Synthesis and Pharmacology of Site-Specific Cocaine Abuse Treatment Agents: Restricted Rotation Analogues of Methylphenidate

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A series of *threo*-1-aza-3 or 4-substituted-5-phenyl[4.4.0]decanes (quinolizidines), which were envisioned as restricted rotational analogues (RRAs) of methylphenidate (MP), was synthesized and tested for inhibitory potency against [^{3}H]WIN35,428, [^{3}H]citalopram, and [^{3}H]nisoxetine binding to the dopamine, serotonin, and norepinephrine transporters, respectively. Two different synthetic schemes were used; a Wittig reaction or acylation (followed by an intramolecular condensation) was a key feature of each scheme. The unsubstituted RRA, *threo(trans*)-1-aza-5-phenyl[4.4.0]decane (**12a**), was equipotent to unconstrained *threo*-MP against [^{3}H]WIN35,428 binding. The extra ring in these RRAs (which reduces the conformational freedom) and the orientation and polarity of substituents at the 4-position on this extra ring are of critical importance to the biological activity. Generally, the RRAs paralleled the corresponding unconstrained MP derivatives in binding affinity to the three transporters. The results suggest that the conformation of MP in which the carbonyl group of the methyl ester is H-bonded to the piperidinyl N−H may be the bioactive form of the molecule.

Introduction

Cocaine (**1**) is a powerfully addictive drug whose abuse continues to be a problem that plagues our society.[1] Drug abuse is not only a health problem, but also a huge economic problem in our society. Compared to non-drug users, cocaine abusers have been shown to have a much higher risk for infectious diseases such as HIV/AIDS and Hepatitis B or C.[2] The economic costs of drug abuse, as developed by the Lewin group in 2001, have increased at a rate of 5.9% annually between 1992 and 1998 in the United States.[3] By 1998 the societal cost of drug abuse including productivity loss, health care, and crime was in excess of $140 billion.

In spite of intensive research in this area[4] and the large economic incentive,[3] there are currently no safe and effective pharmacotherapies available to help habitual users of cocaine who want to stop their usage of the drug. Its reinforcing and stimulant properties are, in part, a consequence of its propensity to inhibit monoamine transport systems, in particular the dopamine transporter (DAT).[5] This inhibition results in an increase in synaptic dopamine levels which then leads to overstimulation of postsynaptic dopamine receptors. However, the importance of serotonergic mechanisms is increasingly being recognized.[6]

Much research has focused on structural analogues of cocaine (**1**) for the development of treatment agents,[4] with the aromatic ring, nitrogen atom, and ester group considered as the important contributors to the pharmacophore in the tropane series.[7] A lack of conformational freedom appears to play a role in the tight binding of these compounds to the DAT. For example, in WIN 35,065-2 (**2**),[8] in which the 4-benzoate group of cocaine is replaced by a directly bonded phenyl group, a 7-fold increase in potency is observed. WIN 35,065-2 has less conformational freedom between the components of the pharmacophore than cocaine. In the more flexible piperidine structure (**3**), which has the same critical functional groups as WIN 35,065-2, binding affinity for the DAT is decreased 33-fold.[9] These results show that rigidity and conformational freedom, which affect the orientation of the functional groups comprising the pharmacophore, can be important factors in determining the potency of binding.

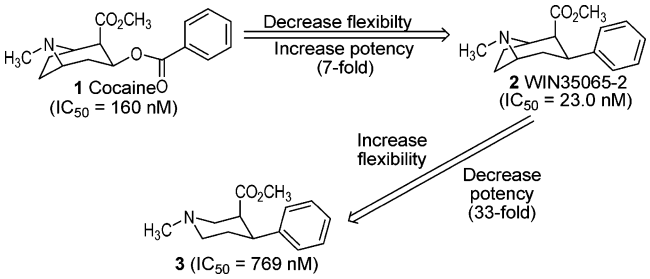

Figure 1. Flexibility in dopamine uptake inhibitors.

The increased flexibility of the piperidine-based ligands also apparently leads to a different structure−activity relationship (SAR) as compared to the tropane ligands. For example, *N*-phenylpropyl or *N*-phenylpentyl tropanes were more potent and *N*-benzyl tropane was less potent for the DAT compared to the corresponding *N*-methyl compound WIN 35,065-2. However, all N-substituted piperidine compounds were significantly less potent for the DAT than the corresponding *N*-methylpiperidine analogue.[4,10] Kozikowski and co-workers have shown, by making rigid cocaine analogues,[11] that the binding selectivity between the monoamine neurotransmitters can be explained in part by the stereochemistry of the nitrogen lone pair. The "back-bridged" analogue **4** is more potent at the DAT while the "front-bridged" analogue **5** is more potent at the serotonin transporter (5-HTT) (Figure 2). Their research has also shown that better selectivity at the 5-HTT can be achieved in a very rigid tricyclic compound **6** with a different arrangement between the functional groups (Figure 2).[12] Therefore, the molecular flexibility as well as the orientation of the critical functional groups can be considered important factors for the development of drugs to be used as treatment agents for cocaine abuse.

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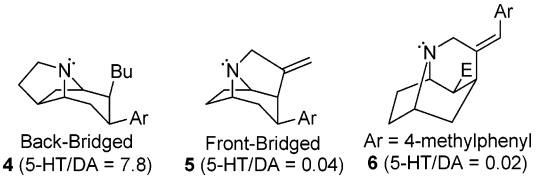
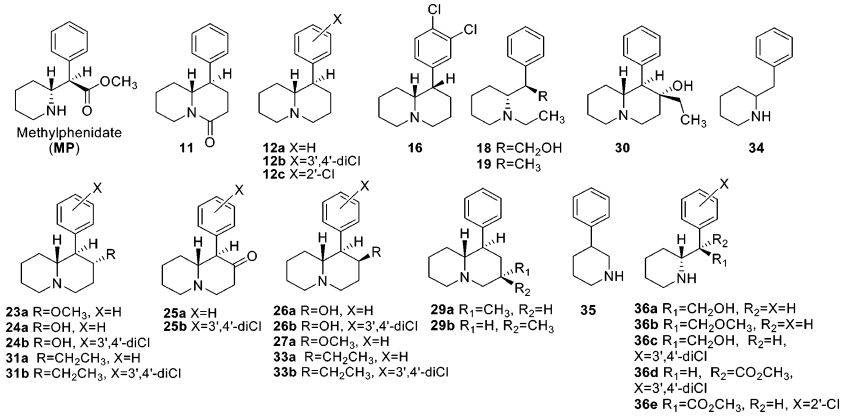


Figure 2. Bridged tropane analogues as a dopamine uptake inhibitor.

MP (**7**) was chosen as a promising candidate for drug development of treatment agents for cocaine abuse for several reasons: (1) decades of clinical experience with MP in the treatment of Attention Deficit Disorder have shown that it is safe and has relatively little abuse potential, when taken orally;[13,14] (2) like cocaine, it binds to the DAT and inhibits dopamine transport;[15,16] (3) in our assays (see Table 1), its rank order of potency at the monoamine transporters differs from that of cocaine (MP: DAT > norepinephrine transporter (NET) >> 5-HTT; cocaine: DAT > 5-HTT > NET), suggesting that derivatives of MP might engender a qualitatively different subjective state compared to cocaine; (4) unlike cocaine,[17] it is not a sodium channel blocker and hence would not be expected to have deleterious effects on nerve conductance, even in overdose. MP also has similar functional groups in its pharmacophore as cocaine and the WIN compounds (a basic nitrogen atom, ester, and an aromatic ring). But in contrast, the functional groups are more flexibly connected than in WIN 35,065-2 and freely rotate through several bonds. Therefore, MP can have many rotational conformers, making it difficult to identify which is the "bioactive" conformation. Our previous results[16] have shown that all derivatives with substituents at the 2′-position of the phenyl ring were much less potent than those with the same substitutents on the 3′- or 4′-positions. We suspected that

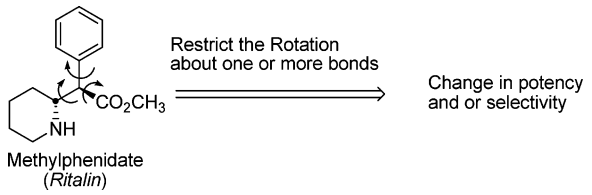
Table 1. Binding and Uptake Inhibition Data for Methylphenidate Analogues and Reference Compounds at the DAT, NET, and 5-HTT



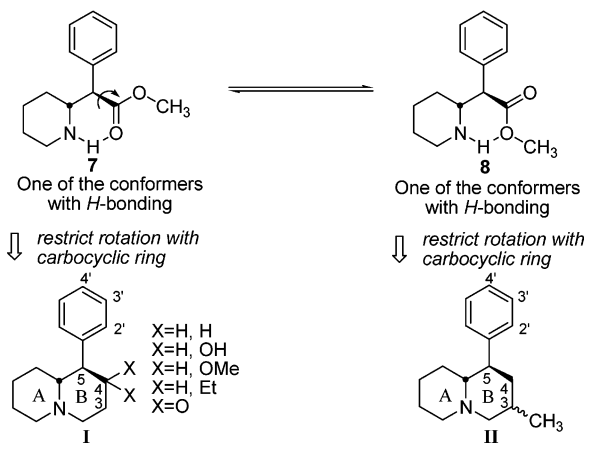
	Binding assays[g]							Selectivity		
	[3H]WIN at the DAT		[3H]NIS at the NET		[3H]CIT at the 5-HTT					
compd[a]	K_i (nM)	n_H	K_i (nM) or % inhibition	n_H	K_i (nM) or % inhibition	n_H	Uptake [3H]DA IC_{50} (nM)	[3H]CIT/ [3H]WIN	[3H]NIS/ [3H]WIN	[3H]CIT/ [3H]NIS
cocaine	156 ± 11	1.03 ± 0.01	1930 ± 360	0.82 ± 0.05	306 ± 13	1.12 ± 0.15	404 ± 26	2.0	12	0.16
MP	74.6 ± 7.4	0.96 ± 0.08	270 ± 23	0.76 ± 0.06	14 ± 8%[f]		230 ± 16	>130	3.6	>37
3′4′-diCl MP	4.76 ± 0.62	2.07 ± 0.05	ND[h]		667 ± 83	1.07 ± 0.04	7.00 ± 0.60	140		
11	6610 ± 440	0.91 ± 0.01	11%[b]		3550 ± 70	1.79 ± 0.55	8490 ± 1800	0.54	>0.76	<0.7
12a	76.2 ± 3.4	1.05 ± 0.05	138 ± 9.0	1.12 ± 0.20	5140 ± 670	1.29 ± 0.40	244 ± 2.5	67	1.8	37
12b	3.39 ± 0.77	1.25 ± 0.29	28.4 ± 2.5	1.56 ± 0.80	121 ± 17	1.16 ± 0.31	11.0 ± 0.00	36	8.4	4.3
12c	480 ± 46	1.00 ± 0.09	2750, 58%[b]	0.96	1840 ± 70	1.18 ± 0.06	1260 ± 290	3.8	5.7	0.67
16	34.6 ± 7.6	0.95 ± 0.18	160 ± 18	1.28 ± 0.12	102 ± 8.2	1.01 ± 0.02	87.6 ± 0.35	3.0	4.6	0.64
18	2100 ± 697	0.87 ± 0.09	ND[h]		16.2 ± 0.05%[f]		10,400 ± 530	>4.8		
19	7610 ± 800	1.02 ± 0.03	8.3%[b]		11 ± 5%[f]		7960 ± 290	>1.3	≫0.66	
23a[d]	570 ± 49	0.94 ± 0.10	2040, 64 ± 1.7%[b]	0.73	14 ± 3%[f]		1850 ± 160	>18	3.6	>4.9
24a	6250 ± 280	0.86 ± 0.03	23.7 ± 4.1%[b]		1 ± 1%[f]		10700 ± 750	≫1.6	>0.80	
24b	35.7 ± 3.2	1.00 ± 0.09	367 ± 42	1.74 ± 0.87	2050 ± 110	1.15 ± 0.12	ND[h]	57	10	5.6
25a	908 ± 160	0.88 ± 0.05	4030, 52%[b]	1.04	5 ± 1%[f]		12400 ± 1500	≫11	4.4	≫2.5
25b	14.0 ± 1.2	1.27 ± 0.20	280 ± 76	0.68 ± 0.09	54 ± 2%[f]		ND[h]	~710	20	~36
26a	108 ± 7.0	0.89 ± 0.10	351 ± 85	0.94 ± 0.27	12 ± 2%[f]		680 ± 52	>93	3.3	>28
26b	2.46 ± 0.52	1.39 ± 0.20	27.9 ± 3.5	0.70 ± 0.01	168	1.02	ND[h]	68	11	6.0
27a	10.8 ± 0.8	0.97 ± 0.07	63.7 ± 2.8	0.84 ± 0.04	2070, 73 ± 5%[f]	0.90	61.0 ± 9.3	190	5.9	32
29a	178 ± 28	1.23 ± 0.09	694 ± 65	0.88 ± 0.13	427	1.39	368	2.4	3.9	0.62
29b	119 ± 20	1.17 ± 0.12	76.0 ± 12	0.88 ± 0.06	243	1.17	248	2.0	0.64	3.2
30	175 ± 8.0	1.00 ± 0.04	1520 ± 120	0.97 ± 0.06	19 ± 4%[f]		ND[h]	>57	8.69	>6.6
31a	27.6 ± 1.7	1.29 ± 0.05	411 ± 49	1.16 ± 0.19	2390, 80%[f]	1.12	ND[h]	87	15	5.8
31b	3.44 ± 0.02	1.90 ± 0.05	102 ± 19	1.27 ± 0.10	286 ± 47	1.30 ± 0.10	ND[h]	83	30	2.8
33a	5.51 ± 0.93	1.15 ± 0.03	60.8 ± 9.6	0.75 ± 0.07	3550, 86%[f]	0.95	ND[h]	640	11	58
33b	4.12 ± 0.95	1.57 ± 0.00	98.8 ± 8.7	1.07 ± 0.07	199 ± 17	1.24 ± 0.00	ND[h]	48	24	2.0
34	6360 ± 1300	1.00 ± 0.04	36 ± 10%[c]		22 ± 7%[f]		8800 ± 870	>1.6		
35	4560 ± 1100	1.10 ± 0.09	534 ± 210[e]	0.96 ± 0.08	53 ± 6%[f]		1060 ± 115	~2.2	0.12	~19
36a	406 ± 4	1.07 ± 0.08	ND[h]		31.0 ± 1.5%[f]		1520 ± 15	>25		
36b	89.9 ± 9.4	0.97 ± 0.04	ND[h]		47.8 ± 0.7%[f]		281 ± 19	~110		
36c	3.91 ± 0.49	1.21 ± 0.06	ND[h]		276, 94.6%[f]	0.89	22.5 ± 1.4	71		
36d	363 ± 20	1.17 ± 0.41	ND[h]		2570 ± 580	1.00 ± 0.01	317 ± 46	7.1		
36e	1740 ± 200	0.98 ± 0.02	ND[h]		22.2 ± 2.5%[f]		2660 ± 140	>5.7		

[a] Compounds tested as the HCl salts, unless otherwise noted. [b] % inhibition by 5 μM. [c] % inhibition caused by 10 μM, as assayed by SRI (see methods section). [d] Tested as a free base. [e] Assayed by SRI (appropriate correction factor applied; see methods section). [f] % inhibition by 10 μM compound. [g] Values expressed as $x \pm$ SEM of two to five replicates. If no SEM is shown, the value is for an n of 1. [h] ND = not determined.

