Synthesis and Transporter Binding Properties of 3β-(4′-Alkyl-, 4′-alkenyl-, and 4′-alkynylphenyl)nortropane-2β-carboxylic Acid Methyl Esters: Serotonin Transporter Selective Analogs

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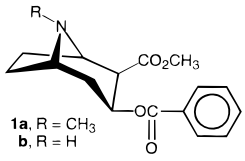
Received June 10, 1996[⊗]

New methods for the synthesis of 3β-(4′-alkyl-, 4′-alkenyl-, and 4′-alkynylphenyl)nortropane-2β-carboxylic acid methyl esters **2**−**4**, respectively, were developed. These methods involved coupling of the appropriate organometallic reagents to 3β-(4′-iodophenyl)tropane-2β-carboxylic acid methyl ester (**6a**, RTI-55) or to an N-protected derivative of **6a** followed by N-demethylation or removal of the protecting group. Some analogs were prepared by catalytic reduction of the alkene and alkyne analogs **3** and **4** or by isomerization of the alkenes **3**. The analogs **2**−**4** were evaluated for inhibition of radioligand binding to the serotonin (5-HT), dopamine (DA), and norepinephrine (NE) transporters. 3β-(4′-Isopropenyl- and 4′-*cis*-propenylphenyl)nortropane-2β-carboxylic acid methyl esters (**3b**,**d**), which possessed IC_{50} values of 0.6 and 1.15 nM, respectively, were the most potent analogs at the 5-HT transporter, and with NE/5-HT IC_{50} ratios of 240 and 128 nM, respectively, they were selective for the 5-HT relative to the NE transporter. Since interaction with the serotonin transporter may modulate the pharmacological effects resulting from binding to the dopamine transporter, 3β-(4′-isopropenylphenyl)tropane-2β-carboxylic acid methyl ester (**11b**) which has good affinity for both the 5-HT and DA transporters but low affinity at the NE transporter may be useful for studying this interaction.

In order to understand the mechanism related to the addictive properties of (−)-cocaine (**1a**), it was necessary to identify the molecular site where this drug interacts to produce its initial physiological effects. (−)-Cocaine has several sites of action in the central nervous system



1a, R = CH_3
b, R = H

of rodents and nonhuman primates, as well as in human brain.[1−7] Of these, the dopaminergic pathway has been implicated in the reinforcing properties of (−)-cocaine.[8,9] The current view, termed "the dopamine hypothesis", is that the behaviors associated with cocaine addiction result, to a large extent, not from a direct message elicited by the binding of (−)-cocaine but rather from the accumulation of dopamine in the synapse and its action at one or more of the D_1−D_5 receptors.[8] Research results from many laboratories have supported this finding and have led to the view that cocaine binds to specific recognition sites located on the dopamine transporter of mesolimbocortical neurons thereby preventing (inhibiting) dopamine reuptake into presynaptic neurons.[8]

Since cocaine also inhibits serotonin reuptake, the effects of compounds that interact with serotonin receptors have been evaluated for efficacy against behavioral effects of cocaine. Serotonin agonists lacking dopaminergic activity have been found not to produce reward or euphoria. However, some evidence suggests that inhibition of serotonin reuptake modulates the reinforcing properties of cocaine.[10,11] If serotonin synapses on the cell body of dopamine neurons regulate reward threshold levels, then cocaine inhibition of serotonin reuptake could enhance or reduce cocaine-induced effects in the dopamine system. Even though the importance of the serotonin transporter in mediating the neurochemical and behavioral actions of cocaine is now recognized, the biochemical mechanism of action and regulation of this transporter is not well understood. The molecular mechanism of action would be better understood if cocaine analogs which bind selectively to the serotonin transporter site were available for pharmacological studies. In a recent study, we reported that 3β-(4′-ethylphenyl)nortropane-2β-carboxylic acid methyl ester (**2a**) showed higher affinity for the serotonin (5-HT) transporter than for the dopamine (DA) transporter, which suggested that appropriate modification of 3β-(substituted phenyl)nortropane-2β-carboxylic acid methyl esters would lead to compounds potent and selective for the 5-HT transporter.[12] In this study, we describe the synthesis of several 3β-(4′-alkyl-, 4′-alkenyl-, and 4′-alkynylphenyl)nortropane-2β-carboxylic acid methyl esters **2**−**4**, respectively, and report that some of the compounds possess good selectivity and potency for the 5-HT transporter. We also report that one compound shows good affinity for both the 5-HT and DA transporters but has low affinity for the norepinephrine (NE) transporter.

Chemistry

Some of the **2**−**4** analogs could be prepared via N-demethylation of the corresponding 3β-(4′-alkyl, 4′-

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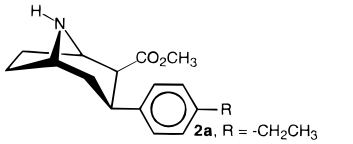
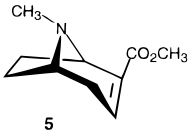
[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

S0022-2623(96)00409-8 CCC: $12.00



2a, R = -CH_2CH_3
b, R = -$CH_2CH_2CH_2$
c, R = -$CH(CH_3)_2$
3a, R = -$CH{=}CH_2$
b, R = -$C(=CH_2)CH_3$
c, R = t-$CH{=}CHCH_3$
d, R = c-$CH{=}CHCH_3$
e, R = $CH_2CH{=}CH_2$
4a, R = C≡CH
b, R = -C≡CCH_3

alkenyl, and 4′-alkynylphenyl)tropane-2β-carboxylic acid methyl esters. However, since the preparation of 3β-(4′-ethylphenyl)tropane-2β-carboxylic acid methyl esters via the 1,4-addition of 4-substituted phenylmagnesium halides to anhydroecgonine methyl ester (**5**) resulted in



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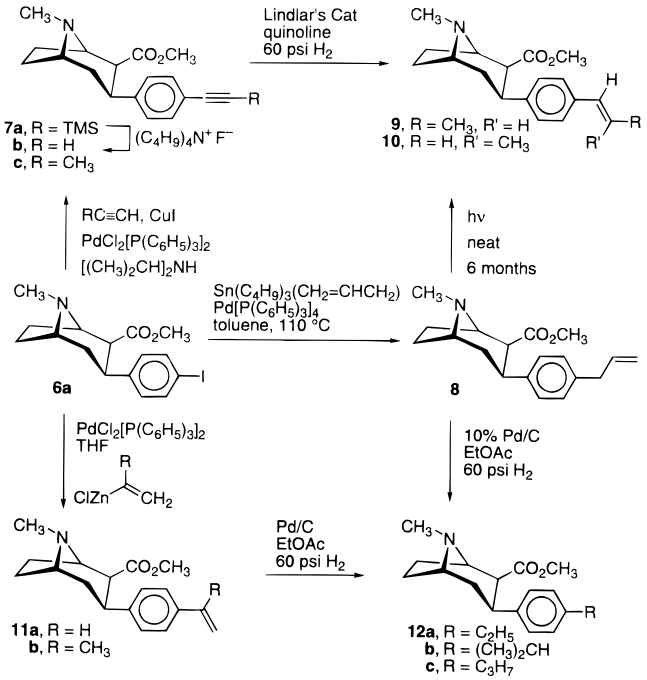
low yields,[12] we developed an alternative approach to synthesize these compounds which relies upon the palladium-catalyzed coupling of organometallic reagents to 3β-(4′-iodophenyl)tropane-2β-carboxylic acid methyl ester (**6a**, RTI-55). Through the use of both Castro−Stevens and Stille-type palladium-catalyzed couplings,[13−15] we were able to synthesize 3β-(4′-alkyl-, 4′-alkenyl-, and 4′-alkynylphenyl)nortropane-2β-carboxylic acid methyl esters **2**−**4** as outlined in Scheme 1. In the case of the 3β-(4′-alkynylphenyl)tropane-2β-carboxylic acid methyl ester derivatives, a Castro−Stevens coupling of a terminal acetylene with **6a** was used (Scheme 1). Thus, reaction of **6a** with trimethylsilylacetylene in the presence of a catalytic amount of copper(I) iodide and bis(triphenylphosphine)palladium(II) chloride in degassed diisopropylamine produced **7a**. Removal of the silyl protection group with tetrabutylammonium fluoride in tetrahydrofuran afforded **7b** in 98% yield. In a similar fashion, reaction of **6a** with propyne provided **7c** in 73% yield.

