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Bioorganic & Medicinal Chemistry 16 (2008) 5529–5535
Bioorganic & Medicinal Chemistry

Synthesis and receptor binding properties of 2β-alkynyl and 2β-(1,2,3-triazol)substituted 3β-(substituted phenyl)tropane derivatives

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Received 6 March 2008; revised 3 April 2008; accepted 4 April 2008
Available online 10 April 2008

Abstract—A series of 2β-alkynyl and 2β-(1,2,3-triazol)substituted 3β-(substituted phenyl)tropanes were synthesized and evaluated for affinities at dopamine, serotonin, and norepinephrine membrane transporters using competitive radioligand binding assays. All tested compounds were found to exhibit nanomolar or subnanomolar affinity for the dopamine transporter (DAT). One of the most potent and selective compounds in the series was 3β-(4-chlorophenyl)-2β-(4-nitrophenylethynyl)tropane (**10c**) that possessed an IC_{50} value of 0.9 nM at the DAT and K_i values of 230 nM and 620 nM at the norepinephrine transporter (NET) and serotonin transporter (5-HTT), respectively.

1. Introduction

Cocaine (**1**, Fig. 1) is one of the most powerful central nervous system (CNS) stimulants with reinforcing properties. While cocaine blocks the presynaptic reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE), numerous studies have strongly supported the hypothesis that the dopamine transporter (DAT) is highly significant in cocaine abuse regarding its reinforcing effects.[1–5] Although other targets may be important to addiction (metabotropic and iontropic glutamate receptors, GABA)[6–8] animal behavioral and clinical finding suggest that the DAT is still an important target.[9–14] Structure–activity relationship (SAR) studies of a number of different classes of DAT inhibitors with the goal of the development of pharmacotherapies to treat cocaine addiction have been reported.[12,15–18] One of the most studied classes of DAT inhibitors are the 3-phenyltropanes.[12,15,19,20] The lead compound was 3β-phenyltropane-2β-carboxylic acid methyl ester (**2a**, WIN 35,065-2).[21,22] A large part of our SAR studies have been directed toward modification of the 4′-methyl and 4′-chloro analogs **2b**,**c**.[12]

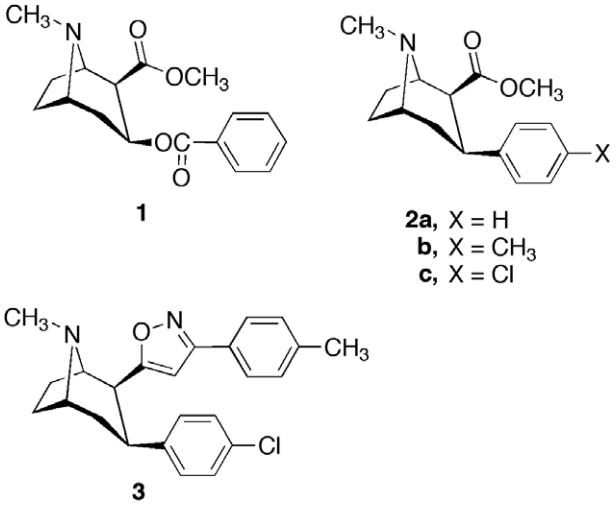

Figure 1. Structures of compounds **1**, **2a–c**, and **3**.

Most of the studies were directed toward changes in the C(2)-position of **2a–c**. SAR studies have revealed that a variety of functional groups and substituents are well tolerated at this position without loss of high-affinity for monoamine transporters. In early studies, we showed that a variety of 2β-esters and amides had high-affinity for the DAT, in some cases, with considerably reduced affinity at the 5-HTT and NET.[12] SAR

