Synthesis, Structure, Dopamine Transporter Affinity, and Dopamine Uptake Inhibition of 6-Alkyl-3-benzyl-2-[(methoxycarbonyl)methyl]tropane Derivatives

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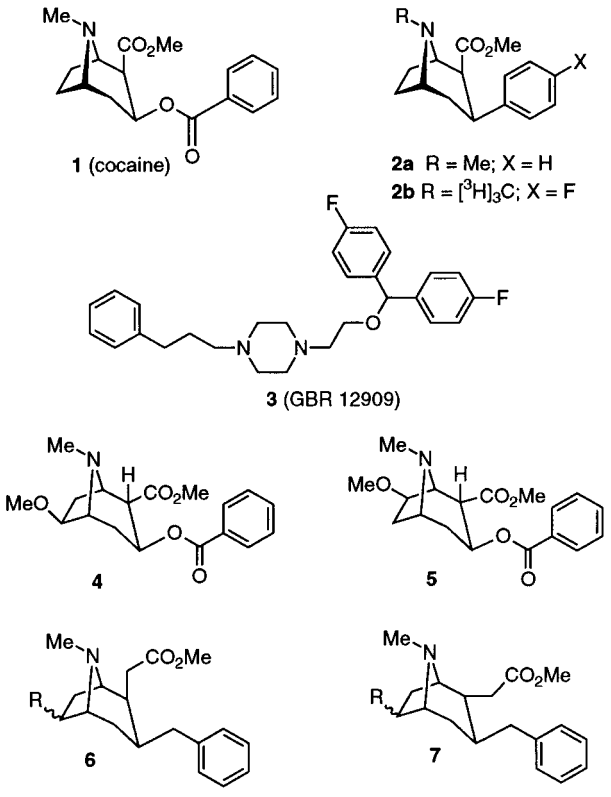
A series of 6-alkyl-3β-benzyl-2-[(methoxycarbonyl)methyl]tropane analogues were synthesized and evaluated as cocaine binding site ligands at the dopamine transporter (DAT). The in vitro affinity (K_i) for the DAT of the 6-alkyl-3β-benzyl-2-[(methoxycarbonyl)methyl]tropane analogues was determined by inhibition of [^{3}H]WIN 35,428 in rat caudate putamen tissue. The inhibition of dopamine uptake (IC_{50}) was also measured for selected compounds which demonstrated moderate affinity for the dopamine transporter. The unsubstituted enantiopure analogues (−)-**19a** (K_i = 33 nM) and surprisingly (+)-**20a** (K_i = 60 nM) were found to be almost equipotent with the high-affinity binding components of cocaine and WIN 35,065-2 and exhibited slightly more potent dopamine uptake inhibition than both cocaine and WIN 35,065-2. In general, substitution at the 6-position of racemic **19a** and **20a** with alkyl groups was found to result in decreased activity relative to increased chain length of the substituent. The 3β-benzyl-2β-[(methoxycarbonyl)methyl]-6β-methyltropane (**21b**; K_i = 57 nM) was the only 6-alkyl derivative to exhibit moderately potent activity. The 6β-isomer **21b** was 4-fold more potent than the 6α-isomer **19b** (K_i = 211 nM) and was nearly equipotent with (−)-**19a** and (+)-**20a** as well as with cocaine and WIN 35,065-2. The results of this study further demonstrate the steric constraints associated with the C(6)−C(7) methylene bridge of the tropane ring system for molecular recognition of cocaine analogues at the cocaine binding site(s) on the DAT.

Introduction

The abuse of cocaine (**1**) is a national health problem of increasing magnitude. Consequently, a considerable effort has been directed toward understanding the pharmacological mechanism of action and the behavioral effects of cocaine. It has been hypothesized that the broad spectrum of reinforcing and stimulant effects associated with cocaine are mediated by the dopaminergic system.[1−4] Cocaine occupation of stereoselective binding site(s) on the dopamine transporter (DAT) has been shown to result in inhibition of dopamine reuptake into presynaptic neurons.[1] This is thought to lead to increased extracellular dopamine concentrations in the synapse resulting in increased dopaminergic neurotransmission.[1−4]

To date the search for compounds to be used in the development of safe and effective treatment strategies for cocaine addiction has led to the synthesis of a number of diverse tropane (**2**)[1,5−18] and non-tropane analogues.[19−25] Among these compounds the disubstituted piperazine derivative **3** (GBR 12909) and the tropane derivatives 6β-methoxypseudococaine (**4**) and 7β-methoxypseudococaine (**5**) have been reported to demonstrate potential as cocaine abuse therapeutic agents. Recent studies have demonstrated that **3** is a high-affinity, DAT selective,[20,26,27] low-intrinsic-activity agonist which attenuated cocaine's ability to elevate extracellular dopamine concentrations.[28,29] Alternatively, the pseudococaine derivatives **4** and **5** were shown to be 2.5 and 4 times weaker as dopamine uptake inhibitors relative to their ability to displace [^{3}H]-mazindol.[5] Although the binding affinities of **4** and **5** at the DAT were low, this was the first report of weak antagonist-like properties for a tropane derivative and suggested that it may be possible to structurally modify



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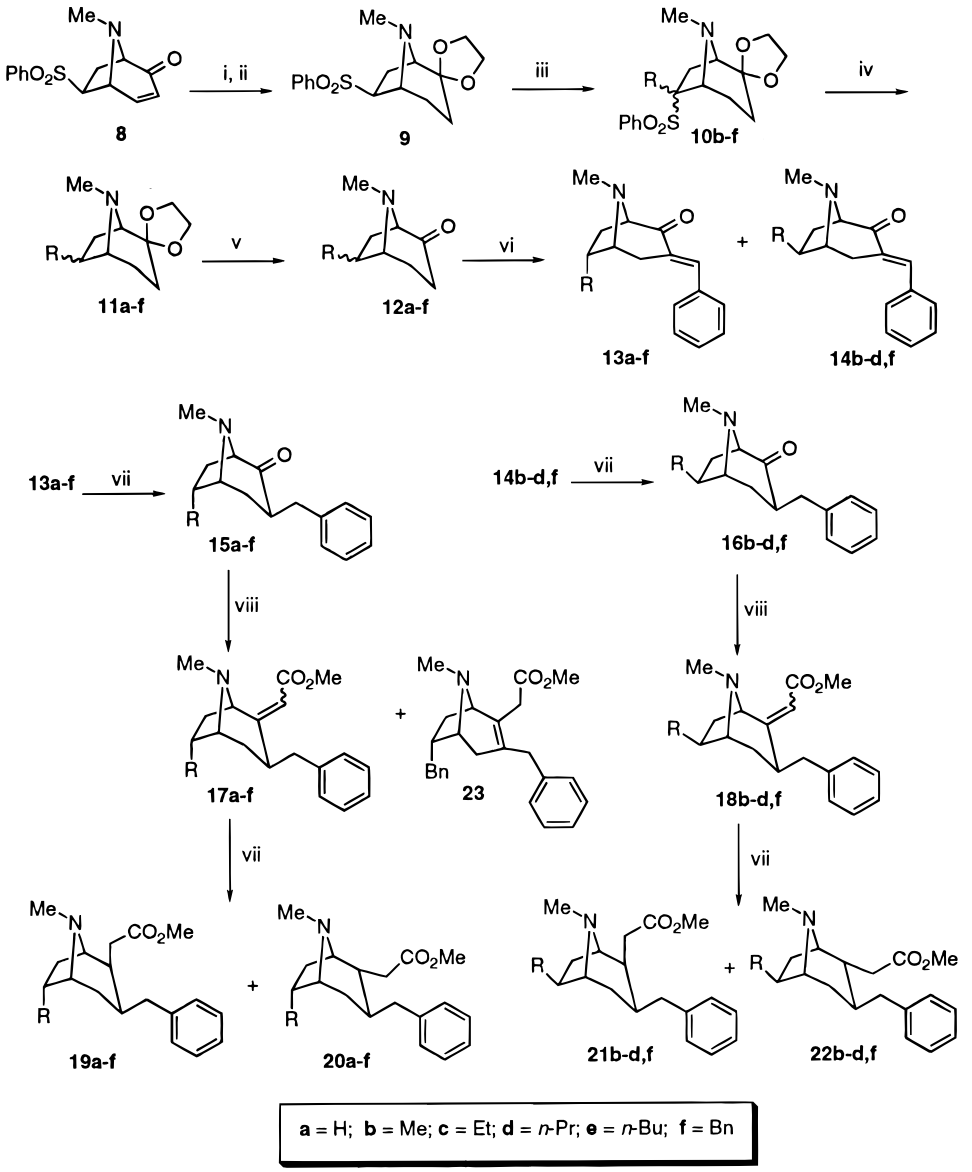
Scheme 1[a]



[a] Reagents: (i) H_2, Pd/C, EtOH/$CHCl_3$; (ii) $(CH_2OH)_2$, *p*-TsOH, benzene, △; (iii) *n*-BuLi, THF, −78 °C, then RX, 0 °C to room temperature; (iv) 40% Na(Hg), MeOH/THF, Na_2HPO_4; (v) 3 N $HClO_4$, 90 °C; (vi) PhCHO, 5 N NaOH, EtOH; (vii) H_2, Pd/C, MeOH; (viii) NaH, $(MeO)_2POCH_2CO_2Me$, DME, 80 °C.

the tropane ring system to obtain compounds with cocaine antagonist activity.