Scheme 1. Restricting Rotation about Bonds



Scheme 2. Design of Rigid Analogues



an intramolecular steric interaction which leads to a lower population of the bioactive conformation might be one of the reasons for this "2′-position" effect. The work reported here was designed to study how the flexibility of MP is related to the binding potency and which conformation is involved (see Schemes 1 and 2).

One approach to the exploration of the issues cited above is the synthesis of more rigid analogues in which the rotation about selected bonds is restricted and a promising rotational conformer of MP is mimicked. Our first attempt was a "bridging" (with two carbon atoms) between the carbonyl carbon of the ester and the nitrogen atom to afford a bicyclo-[4.4.0] structure as shown in Scheme 2. The resulting rigid molecule resembles the conformations assumed by the freely rotating ester upon intramolecular hydrogen bonding between the N−H and the ester group, which could play a role in the bioactive conformation of MP.

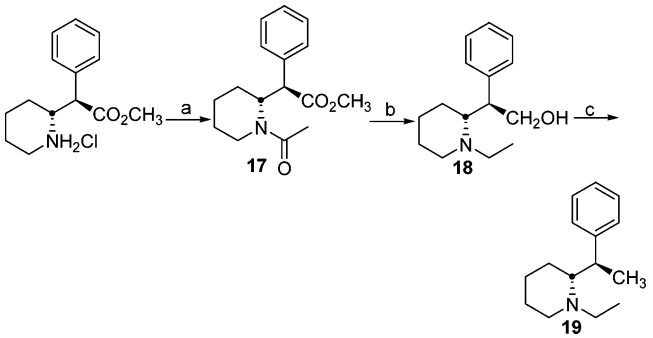
We report here the synthesis and testing of a series of novel bicyclic bioactive analogues of MP, 1-aza-5-aryl-[4.4.0]decahydronaphthalenes, with structures similar to the intramolecularly H-bonded conformers of MP. They are compared with the corresponding unconstrained compounds and with each other for potency at the DAT, NET, and 5-HTT.

Results and Discussion

Chemistry. Two different synthetic pathways were designed to build the 1-aza-5-phenyl[4.4.0]decane structure.[18] The first (Scheme 3) was based on a Wittig reaction in which a carboethoxy ylide ($Ph_3P{=}CHCO_2Et$)[19] was utilized to incorporate two additional carbon atoms into MP at the ester carbonyl carbon. For this reaction, the ester group was converted into an aldehyde (**9** and **13)** which required protection of the secondary amine with the BOC group. This was followed by reduction of the ester to the alcohol with LAH and then reoxidation to the aldehyde with PCC. The Wittig products were always mixtures of isomers with E:Z ratios that varied from 13:1 (**10b**) to 7:1 (**14**), based on ^{1}H NMR analysis after deprotection of the BOC group. The mixtures of *E*/*Z* isomers were hydrogenated to give aminoesters which cyclized to the corresponding lactams (**11a**−**c** and **15**), either during the hydrogenation and evaporation of the solvent or during further treatment with K_2CO_3 in methanol. All the lactams were reduced to the corresponding tertiary amines (**12a**−**c** and **16**) in good yield using diborane in refluxing THF.

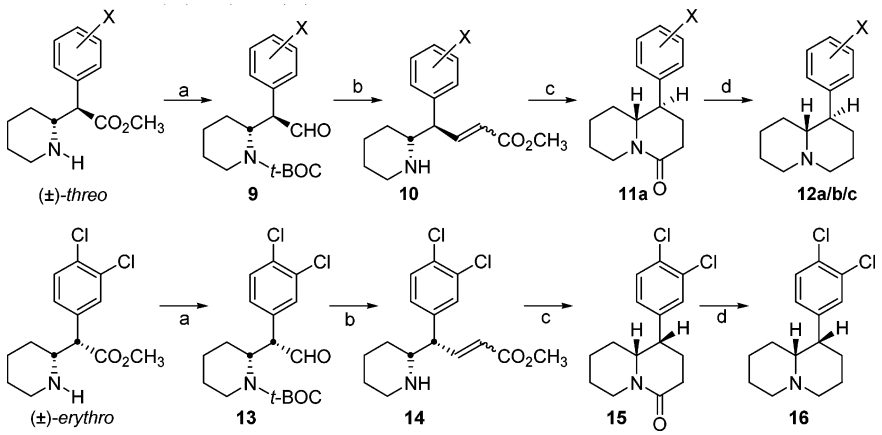
In order to compare these bicyclic analogues of MP to a noncyclized compound without the ester functional group, two "broken ring" analogues were prepared. These two compounds (**18** and **19**) were designed and synthesized as shown in Scheme 4. The acetamide derivative of MP (**17**) was prepared and

Scheme 4[a]



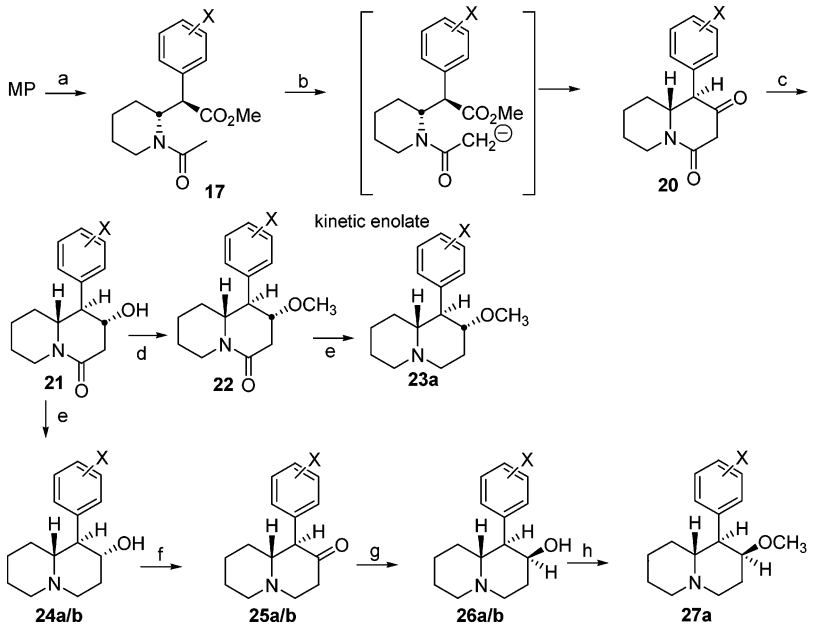
[a] (a) Ac_2O/Pyridine/DMAP; (b) LAH/THF; (c) TsCl/DMAP; LAH reduced to afford *N*-ethylritalinol (**18**). Tosylation of the hydroxy group followed by direct addition of LAH (one-pot reaction)

Scheme 3[a,b]



[a] (a) i) $BoC)_2O$/$NaHCO_3$/NaCl; ii) LAH/THF; iii) PCC; (b) i) $Ph_3PCHCO_2CH_3$; ii) TFA; (c) i) 10% Pd-C/H_2; ii) K_2CO_3/CH_3OH; (d) BH_3/THF. [b] (a, X=H; b, X=3′,4′-diCl; c, X=2′-Cl).

Scheme 5[a,b]



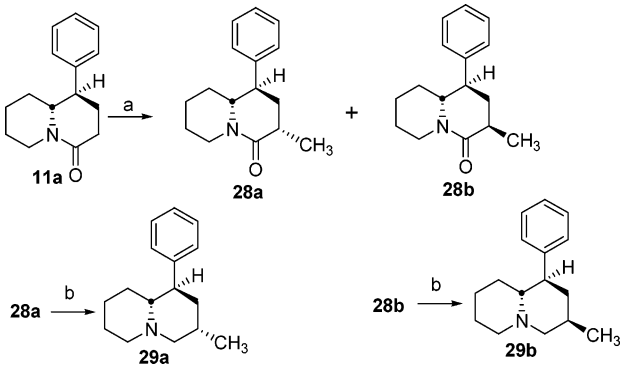
[a] (a) Ac_2O/Pyridine/DMAP; (b) LHMDS/HMPA; (c) $NaBH_4$; (d) LHMDS; MeI; (e) BH_3/THF; (f) $(COCl)_2$/DMSO; Et_3N; (g) K-Selectride, −78 °C; (h) NaH; TBAl/MeI. [b] (a, X = H; b, X = 3′,4′-diCl).

afforded the open-chained compound **19**. The intermediate tosylate was too unstable for isolation.

The second synthetic pathway to the 1-aza-5-phenyl[4.4.0]-decane structure, which would also introduce groups at the C-4 position and mimic the rotational conformer (**7**), is shown in Scheme 5. An intramolecular condensation reaction was designed to afford a carbonyl group at C-4 which could be further transformed to various functional groups. Acylation of the secondary amine of MP gave **17** which incorporated the two additional carbon atoms needed. For the controlled intramolecular condensation between amide and ester groups, the kinetic enolate of **17** was obtained by dropwise addition of LDA to a cold solution of **17** in THF. This afforded the 4-ketoamide (**20**) as the major product. When compound **20** was treated with LAH, no major product could be isolated. However, a stepwise reduction process proved to be successful. When $NaBH_4$ in methanol at 0 °C was used, only the 4-α-hydroxy isomer (**21**) was obtained. The stereochemistry of the hydroxyl group of **21** was easily determined by analysis of the ^{1}H NMR spectrum. The axial benzylic proton (C-5) of hydroxyamide **21a** is a triplet (J = 10.5 Hz) at 2.58 ppm and therefore must be adjacent to two axial protons at C-4 and C-6. The hydroxyl group of **21** was methylated with LDA and methyl iodide to afford **22** in a high yield. One equivalent of the base must be used to reduce the amount of a side reaction, which afforded an α,β-unsaturated lactam. Borane reduction of amides **21** and **22** afforded amines **23** and **24** (4-α orientation).

A Mitsunobu reaction[20] was attempted in order to prepare the 4β-hydroxyamide from 4α-hydroxyamide **21**; however, the acetate group of the reaction product was very easily eliminated to afford the α,β-unsaturated amide during the hydrolysis or reduction steps. Fortunately, another route to the 4β-hydroxyl series was available. Aminoketone **25** was prepared by borane reduction of **21**, followed by Swern oxidation. Reduction of the carbonyl group of **25** using K-Selectride was found to be stereoselective and gave only the β-isomer (**26**) when the reaction was done at −78 °C. The stereochemistry (α or β) of the hydroxyl group was easily determined by examining the splitting patterns in the ^{1}H NMR spectra. In the α isomer (**24a**),

Scheme 6[a]

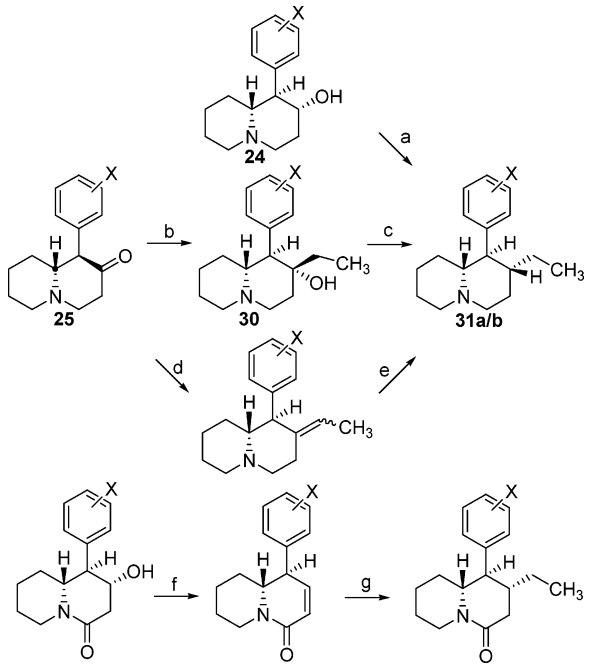


[a] (a) LHMDS, −78 °C; MeI; (b) BH_3/THF

the benzylic proton at C-5 clearly shows a triplet at 2.32 ppm (J = 10.5 Hz), which is very similar to the same proton in **21a**. For the β-isomer (**26a**) the corresponding benzylic proton shows a doublet of doublets at 2.60 ppm (J = 9.0, 2.7 Hz). The carbinol protons at C-4 for both isomers were also consistent with these assignments [**24a** shows a triplet of doublets at 3.67 ppm (J = 10.5, 4.8 Hz) and **26a** a quartet at 3.85 ppm (J = 2.7 Hz)]. The stereoselectivity of the carbonyl group reduction depends on the size of the reducing agent. For example, K-selectride gives only the β-isomer (**26**), whereas DIBAL-H gives a 2:1 ratio of β to α isomers (**24**/**26**). The hydroxyl group of **26** was methylated with LDA and methyl iodide to afford **27** in a moderate yield.

In order to mimic the other rotational conformer (**8** in Scheme 2), the lactam **11a** was methylated with MeI using LHMDS at −78 °C (Scheme 6). This produced a 1:1 mixture of amide isomers (**28a/b**). These isomers were separated by chromatography and their stereochemistry determined using ^{1}H NMR NOESY spectral data. A NOE spectrum of the α-isomer (**28a**) shows a strong interaction between the methyl protons (d, J = 7.5 Hz, 1.29 ppm) at C-3 and the benzylic proton at C-5. This is expected because the methyl group and the benzylic proton are cis and close to each other (estimated distance using CHEM 3D is 2.8 Å). However, the methyl protons of the β-isomer (**28b**)

Scheme 7[a,b]



[a] (a) MsCl/Et_3N/DMAP; EtMgBr/THF; (b) EtMgBr/THF; (c) i) NaH/Imidazole/THF; CS_2; MeI; (d) Ph_3PEtBr/LHMDS; (e) 10% Pd-C/H_2; (f) Ac_2O/Pyridine/DMAP; (g) EtMgBr/$CuBrMe_2S$, HMPA. [b] (a, X=H; b, X=3′,4′-diCl).

(d, $J = 6.9$ Hz, 1.23 ppm) do not show this interaction, because of the trans-orientation of these groups (estimated distance using CHEM 3D is 4.4 Å). Each lactam, **28a** and **28b**, was separately reduced to afford the amines **29a** and **29b** in high yield.