Keywords: Monoamine transporters; 3-Phenyltropanes; Alkynes; 1,2,3-Triazoles; Cocaine; Addiction.
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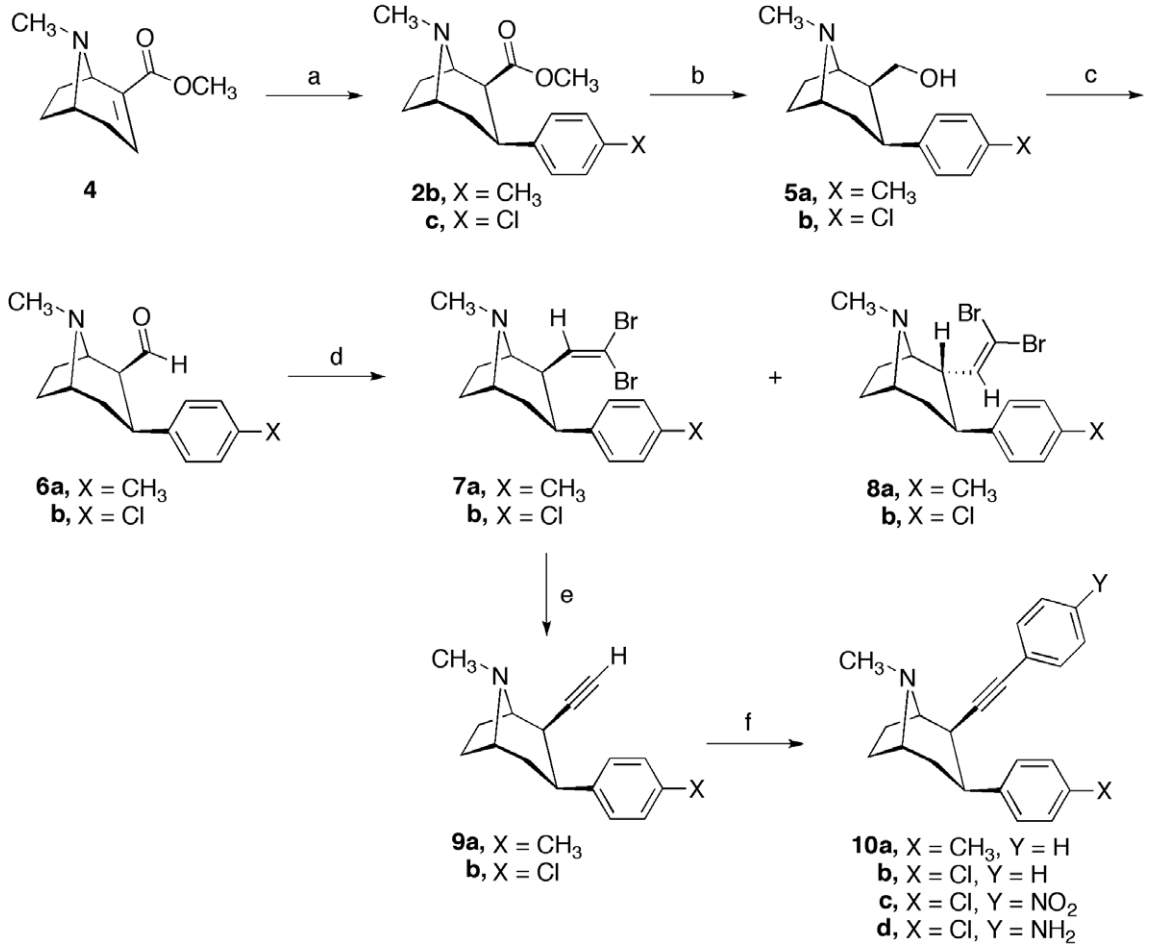
doi:10.1016/j.bmc.2008.04.008

studies from other groups and us also revealed that large lipophilic groups on the 2β-position, including alkyl, alkenyl and aryl substituents retained high DAT binding affinity.[12,23–25] In addition, exchange of the 2β-carbomethoxy group with bioisosteric heterocyclic groups led to analogs with high-affinity and selectivity for the DAT. One of the most studied compounds in this series is the DAT selective 3-phenyltropane analog, RTI-336 (**3**). RTI-336 is currently in advanced preclinical development.[10–12]

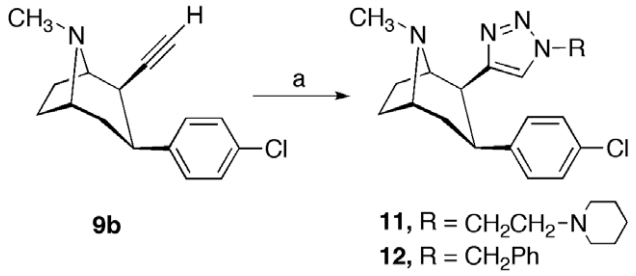
Despite extensive efforts directed toward the development of a pharmacotherapy for cocaine abuse, at present no clinically approved drugs are available. In order to gain a better understanding of the molecular mechanisms of cocaine actions in the brain and find highly potent and selective monoamine uptake inhibitors, we have continued the investigation on modification of **2a**. The present study was undertaken to further explore the SAR of 2-substituents of the 3β-phenyltropanes. In this paper, we describe the synthesis and monoamine transporter binding properties of several 2β-alkynyl and 2β-(1,2,3-triazol)substituted 3β-(substituted phenyl)tropane derivatives, and report that 3β-(4-chlorophenyl)-2β-(4-nitrophenylethynyl)tropane (**10c**) has high potency and good selectivity for the DAT relative to the 5-HTT and NET.

