Synthesis and Dopamine Transporter Affinity of 2-(Methoxycarbonyl)-9-methyl-3-phenyl-9-azabicyclo[3.3.1]nonane Derivatives

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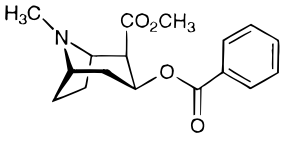
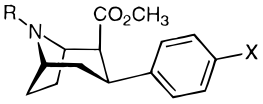
A series of 9-methyl-3β-phenyl-2-substituted-9-azabicyclo[3.3.1]nonane derivatives were synthesized and evaluated as cocaine-binding site ligands at the dopamine transporter (DAT). The conformation of the bicyclic structures and the stereochemistry of the substituents were determined by NMR and X-ray crystallography. The *in vitro* binding affinity (K_i) of the 9-azabicyclo[3.3.1]nonane derivatives was measured in rat caudate-putamen tissue, and they were found to be 100-fold ($K_i = 2-14\ \mu$M) less potent than cocaine and other tropane analogs. From these results it is evident that the cocaine-binding site at the DAT is very sensitive to structural modifications of the unsubstituted methylene bridge [C(6)−C(7)] of cocaine and cocaine-like compounds.

Introduction

The pharmacologic spectrum of activity exhibited by cocaine (**1**) has been shown to be mediated by occupation of binding sites on biogenic amine transporters in mammalian central nervous systems.[1−3] The positive reinforcing effect of **1** is believed to be due to inhibition of dopamine uptake at dopamine transporters (DAT).[4−6] A number of structure−activity relationship (SAR) studies of cocaine analogs and 2-substituted-3β-aryltropanes have provided insight into the structural criteria for high-affinity efficacious ligands at DAT.[7−13] These SAR studies have demonstrated profound stereochemical effects and substituent effects at C(2), C(3), C(6), C(7), and N(8) of the tropane nucleus of cocaine-related drugs. From these studies the 2β-(methoxycarbonyl)-3β-phenyltropane derivatives **2** have been found to be among some of the most potent ligands for cocaine-binding sites at DAT.[7,9]

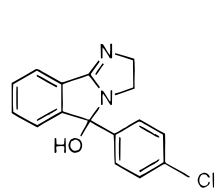


(-)-cocaine **1**



2a X = H; R = CH_3
2b X = F; R = C^3H_3

In addition to tropane derivatives, several other classes of ligands have been reported to be potent inhibitors of [^{3}H]cocaine binding at DAT. These ligands include mazindol (**3**),[14] GBR compounds **4**,[15] and some benztropine analogs **5**.[16,17] The diversity of structures which demonstrate high binding affinity has led to the formulation of a cocaine-binding site model which is composed of alternative and possibly multiple binding domains.[7,10,16,17] These ligands competitively inhibit [^{3}H]cocaine binding yet, on a molecular level, probably interact with the DAT differently from each other. It has been proposed that these ligands which access alternative binding domains may be useful as treatments for drug addiction. These drugs may inhibit cocaine binding while not inhibiting dopamine uptake at DAT and allow sufficient potentiation of the dopaminergic system to maintain extracellular concentrations of dopamine.[16−18]



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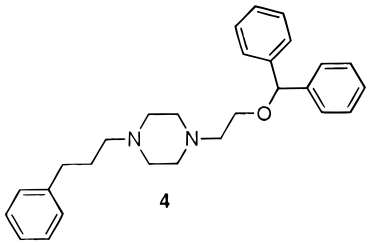

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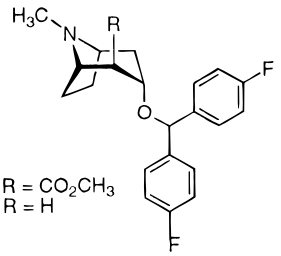
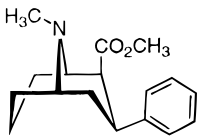


5a R = CO_2CH_3
5b R = H



6

As part of an ongoing program of research aimed at the structural elucidation of the cocaine pharmacophore and the development of treatments for cocaine abuse, it was of interest to explore the effects of structural modification of the tropane ring system of the potent 2β-(methoxycarbonyl)-3β-phenyltropane derivatives. The (1*R*)-2β-(methoxycarbonyl)-9-methyl-3β-phenyl-9-azabicyclo[3.3.1]nonane (**6**) is a homolog of **2a** (WIN 35,065-2)[19] and was envisaged as an attractive drug candidate to explore the effect of structural modification of the C(6)−C(7) methylene bridge of the 2β-(methoxycarbonyl)-3β-phenyltropane analogs. In addition, on the basis of studies with C(6)- and C(7)-methoxy pseudococaine analogs which have been described as weak cocaine antagonists,[10] the stereoisomers of **6** were also of interest. Herein we wish to report the synthesis, structural features, and DAT binding affinity of a series