The 3β-(4′-allylphenyl)tropane-2β-carboxylic acid methyl ester (**8**) was synthesized via a Stille[16] coupling of allyltributyltin with **6a** using tetrakis(triphenylphosphine)palladium as catalyst in refluxing toluene (Scheme 1). Isomerization of the double bond of **8** into conjugation with the aromatic ring occurred upon standing at room temperature over 6 months, affording (*E*)-3β-(4′-propenylphenyl)tropane-2β-carboxylic acid methyl ester (**9**). The isomerization may have been assisted by small amounts of palladium metal contaminant. The *Z* analog **10** was prepared by partial reduction of 3β-(4′-propynylphenyl)tropane-2β-carboxylic acid methyl ester (**7c**) using Lindlar's catalyst and a small amount of quinoline. The resulting double bond was resistant to further reduction, and no overreduction was observed, even under 60 psi of hydrogen.

The remaining 3β-(4′-alkenylphenyl)tropane-2β-carboxylic acid methyl ester derivatives were prepared by utilizing a Stille-type coupling between an alkenylzinc chloride and **6a**. Thus, reaction of **6a** and vinylzinc chloride, generated by the addition of zinc chloride to a solution of vinylmagnesium bromide in THF, in the

Scheme 1



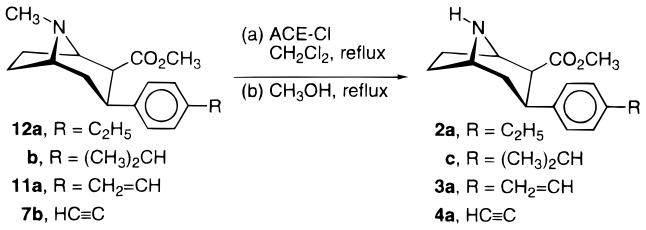
presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride afforded the 4′-vinyl analog **11a**. A similar reaction performed with isopropenylzinc chloride, prepared from isopropenyllithium and zinc chloride, afforded the isopropenyl analog **11b**. Surprisingly, attempts to synthesize the olefins by coupling tributylvinyltin or tributylisopropenyltin and **6a** with bis(triphenylphosphine)palladium(II) chloride or tetrakis(triphenylphosphine)palladium catalyst failed. Increasing the temperature from 60 to 110 °C caused decomposition. A coupling reaction was observed with tetravinyltin and **6a** in refluxing toluene with tetrakis(triphenylphosphine)palladium as the catalyst. However, there was extensive decomposition, and the product yield was only 6%. The observed decomposition was unexpected since allyltributyltin had coupled cleanly in refluxing toluene with little decomposition of **6a**. Apparently, either the palladium intermediate was unstable or the vinylstannane reagent and heating caused decomposition of the tropane ring system.

The ethyl, isopropyl, and *n*-propyl analogs **12a**−**c** were synthesized by catalytic hydrogenation of **11a**,**b** and **8** with palladium on carbon in ethyl acetate under 60 psi of hydrogen (Scheme 1). The 4′-ethyl has also been prepared in 8% yield by the addition of 4-ethylphenylmagnesium bromide to **5**.[12]

The 3β-(4′-ethyl-, 4′-isopropyl-, 4′-vinyl-, 4′-allyl-, and 4′-ethynylphenyl)nortropane-2β-carboxylic acid methyl esters (**2a**,**c**, **3a**, and **4a**) were prepared by direct N-demethylation of the *N*-methyl compounds. Thus, reaction of **12a**,**b**, **11a**, and **7b** with chloroethyl chloroformate (ACE-Cl) in refluxing dichloroethane followed by reaction in refluxing methanol afforded **2a**,**c**, **3a**, and **4a** (Scheme 2).

Attempts to remove the *N*-methyl group from 3β-(4′-isopropenylphenyl)tropane-2β-carboxylic acid methyl ester (**11b**) via ACE-Cl resulted in loss of the isopropenyl moiety and decomposition. Since the N-demethylation had failed and since these reactions sometimes resulted in lower yields than desired, we investigated

Scheme 2



an alternative route using (2,2,2-trichloroethyl)carbamate (Troc)-protected intermediate *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-iodophenyl)nortropane-2β-carboxylic acid methyl ester (**13**) (Scheme 3). Reaction of **6a** with *N*-2,2,2-trichloroethyl chloroformate (Troc-Cl) in refluxing dichloroethane afforded **13** in 96% yield. The isopropenyl analog **14a** was then synthesized by reaction of **13** with isopropenylzinc chloride and bis(triphenylphosphine)palladium(II) chloride using conditions similar to those used for the preparation of **11a**. The *N*-(2,2,2-trichloroethyl)carbamoyl group was also compatible with the Castro−Stevens coupling reactions forming **14b**. The *N*-(2,2,2-trichloroethyl)carbamoyl group was removed using either zinc/acetic acid or 10% lead oxide−cadmium[17] in tetrahydrofuran ammonium acetate providing the 3β-(4′-substituted phenyl)nortropane-2β-carboxylic acid methyl ester analogs **3b** and **4b**.

Reduction of **4b** using either palladium on carbon or Lindlar's catalyst afforded **2b** and **3d**, respectively. Isomerization of the allyl group in **14c** using rhodium trichloride in refluxing ethanol followed by removal of the Troc group afforded **3c**. Reaction of 3β-(4′-allylphenyl)tropane-2β-carboxylic acid methyl ester (**8**) with Troc-Cl in refluxing dichloroethane formed **14c** in 72% yield. The *N*-(2,2,2-trichloroethyl)carbamoyl group was removed with 10% lead oxide−cadmium as outlined previously producing **3e**.

The structural assignments for key compounds **2c**, **3a**−**e**, **4a**,**b**, **7b**,**c**, **8**, **9**, **11a**,**b**, and **12b**,**c** were based largely on the method of synthesis and elemental and ^{1}H NMR analyses. The chemical shift and coupling pattern of the C-2 and C-3 protons were consistent with previously reported compounds[12,18] and with β-stereochemistry. All other distinctive NMR resonances for **2c**, **3a**−**e**, **4a**,**b**, **7b**,**c**, **8**, **9**, **11a**,**b**, and **12b**,**c** as well as for intermediates are given in the Experimental Section.

