Synthesis, Dopamine Transporter Affinity, Dopamine Uptake Inhibition, and Locomotor Stimulant Activity of 2-Substituted 3β-Phenyltropane Derivatives

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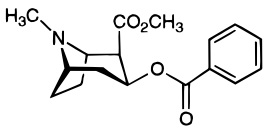
Received October 23, 1996[⊗]

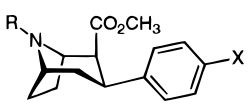
A series of 2β-substituted 3β-phenyltropanes were synthesized as analogs of cocaine and tested *in vitro* for their ability to displace bound [^{3}H]WIN 35,428 (**2b**) and inhibit dopamine uptake in rat caudate-putamen tissue. The analogs bound with high affinity (K_i = 11−22 nM) to the dopamine transporter. Increased lipophilicity at the β-C(2)-position was found to lead to increased binding affinity and increased dopamine uptake potency. However, a direct correlation between clogP values and binding affinity and potency of uptake inhibition was not observed. The unsaturated ester **7** was found to possess weak dopamine uptake inhibition relative to the high binding affinity (IC_{50}/K_i = 10.2). *In vivo* measurement of stimulated locomotor activity and drug discrimination against cocaine (10 mg/kg, ip) with selected analogs (**4**, **6**, and **7**) demonstrated that the behavioral effects of these drugs were approximately equipotent with those of cocaine. The structure−activity relationships of this series of cocaine analogs supports a pharmacophore model in which lipophilic interactions between the β-C(2)-position of 3β-phenyltropanes and the cocaine binding site on the dopamine transporter lead to enhanced potency while electrostatic interactions have a nonspecific effect.

Introduction

The structural elucidation of the cocaine pharmacophore has been the subject of numerous studies. Derivatives of cocaine (**1**) and 2-substituted 3-phenyltropanes (**2**) have proven to be useful probes for exploring the topology of the cocaine binding sites on biogenic amine transporters.[1−12] To date, most of these studies have focused on the structure−activity relationships (SAR) of these tropane derivatives at the cocaine binding site on the dopamine transporter (DAT) due to evidence which closely links inhibition of dopamine uptake with the reinforcing properties and other behavioral effects of cocaine.[13−16]



(-)-cocaine **1**



2a X = H; R = CH_3
2b X = F; R = C[^{3}H]$_3$

Our initial work in this area was to explore the relative proximal effect of the 2β-carbomethoxy group of several 3β-phenyltropane derivatives on binding affinity and [^{3}H]dopamine uptake inhibition.[8] From this study we proposed that a large lipophilic pocket was present at the binding site capable of accommodating large substituents at the β-C(2)-position of the ligand. In addition, we concluded that lipophilicity of substituents at the β-C(2)-position of 3β-phenyltropanes was important for binding while H-bonding between the substituent and the binding site was not an essential feature for high-affinity binding. This latter point has been illustrated by a series of 2β-alkyl-3β-phenyltropane derivatives prepared and studied by Kozikowski *et al.*[3,4,10] Additional studies have also demonstrated the importance of lipophilicity at the β-C(2)-position on DAT selectivity.[9] However, a recent study by Carroll *et al.* has demonstrated for a series of 2β-heterocyclic 3β-(4′-substituted phenyl)tropane derivatives that electrostatic interactions between the β-C(2)-substituent and the binding site significantly contributed to the binding potency of the ligands while lipophilic interactions were of less importance.[6,12]

It was of interest to explore the apparent dichotomy of substituent effects on binding affinity. To that end, a series of 2β-substituted congeners were synthesized with substituents that varied in lipophilicity. The biological activity of these compounds was assessed by examining the affinity at cocaine binding sites on the DAT, and biological function was assessed by examining the inhibition of dopamine uptake *in vitro* as well as examining the behavioral effects of selected analogs.

Chemistry

The 2β-substituted 3β-phenyltropane derivatives were prepared from 2β-carbomethoxy-3β-phenyltropane (WIN 35,065-2, **2a**.)[17] Multiple gram quantities of **2a** were readily available from the degradation of cocaine (**1**) using an improved synthetic procedure recently reported from these laboratories.[18] As illustrated in Scheme 1, the ester homologs **4**, **5**, **7**, and **8** as well as the alcohol derivatives **3**, **6**, and **9** were prepared by the synthetic strategy previously reported.[8] The ester **2a** was reduced with $LiAlH_4$ to furnish the alcohol **3** in 94% yield. Swern oxidation of **3** followed by Musamune−Rousch olefination afforded the α,β-unsaturated ester **4** stereospecifically in 65% overall yield. Hydrogenation (1 atm) of the ester **4** over 10% palladium on carbon gave