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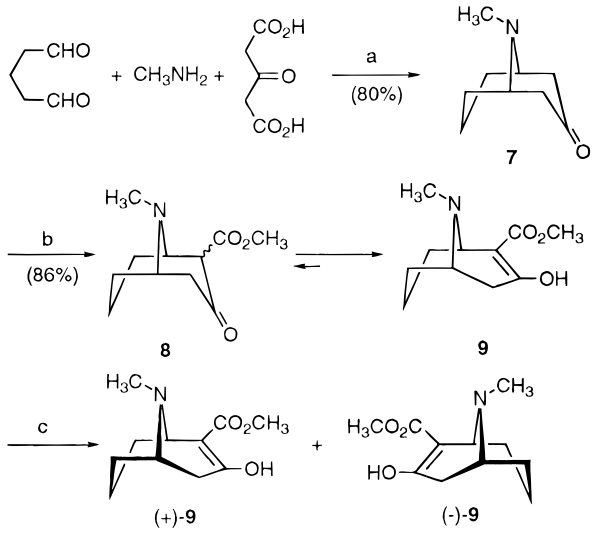
Scheme 1[a]



[a] Reagents: (a) H_2O, Na_2HPO_4, 24 h, then HCl, Δ, 1 h; (b) NaH, $(CH_3O)_2CO$, cyclohexane, Δ; (c) tartaric acid.

of 9-methyl-3-phenyl-2-substituted-9-azabicyclo[3.3.1]-nonane derivatives.

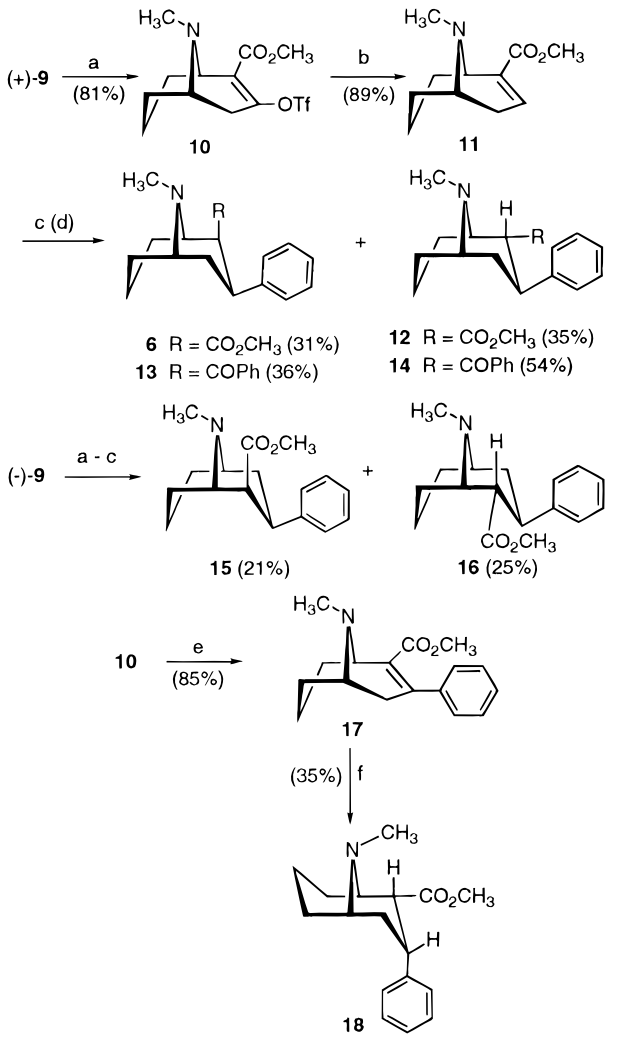
Chemistry

The 9-azabicyclo[3.3.1]nonane is an important substructure of a variety of compounds which possess neuroleptic,[20,21] antiparkinsonian,[22] and hypotensive activity.[23] As a result, the synthesis of 9-azabicyclo-[3.3.1]nonane derivatives has been the subject of numerous studies. The most efficient synthetic method for the preparation of the 9-azabicyclo[3.3.1]nonane ring system is *via* the synthesis of 9-methyl-9-azabicyclo-[3.3.1]nonan-3-one (**7**, pseudopellitierene), an alkaloid obtained from the bark of the pomegranate tree.[24,25] The construction of the 9-azabicyclo[3.3.1]nonane ring was achieved with a modification of Robinson's procedure for the preparation of **7**.[25] As illustrated in Scheme 1, the biomimetic reaction of the glutaraldehyde, methylamine, and acetonedicarboxylic acid gave **7** in 80% yield. The ketone **7** was then converted into the β-keto ester **8** with dimethyl carbonate using an established procedure.[16,26–28] Spectroscopic data (^{1}H and ^{13}C NMR) suggested that the β-keto ester **8** existed almost entirely in the enol tautomeric form **9** (Scheme 1).