It was of interest to explore the structure−activity relationships (SAR) of substitution at the 6- and 7-positions of the tropane ring system relative to the development of high-affinity analogues with weak or no inhibition of dopamine uptake. To this end, an investigation of the synthesis and SAR of 6-alkyltropane derivatives was initiated. The 6-alkyl-3β-benzyl-2-[(methoxycarbonyl)methyl]tropane derivatives **6** and **7** were identified as suitable candidates to explore the effect of C(6)-substitution on the binding affinity of cocaine- and pseudococaine-related derivatives. The syntheses of the homologues **6** and **7** were envisaged to be facile and straightforward from a common readily available intermediate. The 2β-benzyl group and the 2β-(methoxycarbonyl)methyl group were chosen as ancillary substituents to facilitate the syntheses of 6-alkyltropane derivatives. In addition, the 3β-benzyl group was envisaged as isosteric with the 3β-benzoyloxy group of the cocaine analogues **4** and **5**, and the 2β-(methoxycarbonyl)methyl group was not expected to significantly diminish binding affinity.[10,16] Therefore, it was believed that the biological activity of **6** and **7** would primarily reflect the effect of the 6-alkyl group at the DAT. Herein we wish to describe the synthesis, binding site affinity, and dopamine uptake inhibition of the 6-alkyl-3β-benzyl-2-[(methoxycarbonyl)methyl]tropanes, a new class of cocaine analogues.

Chemistry

Despite numerous synthetic methods for the construction of the tropane ring system,[30−34] there are few synthetic methods which allow direct functionalization of the C(6)- and C(7)-positions of the tropane ring.[30,35−38] As illutrated in Scheme 1, the synthesis of the 6-alkyltropane derivatives was envisaged to proceed via alkylation/desulfonylation of the 6β-(phenylsulfonyl)-8-methyl-8-azabicyclo[3.2.1]octan-2-one ethylene acetal (**9**).[36] The acetal **9** was prepared from readily available **8** in a straightforward fashion.[37] Treatment of **9** with

Table 1. Stereoselectivity and Overall Yields of the Olefination/Hydrogenation of **15a**−**f** and **16b**−**d,f**

products	2β:2α[a]	yield (%)[b]
19a/20a	1:3	61
19b/20b	1:3	55
19c/20c	1:3	47
19d/20d	1:4	65
19e/20e	1:5	78
19f/20f	1:1	32
21b/22b	1:3	66
21c/22c	1:3	44
21d/22d	1:4	53
21f/22f	1:3	60

[a] Isomer ratios were determined from isolated yields. [b] Overall yield; reaction conditions were not optimized.

n-butyllithium at −78 °C in dry THF and concomitant addition of an alkyl halide furnished the alkylated sulfone derivatives **10b**−**f** as a mixture of isomers in high yields.[39]

The desulfonylation of **9** and the alkylated products **10b**−**f** was achieved with 40% Na(Hg) in Na_2HPO_4-buffered methanol/THF to afford the tropane derivatives **11a**−**f** in high yields (80−91%).[39] The compounds **11b**−**f** were characterized as a mixture of isomers, and the 6α-isomers of **11b**−**f** were found to be the major products. Conversion of **11a**−**f** into the corresponding tropanones **12a**−**f** (72−87% yield) followed by condensation with benzaldehyde gave the benzylidene derivatives **13a**−**f** and **14b**−**d**,**f** (70−82% yield; Scheme 1).[39] The 6α-isomers **13b**−**f** and 6β-isomers of **14b**−**d**,**f** were then easily separated by column chromatography and obtained in pure form. Hydrogenation of the carbon−carbon double bond of **13a**−**f** afforded the 3β-benzyl derivatives **15a**−**f** stereoselectively.[39]

Wadsworth−Emmons olefination of the ketones **15a**−**f** furnished the intermediate alkylidine esters **17a**−**f**. The unsaturated analogue **23**, was isolated as a byproduct (41% yield) from the olefination of **15f** (Scheme 1). Presumably, the formation of **23** resulted from the base-catalyzed isomerization of the alkylidine **17f** in situ. This isomerization was only observed with the dibenzyl derivative **17f**.

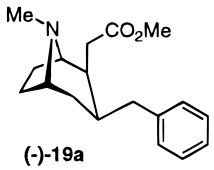
Subsequent hydrogenation of the alkylidine esters **17a**−**f** over 10% palladium on carbon afforded a mixture of the 2β- and 2α-isomers **19a**−**f**:**20a**−**f** in 32−78% overall yield (Table 1). In all cases, the 2α-isomer was the major isomer formed. The isomers were then separated by column chromatography. The relative stereochemistry of each isomer was determined by $^1H-^1H$ COSY NMR experiments. In addition, it is noteworthy that the stereochemistry at C(2) could be easily established by means of a simple chemical test. Treatment of the 2α-isomers with excess ethyl iodide in acetone readily formed the corresponding quaternary ammonium iodide salt. However, quaternization of the 2β-isomer was not possible due to steric constraints imposed by the 2β-(methoxycarbonyl)methyl group.[40] The minor benzylidine isomers **14b**−**d**,**f** were also converted into the 6β-alkyl analogues **21b**−**d**,**f** and **22b**−**d**,**f** in a similar fashion (Scheme 1, Table 1).

The enantiopure parent compounds (−)-**19a** and (+)-**20a** were prepared in similar fashion to that described above for **19a** and **20a** from (+)-2-tropinone.[41] The structures of (−)-**19a** and (+)-**20a** were unequivocally confirmed by single-crystal X-ray analysis.

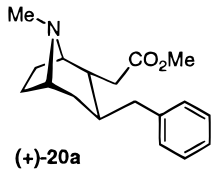
Table 2. Inhibition of [^{3}H]WIN 35,428 (**2b**) Binding and Inhibition of [^{3}H]Dopamine Uptake

compd[a]	K_i (nM)[b]	[^{3}H]DA inhibition IC_{50} (nM)[b]
1[c]	32 ± 5	405 ± 91
	338 ± 221	
2a[c]	33 ± 17	373 ± 10
	314 ± 222	
(−)-**19a**[d]	33 ± 5	161 ± 100
19a[d]	91 ± 10	94 ± 26
19b	211 ± 23	
19c	307 ± 28	
19d	4180 ± 418	
19e	8580 ± 429	
19f	3080 ± 277	
(+)-**20a**[d]	60 ± 6	208 ± 63
20a[d]	108 ± 14	457 ± 104
20b	531 ± 64	
20c	1150 ± 135	
20d	7240 ± 376	
20e	19700 ± 350	
20f	7590 ± 531	
21b[e]	57 ± 5	107 ± 36
21c[d]	3110 ± 187	
21d[d]	5850 ± 702	
21f	1560 ± 63	
22b	294 ± 29	532 ± 136
22c[d]	6210 ± 435	
22d[d]	57300 ± 3440[f]	
22f[d]	3080 ± 277	
23[d]	4830 ± 434	

[a] All compounds were tested as the oxalate salt unless otherwise noted. [b] All values are the mean ± SEM of three experiments performed in triplicate using protocol previously described in ref 42. [c] The K_i values and IC_{50} values for these drugs are reproduced from ref 42 and were collected under conditions identical with the present ones. [d] Tested as the hydrochloride salt. [e] Tested as the fumarate salt. [f] Only 64% inhibition at 100 μM.



(-)-19a



(+)-20a

Biology

The compounds (−)-**19a**, **19a**−**f**, (+)-**20a**, **20b**−**f**, **21b**−**d**,**f**, **22b**−**d**,**f**, and **23** were tested for their ability to displace [^{3}H]WIN 35,428 (**2b**) from rat caudate putamen tissue. The K_i values reported in Table 2 are inhibition constants derived for the unlabeled ligands. In addition, selected high-affinity compounds were tested for their ability to inhibit uptake of [^{3}H]dopamine into rat caudate putamen tissue.[42] The linear portions of the inhibition curves were analyzed using analysis of variance and linear regression techniques, and the IC_{50} values are reported in Table 2. As noted previously, cocaine (**1**) and WIN 35,065-2 (**2a**) modeled better for two binding sites than one; as a consequence, their high-affinity and low-affinity K_i values are given in Table 2.[8,16,42] All of the 3β-benzyl-2-[(methoxycarbonyl)methyl]tropane derivatives prepared for this study were best fit by a single-component model, and as such, single K_i values are reported in Table 2.

Discussion

The binding affinity of the enantiopure unsubstituted analogue (−)-**19a** was found to be equipotent with the high-affinity binding component of cocaine (**1**) and WIN

35,065-2 (**2a**). In addition, (−)-**19a** was found to be slightly more potent toward [^{3}H]dopamine uptake inhibition than **1** and **2a**. Moreover, racemic **19a** exhibited comparable potency to (−)-**19a** for dopamine uptake inhibition, and as expected (−)-**19a** was 3-fold more potent than **19a** for inhibition of [^{3}H]WIN 35,428 binding. These results demonstrated that the one-carbon homologation at the 2β- and 3β-positions of **2a** did not adversely affect binding affinity or inhibition of [^{3}H]dopamine uptake of (−)-**19a** compared to **1** and **2a**.