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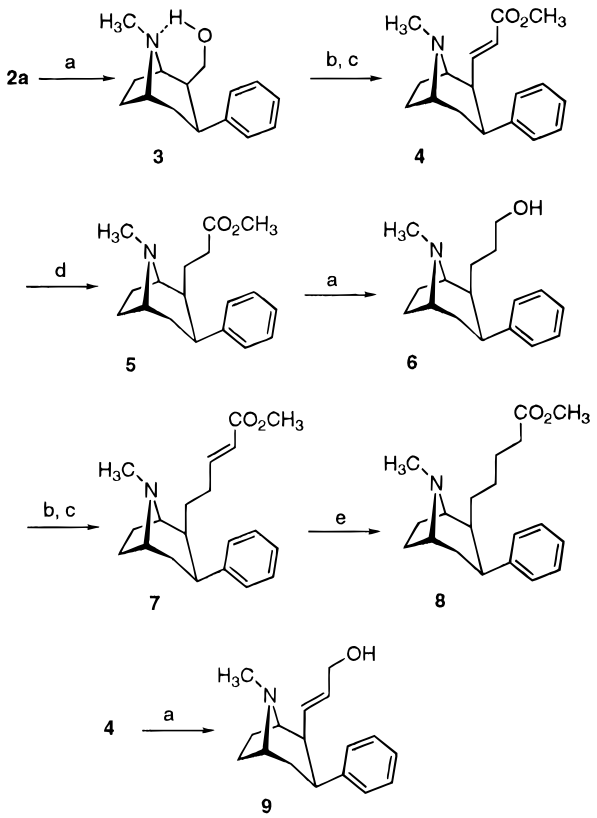
[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1997.

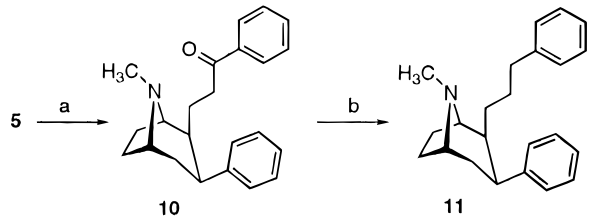
S0022-2623(96)00739-X CCC: $14.00

Scheme 1[a]



[a] Reagents: (a) $LiAlH_4$, Et_2O, 0 °C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) $(CH_3O)_2POCH_2CO_2CH_3$, *i*-Pr_2NEt, LiCl, CH_3CN, 25 °C; (d) H_2, 10% Pd/C, CH_3OH; (e) H_2, PtO_2, CH_3OH.

Scheme 2[a]



[a] Reagents: (a) PhMgBr, Et_2O, 0 °C; (b) NH_2NH_2, KOH, Δ.

the saturated ester **5** in quantitative yield. Reduction of **5** gave the alcohol **6** which was further converted sequentially into the α,β-unsaturated ester **7** (89%) and the saturated ester **8** (95%). Reduction of **4** with $LiAlH_4$ gave the allyl alcohol **9** in 94% yield.

The phenyl ketone **10** was synthesized from **5** by a 1,2-addition reaction of phenylmagnesium bromide. The deoxygenation of the ketone **10** to furnish the saturated derivative **11** was achieved by a Wolff−Kishner reaction (Scheme 2).

Biology

The 2β-substituted 3β-phenyltropanes were tested for their ability to displace bound [^{3}H]WIN 35,428 (**2b**) from rat caudate-putamen tissue.[8,19] The K_i values reported in Table 1 are inhibition constants derived for the unlabled ligands. In addition, the compounds were tested for their ability to inhibit uptake of [^{3}H]dopamine into rat caudate-putamen tissue.[8,19] The linear portion of the inhibition curves were analyzed using analysis of variance and linear regression techniques, and the IC_{50} values are reported in Table 1. As noted previously, cocaine and **2a** modeled better for two binding sites than for one; as a consequence, their high affinity and low affinity K_i values are given in Table 1.[8,19] All of the higher order analogs (**4**−**11**) prepared for this study were best fit by a single-component model, and as such, a single K_i value is provided in Table 1.