Racemic **9** was easily resolved into the enantiomers (+)- and (−)-**9** by recrystallization with L-(+)- and D-(−)-tartaric acid, respectively.[28] The absolute configuration of (+)-**9** was assigned as having C(1*R*)-stereochemistry analogous to the (+)-isomer of the corresponding 8-azabicyclo[3.2.1]octane system,[16,26] while the (−)-**9** was assigned as having *C(1S)*-stereochemistry. Unequivocal assignment of the absolute configuration of (+)-**9** was achieved by X-ray crystallographic analysis of the (+)-**9**·L-tartrate salt.[29]

With (+)-**9** in hand conversion into the vinyl triflate **10** was achieved in high yield (81%) by addition of trifluoromethanesulfonic anhydride to a solution of (+)-**9** and pyridine in CH_2Cl_2 (Scheme 2).[30] The vinyl triflate **10** was then converted into the alkene **11** using Cacchi's procedure in analogous fashion to the synthesis of anhydroecgonine methyl ester recently reported by Carroll *et al.*[31,32] Conjugate addition of 1 equiv of phenylmagnesium bromide to **11** provided the desired

Scheme 2[a]



[a] Reagents: (a) $(CF_3SO_2)_2O$, pyridine; (b) HCO_2H, $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 60 °C; (c) PhMgBr (1 equiv), Et_2O, −40 °C, TFA, −70 °C; (d) PhMgBr (2 equiv), Et_2O, −40 to 25 °C, TFA, −70 °C; (e) LiCl, Na_2CO_3, $Pd_2(dba)_3$, DME, $C_6H_5B(OH)_2$; (f) PtO_2, H_2 (50 psi), EtOH.

products **6** and **12** in 30% and 35% yields, respectively, after chromatography. In addition, treatment of **11** with 2 equiv of phenylmagnesium bromide afforded the phenyl ketones **13** (36%) and **14** (54%) (Scheme 2). Alternatively, the enantiomers **15** and **16** were prepared in similar fashion from (−)-**9** (Scheme 2).

A coupling reaction of the vinyl triflate **10** with phenylboronic acid in refluxing dimethoxyethane using tris(dibenzylideneacetone)dipalladium(0) as a catalyst gave **17** in 80% yield.[33] Hydrogenation (50 psi) of **17** over PtO_2 provided **18** as the major product (30%) along with unreacted **17** and trace amounts of other isomers.

^{1}H and ^{13}C NMR spectroscopy has been found to be very useful for the stereochemical and conformational analysis of the 9-azabicyclo[3.3.1]nonane derivatives.[34–37] Accordingly, the stereochemical and conformational assignments of stereoisomers of **6**, **12**−**16**, and **18** were made on the basis of NMR data in similar fashion. For compounds **6** and **12**−**16**, H(2), H(3), H(4a) and H(4e) were easily differentiated from other ring protons because of the C(2)- and C(3)-substituents. The values of the coupling constants of $J_{2,3}$, $J_{3,4a}$, and $J_{3,4e}$ were consistent with the conformations assigned to related

Table 1. K_i Values for Displacement of Bound [^{3}H]WIN 35,428 (**2b**)[a]

analog	K_i (μM)
1[b]	0.032 ± 0.005
	0.39 ± 0.22
2a[b]	0.033 ± 0.017
	0.31 ± 0.22
6[c]	4.60 ± 0.51
(+)-**9**[d]	>100[e]
12[c]	5.73 ± 0.57
13[c]	3.97 ± 0.36
14[c]	1.91 ± 0.10
15[c]	3.45 ± 0.31
16[c]	3.47 ± 0.35
18[c]	13.9 ± 2.01

[a] All values are the mean ± SEM of three experiments performed in triplicate. [b] The K_i values for these drugs are reproduced from ref 38 and were collected under conditions identical with the present ones. [c] Tested as the fumarate salt. [d] Tested as the tartrate salt. [e] No inhibition at concentrations up to 100 μM.

bicyclic ring systems.[34−37] A value of ~13 Hz indicated a *trans*-diaxial relationship, while ~6 Hz corresponded to a *cis*-axial−equatorial or a *trans*-diequatorial relationship. For example, in compound **12**, H(3) exhibited a *trans*-diaxial relationship with H(2) (J = 12.5 Hz) and H(4a) (J = 12.7 Hz) and a *cis*-axial−equatorial relationship with H(4e) (J = 6.5 Hz). Similar to the 2β-(methoxycarbonyl)-3β-phenyltropanes, the 2β-ester group resulted in an upfield shift of the NCH_3 signal (^{1}H NMR) of **6** (δ 2.53 ppm) relative to the NCH_3 signal of **12** (δ 2.61 ppm).[19] Based on coupling constants it is believed that in solution **6** and **12** exist in a chair−chair conformation while **18** was observed to exist in a chair−boat conformation. The major difference between these two conformations was the ^{13}C NMR chemical shifts of C(7). An upfield shift of the C(7) signal of **18** (δ 15.2 ppm) relative to **6** (δ 21.5 ppm) and **12** (δ 28.3 ppm), respectively, indicated that the 3α-phenyl group forced the unsubstituted ring to flip into a boat conformation to alleviate steric interactions. This observation was consistent with Wiseman's conformational study of the 9-azabicyclo[3.3.1]nonane derivatives.[34,35] The structural assignments of **12** and **14** determined by NMR were unequivocally confirmed by X-ray crystallography.[29]