2. Chemistry

The synthesis of 2β-alkynyl-3β-(substituted phenyl)tropane analogs **9a**,**b** and **10a–d** starting with anhydroecgonine methyl ester (**4**) is outlined in Scheme 1. The 1,4-addition of **4** with the appropriate Grignard reagent at −45 °C in ethyl ether followed by trifluoroacetic acid (TFA) led to the corresponding 3β-aryl substituted compounds **2b,c**.[26] Lithium aluminum hydride ($LiAlH_4$) reduction of the 2β-ester group of **2b,c** afforded alcohols **5a,b**. Swern oxidation of **5a,b** provided aldehydes **6a,b**. The aldehydes **6a,b** were not stable and underwent epimerization at the C(2)-position during silica gel chromatography. Therefore, crude **6a,b**, used without purification, were treated with carbon tetrabromide, triphenylphosphine, and zinc to give the 2β-isomers **7a,b** in the order of 54–56% yield as well as the minor 2α-isomers **8a,b** in 1.7% and 1.4% yield, respectively, after column chromatography. With the C(2)-position no longer susceptible to epimerization, **7a,b** were treated with 2 equivalents of butyl lithium to afford 2β-ethynyltro-



Scheme 1. Reagents and conditions: (a) Grignard reagent, −45 °C, 2 h, then −78 °C, TFA; (b) $LiAlH_4$ THF, room temperature; (c) Swern oxidation; (d) CBr_4, PPh_3, Zn, CH_2Cl_2, room temperature; (e) BuLi, THF, −78 °C to room temperature; (f) ArI, $Pd(PPh_3)_4$, CuI, benzene–Et_3N, 40 °C.



Scheme 2. Reagents and conditions: (a) azide, $CuSO_4$, sodium ascorbate, *t*BuOH-H_2O, room temperature.

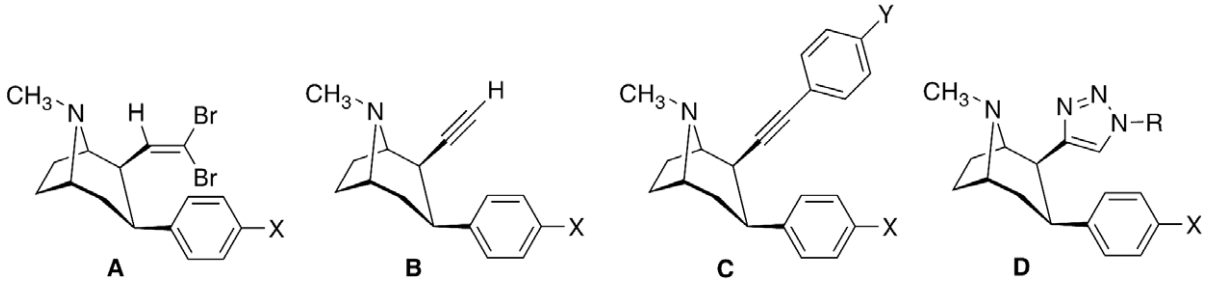
panes **9a,b** exclusively. Sonogashira coupling of ethyne **9a** or **9b** with iodobenzene using tetrakis(triphenylphosphine)palladium(0), and copper(I) iodide in 1:1 mixture of benzene-triethylamine gave 2β-phenylethynyltropanes **10a** and **10b**, respectively. Finally, coupling of **9b** with 1-iodo-4-nitrobenzene or 4-iodoaniline furnished **10c** and **10d**. The relative stereochemistry of each compound was determined by ^{1}H NMR spectral analysis, particularly with the aid of coupling constants of C(2)–H and C(3)–H. The vicinal couplings of $J_{2eq,3ax}$ = 5.4–5.7 Hz and $J_{2ax,3ax}$ = 11.5–11.9 Hz for the 2β- and 2α-substituents, respectively, are in good agreement with stereochemical assignments.

