Chemical Synthesis and Pharmacology of 6- and 7-Hydroxylated 2-Carbomethoxy-3-(*p*-tolyl)tropanes: Antagonism of Cocaine's Locomotor Stimulant Effects

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In our efforts to identify molecules that might act as cocaine antagonists or cocaine partial agonists, efforts were made to further capitalize on our earlier finding regarding the ability of a 7-methoxylated pseudococaine analogue to act as a weak cocaine functional antagonist. Herein, a series of the 6- and 7-hydroxylated WIN analogues possessing a boat or chair conformation of the tropane ring were prepared and tested for their ability to displace [^{3}H]mazindol binding and to inhibit high-affinity monoamine uptake into rat brain nerve endings. These 6- and 7-hydroxylated WIN analogues were readily prepared by use of a classical Willstätter synthesis to construct an appropriately functionalized tropane ring followed by use of a Suzuki coupling reaction to introduce the aryl group at position 3. Reduction of the resulting tropene by use of SmI_2 or by catalytic hydrogenation followed by deprotection delivered the final target compounds. Some of these compounds were found to retain considerable affinity as inhibitors of the dopamine transporter (DAT) and the norepinephrine transporter (NET), but they were less potent inhibitors of the serotonin transporter (SERT). None of the compounds of the present series revealed any substantial potency difference in [^{3}H]mazindol binding versus [^{3}H]DA uptake, and failed to show "cocaine antagonism" when tested for their ability to prevent cocaine's inhibition of DA transport. However, one of these hydroxylated WIN analogues, namely **12b**, which possesses nanomolar potency at the DAT and NET and micromolar potency at the SERT, when tested in vivo, was found capable of attenuating cocaine's locomotor activity (AD_{50} = 94 mg/kg). Taken together, this work provides further support for our hypothesis that drugs that lack the ability to inhibit transport by all three monoaminergic transporters may exhibit "partial" cocaine-like properties, but act as cocaine antagonists. Consequently, it may prove valuable to examine the behavioral activity of other 6- and 7-substituted tropanes in animal behavioral paradigms in the search for a cocaine medication.

Introduction

Immediate therapies are needed for the treatment of cocaine abuse worldwide.[1] It has been estimated, for example, that there are at present over 1.5 million cocaine abusers in the United States alone, and that approximately one-third of these users are consistent or hard core users. Undoubtedly, cocaine abuse has a tremendous negative impact on our society, for it has been estimated that the health and crime costs associated with cocaine abuse amount to about 100 billion dollars per year. Moreover, it has been reported that approximately one-half million Americans ended up in hospital emergency rooms last year. Cocaine use figured into about 28% of these emergency visits, up by 15% from 1993. At present there are no effective medications available to treat cocaine addiction, although selegeline is in phase III trials.[1]

To develop agents that might find use in the treatment of cocaine abuse, the search for both cocaine antagonists and partial agonists is being pursued. While antagonists are more likely to find use in situations of cocaine overdose, the partial agonist approach may prove more useful in maintenance programs. Compounds that possess the ability to mimic partially the effects of cocaine may help to maintain individuals in treatment programs in a manner analogous to methadone, a drug widely used in the treatment of opiate abuse. Alternatively, or in addition, such "partial agonists" may be able to prevent the effects of cocaine.

In pursuit of possible medications we have focused much of our chemistry efforts on the modification of cocaine itself, in the belief that appropriate structural alterations may lead to the desired type of partial agonist or antagonist activity we seek. In fact, some time ago we reported the ability of a 7-methoxylated analogue of pseudococaine to act as weak antagonist of cocaine, in that it was able to inhibit cocaine's ability to block dopamine reuptake.[2] Based upon this interesting finding, it became attractive to investigate the activity of other 6- and 7-substituted cocaine analogues. In particular, we chose to explore these modifications in the higher affinity WIN series, in which the 3-position of

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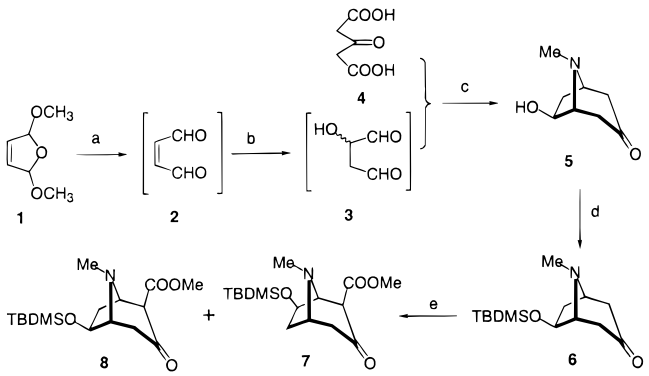
Scheme 1[a]



[a] Reagents and conditions: (a) 3 N HCl, rt, 12 h; (b) neutralization with 6 N NaOH; (c) NaOAc, CH_3NH_2·HCl, rt, 2 d; (d) TBDMSCl, imidazole, DMF, rt, 12 h; (e) LDA, NC−COOMe, THF, −78 °C, 1 h.

the tropane ring bears phenyl in place of cocaine's benzoate group. While we have reported to date on the synthesis of a variety of such 6- and 7-substituted tropanes through use of an oxidopyridinium-based cycloaddition strategy, we found this method to be cumbersome in achieving our present objective, which was the construction of all possible 6- and 7-substituted tropanes of both chair and boat conformation.[3] Herein, we report on the chemical synthesis and pharmacological characterization of a series of hydoxylated WIN derivatives, and in one case we also present data showing the ability of one of these derivatives to antagonize cocaine's stimulant effects in a rat locomotor assay. As will become apparent, the present work provides further support for our hypothesis that drugs that lack the ability to inhibit transport by all three monoaminergic transporters may exhibit only "partial" cocaine-like properties.[4] That is, drugs that are selective for SERT and NET, or DAT and NET, or SERT and DAT may have properties that could act either alone or in combination with an "antagonist" to reduce cocaine self-administration.

Chemistry. In terms of developing a chemical approach to the 6- and 7-substituted WIN analogues, we initially attempted to use cocaine itself, investigating the possibility to bring about the remote functionalization of this molecule by tethering appropriate functionality to the nitrogen atom. Unfortunately, such efforts did not meet with success. We then modifed our approach by adapting the route devised by Willstätter nearly eight decades ago for the synthesis of cocaine itself.[5] The chemical route used to generate the required 6- and 7-hydroxylated tropinones is shown in Scheme 1, and it resembles closely the approach we first used to prepare the methoxylated pseudococaine derivative metioned in the Introduction.[6]

Accordingly, commercially available 2,5-dimethoxy-2,5-dihydrofuran (**1**) was stirred in 3 N HCl overnight at room temperature and then neutralized by the addition of 6 N NaOH. This mixture was then added to a solution of acetonedicarboxylic acid, methylamine hydrochloride, and sodium acetate in water (pH approximately 4.3). The resulting mixture was then stirred for 2 days at room temperature. The crude product thus obtained was recrystallized from 2-propanol to afford 6β-hydroxytropinone (**5**) as a white solid in 42% yield.

The hydroxytropinone **5** was protected in turn as its *tert*-butyldimethylsilyl ether **6** using *tert*-butyldimethylsilyl chloride and imidazole in DMF at room temperature for 12 h. This intermediate then was deprotonated with lithium diisopropylamine (LDA) in the same manner as described by Majewski for tropinone.[7] Ketone **6** was treated with LDA in THF at −78 °C, and the resulting enolate was reacted with methyl cyanoformate to afford the corresponding racemic carbomethoxylated derivatives **7** and **8** in 64% yield and in a ratio of 9:7. The two isomers can be separated by careful flash column chromatography, and the structure of compound **7**, which exists as its enol after removal of the TBDMS group, was assigned by X-ray analysis.[8] The keto esters **7** and **8** served as key intermediates in the synthesis of 6- and 7-hydroxylated WIN type analogues of cocaine.

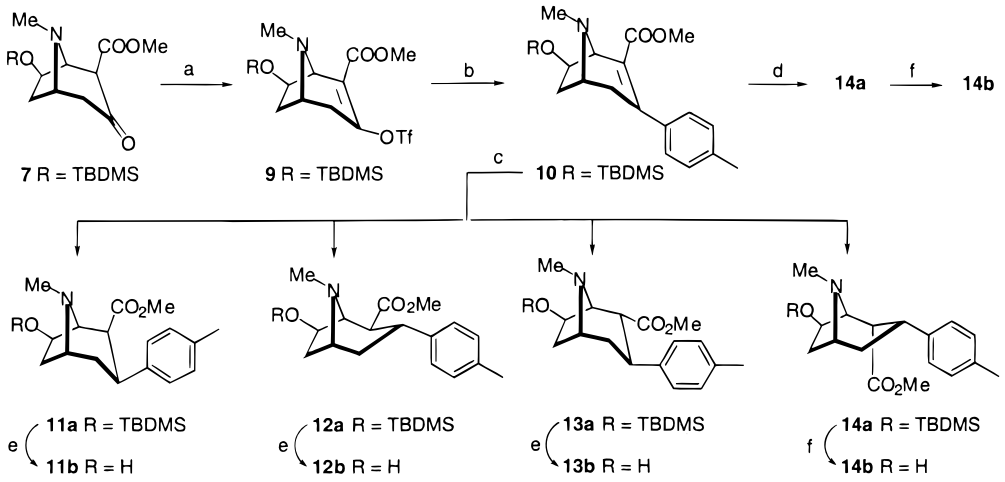
From this point, a Suzuki coupling protocol was used to install the tolyl group following a protocol much like that first reported by Carroll in his synthesis of other cocaine analogues.[9] Hence, the enol triflate **9** was readily obtained in 73% yield by the addition of *N*-phenyltrifluoromethanesulfonimide to a THF solution of ketone **7** containing sodium bis(trimethylsilyl)amide at −78 °C (Scheme 2). Reaction of **9** with 4-methylphenylboronic acid, which was prepared from triisopropyl borate,[10] in 1,2-dimethoxyethane using tris(dibenzylideneacetone)dipalladium(0) as catalyst together with sodium carbonate and lithium chloride at reflux gave **10** in 98% yield.

Reduction of **10** with samarium iodide in THF at −78 °C using methanol as the proton source followed by quenching with acetic acid provided a mixture of the desired tropanes **11a** (22.5%), **12a** (32.5%), **13a** (17.5%), and **14a** (12.5%) in a total yield of 85%. These products are readily separable by flash column chromatography. On the other hand, hydrogenation of **10** over 10% Pd/C in methanol gives rise to a single product in 80% yield to which we assign 2α,3α-stereochemistry (compound **14a**) in accordance with literature precedent.[11] Under basic conditions (NaOMe, MeOH, reflux, 24 h; 83%), **14a** is converted to the more stable 2β,3α-isomer **12a**. Compounds **11a** and **13a** are therefore the other two isomers. Since **11a** epimerizes to **13a** with NaOMe in methanol, **13a** must be the 2α,3β-isomer, and **11a** the 2β,3β-isomer.

Finally, the TBDMS group of each of the compounds **11a**, **12a**, and **13a** was removed in high yield with *n*-Bu_4NF in THF at room temperature to give the corresponding products **11b**−**13b** (87, 99, and 85%, respectively). However, when compound **14a** was treated with *n*-Bu_4NF in THF, only **12b** was obtained as the product. To avoid this epimerization, which was obviously a consequence of the basicity of the fluoride anion, compound **14a** was instead deprotected with 48% HF to afford 7β-hydroxy-3α-(*p*-tolyl)tropane-2α-carboxylic acid methyl ester (**14b**) in 79% yield. The structure of **12b** was confirmed by X-ray analysis (Figure 1).