Biological Results and Discussion

The 9-azabicyclo[3.3.1]nonane derivatives were tested *in vitro* for their ability to displace bound [^{3}H]WIN 35,428 (**2b**) from rat caudate-putamen tissue.[38] The K_i values reported in Table 1 are dissociation constants derived for the unlabeled ligands. Both cocaine (**1**) and **2a** modeled better for two binding sites than for one, and therefore two K_i values are given in Table 1.[11,38] In contrast compounds **6**, **9**, and **12**−**18** did not model for two sites better than for one. The low binding affinity of the 9-azabicyclo[3.3.1]nonane derivative **6** was very surprising considering that the difference between **2a** and **6** was only the addition of a single methylene unit which resulted in a 100-fold decrease in binding site affinity. Comparison of the K_i values of **6** with high-affinity 2β-(methoxycarbonyl)-3β-phenyltropanes and of **13** with 2β-acyl-3β-aryltropanes clearly illustrates the sensitivity of the binding site to structural modification of the unsubstituted methylene bridge of the 8-azabicyclo-[3.2.1]octane ring system of cocaine analogs.[7,9] The low binding affinity of the 9-azabicyclo[3.3.1]nonane analogs did not warrant further study of these compounds as dopamine uptake inhibitors.

Unlike the SAR of (−)-cocaine and (*R*)-2β-substituted-3β-phenyltropane derivatives, the C(2)-stereoisomer **12** and the enantiomers **15** and **16** were equipotent to **6**, albeit about 100-fold less potent than **2a**. No stereoselectivity or enantioselectivity for binding sites on the DAT was observed for these compounds. In addition, the phenyl ketone derivatives **13** and **14** exhibited K_i values on the same order magnitude as **6**. It is noteworthy that the 2α-isomer **14** was slightly more potent than any of the other analogs. This suggests that the binding criteria for the 2-substituted-3β-phenyl-9-azabicyclo[3.3.1]nonane analogs are different than that of the corresponding (*R*)-2β-substituted-3β-phenyltropane derivatives. Therefore similar to the results observed for difluoropine (**5a**), in which the lipophilic 3α-diarylmethoxy substituent is thought to occupy the lipophilic region of the binding site associated with the 2β-substituents of (*R*)-cocaine analogs, the increased lipophilicity in the 2α-position of **14** may allow the ligand to adopt a conformation which facilitates binding.[16] Moreover, based on the diverse number of structures which bind to the cocaine-binding site and recent reports which identify binding site heterogeneity, it is possible to speculate that compounds such as **5a** and **14** may bind at a different domain(s) of a single binding site or bind to an alternative binding site on the DAT.[16,17,38]

Similar to the SAR of cocaine, the enol (+)-**9** and the 2α,3α-isomer **18** were the least potent of the 9-azabicyclo-[3.3.1]nonane analogs.[7] In addition, the SAR of the 9-azabicyclo[3.3.1]nonane derivatives was similar to the findings reported by Kozikowski *et al.* for the racemic series of C(6)- and C(7)-methoxy cocaine analogs.[10] These analogs were also found to exhibit low binding affinities (micromolar range) at DAT. Clearly from these two independent studies, it is evident that structural modification of the methylene bridge of 2β-substituted-3β-phenyltropane derivatives **2** has a profound effect on binding affinity. In fact, the binding site appears to be more sensitive to substituents in this region of the molecule than any other region of the 2β-substituted-3β-phenyltropane.

In conclusion, the results of this study clearly demonstrate that the unsubstituted methylene bridge [C(6)-C(7)] of cocaine and cocaine-like compounds appears to be a vital feature for molecular recognition at the cocaine-binding site on DAT. The sensitivity of the binding site toward structural modification of the methylene bridge [C(6)-C(7)] of derivatives of cocaine suggests that it may be possible to attenuate the potency as well as the activity (agonist to antagonist) of cocaine-binding site ligands with the appropriate use of substituents at C(6) and/or C(7). In addition, further studies of the effects of substituents at C(6) and C(7) of 2-substituted-3-aryltropane derivatives may provide additional information about the apparent heterogeneity of the cocaine-binding site at DAT.