It was quite surprising to find that unlike the SAR of cocaine analogues and 2-substituted-3β-aryltropanes, the 2α-isomer **20a** was equipotent with the 2β-isomer **19a**. In addition, the enantiopure 2α-isomer (+)-**20a** was only one-half as potent as the 2β-isomer (−)-**19a** as well as **1** and **2a**. Among other cocaine and 3β-aryltropane analogues, the 2α-isomers typically have been reported to be at least 30−100-fold less potent than the corresponding 2β-isomers.[1,10,14]

Based on the structural similarities of (−)-**19a** to **1** and **2a** and the fact that (−)-**19a** was found to be equipotent with **1** and **2a**, it is believed that the homologues bind in similar fashion at the DAT. Therefore, since the racemic analogue **19a** exhibited only a moderate decrease in binding affinity and no significant loss of potency in dopamine uptake inhibition relative to the enantiopure analogue (−)-**19a**, the biological activity of the racemic 6-alkyl-3β-benzyl-2-[(methoxycarbonyl)-methyl]tropane derivatives is thought to primarily be a reflection of the effect of the 6-alkyl group, which in turn can be extrapolated to provide some general insight into the effects of 6-alkyl substitution on cocaine and 2β-carbomethoxy-3β-phenyltropane analogues.

In general, the binding affinity of the racemic 6α-alkyl-2β-(methoxycarbonyl)methyl congeners **19b**−**f** decreased relative to the unsubstituted derivative **19a** as the chain length of the alkyl substituent increased. A dramatic decrease was observed when the chain length was extended by one methylene unit from ethyl (**19c**) to *n*-propyl (**19d**). The 6α-alkyl-2α-(methoxycarbonyl)-methyl congeners **20b**−**f** exhibited a similar trend in binding affinity albeit being approximately 2-fold less potent than the corresponding 2β-congeners **19b**−**f**. It is noteworthy that the *n*-propyl and benzyl analogues **19d**,**f** and **20d**,**f** were of similar potency, while the *n*-butyl analogues **19e** and **20e** were greater than 2-fold less potent, respectively. In addition, the unsaturated 6-benzyl analogue **23** possessed similar binding affinity to **19d** and **19f** despite the loss of stereochemistry at C(2) and C(3).

The 6β-alkyl-3β-benzyl-2-[(methoxycarbonyl)methyl]-tropanes were found to be more sensitive to binding site constraints than the corresponding 6α-isomers. Only the 6β-methyl analogue **21b** exhibited potent binding affinity, while the binding affinity decreased considerably for the 6β-ethyl analogue **21c** and the *n*-propyl analogue **21d**. Even as the racemate, the binding affinity and the dopamine uptake inhibition of **21b** were equipotent with those of the unsubstituted analogue (−)-**19a** as well as with those of the high-affinity binding components of **1** and **2a**. In addition, **21b** was 4-fold more potent than the corresponding 6α-methyl analogue **19b**. The 6β-alkyl-2α-(methoxycarbonyl)methyl congeners **22b**,**c**,**f** again were consistently only 2-fold less potent than the corresponding 2β-isomers **21b**,**c**,**f**, while the binding affinity of *n*-propyl derivative **22d** was greatly diminished.

Among the 6-alkyl derivatives the 6-benzyl analogues **19f**, **20f**, **21f**, and **22f** exhibited anomalous binding affinity. In all cases, the benzyl derivatives exhibit higher affinity than would be expected based on simple steric and lipophilic trends. This suggests that there may be a significant electrostatic interaction between the binding site and the aromatic π-system of the benzyl group at the 6-position. Such an interaction could be the source of the enhanced affinity of the 6-benzyl derivatives relative to the alkyl analogues **19e**, **20e**, **21d**, and **22d**. This effect seemed to be especially significant when the benzyl group was in the 6β-position; **21f** was the most potent of the four 6-benzyl diastereoisomers. Alternatively, it may be possible that the 6-benzyl group facilitates binding of the analogue to a different domain on the dopamine transporter than the 6-alkyl analogues and thus leads to the observed differences in binding affinity.[43] However, heterogeneous binding affinity was not observed for the 6-benzyl analogues, so it is not possible to establish the presence of an alternate binding domain accessed by the 6-substituted compounds at this time.[43]

From the SAR data it is apparent that substitution in the 6-position inhibits binding at the dopamine transporter. This is consistent with the effect of the methoxy group on the binding affinity of the corresponding cocaine derivatives.[5] For the 6-alkyl-2-[(methoxycarbonyl)methyl]-3β-benzyltropanes, only a small substituent (**21b**, Me) in the 6β-position was tolerated without loss of activity. The 6α-position was slightly more tolerant of substituents; the methyl (**19b**) and ethyl (**19c**) analogues exhibited moderate binding affinity; however, when the 6-alkyl chain was *n*-propyl (**19d**) the activity decreased dramatically. Based on this SAR, it is apparent that the binding site is sensitive to the steric bulk of the 6-alkyl substituent and suggests that the region occupied by the 6-alkyl substituent has a defined volume which will not tolerate substituents larger than 6β-methyl and 6α-ethyl. As a result of increasing the size of the 6-alkyl group, it appears that the ligand may not be able to align itself properly in the binding site and as a result the affinity was reduced. The sensitivity of the cocaine binding site to substituents at the 6α- and 6β-position is also consistent with the decreased binding affinity observed for 2β-(methoxycarbonyl)-3β-phenyl-9-methyl-9-azabicyclo[3.3.1]-nonane recently reported from these laboratories.[44] The SAR of the 6-alkyl-3β-benzyl-2-[(methoxycarbonyl)-methyltropanes further demonstrates the steric constraints associated with the C(6)−C(7) methylene bridge of the tropane ring system for molecular recognition of cocaine analogues at the cocaine binding site(s) on the DAT.

It is apparent from biological data of the 6-alkyl analogues (Table 2) that those compounds which maintained high binding affinity relative to cocaine for the DAT (**21b** and **22b**) also exhibited relatively potent dopamine uptake inhibition. In fact, **21b** and **22b** were comparable in potency as dopamine uptake inhibitors to cocaine (**1**) and were at least 1000-fold more potent than **4** (K_i = 510 μM).[5] These result are consistent with much of the SAR of cocaine and phenyltropane deriva-

tives, such that high-affinity ligands at the DAT are generally potent dopamine uptake inhibitors.[1,5−18,42−44]

In summary, the 3β-benzyl-2-[(methoxycarbonyl)-methyl]tropane system has been identified as a new class of dopamine uptake inhibitors. The unsubstituted enantiopure analogues (−)-**19a** and surprisingly (+)-**20a** were found to be nearly equipotent with the high-affinity binding components of cocaine and WIN 35,065-2 and exhibited slightly more potent dopamine uptake inhibition than both cocaine and WIN 35,065-2. Substitution at the 6-position of **19a** and **20a** with alkyl groups was found to result in decreased activity relative to the chain length of the substituent. These results further demonstrate the steric constraints associated with the C(6)−C(7) methylene bridge of the tropane ring system for molecular recognition of cocaine analogues at the cocaine binding site(s) on the DAT. All of the high-affinity analogues tested for dopamine uptake inhibition were nearly equipotent to cocaine. Therefore, it seems unlikely that alkyl group substitution at the 6-position of the 3β-benzyl-2-[(methoxycarbonyl)methyl]tropanes as well as analogues of cocaine and 3β-phenyl-2-(methoxycarbonyl)tropanes will diminish dopamine uptake inhibition relative to DAT binding affinity and lead to compounds with antagonist-like activity.

Experimental Section

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. DME and THF were dried by distillation over Na/benzophenone. MeOH was dried by distillation over Drierite. Chromatography refers to flash chromatography on silica gel (silica gel 60, 230−400 mesh; E. M. Science) and petrol refers to petroleum ether (pentanes) with a boiling point range of 30−60 °C. Reported melting points are uncorrected. NMR spectra were recorded on a Varian-Gemini 300 MHz multiprobe spectrometer or as noted on a Varian-Gemini 400 MHz spectrometer. Chemical shifts are reported as δ values with chloroform, or as noted, tetramethylsilane (TMS) was employed as the internal standard. Mass spectra (LRMS) were recorded on a Hewlett-Packard 5855 GC−MS. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA. The physical data and experimental details for the preparation of **13a**−**f** and **14b**−**d**,**f** are described in ref 39.

General Procedure for the Preparation of Hydrochloride Salts. Some of the compounds were converted into the corresponding hydrochloride salts for ease of handling and storage as well as for biological testing. The base (100 mg) was dissolved in a minimum amount of tetrahydrofuran (1−2 mL) and added to an etheral solution (1−2 mL) of hydrogen chloride (saturated). The hydrochloride salts then crystallized upon standing at room temperature and were collected by vacuum filtration. Fractional moles of water in some of the analytical samples could not be prevented despite vigorous drying (65 °C, 18 h) under vacuum (0.01 mmHg).