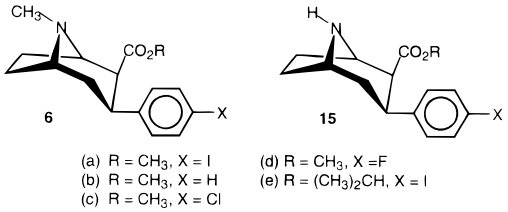
Biological Evaluation

Competitive radioligand binding assays were used to determine the affinities of target compounds. 5-HT, DA, and NE transporter binding studies were performed as previously described[18] using [^{3}H]paroxetine, [^{3}H]WIN 35,428, and [^{3}H]nisoxetine in frontal cortex, striati, and midbrain from rats, respectively. The ratio of IC_{50} values DA/5-HT and NE/5-HT were used as a measure of the in vitro selectivity of the compounds for the 5-HT transporter relative to the DA and NE transporters. The results of the binding studies are summarized in Table 1 along with the data for cocaine and norcocaine (**1a**,**b**) for comparison.

Results and Discussion

Cocaine (**1a**) is an inhibitor of the neuronal transport of norepinephrine, dopamine, and serotonin at roughly similar concentrations.[19] Biochemical binding studies indicate slight DA selectivity.[9,20] In recent years, structure−activity relationship studies of cocaine analogs (**6b**, WIN 35,065-2) for binding at monoamine transporters, particularly at the dopamine transporter, have been explored,[21−24] and some structural modifications that result in selectivity for the dopamine transporter over the norepinephrine and serotonin transporters have been reported.[25−27]

Early reports showed that replacement of the *N*-methyl group by hydrogen in **6b**, to give **15b** (WIN 35,981), resulted in enhanced affinity for binding at the 5-HT and NE transporters with virtually no change in binding affinity at the DA transporter, leading to increased selectivity for the 5-HT and NE transporters over the DA transporter.[1,20] An analogous effect was observed upon replacement of the *N*-methyl group in



cocaine (**1a**) by hydrogen to give norcocaine (**1b**), but in this case, while affinity at NE and 5-HT transporters was enhanced, it was decreased at the DA transporter.[1,12,20] In addition, our examination of the potency of several 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters, **6a**,**c**−**e** and **12a**, relative to their nortropane analogs revealed that replacement of the *N*-methyl group by hydrogen generally enhances selectivity for 5-HT and NE relative to DA transporters.[12] In this study, we also found that changing the *N*-methyl group of all of the 3β-(4′-alkyl-, 4′-alkenyl-, and 4′-alkynylphenyl)tropane-2β-carboxylic acid methyl esters to hydrogen to afford the nortropane analogs resulted in increased potency at the 5-HT transporter. It is interesting that 2-carbon 4′-substituent analogs **2a**, **3a**, and **4a** have potency for the DA transporter similar to their *N*-methyl derivatives **12a**, **11a**, and **7b**.

As noted in the introduction, the 4′-ethyl analog **2a** showed relatively weak binding to the DA transporter while having reasonable binding to the 5-HT transporter. In this study, we found that changing the 4′-substituents to alkyl groups larger than ethyl, such as the propyl and isopropyl analogs **2b**,**c**, respectively, resulted in lower affinity for the 5-HT transporter. In contrast, both two- and three-carbon olefin analogs showed good affinity for the 5-HT transporter. The 4′-olefinic substituents (**3a**−**d**), which are in conjugation with the phenyl ring, all showed IC_{50} values of less than 2.25 nM at the 5-HT transporter. However, even the 4′-allyl analog **3e**, with an IC_{50} value of 6.2 nM, was more potent than the *n*-propyl and isopropyl analogs **2b**,**c**, suggesting that some of the reduction in potency might be due to steric factors. The nortropane analogs **2**−**4** were more selective for the 5-HT and NE transporters relative to the DA transporter; however, none of the analogs were highly selective for the 5-HT transporter relative to the DA transporter. Nevertheless, it is interesting to note that the *trans*- and *cis*-4′-propene analogs **3c**,**d** have similar potencies, but the cis isomer **3d** is 3 times more selective relative to the NE transporter than the trans isomer **3c**. Compound

Scheme 3

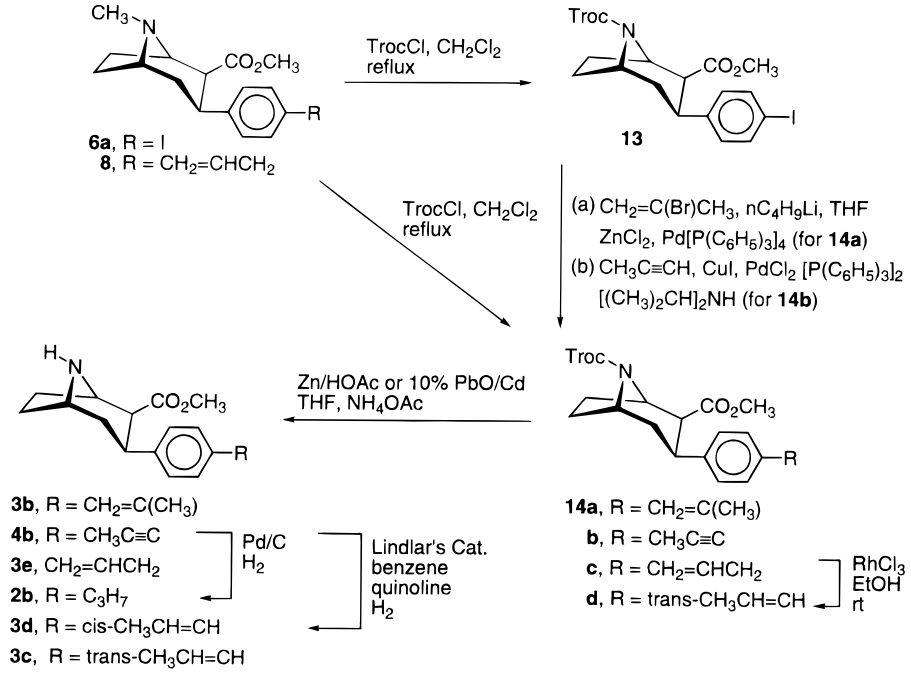
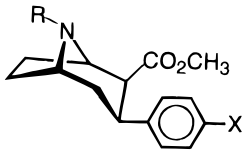


Table 1. Comparison of Transporter Binding Potencies for 3β-(4′-Alkyl-, 4′-alkenyl-, and 4′-alkynylphenyl)tropane-2β-carboxylic Acid Methyl Esters and Their Nortropane Analogs[a]