To access the 7α-epimers, the TBDMS group of compound **10** was removed with *n*-Bu_4NF in THF at room temperature. The resulting alcohol **15** (91% yield) was subjected to a Swern oxidation,[12] which delivered the ketone **16** in 97% yield. Reduction of **16** with $NaBH_4$ in methanol gave a 15:1 mixture of the alcohols **17** and **15** in 91% yield. These two compounds were readily

Scheme 2[a]



[a] Reagents and conditions: (a) $NaN(TMS)_2$, $PhNTf_2$, THF, −78 °C to rt, overnight; (b) *p*-tolylboronic acid, Pd_2dba_3, Na_2CO_3, LiCl, DME, 1 h; (c) SmI_2, MeOH, THF, −78 °C, 1 h; (d) H_2 (40 psi), 10% Pd/C, MeOH, 12 h; (e) *n*-Bu_4NF, THF, rt, 12 h; (f) 48% HF, CH_3CN, rt, overnight.

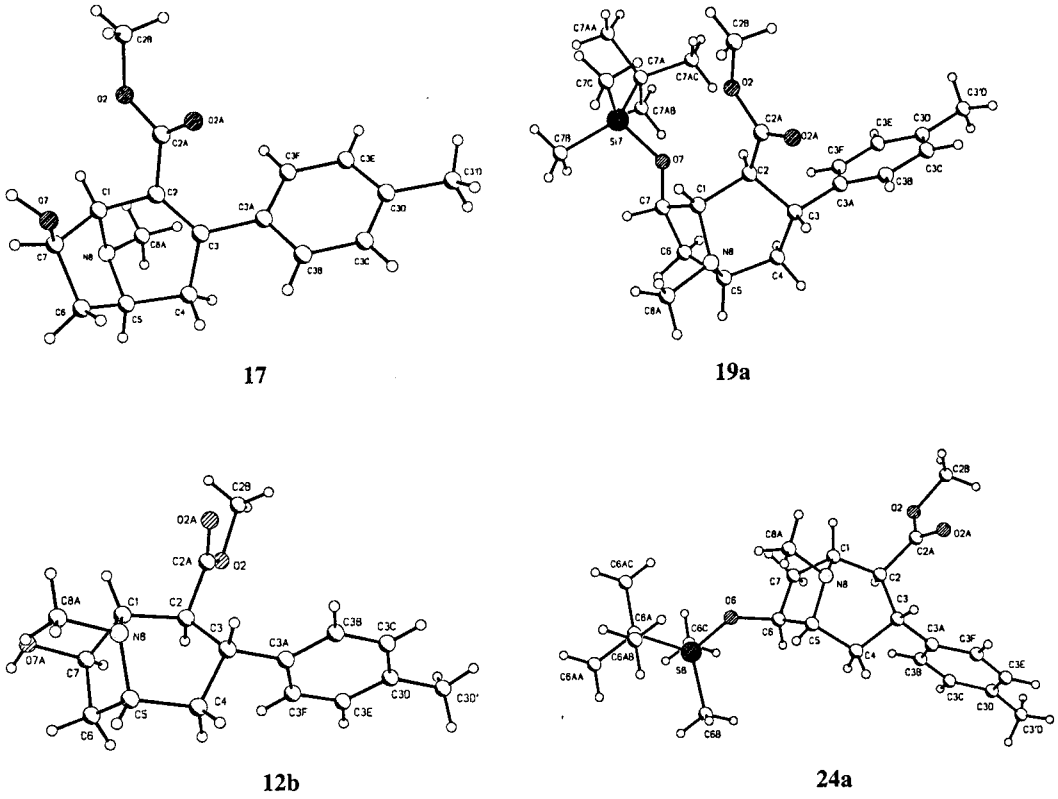
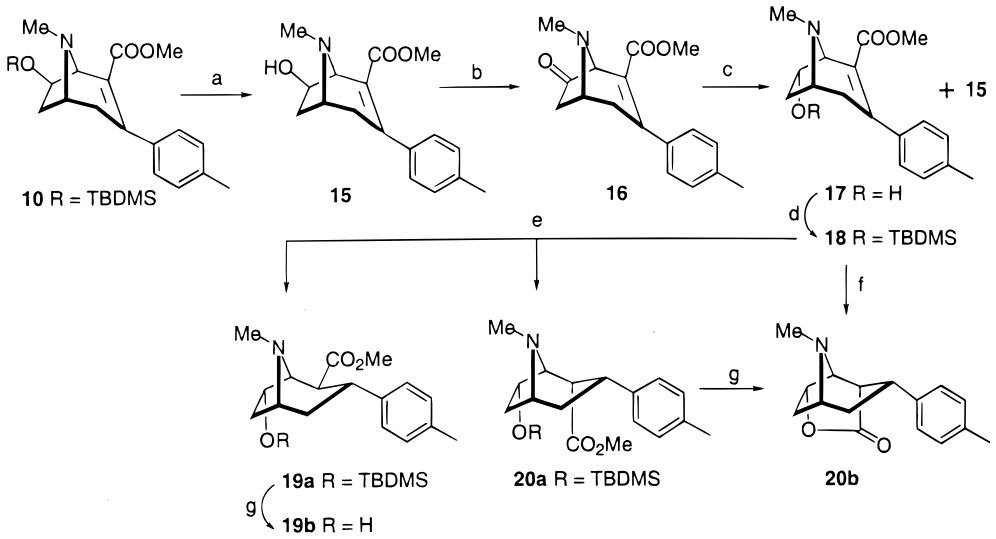


Figure 1. ORTEP drawings of compounds **17**, **19a**, **12b**, and **24a**.

separated by flash chromatography, and the structure of **17** was established by X-ray analysis (Figure 1). Attempts at saturating the double bond in the free alcohol **17** with SmI_2 as described above were unsuccessful. Therefore, compound **17** was converted to its *tert*-butyldimethylsilyl ether **18**, and this intermediate was reacted with SmI_2 in THF/MeOH. Of the reduction products, only the major isomer **19a** was obtained in pure form in 66% yield while the minor stereoisomers formed an inseparable mixture. Upon treatment with NaOMe in MeOH at reflux, approximately 75% of this mixture was converted to compound **19a**. The remaining material exhibited a complex ^1H NMR spectrum and was not further investigated. If the mixture of minor products was deprotected with *n*-Bu_4NF in THF, most of it was transformed into the lactone **20b**. Hydrogenation (40 psi) of **18** over 10% Pd/C in methanol gave the same lactone directly. We conclude that the predominant isomer among the minor products has 2α,3α-configuration and that compound **19a** has 2*β*,3α-configuration. The structure of **19a** was subsequently confirmed by X-ray crystallographic analysis (Figure 1). Deprotection of **19a** with *n*-Bu_4NF in THF provided the desired compound **19b** (Scheme 3).

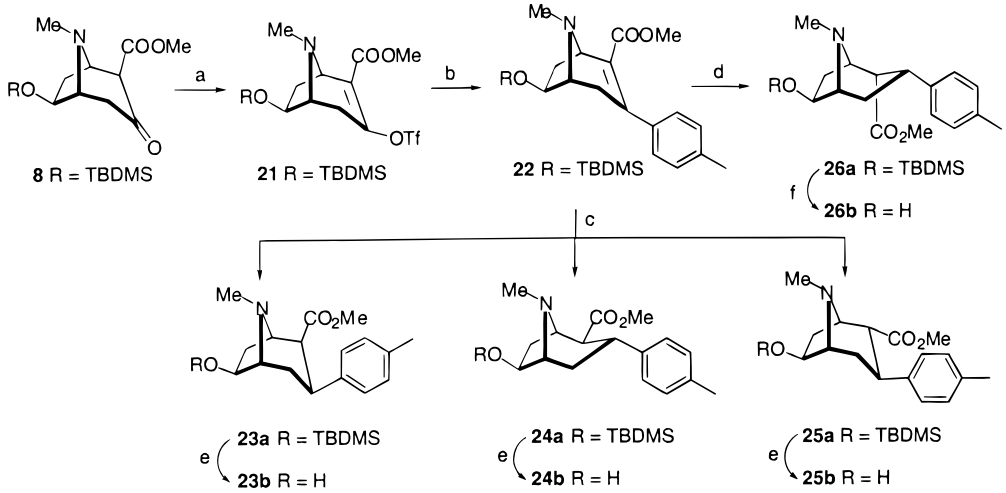
In the same manner as described above, compound **8** was converted into its enol triflate **21** in 62% yield, which was coupled with *p*-tolylboronic acid to produce the aryl olefin **22** in high yield (Scheme 4). Reduction

Scheme 3[a]



[a] Reagents and conditions: (a) *n*-Bu_4NF, THF, rt, 12 h; (b) oxalyl chloride, DMSO, −78 °C, 30 min; (c) MeOH, $NaBH_4$, 0 °C−rt, overnight; (d) TBDMSCl, imidazole, DMF, rt, 12 h; (e) SmI_2, MeOH, THF, −78 °C, 1 h; (f) H_2 (30 psi), 10% Pd/C, MeOH, 12 h; (g) *n*-Bu_4NF, THF, rt, 12 h.

Scheme 4[a]



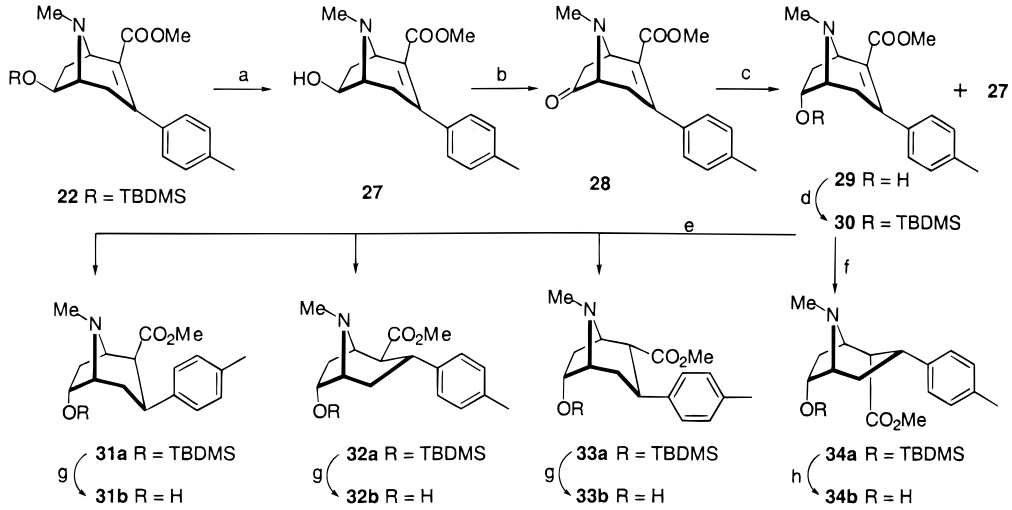
[a] Reagents and conditions: (a) $NaN(TMS)_2$, $PhNTf_2$, THF, −78 °C to rt, overnight; (b) *p*-tolylboronic acid, Pd_2dba_3, Na_2CO_3, LiCl, DME, 1 h; (c) SmI_2, MeOH, THF, −78 °C, 1 h; (d) H_2 (30 psi), 10% Pd/C, MeOH, 12 h; (e) *n*-Bu_4NF, THF, rt, 12 h; (f) 48% HF, CH_3CN, rt, overnight.

of **22** with SmI_2 at −78 °C in THF/MeOH gave the saturated tropane analogues **23a** (38%), **24a** (48%), and **25a** (5%). Intermediate **23a** was converted to **25a** in high yield by treatment with NaOMe in MeOH at reflux. Hydrogenation of **22** over 10% Pd/C, on the other hand, provided the 2α,3α-isomer **26a** exclusively. The structure of compound **24a** was confirmed by X-ray analysis (Figure 1).[13] Finally, the TBDMS group of each of the compounds **23a**, **24a**, and **25a** was removed in high yield with *n*-Bu_4NF in THF to give the desired products **23b**, **24b**, and **25b**, respectively. The remaining isomer **26b** was obtained in 92% yield by treatment of **26a** with 48% HF.