Table 1. clogP Values, K_i Values for Displacement of Bound [^{3}H]WIN 35,428 (**2b**), and IC_{50} Values for Inhibition of [^{3}H]Dopamine Uptake

compd	clogP	K_i (nM)[a,b]	IC_{50} (nM)[a,b]
1[c]		32 ± 5 388 ± 221	405 ± 91
2[c]		33 ± 17 314 ± 222	373 ± 100
4	3.22	22 ± 2	123 ± 65
5	3.13	23 ± 2	166 ± 68
6	2.71	11 ± 1	64 ± 32
7	4.27	20 ± 2	203 ± 77
8[d,e]	4.19	30 ± 2	130 ± 27
9	2.23	26 ± 3	159 ± 43
10	4.53	28 ± 2	47 ± 15
11	6.12	16 ± 2	43 ± 13

[a] All values are the mean ± SEM of three experiments performed in triplicate. [b] All compounds were tested as the HCl salt unless otherwise noted. [c] The K_i and IC_{50} values of these drugs are reproduced from ref 19 and were collected under identical conditions. [d] Tested as the fumarate salt. [e] Uptake inhibition curves were significantly different from linear and as a consequence the IC_{50} values are only estimates.

Table 2. ED_{50} Values and Maximal Effects for Stimulation of Locomotor Activity of Mice and ED_{50} Values for Substitution for Cocaine in Rats Trained to Discriminate Cocaine from Saline

	locomotor activity		
compd	ED_{50} value[a] (μmol/kg)	maximal effect[b] (counts/10 min)	drug discrimination ED_{50} value[a] (μmol/kg)
4	4.74 (3.48−6.47)	14996 ± 1774	12.78 (10.55−15.47)
6	11.98 (9.29−15.45)	20820 ± 1379	12.92 (6.36−26.30)
7	9.21 (7.06−12.00)	17327 ± 1413	15.04 (14.70−15.37)
cocaine	20.79 (13.26−32.62)	12518 ± 1647	8.74 (6.18−12.18)

[a] Parenthetical values represent 95% confidence limits. [b] Values represent number of horizontal activity counts per 10 min ± 1 SEM.

Selected compounds (**4**, **6**, and **7**) were then tested *in vivo* and compared with cocaine for their effectiveness for stimulating locomotor activity. Their ED_{50} values for the stimulation of activity were derived as previously described[19] and are reported in Table 2.[20] The maximal stimulant effects and durations of action were also assessed and compared with those measured for cocaine (Table 2).[20] Drug discrimination studies were conducted with the selected compounds; rats were trained to discriminate 10 mg/kg of cocaine (ip) from saline[21,22] and the novel analogs were examined for their potency and efficacy in substituting for cocaine in test sessions according to published methods.[21]

Results and Discussion

All of the analogs **4**−**11** exhibited high binding affinities at DAT, greater than that measured for the parent ester **2a**.[8,19] The binding affinities of the ligands **4**−**11** fit a single-site model better than a two-site model, with an affinity comparable to the high-affinity binding components of cocaine and **2a**. Within this

series of compounds, there was relatively little variation in binding affinity; the K_i values varied over only an approximate 3-fold range and exhibited no correlation with calculated partition coefficients (clogP) determined for the compounds (Table 1).[23]

The binding data demonstrate that large, long-chain substituents at the β-C(2)-position of 3β-aryltropanes are readily tolerated by the cocaine binding site on the DAT. This supports the pharmacophore models which describe the region occupied by the 2β-substituent as a lipophilic/hydrophobic pocket or cleft in the DAT protein.[8,10] It was interesting to note that although the magnitudes of the binding affinity (K_i values) were nearly equal among the different analogs **4**−**11**, there was somewhat more variance among the IC_{50} values for dopamine uptake inhibition. The IC_{50} values varied over an approximate 5-fold range of potencies (Table 1). The unsaturated ester **7** was found to be the least potent uptake inhibitor of the series, while the alcohol **6** and the propylphenyl analogs **10** and **11** were 3−4-fold more potent than **7**.

The high binding affinities and uptake inhibition potencies of **6** and **11** could not easily be ascribed to the influence of electrostatic (*H*-bond) interactions between the 2β-substituent of the ligands and the binding site nor could they be directly correlated with lipophilic parameters, clogP values (Table 1). The potent activity observed for **6** is believed not to be due to the presence of the hydrophilic hydroxyl group since the unsaturated alcohol **9** exhibited diminished activity. Alternatively, the increased lipophilic character of **6** and **11** relative to **9** and **10** (clogP values, Table 1), respectively, clearly resulted in increased binding affinity. In addition, the saturated alcohol **6** and ester **8** exhibited 2-fold more potent dopamine uptake inhibition relative to **9** and **7**, respectively, while the more lipophilic **10** and **11** were equipotent. Comparison of the binding affinities and dopamine uptake potencies observed for **4**−**11** (Table 1) suggests that any electrostatic or *H*-bonding interaction between the hydroxyl of **6** and the binding site is nonspecific while, in general, it appears that lipophilic β-C(2)-substituents lead to increased high binding affinity and potent dopamine uptake inhibition.