				IC_{50} (nM)				
RTI no.	compd	X	R	5-HT [^{3}H]paroxetine	DA [^{3}H]WIN 35,428	NE [^{3}H]nisoxetine	DA/5-HT[b] ratio	NE/5-HT[b] ratio
	1a (cocaine)			1045 ± 78[c]	89 ± 4.8[c]	3298 ± 293[c]	0.09	3.2
	1b			127 ± 13[c]	206 ± 29[c]	139 ± 9[c]	1.6	1.1
83	**12a**	C_2H_5	CH_3	28.4 ± 3.8	55 ± 2	4030 ± 381	1.9	142
173	**2a**	C_2H_5	H	8.13 ± 0.30	49.9 ± 7.3	122 ± 12	6.1	15
282	**12c**	*n*-C_3H_7	CH_3	70.4 ± 4.1	68.5 ± 7.1	3920 ± 130	0.97	56
364	**2b**	*n*-C_3H_7	H	26 ± 1.3	212 ± 17	532 ± 8.1	8.2	21
302	**12b**	$CH(CH_3)_2$	CH_3	191 ± 9.5	597 ± 52	75000 ± 5820	3.1	392
330	**2c**	$CH(CH_3)_2$	H	15.1 ± 0.97	310 ± 21	ND	21	
359	**11a**	$CH{=}CH_2$	CH_3	9.5 ± 0.8	1.24 ± 0.2	78 ± 4.1	0.13	8.2
309	**3a**	$CH{=}CH_2$	H	2.25 ± 0.17	1.73 ± 0.05	14.9 ± 1.18	0.77	6.6
283	**11b**	$C(=CH_2)CH_3$	CH_3	3.13 ± 0.16	14.4 ± 0.30	1330 ± 333	4.6	425
357	**3b**	$C(=CH_2)CH_3$	H	0.6 ± 0.06	23 ± 0.9	144 ± 12	38	240
296	**9**	*t*-$CH{=}CHCH_3$	CH_3	11.4 ± 0.28	5.29 ± 0.53	1590 ± 93	0.46	140
368	**3c**	*t*-$CH{=}CHCH_3$	H	1.3 ± 0.1	28.6 ± 3.1	54 ± 16	22	42
304	**10**	*c*-$CH{=}CHCH_3$	CH_3	7.09 ± 0.71	15 ± 1.2	2800 ± 300	2.1	395
358	**3d**	*c*-$CH{=}CHCH_3$	H	1.15 ± 0.1	31.6 ± 2.2	147 ± 4.3	28	128
301	**8**	$CH_2CH{=}CH_2$	CH_3	28.4 ± 2.4	32.8 ± 3.1	2480 ± 229	1.16	87
369	**3e**	$CH_2CH{=}CH_2$	H	6.2 ± 0.3	56.5 ± 5.6	89.7 ± 9.6	9.1	15
360	**7b**	$C{\equiv}CH$	CH_3	4.4 ± 0.4	1.2 ± 0.1	83.2 ± 2.8	0.27	19
305	**4a**	$C{\equiv}CH$	H	1.59 ± 0.2	1.24 ± 0.11	21.8 ± 1.0	0.78	13.7
281	**7c**	$C{\equiv}CCH_3$	CH_3	15.7 ± 1.5	2.37 ± 0.2	820 ± 46	0.15	52
307	**4b**	$C{\equiv}CCH_3$	H	3.16 ± 0.33	6.11 ± 0.67	116 ± 5.1	1.93	37

[a] Data are mean ± standard error of three or four experiments performed in triplicate. [b] 5-HT/DA and NE/DA are ratios of IC_{50} values. [c] Reference 9.

3b which is isomeric with **3c**,**d** is both more potent and more selective for the 5-HT transporter relative to the NE transporter.

In conclusion, we have developed new methods for the syntheses of 3β-(substituted phenyl)nortropane-2β-carboxylic acid methyl esters. These methods involve coupling of the appropriate organostannane or zinc reagent with RTI-55 (**6a**) or with an *N*-(2,2,2-trichloroethyl)carbamoyl (Troc) derivative of **6a** followed by N-demethylation or removal of the Troc protecting group. 3β-(4′-Isopropenyl- and 4′-*cis*-propenylphenyl)-nortropane-2β-carboxylic acid methyl esters (**3b**,**d**) showed the highest potency and selectivity for the 5-HT transporter. Since, as pointed out in the introduction section, some reports suggest that inhibition of serotonin reuptake modulates the reinforcing properties of cocaine,[10] these compounds may be useful for cocaine abuse studies. In addition, 3β-(4′-isopropenylphenyl)-

tropane-2β-carboxylic acid methyl ester (**11b**) with IC_{50} values of 3.13, 14.4, and 1330 nM for 5-HT, DA, and NE transporters, respectively, may also be a useful compound for further investigation.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 250 MHz (Bruker AM-250) spectrometer. Chemical shift data for the proton resonances were reported in parts per million (δ) relative to internal $(CH_3)_4Si$ (δ 0.0). Optical rotations were measured on an AutoPol III polarimeter, purchased from Rudolf Research. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Analytical thin-layer chromatography (TLC) was carried out on plates precoated with silica gel GHLF (250 μm thickness). TLC visualization was accomplished with a UV lamp. Flash column chromatography was performed as described by Still.[28] All moisture-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. The pressurized reactions were performed in a thick-walled pressure tube purchased from ACE glass. The hydrogenations were performed by attaching a gauge assembly to the top of the pressure tube and introducing the hydrogen from a lecture bottle. The gauge assembly was made to fit the top of the tube by drilling a hole in the Teflon cap and threading it for a standard gauge assembly.

Tetrahydrofuran (THF) was distilled just prior to its use (sodium benzophenone ketyl). Anhydrous methylene chloride, toluene, and ethyl acetate were purchased from Aldrich Chemical Co. Triethylamine and diisopropylamine were distilled from CaH_2 and stored.

3β-(4′-Ethynylphenyl)tropane-2β-carboxylic Acid Methyl Ester (7b). A solution of 1.08 g (0.0028 mol) of **6a** in 28 mL of diisopropylamine in an ACE pressure tube was deaerated by bubbling nitrogen through the mixture for 30 min. To the stirred solution were added 30 mg (0.14 mmol) of copper(I) iodide and 196 mg (0.28 mmol) of bis(triphenylphospine)palladium(II) chloride followed by 0.40 mL (2.8 mmol) of trimethylsilylacetylene. The solution became dark quickly and solidified. Additional diisopropylamine was added, and the solution was briefly degassed as before. The vessel was sealed with a Teflon cap, and the mixture was stirred overnight. The resulting slurry was concentrated under reduced pressure and then diluted with ethyl acetate and a little triethylamine and filtered through a plug of silica gel. The solution was concentrated under reduced pressure.

To the crude acetylene in 20 mL of tetrahydrofuran at 0 °C was added 3.60 mL (3.60 mmol) of 1.0 M tetrabutylammonium fluoride in tetrahydrofuran dropwise. The solution was stirred for 2 h with warming to room temperature. The solution was diluted with saturated aqueous sodium bicarbonate, and the aqueous layer was extracted three times with methylene chloride. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude yellow oil was purified by column chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with an additional 1% of triethylamine afforded 0.766 g (98% yield) of 3β-(4′-ethynylphenyl)tropane-2β-carboxylic acid methyl ester (**7b**): ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 1H, C≡C*H*), 6.95 (d, 2H, J = 8.3 Hz, aryl H), 7.14 (d, 2H, J = 8.0 Hz, aryl H).

The free base was converted to the tartrate salt: mp 150 °C dec; $[\alpha]^{27}_D$ −75.2° (*c* 0.105, MeOH). Anal. ($C_{22}H_{27}NO_8\cdot 1.0H_2O$) C, H, N.