Experimental Section

All chemicals and reagents not otherwise noted were purchased from Aldrich Chemical Co., Milwaukee, WI. Dichloromethane (E. M. Science) was dried over P_2O_5 and distilled under nitrogen before use. Tetrahydrofuran (THF; Baker) and benzene (E. M. Science) were dried by distillation from sodium

and benzophenone. Methanol was dried by distillation over magnesium metal. Dimethyl sulfoxide (DMSO) was dried by distillation under high vacuum over CaH_2. Ethyl acetate (E. M. Science) and 30−60 °C petroleum ether (E. M. Science) were distilled prior to use. Chromatography refers to flash chromatography with silica gel (Silica Gel 60, 230−400 mesh; E. M. Science). Silica gel TLC plates (E. M. Science; Kiesel gel 60, F_{254}, 0.2 mm layer, plastic and/or glass back) were purchased from Curtin-Matheson Scientific and visualized under UV light. NMR spectra were recorded using a Varian Gemini 300 MHz spectrometer. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrometer. The fumarate salts of **6**, **12**−**16**, and **18** were obtained from a mixture of the base (1 equiv) and fumaric acid (1 equiv) in hot 2-propanol. The salt was recrystallized twice from 2-propanol. Optical rotations of compounds **6**, **12**−**16**, and **18** were determined as the fumarate salt and measured on a Rudolph Autopol III polarimeter. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

9-Methyl-9-azabicyclo[3.3.1]nonan-3-one (Pseudopelletierine, 7). See ref 25 for experimental details: (61 g, 80%); mp 48−52 °C (lit.[24,25] mp 47−53 °C); ^{1}H NMR ($CDCl_3$) δ 3.27 (br s, 2H), 2.80−2.68 (dd, J = 16.6, 6.4 Hz, 2H), 2.59 (s, 3H), 2.25 (s, 1H), 2.19 (s, 1H), 1.93 (m, 2H), 1.60−1.46 (m, 3H), 1.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 210.7, 55.8, 42.0, 41.4, 29.7, 16.2.

2-(Methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (9). A solution of **7** (23 g, 0.15 mol) in cyclohexane (140 mL) was added dropwise to a mixture of prewashed (petroleum ether) NaH (12 g, 60% dispersion, 0.30 mol) and dimethyl carbonate (25 mL, 0.30 mol) in cyclohexane (60 mL) at a gentle reflux. Methanol (0.5 mL) was then added at the end of the addition. The reaction mixture was heated at reflux until effervescence ceased. Water (250 mL) was added after the reaction mixture had cooled to room temperature. The layers were separated, and the cyclohexane layer was washed with additional water (2 × 100 mL). The combined aqueous layers were saturated with NH_4Cl (120 g) and extracted with dichloromethane (8 × 100 mL). The combined organic extracts were dried (K_2CO_3), and the solvent was removed under reduced pressure to afford **8**. The β-keto ester **8** was found to exist almost entirely (>97%; **8** was not observed by ^{1}H NMR) in the tautomeric enol form **9** as a white crystalline material (26 g, 81%): mp 126−127 °C; ^{1}H NMR ($CDCl_3$) δ 12.1 (s, 1H), 3.74 (s, 3H), 3.61 (s, 1H), 3.07 (s, 1H), 2.65 (dd, J = 19.2, 7.3 Hz, 1H), 2.32 (s, 3H), 1.93−1.70 (m, 3H), 1.53−1.43 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.7, 96.9, 53.2, 52.6, 51.4, 41.8, 32.6, 29.3, 28.1, 14.9. Anal. ($C_{11}H_{17}NO_3$) C, H, N.

Resolution of (±)-2-(Methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one (9). (+)-2-(Methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one [(+)-9]. L-(+)-Tartaric acid (9.0 g, 0.060 mol) was added to (±)-**9** (12.6 g, 0.060 mol) in ethanol (100 mL). Ethanol was removed under reduced pressure after all the tartaric acid had dissolved. The residue was recrystallized from acetone/water (10:1, 440 mL) to afford (+)-2-(methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one tartrate as a pale crystalline solid. The solid was recrystallized until a constant rotation was obtained $[\alpha]^{21}_D$ = +13° (c 1.0, H_2O); mp 60−63 °C. Anal. ($C_{11}H_{17}NO_3 \cdot C_4H_6O_6 \cdot {}^1/_2H_2O$) C, H, N.

The salt **9**·$C_4H_6O_6$ was dissolved in saturated Na_2CO_3 (50 mL), and the free base was extracted with dichloromethane (2 × 100 mL). The combined extracts were dried (K_2CO_3) and then concentrated to afford (+)-2-(methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one [(+)-**9**] (4.2 g, 30%) as a white solid: mp 93−95 °C; $[\alpha]^{21}_D$ = +28° (c 1.0, CH_3OH). Anal. ($C_{11}H_{17}NO_3$) C, H, N.