The results of this study are consistent with our original pharmacophore model[8] as well as the model proposed by Kozikowski *et al.*[10] while a correlation to the Carroll *et al.* pharmacophore model based on enhanced electrostatic interactions was not observed.[12] In addition, in contrast to the pharmacophore model proposed by Crippen *et al.*,[24] it is apparent from the dopamine uptake inhibition data for **4**−**11** that the substituents at the β-C(2)-position do impart significant activity at the DAT. Moreover, the effects of aqueous solvation of the ligand does not correlate with the *in vitro* activity measured for **4**−**11**.[25] If aqueous solvation effects contributed toward the activity of these compounds, a much greater difference in binding affinity (K_i) and uptake inhibition (IC_{50}) between **6** and **11** would be anticipated.

No heterogeneous binding could be detected *in vitro* for the analogs **4**−**11**.[26] This suggests that the compounds despite different lipophilicity at the β-C(2)-position, either (1) bind to a single site; (2) bind to a single site at different domains with equal affinity; or (3) bind at two different sites with equal affinity.[26] In any case, it is apparent that the resolution of the heterogeneous nature of the cocaine binding site on DAT cannot be readily achieved by variation of the lipophilicity of the 2β-substituent of 3β-phenyltropane derivatives. It is believed that access to different domains of the cocaine binding site or an alternative binding site on DAT will require compounds of more diverse structure.[27−30]

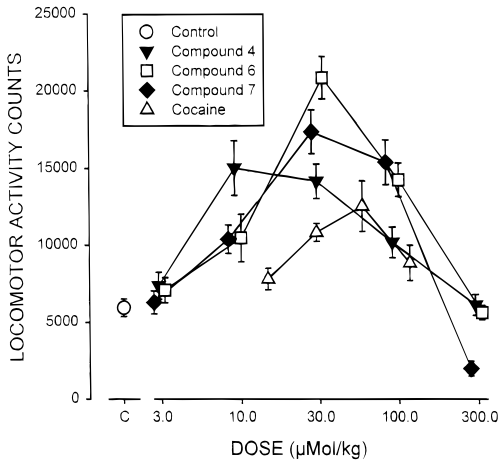


Figure 1. The dose−response effect of compounds **4**, **5**, and **7** on locomotor activity in mice. Ordinates: horizontal activity counts after drug administration. Abscissae: dose of drug in μmol/kg (log scale). The point above C represents the effects of saline vehicle controls. Each point represents the average effect determined in eight mice. The data shown are from the first 30 min periods after drug administration, in which the greatest stimulant effects were obtained.

To further investigate the SAR of 2β-substituents, three compounds from the series with differing lipophilicity and potency were selected for *in vivo* testing. Compounds **4**, **6**, and **7** were believed to be a representative cross section of the *in vitro* activity observed for this series having high binding affinity (K_i = 11−22 nM) with moderate, high, and low uptake inhibition, respectively (Table 1). In addition, **7** was of interest because it has been suggested that compounds which exhibit a significant difference between potency for inhibition and DAT binding affinity (IC_{50}/K_i) may produce antagonist-like effects.[28] The ratio calculated for the unsaturated ester **7** (IC_{50}/K_i = 10.2) was among the highest ratios reported for derivatives of cocaine.[1]

The selected compounds (**4**, **6**, and **7**) were tested *in vivo* for stimulation of locomotor activity. All three compounds were found to be locomotor stimulants, with **4** the most potent; approximately 2−3 times more potent than **6** or **7** and approximately 5 times more potent than cocaine (Figure 1, Table 2). There were also significant differences in the maximal stimulation produced by the compounds. A one-way ANOVA of the maximal effects produced by each compound was significant ($F_{3,28}$ = 5.115, p = 0.006). Posthoc comparisons (Tukey−Kramer multiple comparisons)[31] to determine which of the maximal effects were significant indicated that **6** had a maximal effect that was significantly greater than that for cocaine (Table 2), but not different from that of **4** or **7**. Neither compound **4** nor **7** was different from cocaine in terms of maximal stimulation.