Compounds of the 6α-series were prepared, like their 7α-isomers, by stereochemical inversion at the oxygen-bearing carbon atom. Thus, compound **22** was deprotected with *n*-Bu_4NF and the resulting alcohol **27** converted by Swern oxidation to ketone **28**, which upon $NaBH_4$ reduction afforded **27** and its 6α-isomer **29** in a ratio of 1:5.3. After hydroxyl protection as the silyl ether **30**, the double bond was reduced with SmI_2 in THF/MeOH to afford the saturated products **31a** (6%), **32a** (69%), and **33a** (17%). Hydrogenation of **30** gave the 2α,3α-isomer **34a** in 89% yield. Finally, all of these four intermediates were deprotected with *n*-Bu_4NF or 48% HF to give the desired products **31b**−**34b** (Scheme 5).

Biology. All of the hydroxylated tropanes described herein were tested for their ability to displace [^{3}H]mazindol binding. Mazindol has been shown to label the cocaine binding site on the dopamine transporter of rat striatal membranes.[14] This ligand binds with high affinity (K_d = 8.63 ± 0.53 nM) to a single, sodium-dependent site in striatal membranes, representing the dopamine carrier. Additionally, these compounds were tested for their ability to inhibit high-affinity uptake of DA, 5-HT, and NE into nerve endings (synaptosomes) which were prepared from various regions of the rat brain that are enriched with the particular transporter under study.[15] Comparison of the K_i values for inhibition of monoamine uptake and mazindol binding was facili-

Scheme 5[a]



[a] Reagents and conditions: (a) *n*-Bu_4NF, THF, rt, 12 h; (b) oxalyl chloride, DMSO, −78 °C, 30 min; (c) $NaBH_4$, MeOH 0 °C-rt, overnight; (d) TBDMSCl, imidazole, DMF, rt, 12 h; (e) SmI_2, MeOH, THF, −78 °C, 1 h; (f) H_2 (30 psi), 10% Pd/C, MeOH, 12 h; (g) *n*-Bu_4NF, THF, rt, 12 h; (h) 48% HF, CH_3CN, rt, overnight.

Table 1. K_i Values for 6- and 7-Hydroxylated Tropane Analogues in the Inhibition of [^{3}H]Mazindol Binding and in the Inhibition of Radiolabeled DA, 5-HT, and NE Uptake[a]

compound	[^{3}H]mazindol binding	[^{3}H]dopamine uptake	[^{3}H]5-HT uptake	[^{3}H]NE uptake
cocaine	230 ± 16 nM	423 ± 147 nM	155 ± 0.4 nM	108 ± 4 nM
WIN 35065-2[b]	89.4 nM	49.8 ± 2.2 nM	173 ± 13 nM	37.2 ± 5.2 nM
11b	25.2 ± 2.5 nM	39.2 ± 2.6 nM	581 ± 57 nM	44.7 ± 9.5 nM
12b	135 ± 15 nM	156 ± 25 nM	5.9 ± 0.1 μM	60.9 ± 3.5 nM
13b	2.9 ± 0.1 μM	5.6 ± 0.2 μM	≈3 μM	≈1 μM
14b	1.4 ± 0.3 μM	2.9 ± 0.3 μM	>100 μM	≈300 nM
19b	540 ± 53 nM	676 ± 43 nM	NT	NT
20b	14.5 ± 0.2 μM	25 ± 1 μM	NT	NT
23b	126 ± 18 nM	292 ± 80 nM	6.7 ± 0.4 μM	154 ± 23 nM
24b	659 ± 39 nM	996 ± 11 nM	NT	NT
25b	13.2 ± 3.0 μM	3.1 ± 0.3 μM	NT	NT
26b	5.1 ± 0.1 μM	1.9 ± 0.3 μM	NT	NT
31b	1.8 ± 0.1 μM	2.3 ± 0.1 μM	NT	NT
32b	13.2 ± 1.0 μM	11.7 ± 1.7 μM	NT	NT
33b	>100 μM	97.2 ± 5.6 μM	NT	NT
34b	54 ± 3 μM	64 ± 2 μM	NT	NT
35[c]	21.0 ± 2.3 nM	51.8 ± 2.1 nM	80.2 ± 1.1 nM	6.3 ± 1.6 nM

[a] K_i values are mean ± SE from 2 to 4 independent experiments, each consisting of six drug concentrations (in triplicate) that were selected on the basis of preliminary screening experiments to bracket the approximate IC_{50} value. [b] WIN 35065-2 is 2β-carbomethoxy-3β-phenyltropane. [c] Compound **35** is (1*R*,5*S*)-2α-*n*-propyl-3β-*p*-tolyltropane.

tated by the use of the same buffer in all assays. The binding and uptake data are provided in Table 1 along with comparison data for cocaine.

As is apparent from the accompanying table, of the 7-hydroxylated tropanes, only **11b** and **12b**, the former with the chair conformation and the latter with the boat conformation, were found to have nanomolar range potencies in binding and uptake. The chair tropane **11b** is particularly potent, with a K_i of 25 nM in mazindol binding. The DAT and NET potencies are comparable (39 and 45 nM) and about 10-fold better than the SERT potency. On the other hand, the NET potency of **12b** is 2-fold better than its DAT potency, while its SERT potency is in the 6 μM range. Both of the 7β-hydroxylated analogues **13b** and **14b**, which have an α-oriented ester group, exhibit only micromolar potencies at all three transporters. The 7α-hydroxylated boat tropane **19b** is less active than cocaine in the DAT assay, with a K_i of about 0.7 μM, with very little activity being shown by the lactone **20b**. During the course of our work, Meltzer has also reported on the activity of some 7-hydroxylated WIN analogues, finding that a 7β-hydroxy-3α-(3,4-dichlorophenyl) substituted tropane has both high affinity and selectivity for DAT over the SERT (IC_{50} = 1.2 nM vs 1390 nM). The chemical route used by Meltzer also makes use of the Willstätter approach first employed by us in combination with the Suzuki coupling chemistry.[16]

Of the 6-hydroxylated compounds, only the tropane **23b** of chair conformation had activity in the nanomolar range (290 nM) at the DAT, while all other 6-hydroxylated derivatives exhibited binding and uptake data in the micromolar range. The NET activity of **23b** is also good, while this compound shows poor activity at the SERT. Compound **23b** is thus DAT + NET selective.

From the present study one may make the observation that the mazindol and DA recognition sites are more tolerable for the 6- and 7-hydroxylated tropanes that possess a β-oriented hydroxyl group. From a structural standpoint, this is reasonable, as the nitrogen atom and *N*-methyl group that make up the tropane ring already provide some steric bulk to this face of the seven-membered carbocycle, and the presence of the extra hydroxy group causes little further "steric dis-

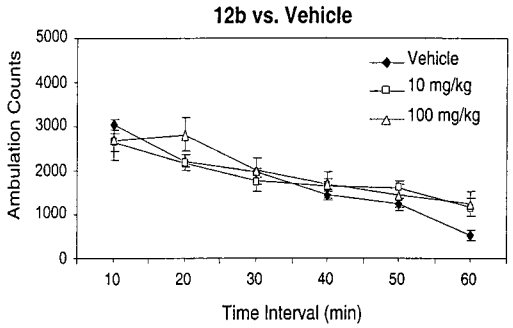


Figure 2. Time course of effects of **12b** on horizontal activity counts/10 min.

turbance". Also, for the three ligands showing 300 nM or better DAT potency, their SERT potency is 15- to 50-fold less. Thus, the 6- or 7-hydroxy group causes a reduction in activity at the SERT in comparison to the activity found for cocaine itself or for a 6/7-unsubsituted WIN analogue. As can be seen from Table 1, cocaine shows better activity at the SERT than the DAT. Data are also provided for the WIN analogue **35** bearing an α-oriented *n*-propyl group at the 2-position. The DAT and SERT potencies are comparable in this case, whereas the compound is more active at the NET.

Unfortunately, based upon a comparison of binding and uptake data, it appeared that none of our hydroxylated WIN type compounds might act as a cocaine antagonist by binding to the mazindol site more avidly than the DA site on DAT. Even when tested as such, in contrast to what we found previously for the 7α-methoxylated pseudococaine analogue which possesses low binding affinity, no functional antagonism was observed.[2a] Nonetheless, from our prior experience with a DAT/NET-selective piperidine-based ligand that shows no functional antagonism in vitro, but yet is able to antagonize the effects of cocaine in vivo in locomotor studies, we chose to scale-up two of the more active of these compounds, **11b** and **12b**, to allow for in vivo studies.[2b] Compound **12b** was chosen based both upon its DAT potency and its selectivity for the DAT over the SERT.

Locomotor Study of 11b and 12b. Tropanes **11b** and **12b** were tested in nonhabituated male Swiss-Webster mice in the locomotor assay using the standard operating procedure developed by the Medications Development Division of the National Institute on Drug Abuse. Not unexpectantly, the more DAT-potent ligand **11b** had an efficacy similar to cocaine when it was tested alone at a dose range of 3−100 mg/kg, and it was found to stimulate locomotor activity with an ED_{50} value of 14.03 mg/kg and a maximal effect/cocaine mixmal effect ratio of 0.88. As a consequence of this activity profile, **11b** was not tested for its ability to attenuate cocaine-induced locomotor activity. On the other hand, the less DAT-active ligand **12b** proved to be more interesting. Figure 2 shows the average horizontal activity counts/10 min as a function of time, immediately following injection of **12b** or vehicle. Since **12b** did not affect spontaneous locomotor activity in the dose range finding experiment, a cocaine interaction study was conducted next. Figure 3 shows the average horizontal activity counts/10 min for the different treatment groups as a function of time, starting 20 min after pretreatment with **12b**. The period of 0−30 min was selected for

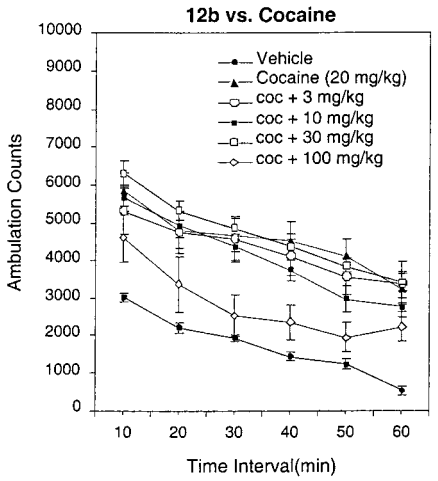


Figure 3. Interaction between **12b** and cocaine on LMA: time course of effect.