(−)-2-(Methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one [(−)-9]. The filtrates from the resolution with L-(+)-tartaric acid were concentrated to dryness. The residue obtained was dissolved in saturated Na_2CO_3 (50 mL), and the free base was extracted with dichloromethane (3 × 100 mL). The dried (K_2CO_3) organic extract was concentrated to dryness under reduced pressure. The residue (2.1 g, 0.11 mol) and D-(−)-tartaric acid (1.5 g, 0.13 mol) were dissolved in absolute ethanol. Ethanol was then removed under reduced pressure, and the residue was recrystallized from an acetone/water mixture (10:1, 110 mL) until a constant rotation was obtained. This afforded the (−)-2-(methoxycarbonyl)-9-methyl-9-azabicyclo-[3.3.1]nonan-3-one tartrate as a white crystalline solid. The solid was recrystallized until a constant rotation was obtained: $[\alpha]^{21}_D$ = −15° (c 1.0, H_2O); mp 64−66 °C. Anal. ($C_{11}H_{17}NO_3 \cdot C_4H_6O_6 \cdot {}^1/_2H_2O$) C, H, N.

The free base was generated by the same procedure described above to give (−)-2-(methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-one [(−)-**9**] (1.1 g, 10%) as a white solid: mp 91−94 °C; $[\alpha]^{21}_D$ = −28° (c 1.0, CH_3OH). Anal. ($C_{11}H_{17}NO_3$) C, H, N.

(+)-2-(Methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]non-2-ene 3-Trifluoromethylsulfonate (10). To a stirred solution of (+)-**9** (10.8 g, 51 mmol) and pyridine (20 mL) at 0 °C was added trifluoromethanesulfonic anhydride (9.3 mL, 55 mL) was added *via* syringe. The solution was allowed to warm slowly to room temperature and maintained at room temperature for 12 h. The volume of the reaction mixture was reduced on a rotoevaporatory instrument to about 15 mL, and then the pink solution was directly chromatographed (ethyl acetate:petroleum ether 2:1) to furnish **10** as a yellow oil (14.1 g, 81%): ^{1}H NMR ($CDCl_3$) δ 3.89 (br, 1H), 3.80 (s, 3H), 3.22 (br, 1H), 2.77 (dd, J = 19.5, 7.2 Hz, 1H), 2.36 (s, 3H), 2.17−1.53 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 164.1, 150.7, 121.9, 120.5, 116.2, 57.0, 53.6, 52.1, 41.6, 32.6, 28.2, 28.1, 14.6. Anal. ($C_{12}H_{16}F_3NO_5S$) C, H, N.

(+)-2-(Methoxycarbonyl)-9-methyl-9-azabicyclo[3.3.1]non-2-ene (11). A solution of **10** (13 g, 42 mmol), triethylamine (24 mL), palladium acetate (0.3 g), and triphenylphosphine (0.6 g) in DMF (80 mL) was stirred under nitrogen. Formic acid (4 mL, 99%) was added dropwise *via* syringe over 2−3 min. The resulting mixture was warmed in an oil bath at 60 °C for 1 h. During this period the mixture became black. The contents of the flask were poured into water (50 mL) and extracted with ether (5 × 100 mL). The combined etheral portions were dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by chromatography (petroleum ether:ether:triethylamine, 4:5:1) to furnish **11** as a colorless oil (6.9 g, 89%): ^{1}H NMR ($CDCl_3$) δ 7.12 (t, J = 3.69 Hz, 1H), 3.60 (s, 3H), 3.51 (br, 1H), 2.83 (br, 1H), 2.45 (m, 1H), 2.18 (s, 3H), 1.80−1.27 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 166.5, 139.9, 128.6, 53.7, 51.4, 51.2, 41.4, 32.7, 27.8, 25.8; $[\alpha]^{22}_D$ = +4.4° (c 0.20, $CHCl_3$). Anal. ($C_{11}H_{17}NO_2$) C, H, N.

(+)-2β-(Methoxycarbonyl)-9-methyl-3β-phenyl-9-azabicyclo[3.3.1]nonane (6). To a 300 mL flame-dried, round-bottomed flask were added anhydrous ether (120 mL) and phenylmagnesium bromide (3.50 mL, 10.5 mmol, 3 M in Et_2O) under nitrogen. The solution was cooled to −40 °C, and **11** (1.95 g, 10.0 mmol) in anhydrous ether (120 mL) was added slowly. The reaction mixture was stirred for 2 h at −40 °C and cooled to −78 °C; the reaction was quenched with trifluoroacetic acid (1 mL, 12 mmol), and the mixture was allowed to warm to room temperature. The yellow mixture was then diluted with water and acidified to pH = 1 with concentrated HCl, and the etheral portion was discarded. The aqueous solution was basified with NH_4OH (pH >10) and extracted with dichloromethane (3 × 100 mL). The organic phase was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was chromatographed (petroleum ether:ether:triethylamine, 4:5:1) to afford a colorless oil (0.82 g, 31%): ^{1}H NMR (CD_2Cl_2) δ 7.29−7.15 (m, 5H), 3.76 (ddd, J = 13.5, 5.6, 5.6 Hz, 1H, H3), 3.39 (s, 3H, OCH_3), 3.23 (d, J = 5.3 Hz, 1H, H5), 3.14 (d, J = 5.6 Hz, 1H, H2), 3.03 (br, 1H, H1), 2.85 (dt, J = 13.3, 12.8, 5.1 Hz, 1H, H4a), 2.53 (s, 3H, NCH_3), 2.31−2.02 (m, 3H), 1.88 (dd, J = 12.6, 5.1 Hz, 1H, H4e), 1.74 (m, 1H), 1.48 (dd, J = 14.6, 6.57 Hz, 1H), 1.31 (m, 1H); ^{13}C NMR (CD_2Cl_2) δ 173.3, 144.8, 128.2, 127.3, 126.0, 56.6, 53.0, 52.5, 51.2, 41.1, 36.7, 32.6, 21.5, 21.2, 20.6. **6**·$C_4H_4O_4$: mp 127−128 °C; $[\alpha]^{22}_D$ = +5.0° (c 1.0, CH_3OH). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