3β-(4′-Propynylphenyl)tropane-2β-carboxylic Acid Methyl Ester (7c). A solution of 1.0 g (0.0026 mol) of **6a** in 13.0 mL of triethylamine in an ACE pressure tube was deaerated by bubbling nitrogen through the mixture for 30 min. To the stirred solution were added a catalytic amount of copper(I) iodide and bis(triphenylphospine)palladium(II) chloride. The gauge assembly was fitted on top, and a lecture bottle of propyne gas was attached via a tygon hose. The vessel was evacuated via an aspirator followed by introduction of the propyne gas. This procedure was repeated three times to ensure total saturation. The apparatus was then pressurized as much as possible (5 psi) with propyne gas, sealed, and stirred overnight. The mixture turned dark immediately after the addition of propyne. The vessel was vented, and the resulting slurry was concentrated under reduced pressure. The crude oil was diluted with ethyl acetate and a little triethylamine and filtered through a plug of silica gel. The solution was concentrated under reduced pressure. The crude yellow oil was purified by column chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with an additional 1% of triethylamine afforded 0.565 g (73% yield) of 3β-(4′-propynylphenyl)tropane-2β-carboxylic acid methyl ester (**7c**): ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, C≡CC*H*$_3$), 7.15 (d, 2H, J = 8.0 Hz, aryl H), 7.28 (d, 2H, J = 8.0 Hz, aryl H).

The free base was converted to the tartrate salt: mp 137−139 °C; $[\alpha]^{27}_D$ −80.98° (c 0.425, MeOH). Anal. ($C_{23}H_{29}NO_8\cdot 0.5H_2O$) C, H, N.

3β-(4′-Allylphenyl)tropane-2β-carboxylic Acid Methyl Ester (8). To a solution of 150 mg (0.389 mmol) of 3β-(4′-iodophenyl)tropane-2β-carboxylic acid methyl ester (**6a**) in 4 mL of dry toluene under a nitrogen atmosphere was added 0.145 mL (0.467 mmol) of allyltributyltin followed by 60 mg of tetrakis(triphenylphosphine)palladium. The mixture was heated to reflux for 12 h, until the solution became dark from the precipitation of palladium(0). The mixture was concentrated under reduced pressure. The dark yellow oil was dissolved in diethyl ether, and the organic layer was extracted with 1 M aqueous hydrochloric acid (3×). The combined aqueous layers were basified with saturated aqueous sodium carbonate and extracted with methylene chloride (5×). The combined extract was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 0.104 g (89% yield) of 3β-(4′-allylphenyl)tropane-2β-carboxylic acid methyl ester (**8**): ^{1}H NMR ($CDCl_3$) δ 3.22 (d, 2H, J = 6.0 Hz, CH_2CH), 5.00 (s, 1H, one of CH=CH_2), 5.06 (d, 1H J = 7.2 Hz, one of CH=CH_2), 5.85−6.01 (m, 1H C*H*=CH$_2$), 7.08 (d, 2H, J = 7.4 Hz, aryl H), 7.18 (d, 2H, J = 7.7 Hz, aryl H).

The free base was converted to the tartrate salt: mp 114−116 °C; $[\alpha]^{27}_D$ −87.3° (*c* 0.77, MeOH). Anal. ($C_{23}H_{33}NO_8\cdot 0.25H_2O$) C, H, N.

(*E*)-3β-(4′-Propenylphenyl)tropane-2β-carboxylic Acid Methyl Ester (9). A crude sample of 3β-(4′-allylphenyl)-tropane-2β-carboxylic acid methyl ester (**8**) was stored neat on the bench in light. After 6 months, the olefin had completely isomerized. The crude material was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 0.134 g (100% yield) of (*E*)-3β-(4′-propenylphenyl)tropane-2β-carboxylic acid methyl ester (**9**): ^{1}H NMR ($CDCl_3$) δ 1.77 (d, 3H, J = 6.3 Hz, CHC*H*$_3$), 6.08 (dq, 1H, J = 6.2, 15.7 Hz, C*H*CH$_3$), 6.27 (d, 1H, J = 16 Hz, C*H*=CHCH$_3$), 7.09 (d, 2H, J = 8.5 Hz, aryl H), 7.15 (d, 2H, J = 8.4 Hz, aryl H).

The free base was converted to the tartrate salt: mp 142 °C dec; $[\alpha]^{27}_D$ −96.5° (*c* 0.920, MeOH). Anal. ($C_{23}H_{31}NO_8\cdot 0.5H_2O$) C, H, N.

(*Z*)-3β-(4′-Propenylphenyl)tropane-2β-carboxylic Acid Methyl Ester (10). To a solution of 0.171 g of 3β-(4-propynylphenyl)tropane-2β-carboxylic acid methyl ester (**7c**) in 7.0 mL of benzene in an ACE pressure tube was added 1 small drop of quinoline followed by a catalytic amount of Lindlar's catalyst. The gauge assembly was fitted on top, and the tube was pressurized with 60 psi of hydrogen gas. The slurry was stirred overnight. The tube was vented, and the slurry was filtered through a plug of Celite to remove the catalyst. The solution was concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 0.080 g (47% yield) of (*Z*)-3β-(4′-propenylphenyl)tropane-2β-carboxylic acid methyl ester: ^{1}H NMR ($CDCl_3$) δ 1.89 (d, 3H, J = 7.2 Hz, CHC*H*$_3$), 5.73 (dq, 1H, J = 7.3, 11.6 Hz, C*H*CH$_3$), 6.37 (d, 1H, J = 11.5 Hz, C*H*=CHCH$_3$), 7.21 (s, 4H, aryl H).

The free base was converted to the tartrate salt: mp 128−130 °C; $[\alpha]^{27}_D$ −101.7° (*c* 0.120, MeOH). Anal. ($C_{23}H_{31}NO_8\cdot 1.25H_2O$) C, H, N.

3β-(4′-Vinylphenyl)tropane-2β-carboxylic Acid Methyl Ester (11a). To a solution of 7.78 mL (7.78 mmol) of 1.0 M vinylmagnesium bromide in tetrahydrofuran at −78 °C under a nitrogen atmosphere was added 19.5 mL of dry tetrahydrofuran followed by 15.5 mL (7.78 mmol) of 0.5 M zinc chloride in tetrahydrofuran. The mixture was stirred for 15 min; then 1.5 g (3.89 mmol) of **6a** in 5 mL of dry tetrahydrofuran was added dropwise followed by the additon of 90 mg of bis-(triphenylphosphine)palladium(II) chloride. The mixture was stirred overnight with warming to room temperature. The mixture turned dark soon after reaching room temperature. The mixture was concentrated under reduced pressure. The dark yellow oil was dissolved in diethyl ether, and the organic layer was extracted with 1 M aqueous hydrochloric acid (3×). The combined aqueous layers were basified with saturated aqueous sodium carbonate and extracted with methylene chloride (5×). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 1.05 g (95% yield) of 3β-(4′-vinylphenyl)-tropane-2β-carboxylic acid methyl ester (**11a**): ^{1}H NMR ($CDCl_3$) δ 5.17 (d, 1H, J = 10.9 Hz, one of CH=CH_2), 5.68 (d, 1H, J = 17.6 Hz, one of CH=CH_2), 6.66 (dd, 1H, J = 10.8, 17.6 Hz CH=CH$_2$), 7.20 (d, 2H, J = 8.2 Hz, aryl H), 7.31 (d, 2H, J = 8.2 Hz, aryl H).

The free base was converted to the tartrate salt: mp 129−131 °C; $[\alpha]^{27}_D$ −90.1° (*c* 0.70, MeOH). Anal. ($C_{22}H_{29}NO_8$·0.5H_2O) C, H, N.