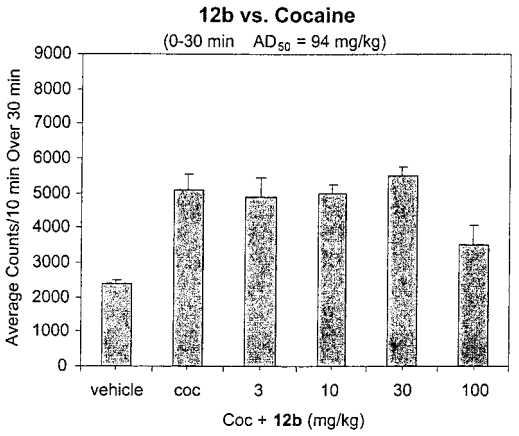


Figure 4. Interaction between **12b** and cocaine on LMA: dose response during first 30 min after a 20 min pretreatment.

analysis of the dose−response data because this is the time period in which cocaine produced its maximal effects. Figure 4 shows the average horizontal activity counts/10 min over 30 min as a function of the dose condition, 20 min after pretreatment with **12b**. The bar above "vehicle" represents the effect of vehicle 20 min prior to saline injection. The bar above "coc" represents the effect of vehicle 20 min prior to injection of 20 mg/kg cocaine. The bars above "3, 10, 30, and 100" represent the effects of **12b** at the designated doses 20 min prior to injection of 20 mg/kg cocaine. The mean average horizontal activity counts/10 min on the descending portion of the dose−effect curve (30 to 100 mg/kg dose range) for this 30 min period were fit to a linear function of log dose, and the AD_{50} (dose attenuating cocaine-induced stimulation by 50%) was calculated to be 94 mg/kg. [The ordinate value for the AD_{50} was calculated using the mean of the vehicle + 0.9% saline (vehicle) group as the minimum value, and the mean of the vehicle plus 20 mg/kg cocaine group as the maximum value.]

A one-way analysis of variance conducted on log horizontal activity counts for the 0−30 min time period indicated a significant overall effect of the treatment group $F(5,42) = 7.90$, $p < 0.05$; planned comparisons (a priori contrast) against the cocaine group showed significant differences for vehicle and the 100 mg/kg dose (all p values < 0.05 denoted in Figure 3 with an

asterisk). However, as the difference between the "no effect" dose of **12b** at 100 mg/kg alone and the antagonism result is only a difference of outcome at the 100 mg/kg dose, it is important that these studies be extended further. Nonetheless, the present results do suggest that these hydroxylated tropanes are worthy of further exploration.

Conclusions

The present work details the synthesis of a series of the 6- and 7-hydroxlated WIN analogues possessing a boat or chair conformation of the tropane ring. Some of these compounds retain considerable DAT and NET potency, with diminished activity at the SERT. While previously we had found that a methoxylated pseudococaine analogue was able to antagonize cocaine's inhibition of dopamine reuptake, none of the compounds of the present series revealed any substantial difference in binding versus uptake, and they failed to show "cocaine antagonism" when tested for such. However, one of the hydroxylated WIN analogues, namely **12b**, was tested in vivo and found capable of attenuating cocaine's locomotor activity. When the compound was tested alone at a dose range of 3−100 mg/kg, the compound was found to have no effect on locomotor activity. When tested in animals that had been treated with 20 mg/kg (i.p.), **12b** was able to attenuate locomotor activity with an AD_{50} of 94 mg/kg. In contrast, locomotor studies using the more DAT-active ligand **11b** revealed this compound to be cocaine-like in its action (maximal effect/cocaine miximal effect ratio of 0.88).

The present finding suggests that it may prove valuable to examine the behavioral activity of other 6- and 7-substituted tropanes in animal behavioral paradigms in the search for a cocaine medication. Of interest in this connection is our related finding concerning the action of 7α-fluoro-3α-(*p*-fluorophenyl)-2*β*-propyltropane. This compound was evaluated in the brain stimulation reward paradigm, a behavioral screen that allows measuring the intrinsic hedonic properties of compounds separately from the concomitant changes in the rate of responding.[17] The fluorinated tropane was found to be unrewarding when administered alone, with only a slight increase in reward at 20 mg/kg (i.p.), the highest dose tested to date. However, when 5 mg/kg or 10 mg/kg i.p. of this tropane was combined with 10 mg/kg cocaine (i.p.), a reduction in cocaine-induced reward-enhancement (by approximately 60%) was noted. No changes in motor/performance capacity were observed, either when the derivative was administered alone or in combination with cocaine. Like **12b**, this fluorinated tropane also shows better activity at the DAT and NET versus the SERT (49, 52, and 560, respectively).[18]

Thus, taken together this work provides further support for our hypothesis that drugs that lack the ability to inhibit transport by all three monoaminergic transporters may exhibit only "partial" cocaine-like properties. It is our intention to further explore this hypothesis using other tropanes showing varying levels of transporter selectivity.

Last, we call attention to the fact that the hydroxlated tropanes reported herein have been made in racemic form. Based upon the encouraging behavioral results, it is our plan to prepare the more potent compounds in optically pure form using enzymatic methods (PLE) as previously described.[19]

Experimental Section

Chemical Methods. General. Diethyl ether was distilled from phosphorus pentoxide. THF was freshly distilled under N_2 from sodium benzophenone. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ with a Varian Unity Inova instrument at nominal frequencies of 300 and 75 MHz, respectively. ^{1}H chemical shifts (δ) are reported in ppm downfield from internal TMS. ^{13}C chemical shifts are referenced to $CDCl_3$ (central peak, δ = 77.0 ppm). Melting points were determined in Pyrex capillaries with a Thomas-Hoover Unimelt apparatus and are uncorrected. Mass spectra were measured in the EI mode at an ionization potential of 70 eV. X-ray data were collected on a computer controlled Bruker P4 automatic 4-circle diffractometer. The structures were solved by direct methods and refined, using all independent data, with full matrix least-squares on F2 values using the SHELXTL program package. TLC was performed on Merck silica gel $60F_{254}$ glass plates. Column chromatography (CC) was performed using Merck silica gel (60−200 mesh).

(±)-6*β*-Hydroxytropan-3-one (5). A solution of 2,5-dimethoxy-2,5-dihydrofuran (2.6 g, 20 mmol) in 3 N HCl (36 mL) was stirred at room temperature for 16 h, neutralized with 6 N NaOH (about 18 mL) and added to a solution of sodium acetate (13.6 g, 168 mmol), methylamine hydrochloride (2.72 g, 40 mmol), and acetonedicarboxylic acid (5.84 g, 40 mmol) in water (320 mL). The mixture was left standing for 2 d, during which time its pH increased from 3.0 to 4.9. K_2CO_3 and NaCl (100 g each) were added, and the solution was extracted with chloroform (4 × 150 mL). The combined chloroform extracts were dried over $MgSO_4$ and concentrated. The residue was crystallized from 2-propanol to give the product (1.30 g, 42%) as a white solid: mp 107−108 °C (lit. mp,[5f] 108−109 °C). ^{1}H NMR δ 4.14 (dd, 1H), 3.61 (m, 1H), 3.38 (d, 1H), 2.78−2.55 (m, 2H), 2.67 (s, 3H), 2.45 (br s, 1H), 2.28−1.92 (m, 4H).

(±)-6*β*-(*tert*-Butyldimethylsilyloxy)tropan-3-one (6). A solution of **5** (132 mg, 0.85 mmol), imidazole (68 mg, 1.0 mmol), and *tert*-butyldimethylsilyl chloride (150 mg, 1.0 mmol) in DMF (2 mL) was stirred under N_2 at room temperature for 32 h. The mixture was diluted with ether, and the solution was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated. CC of the residue (Et_2O/Et_3N 99:1−19:1) gave compound **6** (218 mg, 95%) as a clear oil: ^{1}H NMR δ 4.11 (dd, J = 3.6, 6.3 Hz, 1H), 3.59 (m, 1H), 3.25 (m, 1H), 2.67 (s, 3H), 2.72−2.60 (m, 2H), 2.30−2.00 (m, 4H), 0.88 (s, 9H), 0.23 (s, 6H).

(±)-7*β*-(*tert*-Butyldimethylsilyloxy)-2*β*-(methoxycarbonyl)tropan-3-one (7) and (±)-6*β*-(*tert*-Butyldimethylsilyloxy)-2*β*-(methoxycarbonyl)tropan-3-one (8). A solution of diisopropylamine (155 μL, 1.1 mmol) in THF (5 mL) was cooled to 0 °C, and *n*-butyllithium (0.48 mL, 2.3 M solution in hexane, 1.1 mmol) was added. The solution was stirred for 25 min at 0 °C and then cooled to −78 °C. Ketone **6** (269 mg, 1.0 mmol) dissolved in THF (2 mL) was added dropwise over 15 min. The resulting mixture was stirred for 45 min at −78 °C, and then methyl cyanoformate (0.1 mL, 1.3 mmol) was added dropwise at −78 °C. Stirring was continued at −78 °C for 20 min. Glacial acetic acid (1.0 mL) and then silver acetate (168 mg, 1.0 mmol) in glacial acid (1.0 mL) were added at −78 °C. The mixture was warmed to room temperature and stirred for another 30 min, then concentrated NH_4OH was added until the mixture became clear. The resulting solution was extracted with $CHCl_3$ (5 × 30 mL). The combined organic extracts were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was subjected to CC (CH_2Cl_2 saturated with concentrated NH_4OH) to give the *β*-ketoesters **7** (117 mg, 36%) and **8**[20] (93 mg, 28%). Compound **7**: ^{1}H NMR δ 4.13 (dd, J = 1.5, 6.6 Hz, 1H), 3.78 (s, 3H), 3.67 (br s, 1H), 3.45 (m, 1H), 2.72−2.60 (m, 2H), 2.43 (s, 3H), 2.14−2.04 (m, 1H), 1.97 (dd, J = 6.9, 13.8 Hz, 1H), 1.74 (d, J = 18.6 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). Compound **8**:^{1}H NMR δ 4.14 (dd, J = 4.2, 7.5 Hz, 1H), 3.85 (d, J = 5.7 Hz,

1H), 3.76 (s, 3H), 3.17 (d, J = 5.4 Hz, 1H), 2.76−2.60 (m, 2H), 2.42 (s, 3H), 2.45−2.20 (m, 1H), 2.12−1.96 (m, 1H), 1.91 (d, J = 20.7 Hz, 1H), 0.88 (s, 9H), 0.05 (s, 6H).

(±)-Methyl 7β-(*tert*-Butyldimethylsilyloxy)-8-methyl-3-(trifluoromethanesulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (9). Sodium bis(trimethylsilyl)amide (1.0 M in THF, 1.7 mL) was added dropwise to a solution of **7** (462 mg, 1.41 mmol) in THF (5 mL) at −78 °C under N_2. After 30 min of stirring, *N*-phenyltrifluoromethanesulfonimide (555 mg, 1.55 mmol) was added in one portion at −78 °C. The mixture was allowed to warm to room temperature and was then stirred overnight. The solvent was removed, the residue was dissolved in CH_2Cl_2, and the solution was washed with water and brine and dried over $MgSO_4$. The organic phase was concentrated, and the residue was purified by CC (hexane/EtOAc 8:1−4:1) to afford the product (471 mg, 73%) as an oil: ^{1}H NMR δ 4.28 (dd, J = 2.1, 6.9 Hz, 1H), 3.83 (s, 3H), 3.53 (m, 1H), 2.78 (dd, J = 4.2, 18.6 Hz, 1H), 2.20−1.91 (m, 1H), 1.85 (d, J = 18.6 Hz, 1H), 0.89 (s, 9H), 0.10 (s, 6H).