Recently, the copper(I)-catalyzed 1,2,3-triazole formation from terminal alkynes and azides, also known as the 'click reaction', has found growing applications in drug discovery due to the favorable physicochemical properties of triazole, which can readily associate with biological targets through hydrogen bonding and dipole interactions.[27,28] Accordingly, 2β-(1,2,3-triazol)substituted tropanes **11** and **12** were synthesized by treatment of **9b** with 1-(2-azidoethyl)piperidine or benzylazide in the presence of copper sulfate and sodium ascorbate (Scheme 2).

3. Biology

The binding affinities for the target compounds at the DAT, NET, and 5-HTT were determined via competitive binding assays using the previously reported procedures.[29,30] The final concentration of radioligands in the assays was 0.5 nM [^{3}H]WIN35,428 for the DAT, 0.5 nM [^{3}H]nisoxetine for the NET, and 0.2 nM [^{3}H]paroxetine for the 5-HTT. The results of the binding studies, along with binding data of cocaine and **2a**[10] for comparison are listed in Table 1. Since the NET and 5-HTT have only one binding site, K_i values were calculated for inhibition of binding at these two transporters.

Table 1. Monoamine transporter binding potencies for 2β-substituted 3β-(substituted phenyl)tropane derivatives



Compound[a]	*c*log *P*	Structure	X	Y	R	DAT, IC_{50}[d] (nM) [^{3}H]WIN35,428	NET, K_i[d] (nM) [^{3}H]nisoxetine	5-HTT, K_i[d] (nM) [^{3}H]paroxetine
Cocaine[b]						89.1	1990	95
2a	—	—	—	—	—	23	556	182
7a	5.21	A	CH_3			0.23 ± 0.05	3.4 ± 0.6	39 ± 10
7b	5.35	A	Cl			0.32 ± 0.05	3.5 ± 0.3	7 ± 2
8a	5.21	A[c]	CH_3			3.6 ± 1.1	55 ± 2	252 ± 13
8b	5.35	A[c]	Cl			1.4 ± 0.2	49 ± 2	76 ± 9
9a	3.40	B	CH_3			11 ± 3	150 ± 20	54 ± 15
9b	3.53	B	Cl			3.6 ± 0.4	75 ± 13	18 ± 2
10a	5.87	C	CH_3	H		0.8 ± 0.3	31 ± 1	730 ± 190
10b	6.01	C	Cl	H		0.8 ± 0.2	14 ± 2	81 ± 4
10c	5.74	C	Cl	NO_2		0.9 ± 0.2	230 ± 20	620 ± 150
10d	4.73	C	Cl	NH_2		2.2 ± 0.5	50 ± 3	19 ± 3
11	3.89	D	Cl		NCH_2CH_2	8 ± 1	430 ± 50	138 ± 11
12	4.25	D	Cl		$C_6H_5CH_2$	47 ± 12	2560 ± 130	161 ± 27

[a] All compounds were tested as the HCl salt.
[b] Data taken from Ref. 9.
[c] 2α-Stereoisomer.
[d] All values are means ± standard error of three or four experiments performed in triplicate.

4. Results and discussion

One of the most interesting features of the SAR of 3-phenyltropane analogs for the DAT is that exchanging the 2β-ester group in WIN 35,065-2, with amide, ether, heterocyclic, keto, alkyl, alkenyl, or aryl substituents at the C(2)-position provides compounds with equal or greater affinity than that of WIN 35,065-2 at the DAT.[12] Although the DAT tolerates ligands having a broad variety of 2β-substituents with little change in the affinity of the ligand, the nature of the substituents has a profound effect on the monoamine selectivity. In order to gain additional information on the structural requirements for high-affinity and good selectivity at the C(2)-position, we designed and synthesized a new series of 2-substituted 3β-(substituted phenyl)tropane derivatives.

All the compounds possessed high affinities at the DAT with nanomolar or subnanomolar IC_{50} values ranging from 0.23 nM to 47 nM. No correlation was observed between the DAT binding affinities with the calculated partition coefficients ($c\log P$) of the compounds. Generally, the 3β-(4-chlorophenyl) substituted tropanes except **7b** were equal or more potent than the compounds with a 3β-(4-methylphenyl) substitution. The 2α-isomers **8a** and **8b** were approximately 16- and 4-fold less potent than the corresponding 2β-isomers **7a** and **7b**, respectively. This was consistent with the previous findings that exchange of the 2β-substituent in the tropane derivatives with the 2α moiety decreased the relative binding affinity for the DAT.[31]