The onset of locomotor stimulant effects of cocaine was rapid with maximum effects occurring within 10 min after injection (Figure 2). In contrast, for analogs **4**, **6**, and **7**, the maximal stimulation of the locomotor

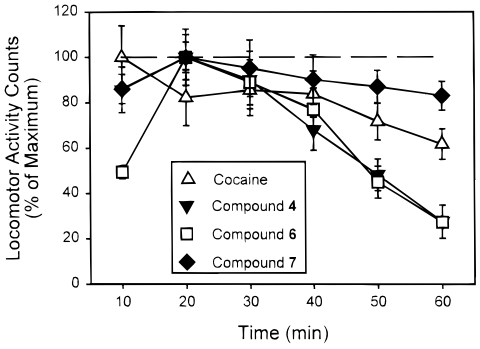


Figure 2. Time-dependent effects of compounds **4**, **6**, **7**, and cocaine on locomotor activity in mice. Ordinates: horizontal activity counts after drug administration expressed as a percentage of the maximum obtained in any 10 min period for that dose of the compound. Abscissae: time after injection. The dashed horizontal line represents the effects of saline vehicle controls. Each point represents the average effect determined in eight mice. The data shown are from the dose producing maximal stimulant effects for each of the compounds; the doses were as follows: **4**, 9.1 μmol/kg; **6**, 33.3 μmol/kg; **7**, 27.9 μmol/kg; cocaine, 58.8 μmol/kg.

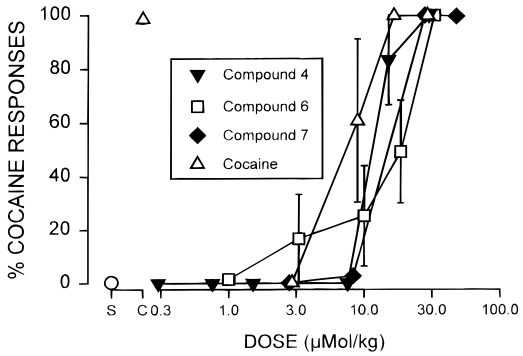


Figure 3. Effects of compounds **4**, **6**, and **7** in rats trained to discriminate injections of cocaine (10 mg/kg) from equal volumes of saline. Ordinates: percentage of total responses on the cocaine-appropriate lever. Abscissae: drug dose in μmol/kg (log scale). Ordinates: percentage of responses emitted on the lever on which rats were trained to respond after injections of cocaine. The lever selection was not considered reliable if the subject responded at a rate below 0.02 responses per second, and a point was not plotted on the graph if fewer than half of the subjects responded above this criterion response rate. Each point represents the effect in four to six rats.

activity occurred between 10 and 20 min after injection. Consistent with its duration of action, the effects of cocaine diminished over the course of the 60 min session. Diminished activity was also observed over the session with compounds **4** and **6**. However, **7** showed the least loss of activity during the session (Figure 2). The source of the prolonged duration of activity is unclear at this time. However, the lipophilic 2β-side chain of **7** may enhance the solubility of the drug in fat tissue and thereby avoid rapid hydrolysis by esterase enzymes. As a result, slow release of the dissolved drug from fat tissue may supply sufficient concentrations of the drug to maintain the observed prolonged activity. Similar results were observed by Kozikowski *et al.* for lipophilic, esterase-resistant analogs.[10]

Each of the three analogs produced a dose-related substitution for cocaine in rats trained to discriminate 10 mg/kg doses of cocaine from saline (Figure 3). Cocaine had the greatest potency which was significantly greater than **7**, but not significantly different from the others (see 95% confidence limits in Table 2). In addition, all of the compounds at least at one dose produced a complete substitution for the training dose of cocaine, indicating that they were as effective as cocaine in producing cocaine-like subjective effects in animals. Taken together with the stimulation of locomotor activity produced by the compounds, these results indicate that the 2β-substituted analogs each possess a cocaine-like pharmacology and differ substantially from cocaine only in their affinity for the DAT and possibly in their pharmacokinetics. In addition, it is noteworthy that the IC_{50}/K_i ratios of approximately 10 for **7** did not confer to it any qualitative or quantitative differences in agonist activity. This result strongly suggests a lack of utility of the IC_{50}/K_i ratios as a screen for potential cocaine antagonists.