(±)-Methyl 7β-(*tert*-Butyldimethylsilyloxy)-8-methyl-3-(*p*-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (10). The triflate **9** (470 mg, 1.02 mmol), *p*-tolylboronic acid (184 mg, 1.35 mmol), LiCl (95 mg, 2.05 mmol), tris(dibenzylideneacetone)dipalladium(0) (41 mg, 45 μmol), and Na_2CO_3 (0.99 mL, 2.0 M aqueous solution) were combined in 1,2-dimethoxyethane (5 mL) under Ar and heated at reflux for 1 h. The mixture was cooled to room temperature, filtered through Celite, and washed with ether. The mixture was basified with concentrated NH_4OH and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated to dryness. The residue was purified by CC (hexane/EtOAc 2:1) to afford **10** (405 mg, 98%) as a yellowish solid: mp 45−46 °C; ^{1}H NMR δ 7.13 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 4.36 (dd, J = 1.8, 6.3 Hz, 1H), 3.77 (s, 1H), 3.55 (s, 3H), 3.51 (m, 1H), 2.72 (dd, J = 4.2, 18.9 Hz, 1H), 2.56 (s, 3H), 2.35 (s, 3H), 2.23−2.00 (m, 2H), 1.91 (d, J = 18.9 Hz, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ −5.1, −4.6, 18.4, 21.2, 26.0 (3C), 34.8, 35.5, 43.5, 51.3, 57.0, 68.3, 78.8, 126.2, 126.5 (2C), 128.7 (2C), 137.3, 137.8, 144.8, 168.3. Anal. ($C_{23}H_{35}NO_3Si$) C, H, N.

(±)-Methyl 7β-(*tert*-Butyldimethylsilyloxy)-3β-(*p*-tolyl)-tropane-2β-carboxylate (11a), (±)-Methyl 7β-(*tert*-Butyldimethylsilyloxy)-3α-(*p*-tolyl)tropane-2β-carboxylate (12a), (±)-Methyl 7β-(*tert*-Butyldimethylsilyloxy)-3β-(*p*-tolyl)-tropane-2α-carboxylate (13a), and (±)-Methyl 7β-(*tert*-Butyldimethylsilyloxy)-3α-(*p*-tolyl)tropane-2α-carboxylate (14a). To a solution of the aryl olefin **10** (40 mg, 0.10 mmol) in THF (2 mL) at −78 °C under N_2 was added SmI_2 (4.5 mL, 0.1 M in THF, 0.45 mmol). After stirring for 30 min, MeOH (anhydrous, 0.5 mL) was added. The mixture was stirred at −78 °C for another 2 h, then the reaction was quenched with acetic acid (0.5 mL). The mixture was basified with NH_4OH and extracted with ether, and the organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC (hexane/EtOAc 2:1), and the products **11a**−**14a** were obtained in a total yield of 85%. Compound **11a** (9 mg, 22.5%): white solid, mp 108−109 °C; ^{1}H NMR δ 7.14 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 4.42 (dd, J = 3.0, 6.9 Hz, 1H), 3.56 (m, 1H), 3.52 (s, 3H), 3.42 (m, 1H), 3.00 (m, 1H), 2.74−2.62 (m, 1H), 2.53 (s, 3H), 2.52−2.44 (m, 1H), 2.30 (s, 3H), 2.26−2.10 (m, 1H), 2.04 (dd, J = 7.2, 13.8 Hz, 1H), 1.59 (dt, J = 3.6 Hz (t), 12.3 Hz (d), 1H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR δ −4.8, −4.7, 17.8, 21.0, 25.7 (3C), 33.0, 34.5, 38.8, 43.0, 50.2, 63.5, 77.6, 127.1 (2C), 128.7 (2C), 135.3, 139.6, 171.6. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N. Compound **12a** (13 mg, 32.5%): yellowish solid, mp 74−75 °C; ^{1}H NMR δ 7.08 (s, 4H), 4.31 (dd, J = 3.0, 6.9 Hz, 1H), 3.50−3.28 (m, 2H), 3.20 (s, 1H), 2.58 (s, 3H), 2.56−2.49 (m, 1H), 2.45−2.33 (m, 1H), 2.30 (s, 3H), 2.18−2.06 (m, 1H), 1.98 (dd, J = 6.9, 13.8 Hz, 1H), 1.29 (m, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ −4.9, −4.8, 17.9, 21.0, 25.8 (3C), 36.2, 37.9, 41.9, 42.1, 51.8, 52.3, 60.2, 72.2, 81.5, 127.5 (2C), 129.0 (2C), 135.7, 140.7, 174.7. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N. Compound **13a** (7 mg, 17.5%): white solid, mp 90−92 °C; ^{1}H NMR δ 7.13 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 4.57 (dd, J = 2.7, 12.0 Hz, 1H), 3.54 (s, 3H), 3.43 (m, 1H), 3.27 (d, J = 2.4 Hz, 1H), 3.04 (dd, J = 2.7, 12.0 Hz), 2.90 (dt, J = 5.7 Hz (d), 12.3 Hz (t), 1H), 2.65 (s, 3H), 2.30 (s, 3H), 2.22−2.10 (m, 2H), 1.82 (t, J = 12.6 Hz, 1H), 1.56−1.43 (m, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR δ −5.0, −4.9, 18.0, 21.0, 25.8 (3C), 36.4, 37.1, 39.6, 40.3, 48.2, 51.5, 61.6, 71.6, 73.5, 127.4 (2C), 129.1 (2C), 136.0, 140.6, 173.3. Compound **14a** (5 mg, 12.5%): clear oil; ^{1}H NMR δ 7.08 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 4.64 (dd, J = 2.7, 6.9 Hz, 1H), 3.63−3.56 (m, 1H), 3.51 (s, 3H), 3.45−3.36 (m, 3H), 2.61 (s, 3H), 2.42−2.28 (m, 1H), 2.29 (s, 3H), 2.04−1.90 (m, 2H), 1.82 (dd, J = 6.9, 12.3 Hz, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR δ −5.0, −4.8, 17.8, 20.8, 25.8 (3C), 35.0, 35.5, 40.3, 41.6, 47.5, 51.2, 60.8, 70.1, 75.5, 127.3 (2C), 128.5 (2C), 135.1, 140.2, 174.0. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N.

Compound 14a by Hydrogenation of 10. Compound **10** (10 mg, 25 μmol) was dissolved in absolute MeOH (2 mL) and hydrogenated over 10% Pd/C at 40 psi for 8 h. TLC showed almost complete conversion. The catalyst was filtered off over Celite, and the solvent was evaporated. The residue was purified by CC (hexane/EtOAc 2:1−1:1) to give **14a** (8 mg, 80%) as a clear oil exhibiting the same spectroscopic data as above.

General Procedure for the Deprotection of *tert*-Butyldimethylsilyl Ethers. To a solution of the *tert*-butyldimethylsilyl ether in THF was added *n*-Bu_4NF (1.2 equiv, 1 M in THF) under N_2. The mixture was stirred at room temperature overnight and then concentrated, and the residue was dissolved in EtOAc followed by washing with water and brine. The organic phase was dried over $MgSO_4$ and concentrated, and the residue was purified by CC (CH_2Cl_2 saturated with concentrated NH_4OH) to give the free alcohol.

(±)-Methyl 7β-Hydroxy-3β-(*p*-tolyl)tropane-2β-carboxylate (11b). From the silyl ether **11a** (21 mg, 52 μmol), **11b** (13 mg, 87%) was obtained as a white solid: mp 148−149 °C; ^{1}H NMR δ 7.13 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 4.57 (dd, J = 3.9, 6.3 Hz, 1H), 3.64−3.59 (m, 1H), 3.51 (s, 3H), 3.57−3.49 (m, 1H), 3.04 (t, J = 3.9 Hz, 1H), 2.78−2.66 (m, 1H), 2.57 (s, 3H), 2.51 (dd, J = 2.7, 12.6 Hz, 1H), 2.30 (s, 3H), 2.22−2.12 (m, 2H), 1.93 (br s, 1H), 1.60 (dt, J = 3.6 Hz (t), 8.4 Hz (d), 1H); ^{13}C NMR δ 21.0, 32.1, 34.5, 38.3, 42.3, 59.8, 51.2, 63.2, 73.2, 127.0 (2C), 128.7 (2C), 135.4, 139.5, 171.6; MS m/z 289 (M^+), 245, 230, 186, 172, 158, 129, 115, 98, 82, 72, 58, 43. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-Methyl 7β-Hydroxy-3α-(*p*-tolyl)tropane-2β-carboxylate (12b). From the silyl ether **12** (18 mg, 45 μmol), **12b** (11 mg, 85%) was obtained as a white solid: mp 118−119 °C; ^{1}H NMR δ 7.08 (s, 4H), 4.28 (dd, J = 3.0, 5.4 Hz, 1H), 3.60 (s, 3H), 3.54−3.35 (m, 2H), 3.27 (s, 1H), 2.70 (s, 3H), 2.58−2.40 (m, 1H), 2.43−2.33 (m, 1H), 2.31 (s, 3H), 2.13−2.04 (m, 2H), 1.36 (dd, J = 9.3, 14.1 Hz, 1H); ^{13}C NMR δ 21.0, 35.3, 35.6, 39.4, 41.9, 50.7, 51.9, 57.2, 70.3, 79.1, 127.4 (2C), 129.1 (2C), 135.8, 141.3, 175.2; MS m/z 289 (M^+), 245, 230, 186, 170, 158, 145, 129, 112, 98, 82, 72, 58, 42. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-Methyl 7β-Hydroxy-3β-(*p*-tolyl)tropane-2α-carboxylate (13b). From the silyl ether **13** (17 mg, 42 μmol), **13b** (12 mg, 99%) was obtained as a white solid: mp 187−189 °C; ^{1}H NMR δ 7.12 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 4.55 (dd, J = 3.6, 6.3 Hz, 1H), 3.54 (s, 3H), 3.46−3.40 (m, 1H), 3.31 (d, J = 2.7 Hz, 1H), 3.13 (dd, J = 3.0, 12.0 Hz, 1H), 2.98 (dt, J = 6.0 Hz (d), 12.3 Hz (t), 1H), 2.68 (s, 3H), 2.30 (s, 3H), 2.45−2.20 (m, 2H), 2.16−1.80 (m, 2H), 1.44−1.34 (m, 1H); ^{13}C NMR δ 21.0, 32.0, 35.5, 37.1, 40.9, 44.2, 51.7, 59.5, 70.1, 72.4, 127.2 (2C), 129.2 (2C), 136.1, 140.5, 173.6; MS m/z 289 (M^+), 245, 230, 186, 172, 158, 145, 129, 115, 98, 72, 57, 42. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-Methyl 7β-Hydroxy-3α-(*p*-tolyl)tropane-2α-carboxylate (14b). A THF solution (1.0 mL) of silyl ether **14a** (16 mg, 39 μmol) was added to 48% aqueous HF (1.0 mL). After stirring at room temperature overnight, the mixture was poured into NH_4OH (6.0 mL) and extracted with $CHCl_3$. The combined extracts were dried, and the solvent was removed. Purification of the crude product by CC (CH_2Cl_2 saturated with concentrated NH_4OH) gave **14b** (9 mg, 79%) as a white solid: mp 103−104 °C; ^{1}H NMR δ 7.09 (d, J = 8.4 Hz, 2H), 7.04 (d,