3β-(4′-Isopropenylphenyl)tropane-2β-carboxylic Acid Methyl Ester (11b). To a solution of 0.292 mL (3.30 mmol) of 2-bromopropene in 5 mL of dry tetrahydrofuran at −78 °C under a nitrogen atmosphere was added 2.1 mL (3.30 mmol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred for 15 min at −78 °C. To this mixture was added 3.30 mL (3.30 mmol) of 1 M zinc chloride in diethyl ether, and the mixture was stirred for an additional 30 min at −78 °C. Then 0.423 g (1.10 mmol) of **6a** in 5 mL of dry tetrahydrofuran was added dropwise followed by the additon of 60 mg of bis-(triphenylphosphine)palladium(II) chloride. The mixture was stirred overnight with warming to room temperature. The mixture turned dark soon after reaching room temperature. The mixture was concentrated under reduced pressure. The dark yellow oil was dissolved in diethyl ether, and the organic layer was extracted with 1 M aqueous hydrochloric acid (3×). The combined aqueous layers were basified with saturated aqueous sodium carbonate and extracted with methylene chloride (5×). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 0.270 g (84% yield) of 3β-(4′-isopropenylphenyl)tropane-2β-carboxylic acid methyl ester (**11b**): ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, CH_3C=CH_2), 5.02 (s, 1H, one of C=CH_2), 5.33 (s, 1H, one of C=CH_2), 7.21 (d, 2H, J = 8.3 Hz, aryl H), 7.38 (d, 2H, J = 8.4 Hz, aryl H).

The free base was converted to the tartrate salt: mp 86−88 °C; $[\alpha]^{27}_D$ −87.5° (*c* 0.480, MeOH). Anal. ($C_{23}H_{31}$-NO_8·1.0H_2O) C, H, N.

3β-(4′-Ethylphenyl)tropane-2β-carboxylic Acid Methyl Ester (12a). To a solution of 1.05 g (3.68 mmol) of 3β-(4′-vinylphenyl)tropane-2β-carboxylic acid methyl ester (**11a**) in 12.0 mL of ethyl acetate in an ACE pressure tube was added 0.3 g of 10% palladium on carbon (fire hazard). The gauge assembly was fitted on top, and the tube was pressurized with 60 psi of hydrogen gas. The slurry was stirred overnight. The tube was vented, and the slurry was filtered through a plug of Celite to remove the palladium on carbon. The solution was concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 0.857 g (81% yield) of 3β-(4′-ethylphenyl)tropane-2β-carboxylic acid methyl ester (**12a**): ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.6 Hz, CH_2CH_3), 2.52 (q, 2H, J = 7.6 Hz, CH_2CH_3), 7.02 (d, 2H, J = 8.0 Hz, aryl H), 7.10 (d, 2H, J = 8.1 Hz, aryl H). The NMR spectrum was identical with that of an authentic sample.[12]

3β-(4′-Isopropylphenyl)tropane-2β-carboxylic Acid Methyl Ester (12b). To a solution of 398 mg (1.33 mmol) of 3β-(4′-isopropenylphenyl)tropane-2β-carboxylic acid methyl ester (**11b**) in 2.6 mL of ethanol in an ACE pressure tube was added a catalytic amount of 5% palladium on carbon (fire hazard). The gauge assembly was fitted on top, and the tube was pressurized with 60 psi of hydrogen gas. The slurry was stirred overnight. The tube was vented, and the slurry was filtered through a plug of Celite to remove the palladium on carbon. The solution was concentrated under reduced pressure. The pale yellow oil was then dissolved in 2,2′-dimethoxypropane, and a small amount of concentrated hydrochloric acid was added. After stirring overnight, the mixture was dissloved in diethyl ether and basified with aqueous sodium bicarbonate. The aqueous layer was extracted with methylene chloride (5×). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 0.249 g (63% yield) of 3β-(4′-isopropylphenyl)-tropane-2β-carboxylic acid methyl ester (**12b**): ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 6H, J = 6.9 Hz, CH(CH_3)$_2$), 7.12 (d, 2H, J = 8.4 Hz, aryl H), 7.19 (d, 2H, J = 8.4 Hz, aryl H).

The free base was converted to the tartrate salt: mp 130−131 °C; $[\alpha]^{27}_D$ −88.1° (*c* 0.255, MeOH). Anal. ($C_{23}H_{33}NO_8$) C, H, N.

3β-(4′-Propylphenyl)tropane-2β-carboxylic Acid Methyl Ester (12c). To a solution of 104 mg (0.347 mmol) of 3β-(4′-allylphenyl)tropane-2β-carboxylic acid methyl ester (**8**) in 1 mL of ethyl acetate in an ACE pressure tube was added a catalytic amount of 10% palladium on carbon (fire hazard). The gauge assembly was fitted on top, and the tube was pressurized with 60 psi of hydrogen gas. The slurry was stirred overnight. The tube was vented, and the slurry was filtered through a plug of Celite to remove the palladium on carbon. The solution was concentrated under reduced pressure. The pale yellow oil was then dissolved in 2,2′-dimethoxypropane, and a small amount of concentrated hydrochloric acid was added. After stirring overnight, the mixture was dissloved in diethyl ether and basified with aqueous sodium bicarbonate. The aqueous layer was extracted with methylene chloride (5×). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 74 mg (71% yield) of 3β-(4′-propylphenyl)-tropane-2β-carboxylic acid methyl ester (**12c**): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.2 Hz, CH_2CH_3), 2.54 (t, 2H, J = 7.7 Hz, $CH_2CH_2CH_3$), 7.07 (d, 2H, J = 8.1 Hz, aryl H), 7.16 (d, 2H, J = 8.1 Hz, aryl H).

The free base was converted to the tartrate salt: mp 137−139 °C; $[\alpha]^{27}_D$ −80.8° (*c* 0.50, MeOH). Anal. ($C_{23}H_{33}NO_8$·1.0H_2O) C, H, N.

General Procedure for N-Demethylation: 3β-(4′-Ethylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (2a). To a solution of 156 mg (0.543 mmol) of 3β-(4′-ethylphenyl)tropane-2β-carboxylic acid methyl ester (**12a**) in 1 mL of dry 1,2-dichloroethane under nitrogen at room temperature was added 0.175 mL (1.63 mmol) of 1-chloroethyl chloroformate dropwise. The mixture was refluxed overnight. The solution was then concentrated under reduced pressure and dissolved in 5 mL of methanol. This solution was refluxed for 4 h and cooled. The solution was concentrated under reduced pressure, and then the mixture was dissolved in diethyl ether and basified with aqueous sodium bicarbonate. The aqueous layer was extracted with methylene chloride (5×). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 2% additional methanol and 1% additional triethylamine afforded 0.107 g (72% yield) of 3β-(4′-ethylphenyl)nortropane-2β-carboxylic acid methyl ester (**2a**). The NMR spectrum was identical with that of an authentic sample.[12]

3β-(4′-Isopropylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (2c). The procedure for 3β-(4′-ethylphenyl)-nortropane-2β-carboxylic acid methyl ester (**2a**) was followed with 0.350 g (1.2 mmol) of 3β-(4′-isopropylphenyl)tropane-2β-carboxylic acid methyl ester (**12b**) and 0.50 mL (4.65 mmol) of 1-chloroethyl chloroformate affording 0.0931 g (28% yield) of 3β-(4′-isopropylphenyl)nortropane-2β-carboxylic acid methyl ester (**2c**): ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 6H, J = 6.9 Hz, $CH(CH_3)_2$), 7.12 (s, 4H, aryl H).