In order to prepare compounds with appendages at C-4 less polar than the methoxyl groups of **23** and **27**, ethyl analogues were designed and synthesized. Several strategies were utilized, but only the α-isomer (**31**) was obtained using a number of different reactions of cyclic precursors, as shown in Scheme 7. Fortunately, a mixture of isomers, enriched in the *β*-isomer, could be synthesized using the acyclic α,*β*-unsaturated ester **10**. The Michael addition of ethylmagnesium bromide[21] to **10** gave a mixture of isomers (2:7 ratio, Scheme 8). These adducts were treated with trifluoroacetic acid (TFA) and then K_2CO_3 to afford the corresponding mixture of lactams (**32**), which in our hands could not be separated. After reduction, the amine α- and *β*-isomers (**31** and **33**, 2:7 ratio, respectively) could be separated by chromatography. The stereochemistry of these isomers was easily determined by examining the splitting patterns of the benzylic hydrogen in the ^{1}H NMR spectra (see discussion for **24a** and **26a** above).

The analogues 2-benzylpiperidine (**34**)[22] and a 3-phenylpiperidine (**35**)[23] were, respectively, prepared by a catalytic hydrogenation from 2-benzylpyridine and 3-phenylpyridine (Scheme 8). Each of these compounds, **34** or **35**, has only one ring (A or B) of the restricted analogue **12a**. Two additional noncyclized compounds were synthesized to facilitate comparisons. The *erythro* compound **36d** was made as described in our earlier work.[16] Alcohols **36a** and **36c** were synthesized by reduction of MP and 3′,4′-dichloromethylphenidate,[16] respectively. Ether **36b** was made by methylation of **36a** (protected as *N*-benzyl).

The reactions in Schemes 3 and 6 proved to be very useful for the synthesis of RRAs with either no substitution at positions 3 and 4 or for those substituted only at position 3. For analogues substituted at position 4, the reactions summarized in Schemes 5, 7, and 8 worked very well. The stereospecific reductions of the carbonyl group of **20** (with $NaBH_4$) and **25** (with K-selectride) to give the α and *β* hydroxyl isomers, respectively, proved to be extremely useful. All attempts to use the cyclic precursor **25** for the synthesis of 4-ethyl derivatives gave only α isomers under a number of conditions (Scheme 7). The problem of obtaining the *β* isomers was solved by a stereoselective Michael addition to the acyclic ester **10** to yield primarily the *β* isomer.

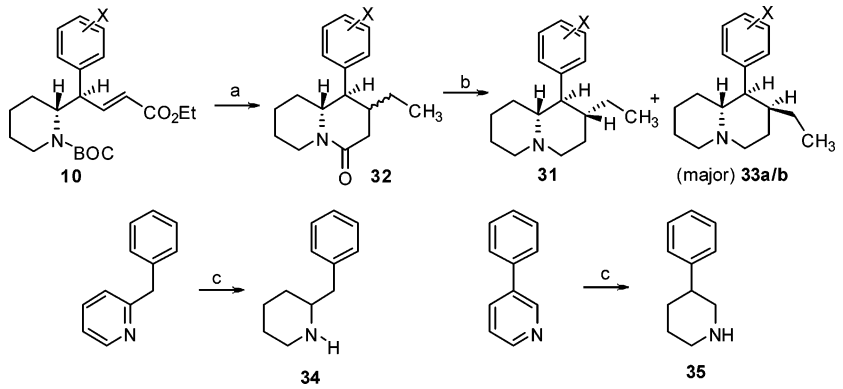
Pharmacology. All of the compounds that were synthesized in this study were tested for their ability to inhibit the binding of [^{3}H]WIN 35,428 (WIN) to rat striatal tissue as a measure of their binding to the DAT. In addition, the uptake of [^{3}H]-dopamine[24] ([^{3}H]DA)into rat striatal synaptosomes was determined for some of the compounds. Binding to the 5-HTT was measured using [^{3}H]citalopram (CIT) and rat cortical tissue. Binding to the NET was measured using [^{3}H]nisoxetine (NIS) and portions of rat cerebrum and brain stem. A 25 mM sodium phosphate buffer, pH 7.70 at 0 °C, was utilized in all three binding assays in order to standardize conditions across assays. The NIS binding assay required that the buffer also contain 5 mM KCl and 120 mM NaCl in order to optimize high affinity specific binding. A more detailed description of the methods used can be found in the experimental section below. The results are summarized in Table 1. Previously published data for the corresponding unconstrained compounds are also included in Table 1 to facilitate comparison.

Inhibition of WIN Binding. Values quoted in the following discussion for the inhibition constants (K_i) are expressed as the mean ± SEM, in nanomolar (nM) units. In general, these RRAs are at least as potent as, and in several cases somewhat more potent than, the corresponding unconstrained MP analogues. For example, the affinity of MP (K_i =74.6 ± 7.4) is virtually identical to the corresponding RRA **12a** (K_i =76.2 ± 3.4). For 3′,4′-dichloromethylphenidate[16] and the corresponding compound **12b**, the K_i values are 4.76 ± 0.62 and 3.39 ± 0.77, respectively. In some cases, the cyclized analogues are more potent; for example **12c** is 3.6-fold more potent than 2′-chloromethylphenidate[16] (K_i = 1740 ± 200) and the *erythro* compound **16** is 10.5-fold more potent than the corresponding *erythro*-3′,4′-dichloromethylphenidate (**36d**) (K_i = 363 ± 20). These RRAs do not have an ester group, which has been considered an essential component of the MP pharmacophore.[16] These results suggest that the ester group of MP might function mostly to control the conformation, rather than in directly contributing to the binding affinity.

The critical importance of conformation is supported by the fact that the potency of the RRAs is decreased when the structures become flexible. For example, the potency of rigid analogue **12a** is reduced by 100-fold when the C−C bond between C-3 and C-4 is disrupted to form the "open ring" compound **19** (K_i = 7610 ± 800). The potency is also greatly decreased (83 and 60-fold, respectively) when either one of the rings (A or B) is removed, as illustrated by compounds **34** (K_i = 6360 ± 1300) or **35** (K_i = 4560 ± 1100).

The importance of other commonly accepted pharmacophoric elements such as a basic nitrogen atom and the *threo* configuration is also indicated. For example, the lack of a basic nitrogen in amide **11** causes the potency (K_i = 6610 ± 440) to decrease 89-fold as compared to **12a**. This is consistent with reports of other investigators for the tropane,[25,28a] benztropine,[26] and MP[28b] series. Clearly, a basic nitrogen atom strongly enhances binding to the DAT.

Scheme 8[a,b]



[a] (a) i) EtMgBr/CuBrMe$_2$S, HMPA; ii) TFA; iii) K_2CO_3/CH_3OH; (b) BH_3/THF; (c) 10% Pt-C/H_2. [b] (a, X=H; b, X=3′,4′-diCl).

The RRA *threo* (*trans*) compound **12b** (K_i =3.39 ± 0.77) is 10-fold more potent than the *erythro*-isomer **16**. A similar, but more pronounced, effect is seen with the corresponding noncyclized isomers, where the 3′4′-dichloro *threo* compound (K_i = 4.76 ± 0.62) is 76-fold more potent than the corresponding noncyclized *erythro*-isomer **36d** (K_i = 363 ± 20).

Examination of the K_is against WIN obtained when ring B is substituted at position 3 or 4 shows that the inhibitory potency of the resulting compounds depends on the nature, position, and orientation of the substituents. Introduction of a methyl group in either orientation at the C-3 position (designed to mimic hydrogen bonding conformer **8** [Scheme 2]) has little effect on binding potency; **29a** (α, K_i =178 ± 28) and **29b** (*β*, K_i =119 ± 20) as compared to the unsubstituted compound **12a** (K_i =76.2 ± 3.4). As will be discussed later in this report, however, selectivity for the DAT over the 5-HTT is greatly reduced.

In contrast, the effects of substituents at C-4 (hydrogen bonding conformer **7**; Scheme 2) depend both on the nature of the group (such as hydroxyl, methoxyl, carbonyl, and ethyl) and the orientation. In general, potency decreased with polarity (CH_2CH_3 > OCH_3 ≥ O ∼ OH). All compounds with polar groups (hydroxyl, carbonyl) were less potent as compared to the parent compound **12a**; all the compounds with either a 4*β*-methoxyl or 4-ethyl group were more potent. For example, 4α-hydroxy compound **24a** (K_i = 6250 ± 280) is 82-fold less potent than the parent compound **12a**. A similar, albeit less pronounced, reduction in binding affinity is also observed for the unconstrained alcohol analogue of MP (**36a**), which is 5.4-fold less potent (K_i = 406 ± 4.0) than MP.[16]

There is, however, a very strong orientation effect at the 4-position of the cyclized structure. In all cases, groups α oriented (*trans* to the phenyl group) yield analogues less potent than when *β* oriented (*cis* to the phenyl group). This orientation effect is very strong for the more polar OH and OCH_3 groups and much less for the nonpolar CH_2CH_3 group. For instance, the 4*β*-hydroxy compound **26a** (K_i =108 ± 7) is 58-fold more potent than the 4α-hydroxy **24a** and only slightly less potent than the parent **12a**. Note that oxo compound **25a**, with a carbonyl group pointing between the α and *β* orientations, has a binding affinity (K_i = 908 ± 160) in between those of the α and *β* hydroxyl compounds [**24a** (K_i = 6250 ± 280), **26a** (K_i = 108 ± 7.0)]. Moreover, if the hydroxylated ring B of the constrained analogue is opened between C3 and C4, the resulting compound (**18**) exhibits an affinity (2100 ± 697) between that of the 4α-hydroxy and 4*β*-hydroxy compounds. The orientation effect is also evident when the aromatic ring of the hydroxylated compounds is chlorinated. Here, the *β*-hydroxy compound **26b** (K_i = 2.46 ± 0.52) is 15-fold more potent than the 4α-hydroxy

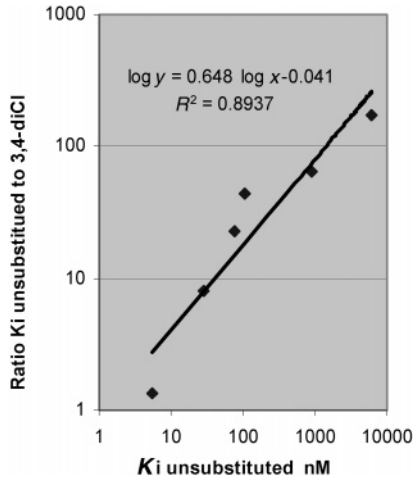


Figure 3. WIN binding for unsubstituted versus enhancement in binding caused by 3,4-diCl substitution.

24b. The advantage of locking the OH group into the *β* orientation can be seen from the fact that **26b** even surpasses the analogous unconstrained compound **36c** in potency. The less polar methyl ethers are both much more potent (∼10-fold) than the corresponding alcohols and show an almost identical orientation effect. Thus, the 4*β*-methoxyl compound **27a** (K_i = 10.8 ± 0.8) is 53-fold more potent than the 4α-methoxyl compound **23a** (K_i = 570 ± 49). The higher potency of methyl ether as opposed to alcohol analogues (4.5-fold) is also observed in the unconstrained MP derivatives **36b** (K_i = 89.9 ± 9.4) and **36a** (K_i = 406 ± 4). With the completely nonpolar ethyl substituents, even more potent compounds were obtained, but the orientation effect was greatly reduced. The 4*β*-ethyl compound **33a** (K_i = 5.51 ± 0.93) is only 5-fold more potent than the 4α-ethyl compound **31a** (K_i = 27.6 ± 1.7). The dramatic loss of affinity (32-fold) due to a polar 4α-hydroxyl group is also shown in **30** (K_i = 175 ± 8.0) as compared to **33a** (K_i = 5.51 ± 0.93) which both have 4*β*-ethyl substituents. Thus, polar groups at position 4 are not well tolerated, but those *trans* to the phenyl group are particularly deleterious to binding efficacy. Nonpolar groups such as ethyl enhance potency in either orientation. In general, these results support the proposition that the methyl ester of MP functions primarily to control conformation through hydrogen bonding and does not contribute directly to the actual binding interactions of MP with the transporter.

For the most part, substitutions on the phenyl ring of these RRAs affect potency in a qualitatively similar manner as those of the analogous nonrigid MP derivatives. For example: 2′-

chloro **12c** is 6-fold less potent than unsubstituted **12a**, while 3′,4′-dichloro substitution of the aromatic ring of the RRAs generally leads to a significant increase in binding affinity. The 3′,4′-dichloro compound **12b** ($K_i = 3.39 \pm 0.77$) is 22-fold more potent than the parent compound **12a**. Other comparisons are: **24b** to **24a** (175-fold), **25b** to **25a** (65-fold), **26b** to **26a** (44-fold), and **31b** to **31a** (8-fold). However, **33b** ($K_i = 4.12 \pm 0.95$) and **33a** ($K_i = 5.51 \pm 0.93$) are essentially identical in binding potency. An increase in affinity upon 3′,4′-dichloro substitution of the aromatic ring is also characteristic of noncyclized MP derivatives; e.g., 3′,4′-dichloromethylphenidate is 16-fold more potent than MP and **36c** is over 100-fold more potent than **36a**. Similar results have been noted for 3,4-dichloro derivatives of meperidine.[27]

Closer inspection of the WIN binding data obtained for the 3′,4′-dichloro analogues reveals an interesting trend. Shown in Figure 3 is a log−log plot of the K_i of various unsubstituted analogues versus the ratio of K_i values for these unsubstituted analogues to the corresponding 3′,4′-dichloro-substituted analogue. This ratio, which varies from 1.3 to 175, is a measure of the enhancement of potency due to 3′,4′-dichloro substitution. Surprisingly, there is a strong correlation between the log of this enhancement ratio and the log of the K_i values of the unsubstituted analogues ($R^2 = 0.89$). Thus, the affinities of compounds with low potency for the DAT are highly enhanced by dichloro substitution, while the more potent compounds show very little enhancement. This effect may be caused, at least in part, by a competition in the mode of binding by the different pharmacophoric elements which is not completely complementary. It is possible that 3′,4′-dichloro-substituted phenyl rings interact with the area of the binding site that recognizes the aromatic ring in a slightly different manner than do unsubstituted phenyl groups. Although the improved interaction of the dichlorinated compounds with the aromatic ring binding pocket confers heightened affinity for this binding domain, it may also force the dichlorinated molecules to bind in a somewhat different orientation that prevents the optimal binding of the other components of the pharmacophore. Low affinity structures, by definition, do not interact optimally with the various binding site domains. Upon 3′,4′-dichloro substitution, large increases in affinity may occur with these low potency compounds because of the dramatic increase in affinity that results from the improved interaction with the aromatic ring binding pocket. This greatly offsets the negative impact on the low affinity interactions of the remaining pharmacophoric elements that is caused by the proposed shift in orientation following chlorine substitution. On the other hand, high affinity unsubstituted compounds presumably already interact near optimally with all domains on the binding site. While introduction of chlorine atoms into the phenyl ring of a high affinity compound may enhance its interaction with the binding pocket for the aromatic moiety, it may also shift the orientation of the molecule so as to disrupt the strong binding interactions of the remaining elements of the pharmacophore with the DAT. Thus, any increase in affinity due to dichloro substitution of the phenyl ring of high affinity compounds will be offset by the negative effect on the interaction of the molecule with the remaining binding domains, with the net result that little change in affinity will occur.