Among the tested 2β-substituted tropanes, the 2β-dibromovinyltropanes **7a** and **7b** possessed the highest potency at the DAT with IC_{50} values of 0.23 nM and 0.32 nM, respectively. Replacement of the vinyl group with the ethynyl substitution afforded **9a** and **9b** with decreased affinities at the DAT (11 nM vs 0.23 nM and 3.6 nM vs 0.32 nM IC_{50}). It is interesting to note that attachment of a phenyl group to the end of the ethyne group gave **10a** and **10b**, which regained the binding affinity by 4- to 14-fold, respectively. In addition, replacing the phenylethynyl group at the C(2)-position of the 3β-(4-chlorophenyl) analogue **10b** (IC_{50} = 0.8 nM) with the 4-nitrophenylethynyl substitution to give **10c** had no effect on binding affinity (IC_{50} = 0.9 nM). However, the addition of a 4-amino group to **10b** resulted in approximately 3-fold loss of binding affinity at the DAT. These findings support previous reports that a large pocket is present in the DAT binding site occupied by the 2β-substituent.[12] The lipophilic interactions as well as the possible π-interactions between the 2β-substituents and the binding site may play an important role for the high affinity of these ligands. Finally, as analogs of the reported 2β-heterocyclic tropanes, the 2β-(1,2,3-triazol)substituted tropane derivatives **11** and **12** also possessed high-affinity at the DAT with IC_{50} values of 8 nM and 47 nM, respectively.

In terms of monoamine selectivity, all the compounds exhibited lower binding affinities at the NET and 5-HTT relative to the DAT. However, no correlation was observed between the 2β-substituents and the monoamine selectivity. 3β-(4-Chlorophenyl)-2β-(4-nitrophenylethynyl)tropane (**10c**) with an IC_{50} value of 0.9 nM at the DAT and K_i values of 230 nM at the NET and 620 nM at the 5-HTT, respectively, was one of the most potent and selective compounds for the DAT relative to the NET and 5-HTT in the series.

In summary, several novel 3β-(substituted phenyl)tropanes with various 2β-alkynyl and 2β-(1,2,3-triazol) substituents were synthesized and evaluated for their monoamine transporter binding affinities. All the tested compounds demonstrated higher potency at the DAT than cocaine and were more selective relative to binding at the NET and 5-HTT. One of the most potent and selective compounds in the series, 3β-(4-chlorophenyl)-2β-(4-nitrophenylethynyl)tropane (**10c**) had an IC_{50} value of 0.9 nM at the DAT and was 256- and 689-fold selective for the DAT over the NET and 5-HTT, respectively. These 2β-substituted tropanes are promising leads for further investigation of highly potent and selective monoamine inhibitors.

5. Experimental

Melting points were determined using a MEL-TEMP II capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained on a Bruker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Mass spectra (MS) were run on a Perkin-Elmer SCIEX API 150 EX mass spectrometer outfitted with ESI (turbospray) source or on a Hewlett Packard 5989A instrument by electron impact. Elemental analysis was performed by Atlantic Microlab Inc., Atlanta, GA. Optical rotations were measured on an AutoPol III polarimeter, purchased from Rudolf Research. Analytical thin-layer chromatography (TLC) was carried out using EMD silica gel 60 F_{254} TLC plates. TLC visualization was achieved with a UV lamp or in an iodine chamber. Flash column chromatography was done on a CombiFlash Companion system using Isco prepacked silica gel columns or using EM Science silica gel 60 Å (230–400 mesh). Unless otherwise stated, reagent-grade chemicals were obtained from commercial sources and were used without further purification. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen.

5.1. 3β-(4-Methylphenyl)-2β-hydroxymethyltropane (5a)

To a stirred solution of **2b**[26] (11.4 g, 0.04 mol) in anhydrous THF (100 mL) at 0 °C under nitrogen was added $LiAlH_4$ (3.04 g, 0.080 mol). After stirring at room temperature for 2 h, the reaction was quenched by slow addition of H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (3 × 50 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded crude **5a** (9.60 g, 98%) as a white solid: mp 78–80 °C; ^{1}H NMR

($CDCl_3$) δ 7.25 (d, J = 8.1 Hz, 2 H), 7.12 (d, J = 8.1 Hz, 2H), 3.75 (dd, J = 10.8, 2.1 Hz, 1H), 3.51–3.45 (m, 1H), 3.39 (dd, J = 10.8, 2.1 Hz, 1H), 3.37–3.29 (m, 1H). 3.05 (ddd, J = 12.9, 5.7, 5.7 Hz, 1H), 2.51 (ddd, J = 12.9, 12.9, 3.0 Hz, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.26–2.04 (m, 2H), 1.82–1.57 (m, 3H), 1.52–1.43 (m, 1H); MS (ESI) m/z 246.4 (M+1). The desired compound was used in the next step without further purification.