The free base was converted to the tartrate salt: mp 130−131 °C dec; $[\alpha]^{27}_D$ −91.4° (*c* 0.5, MeOH). Anal. ($C_{22}H_{31}NO_8 \cdot 0.5H_2O$) C, H, N.

3β-(4′-Vinylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (3a). The procedure for 3β-(4′-ethylphenyl)nortropane-2β-carboxylic acid methyl ester (**2a**) was followed with 0.110 g (0.385 mmol) of 3β-(4′-vinylphenyl)tropane-2β-carboxylic acid methyl ester (**11a**) and 0.166 mL (1.54 mmol) of 1-chloroethyl chloroformate affording 0.0673 g (64% yield) of 3β-(4′-vinylphenyl)nortropane-2β-carboxylic acid methyl ester (**3a**): ^{1}H NMR ($CDCl_3$) δ 5.13 (d, 1H, J = 10.9 Hz, one of $CH{=}CH_2$), 5.63 (d, 1H, J = 17.7 Hz, one of $CH{=}CH_2$), 6.61 (dd, 1H, J = 11.2, 17.8 Hz, $CH{=}CH_2$), 7.08 (d, 2H, J = 8.2 Hz, aryl H), 7.25 (d, 2H, J = 8.2 Hz, aryl H).

The free base was converted to the tartrate salt: mp 135−138 °C; $[\alpha]^{27}_D$ −99.6° (*c* 0.255, MeOH). Anal. ($C_{21}H_{27}NO_8 \cdot 0.5H_2O$) C, H, N.

3β-(4′-Ethynylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (4a). The procedure for 3β-(4′-ethylphenyl)-nortropane-2β-carboxylic acid methyl ester (**2a**) was followed with 0.110 g (0.390 mmol) of 3β-(4′-ethynylphenyl)tropane-2β-carboxylic acid methyl ester (**7b**) and 0.126 mL (1.16 mmol) of 1-chloroethyl chloroformate affording 0.0284 g (28% yield) of 3β-(4′-ethynylphenyl)nortropane-2β-carboxylic acid methyl ester (**4a**): ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 1H, acetylenic H), 7.15 (d, 2H, J = 8.3 Hz, aryl H), 7.42 (d, 2H, J = 8.3 Hz, aryl H).

The free base was converted to the tartrate salt: mp 148−150 °C; $[\alpha]^{27}_D$ −71.4° (*c* 0.070, MeOH). Anal. ($C_{21}H_{25}NO_8 \cdot 0.5H_2O$) C, H, N.

***N*-[(2,2,2-Trichloroethyl)carbamoyl]-3β-(4′-iodophenyl)nortropane-2β-carboxylic Acid Methyl Ester (13).** To a stirred solution of 1.054 g (2.73 mmol) of **6a** in 14 mL of dry dichloroethane was added 1.13 mL (8.20 mmol) of 2,2,2-trichloroethyl chloroformate. The solution was refluxed overnight and cooled to room temperature. The mixture was diluted with diethyl ether (100 mL). The organic layer was extracted with 1 M aqueous hydrogen chloride (2x). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel. Elution with 3:1 hexane−ether afforded 1.425 g (96% yield) of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-iodophenyl)nortropane-2β-carboxylic acid methyl ester (**13**).

***N*-[(2,2,2-Trichloroethyl)carbamoyl-3β-(4′-isopropenylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (14a).** To a solution of 0.233 mL (2.62 mmol) of 2-bromopropene in 5 mL of dry tetrahydrofuran at −78 °C under a nitrogen atmosphere was added 1.64 mL (2.62 mmol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred for 15 min at −78 °C. To this mixture was added 5.25 mL (2.62 mmol) of 0.5 M zinc chloride in tetrahydrofuran, and the mixture was stirred for an additional 30 min with warming to room temperature. Then 0.478 g (0.875 mmol) of **13** in 5 mL of dry tetrahydrofuran was added dropwise followed by the additon of 60 mg of bis(triphenylphosphine)palladium(II) chloride. The mixture was stirred overnight at room temperature. The mixture turned dark soon after reaching room temperature. The mixture was diluted with saturated aqueous sodium bicarbonate and extracted with methylene chloride (5×). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 hexane−ether afforded 0.380 g (93% yield) of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-isopropenylphenyl)nortropane-2β-carboxylic acid methyl ester (**14a**).

***N*-[(2,2,2-Trichloroethyl)carbamoyl]-3β-(4′-propynylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (14b).** A solution of 0.404 g (0.740 mmol) of **13** in 7.0 mL of diisopropylamine in an ACE pressure tube was deaerated by bubbling nitrogen through the mixture for 30 min. To the stirred solution was added 14 mg (0.074 mmol) of copper(I) iodide and 104 mg (0.148 mmol) of bis(triphenylphospine)-palladium(II) chloride. The gauge assembly was fitted on top, and a lecture bottle of propyne gas was attached via a tygon hose. The vessel was evacuated via an aspirator followed by introduction of the propyne gas. This procedure was repeated three times to ensure total saturation. The apparatus was then pressurized as much as possible (5 psi) with propyne gas, sealed, and stirred overnight. The mixture turned green and then black immediately after the addition of propyne. The vessel was vented, and the resulting slurry was concentrated under reduced pressure. The crude oil was diluted with diethyl ether and filtered through a plug of silica gel washing with ether. The solution was concentrated under reduced pressure. The crude yellow oil was purified by column chromatography on silica gel. Elution with 3:1 hexane−ether afforded 0.330 g (97% yield) of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-propynylphenyl)nortropane-2β-carboxylic acid methyl ester (**14b**).

***N*-[(2,2,2-Trichloroethyl)carbamoyl]-3β-(4′-allylphenyl-)nortropane-2β-carboxylic Acid Methyl Ester (14c).** The procedure for *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-iodophenyl)nortropane-2β-carboxylic acid methyl ester (**13**) was followed with 487 mg (1.63 mmol) of **8** in 16 mL of dry dichloroethane and 0.448 mL (3.3 mmol) of 2,2,2-trichloroethyl chloroformate affording 0.536 g (72% yield) of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-allylphenyl)nortropane-2β-carboxylic acid methyl ester (**14c**).

3β-(4′-Isopropenylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (3b). To a stirred slurry of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-isopropenylphenyl)nortropane-2β-carboxylic acid methyl ester (**14a**) in 7.0 mL of glacial acetic acid was added 324 mg (0.703 mmol) of activated zinc. The slurry was stirred overnight and then filtered through a plug of Celite. The aqueous solution was poured slowly into saturated aqueous bicarbonate, and additional bicarbonate was added until basic. The aqueous layer was then extracted with methylene chloride (5×). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 2% additional methanol and 1% additional triethylamine afforded 0.128 g (64% yield) of β-(4′-isopropenylphenyl)nortropane-2β-carboxylic acid methyl ester (**3b**): ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H, $CH_3C{=}CH_2$), 5.05 (s, 1H, one of $C{=}CH_2$), 5.35 (s, 1H, one of $C{=}CH_2$), 7.15 (d, 2H, J = 8.4 Hz, aryl H), 7.39 (d, 2H, J = 8.3 Hz, aryl H).