This "3′,4′-dichloro substitution" effect may in part help to explain the results of Meltzer et al.[28] that show that both tropane and MP ligands without a basic nitrogen, "nonamines", can still have fairly high affinity for the DAT. In both cases, the higher affinity compounds are 3′,4′-dichloro-substituted; the unsubstituted analogues have quite low affinity. For the MP compound without a basic nitrogen[28b], the reported K_i values for binding to the DAT (utilizing a different binding assay than employed in our laboratory) were 3000 nM for the unsubstituted and 29nM for the 3′,4′-dichloro-substituted. Based on the correlation shown in Figure 3, the predicted value for 3′,4′-dichloro-substituted (using the unsubstituted K_i value of 3000 nM) would be 18 nM, in good agreement with the experimental value of 29 nM. Thus, it appears that 3′,4′-dichloro substitution can compensate for the loss or modification of the other essential elements of the pharmacophore common to the various structural classes of stimulant agents.

Inhibition of [^{3}H]DA Uptake. Similar conclusions to those described for WIN binding can be reached when considering the inhibition of [^{3}H]DA uptake, since there is a high correlation between them. Generally, IC_{50}s obtained for the inhibition of [^{3}H]DA uptake were approximately 2- to 3-fold higher than the K_is obtained for the inhibition of WIN binding, similar to unconstrained MP derivatives.[16] It is possible that this systematic difference in values obtained between the two assays is due to the different conditions utilized in the two analyses. The largest departure from this pattern is seen with the 4-oxo compound **25a**, which is 14-fold less potent against [^{3}H]DA uptake ($IC_{50} = 12\,400 \pm 1500$ nM) than WIN binding. Interestingly, this compound closely resembles conformer **8** (the conformer of MP possibly less favored for interaction with the WIN binding site; see later discussion) with respect to the position of its carbonyl group (Scheme 2). **25a** is the least potent of the RRAs tested against [^{3}H]DA uptake and is similar in potency to the 4-α hydroxy compound **24a** against DA transport. In the WIN assay, however, **25a** is almost 7-fold more potent than the 4-α hydroxyl compound.

The only compound that is *less* potent in the WIN binding assay than in the [^{3}H]DA uptake assay is compound **35**, one of the compounds designed to test whether both of the constrained rings contribute to the activity of the RRAs. Its IC_{50} against [^{3}H]DA uptake is 0.23-fold that of its K_i against WIN binding. Compound **35** (which lacks the piperidine ring native to MP) and compound **34** (which retains the original piperidine ring, but lacks the constrained ring B common to the RRAs) exhibit approximately equal, but weak, potency against WIN binding. However, compound **35** is 8.3-fold more potent than **34** against [^{3}H]DA uptake. The significance, if any, of the departure of compounds **25a** and **35** from the typical relationship observed between values of potency obtained for compounds in the [^{3}H]DA uptake and WIN binding assay is unknown at this time.

Inhibition of CIT Binding and Selectivity for WIN over CIT. Most unconstrained MP analogues are quite selective for the DAT as compared to the 5-HTT, as evidenced by the high ratios of CIT to WIN K_i values shown in Table 1. With one exception (discussed below), the RRAs are also more potent at the DAT as compared to the 5-HTT, although in many cases their selectivity is diminished. To illustrate, compare the selectivity of the unconstrained compounds MP (>134) and 3′,4′-diClMP (140) with their corresponding RRAs, **12a** (67) and **12b** (36). In most instances, the decreased selectivity is attributable to increased inhibitory potency against CIT, rather than decreased potency against WIN.

In every case, introduction of 3′,4′-dichloro into the aryl ring increases the potency of the RRAs against CIT binding; e.g., compare **24a** and **24b**. This is observed even for the 4β-ethyl-substituted compound **33b**, the only compound that does not show increased affinity for the WIN and NIS binding site upon

dichloro substitution. Where the data allow quantification, dichloro substitution is found to attenuate the selectivity for the WIN by increasing the inhibitory potency for the CIT binding site to an even greater extent than it enhances potency for the WIN binding site.

Similar to the results seen with WIN binding, the orientation of the methyl substitution at the C-3 position of ring B has little effect on the binding of these compounds to the 5-HTT. Both the α (**29a**) and *β* (**29b**) isomer, however, exhibit greater than a 10-fold increase in potency against CIT binding compared to the unsubstituted **12a**. This increase in potency almost completely removes their selectivity (2.4 and 2.0, respectively). Although a 4-keto, 3-Me-substituted RRA would provide a better test of this hypothesis, these results offer preliminary evidence that hydrogen bonding conformer **8** (Scheme 2), which these compounds resemble, is not the biologically relevant conformation of MP. If it were, these compounds would be expected to have a much lower affinity for the 5-HTT (see discussion below). The dramatic increase in affinity for the CIT binding site seen with the 3-substituted RRAs suggests that they could prove useful in elucidating the structural characteristics of the 5-HTT.

As with the WIN binding results, the orientation of polar substitutions at the C-4 position affects CIT binding, with the *β* orientation favored over the α orientation (compare compounds **23a** and **27a**, **24a** and **26a**, and **24b** and **26b**). This effect is not observed, however, when a nonpolar group is the substituent (compare **31a** and **33a**, and **31b** and **33b**).

A carbonyl at C-4 increases the selectivity substantially compared to the corresponding RRA without a C-4 substitution; e.g., compare **25b** (∼700) to **12b** (36). While **25a** (>>11) appears to show this same pattern with respect to **12a** (67), the low affinity of **25a** for the 5-HTT precludes a definitive comparison. When the aromatic ring is unsubstituted, a 4*β*-ethyl group leads to higher selectivity (**33a**, 640) than a 4α-ethyl group (**31a**, 87); however, when the aromatic ring is 3′,4′-diCl-substituted the effect is lost (48 and 83 for **33b** and **31b**, respectively). The 4*β*-OMe compound (**27a**) also had high selectivity (192); however, for most other compounds the exact selectivity could not be measured, because of their low affinity for the 5-HTT site.

In contrast to all of the other compounds, the amide (**11**), without a basic nitrogen, is slightly *more* selective for the CIT binding site over the WIN binding site (0.5). Moreover, it is approximately equipotent to the amine **12a** at the CIT site (K_is of 3550 ± 70 nM versus 5140 ± 670 nM). This might suggest that 3-methyl amide analogues would have high selectivity for CIT compared to WIN.

The one *erythro*-isomer (**16**) that was studied has very little selectivity (3.0). As above, the loss of selectivity is due more to its gain in affinity for the CIT binding site, rather than its loss of affinity for the WIN binding site.

Inhibition of NIS Binding and Selectivity for WIN Compared to NIS. Both unconstrained and constrained MP analogues generally have low NIS/WIN selectivity. For example, MP itself is only 3.6 times more potent against WIN versus NIS binding, while the unsubstituted rigid analogue **12a** is only 1.8-fold more selective for the WIN site. Since the inhibition of NIS binding generally shows similar trends as WIN binding, selectivity changes little with structure for these compounds. The RRAs showing the greatest selectivity for the WIN over the NIS site are the 4-ethyl and 4-oxo analogues with 3′,4′ dichloro-substituted aryl rings (**31b**, **33b**, and **25b**); they are 30-, 24-, and 20-fold more potent, respectively, at the WIN versus the NIS binding site. Removal of the dichloro substitution from these compounds causes the selectivity to drop by half or more.

Potential Bioactive Conformers. In considering which might be the bioactive conformation of MP at the various transporters, the 4-OMe compounds **23a** and **27a** can be viewed as analogues of H-bonded conformer **7** (Scheme 2), while the 3-Me compounds **29a** and **29b** can be seen as first approximations of conformer **8** (Scheme 2). The pH was purposely held constant across the WIN, CIT, and NIS binding assays so that the distribution of charged species for a given compound would not change because of assay conditions. If it is assumed that the same conformer binds to all three transporters, the data clearly supports conformer **7** as the likely bioactive candidate. Even though neither **23a** nor **27a** has the same affinity for the three transporters as the freely rotating MP, they both exhibit the same relative affinity across the transporter assays as MP, and the affinity of MP for the transporters is bracketed by the values obtained for the α- and *β*-oriented isomers. This bracketing effect likely reflects the fact that the OCH_3 of the freely rotating ester (at an sp^2 carbon) has a "planar" orientation, while the 4-OCH_3 groups in the RRAs have "up and down" orientations at the sp^3 carbon. Compounds **29a** and **29b**, on the other hand, neither bracket the values obtained for MP at all of the transporters nor exhibit the same proportional relative selectivities for the transporters as does MP. This suggests that conformer **8** is not the bioactive conformer if it is stipulated that the same conformer must interact with all three transporters.

Alternatively, it is possible that MP could be influenced by the microenvironment of the individual transporters, so that the optimal conformation might vary depending upon the particular transporter. In this case, the DAT might accept either conformer **7** or **8**. The rationale for conformer **7** is presented above. The 3-Me isomers are fairly close to MP in potency (no more than 2.5-fold less potent), suggesting that conformer **8** might also interact with the DAT. The NIS binding results also indicate that both conformer **7** (discussed above) and **8** might be suitable for binding to the NET. The K_is of **29a** and **29b** for the NET bracket the value obtained for MP, suggesting that conformer **8** may also be able to interact favorably with the NIS binding site. In contrast, the 5-HTT appears to recognize only conformer **7**. This is based on the fact that the potency of compounds **23a** and **27a** closely parallel the results obtained for MP, while **29a** and **29b** are much more potent inhibitors of CIT binding, which does not reflect the results obtained for MP.

Conclusions

Cyclized MP analogues constitute an exciting new category of potential pharmacotherapies for cocaine abuse. These compounds are unique in that their ester function has been removed and the rotational freedom of the resulting molecule is limited. The former alteration may be advantageous, in that removal of the primary site of metabolic attack by esterases may lead to a longer elimination half-life *in vivo*. The latter alteration, combined with the introduction of various substituents at the 3 and 4 positions of the added ring, allows some preliminary conclusions about the bioactive conformation of MP and its mode of binding to the monoamine transporters. A detailed interpretation of the effect of 3′,4′-dichloro substitution has revealed a new picture of how these compounds may uniquely bind to the DAT. Finally, two compounds (**31b** and **33b**), characterized by 3′,4′-dichloro-substituted benzene rings and 4-ethyl groups, have been identified that possess relatively high

affinity and selectivity for the DAT. These compounds may prove useful as selective probes for the DAT.

Experimental Section

Chemistry.

General Methods. Starting materials were purchased from Aldrich Chemical Co. and used without further purification. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl prior to distillation under argon. Flash chromatography was run using 230−400 mesh silica gel. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H (300 or 500 MHz), ^{13}C NMR (75 or 100 MHz), and COSY/NOESY spectra were obtained on either a Varian Gemini-300 or a Bruker DSX-500 Spectrometer. High-resolution mass spectra (EI, CI or FAB) were recorded on a VG Analytical 70-SE mass spectrometer equipped with a 11-250J data system. Elemental analyses were obtained from Atlantic Microlabs, Atlanta, GA. Free bases were dissolved in CH_2Cl_2 and converted to HCl salts by the addition of 1 M HCl (1.5 equiv.) in diethyl ether. The excess HCl was removed under reduced pressure, and the solid was recrystallized from a mixture of MeOH, EtOAc, diethyl ether, or CH_2Cl_2.

General Procedures of 1-Aza-2-oxo-5-(aromatic ring-substituted)[4.4.0]decane (11 and 15). *threo*-1-Aza-2-oxo-5-phenyl-[4.4.0]decane (11a). The HCl salt of *threo*-MP (5.0 g, 18.6 mmol) was dissolved in a mixture of di-*tert*-butyl dicarbonate (4.06 g, 18.6 mmol), sodium bicarbonate (3.61 g, 43.0 mmol), and sodium chloride (4.4 g, 75.1 mmol) in water (50 mL) and chloroform (100 mL). The mixture was heated under reflux until the starting material disappeared as shown by TLC analysis (2 h). After being cooled to RT, the mixture was washed with 1 N HCl solution and water, and the organic layer was dried over $MgSO_4$ and concentrated to afford a crude product (6.2 g, 100%); HRMS (CI) calcd for $C_{19}H_{28}NO_4$ *m*/*z* 334.2018, found 334.2034. Because of the rotamers of the BOC protecting group, a reasonable analysis of the ^{1}H NMR analysis could not be performed.

The crude product was dissolved in THF (30 mL), and solid LAH (740 mg) was added at 0 °C. After 3 h the excess LAH was quenched with ethyl acetate (20 mL), and 1.0 mL of water was added. After 30 min, the mixture was dried over $MgSO_4$ and filtered on a glass filter and the filtrate concentrated to give the crude alcohol (5.22 g, 92% for two steps); HRMS (CI) calcd for $C_{18}H_{28}NO_3$ *m*/*z* 306.2069, found 306.2089.

The crude alcohol (2.08 g, 6.82 mmol) and PCC (2.2 g, 10.2 mmol) in 30 mL of methylene chloride were stirred for 1.5 h at RT, and the mixture was filtered on celite. The filtrate was concentrated and filtered once more on a short column of silica gel to afford the aldehyde **9a** (1.4 g, 67%); R_f value = 0.4 with 1:5 ethyl acetate:hexane. The aldehyde **9a** (1.4 g, 4.62 mmol) and $Ph_3PCHCO_2CH_3$ (1.62 g, 4.85 mmol) in 15 mL of CH_2Cl_2 were stirred for 1.5 days at RT under an argon atmosphere. The mixture was concentrated, redissolved in ether, and washed with water. The ether layer was dried over $MgSO_4$, concentrated, and filtered on a short column of silica gel with ethyl acetate/hexane solution (1:3) to afford a α,*β*-unsaturated ester (1.66 g); R_f value = 0.2 with 1:5 ethyl acetate:hexane. A solution of the α,*β*-unsaturated ester (1.66 g) in 10 mL of trifluoroacetic acid was stirred at 0 °C for 1 h and was concentrated and then treated with a solution K_2CO_3 (pH 10). The aqueous was extracted with CH_2Cl_2 three times, dried over $MgSO_4$, and concentrated to afford **10a** (1.07 g, 86% from **9a**), which was a mixture of *E*/*Z* isomers (>20:1); R_f value = 0.01 with 1:2 ethyl acetate:hexane. The mixture was used without purification.