J = 8.4 Hz, 2H), 4.73 (dd, J = 3.0, 6.9 Hz, 1H), 3.72−3.62 (m, 1H), 3.53 (s, 3H), 3.44−3.36 (m, 2H), 3.36−3.29 (m, 1H), 2.62 (s, 3H), 2.52−2.40 (m, 1H), 2.30 (s, 3H), 1.99−1.78 (m, 4H); ^{13}C NMR δ 20.8, 32.1, 35.4, 37.6, 39.2, 42.0, 51.4, 58.9, 68.8, 74.0, 127.2 (2C), 128.7 (2C), 135.2, 140.8, 174.4; MS m/z 289, 245, 230, 186, 171, 158, 145, 129, 115, 98, 84, 58. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-Methyl 7β-Hydroxy-8-methyl-3-(*p*-tolyl)-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylate (15). Compound **10** (40 mg, 0.10 mmol) was deprotected according to the general procedure to give product **15** (26 mg, 91%) as a white solid: mp 124−126 °C; ^{1}H NMR δ 7.13 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 7.8 H, 2H), 4.29 (dd, J = 3.6, 4.2 Hz, 1H), 3.74 (s, 1H), 3.53 (s, 3H), 3.44−3.36 (m, 1H), 2.66 (dd, J = 4.2, 19.2 Hz, 1H), 2.49 (s, 3H), 2.34 (s, 3H), 2.17 (s, 1H), 2.13−2.05 (m, 2H), 1.88 (d, J = 18.9 Hz, 1H); ^{13}C NMR δ 21.2, 33.4, 33.9, 43.1, 51.4, 55.5, 67.7, 77.7, 125.1, 126.5 (2C), 128.8 (2C), 137.4, 137.6, 144.5, 168.4. Anal. ($C_{17}H_{21}NO_3$) C, H, N.

(±)-Methyl 8-Methyl-7-oxo-3-(*p*-tolyl)-8-azabicyclo[3.2.1]-oct-2-ene-2-carboxylate (16). Oxalyl chloride (122 μL, 1.40 mmol) was dissolved in 5 mL of anhydrous methylene chloride, and the solution was cooled to −78 °C. Dimethyl sulfoxide (0.40 mL, 2.8 mmol) was added. After 5 min, compound **15** (200 mg, 0.70 mmol) in dry CH_2Cl_2 (2.0 mL) was added, and stirring was continued for another 30 min. The reaction was quenched by adding Et_3N (2.0 mL), then the solution was warmed to room temperature and washed with water, and the aqueous phase was extracted several times with CH_2Cl_2. The combined organic phases were washed with saturated NH_4Cl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by CC (Et_2O/Et_3N 99:1−9:1) gave ketone **16** (193 mg, 97%) as a clear oil: ^{1}H NMR δ 7.10 (d, J = 7.8 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 4.10 (s, 1H), 3.50 (s, 3H), 3.68−3.44 (m, 2H), 2.96−2.69 (m, 2H), 2.41 (s, 3H), 2.30 (s, 3H), 2.18 (d, J = 18.3 Hz, 1H), 2.12 (d, J = 19.2 Hz, 1H); ^{13}C NMR δ 21.2, 34.2, 35.7, 42.8, 51.7, 55.0, 65.9, 121.9, 126.5 (2C), 128.8 (2C), 137.3, 137.9, 147.7, 166.6, 207.5; MS m/z 257 (M^+-CO), 242, 229, 210, 198, 182, 167, 157, 141, 128, 115, 105, 91, 42. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

(±)-Methyl 7α-Hydroxy-8-methyl-3-(*p*-tolyl)-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylate (17). $NaBH_4$ (47 mg, 1.33 mmol) was added cautiously with stirring to a solution of ketone **16** (190 mg, 0.67 mmol) in MeOH at 0 °C. The mixture was allowed to warm to room temperature overnight and then concentrated. The residue was dissolved in EtOAc (50 mL), and the solution was washed with water and brine. After drying over $MgSO_4$ and concentration, the residue was purified by CC (CH_2Cl_2 saturated with concentrated NH_4OH) to give the 7α-alcohol **17** (162 mg, 85%) as a white solid together with compound **15** (11 mg, 6%). Compound **17**: mp 113−114 °C; ^{1}H NMR δ 7.13 (d, J = 7.8 Hz, 2H), 7.06 (d, J = 7.8 Hz, 2H), 4.65 (m, 1H), 3.88 (d, J = 5.4 Hz, 1H), 3.48 (s, 3H), 3.31−3.22 (m, 1H), 3.02 (br s, 1H), 2.80 (dd, J = 3.9, 18.9 Hz, 1H), 2.72−2.62 (m, 1H), 2.44 (s, 3H), 2.35 (s, 3H), 2.08 (d, J = 19.2 Hz, 1H), 1.40 (dd, J = 4.5, 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 34.7, 35.1, 40.4, 51.5, 56.5, 64.1, 77.1, 125.3, 126.6 (2C), 128.7 (2C), 137.4, 137.8, 145.0, 170.3. Anal. ($C_{17}H_{21}NO_3$) C, H, N.

(±)-Methyl 7α-(*tert*-Butyldimethylsilyloxy)-8-methyl-3-(*p*-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (18). Compound **17** (160 mg, 0.56 mmol) was silylated in the same manner as described for compound **5** and purified by CC (hexane/EtOAc 2:1−1:1) to furnish the product **18** (89%) as a clear oil: ^{1}H NMR δ 7.14 (d, J = 7.8 Hz, 2H), 7.06 (d, J = 7.8 Hz, 2H), 4.65−4.66 (m, 1H), 4.07 (d, J = 5.4 Hz, 1H), 3.43 (s, 3H), 3.25 (dd, J = 4.8, 6.9 Hz, 1H), 2.68−2.50 (m, 2H), 2.40 (s, 3H), 2.36 (s, 3H), 2.12 (d, J = 18.9 Hz, 1H), 1.36 (dd, J = 4.8, 12.9 Hz, 1H), 0.83 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ −5.2, −5.0, 18.0, 21.2, 25.7 (3C), 34.6, 35.7, 41.0, 50.9, 56.6, 63.6, 77.6, 126.2, 126.9 (2C), 128.6 (2C), 137.0, 138.7, 144.4, 168.9.

(±)-Methyl 7α-(*tert*-Butyldimethylsilyloxy)-3α-(*p*-tolyl)-tropane-2β-carboxylate (19a). The aryl olefin **18** (40 mg, 0.10 mmol) was treated with SmI_2 as described for compound **10**. After purification, compound **19a** was obtained by CC (ether/Et_3N 99:1) as a white solid in a yield of 66%. The mother liquor contained predominantly compound **20a** together with a minor component in a ratio of 3:1 (^{1}H NMR). To a solution of the evaporated mother liquor (20 mg) in dry MeOH (2.0 mL) was added under N_2 30% NaOMe/MeOH (0.1 mL). The mixture was refluxed for 24 h, cooled to room temperature, and concentrated. CH_2Cl_2 and saturated NH_4Cl were added, the phases were separated, and the organic layer was washed with brine and concentrated. Purification of the residue by TLC (ether/Et_3N 99:1) afforded compound **19a** (15 mg, 100%): mp 113−115 °C; ^{1}H NMR δ 7.16 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.63 (m, 1H), 3.55 (s, 3H), 3.57−3.46 (m, 1H), 3.42−3.17 (m, 3H), 2.73−2.60 (m, 1H), 2.56−2.47 (m, 1H), 2.47 (s, 3H), 2.31 (s, 3H), 1.54−1.41 (m, 2H), 0.95 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ −5.1, −4.8, 18.0, 21.0, 25.8 (3C), 35.2, 39.1, 40.0, 41.0, 44.1, 51.4, 57.8, 66.1, 71.2, 128.0 (2C), 129.0 (2C), 135.4, 142.7, 176.6. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N.

(±)-Methyl 7α-Hydroxy-3α-(*p*-tolyl)tropane-2β-carboxylate (19b) was obtained (15 mg, 77%) as an oil in a similar manner as for the prepation of **11b** after purification by CC (CH_2Cl_2 saturated with concentrated NH_4OH): ^{1}H NMR δ 7.17 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 4.80−4.68 (m, 1H), 3.56 (s, 3H), 3.52−3.34 (m, 3H), 3.22 (t, J = 7.8 Hz, 1H), 2.80−2.64 (m, 1H), 2.58−2.47 (m, 1H), 2.45 (s, 3H), 1.82 (br s, 1H), 1.45−1.30 (m, 2H); ^{13}C NMR δ 21.0, 35.3, 39.3, 39.9, 40.2, 44.2, 51.8, 58.0, 66.0, 70.8, 128.0 (2C), 129.1 (2C), 135.7, 141.9, 176.2. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-9-Methyl-3α-(*p*-tolyl)-6-oxa-9-azatricyclo[5.2.1.0^{4,8}]-decan-5-one (20b) was obtained from **18** in 78% yield (9 mg) by catalytic hydrogenation using a procedure similar to that for the conversion of **10** to **14**, or by SmI_2 reduction of **18** followed by treatment of the mixture of minor product stereoisomers with n-Bu_4NF: ^{1}H NMR δ 7.12 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 5.18 (t, J = 7.2 Hz, 1H), 4.02 (m, 1H), 3.60−3.38 (m, 2H), 3.00 (dd, J = 6.9, 8.7 Hz, 1H), 2.58−2.30 (m, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.79 (d, J = 14.4 Hz, 1H), 1.66 (t, J = 13.8 Hz, 1H), 1.59 (br s, 1H); ^{13}C NMR δ 21.1, 33.6, 36.0, 38.0, 41.1, 45.4, 59.6, 66.9, 77.2, 81.7, 128.2 (2C), 128.9 (2C), 136.2, 136.5, 176.4; MS m/z 257 (M^+), 242, 228, 213, 198, 184, 172, 156, 139, 115, 81, 57, 42.

(±)-Methyl 6β-(*tert*-Butyldimethylsilyloxy)-8-methyl-3-(trifluoromethanesulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (21). Using a procedure similar to that for the preparation of **9**, triflate **21** (470 mg, 62%) was obtained after CC (hexane/EtOAc 9:1) as an oil: ^{1}H NMR δ 4.13 (dd, J = 3.9, 7.5 Hz, 1H), 4.01 (d, J = 6.0 Hz, 1H), 3.81 (s, 3H), 3.26 (d, J = 5.4 Hz, 1H), 2.82 (dd, J = 5.4, 18.9 Hz, 1H), 2.50−2.38 (m, 4H), 2.16−2.04 (m, 1H), 1.99 (d, J = 18.9 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ −4.9, −4.8, 18.2, 25.8 (3C), 29.3, 34.9, 47.5, 52.2, 60.4, 66.4, 78.1, 118.2 (q, J = 318 Hz), 125.8, 147.4, 163.6.