The free base was converted to the tartrate salt: mp 103−106 °C; $[\alpha]^{27}_D$ −101.7° (*c* 0.590, MeOH). Anal. ($C_{22}H_{29}NO_8 \cdot 0.5H_2O$) C, H, N.

3β-(4′-Allylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (3e). To a stirred solution of 128 mg (0.28 mmol) of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-allylphenyl)nortropane-2β-carboxylic acid methyl ester (**14c**) in 1.1 mL of tetrahydrofuran and 1.1 mL of 1 M aqueous ammonium acetate was added 0.156 g (1.38 mmol) of 10% PbO/Cd. The slurry was stirred for 1 h and then filtered through Celite. The solution was basified with saturated aqueous bicarbonate and extracted with methylene chloride (5×). The combined extract was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 5% additional methanol and 1% additional triethylamine afforded 0.0382 g (48% yield) of (*E*)-3β-(4′-allylphenyl)nortropane-2β-carboxylic acid methyl ester (**3e**): ^{1}H NMR ($CDCl_3$) δ 3.35 (d, 2H, J = 6.7 Hz, CH_2CH), 5.02 (d, 1H J = 2.7 Hz, one of $CH{=}CH_2$), 5.07 (s, 1H, one of $CH{=}CH_2$), 5.86−6.02 (m, 1H, $CH{=}CH_2$), 7.11 (s, 4H, aryl H).

The free base was converted to the tartrate salt: mp 111−113 °C; $[\alpha]^{27}_D$ −68.6° (*c* 0.28, MeOH). Anal. ($C_{22}H_{29}NO_8 \cdot 0.5H_2O$) C, H, N.

3β-(4′-Propynylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (4b). The procedure for 3β-(4′-isopropenylphen-

yl)nortropane-2β-carboxylic acid methyl ester (**3b**) was followed with 0.212 g (0.462 mmol) of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-propynylphenyl)nortropane-2β-carboxylic acid methyl ester (**14b**) and 0.151 g (2.31 mmol) of activated zinc in 3 mL of glacial acetic acid affording 0.081 g (62% yield) of 3β-(4′-propynylphenyl)nortropane-2β-carboxylic acid methyl ester (**4b**): ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H, CCH_3), 7.02 (d, 2H, J = 8.2 Hz, aryl H), 7.23 (d, 2H, J = 8.1 Hz, aryl H).

The free base was converted to the tartrate salt: mp 168−170 °C; $[\alpha]^{27}_D$ −106.0° (*c* 0.465, MeOH). Anal. ($C_{22}H_{27}NO_8\cdot 0.75H_2O$) C, H, N.

3β-(4′-Propylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (2b). To a solution of 0.1112 g (0.392 mmol) of 3β-(4′-propynylphenyl)nortropane-2β-carboxylic acid methyl ester (**4b**) in 1.0 mL of ethyl acetate in a round-bottom flask was added 0.1 g of 10% palladium on carbon (fire hazard). The hydrogen atmosphere was added via a hydrogen-filled balloon, and the slurry was stirred overnight. The slurry was filtered through a plug of Celite to remove the palladium on carbon. The solution was concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 1% additional triethylamine afforded 0.082 g (73% yield) of 3β-(4′-propylphenyl)nortropane-2β-carboxylic acid methyl ester (**2b**): ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, J = 7 Hz, CH_2CH_3), 2.54 (t, 2H, J = 8 Hz, $CH_2CH_2CH_3$), 7.09 (s, 4H, aryl H).

The free base was converted to the tartrate salt: mp 138−140 °C; $[\alpha]^{27}_D$ −73.6° (*c* 0.46, MeOH). Anal. ($C_{22}H_{31}NO_8\cdot 0.5H_2O$) C, H, N.

(*Z*)-3β-(4′-Propenylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (3d). To a solution of 0.0812 g (0.286 mmol) of 3β-(4′-propynylphenyl)nortropane-2β-carboxylic acid methyl ester (**4b**) in 3.0 mL of benzene in an ACE pressure tube was added 1 small drop (7 μL) of quinoline followed by 183 mg of Lindlar's catalyst. The gauge assembly was fitted on top, and the tube was pressurized with 60 psi of hydrogen gas. The slurry was stirred for 3.5 h. The tube was vented, and the slurry was filtered through a plug of Celite to remove the catalyst. The solution was concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 5% additional methanol and 1% additional triethylamine afforded 0.0612 g (75% yield) of (*Z*)-3β-(4′-propenylphenyl)-nortropane-2β-carboxylic acid methyl ester (**3d**): ^{1}H NMR ($CDCl_3$) δ 1.89 (d, 3H, J = 7.2 Hz, CHCH_3), 5.76 (dq, 1H, J = 7.2, 11.6 Hz, CHCH$_3$), 6.38 (d, 1H, J = 11.5 Hz, CH=CHCH$_3$), 7.15 (d, 2H, J = 8.3 Hz, aryl H), 7.22 (d, 2H, J = 8.3 Hz, aryl H).

The free base was converted to the tartrate salt: mp 107−108 °C; $[\alpha]^{27}_D$ −104.2° (*c* 0.310, MeOH). Anal. ($C_{22}H_{29}NO_8\cdot 0.5H_2O$) C, H, N.

(*E*)-3β-(4′-Propenylphenyl)nortropane-2β-carboxylic Acid Methyl Ester (3c). To a stirred solution of 0.273 g (0.59 mmol) of *N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-allylphenyl)nortropane-2β-carboxylic acid methyl ester (**14c**) in 7.0 mL of ethanol was added 100 mg of rhodium(III) chloride. The slurry was heated to reflux overnight and cooled. The slurry was filtered through a plug of silica gel and concentrated under reduced pressure affording 0.131 g (48% yield) of crude (*E*)-*N*-[(2,2,2-trichloroethyl)carbamoyl]-3β-(4′-propenylphenyl)nortropane-2β-carboxylic acid methyl ester (**14d**).

To the crude carbamate in 1.4 mL of tetrahydrofuran and 1.4 mL of saturated aqueous ammonium acetate was added 0.160 g (1.42 mmol) of 10% PbO/Cd. The slurry was stirred for 1 h and then filtered through Celite. The solution was basified with saturated aqueous bicarbonate and extracted with methylene chloride (5×). The combined extract was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography on silica gel. Elution with 3:1 ethyl acetate−hexane with 5% additional methanol and 1% additional triethylamine afforded 0.0381 g (47% yield) of (*E*)-3β-(4′-propenylphenyl)nortropane-2β-carboxylic acid methyl ester (**3c**): ^{1}H NMR ($CDCl_3$) δ 1.87 (d, 3H, J = 6.1 Hz, CHCH_3), 6.19 (dq, 1H, J = 6.0, 15.8 Hz, CHCH$_3$), 6.36 (d, 1H, J = 16.0 Hz, CH=CHCH$_3$), 7.10 (d, 2H, J = 8.3 Hz, aryl H), 7.26 (d, 2H, J = 8.9 Hz, aryl H).

The free base was converted to the tartrate salt: mp 160−162 °C; $[\alpha]^{27}_D$ −102.4° (*c* 0.62, MeOH). Anal. ($C_{22}H_{29}NO_8\cdot H_2O$) C, H, N.

Acknowledgment. This work was supported in part by the National Institute on Drug Abuse, Grant No. DA05477.

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JM960409S