The *E*/*Z* mixture of **10a** (1.07 g, 3.98 mmol) was dissolved in methanol (15 mL), 10% Pd/C (200 mg) was added, and it was agitated under a hydrogen atmosphere until the pressure stopped changing. It was filtered, concentrated, and recrystallized using a 2:1 mixture of ethyl acetate to hexane. This afforded the lactam **11a** (839 mg, 92%): mp 72−73 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.35−7.18 (m, 5H), 4.85 (dt, *J* = 13.2, 2.1 Hz, 1H), 3.26 (td, *J* = 9.6, 2.4 Hz, 1H), 2.63 (ddd, *J* = 11.4, 9.3, 4.2 Hz, 1H), 2.57−2.36 (m, 3H), 2.04−1.85 (m, 2H), 1.76−1.63 (m, 3H), 1.44−1.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 168.9, 142.5, 128.7, 127.7, 127.0, 62.6, 48.3, 42.5, 32.6, 32.5, 27.7, 25.1, 24.2; Anal. ($C_{15}H_{19}NC$) C, H, N.

***threo*-1-Aza-2-oxo-5-(3,4-dichlorophenyl)[4.4.0]decane (11b).** Using a procedure similar to that for **11a**, *threo*-3,4-dichloromethylphenidate was converted to **11b** (38.4% for six steps): mp 119−120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.39 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.04 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.85 (d, *J* = 13.2 Hz, 1H), 3.20 (td, *J* = 11.2, 2.7 Hz, 1H), 2.63 (ddd, *J* = 14.7, 9.6, 4.2 Hz, 1H), 2.52−2.35 (m, 3H), 1.95−1.86 (m, 2H), 1.77−1.61 (m, 3H), 1.40−1.11 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 168.6, 142.8, 132.9, 131.1, 130.7, 129.6, 127.1, 62.2, 47.6, 42.5, 32.5, 32.4, 27.5, 25.0, 24.1; MS (EI) *m*/*e* 297.0 (39.74), 299.0 (24.55) for $C_{15}H_{17}NOCl_2$; HRMS (EI) calcd for $C_{15}H_{17}NOCl_2$ *m*/*z* 297.0687, found 297.0676.

***threo*-1-Aza-2-oxo-5-(2-chlorophenyl)[4.4.0]decane (11c).** Using a procedure similar to that for **11a**, *threo*-2-chloromethylphenidate was converted to **11c** (41.8% for six steps): ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.39−7.14 (m, 4H), 4.85 (d, *J* = 14.7 Hz, 1H), 3.39−3.23 (m, 2H), 2.64−2.39 (m, 3H), 2.00−1.85 (m, 2H), 1.77−1.60 (m, 3H), 1.43−1.13 (m, 3H).

***erythro*-1-Aza-2-oxo-5-(3,4-dichlorophenyl)[4.4.0]decane (15).** Using a procedure similar to that for **11a**, *erythro*-3,4-dichloromethylphenidate was converted to **15** (32.5% for six steps): ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.39 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.76 (d, *J* = 12.9 Hz, 1H), 3.45 (m, 1H), 3.27 (ddd, *J* = 13.2, 6.0, 3.0 Hz, 1H), 2.65−2.41 (m, 3H), 2.19 (dtd, *J* = 12.9, 12.0, 2.4 Hz, 1H), 1.87 (m, 2H), 1.62 (m, 2H), 1.42−1.04 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 167.8, 141.0, 131.0, 130.5 (2C), 129.8, 127.2, 61.7, 44.7, 42.3, 32.3, 26.9, 25.5, 24.9, 21.7; MS (EI) *m*/*e* 297.1 (38.99), 299.1 (25.19) for $C_{15}H_{17}NOCl_2$; HRMS (EI) calcd for $C_{15}H_{17}NOCl_2$ *m*/*z* 297.0687, found 297.0699.

General Procedure for the Reduction Lactams to *tert*-Amines (12 and 16). *threo*-1-Aza-5-phenyl[4.4.0]decane (12a). A mixture of lactam **11a** (700 mg, 3.05 mmol) and BH_3·THF (1 M, 3.5 mL) in THF (10 mL) was heated to 50 °C overnight, cooled to RT, and quenched with concd HCl (1.0 mL) and water (10 mL). The mixture was treated with KOH to pH >10, stirred for 2 h, and then extracted with chloroform three times. The organic layer was dried over $MgSO_4$ and concentrated to afford **12a** (472 mg, 72%): ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.39−7.24 (m, 2H), 7.20−7.13 (m, 3H), 2.87 (m, 2H), 2.40 (td, *J* = 12.6, 3.3 Hz, 1H), 2.17 (td, *J* = 11.4, 3.9 Hz, 1H), 2.06 (m, 2H), 1.93−1.68 (m, 4H), 1.55 (m, 3H), 1.25 (m, 1H), 1.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 144.9, 128.7, 128.3, 126.6, 67.9, 57.3, 57.2, 50.4, 34.1, 31.0, 26.2, 26.0, 25.0; MS (EI) *m*/*e* 215.2 (54.2) for $C_{15}H_{21}N$; HRMS (EI) calcd for $C_{15}H_{21}N$ *m*/*z* 215.1624, found 215.1672. The *tert*-amine **12a** was converted to HCl salt and recrystallized from methylene chloride/ethyl ether to afford a **12a**·HCl: mp 215−229 °C; ^{1}H NMR (D_2O, 300 MHz) *δ* 7.30−7.14 (m, 5H), 3.30 (d, *J* = 12.3 Hz, 2H), 3.16 (td, *J* = 11.4, 3.0 Hz, 1H), 3.00 (td, *J* = 12.6, 3.3 Hz, 1H), 2.89 (td, *J* = 12.6, 3.3 Hz, 1H), 2.62 (td, *J* = 11.7, 3.9 Hz, 1H), 1.91−1.67 (m, 5H), 1.62−1.54 (m, 2H), 1.43 (d, *J* = 13.2 Hz, 1H), 1.27−1.14 (m, 2H). Anal. ($C_{15}H_{22}NCl$·0.4 H_2O) C, H, N, Cl.

***threo*-1-Aza-5-(3,4-dichlorophenyl)[4.4.0]decane·HCl (12b·HCl).** Using a procedure similar to that for **12a**·HCl, **11b** was converted to **12b**·HCl (67%): mp 247−250 °C; ^{1}H NMR (D_2O, 300 MHz) *δ* 7.32 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.1 Hz, 1H) 3.25 (d, *J* = 12.0 Hz, 2H), 3.07 (td, *J* = 11.4, 3.0 Hz, 1H), 2.93 (td, *J* = 12.0, 2.7 Hz, 1H), 2.83 (td, *J* = 12.9, 3.3 Hz, 1H), 2.62 (td, *J* = 11.4, 3.3 Hz, 1H), 1.86−1.64 (m, 5H), 1.60−1.48 (m, 2H), 1.9 (d, *J* = 12.3 Hz, 1H), 1.22−1.11 (m, 2H); HRMS (EI) calcd for $C_{15}H_{19}NCl_2$ *m*/*z* 283.0895, found 283.0885. Anal. ($C_{15}H_{20}NCl_3$·0.6 H_2O) C, H, N, Cl.

***threo*-1-Aza-5-(2-chlorophenyl)[4.4.0]decane·HCl (12c·HCl).** Using a procedure similar to that for **12a**·HCl, **11c** afforded **12c**·HCl (65% from): mp 233−235 °C; ^{1}H NMR (D_2O, 300 MHz) *δ* 7.31 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 4.2 Hz, 1H), 7.13−7.07 (m, 2H), 3.36−3.27 (m, 3H), 3.15 (td, *J* = 11.4, 3.3 Hz, 1H) 2.97 (td, *J* = 12.6, 3.3 Hz, 2H), 2.85 (td, *J* = 12.9, 3.3 Hz, 1H), 1.88−1.64

(m, 4H), 1.60−1.33 (m, 4H), 1.30−1.17 (m, 2H); HRMS (EI) calcd for $C_{15}H_{20}NCl$ *m*/*z* 249.1284, found 249.1293. Anal. ($C_{15}H_{21}NCl_2 \cdot 0.19\ H_2O$) C, H, N, Cl.

***erythro*-1-Aza-5-(3,4-dichlorophenyl)[4.4.0]decane·HCl (16·HCl).** Using a procedure similar to that for **12a**·HCl, **15** afforded **16**·HCl (68%): mp 227−230 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.35 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.01 (dd, J = 8.7, 1.8 Hz, 1H) 3.49 (t, J = 12.9 Hz, 2H), 3.13−3.06 (m, 3H), 2.94 (d, J = 11.4 Hz, 1H), 2.01−1.49 (m, 8H), 1.17−0.99 (m, 3H): HRMS (EI) calcd for $C_{15}H_{19}NCl_2$ *m*/*z* 283.0895, found 283.0893. Anal. ($C_{15}H_{20}NCl_3$) C, H, N, Cl.

***threo*-*N*-ethylritalinol (18).** A mixture of MP (900 mg, 3.86 mmol), acetic anhydride (1.8 mL, 19.3 mmol), pyridine (1.8 mL, 38.3 mmol), and DMAP (cat. amount) in methylene chloride (10 mL) was stirred for 2 days at RT, quenched with 3 N HCl, and diluted with ethyl acetate. The mixture was washed with water, and the organic layer was dried and concentrated under a vacuum overnight to afford the amide **17** (1.06 g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H); MS (CI: isobutane) *m*/*e* 276.2; FT-IR (NaCl) 1738, 1645 cm^{-1}. The unpurified amide was dissolved in THF (10 mL), and solid LAH (300 mg, 7.89 mmol) was added at RT. After heating at 55 °C overnight, the mixture was cooled to RT and the excess LAH quenched with ethyl acetate and a few drops of water. The mixture was filtered and concentrated to afford the alcohol **18** (835 mg, 93% for two steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.10 (m, 5H), 3.95 (t, J = 10.5 Hz, 1H), 3.72 (dd, J = 10.5, 3.3 Hz, 1H), 3.41 (td, J = 10.8, 3.3 Hz, 1H), 3.30−3.16 (m, 2H), 2.85 (q, J = 7.2 Hz, 2H), 2.76 (d, J = 13.8 Hz, 1H), 1.67−1.24 (m, 6H), 1.17 (t, J = 7.2 Hz, 3H), 0.92−0.86 (m, 1H). **18**·HCl, Anal. ($C_{15}H_{24}NOCl \cdot 0 \cdot 0.25\ H_2O$) C, H, N, Cl.

***threo*-*N*-Ethyl-2-(1-methylbenzyl)piperidine (19).** A mixture of **18** (400 mg, 1.72 mmol) and a catalytic amount of DMAP was dissolved in THF (5 mL), followed by the addition of TsCl (492 mg, 2.58 mmol) and triethylamine (3 mL) at RT. After 30 min, LAH (100 mg, 2.63 mmol) was slowly added to the reaction mixture and stirred another 2 h. The mixture was quenched with ethyl acetate/water (a few drops), filtered, and concentrated. The concentrate was chromatographed with 1:1 (ethyl acetate:hexane) eluting solvent to afford the starting material **18** (220 mg, 55%) and *threo*-*N*-ethyl-2-(1-methylbenzyl)piperidine (**19**) (149 mg, 40%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.13 (m, 5H), 3.10−2.97 (m, 2H), 2.79 (dq, J = 15.9, 7.2 Hz, 1H), 2.62 (dq, J = 15.9, 7.5 Hz, 1H), 2.55 (td, J = 12.6, 5.1 Hz, 1H), 2.54 (qd, J = 13.2, 4.5 Hz, 1H), 1.74−1.68 (m, 2H), 1.42−1.20 (m, 2H), 1.27 (d, J = 6.9 Hz, 3H), 1.09−0.98 (m, 1H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9, 128.2, 127.9, 125.9, 65.3, 49.4, 43.0, 40.5, 23.6, 23.3, 20.8, 19.2, 12.6; MS (CI: isobutane) *m*/*e* 218.2 for $C_{15}H_{24}N$; HRMS (CI) calcd for $C_{15}H_{24}N$ *m*/*z* 218.1909, found 218.1917. *threo*-*N*-Ethyl-2-(1-methylbenzyl)piperidine·HCl (**19·HCl**): mp 162−163 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.28−7.11 (m, 5H), 3.49−3.15 (m, 4H), 3.01−2.85 (m, 2H), 2.05−1.96 (m, 0.5H), 1.72−1.09 (m, 11.5H). Anal. ($C_{15}H_{24}NCl \cdot 0.18H_2O$) C, H, N, Cl.

***threo*-1-Aza-2-oxo-4α-hydroxy-5-phenyl[4.4.0]decane (21a).** A solution of amide **17a** (1.97 g, 7.16 mmol) in THF (55 mL) and HMPA (5 mL) was added dropwise to a solution of LDA (1 M, 30 mL) for 8 h at - 78 °C. The mixture was stirred overnight while the bath was warmed up to RT, quenched with water, and concentrated to remove the solvent, THF. The concentrate was diluted with water, treated with concd HCl to pH 2, and extracted with ethyl acetate by three times. The organic layer was dried over $MgSO_4$, concentrated, and filtered on a short silica gel column with 1:1 solution of ethyl acetate/hexane. The filtrate was concentrated and triturated with 1:1 solution of ethyl acetate/hexane to afford a white solid **20a** (1.18 g, 68%): mp 154−155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.47 (s, 0.2H: enol form hydroxy proton), 5.05 (s, 0.2H: enol form vinyl proton), 3.29 (s, 1.6H) methylene protons); MS (EI) *m*/*e* 243.1 (80.15), 118.0 (50.57), 84.1 (100) for $C_{15}H_{17}NO$; HRMS (EI) calcd for $C_{15}H_{17}NO$ *m*/*z* 243.1259, found 243.1263. The β-ketoamide **20a** (1.18 g, 4.86 mmol) was dissolved in methanol (15 mL), and $NaBH_4$ (184 mg, 4.86 mmol) was added to the solution. After 30 min, the mixture was quenched with water and extracted with methylene chloride three times to afford a hydroxy amide **21a** (1.18 g) in quantitative yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (t, J = 7.25 Hz, 2H), 7.32 (t, J = 7.35 Hz, 1H), 7.25 (d, J = 8.18 Hz, 2H), 4.82 (dp, J = 13.42, 1.78 Hz, 1H), 4.10 (tdd, J = 10.92, 5.02, 2.38 Hz, 1H), 3.24 (td, J = 10.57, 2.16 Hz, 1H), 2.90 (dd, J = 16.71, 4.98 Hz, 1H), 2.58 (t, J = 10.50 Hz, 1H), 2.49 (dd, J = 16.81, 11.15 Hz, 1H), 2.42 (td, J = 13.83, 2.33 Hz, 1H), 1.78−1.49 (m, 4H), 1.37 (qt, J = 12.93, 3.78 Hz, 1H), 1.25 (qt, J = 12.81, 3.35 Hz, 1H), 1.16 (qd, J = 11.88, 3.46 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 138.0, 129.3, 128.8, 128.1, 67.5, 60.5, 56.8, 42.4, 40.5, 32.3, 24.9, 24.3; MS (EI) *m*/*e* 245.1 (22.5), 22.1 (33.1), 144.0 (100.0) for $C_{15}H_{19}NO_2$; HRMS (FAB) calcd for $C_{15}H_{20}NO_2$ *m*/*z* 246.1494, found 246.1481.