(+)-2α-Methoxycarbonyl-9-methyl-3β-phenyl-9-azabicyclo[3.3.1]nonane (12). Compound **12** was obtained after **6** in the elution sequence as a colorless oil (0.96 g, 35%).

^{1}H NMR (CD_2Cl_2) δ 7.29−7.16 (m, 5H), 3.76 (ddd, J = 13.5, 12.7, 6.4 Hz, 1H, H3), 3.51 (s, 3H, OCH_3), 3.35 (dd, J = 12.3, 5.0 Hz, 1H, H2), 3.14 (br, 1H, H1), 2.86 (br, 1H, H5), 2.61 (s, 3H, NCH_3), 2.08−1.80 (m, 4H), 1.71 - 1.45 (m 4H); ^{13}C NMR ($CDCl_3$) δ 174.7, 146.9, 128.8, 127.8, 126.6, 56.0, 53.3, 51.7, 46.8, 41.2, 40.3, 33.7, 28.3, 25.4, 20.2. **12**·$C_4H_4O_4$: mp 148−151 °C; $[\alpha]^{22}_D$ = +2.2° (*c* 1.2, CH_3OH). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

(+)-2*β*-Benzoyl-9-methyl-3*β*-phenyl-9-azabicyclo[3.3.1]-nonane (13). To a 300 mL flame-dried, round-bottomed flask were added anhydrous ether (120 mL) and phenylmagnesium bromide (10.0 mL, 30.0 mmol, 3 M in Et_2O). The solution was cooled to −40 °C, and **11** (2.92 g, 15.0 mmol) in anhydrous ether (120 mL) was added slowly. The reaction mixture was stirred for 1 h at −40 °C. The solution was allowed to warm up to room temperature and stirred for 12 h. The reaction mixture was then cooled to −78 °C, the reaction quenched with trifluoroacetic acid, and the mixture allowed to warm to room temperature. The yellow mixture was then diluted with water and acidified to pH = 1 with concentrated HCl, and the etheral portion was discarded. The aqueous solution was basified with NH_4OH (30%) and extracted with dichloromethane. The organic phase was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by chromatography (petroleum ether:ether:triethylamine, 4:5:1) to furnish **13** as a white solid (1.4 g, 35%): ^{1}H NMR (CD_2Cl_2) δ 7.74 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.41−7.32 (m, 4H), 7.22 (t, J = 7.5 Hz, 2H), 7.08 (t, J = 7.2 Hz, 1H), 4.20 (d, J = 5.9 Hz, 1H), 3.91 (m, 1H), 3.15−3.00 (m, 3H), 2.42 (s, 3H), 2.41−1.57 (m, 7H); ^{13}C NMR (CD_2Cl_2) δ 199.6, 145.2, 132.6, 128.9, 128.2, 127.3, 125.8, 55.9, 52.9 52.8, 41.2, 37.2, 33.2, 21.4, 21.2, 20.8. **13**·$C_4H_4O_4$: mp 135−138 °C; $[\alpha]^{22}_D$ = +8.5° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{25}NO$) C, H, N.

(+)-2α-Benzoyl-9-methyl-3*β*-phenyl-9-azabicyclo[3.3.1]-nonane (14). Compound **14** was obtained after **15** in the elution sequence as a white solid (1.72 g, 54%). ^{1}H NMR (CD_2Cl_2) δ 7.86 (d, J = 8.6 Hz, 2H), 7.52 (t, J = 7.0 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 7.34 (d, J = 7.8 Hz, 2H), 7.23 (t, J = 7.3 Hz, 2H), 7.11 (t, J = 7.1 Hz, 1H), 4.47 (dd, J = 11.7, 4.6 Hz, 1H), 4.11 (ddd, J = 12.3, 12.5, 6.3 Hz, 1H), 3.19 (br, 1H), 2.94 (br, 1H), 2.73 (s, 3H), 2.24−1.34 (m, 7H); ^{13}C NMR (CD_2Cl_2) δ 201.5, 147.1, 137.2, 133.2, 129.9, 129.0, 128.7, 128.4, 127.8, 126.5, 56.3, 48.9, 41.2, 39.3, 33.9, 28.2, 24.7, 19.8. **14**·$C_4H_4O_4$: mp 164−165 °C; $[\alpha]^{22}_D$ = +4.6° (*c* 0.5, CH_3OH). Anal. ($C_{22}H_{25}NO$) C, H, N.