Conclusion

Despite the difference in the lipophilic character of the substituents at the β-C(2)-position of the 3β-phenyltropanes tested in this study, all the analogs exhibit homogeneous potent binding affinity. The *in vivo* activity of the compounds **4**, **6**, and **7** exhibited pharmacological profiles very similar to cocaine. These results further support a pharmacophore model in which lipophilic interactions between 2β-substituents and the cocaine binding site contribute to enhanced potency. However, while electrostatic (H-bonding) interactions may be significant at the α-carbon atom of some 2β-substituents,[12] they appear to be of lesser importance when electron-rich groups are removed from proximity of the tropane nucleus. In addition, substantial lipophilicity was found to lead to prolonged duration of action of the drug (**7**). Finally, the heterogeneous nature of the cocaine binding site was found to be insensitive to the lipophilicity of substituents at the β-C(2)-position of the 3β-phenyltropanes. Further studies to address the heterogeneity of the cocaine binding site are currently under investigation.

Experimental Section

Melting points were determined on a Mel-Temp II capillary tube apparatus (uncorrected). Optical rotations were determined at the sodium D line using an Autopol III automatic polarimeter. NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer using tetramethylsilane as an internal standard. All chemicals and reagents were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Tetrahydrofuran and ether were dried by distillation over sodium/benzophenone. Chromatography refers to flash chromatography on silica gel (silica gel 60, E. M. Science, 230−400 mesh) and TLC plates (E. M. Science, Kiesel gel 60, F_{254}, 0.2 mm layer glassback) were purchased from Curtin−Matheson Scientific. Elemental analyses were determined by Atlantic Microlab Inc., Norcross, GA. The compounds (**4**−**7** and **9**−**11**) were converted into the corresponding hydrochloride salts by addition of a solution of the base to a saturated solution of etheral hydrogen chloride (anhydrous). The salt was collected by filtration and dried under vacuum (56 °C, 0.1 mmHg) for 3 h.

General Method A. To a stirred suspension of $LiAlH_4$ (76 mg, 2 mmol) in dry Et_2O (10 mL) at 0 °C under a nitrogen atmosphere was added a solution of the ester (2 mmol) in dry ether (5 mL) dropwise through a syringe, and stirring was continued overnight at room temperature. The reaction mixture was cooled to 0 °C, and an aqueous solution of NaOH was added dropwise. The reaction mixture was filtered and the residue was washed with ether. The combined filtrate and

washings were concentrated under reduced pressure to furnish the alcohol. The alcohol was then purified by chromatography.

General Method B. To a solution of oxalyl chloride (1.2 mL, 2.0 M solution in CH_2Cl_2, 2.2 mmol) under nitrogen (−60 °C) was added a solution of DMSO (0.31 mL, 343 mg, 4.4 mmol) in dry CH_2Cl_2 (1 mL). After 0.5 h, a solution of the alcohol (2 mmol) in dry CH_2Cl_2 (3 mL) was added and stirring was continued for 1 h at −60 °C followed by addition of triethylamine (1.3 mL, 9.2 mmol) at the same temperature. The reaction mixture was allowed to warm to room temperature and diluted with water. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield the corresponding aldehyde (95%). The material was then carried on to the olefination step without further purification.

General Method C. To a stirred suspension of lithium chloride (0.10 g, 2.4 mmol) in dry acetonitrile (10 mL) at room temperature under a nitrogen atmosphere were added trimethyl phosphonoacetate (0.437 g, 2.4 mmol), *N,N*-diisopropylethylamine (0.26 g, 2.0 mmol), and the aldehyde (2.0 mmol). The reaction mixture was allowed to stir for 24 h, after which acetonitrile was removed under reduced pressure and the residue was diluted with water and extracted with ether (3 × 40 mL). The combined organic layers were washed with water and brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure and purification of the crude product by chromatography (ether:triethylamine, 9:1) gave the corresponding unsaturated ester.

General Method D. A solution of the unsaturated compound (2.0 mmol) in dry methanol (20 mL) was hydrogenated (1 atm) over 10% palladium on carbon (15% by w/w). After the hydrogenation was complete (^{1}H NMR), the reaction mixture was filtered and the solvent was evaporated under reduced pressure to give the saturated analog.