***threo*-1-Aza-2-oxo-4α-hydroxy-5-(3,4-dichlorophenyl)[4.4.4.0]-decane (21b).** Using a procedure similar to that for **21a**, **17b** was converted to **21b** (61% for two steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.19 (dd, J = 8.1, 2.1 Hz, 1H), 4.78 (dp, J = 8.7, 1.5 Hz, 1H), 4.05 (td, J = 6.6, 3.6 Hz, 1H), 3.17 (td, J = 10.2, 3.0 Hz, 1H), 2.88 (dd, J = 13.5, 4.8 Hz, 1H), 2.57 (t, J = 10.5 Hz, 1H),), 2.49 (dd, J = 16.5, 10.8 Hz, 1H), 2.42 (td, J = 14.1, 2.4 Hz, 1H), 1.80−1.05 (m, 7H).

***threo*-1-Aza-2-oxo-4α-methoxy-5-phenyl[4.4.0]decane (22a).** The hydroxy amide **21a** (365 mg, 1.49mmol) was dissolved in THF (10 mL) at RT, and 1.5 mL of $LiN(TMS)_2$ (1 M in THF) was added to the solution at 0 °C under an argon atmosphere. After 30 min, 0.3 mL of MeI (4.82 mmol) was added to the mixture under the darkness. After overnight at RT, the mixture was quenched with water, extracted with methylene chloride, and purified by a flash chromatography (2:1 solution of ethyl acetate to hexane) to afford a methoxy amide **22a** (328 mg, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.19 (m, 5H), 4.80 (dp, J = 13.2, 2.1 Hz, 1H), 3.65 (td, J = 10.5, 4.5 Hz, 1H), 3.24 (td, J = 10.2, 2.7 Hz, 1H), 3.10 (s, 3H), 2.95 (dd, J = 16.8, 4.8 Hz, 1H), 2.67 (t, J = 10.2 Hz, 1H), 2.41 (td, J = 13.2, 2.1 Hz, 1H), 2.49 (dd, J = 16.5, 10.5 Hz, 1H), 1.76−1.59 (m, 3H), 1.37 (qt, J = 12.6, 3.6 Hz, 1H), 1.25 (qt, J = 12.9, 2.7 Hz, 1H), 1.16 (qd, J = 11.4, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 139.6, 128.7, 128.3, 127.2, 76.4, 61.0, 57.0, 54.3, 42.5, 37.8, 32.4, 24.9, 24.5; FT-IR (NaCl) 1650 cm^{-1}.

***threo*-1-Aza-4α-methoxy-5-phenyl[4.4.0]decane (23a).** Using a procedure similar to that for **12a**, **22a** was converted to **23a** (82%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.15 (m, 5H), 3.30 (td, J = 10.5, 4.5 Hz, 1H), 3.03 (s, 3H), 2.97−2.80 (m, 2H), 2.43 (t, J = 10.5 Hz, 1H), 2.21 (td, J = 12.9, 2.7 Hz, 1H), 2.21−2.12 (m, 1H), 2.06−1.97 (m, 1H), 1.88 (td, J = 10.2, 2.4 Hz, 1H), 1.75−1.53 (m, 4H), 1.12−0.99 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.3, 128.2, 128.0, 126.4, 82.1, 66.1, 56.6, 56.5, 56.3, 56.1, 54.5, 30.4, 25.5, 24.1; MS (EI) *m*/*e* 245.2 (23.2), 214.2 (100) for $C_{16}H_{23}NO$; HRMS (EI) calcd for $C_{16}H_{23}NO$ *m*/*z* 245.1780, found 245.1796. Anal. ($C_{16}H_{23}NO \cdot 0.4H_2O$) C, H, N.

***threo*-1-Aza-4α-hydroxy-5-phenyl[4.4.0]decane (24a).** Using a procedure similar to that for **12a**, **21b** was converted to **24a** (86%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.16 (m, 5H), 3.67 (td, J = 10.5, 4.8 Hz, 1H), 2.92−2.86 (m, 2H), 2.32 (t, J = 10.5 Hz, 1H), 2.21 (td, J = 12.9, 2.4 Hz, 1H), 2.07−1.96 (m, 1H), 1.89 (td, J = 10.2, 2.7 Hz, 1H), 1.83−1.50 (m, 4H), 1.12−0.99 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.9, 128.7, 128.5, 127.1, 73.3, 65.3, 58.4, 56.2, 54.4, 33.2, 30.4, 25.4, 24.1; MS (EI) *m*/*e* 232.1 (70.90), 231.1 (19.27), 83.1 (100) for $C_{15}H_{21}NO$; HRMS (EI) calcd for $C_{15}H_{21}NO$ *m*/*z* 232.1701, found 232.1698. **24a**·HCl: ^{1}H NMR (D_2O, 300 MHz) δ 7.32−7.15 (m, 5H), 3.98 (td, J = 10.8, 4.5 Hz, 1H), 3.43−3.34 (m, 2H), 3.25−3.08 (m, 2H), 2.85 (td, J = 12.9, 3.0 Hz, 1H), 2.52 (t, J = 10.5 Hz, 1H), 2.21−2.15 (m, 1H), 1.78−1.67 (m, 2H), 1.62−1.48 (m, 2H), 1.41−1.32 (m, 2H), 1.28−1.16 (m, 2H). Anal. ($C_{15}H_{22}NOCl \cdot 0.21H_2O$) C, H, N, Cl.

***threo*-1-Aza-4α-hydroxy-5-(3,4-dichlorophenyl)[4.4.0]decane (24b).** Using a procedure similar to that for **12a**, **21b** was converted to **24b** (75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.1, 2.1 Hz, 1H), 3.65 (td, J = 10.5, 4.8 Hz, 1H), 2.93−2.86 (m, 2H), 2.32 (t, J = 10.5 Hz, 1H), 2.23 (td, J = 12.3, 2.4 Hz, 1H), 2.08−1.98

(m, 2H), 1.88−1.70 (m, 2H), 1.64−1.38 (m, 4H), 1.20−1.00 (m, 3H); MS (EI) *m*/*e* 298.8 (33.3), 281.8 (31.4), 83 (100) for $C_{15}H_{19}NOCl_2$; HRMS (EI) calcd for $C_{15}H_{19}NOCl_2$ *m*/*z* 299.0844, found 299.0817. **24b**·HCl: mp 257.5−259 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.39 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.03 (dd, J = 8.4, 1.8 Hz, 1H), 3.89 (td, J = 10.8, 4.8 Hz, 1H), 3.38−3.25 (m, 2H), 3.18−3.03 (m, 2H), 2.85 (td, J = 12.9, 3.0 Hz, 1H), 2.50 (t, J = 10.8 Hz, 1H), 2.15 (dd, J = 13.8, 3.9 Hz, 1H), 1.78−1.67 (m, 2H), 1.58−1.32 (m, 4H), 1.21−1.13 (m, 2H). Anal. ($C_{15}H_{20}NOCl_3$·0.07H_2O) C, H, N, Cl.

***threo*-1-Aza-4-oxo-5-phenyl[4.4.0]decane (25a).** DMSO (1 mL, 14.08 mmol) was added to a solution of oxalyl chloride (1.25 mL, 14.33 mmol) in methylene chloride (15 mL) at −55 °C and stirred for 2 min. A solution of β-hydroxy amine **24a** (500 mg, 2.16 mmol) in methylene chloride (5 mL) was added to the mixture and stirred for 5 min, followed by 3 mL of triethylamine (21.6 mmol). After being stirred for another 10 min, the reaction mixture was slowly warmed up to RT (2 h) and stirred another 0.5 h. It was quenched with saturated sodium bicarbonate solution and extracted with chloroform, and the organic layer was concentrated. After filtration on a short column of silica gel, the filtrate was purified by a flash chromatography with ethyl acetate to afford β-amino ketone **25a** (366 mg, 74%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (tt, J = 6.6, 1.5 Hz, 2H), 7.24 (tt, J = 8.1, 1.5 Hz, 1H), 7.03 (dt, J = 6.3, 1.8 Hz, 2H), 3.39 (d, J = 10.5 Hz, 1H), 3.17 (ddd, J = 11.4, 6.6, 1.8 Hz, 1H), 3.04−2.98 (m, 1H), 2.85 (tdd, J = 12.9, 5.7, 1.2 Hz, 1H), 2.61−2.45 (m, 2H), 2.26 (td, J = 10.5, 2.7 Hz, 1H), 2.12 (td, J = 11.7, 3.6 Hz, 1H),1.69−1.53 (m, 3H), 1.33−0.97 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.5, 135.7, 129.8, 128.3, 127.1, 67.7, 63.4, 55.9, 55.8, 41.5, 32.1, 25.4, 23.4; FT-IR (NaCl) 1717 cm^{-1}; MS (EI) *m*/*e* 229.2 (100) for $C_{15}H_{19}NO$; HRMS (EI) calcd for $C_{15}H_{19}NO$ *m*/*z* 229.1467, found 229.1464. **25a**·HCl: mp 152−156 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.33−7.05 (m, 5H), 3.87−2.64 (m, 5H), 2.81 (d, J = 12.0 Hz, 1H), 2.07 (dd, J = 7.5, 3.0 Hz, 1H), 1.79 (m, 1H), 1.68−1.01 (m, 6H). Anal. ($C_{15}H_{20}NOCl$·0.57H_2O·0.2HCl) C, H, N, Cl.

***threo*-1-Aza-4-oxo-5-(3,4-dichlorophenyl)[4.4.0]decane (25b).** Using a procedure similar to that for **25a**, **24b** was converted to **25b** (82%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 2.1 Hz, 1H), 6.88 (dd, J = 8.1, 2.1 Hz, 1H), 3.37 (d, J = 10.5 Hz, 1H), 3.16 (ddd, J = 11.7, 6.3, 2.1 Hz, 1H), 3.00 (m, 1H), 2.89−2.77 (m, 1H), 2.56 (dd, J = 11.7, 3.0 Hz, 1H), 2.50 (ddt, J = 11.4, 13.5, 2.7 Hz, 1H), 2.20 (td, J = 10.5, 3.0 Hz, 1H), 2.11 (td, J = 11.1, 3.3 Hz, 1H), 2.10−1.52 (m, 3H), 1.33−1.01 (m, 3H); MS (EI) *m*/*e* 297.0 (71.9), 83.0 (100) for $C_{15}H_{17}NOCl_2$; HRMS (EI) calcd for $C_{15}H_{17}NOCl_2$ *m*/*z* 297.0687, found 297.0652. **25b**·HCl: mp 219−221 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.42−6.92 (m, 3H), 3.84−2.58 (m, 4H), 2.92 (t, J = 11.7 Hz, 1H), 2.77 (d, J = 11.1 Hz, 1H), 2.02 (d, J = 5.1 Hz, 2H), 1.75 (d, J = 14.4 Hz, 1H), 1.60−1.08 (m, 5H). Anal. ($C_{15}H_{18}NOCl_3$·0.3H_2O) C, H, N, Cl.

***threo*-1-Aza-4β-hydroxy-5-phenyl[4.4.0]decane (26a).** To a solution of amino ketone **25a** (81 mg, 0.35 mmol) in THF (3 mL) at −78 °C was added 0.7 mL of K-Selectride (1 M). After 2 h, the mixture was warmed up to RT, quenched with water, and treated with KOH. The mixture was stirred overnight, extracted with chloroform three times, and purified by a flash chromatography with 1:1:6 MeOH/EtOAc/hexane to afford a white solid **26a** (72 mg, 88%): mp 164−165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.19 (m, 5H), 3.85 (q, J = 2.7 Hz, 1H), 2.62 (td, J = 10.8, 2.1 Hz, 1H), 2.60 (dd, J = 9.0, 2.7 Hz, 1H), 2.53 (td, J = 10.8, 2.4 Hz, 1H), 2.18 (td, J = 9.6, 4.2 Hz, 1H), 2.06 (tdd, J = 13.5, 9.0, 2.7 Hz, 1H), 1.89 (dq, J = 13.8, 3.0 Hz, 1H), 1.74 (br s, 1H), 1.64−1.52 (m, 5H), 1.41 (m, 1H), 1.21 (m, 1H), 1.02−0.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.0, 128.7, 128.5, 126.7, 68.7, 59.2, 56.6, 54.4, 49.8, 32.1, 30.8, 25.8, 24.7; MS (EI) *m*/*e* 231.1 (62.1), 214.1 (55.6), 83.1 (100) for $C_{15}H_{21}NO$; HRMS (EI) calcd for $C_{15}H_{21}NO$ *m*/*z* 231.1623, found 231.1613. **26a**·HCl: mp 214.5−216 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.30−7.05 (m, 5H), 3.90 (br s, 1H), 3.62−2.83 (m, 7H), 2.09−1.06 (m, 7H). Anal. ($C_{15}H_{22}NOCl$·0.15H_2O) C, H, N.

***threo*-1-Aza-4β-hydroxy-5-(3,4-dichlorophenyl)[4.4.0]decane (26b)**. Using a procedure similar to that for **26a**, **25b** was converted **26b** (86%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, J = 8.1 Hz, 1H), 7.34 (br s, 1H), 7.07 (d, J = 8.1 Hz, 1H), 3.86 (q, J = 2.7 Hz, 1H), 2.90 (d, J = 10.2 Hz, 1H), 2.68−2.49 (m, 4H), 2.21 (m, 1H), 2.07 (m, 1H), 1.84 (dq, J = 14.1, 3.0 Hz, 1H), 1.62 (m, 4H), 1.34 (dd, J = 13.2, 2.4 Hz, 1H), 1.24−0.94 (m, 2H); MS (EI) *m*/*e* 298.8 (41.2), 281.8 (39.2) 83.0 (100) for $C_{15}H_{19}NOCl_2$; HRMS (EI) calcd for $C_{15}H_{19}NOCl_2$ *m*/*z* 299.0844, found 299.0840. **26b**·HCl: mp 214.5−216 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.35 (d, J = 8.4 Hz, 1H), 7.30 (br s, 1H), 7.02 (d, J = 8.7 Hz, 1H), 3.85 (d, J = 1.8 Hz, 1H), 3.53 (t, J = 11.7 Hz, 1H), 3.31 (d, J = 10.8 Hz, 1H), 3.22−3.12 (m, 2H), 2.94 (t, J = 12.6, 1H), 2.83 (d, J = 11.7 Hz, 1H), 2.05−1.06 (m, 9H). Anal. ($C_{15}H_{20}NOCl_3$·0.024HCl) C, H, N, Cl.