(±)-Methyl 6β-(*tert*-Butyldimethylsilyloxy)-8-methyl-3-(*p*-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (22). Using a procedure similar to that for the preparation of **10**, aryl olefin **22** (400 mg, 97%) was obtained after CC (silica gel, hexane/EtOAc 2:1) as an oil: ^{1}H NMR δ 7.13 (d, J = 7.8 Hz, 2H), 7.03 (d, J = 7.8 Hz, 2H), 4.22 (dd, J = 3.6, 7.2 Hz, 1H), 3.92 (d, J = 6.0 Hz, 1H), 3.51 (s, 3H), 3.19 (d, J = 5.1 Hz, 1H), 2.72 (dd, J = 5.4, 19.5 Hz, 1H), 2.51 (s, 3H), 2.47 (dd, J = 4.5, 12.6 Hz, 1H), 2.35 (s, 3H), 2.16−2.08 (m, 1H), 2.04 (d, J = 19.2 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ −4.7 (2C), 18.3, 21.2, 25.9 (3C), 33.0, 35.7, 47.2, 51.3, 60.9, 66.6, 79.0, 126.6 (2C), 128.7 (2C), 130.5, 137.4, 137.7, 142.2, 168.5.

(±)-Methyl 6β-(*tert*-Butyldimethylsilyloxy)-3β-(*p*-tolyl)-tropane-2β-carboxylate (23a), (±)-Methyl 6β-(*tert*-Butyldimethylsilyloxy)-3α-(*p*-tolyl)tropane-2β-carboxylate (24a), and (±)-Methyl 6β-(*tert*-Butyldimethylsilyloxy)-3β-(*p*-tolyl)tropane-2α-carboxylate (25a) were obtained from **22** using a procedure similar to that for the preparation of **11a**-**14a**. Compound **23a** (38 mg, 38%): mp 68−70 °C; ^{1}H NMR δ 7.13 (d, 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.33 (dd, J = 3.0, 6.9 Hz, 1H), 3.77 (d, J = 5.4 Hz, 1H), 3.50 (s, 3H), 3.23 (br s, 1H), 2.86−2.80 (m, 1H), 2.80−2.68 (m, 1H), 2.55 (s, 3H), 2.55−2.44 (m, 1H), 2.30 (s, 3H), 2.25 (dd, J = 3.0, 6.9 Hz, 1H),

2.17 (dd, J = 6.9, 12.6 Hz, 1H), 1.76 (dt, J = 3.9 Hz (t), 12.6 Hz (d), 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ −4.9 (2C), 17.8, 20.9, 25.7 (3C), 31.2, 34.2, 39.2, 43.1, 51.1, 51.8, 66.4, 70.9, 77.4, 126.9 (2C), 128.7 (2C), 135.3, 139.5, 172.0. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N. Compound **24a** (48 mg, 48%): mp 96−97 °C; ^{1}H NMR δ 7.08 (s, 4H), 4.21 (dd, J = 2.7, 6.6 Hz, 1H), 3.59 (s, 3H), 3.58−3.48 (m, 1H), 3.35 (dd, J = 9.6, 18.0 Hz, 1H), 3.14 (d, J = 9.3 Hz, 1H), 2.30 (s, 3H), 2.26−2.14 (m, 1H), 2.08 (dd, J = 6.9, 13.8 Hz, 1H), 1.42−1.23 (m, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ −4.9 (2C), 17.8, 20.9, 25.7 (3C), 34.9, 36.4, 42.1, 42.3, 51.7, 55.3, 63.8, 68.3, 81.5, 127.4 (2C), 129.0 (2C), 135.7, 140.6, 175.0. Compound **25a** (5.2 mg, 5.2%): mp 195−198 °C; ^{1}H NMR δ 7.14 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.35 (dd, J = 2.7, 7.5 Hz, 1H), 3.65−3.56 (m, 1H), 3.51 (s, 3H), 3.09 (m, 1H), 3.04 (dd, J = 2.7, 11.7 Hz, 1H), 2.85 (dt, J = 6.3 Hz (d), 12.0 Hz (t), 1H), 2.66 (s, 3H), 2.39 (dd, J = 7.5, 14.1 Hz, 1H), 2.30 (s, 3H), 1.97 (ddd, J = 2.4, 6.9, 13.8 Hz, 1H), 1.79 (dt, J = 3.0 Hz (d), 13.2 Hz (t), 1H), 1.61 (ddd, J = 2.7, 6.0, 13.5 Hz, 1H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ −4.8, −4.7, 18.0, 21.0, 28.8 (3C), 34.3, 36.9, 37.2, 39.4, 48.9, 51.5, 64.2, 69.4, 76.7, 127.4 (2C), 129.1 (2C), 136.0, 140.5, 173.4.

(±)-Methyl 6*β*-(*tert*-Butyldimethylsilyloxy)-3α-(*p*-tolyl)-tropane-2α-carboxylate (26a). Using a hydrogenation reaction similar to that described for the preparation of **14a**, **26a** (15 mg, 76%) was obtained from **22** after CC (hexane/EtOAc 1:1) as an oil: ^{1}H NMR δ 7.10 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 4.03 (dd, J = 3.3, 7.2 Hz, 1H), 3.78−3.66 (m, 1H), 3.60−3.50 (m, 1H), 3.50−3.38 (m, 4H), 3.09 (d, J = 5.7 Hz, 1H), 2.62 (s, 3H), 2.29 (s, 3H), 2.42−2.29 (m, 2H), 2.08−1.96 (m, 1H), 0.80 (s, 9H), −0.06 (s, 3H), −0.07 (s, 3H); ^{13}C NMR δ −5.0, −4.9, 17.9, 20.8, 25.7 (3C), 32.5, 34.8, 37.0, 41.1, 48.3, 51.1, 62.1, 68.9, 79.0, 127.3 (2C), 128.5 (2C), 135.1, 139.9, 174.0. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N.

(±)-Methyl 6*β*-Hydroxy-3*β*-(*p*-tolyl)tropane-2*β*-carboxylate (23b), (±)-Methyl 6*β*-Hydroxy-3*β*-(*p*-tolyl)tropane-2α-carboxylate (24b), and (±)-Methyl 6*β*-Hydroxy-3α-(*p*-tolyl)tropane-2*β*-carboxylate (25b) were from **23a**, **24a**, and **25a**, respectively, by the General Procedure for desilylation with n-Bu$_4$NF. Compound **23b** (13 mg, 91%): mp 169−171 °C; ^{1}H NMR δ 7.12 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 4.47 (dd, J = 3.9, 6.0 Hz, 1H), 3.83 (br s, 1H), 3.50 (s, 3H), 3.31 (br s, 1H), 2.83 (m, 1H), 2.75 (m, 1H), 2.58 (s, 3H), 2.51 (dd, J = 3.3, 12.6 Hz, 1H), 2.30 (s, 3H), 2.27 (m, 2H), 1.86 (br s, 1H), 1.78 (m, 1H); ^{13}C NMR δ 21.0, 30.7, 38.7, 42.5, 51.2, 51.4, 66.2, 70.6, 77.3, 126.9 (2C), 128.7 (2C), 135.4, 139.5, 172.0. Anal. ($C_{17}H_{23}NO_3$) C, H, N. Compound **24b** (12 mg, 93%): mp 102−104 °C; ^{1}H NMR δ 7.09 (br s, 4H), 4.25 (br s, 1H), 3.64 (m, 1H), 3.61 (s, 3H), 3.45 (m, 1H), 3.20 (d, J = 9.0 Hz, 1H), 2.68 (s, 3H), 2.47 (d, J = 9.0 Hz, 1H), 2.35 (m, 1H), 2.18 (m, 2H), 1.98 (br s, 1H), 1.39 (m, 1H); ^{13}C NMR δ 20.9, 33.0, 35.7, 40.6, 42.2, 51.8, 54.3, 62.0, 67.3, 79.9, 127.4 (2C), 129.1 (2C), 135.8, 141.0, 175.1. Anal. ($C_{17}H_{23}NO_3$) C, H, N. Compound **25b** (11 mg, 97%): mp 222−223 °C; ^{1}H NMR δ 7.13 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 4.34 (br d, J = 6.0 Hz, 1H), 3.58 (br d, J = 6.9 Hz, 1H), 3.52 (s, 3H), 3.14 (m, 2H), 2.93 (ddd, J = 6.0, 12.0, 12.6 Hz, 1H), 2.70 (s, 3H), 2.52 (dd, J = 7.2, 14.1 Hz, 1H), 2.30 (s, 3H), 2.18 (br s, 1H), 1.87 (m, 2H), 1.55 (ddd, J = 2.1, 6.0, 13.8 Hz, 1H); ^{13}C NMR δ 21.0, 30.0, 35.4, 37.2, 37.6, 44.6, 51.6, 62.3, 67.8, 75.5, 127.3 (2C), 129.2 (2C), 136.1, 140.6, 173.7. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-Methyl 6*β*-Hydroxy-3α-(*p*-tolyl)tropane-2α-carboxylate (26b) was obtained (13 mg, 90%) from **26a** by desilylation with HF as described for the preparation of **14b**: mp 107−109 °C; ^{1}H NMR δ 7.09 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 4.09 (dd, J = 3.0, 7.2 Hz, 1H), 3.74 (m, 1H), 3.63 (m, 1H), 3.48 (s, 3H), 3.46 (m, 1H), 3.17 (m, 1H), 2.68 (s, 3H), 3.63 (dd, J = 6.9, 14.4 Hz, 1H), 2.46 (m, 1H), 2.32 (br s, 1H), 2.00 (m, 2H); ^{13}C NMR δ 20.8, 30.4, 34.8, 37.1, 38.5, 44.6, 51.3, 60.8, 68.1, 77.2, 127.4 (2C), 128.7 (2C), 135.4, 139.9, 173.9. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-Methyl 6*β*-Hydroxy-8-methyl-3-(*p*-tolyl)-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylate (27). Compound **27** (279 mg) was obtained from **22** in 97% yield by desilylation with n-Bu$_4$NF: mp 144−146 °C; ^{1}H NMR δ 7.13 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 4.23−4.10 (m, 1H), 3.93 (d, J = 6.6 Hz, 1H), 3.50 (s, 3H), 3.21 (d, J = 5.4 Hz, 1H), 2.67 (dd, J = 5.1, 19.5 Hz, 1H), 2.54 (dd, J = 7.5, 13.2 Hz, 1H), 2.47 (s, 3H), 2.34 (s, 3H), 2.09 (d, J = 19.5 Hz, 1H), 2.06−1.98 (m, 1H); ^{13}C NMR δ 21.2, 31.5, 34.3, 51.3, 59.9, 66.0, 77.9, 126.5 (2C), 128.7 (2C), 129.5, 137.4 (2C), 142.4, 168.4.