(−)-2*β*-(Methoxycarbonyl)-9-methyl-3*β*-phenyl-9-azabicyclo[3.3.1]nonane (15): prepared from (−)-**9** using the same procedures employed for the synthesis of **6** to furnish **15** as a colorless oil (0.15 g, 21%). **15**·$C_4H_4O_4$: mp 132−134 °C; $[\alpha]^{22}_D$ = −5.2° (*c* 1.1, CH_3OH). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

(−)-2α-(Methoxycarbonyl)-9-methyl-3*β*-phenyl-9-azabicyclo[3.3.1]nonane (16): prepared from (−)-**9** using the same procedures employed for the synthesis of **12** to furnish **16**:as a colorless oil (0.17 g, 25%). **16**·$C_4H_4O_4$: mp 153−155 °C; $[\alpha]^{22}_D$ = −2.4° (*c* 1.1, CH_3OH). Anal. ($C_{17}H_{23}NO_2$) C, H, N.

(−)-2-(Methoxycarbonyl)-9-methyl-3-phenyl-9-azabicyclo[3.3.1]non-2-ene (17). A solution of (+)-**10** (3.43 g, 10.0 mmol), Na_2CO_3 (15 mL, 2 M), 1-phenylboronic acid (2.47 g, 14.4 mmol), LiCl (1.30 g, 30.8 mmol), and tris(dibenzylideneacetone)dipalladium (0.2 g, 0.5 mmol) in DME (35 mL) was heated to reflux with vigorous stirring. After 2 h the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was chromatographed (triethylamine:petroleum ether, 1:9) to afford (−)-**17** as an oil (2.30 g, 85%): ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 3H), 7.16 (d, J = 7.3 Hz, 2H), 3.73 (br, 1H), 3.41 (s, 3H), 3.07 (br, 1H), 2.67 (dd, J = 19.8, 7.2 Hz, 1H), 2.41 (s, 3H), 2.09−1.52 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 168.8, 147.4, 141.9, 127.9, 127.2, 126.6, 126.5, 56.1, 52.6, 51.1, 41.6, 33.0, 31.6, 28.5, 15.2; free base $[\alpha]^{22}_D$= −14.0° (*c* 0.95, CH_3OH). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

(+)-2-(Methoxycarbonyl)-9-methyl-3-phenyl-9-azabicyclo[3.3.1]nonane (18). A solution of **17** (0.56 g, 2 mmol) in absolute ethanol (10 mL) was hydrogenated (50 psi) over PtO_2 (0.05 g) on a Parr hydrogenation apparatus for 12 h. The catalyst was removed by filtration through Celite and washed with ethanol (2 × 5 mL). After removal of the solvent under reduced pressure, the residue was chromatographed (triethylamine:petroleum ether, 1:9) to afford **18** as a colorless oil (0.2 g, 35%): ^{1}H NMR (CD_2Cl_2) δ 7.28−7.13 (m, 5H), 3.72 (dd, J = 10.3, 8.0 Hz, 1H, H2), 3.51 (ddd, J = 13.3, 8.0, 5.0 Hz, 1H, H3), 3.34 (s, 3H, OCH_3), 3.30 (br, 1H, H1), 3.08 (br, 1H, H5), 2.56 (s, 3H, NCH_3), 2.41 (ddd, J = 13.5, 13.3, 5.0 Hz, 1H, H4a), 2.23−2.15 (m, 2H), 2.02 −1.90 (m, 2H), 1.42 (m, 1H), 1.13 (d, J = 13.5 Hz, 1H, 4He), 1.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.2, 143.0, 127.9, 127.7, 125.8, 52.8, 51.3, 50.7, 49.6, 40.2, 35.1, 26.8, 22.6, 20.4, 15.2. **18**·$C_4H_4O_4$: mp 130−132 °C; $[\alpha]^{22}_D$ = +10.8° (*c* 1.0, CH_3OH). Anal. ($C_{17}H_{23}NO_2 \cdot {}^1/_2H_2O$) C, H, N.

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Supporting Information Available: X-ray crystallographic data, ORTEP drawings, and tables of bond distances, bond angles, and positional parameters for (+)-**9**·L-tartrate, **12**, and **14** (29 pages). Ordering information is given on any current masthead page.

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