***threo*-1-Aza-4β-methoxy-5-phenyl[4.4.0]decane (27a).** A mixture of β-amino alcohol **26a** (100 mg, 0.43 mmol), NaH (40 mg, 60% in mineral oil), and a catalytic amount of tetrabutylamonium iodide (10 mg) in THF (5 mL) was stirred for 2 h at RT under an argon atmosphere. MeI (32 mL, 0.51 mmol) was added to the mixture, and the flask was wrapped with Al foil and stirred overnight. It was quenched with water, extracted, with chloroform three times, and purified by a flash chromatography with 1:1:10 MeOH/EtOAc/hexane to afford material (25 mg, 25%) and methyl ether **27a** (42 mg, 40%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.19 (m, 5H), 3.85 (q, J = 2.4 Hz, 1H), 3.1 (s, 3H), 2.86 (dq, J = 11.4, 2.4 Hz, 1H), 2.68−2.48 (m, 4H), 2.23−2.14 (m, 1H), 2.00 (dq, J = 11.1, 3.0 Hz, 1H), 1.86 (tdd, J = 14.1, 5.7, 2.4 Hz, 1H), 1.64−1.55 (m, 3H), 1.28 (dd, J = 13.2, 2.4 Hz, 1H), 1.23−1.08 (m, 1H), 0.94 (tdd, J = 12.6, 9.9, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.3, 129.5, 127.8, 126.2, 78.1, 60.4, 57.1, 57.0, 56.5, 53.9, 50.1, 30.8, 28.3, 25.8, 24.6; MS (EI) *m*/*e* 293.1 (22.2), 149.0 (100) for $C_{15}H_{21}NO$; HRMS (EI) calcd for $C_{16}H_{23}NO$ *m*/*z* 245.1780, found 245.1782. **27a**·HCl: mp 225−227 °C; ^{1}H NMR (D_2O, 300 MHz) δ 7.28−7.16 (m, 5H), 3.58−3.45 (m, 2H), 3.31 (d, J = 12.3 Hz, 1H), 3.19−3.14 (m, 2H), 2.97 (s, 3H), 2.95−2.89 (m, 1H), 2.85 (dd, J = 12.0, 2.4 Hz, 1H), 2.18 (dd, J = 16.2, 3.0 Hz, 1H), 1.91−1.74 (m, 2H), 1.62−1.49 (m, 3H), 1.40−1.27 (m, 1H), 1.18−0.98 (m, 1H). Anal. ($C_{16}H_{24}NOCl$·0.57H_2O) C, H, N.

***threo*-1-Aza-2-oxo-3-methyl-5-phenyl[4.4.0]decane (28).** To a solution of lactam **11a** (86 mg, 0.38 mmol) in THF (3 mL) was added $LiN(TMS)_2$ (1 M, 560 μL) at −78 °C. After 3 h, MeI (25 μL, 0.38 mmol) was added to the mixture and slowly warmed to RT overnight. The mixture was quenched with water, extracted with chloroform, and purified by a flash chromatography with 1:2 ethyl acetate/hexane to afford *threo*-1-aza-2-oxo-3α-methyl-5-phenyl-[4.4.0]decane (**28a**: 30 mg, 33%): R_f value = 0.45, 1:2 ethyl acetate: hexane; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.18 (m, 5H), 4.82 (dq, J = 12.9, 1.8 Hz, 1H), 3.28 (td, J = 8.7, 2.4 Hz, 1H), 2.83 (ddd, J = 11.4, 8.4, 3.3 Hz, 1H), 2.59−2.52 (m, 1H), 2.41 (td, J = 12.6, 2.7 Hz, 1H), 2.11 (ddd, J = 11.4, 13.2, 5.7 Hz, 1H), 1.72 (dt, J = 13.5, 3.6 Hz, 2H), 1.65 (d, J = 13.5 Hz, 2H), 1.29 (d, J = 7.5 Hz, 3H), 1.40−1.53 (m, 3H); and *threo*-1-aza-2-oxo-3β-methyl-5-phenyl[4.4.0]decane (**28b**: 35 mg, 38%): R_f = 0.25, 1:2 ethyl acetate:hexane; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.18 (m, 5H), 4.83 (dq, J = 13.5, 1.8 Hz, 1H), 3.24 (td, J = 10.2, 2.1 Hz, 1H), 2.68 (ddd, J = 12.6, 10.5, 3.3 Hz, 1H), 2.49−2.35 (m, 1H), 2.38 (td, J = 12.9, 2.7 Hz, 1H), 1.92−1.77 (m, 2H), 1.73−1.62 (m, 3H), 1.22 (d, J = 6.9 Hz, 3H), 1.42−1.02 (m, 3H).

***threo*-1-Aza-3α-methyl-5-phenyl[4.4.0]decane (29a)**. Using a procedure similar to that for **12a**, **28a** was converted to **29a** (91%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28−7.23 (m, 2H), 7.19−7.14 (m, 3H), 2.74 (ddd, J = 11.4, 4.8, 3.0 Hz, 1H), 2.67−2.58 (m, 2H), 2.32 (dd, J = 8.4, 3.6 Hz, 1H), 1.99−1.90 (m, 2H), 1.84−1.72 (m, 2H), 1.63−1.52 (m, 3H), 1.27−1.16 (m, 1H), 1.21 (d, J = 8.4 Hz, 3H), 1.06−0.98 (m, 2H); ^{13}C NMR (D_2O, 75 MHz) δ 145.1, 128.5, 128.3, 126.3, 68.4, 62.6, 57.5, 44.7, 39.7, 30.7, 28.6, 26.1, 25.0, 18.8. **29a**·HCl: hydroscopic, ^{1}H NMR (D_2O, 300 MHz) δ 7.29−7.15 (m, 5H), 3.29 (d, J = 12.3 Hz, 1H), 3.24−3.08 (m, 3H), 2.86 (q, J = 13.2 Hz, 2H), 2.24 (br s, 1H), 1.96 (td, J = 11.7, 4.2 Hz, 1H), 1.76−1.54 (m, 4H), 1.41 (d, J = 10.5 Hz, 1H), 1.28−

1.16 (m, 2H), 1.10 (d, $J = 7.2$ Hz, 3H). Anal. ($C_{16}H_{24}NCl \cdot 1.4H_2O \cdot 0.09HCl$) C, H, N, Cl.

***threo*-1-Aza-3β-methyl-5-phenyl[4.4.0]decane (29b)**. Using a procedure similar to that for **12a**, **28b** was converted to **29b** (97%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.23 (m, 2H), 7.19−7.12 (m, 3H), 2.83 (tq, $J = 11.4$, 2.1 Hz, 2H), 2.45 (ddd, $J = 9.6$, 9.9, 3.3 Hz, 1H), 2.09−2.00 (m, 1H), 1.93−1.77 (m, 4H), 1.63−1.52 (m, 3H), 1.29−0.99 (m, 4H), 0.87 (d, $J = 6.0$ Hz, 3H). **29b**·HCl: hydroscopic, ^{1}H NMR (D_2O, 300 MHz) δ 7.29−7.13 (m, 5H), 3.31 (d, $J = 11.1$ Hz, 1H), 3.22 (d, $J = 12.3$ Hz, 1H), 3.09 (t, $J = 11.4$ Hz, 1H), 2.88 (td, $J = 13.2$, 3.6 Hz, 1H), 2.73−2.61 (m, 2H), 1.98−1.05 (m, 10H), 0.83 (d, $J = 6.3$ Hz, 3H). Anal. ($C_{16}H_{24}NCl \cdot 0.7H_2O$) C, H, N, Cl.

***threo*-1-Aza-4α-hydroxy-4β-ethyl-5-phenyl[4.4.0]decane (30).** To a solution of *threo*-1-Aza-4-oxo-5-phenyl[4.4.0]decane (**25a**; 199 mg, 0.869 mmol) in 5 mL of THF was added 0.6 mL of ethylmagnesium bromide (2 M) at 0 °C. After being stirred 2 h at RT, the mixture was quenched with water, extracted with chloroform, and purified with by a flash chromatography with 1:1:6 MeOH/EtOAc/hexane to afford **30** as a white solid (203 mg, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.18 (m, 4H), 7.06−7.04 (m, 1H), 2.94 (dd, $J = 10.8$, 1.5 Hz, 1H), 2.77 (ddd, $J = 11.4$, 4.5, 2.4 Hz, 1H), 2.65 (td, $J = 12.6$, 2.7 Hz, 1H), 2.54 (m, 2H), 2.20 (td, $J = 11.7$, 3.9 Hz, 1H), 1.90 (dt, $J = 13.5$, 2.7 Hz, 1H), 1.60 (m, 3H), 1.25−0.97 (m, 6H), 0.77 (t, $J = 7.2$ Hz, 3H); MS (EI) *m*/*e* 259.2 (70.6), 111.1 (100) for $C_{17}H_{25}NO$; HRMS (EI) calcd for $C_{17}H_{25}NO$ *m*/*z* 259.1936, found 259.11942. **30**·HCl: ^{1}H NMR (D_2O, 300 MHz) δ 7.20 (br s, 4H), 7.06 (s, 1H), 3.54 (br s, 1H), 3.34−3.21 (m, 3H), 2.92 (br s, 1H0, 2.65 (d, $J = 11.7$ Hz, 1H), 1.90−1.68 (m, 3H), 1.58−1.46 (m, 2H), 1.34−0.98 (m, 5H), 0.62 (br s, 3H). Anal. ($C_{17}H_{26}NOCl \cdot 0.8H_2O$) C, H.

***threo*-1-Aza-4-ethyl-5-phenyl[4.4.0]decanes (31a** and **33a).** To a solution of ethylmagnesium chloride (2 M, 2.8 mL), $CuBr \cdot Me_2S$ (75 mg, 0.36 mmol), and HMPA (580 μL, 3.24 mmol) in THF (5 mL) was added dropwise a mixture of α,β-unsaturated ester **10** (400 mg, 1.11 mmol) and TMSCl (600 μL, 4.73 mmol) in THF (3 mL) at −78 °C. After 3 h, it was quenched with brine and extracted with methylene chloride. The organic layer was concentrated and treated with 2 mL of trifluoroacetic acid at 0 °C for 2 h. The mixture was concentrated and treated with K_2CO_3 in methanol, and water was added and extracted with chloroform to afford amides **32** (3:1 ratio of β/α isomers). The mixture of amides **32** (β-isomer at 0.85 ppm, t, $J = 7.2$ Hz; α-isomer at 0.70 ppm, t, $J = 6.9$ Hz) could not be separated by flash chromatography.

Amides **32** were treated with BH_3 (1 M, 3 mL) in THF (5 mL) at 55 °C overnight and quenched with 10% HCl. After 10 min, KOH was added to the mixture until pH 10 and stirred for 2 h. The mixture was extracted with chloroform, concentrated, and purified by a flash silica gel column chromatography using 40% acetone in ether to afford a *threo*-1-aza-4α-ethyl-5-phenyl[4.4.0]-decane, **31a**, ($R_f = 0.33$, 65 mg, 24% for four steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (br s, 2H), 7.2 (tt, $J = 1.3$, 7.3 Hz, 1H), 7.14 (br s, 2H), 2.96 (dt, $J = 2.9$, 11.6 Hz, 1H), 2.91 (dq, $J = 3.2$, 11.3 Hz, 1H), 2.25 (ddd, $J = 2.8$, 11.7, 11.9 Hz, 1H), 2.15 (t, $J = 10.2$ Hz, 1H), 2.07 (m, 1H), 1.90 (dd, $J = 2.8$, 9.7 Hz, 1H), 1.87 (m, 1H), 1.64−1.44 (m, 5H), 1.19−0.99 (m, 4H), 0.89 (m, 1H), 0.74 (t, $J = 7.4$ Hz, 3H); MS (EI) *m*/*e* 243.2 (71.5), 214.2 (60.5), 111.2 (100.0) for $C_{17}H_{25}N$; HRMS (EI) calcd for $C_{17}H_{25}N$ *m*/*z* 243.2005, found 243.1987. **31a**·HCl: Anal. ($C_{17}H_{25}N \cdot HCl \cdot 1.2H_2O$) C, H, N, Cl. *threo*-1-Aza-4β-ethyl-5-phenyl[4.4.0]decane, **33a** ($R_f = 0.31$, 186 mg, 69% for four steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.22 (m, 2H), 7.14 (tt, $J = 1.5$, 7.2 Hz, 1H), 7.05 (d, $J = 6.9$ Hz, 2H), 2.85 (dd, $J = 1.5$, 11.1 Hz, 1H), 2.78 (dd, $J = 4.5$, 11.1 Hz, 1H), 2.58 (td, $J = 3.3$, 11.7 Hz, 1H), 2.38−2.28 (m, 2H), 2.13 (m, 1H), 1.93 (tt, $J = 4.5$, 13.5 Hz, 1H), 1.80 (qd, $J = 2.7$, 13.5 Hz, 1H), 1.58 (m, 5H), 1.40 (m, 1H), 1.18 (m, 2H), 0.92 (m, 1H), 0.68 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6, 129.4, 127.8, 125.7, 59.8, 56.9, 53.4, 50.3, 40.5, 31.1, 27.5, 25.9, 24.8, 17.8, 12.1. **33a**·HCl: Anal. ($C_{17}H_{25}N \cdot HCl \cdot 1.0H_2O$) C, H, N, Cl.