General Procedure for the Preparation of Oxalate and Fumarate Salts. Some of the final compounds were converted into the corresponding oxalate and fumarate salts for biological testing. The base (1 equiv) was dissolved in a minimum amount of propanol (1−2 mL) and added to a solution (2 mL) of the corresponding acid (1.2 equiv). The salts then crystallized upon standing at room temperature and were collected by vacuum filtration. Fractional moles of water in some of the analytical samples could not be prevented despite vigorous drying (65 °C, 18 h) under vacuum (0.01 mmHg).

Hydrogenolysis of Benzylidenes 13a−f and 14b−d,f (General Procedure A). To a slurry of 10%, Pd/C (10% w/w) in MeOH (15 mL) was added a solution of the benzylidene (3.0 mmol) in MeOH (15 mL). The mixture was hydrogenated on a Parr hydrogenation apparatus (15 psi) overnight. The catalyst was removed by filtration through Celite. The filter cake was rinsed with MeOH (30 mL), and the combined organic portions were concentrated under reduced pressure. The resulting residue was purified by chromatography (SiO_2) to afford **15a**−**f** and **16b**−**d**,**f**, respectively.

Homologation of Ketones 15a−f and 16b−d,f (General Procedure B). NaH (60%, (4.4 mmol) in a round-bottomed flask equipped with a condensor under an atmosphere of N_2 was rinsed with dry hexane (3 mL). Dried 1,2-dimethoxyethane (DME) (30 mL) was then added followed by $(CHO_3)_2$-$P(O)CH_2CO_2CH_3$ (4.0 mmol) via syringe. Immediately a white precipitate formed, and the suspension was stirred for 45 min, afterwhich a solution of the ketone (2.0 mmol) in DME (4.5 mL) was added via cannula and the reaction mixture was heated at 85 °C for 24 h. The reaction mixture was allowed to cool to room temperature and poured into H_2O (100 mL). The aqueous layer was extracted with Et_2O (4 × 100 mL). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was chromatographed (SiO_2) to afford the α,β-unsaturated esters **17a**−**f** and **18b**−**d**,**f** in sufficient purity for the next step.

Hydrogenolysis of α,β-Unsaturated Esters 17a−f and 18b−d,f (General Procedure C). To a suspension of 10%, Pd/C (10% w/w) in MeOH (10 mL) was added a solution of the α,β-unsaturated ester (1.0 mmol) in MeOH (5 mL). The mixture was hydrogenated on a Parr hydrogenation apparatus (15 psi) for 24 h. The catalyst was removed by filtration through Celite. The filter cake was rinsed with MeOH (15 mL), and the combined organic portions were concentrated under reduced pressure. The resulting residue was purified by chromatography (SiO_2) to afford **19a**−**f**, **20a**−**f**, **21b**−**d**,**f**, and **22b**−**d**,**f**.

3β-Benzyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (15a): general procedure A, 530 mg, 77% (SiO_2, EtOAc), mp 192−194 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.26 (t, J = 7.3 Hz, 2H), 7.19 (d, J = 7.0 Hz, 1H), 7.13 (d, J = 7.4 Hz, 2H), 3.33 (m, 3H), 2.55 (m, 1H), 2.41 (m, 1H), 2.36 (s, 3H), 2.16 (m, 2H), 1.86 (m, 1H), 1.72 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 210.3, 139.7, 128.9 (2C), 128.2 (2C), 125.9, 71.3, 59.6, 43.3, 37.4, 36.9, 34.7, 26.6, 26.3. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

3β-Benzyl-6α,8-dimethyl-8-azabicyclo[3.2.1]octan-2-one (15b): general procedure A, 560 mg, 77% (SiO_2, EtOAc), mp 193−194 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.27 (t, J = 6.8 Hz, 2H), 7.16 (m, 3H), 3.30 (m, 2H), 3.04 (br s, 1H), 2.70−2.46 (m, 3H), 2.41 (s, 3H), 2.37 (m, 1H) 1.84 (m, 2H), 1.31 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 211.7, 139.5, 128.8 (2C), 128.2 (2C), 125.9, 70.6, 62.6, 43.5, 36.4, 35.1, 34.8, 33.9, 30.8, 15.8. Anal. ($C_{16}H_{21}NO$·HCl·$^1/_4H_2O$) C, H, N.

3β-Benzyl-6α-ethyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (15c): general procedure A, 450 mg, 58% (SiO_2, EtOAc), mp 186−187 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.28 (t, J = 6.8 Hz, 2H), 7.19 (d, J = 6.8 Hz, 1H), 7.15 (d, J = 7.2 Hz, 2H), 3.30 (m, 2H), 3.10 (br s, 1H), 2.64 (m, 1H), 2.45 (m, 3H), 2.40 (s, 3H), 1.85 (m, 2H), 1.44−1.28 (m, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 211.7, 139.6, 128.8 (2C), 128.2 (2C), 125.9, 70.4, 61.7, 43.6, 42.0, 36.5, 35.2, 33.2, 31.0, 24.3, 13.5. Anal. ($C_{17}H_{23}NO$·HCl) C, H, N.

3β-Benzyl-8-methyl-6α-propyl-8-azabicyclo[3.2.1]octan-2-one (15d): general procedure A, 550 mg, 67% (SiO_2, EtOAc), mp 176−177 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.26 (t, J = 7.3 Hz, 2H), 7.16 (m, 3H), 3.29 (m, 2H), 3.07 (br s, 1H), 2.69 (m, 1H), 2.47−2.35 (m, 3H), 2.38 (s, 3H), 1.82 (m, 2H), 1.36−1.22 (m, 5H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 211.8, 139.6, 128.8 (2C), 128.2 (2C), 125.9, 70.4, 61.8, 43.6, 39.8, 36.5, 35.1, 33.6, 33.4, 31.0, 22.1, 14.1. Anal. ($C_{18}H_{25}NO$·HCl) C, H, N.

3β-Benzyl-6α-butyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (15e): general procedure A, 570 mg, 67% (SiO_2, EtOAc), mp 92−93 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.27 (t, J = 6.9 Hz, 2H), 7.19 (d, J = 7.1 Hz, 1H), 7.15 (d, J = 7.3 Hz, 2H), 3.30 (m, 2H), 3.10 (br s, 1H), 2.69 (m, 1H), 2.44 (m, 3H), 2.40 (s, 3H), 1.84 (m, 2H), 1.37−1.21 (m, 7H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 211.1, 139.3, 128.5 (2C), 127.9 (2C), 125.6, 88.1, 70.6, 70.1, 61.5, 43.4, 39.7, 36.2, 34.8, 33.2, 30.9, 22.4, 13.5. Anal. ($C_{19}H_{27}NO$·HCl·$2H_2O$) C, H, N.

3β,6α-Dibenzyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (15f): general procedure A, 630 mg, 66% (SiO_2, EtOAc−

petrol, 1:1), mp 58−59 °C; ^{1}H NMR ($CDCl_3$) δ 7.34−7.07 (m, 10H), 3.36 (dd, J = 3.9, 14.1 Hz, 1H), 3.31 (d, J = 8.4 Hz,1H), 3.08 (br s, 1H), 2.86 (m, 2H), 2.71 (d, J = 8.1 Hz, 2H), 2.45 (m, 2H), 2.38 (s, 3H), 1.96−1.80 (m, 2H), 1.46 (dd, J = 6.3, 13.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 211.8, 140.6, 139.8, 129.0 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 126.2 (2C), 70.5, 61.7, 43.9, 41.2, 37.3, 36.5, 35.1, 33.2, 31.3. Anal. ($C_{22}H_{25}NO\cdot{}^1/_4H_2O$) C, H, N.

3*β*-Benzyl-6*β*,8-dimethyl-8-azabicyclo[3.2.1]octan-2-one (16b): general procedure A, 450 mg, 61% (SiO_2, EtOAc), mp 75−77 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (t, J = 7.5 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 7.3 Hz, 2H), 3.28 (m, 2H), 2.84 (br s, 1H), 2.64 (m, 1H), 2.45 (m, 1H), 2.41 (s, 3H), 2.20 (m, 1H), 2.06−1.90 (m, 2H), 1.78−1.62 (m, 2H), 1.15 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 213.4, 139.8, 129.1 (2C), 128.3 (2C), 126.0, 71.5, 65.4, 44.4, 36.5 (2C), 35.3, 35.0, 34.6, 23.0. Anal. ($C_{16}H_{21}NO$) C, H, N.

3*β*-Benzyl-6*β*-ethyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (16c): general procedure A, 630 mg, 81% (SiO_2, EtOAc−petrol, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.27 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 7.15 (d, J = 7.1 Hz, 2H), 3.34−3.28 (m, 2H), 2.97 (br s, 1H), 2.65 (m, 1H), 2.45 (m, 1H), 2.41 (s, 3H), 2.05−1.92 (m, 3H), 1.74 (m, 2H), 1.59−1.40 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 213.5, 139.8, 129.1 (2C), 128.3 (2C), 126.0, 71.0, 63.1, 44.4, 44.3, 35.3 (2C), 34.6, 34.4, 30.0, 12.8. Anal. ($C_{17}H_{23}NO$) C, H, N.