2β-(2′-(Methoxycarbonyl)eth-1′-enyl)-3β-phenyltropane (4). General method B and C from **3**[8,17] gave **4** as a solid (0.37 g, 65%): 86−87 °C (free base); ^{1}H NMR ($CDCl_3$) δ 7.22−7.10 (m, 5H, Ph), 7.10 (d, J = 15.8 Hz, 1H), 5.40 (d, J = 15.8 Hz, 1H), 3.60 (s, 3H, OCH_3), 3.36 (m, 1H), 3.14 (m, 2H), 2.48 (m, 1H), 2.25 (s, 3H, NCH_3), 2.22−2.06 (m, 3H), 1.81−1.62 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 167.2, 150.7, 142.9, 128.7, 128.3, 126.7, 122.1, 67.9, 62.7, 52.2, 51.8, 42.2, 37.3, 35.1, 27.1, 25.5; $[\alpha]^{20}_D$ = −107° (*c* 0.015, CH_2Cl_2, free base). Anal. ($C_{18}H_{23}NO_2 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

2β-(2′-(Methoxycarbonyl)ethyl)-3β-phenyltropane (5). General method D from **4** gave **5** as an oil (0.57 g, 99%). ^{1}H NMR ($CDCl_3$) δ 7.30−7.18 (m, 5H, Ph), 3.57 (s, 3H, OCH_3), 3.34 (m, 1H), 3.20 (m, 2H), 2.35 (s, 3H, NCH_3), 2.31−2.21 (m, 4H), 2.10−1.51 (m, 6H), 1.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 174.3, 143.1, 128.3, 127.7, 126.0, 64.0, 62.1, 51.3, 45.5, 42.1, 36.1, 33.3, 32.4, 26.4, 24.8, 22.9; $[\alpha]^{20}_D$ = −95.6° (*c* 0.0025, CH_2Cl_2, free base); mp 190−191 °C (HCl salt). Anal. ($C_{18}H_{25}NO_2 \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

2β-(3′-Hydroxypropyl)-3β-phenyltropane (6). General method A from **5** (SiO_2, $CHCl_3$:CH_3OH, 95:5) gave **6** as an oil (0.51 g, 99%): ^{1}H NMR ($CDCl_3$) δ 7.40−7.08 (m, 5H, Ph), 3.60 (m, 1H), 3.48 (m, 2H), 3.21 (m, 2H), 3.10 (m, 1H), 2.25 (s, 3H, NCH_3), 2.25−2.08 (m, 3H), 1.67 (m, 3H), 1.50 (m, 3H), 1.19 (m, 1H), 0.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 143.4, 128.1, 127.8, 125.9, 64.6, 62.8, 62.0, 46.1, 42.1, 36.3, 33.3, 30.8, 26.5, 24.0, 23.1; $[\alpha]^{20}_D$ = −86.3° (*c* 0.043, CH_2Cl_2, free base); mp 205−206 °C (HCl salt). Anal. ($C_{17}H_{25}NO \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

2β-(4′-(Methoxycarbonyl)but-3′-enyl)-3β-phenyltropane (7). General methods B and C from **6** (SiO_2, ether:triethylamine, 9:1) gave **7** as an oil (0.55 g, 89%): ^{1}H NMR ($CDCl_3$) δ 7.21−7.11 (m, 5H, Ph), 6.60 (m, 1H), 5.55 (d, J = 14 Hz, 1H), 3.51 (s, 3H, OCH_3), 3.33 (m, 1H), 3.20 (m, 1H), 3.08 (m, 1H), 2.39 (s, 3H, NCH_3), 2.31−1.90 (m, 5H), 1.61 (m, 4H), 1.50 (m, 1H), 0.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 166.9, 149.4, 142.3, 128.2, 127.7, 126.1, 120.8, 65.1, 62.4, 51.2, 45.3, 41.7, 35.8, 32.6, 30.2, 26.2, 25.5, 24.4; $[\alpha]^{20}_D$ = −58.0° (*c* 0.056, CH_2Cl_3, free base); mp 130−133 °C (HCl salt). Anal. ($C_{20}H_{27}NO_2 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

2β-(4′-(Methoxycarbonyl)butyl)-3β-phenyltropane (8). Ester **7** (0.63 g, 2 mmol) in dry methanol was hydrogenated (1 atm) over PtO_2 (15% w/w). After the hydrogenation was complete (TLC) the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography (SiO_2, ether:triethylamine, 90:10) to afford the ester **11** as an oil (0.60 g, 95%): ^{1}H NMR ($CDCl_3$) δ 7.42−7.10 (m, 5H, Ph), 3.50 (s, 3H, OCH_3), 3.31 (m, 1H), 3.18 (m, 1H), 3.07 (m, 1H), 2.25 (s, 3H, NCH_3), 2.22 (m, 1H), 2.11 (m, 3H), 1.98−1.41 (m, 7H), 1.33 (m, 2H), 0.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.2, 142.4, 128.2, 127.8, 126.1, 65.2, 62.6, 51.4, 45.8, 41.6, 35.9, 33.9, 32.7, 27.1, 26.4, 26.2, 24.7, 24.5; $[\alpha]^{20}_D$ = −61.8° (*c* 0.012, CH_2Cl_2, free base); mp 158−160 °C (fumarate, recrystallized from *i*-PrOH). Anal. ($C_{20}H_{29}NO_2 \cdot C_4H_4O_4$) C, H, N.