***threo*-1-Aza-4-ethyl-5-(3.4-dichlorophenyl)-[4.4.0]decane (31b and 33b)**. Using a procedure similar to that for **33a** and **33c**, **10b** was converted to **31b** and **33b** (1:1 ratio, 86% for four steps). α-ethyl-**31b**, ($R_f = 0.34$): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, $J = 6.9$ Hz, 1H), 7.17 (s, 1H), 6.92 (d, $J = 7.2$, 1H), 2.87 (m, 2H), 2.17 (td, $J = 3.0$, 12.3 Hz, 1H), 2.04 (m, 2H),1.82 (m, 2H), 1.55 (m, 3H), 1.39 (m, 2H), 1.13−0.92 (m, 4H), 0.84 (m, 1H), 0.70 (t, $J = 7.5$ Hz, 3H); **31b**·HCl: Anal. ($C_{17}H_{23}Cl_2N \cdot HCl \cdot 0.75H_2O$) C, H, N, Cl. β-ethyl-**33b**, ($R_f = 0.33$) : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, $J = 8.1$ Hz, 1H), 7.15 (d, $J = 1.5$ Hz, 1H), 6.89 (dd, $J = 1.8$, 8.1 Hz, 1H), 3.00 (d, $J = 11.1$ Hz, 1H), 2.90 (dd, $J = 4.5$, 11.1 Hz, 1H), 2.77 (td, $J = 3.3$, 12.0 Hz, 1H), 2.43 (dt, $J = 2.4$, 11.1 Hz, 1H), 2.36 (dt, $J = 2.7$, 12.0 Hz, 1H), 2.20 (m, 1H), 1.98 (m, 2H), 1.80 (qd, $J = 2.7$, 14.1 Hz, 1H), 1.68−1.02 (m, 8H), 0.69 (t, $J = 6.9$ Hz, 3H). **33b**·HCl: Anal. ($C_{17}H_{23}Cl_2N \cdot HCl \cdot 1.0H_2O$) C, H, N, Cl.

***threo*-Ritalinol (36a).** To the solution of MP (1.61 g, 6.91 mmol) in ether (15 mL) was added lithium aluminum hydride (4.5 mL, 4.5 mmol) *via* syringe at 0 °C under a nitrogen atmosphere. The solution was stirred at RT for 2 h. Water was carefully added drop by drop until no gas was evolved and the flask washed with ether and water. The ether layer was dried ($MgSO_4$) and evaporated to give a white solid (mp 95−97 °C, 0.95 g, 99%). ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 1H, $J = 8.2$ Hz), 7.33 (d, 1H, $J = 2.2$ Hz), 7.09−7.06 (dd, 1H), 3.99−3.93 (dd, 1H), 3.88−3.83 (dd, 1H), 3.11−3.06 (m, 1H), 2.97−2.90 (q, 1H), 2.67−2.55 (m,2H), 1.80−1.76 (m,1H), 1.63−1.59 (m, 1H), 1.45−1.21 (m, 3H). Anal. ($C_{13}H_{19}NO$): C, H, N.

***threo*-Ritalinol Methyl Ether (36b). *threo*-*N*-Benzylmethylphenidate**. MP-HCl (6.0 g, 22.3 mmol) was added to a suspension of potassium carbonate (7.3 g) in DMF (30 mL), and the resulting suspension was stirred at RT for a few minutes. To this suspension was added benzyl bromide (4.0 mL, 33.5 mmol) in one portion, and the mixture was stirred at RT overnight. Diethyl ether (400 mL) was added and decanted from the solids which were rinsed with ether (3 × 30 mL). The combined organic layer was washed with water (6 × 80 mL) and dried ($MgSO_4$). Evaporation afforded a yellow solid, which was purified by crystallization in EtOAc/hexane (1:99) to give the *N*-benzyl compound as a white solid (mp 71−73 °C, 6.45 g, 89%). ^{1}H NMR ($CDCl_3$) δ 7.35−7.14 (m, 10H), 4.13 (d, 1H, $J = 7.8$ Hz), 3.88 (d, 1H, $J = 13.5$ Hz), 3.72 (d, 1H, $J = 13.5$ Hz), 3.58 (s, 3H), 3.46−3.42 (m, 1H), 2.91−2.87 (m, 1H), 2.56−2.46 (m, 1H), 1.59−0.79 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.1, 140.4, 137.1, 128.8, 128.6, 128.1, 127.4, 126.8, 62.6, 56.3, 53.1, 51.7, 44.8, 21.1, 20.7, 19.4. ***threo*-*N*-Benzylritalinol**. Using a procedure similar to that for **36a**, the above *N*-benzyl ester (6.45 g, 20 mmol) afforded a white solid, mp 76−77 °C, (6.01 g, 100%). ^{1}H NMR ($CDCl_3$) δ 7.40−7.17 (m, 8H), 7.04 (d, 2H, $J = 8.1$ Hz), 4.00 (s, 2H), 3.83 (t, 1H, $J = 11.0$ Hz), 3.70 (dd, 1H, $J = 3.3$, 11.0 Hz), 3.52−3.44 (m, 1H), 3.32−3.18 (m, 2H), 2.74 (m, 1H), 1.77−1.50 (m, 4H), 1.35−0.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 141.0, 138.6, 129.2, 128.7, 127.9, 126.8, 123.2, 70.0, 63.0, 57.2, 45.2, 44.9, 20.4, 19.9, 18.8. ***threo*-*N*-Benzylritalinol Methyl Ether**. To 3 mL of DMSO was added KOH (68 mg, powder, 1.21 mmol). After the mixture was stirred for 20 min at RT, the above alcohol (100 mg, 0.34 mmol) in DMSO (3 mL) was added in one portion, followed immediately by methyl iodide (45 μL, 0.73 mmol). The mixture was stirred at RT for 24 h, and methylene chloride (60 mL) added and washed with water (6 × 20 mL). Evaporation gave a pale yellow solid (113 mg), which was purified by chromatography on a silica gel (EtOAc/hexane, 3:97), to afford pure methyl ether as a white solid (90.2 mg, 86%). ^{1}H NMR ($CDCl_3$) δ 7.38−7.18 (m, 10H), 4.01−3.97 (m, 2H), 3.77 (d, 1H, $J = 13.2$ Hz), 3.65 (t, 1H, $J = 9.3$ Hz), 3.45−3.37 (m, 1H), 3.27 (s, 3H), 3.01−2.92 (m, 1H), 2.53−2.47 (m, 1H), 1.70−1.05 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 142.4, 140.6, 128.7, 128.6, 128.3, 128.2 126.8, 126.4, 75.2, 61.1, 58.9, 55.3, 47.4, 46.1, 22.0, 21.8, 20.0. It was then converted to its HCl salt using anhydrous HCl solution in ether (mp 228−229 °C), a portion (68 mg, 0.20 mmol) was dissolved in methanol (5 mL), and palladium hydroxide (20 mg, 20% Pd, wet) was then added. Hydrogenation was carried out at 45 psi for 2 h.

Filtration and evaporation afforded pure **36b**·HCl as a white solid (mp 154−155 °C, 50 mg, 99.4%). ^{1}H NMR (D_2O) δ 7.32−7.14 (m, 5H), 3.76 (dd, 1H, J = 8.2, 9.9 Hz), 3.73 (dd, 1H, J = 6.0, 9.9 Hz), 3.43−3.37 (m, 1H), 3.23−3.21 (m, 4H), 3.10−3.03 (m, 1H), 2.91−2.82 (m, 1H), 1.65−1.17 (m, 6H): Anal. ($C_{14}H_{21}N$)·HCl) C, H, N, Cl

***threo*-3,4-Dichlororitalinol (36c)**. Using a procedure similar to that for **36a**, but maintaining the temperature at 0 °C for 45 min and then at rt for 15 min, 3,4-dichloromethylphenidate (162 mg, 0.54 mmol) gave **36c** as a white solid (mp 122−124 °C, 146 mg, 99%). ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 1H, J = 8.2 Hz), 7.33 (d, 1H, J = 2.2 Hz), 7.08 (dd, 1H, J = 2.2, 8.2 Hz), 3.97 (dd, 1H, J = 7.7, 11.0 Hz), 3.86 (dd, 1H, J = 3.7, 11.0 Hz), 3.11−3.06 (m, 1H), 2.97−2.90 (m, 1H), 2.67−2.55 (m, 2H), 1.80−1.76 (m, 1H), 1.63−1.59 (m, 1H), 1.45−1.21 (m, 3H); MS *m*/*z* 274 (M + 1): Anal.-($C_{13}H_{17}Cl_2NO$) C, H, N, Cl.

***erythro*-3,4-Dichloromethylphenidate (36d)**. Using exactly the same procedure as described in reference 16, 3,4-dichlorobenzyl cyanide (5.0 g, 0.027 mol) gave 1.9 g (21% overall yield) of the title compound, **36d**·HCl, mp 196−197 °C. ^{1}H NMR (D_2O) δ 7.38−7.02 (m, 3H), 3.82 (d, J = 8.9 Hz, 1H), 3.68−3.62 (m, 1H), 3.56 (s, 3H), 3.16−3.11 (m, 1H), 2.83−2.75 (m, 1H), 1.92−1.36 (m, 6H): Anal. ($C_{14}H_{17}Cl_2NO_2$·HCl·0.5H_2O) C, H, N, Cl.

2-Phenylpiperidine (34). A 1.5 g amount of 2-phenylpyridine was mixed with 50 mg of 5% Pt/C in 50 mL of acetic acid and stirred with hydrogen at 50 psi for 6 h. After filtration over celite, the acetic acid was evaporated under reduced pressure. Excess HCl was added and the mixture evaporated again. The residue was recrystallized from ethyl acetate containing about 5% chloroform. This gave 1.1 g of white solid, mp 142.5−143 °C (lit. 144 °C).

1-Benzylpiperidine (35). Using the same procedure as in the synthesis of **34**, 1.5 g of 1-benzylpyridine gave a solid residue which was washed with ethyl ether/ethyl acetate (1:1). This gave 1.5 g of white solid, mp 141.5−142.5 °C (lit. 141 °C).

Pharmacology.

Animals. Male Sprague−Dawley rats (Harlan Sprague−Dawley, Indianapolis, IN), weighing 150−300 g, were anesthetized using CO_2 gas and sacrificed by decapitation. Their brains were quickly removed and placed in ice-cold 0.32 M sucrose. The tissue needed for a given assay was quickly dissected out and utilized in the various assays as described below.

[^{3}H]WIN 35,428 Binding to the DAT. The synthesized compounds were screened for activity in a disrupted crude striatal synaptosomal membrane preparation by a previously described method.[29] Briefly, a P_2 fraction prepared from rat striatal tissue was homogenized in 25 mM sodium phosphate buffer, pH 7.7, at 0 °C using a Tekmar tissuemizer. Binding to the tissue preparation in the presence of 2 nM [^{3}H]WIN was determined after a 2 h incubation at 0 °C by rapid filtration through glass microfiber filters using Millipore filtration manifolds. Amfonelic acid (10 μM final concentration) was used to define nonspecific binding. The K_D for [^{3}H]WIN binding was 18.3 ± 0.9 nM.

[^{3}H]Nisoxetine Binding to the NET. A modification of the method described by Dutta et al. was utilized.[30] Tissue from three rat brains (cerebrum and brain stem) minus the striatum, hypothalamus, olfactory tubercles, cerebellum, and medial cortex extending to approximately 1 mm on either side of the interhemispheric fissure was distributed approximately evenly between two Potter-Elvejhm glass/Teflon homogenizers which contained 20 mL each of 0.32 M sucrose and homogenized by 10 up/down strokes of the motorized pestle set at medium speed. The resulting tissue homogenate was adjusted to a 1:20 wet weight tissue:volume ratio with 0.32 M sucrose and then centrifuged at 1000*g* for 10 min at 0 °C. The pellet (P_2 fraction) obtained by centrifugation of the supernatant from the low-speed spin at 20 000*g* for 20 min at 0 °C was suspended in 10 volumes of ice-cold assay buffer (25 mM sodium phosphate/5 mM KCl/120 mM NaCl, pH 7.70 at 0 °C) using an Ultra-Turrax tissue homogenizer. Binding was initiated by addition of 300 μL of the P_2 suspension to samples containing 600 μL of assay buffer, 50 μL of the test compound, 25 μL of water or desipramine (to define nonspecific binding; final concentration, 500 nM), and 25 μL of [^{3}H]NIS (final concentration, 1 nM). [^{3}H]NIS (nisoxetine HCl [*N*-methyl-^{3}H]-) had a specific activity of 70−87 Ci/mmol and was purchased from Perkin-Elmer (Boston, MA). Test compounds were dissolved in water or dilute DMSO (≤0.5% by volume in the final sample). The samples were incubated for 3 h at 0 °C. The reaction was terminated by addition of 5 mL ice-cold assay buffer to the assay tubes, followed by rapid filtration through glass microfiber filter strips (presoaked in 0.05% polyethyleneimine) under reduced pressure using a Brandel cell harvester (Brandel Inc., Gaithersburg, MD). Assay tubes were washed with an additional 5 mL aliquot of ice-cold assay buffer. The filters were transferred to scintillation vials, soaked overnight in 8 mL of Ready-Safe scintillation cocktail (Beckman, Fullerton, CA), shaken vigorously for 60 min, and counted on a Beckman LS6000IC scintillation counter. After correction of the data for displacement of filter binding, IC_{50} values and Hill coefficients were determined as described below. The K_D for [^{3}H]NIS binding was 2.32 ± 0.12 nM.

One of the compounds was outsourced for analysis by SRI International (Menlo Park, CA), as noted in Table 1. Essentially the same procedure was followed for the outsourced compound, except that a final concentration of 1000 nM rather than 500 nM desipramine was used to define nonspecific binding. Four criterion compounds analyzed in the author's laboratory (MS) gave K_i values that were 1.45 ± 0.24 (x ± SD) of the values obtained by SRI International for the same compounds. This correction factor was therefore applied to the K_is provided by SRI International before their inclusion with the results generated by our laboratory.

[^{3}H]Citalopram Binding to the 5-HTT. The method used here was as described previously.[31] Briefly, a P_2 fraction prepared from selected rat cortical tissue was homogenized in 25 mM sodium phosphate buffer, pH 7.7 at 0 °C. Binding to the tissue preparation in the presence of 2 nM [^{3}H]CIT was determined after a 3 h incubation at 0 °C by rapid filtration through glass microfiber filter strips under reduced pressure using a Brandel cell harvester (Brandel Inc., Gaithersburg, MD). Clomipramine (1 μM final concentration) was used to define nonspecific binding. Test compounds were dissolved in water, dilute DMSO, or dilute methanol, with the concentration of organic solvent in any assay tube limited to 0.3% by volume. After correction of the data for displacement of filter binding by clomipramine and/or the test drug, IC_{50} values and Hill coefficients were determined as described below. The K_D for [^{3}H]-CIT binding was 6.65 ± 1.05 nM (x ± SEM).

[^{3}H]DA Uptake. Accumulation of [^{3}H]DA by the S_1 fraction of a striatal homogenate was determined as previously described.[30]

Data Analysis. IC_{50}s (the concentration of compound that inhibits specific binding to the receptor by 50%) and Hill coefficients were calculated from curves fit by nonlinear regression using the GraphPad Prism program. Usually, six drug concentrations were assayed in triplicate to generate a dose−response curve, and each assay was conducted at least twice. K_is were calculated from the IC_{50}s with the equation $K_i = IC_{50}/(1 + [L/K_D])$ where L is the radioligand concentration used in the radioreceptor assay and K_D is the dissociation constant of the radioligand utilized in the assay. Results are expressed as x ± SEM.

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