3*β*-Benzyl-8-methyl-6*β*-propyl-8-azabicyclo[3.2.1]octan-2-one (16d): general procedure A, 630 mg, 77% (SiO_2, EtOAc−petrol, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.28 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 6.9 Hz, 1H), 7.15 (d, J = 7.3 Hz, 2H), 3.34−3.28 (m, 2H), 2.95 (br s, 1H), 2.64 (m, 1H), 2.44 (m, 1H), 2.41 (s, 3H), 2.05−1.93 (m, 3H), 1.75 (m, 2H), 1.60−1.23 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 213.6, 139.8, 129.1 (2C), 128.3 (2C), 126.0, 71.1, 63.5, 44.4, 42.1, 39.5, 35.3 (2C), 34.7 (2C), 21.5, 14.1. Anal. ($C_{18}H_{25}NO$) C, H, N.

3*β*,6*β*-Dibenzyl-8-methyl-8-azabicyclo[3.2.1]octan-2-one (16f): general procedure A, 740 mg, 77% (SiO_2, EtOAc−petrol, 3:1); ^{1}H NMR ($CDCl_3$) δ 7.29−7.11 (m, 10H), 3.35−3.25 (m, 2H), 3.02 (br s, 1H), 2.90−2.60 (m, 3H), 2.46−2.38 (m, 1H), 2.43 (s, 3H), 2.10−1.80 (m, 4H), 1.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 213.3, 140.8, 139.7, 129.1 (2C), 128.9 (2C), 128.4 (2C), 128.3 (2C), 126.1, 126.0, 70.9, 62.5, 44.2, 43.4, 42.6, 34.9, 34.8, 34.5, 34.1. Anal. ($C_{22}H_{25}NO\cdot{}^1/_4H_2O$) C, H, N.

3*β*-Benzyl-2-(carbomethoxymethylidene)-8-methyl-8-azabicyclo[3.2.1]octane (17a): general procedure B, 370 mg, 64% (SiO_2, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.29 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 7.3 Hz, 2H), 5.78 (br s, 1H), 5.81 (d, J = 6.6 Hz, 1H), 3.71 (s, 3H), 3.19−3.07 (m, 2H), 2.62 (m, 1H), 2.39 (m, 1H), 2.35 (s, 3H), 2.18−2.01 (m, 2H), 1.72−1.50 (m, 3H), 1.38−1.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 166.9, 163.6, 139.6, 129.5, 128.9 (2C), 128.4 (2C), 126.1, 111.6, 59.8, 59.7, 51.1, 37.8, 37.1, 36.2, 27.7, 27.6; MS (CI, CH_4) m/z 286 ($M^+ + 1$).

3*β*-Benzyl-2-(carbomethoxymethylidene)-6α,8-dimethyl-8-azabicyclo[3.2.1]octane (17b): general procedure B, 490 mg, 82% (SiO_2, EtOAc−petrol, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.27 (t, J = 7.3 Hz, 2H), 7.20 (d, J = 6.8 Hz, 1H), 7.13 (d, J = 7.3 Hz, 2H), 5.82 (s, 1H), 5.13 (d, J = 6.8 Hz, 1H), 3.77 (m, 1H), 3.67 (s, 3H), 3.10 (dd, J = 13.0, 3.9 Hz, 1H), 2.83 (br s, 1H), 2.68 (m, 1H), 2.46 (m, 1H), 2.38−2.31 (m, 1H), 2.37 (s, 3H), 1.57 (m, 1H), 1.41 (m, 1H), 1.21 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.8, 139.5, 129.3, 128.6 (2C), 128.3 (2C), 126.1, 112.1, 62.5, 59.3, 50.9, 38.0, 36.5, 36.2, 35.8, 34.5, 30.9, 15.0; MS (CI, CH_4) m/z 300 ($M^+ + 1$).

3*β*-Benzyl-2-(carbomethoxymethylidene)-6α-ethyl-8-methyl-8-azabicyclo[3.2.1]octane (17c): general procedure B, 460 mg, 74% (SiO_2, EtOAc−petrol, 1:1), mp 107 °C dec ($C_4H_4O_4$ salt); ^{1}H NMR ($CDCl_3$) δ 7.28 (t, J = 6.8 Hz, 2H), 7.21 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 6.8 Hz, 2H), 5.82 (s, 1H), 5.14 (d, J = 7.3 Hz, 1H), 3.69 (s, 3H), 3.12 (m, 1H), 2.92 (br s, 1H), 2.72 (m, 1H), 2.38 (s, 3H), 2.42−2.33 (m, 3H), 1.57 (m, 1H), 1.36−1.21 (m, 4H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.8, 163.5, 139.4, 128.5 (2C), 128.3 (2C), 126.0, 112.0, 61.4, 58.9, 50.9, 42.6, 38.0, 36.5, 35.8, 34.3, 31.0, 23.4, 13.4; MS (CI, CH_4) m/z 314 ($M^+ + 1$).

3*β*-Benzyl-2-(carbomethoxymethylidene)-8-methyl-6α-propyl-8-azabicyclo[3.2.1]octane (17d): general procedure B, 520 mg, 79% (SiO_2, EtOAc−petrol, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.28 (t, J = 7.3 Hz, 2H), 7.18 (d, J = 6.2 Hz, 1H), 7.13 (d, J = 7.3 Hz, 2H), 5.81 (s, 1H), 5.13 (d, J = 6.4 Hz, 1H), 3.78 (m, 1H), 3.69 (s, 3H), 3.10 (m, 1H), 2.90 (br s, 1H), 2.72 (m, 1H), 2.39−2.32 (m, 2H), 2.37 (s, 3H), 1.56 (m, 1H), 1.40−1.14 (m, 6H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 163.7, 139.5, 128.6 (2C), 128.4 (2C), 126.1, 112.1, 61.6, 59.0, 51.0, 40.4, 38.0, 36.7, 35.9, 34.8, 32.9, 31.2, 22.1, 14.2; MS (CI, CH_4) m/z 328 ($M^+ + 1$).

3*β*-Benzyl-6α-butyl-2-(carbomethoxymethylidene)-8-methyl-8-azabicyclo[3.2.1]octane (17e): general procedure B, 560 mg, 82% (SiO_2, EtOAc−petrol, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.28 (t, J = 7.1 Hz, 2H), 7.20 (d, J = 6.9 Hz, 1H), 7.12 (d, J = 7.1 Hz, 2H), 5.81 (s, 1H), 5.14 (d, J = 6.8 Hz, 1H), 3.79 (m, 1H), 3.70 (s, 3H), 3.12 (m, 1H), 2.92 (br s, 1H), 2.72 (m, 1H), 2.42−2.34 (m, 2H), 2.38 (s, 3H), 1.56 (m, 1H), 1.38 (m, 1H), 1.26−1.11 (m, 7H), 0.78 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 139.5, 128.6 (2C), 128.4 (2C), 126.1, 112.1, 67.9, 61.6, 59.0, 51.0, 40.6, 38.0, 36.7, 35.9, 34.8, 31.1, 30.1, 25.5, 22.7, 13.8; MS (CI, CH_4) m/z 342.51 ($M^+ + 1$).

2-(Carbomethoxymethylidene)-3*β*,6α-dibenzyl-8-methyl-8-azabicyclo[3.2.1]octane (17f): general procedure B, 250 mg, 33% (SiO_2, EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.32 (t, J = 7.2 Hz, 2H), 7.25 (d, J = 7.2 Hz, 1H), 7.20−7.09 (m, 5H), 6.95 (d, J = 7.2 Hz, 2H), 5.85 (s, 1H), 5.16 (d, J = 7.5 Hz, 1H), 3.69 (s, 3H), 3.13 (dd, J = 13.1, 3.9 Hz, 1H), 2.82−2.67 (m, 4H), 2.54−2.28 (m, 3H), 2.35 (s, 3H), 1.51 (m, 2H), 1.37 (dd, J = 13.7, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 166.9, 163.3, 140.9, 139.7, 128.8 (2C), 128.5 (2C), 128.4 (2C), 128.2 (2C), 126.2, 125.8, 112.1, 61.1, 59.1, 50.9, 41.5, 37.8, 37.1, 36.4, 35.7, 34.4, 31.1; MS (CI, CH_4) m/z 376 ($M^+ + 1$).

3*β*-Benzyl-2-(carbomethoxymethylidene)-6*β*,8-dimethyl-8-azabicyclo[3.2.1]octane (18b): general procedure B, 430 mg, 71% (SiO_2, EtOAc−petrol, 1:1); ^{1}H NMR ($CDCl_3$) δ 7.28 (t, J = 7.7 Hz, 2H), 7.18 (d, J = 6.9 Hz, 1H), 7.12 (d, J = 7.2 Hz, 2H), 5.68 (s, 1H), 5.12 (d, J = 6.8 Hz, 1H), 3.70 (s, 3H), 3.09 (dd, J = 13.1, 4.0 Hz, 1H), 2.69 (m, 2H), 2.38 (s, 3H), 1.95 (m, 2H), 1.69 (m, 2H), 1.25 (m, 2H), 1.09 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.8, 162.9, 139.6, 128.8 (2C), 128.3 (2C), 128.1, 126.1, 112.8, 65.6, 59.8, 51.0, 38.1, 37.7, 37.0, 36.9, 34.2, 23.0; MS (CI, CH_4) m/z 300 ($M^+ + 1$).