2β-(3′-Hydroxyprop-1′-enyl)-3β-phenyltropane (9). General method A from **4** (SiO_2, $CHCl_3$:CH_3OH, 95:5) gave **9** as an oil (0.49 g, 95%): ^{1}H NMR ($CDCl_3$) δ 7.40−7.10 (m, 5H, Ph), 5.80 (dd, J = 16.0, 6.6 Hz, 1H), 5.25 (m, 1H), 3.85 (m, 2H), 3.30 (m, 1H), 3.14 (m, 2H), 2.15 (m, 4H), 2.25 (s, 3H, NCH_3), 1.80−1.50 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 142.9, 133.1, 130.3, 127.9, 127.7, 125.8, 68.1, 63.7, 62.3, 50.4, 42.1, 36.6, 34.3, 26.6, 25.0; $[\alpha]^{20}_D$ = −93.7° (*c* 0.007, CH_2Cl_2, free base); mp 90−94 °C (HCl salt). Anal. ($C_{17}H_{23}NO \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

2β-(3′-Phenyl-3′-oxopropyl)-3β-phenyltropane (10). To a solution of **5** (0.58 g, 2.0 mmol) in dry ether (20 mL) was added a solution of phenylmagnesium bromide (0.8 mL, 3 M in ether). The mixture was refluxed for 3 h under an atmosphere of nitrogen. The reaction mixture was poured in water (30 mL), and the aqueous layer was extracted with ether (3 × 50 mL). The combined ether layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was chromatographed (SiO_2, $CHCl_3$:CH_3OH, 9:1) to give **10** as an oil (0.58 g, 87%): ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 7.2 Hz, 2H), 7.51−7.08 (m, 8H), 3.25 (m, 1H), 3.09 (m, 2H), 2.55 (m, 1H), 2.29 (s, 3H, NCH_3), 2.25−1.87 (m, 4H), 1.80−1.32 (m, 5H), 1.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 200.6, 143.2, 136.7, 132.8, 128.2, 128.1, 127.9, 127.5, 125.8, 65.5, 64.7, 61.9, 45.8, 42.0, 36.0, 33.2, 26.2, 24.7, 23.0; $[\alpha]^{25}_D$ = −109° (*c* 0.5, CH_2Cl_2, free base); mp 238−241 °C (HCl salt). Anal. ($C_{23}H_{27}NO \cdot HCl \cdot 0.75H_2O$) C, H, N.

2β-(3′-Phenylpropyl)-3β-phenyltropane (11). A solution of **10** (0.41 g, 1.2 mmol), KOH (1.7 g, 3.6 mmol), and hydrazine hydrate (1.0 mL) in diethylene glycol (10 mL) was heated to 150 °C overnight. The mixture was allowed to cool to room temperature and poured in water (150 mL). The aqueous solution was extracted with ether (5 × 50 mL). The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was chromatographed (SiO_2, $CHCl_3$:CH_3OH, 9:1) to afford **11** as an oil (0.26 g, 68%): ^{1}H NMR ($CDCl_3$) δ 7.39−7.01 (m, 10H), 3.29 (s, 1H), 3.18 (m, 1H), 3.05 (m, 1H), 2.42 (m, 2H), 2.31 (s, 3H, NCH_3), 2.30−2.01 (m, 3H), 1.78−1.42 (m, 6H), 1.17 (m, 1H), 0.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 143.8, 143.2, 128.4, 128.2, 128.0, 127.9, 125.9, 125.5, 65.0, 62.1, 46.4, 42.2, 36.5, 36.3, 33.7, 30.3, 27.4, 26.6, 25.0; $[\alpha]^{25}_D$ = −69.2° (*c* 0.5, CH_2Cl_2, free base); mp 235−236 °C (HCl salt). Anal. ($C_{23}H_{29}NO \cdot HCl$) C, H, N.

Acknowledgment. We are grateful to the National Institute on Drug Abuse (NIDA First Award R29 DA08055) for the financial support of this research. We also thank Mr. Brett Heller, Ms. Julie Haak, and Ms. Lu Espina for technical assistance.

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JM960739C