(±)-Methyl 8-Methyl-6-oxo-3-(*p*-tolyl)-8-azabicyclo[3.2.1]-oct-2-ene-2-carboxylate (28) was prepared from **27** in 97% (268 mg) yield using a procedure similar to that for the preparation of **16**: ^{1}H NMR δ 7.12 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 4.17 (d, J = 6.3 Hz, 1H), 3.50 (s, 3H), 3.45 (d, J = 5.4 Hz, 1H), 2.83 (dd, J = 6.3, 17.4 Hz, 1H), 2.70 (dd, J = 5.7, 19.5 Hz, 1H), 2.53 (s, 3H), 2.52−2.42 (m, 1H), 2.34 (s, 3H), 2.28 (d, J = 19.5 Hz, 1H); ^{13}C NMR δ 21.1, 29.8, 34.9, 47.7, 51.4, 58.6, 64.5, 126.5 (2C), 128.7 (2C), 129.4, 136.8, 137.7, 144.2, 167.8, 215.5. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

(±)-Methyl 6α-Hydroxy-8-methyl-3-(*p*-tolyl)-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylate (29) was obtained from **28** in 77% yield (202 mg) besides 15% of **27** by $NaBH_4$ reduction as described in the preparation of compound **17**: ^{1}H NMR δ 7.12 (d, J = 7.8 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 4.66−4.54 (m, 1H), 3.75 (d, J = 6.6 Hz, 1H), 3.54 (m, 1H), 3.48 (s, 1H), 3.38 (m, 1H), 2.70 (d, J = 19.5 Hz, 1H), 2.65−2.53 (m, 1H), 2.46 (s, 3H), 2.34 (s, 3H), 2.46−2.37 (m, 1H), 1.65 (dd, J = 1.8, 13.2 Hz, 1H); ^{13}C NMR δ 21.1, 26.7, 34.7, 43.5, 51.2, 59.1, 61.6, 72.1, 126.5 (2C), 128.5 (2C), 129.0, 137.2, 137.7, 145.0, 168.6. Anal. ($C_{17}H_{21}NO_3$) C, H, N.

(±)-Methyl 6α-(*tert*-Butyldimethylsilyloxy)-8-methyl-3-(*p*-tolyl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylate (30) was obtained in 85% yield (119 mg) by silylation of **29** in a similar fashion as described in the preparation of **18**: ^{1}H NMR δ 7.14 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 4.64−4.54 (m, 1H), 3.76 (d, J = 6.6 Hz, 1H), 3.50 (s, 3H), 3.33 (dd, J = 5.4, 5.7 Hz, 1H), 2.67 (d, J = 19.2 Hz, 1H), 2.61−2.50 (m, 1H), 2.48 (s, 3H), 2.36 (s, 3H), 1.64 (dd, J = 5.4, 12.6 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ −5.0, −4.8, 18.0, 21.2, 25.9 (3C), 27.5, 35.0, 44.1, 51.2, 59.2, 62.0, 73.2, 126.5 (2C), 128.6 (2C), 129.0, 136.9, 138.6, 146.1, 168.4.

(±)-Methyl 6α-(*tert*-Butyldimethylsilyloxy)-3*β*-(*p*-tolyl)-tropane-2*β*-carboxylate (31a), (±)-Methyl 6α-(*tert*-Butyldimethylsilyloxy)-3α-(*p*-tolyl)tropane-2*β*-carboxylate (32a), and (±)-Methyl 6α-(*tert*-Butyldimethylsilyloxy)-3*β*-(*p*-tolyl)tropane-2α-carboxylate (33a) were obtained in 6, 69, and 17.5% yield, respectively, by SmI_2 reduction of **30** (297 μmol) using a similar procedure as in the preparation of **11a**. The products were purified by CC (hexane/EtOAc 2:1−1:1). Compound **31a**: ^{1}H NMR δ 7.18 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 4.74 (m, 1H), 3.50 (s, 3H), 3.50−3.40 (m, 1H), 3.19 (m, 1H), 2.95 (m, 1H), 2.80−2.64 (m, 1H), 2.43 (dt, J = 3.3 Hz (d), 12.9 Hz (t), 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.06 (dt, J = 3.6 Hz (t), 12.3 Hz (d), 1H), 1.58 (dd, J = 3.3, 13.8 Hz, 1H), 0.85 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ −5.0, −4.9, 17.9, 21.0, 25.8 (3C), 28.3, 33.6, 36.3, 42.0, 51.0, 52.4, 64.2, 64.9, 71.7, 127.1 (2C), 128.6 (2C), 134.8, 140.5, 172.6. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N. Compound **32a**: ^{1}H NMR δ 7.16 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.59 (m, 1H), 3.56 (s, 3H), 3.36−3.14 (m, 3H), 2.80−2.66 (m, 1H), 2.52 (d, J = 11.1 Hz, 1H), 2.31 (s, 3H), 2.34−2.25 (m, 1H), 1.99 (dt, J = 8.7 Hz (t), 14.1 Hz (d), 1H), 1.46 (dd, J = 3.9, 13.5 Hz, 1H), 0.93 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ −5.0, −4.8, 18.0, 21.0, 25.8 (3C), 27.1, 36.0, 40.7, 40.8, 51.6, 57.1, 61.9, 62.1, 71.0, 127.9 (2C), 129.0 (2C), 135.6, 142.0, 175.4. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N. Compound **33a**: ^{1}H NMR δ 7.18 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 4.60 (m, 1H), 3.51 (s, 3H), 3.62−3.40 (m, 2H), 3.37−3.24 (m, 1H), 3.18 (m, 1H), 2.62 (s, 3H), 2.46−2.35 (m, 1H), 2.31 (s, 3H), 1.94−1.76 (m, 3H), 0.95 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ −5.1, −4.8, 18.0, 21.1, 29.9 (3C), 28.7, 35.3, 36.1, 37.0, 45.8, 51.4, 61.8, 63.0, 71.7, 127.4 (2C), 129.2 (2C), 135.8, 141.6, 173.9.

(±)-Methyl 6α-(*tert*-Butyldimethylsilyloxy)-3α-(*p*-tolyl)-tropane-2α-carboxylate (34a) was obtained (18 mg, 89%) from **30** by hydrogenation similarly as described for the preparation of **14a**: ^{1}H NMR δ 7.30 (d, J = 8.1 Hz, 2H), 7.03

(d, J = 8.1 Hz, 2H), 4.55 (m, 1H), 3.63−3.44 (m, 2H), 3.34 (dd, J = 6.6, 6.9 Hz, 1H), 3.28 (s, 3H), 3.09 (t, J = 6.9 Hz, 1H), 2.58−2.50 (m, 1H), 2.48 (s, 3H), 2.44−2.33 (m, 1H), 2.28 (s, 3H), 2.14−2.02 (m, 1H), 1.91 (dd, J = 5.4, 14.4 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ −5.0, −4.9, 18.0, 20.9, 23.2, 25.8 (3C), 33.1, 34.2, 38.7, 47.3, 50.6, 59.6, 61.9, 71.8, 128.4 (2C), 128.6 (2C), 135.0, 140.9, 173.3. Anal. ($C_{23}H_{37}NO_3Si$) C, H, N.

(±)-Methyl 6α-Hydroxy-3β-(*p*-tolyl)tropane-2β-carboxylate (31b), (±)-Methyl 6α-Hydroxy-3α-(*p*-tolyl)tropane-2β-carboxylate (32b), and (±)-Methyl 6α-Hydroxy-3β-(*p*-tolyl)tropane-2α-carboxylate (33b) were obtained from **31a**, **32a**, and **33a**, respectively, by the General Procedure for desilylation with n-Bu_4NF in yields of 85%, 88%, and 82%. Compound **31b** (7.3 mg): ^{1}H NMR δ 7.18 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.88 (m, 1H), 3.50 (s, 3H), 3.58−3.40 (m, 1H), 3.28 (m, 1H), 3.00 (m, 1H), 2.80 (ddd, J = 7.5, 10.5, 14.1 Hz, 1H), 2.52 (dd, J = 6.3, 12.6 Hz, 1H), 2.34 (s, 3H), 2.99 (s, 3H), 2.08 (dt, J = 3.9 Hz (t), 12.6 Hz (d), 1H), 1.69 (dd, J = 3.9, 14.1 Hz, 1H), 1.64 (s, 1H); ^{13}C NMR δ 21.0, 27.7, 33.5, 35.6, 42.0, 51.1, 52.4, 64.2, 64.4, 71.7, 127.0 (2C), 128.6 (2C), 135.0, 140.1, 172.5. Anal. ($C_{17}H_{23}NO_3$) C, H, N. Compound **32b** (14 mg): mp 123−124 °C; ^{1}H NMR δ 7.19 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 4.73 (m, 1H), 3.59 (s, 3H), 3.43−3.23 (m, 3H), 2.83 (ddd, J = 7.5, 9.6, 13.8 Hz, 1H), 2.60 (d, J = 10.5 Hz, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 2.28−2.16 (m, 1H), 2.14−2.00 (m, 1H), 1.71 (s, 1H), 1.53 (dd, J = 4.2, 13.8 Hz, 1H); ^{13}C NMR δ 21.0, 27.2, 35.9, 39.8, 40.9, 51.7, 56.7, 61.8, 62.1, 70.8, 127.9, 129.1, 135.8, 141.4, 175.3. Anal. ($C_{17}H_{23}NO_3$) C, H, N. Compound **33b** (8.8 mg): mp 153−154 °C; ^{1}H NMR δ 7.20 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 4.70 (m, 1H), 3.52 (s, 3H), 3.57−3.44 (m, 1H), 3.40 (dd, J = 2.4, 7.2 Hz, 1H), 2.25 (dd, J = 2.7, 12.0 Hz, 1H), 3.21 (dd, J = 3.0, 6.3 Hz, 1H), 2.63 (s, 3H), 2.47 (ddd, J = 7.5, 10.5, 13.5 Hz, 1H), 2.31 (s, 3H), 1.93−1.74 (m, 2H), 1.62 (br s, 1H); ^{13}C NMR δ 21.0, 28.3, 34.7, 36.2, 37.0, 46.0, 51.5, 61.8, 62.5, 71.7, 127.4 (2C), 129.1 (2C), 135.9, 141.2, 173.9. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(±)-Methyl 6α-Hydroxy-3α-(*p*-tolyl)tropane-2α-carboxylate (34b) was obtained (11 mg, 77%) from **34a** by desilylation with HF as described for the preparation of **14b**: ^{1}H NMR δ 7.17 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 4.63 (m, 1H), 3.66−3.42 (m, 3H), 3.39 (s, 3H), 3.31 (dd, J = 7.8, 8.1 Hz, 1H), 3.01 (br s, 1H), 2.64−2.49 (m, 2H), 2.41 (s, 3H), 2.31 (s, 3H), 2.08 (dt, J = 8.1 Hz (t), 14.4 Hz (d), 1H), 1.52 (dd, J = 2.7, 15.0 Hz, 1H); ^{13}C NMR δ 20.8, 23.8, 34.0, 34.2, 40.5, 50.4, 51.5, 60.0, 62.2, 71.4, 128.0 (2C), 128.8 (2C), 135.7, 138.7, 175.5. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

Locomotor Assay Method. The dose range finding experiment for **12b** was conducted according to the MDD locomotor activity studies standard operating procedure (SOP, Nov. 13, 1992). The study was conducted using 16 Digiscan locomotor activity testing chambers (40.5 × 40.5 × 30.5 cm). Panels of infrared beams (16 beams) and corresponding photodetectors were located in the horizontal direction along the sides of each activity chamber. Separate groups of eight nonhabituated male Swiss-Webster mice were injected via the intraperitoneal (i.p.) route with either vehicle (methylcellulose) or **12b** (10 or 100 mg/kg), immediately prior to locomotor activity testing. In all studies, horizontal activity (interruption of 1 photocell beam) was measured for 1 h within 10 min sample periods. Testing was conducted with one mouse per activity chamber.

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Supporting Information Available: X-ray structures of compounds **17**, **19a**, **12b**, and **24a**, tables of crystal data, atomic coordinates, bond lengths and angles, anisotropic and isotropic displacement parameters, and hydrogen coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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