3*β*-Benzyl-2-(carbomethoxymethylidene)-6*β*-ethyl-8-methyl-8-azabicyclo[3.2.1]octane (18c): general procedure B, 400 mg, 64% (SiO_2, EtOAc−petrol, 1:3); ^{1}H NMR ($CDCl_3$) δ 7.33−7.13 (m, 5H), 5.87 (s, 1H), 5.10 (d, J = 6.4 Hz, 1H), 3.71 (s, 3H), 3.12 (dd, J = 13.1, 4.0 Hz, 1H), 2.82 (br s, 1H), 2.65 (m, 1H), 2.37 (s, 3H), 2.35 (m, 1H), 1.95−1.68 (m, 4H), 1.52−1.36 (m, 2H), 1.23 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 139.7, 129.2, 128.9 (2C), 128.4 (2C), 128.2, 126.1, 113.0, 63.4, 59.4, 51.0, 44.9, 37.8, 37.0, 36.1, 34.6, 30.0, 12.8; MS (CI, CH_4) m/z 314 ($M^+ + 1$).

3*β*-Benzyl-2-(carbomethoxymethylidene)-8-methyl-6*β*-propyl-8-azabicyclo[3.2.1]octane (18d): general procedure B, 480 mg, 73% (SiO_2, EtOAc−petrol, 1:3); ^{1}H NMR ($CDCl_3$) δ 7.30−7.20 (m, 3H), 7.12 (d, J = 7.3 Hz, 2H), 5.85 (br s, 1H), 5.09 (d, J = 6.7 Hz, 1H), 3.69 (s, 3H), 3.08 (dd, J = 13.4, 4.2 Hz, 1H), 2.78 (s, 1H), 2.65 (m, 1H), 2.35 (s, 3H), 2.33 (m, 1H), 1.88−1.65 (m, 4H), 1.52−1.15 (m, 5H), 0.84 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 163.0, 139.6, 128.9 (2C), 128.3 (2C), 126.1, 113.0, 63.7, 59.3, 51.0, 42.7, 39.6, 37.8, 36.9, 36.2, 34.5, 34.3, 21.4, 14.1; MS (CI, CH_4) m/z 328 ($M^+ + 1$).

2-(Carbomethoxymethylidene)-3*β*,6*β*-dibenzyl-8-methyl-8-azabicyclo[3.2.1]octane (18f): general procedure B, 470 mg, 63% (SiO_2, EtOAc−petrol, 1:3); ^{1}H NMR ($CDCl_3$) δ 7.30−7.20 (m, 10H), 5.88 (s, 1H), 5.19 (br s, 1H), 3.70 (s, 3H), 3.22 (m, 1H), 3.10 (dd, J = 13.3, 4.0 Hz, 1H), 2.82 (m, 2H), 2.70 (m, 2H), 2.42 (s, 3H), 2.25 (m, 1H), 1.85 (m, 2H), 1.70 (m, 1H), 1.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 166.8, 141.2, 139.5, 129.1, 128.9 (2C), 128.8 (2C), 128.4 (2C), 128.3 (2C), 128.2, 126.1, 125.8, 113.3, 62.9, 59.3, 51.1, 44.0, 43.0, 37.8, 36.9, 35.9, 34.4; MS (CI, CH_4) m/z 376 ($M^+ + 1$).

3*β*-Benzyl-2*β*-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane (19a) and 3*β*-Benzyl-2α-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]-octane (20a): general procedure C, 280 mg, 96% (60 × wt

SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 90:9:1). **19a:** mp 208−209 °C (HCl salt); ^1H NMR ($CDCl_3$) δ 7.25 (t, J = 7.2 Hz, 2H), 7.16 (d, J = 7.0 Hz, 1H), 7.10 (d, J = 7.0 Hz, 2H), 3.65 (s, 3H), 2.99 (m, 2H), 2.72 (dd, J = 15.2, 9.1 Hz, 1H), 2.51 (dd, J = 13.4, 5.0 Hz, 1H), 2.39 (dd, J = 15.1, 4.2 Hz, 1H), 2.28 (m, 1H), 2.13 (s, 3H), 1.99 (m, 3H), 1.85 (m, 1H), 1.50 (m, 1H), 1.36 (m, 2H), 1.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 174.7, 140.5, 128.8 (2C), 128.2 (2C), 125.8, 65.7, 62.0, 51.4, 42.0, 41.1, 39.3, 35.6, 32.5, 32.2, 25.9, 24.8. Anal. ($C_{18}H_{25}NO_2$·HCl) C, H, N. **20a:** mp 201−202 °C (HCl salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 6.9 Hz, 2H), 7.16 (t, J = 6.9 Hz, 1H), 7.09 (d, J = 7.1 Hz, 2H), 3.68 (s, 3H), 3.06 (br s, 1H), 2.99 (d, J = 6.2 Hz, 1H), 2.90 (d, J = 11.5 Hz, 1H), 2.58 (m, 1H), 2.26 (s, 3H), 2.21−2.08 (m, 3H), 1.99−1.78 (m, 2H), 1.55 (m, 1H), 1.41−1.22 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 173.3, 140.3, 129.0 (2C), 128.2 (2C), 125.8, 64.7, 61.1, 51.6, 42.5, 40.1, 37.3, 36.2, 35.4, 25.8, 22.0. Anal. ($C_{18}H_{25}NO_2$·HCl) C, H, N.

(1*R*)-3*β*-Benzyl-2*β*-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane [(−)-19a]: mp 196−198 °C (HCl salt); $[\alpha]^{25}_D$ = −26 (*c* 0.1, EtOH). Anal. ($C_{18}H_{25}NO_2$·HCl·$^1/_3H_2O$) C, H, N.

(1*R*)-3*β*-Benzyl-2α-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane [(+)-20a]: mp 158−159 °C (HCl salt); $[\alpha]^{25}_D$ = +66 (*c* 0.1, EtOH). Anal. ($C_{18}H_{25}NO_2$·HCl) C, H, N.

3*β*-Benzyl-2*β*-[(methoxycarbonyl)methyl]-6α,8-dimethyl-8-azabicyclo[3.2.1]octane (19b) and 3*β*-Benzyl-2α-[(methoxycarbonyl)methyl]-6α,8-dimethyl-8-azabicyclo[3.2.1]-octane (20b): general procedure C, 200 mg, 67% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 90:9:1). **19b:** mp 189−190 °C ($C_2H_2O_4$ salt); ^1H NMR (C_6D_6, TMS) δ 7.13 (t, J = 7.4 Hz, 2H), 7.04 (d, J = 7.3 Hz, 1H), 6.97 (d, J = 7.3 Hz, 2H), 3.40 (s, 3H), 3.03 (br s, 2H), 2.44 (m, 4H), 2.16−2.02 (m, 4H), 2.11 (s, 3H), 1.31 (m, 2H), 0.97 (dd, J = 12.5, 5.7 Hz, 1H), 0.76 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.7, 140.5, 128.7 (2C), 128.3 (2C), 125.9, 65.8, 65.1, 51.4, 41.7, 40.9, 39.7, 33.9, 33.0, 32.3, 30.9, 30.8, 13.6. Anal. ($C_{19}H_{27}NO_2$·$C_2H_2O_4$·$^1/_3H_2O$) C, H, N. **20b:** mp 168−170 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 8.4 Hz, 2H), 7.18 (d, J = 6.8 Hz, 1H), 7.11 (d, J = 7.1 Hz, 2H), 3.67 (s, 3H), 2.96 (m, 2H), 2.77 (br s, 1H), 2.54 (dd, J = 14.9, 3.4 Hz, 1H), 2.46 (m, 1H), 2.36 (s, 3H), 2.23−2.02 (m, 4H), 1.51 (m, 1H), 1.33 (m, 2H), 1.08 (dd, J = 13.4, 6.3 Hz, 1H), 0.88 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 140.3, 128.7 (2C), 128.1 (2C), 125.7, 64.0, 63.8, 51.4, 40.6, 40.5, 38.9, 36.0, 35.8, 32.2, 31.0, 30.6, 13.9. Anal. ($C_{19}H_{27}NO_2$·$C_2H_2O_4$·$^1/_2H_2O$) C, H, N.

3*β*-Benzyl-2*β*-[(methoxycarbonyl)methyl]-6α-ethyl-8-methyl-8-azabicyclo[3.2.1]octane (19c) and 3*β*-Benzyl-2α-[(methoxycarbonyl)methyl]-6α-ethyl-8-methyl-8-azabicyclo[3.2.1]octane (20c): general procedure C, 200 mg, 63% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 90:9:1). **19c:** mp 178−179 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.24 (t, J = 6.9 Hz, 2H), 7.16 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.3 Hz, 2H), 3.65 (s, 3H), 3.02 (br s, 1H), 2.84 (br s, 1H), 2.78 (m, 1H), 2.50 (m, 2H), 2.32−2.14 (m, 4H), 2.27 (s, 3H), 2.01 (m, 1H), 1.38−1.18 (m, 5H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.6, 140.3, 128.7 (2C), 128.3 (2C), 125.9, 65.5, 64.0, 51.4, 41.6, 40.8, 39.5, 39.2, 32.9, 32.3, 32.1, 30.9, 22.2, 14.2. Anal. ($C_{20}H_{29}NO_2$·$C_2H_2O_4$·$^1/_4H_2O$) C, H, N. **20c:** mp 156−157 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.24 (t, J = 7.6 Hz, 2H), 7.13 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 7.3 Hz, 2H), 3.66 (s, 3H), 3.01 (d, J = 6.6 Hz, 1H), 2.92 (m, 2H), 2.52 (dd, J = 15.1, 3.5 Hz, 1H), 2.37 (s, 3H), 2.23−2.00 (m, 5H), 1.50 (m, 1H), 1.34 (m, 2H), 1.21 (m, 2H), 1.10 (dd, J = 13.0, 6.4 Hz, 1H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.1, 140.1, 128.7 (2C), 128.1 (2C), 125.8, 63.7, 62.9, 51.5, 40.6, 40.4 (2C), 38.9, 35.9, 35.8, 31.0, 28.6, 22.2, 13.8. Anal. ($C_{20}H_{29}NO_2$·$C_2H_2O_4$·$^1/_4H_2O$) C, H, N.

3*β*-Benzyl-2*β*-[(methoxycarbonyl)methyl-8-methyl]-6α-propyl-8-azabicyclo[3.2.1]octane (19d) and 3*β*-Benzyl-2α-[(methoxycarbonyl)methyl]-8-methyl-6α-propyl-8-azabicyclo[3.2.1]octane (20d): general procedure C, 270 mg, 82% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 90:9:1). **19d:** mp 129−130 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 7.0 Hz, 2H), 7.18 (d, J = 7.0 Hz, 1H), 7.13 (d, J = 7.4 Hz, 2H), 3.66 (s, 3H), 2.98 (br s, 1H), 2.81 (m, 1H), 2.74 (m, 1H), 2.54 (dd, J = 12.8, 5.4 Hz, 1H), 2.44 (dd, J = 15.2, 4.7 Hz, 1H), 2.32−2.19 (m, 4H), 2.26 (s, 3H), 2.00 (m, 1H), 1.35−1.17 (m, 7H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.7, 140.3, 128.6 (2C), 128.2 (2C), 125.8, 65.4, 64.0, 51.4, 41.7, 40.8 (2C), 39.5, 36.9, 32.9, 32.4, 31.6, 31.0, 22.9, 14.4. Anal. ($C_{21}H_{31}NO_2$·$C_2H_2O_4$·$^1/_2H_2O$) C, H, N. **20d:** mp 98−100 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 6.9 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.3 Hz, 2H), 3.67 (s, 3H), 3.00 (d, J = 6.6 Hz, 1H), 2.91 (dd, J = 13.6, 3.3 Hz, 1H), 2.85 (br s, 1H), 2.54 (dd, J = 15.0, 3.4 Hz, 1H), 2.37 (s, 3H), 2.25−2.01 (m, 5H), 1.54 (m, 1H), 1.38−1.08 (m, 7H), 0.83 (t, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 140.3, 128.8 (2C), 128.2 (2C), 125.9, 63.8, 63.0, 51.6, 40.7, 40.4, 39.0, 38.2, 36.1, 35.9, 31.7, 31.2, 29.1, 22.5, 14.3. Anal. ($C_{21}H_{31}NO_2$·$C_2H_2O_4$·$^1/_2H_2O$) C, H, N.

3*β*-Benzyl-6α-butyl-2*β*-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane (19e) and 3*β*-Benzyl-6α-butyl-2α-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane (20e): general procedure C, 330 mg, 95% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 90:9:1). **19e:** mp 120−122 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 7.1 Hz, 2H), 7.17 (d, J = 6.9 Hz, 1H), 7.14 (t, J =7.1 Hz, 2H), 3.67 (s, 3H), 3.00 (br s, 1H), 2.79 (m, 2H), 2.56 (dd, J = 12.6, 5.0 Hz, 1H), 2.45 (dd, J = 15.3, 4.6 Hz, 1H), 2.31−2.16 (m, 5H), 2.26 (s, 3H), 2.02 (m, 1H), 1.36−1.13 (m, 8H), 0.80 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.7, 140.4, 128.6 (2C), 128.2 (2C), 125.9, 65.4, 64.0, 51.4, 41.7, 40.9, 39.6, 37.1, 32.9, 32.5 (2C), 31.9, 30.8, 28.8, 22.9, 13.9. Anal. ($C_{22}H_{33}NO_2$·$C_2H_2O_4$·$^2/_3H_2O$) C, H, N. **20e:** mp 155−156 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 6.5 Hz, 2H), 7.17 (d, J = 7.4 Hz, 1H), 7.10 (d, J = 7.2 Hz, 2H), 3.67 (s, 3H), 3.50 (d, J = 6.0 Hz, 1H), 3.25 (br s, 1H), 2.95 (dd, J = 13.5, 3.3 Hz, 1H), 2.64−2.45 (m, 3H), 2.62 (s, 3H), 2.29 (m, 2H), 2.08 (m, 1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.45−1.09 (m, 8H), 0.77 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 139.1, 128.7 (2C), 128.5 (2C), 126.3, 64.2, 64.1, 52.0, 39.3, 39.1, 37.4, 34.9 (2C), 30.8 (2C), 28.5, 28.2, 28.0, 22.6, 13.7. Anal. ($C_{22}H_{33}NO_2$·$C_2H_2O_4$·$^1/_4H_2O$) C, H, N.

3*β*,6α-Dibenzyl-2*β*-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane (19f) and 3*β*,6α-Dibenzyl-2α-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]-octane (20f): general procedure C, 370 mg, 98% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH, 19:1). **19f:** mp 139−140 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.30 (t, J = 7.2 Hz, 2H), 7.24−7.12 (m, 6H), 6.97 (d, J = 7.2 Hz, 2H), 3.66 (s, 3H), 3.00 (d, J = 5.6 Hz, 1H), 2.80−2.61 (m, 5H), 2.51−2.43 (m, 2H), 2.31−2.23 (m, 6H), 2.08 (m, 1H), 1.43 (m, 1H), 1.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.6, 141.7, 140.5, 128.7 (2C), 128.3 (4C), 128.2 (2C), 125.9, 125.7, 65.5, 63.8, 51.3, 41.7, 41.1, 39.6, 38.6, 35.3, 33.0, 32.9, 32.3, 30.9. Anal. ($C_{25}H_{31}NO_2$·$C_2H_2O_4$·$^1/_4H_2O$) C, H, N. **20f:** mp 178−179 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.31 (t, J = 7.6 Hz, 2H), 7.23−7.12 (m, 6H), 7.00 (d, J = 7.6 Hz, 2H), 3.69 (s, 3H), 3.10 (d, J = 6.0 Hz, 1H), 3.02 (dd, J = 13.2, 3.2 Hz, 1H), 2.87 (br s, 1H), 2.77 (m, 1H), 2.61 (m, 2H), 2.48 (dd, J = 14.0, 7.6 Hz, 1H), 2.40 (s, 3H), 2.26 (m, 2H), 2.14 (m, 2H), 1.65 (m, 1H), 1.43 (m, 2H), 1.29 (dd, J = 13.6, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.9, 141.0, 140.1, 128.8 (2C), 128.3 (2C), 128.2 (4C), 126.0, 125.8, 64.0, 62.9, 51.6, 40.4, 40.1, 39.5, 38.8, 36.1, 35.8, 35.3, 31.1, 28.7. Anal. ($C_{25}H_{31}NO_2$·$C_2H_2O_4$) C, H, N.

3*β*-Benzyl-2*β*-[(methoxycarbonyl)methyl]-6*β*,8-dimethyl-8-azabicyclo[3.2.1]octane (21b) and 3*β*-Benzyl-2α-[(methoxycarbonyl)methyl]-6*β*,8-dimethyl-8-azabicyclo[3.2.1]-octane (22b): general procedure C, 280 mg, 93% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 90:9:1). **21b:** mp 159−160 °C ($C_4H_4O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 7.6 Hz, 2H), 7.18 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.0 Hz, 2H), 3.67 (s, 3H), 3.11 (d, J = 5.3 Hz, 1H), 2.80 (s, 1H), 2.73 (dd, J = 15.2, 9.5 Hz, 1H), 2.53 (dd, J = 13.3, 5.1 Hz, 1H), 2.42 (s, 3H), 2.36 (m, 1H), 2.26 (m, 1H), 2.08−1.80 (m, 5H), 1.37 (m, 1H), 1.26 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.7, 140.6, 128.8 (2C), 128.2 (2C), 125.8, 69.5, 67.1, 51.3, 43.6, 40.9, 39.4, 37.0, 36.1, 36.0, 32.9, 32.3, 24.0. Anal. ($C_{19}H_{27}NO_2$·$C_4H_4O_4$·$^3/_4H_2O$) C, H, N. **22b:** mp 150−151 °C ($C_2H_2O_4$ salt); ^1H NMR ($CDCl_3$) δ 7.26 (t, J = 7.6 Hz, 2H), 7.18 (d, J = 6.3 Hz, 1H), 7.10 (d, J = 7.3 Hz, 2H), 3.68 (s, 3H), 3.10 (d, J

= 5.1 Hz, 1H), 2.88 (d, J = 13.2 Hz, 1H), 2.72 (s, 1H), 2.57 (dd, J = 15.4, 3.7 Hz, 1H), 2.51 (s, 3H), 2.23 (m, 2H), 2.12 (m, 1H), 1.89 (m, 2H), 1.47 (m, 3H), 1.11 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 140.2, 129.0 (2C), 128.2 (2C), 125.9, 66.6, 64.2, 51.6, 40.1, 36.6, 36.5, 36.4, 36.3, 36.1, 33.1, 32.1, 23.2. Anal. ($C_{19}H_{27}NO_2 \cdot C_2H_2O_4$) C, H, N.

3β-Benzyl-6β-ethyl-2β-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane (21c) and 3β-Benzyl-6β-ethyl-2α-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane (22c): general procedure C, 220 mg, 69% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 95:4:1). **21c:** mp 209−212 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.25 (t, J = 7.2 Hz, 2H), 7.17 (d, J = 7.2 Hz, 1H), 7.10 (d, J = 7.2 Hz, 2H), 3.65 (s, 3H), 3.04 (br s, 1H), 2.84 (br s, 1H), 2.68 (dd, J = 15.2, 9.4 Hz, 1H), 2.52 (dd, J = 13.2, 5.2 Hz, 1H), 2.38 (m, 1H), 2.34 (s, 3H), 2.27 (m, 1H), 2.00 (m, 2H), 1.78 (m, 2H), 1.65 (m, 1H), 1.50−1.32 (m, 3H), 1.22 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.8, 140.6, 128.8 (2C), 128.2 (2C), 125.8, 67.4, 66.6, 51.3, 45.6, 43.4, 40.9, 39.5, 36.5, 33.8, 32.9, 32.4, 31.5, 13.6. Anal. ($C_{20}H_{29}NO_2 \cdot HCl$) C, H, N. **22c:** mp 205−208 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.27 (t, J = 6.9 Hz, 2H), 7.18 (t, J = 6.8 Hz, 1H), 7.11 (d, J = 7.3 Hz, 2H), 3.68 (s, 3H), 3.03 (d, J = 6.5 Hz, 1H), 2.88 (d, J = 11.3 Hz, 1H), 2.79 (s, 1H), 2.57 (dd, J = 14.8, 3.7 Hz, 1H), 2.49 (m, 1H), 2.46 (s, 3H), 2.27−2.19 (m, 2H), 2.10 (m, 1H), 1.84 (dd, J = 12.5, 8.1 Hz, 1H), 1.57−1.40 (m, 5H), 1.05 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 140.3, 129.0 (2C), 128.1 (2C), 125.8, 64.3, 63.6, 51.5, 44.8, 40.3, 36.6 (2C), 36.5, 36.2, 32.5, 31.1, 30.4, 12.9. Anal. ($C_{20}H_{29}NO_2 \cdot HCl$) C, H, N.

3β-Benzyl-2β-[(methoxycarbonyl)methyl-8-methyl]-6β-propyl-8-azabicyclo[3.2.1]octane (21d) and 3β-Benzyl-2α-[(methoxycarbonyl)methyl]-8-methyl-6β-propyl-8-azabicyclo[3.2.1]octane (22d): general procedure C, 240 mg, 72% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH−NH_4OH, 95:4:1). **21d:** mp 86−87 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.26 (t, J = 7.2 Hz, 2H), 7.18 (d, J = 7.1 Hz, 1H), 7.12 (d, J = 7.2 Hz, 2H), 3.63 (s, 3H), 3.06 (br s, 1H), 2.85 (br s, 1H), 2.71 (dd, J = 15.1, 9.2 Hz, 1H), 2.51 (dd, J = 13.2, 5.3 Hz, 1H), 2.41 (m, 1H), 2.36 (s, 3H), 2.29 (m, 1H), 2.00 (m, 2H), 1.79 (m, 3H), 1.50−1.19 (m, 6H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.7, 140.5, 128.8 (2C), 128.2 (2C), 125.8, 67.7, 66.5, 51.3, 43.5, 43.3, 41.1, 40.8, 39.4, 36.4, 34.1, 32.8, 32.3, 22.4, 14.2. Anal. ($C_{21}H_{31}NO_2 \cdot HCl \cdot {}^2/_3H_2O$) C, H, N. **22d:** mp 107−110 °C (HCl salt); ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 2H), 7.17 (t, J = 6.7 Hz, 1H), 7.10 (d, J = 7.3 Hz, 2H), 3.67 (s, 3H), 3.03 (dd, J = 6.3, 2.1 Hz, 1H), 2.88 (d, J = 12.0 Hz, 1H), 2.77 (s, 1H), 2.57 (dd, J = 15.0, 3.7 Hz, 1H), 2.47 (s, 3H), 2.27−2.13 (m, 2H), 2.09 (dd, J = 15.0, 9.2 Hz, 1H), 1.83 (dd, J = 12.8, 8.9 Hz, 1H), 1.62 (m, 1H), 1.50−1.20 (m, 7H), 1.05 (m, 1H), 0.84 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 140.2, 128.9 (2C), 128.1 (2C), 125.7, 64.6, 63.5, 51.5, 51.4, 42.5, 40.2, 40.0, 36.5, 36.4, 36.1, 32.3, 31.3, 21.6, 14.1. Anal. ($C_{21}H_{31}NO_2 \cdot HCl \cdot H_2O$) C, H, N.

3β,6β-Dibenzyl-2β-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octane (21f) and 3β,6β-Dibenzyl-2α-[(methoxycarbonyl)methyl-8-methyl]-8-azabicyclo[3.2.1]-octane (22f): general procedure C, 360 mg, 95% (60 × wt SiO_2, gravity, $CHCl_3$−MeOH, 19:1). **21f:** mp 85−89 °C ($C_2H_2O_4$ salt); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.28−7.08 (m, 10H), 3.65 (s, 3H), 3.14 (br s, 1H), 2.97 (s, 1H), 2.79−2.71 (m, 3H), 2.51 (s, 3H), 2.42 (m, 1H), 2.39 (dd, J = 15.2, 5.2 Hz, 1H), 2.29 (dd, J = 13.2, 8.4 Hz, 1H), 2.17 (m, 1H), 2.12 (m, 1H), 1.94 (m, 2H), 1.77 (dd, J = 13.6, 9.2 Hz, 1H), 1.20 (m, 1H), 1.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 174.6, 141.5, 140.3, 128.8 (2C), 128.6 (2C), 128.3 (2C), 128.2 (2C), 125.8 (2C), 67.1, 66.7, 51.3, 44.6, 44.2, 43.5, 40.6, 39.3, 36.3, 34.9, 32.7, 32.2. Anal. ($C_{25}H_{31}NO_2 \cdot C_2H_2O_4 \cdot {}^3/_4H_2O$) C, H, N. **22f:** mp 72−74 °C (HCl salt); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.26−7.07 (m, 10H), 3.64 (s, 3H), 3.13 (dd, J = 6.4, 2.4 Hz, 1H), 2.87−2.75 (m, 3H), 2.66 (m, 1H), 2.54 (s, 3H), 2.52 (m, 1H), 2.24 (m, 2H), 2.05 (m, 2H), 1.76 (dd, J = 13.6, 8.8 Hz, 1H), 1.57 (m, 1H), 1.50 (m, 2H), 1.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.0, 141.0, 139.8, 128.9 (2C), 128.6 (2C), 128.0 (4C), 125.7, 125.6, 63.6, 63.2, 51.4, 43.5, 42.8, 39.9, 36.2, 35.7, 35.3, 35.2, 31.0, 30.8. Anal. ($C_{25}H_{31}NO_2 \cdot HCl \cdot {}^2/_3H_2O$) C, H, N.

3,6α-Dibenzyl-2-[(methoxycarbonyl)methyl]-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (23): general procedure B, 300 mg, 40% (SiO_2, $CHCl_3$−MeOH, 9:1), mp 122−123 °C (HCl salt); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.34 (t, J = 7.2 Hz, 2H), 7.26−7.10 (m, 6H), 6.88 (d, J = 7.6 Hz, 2H), 3.71 (s, 3H), 3.59 (d, J = 14.4 Hz, 1H), 3.44 (d, J = 15.6 Hz, 1H), 3.34 (d, J = 6.8 Hz, 1H), 3.23 (t, J = 5.6 Hz, 1H), 3.16 (d, J = 14.8 Hz, 1H), 3.06 (d, J = 15.6 Hz, 1H), 2.92 (m, 1H), 2.48 (s, 3H), 2.45−2.30 (m, 3H), 2.18 (dd, J = 18.4, 4.8 Hz, 1H), 1.79 (d, J = 18.4 Hz, 1H), 1.45 (dd, J = 12.0, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.6, 140.9, 139.4, 130.1, 128.8 (2C), 128.5 (2C), 128.4 (2C), 128.3 (3C), 126.4, 125.8, 62.5, 60.6, 51.7, 41.1, 38.4, 37.6, 37.5, 36.3, 34.7, 26.2; MS (CI, CH_4) m/z 376 ($M^+ + 1$). Anal. ($C_{25}H_{29}NO_2 \cdot HCl \cdot H_2O$) C, H, N.

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Supporting Information Available: Crystal structure data for (−)-**19a** and (+)-**20a**, including ORTEP diagrams, tables of crystallographic data, fractional coordinates and thermal parameters, bond lengths, and bond angles (14 pages). Ordering information can be found on any current masthead page.

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