5.2. 3β-(4-Chlorophenyl)-2β-hydroxymethyltropane (5b)

The procedure for **5a** was followed using 10.0 g (0.034 mol) of **2c**[26] to give 8.90 g (99%) of **5b** as a white solid: mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.38–7.25 (m, 4H), 3.75 (dd, J = 11.1, 2.1 Hz, 1H), 3.50–3.42 (m, 1H), 3.38–3.28 (m, 2H), 3.12–3.00 (m, 1H), 2.49 (ddd, J = 12.9, 12.9, 3.2 Hz, 1H), 2.27 (s, 3H), 2.26–2.04 (m, 2H), 1.80–1.57 (m, 3H), 1.50–1.44 (m, 1H); MS (ESI) m/z 266.3 (M+1). The desired compound was used in the next step without further purification.

5.3. 3β-(4-Methylphenyl)-2β-(2,2-dibromovinyl)tropane (7a) and 3β-(4-methylphenyl)-2α-(2,2-dibromovinyl)tropane (8a)

To a stirred solution of oxalyl chloride (2 M solution, 16.5 mL, 33.0 mmol) in anhydrous CH_2Cl_2 (100 mL) at −78 °C under nitrogen was added anhydrous DMSO (4.68 mL, 66.0 mmol). After stirring for 15 min, a solution of **5a** (5.40 g, 22.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was added and the reaction mixture was stirred at −78 °C for another 30 min. TEA (18.4 mL, 132 mmol) was then added and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by addition of H_2O (10 mL). The organic layer was separated and washed with NH_4Cl (3 × 50 mL), brine (50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded aldehyde **6a** (5.42 g) as an oil, which was used in the next step without further purification.

To a stirred solution of CBr_4 (14.6 g, 0.044 mol) in anhydrous CH_2Cl_2 (165 mL) at 0 °C under nitrogen was added PPh_3 (11.5 g, 0.044 mol) followed by zinc dust (2.88 g, 0.044 mol). After stirring at room temperature for 16 h, the reaction mixture was cooled to 0 °C and a solution of aldehyde **6a** (5.42 g) was added. The reaction mixture was stirred at room temperature for 1 h and filtered through a short pad of Celite. The filtrate was washed with brine (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography on silica gel (300 g) using 0 → 30% ether in hexanes with 5% TEA afforded 2β-isomer **7a** (4.94 g, 56%) and 2α-isomer **8a** (0.15 g, 1.7%). Compound **7a:** white solid; mp 48–50 °C; ^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 6.70 (d, J = 9.4 Hz, 1H), 3.35–3.26 (m, 1H), 2.19–2.13 (m, 1H), 3.07 (ddd, J = 12.6, 5.7, 5.7 Hz, 1H), 2.64 (ddd, J = 5.7, 3.5, 9.4 Hz, 1H), 2.31 (s, 3H), 2.22 (s, 3H), 2.21–2.01 (m, 3H), 1.80–1.58 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 139.8, 138.9, 135.8, 129.0, 127.8, 87.7, 66.1, 62.4, 51.5, 42.2, 35.9, 35.1, 26.6, 25.2, 21.2; MS (ESI) m/z 400.2 (M+1). The free base was converted to the hydrochloride salt: mp 241 °C (dec); $[\alpha]_D^{20}$ −41.67° (c 0.24, CH_3OH); Anal. Calcd for $C_{17}H_{21}Br_2N{\cdot}HCl{\cdot}0.75H_2O$: C, 45.46; H, 5.27; N, 3.12. Found: C, 45.32; H, 5.35; N, 3.01.

Compound **8a:** white solid; mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ 7.07 (s, 4H), 6.09 (d, J = 9.1 Hz, 1H), 3.30–3.16 (m, 2H), 3.03 (ddd, J = 11.5, 2.6, 9.1 Hz, 1H), 2.60 (ddd, J = 11.5, 11.7, 5.4 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 2.20–1.94 (m, 2H), 1.87 (ddd, J = 11.7, 11.7, 2.4 Hz, 1H), 1.77–1.54 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 140.1, 140.0, 136.2, 129.4, 127.7, 89.9, 64.4, 61.4, 49.7, 40.4, 39.9, 39.7, 26.4, 23.7, 21.2; MS (ESI) m/z 400.3 (M+1). The free base was converted to the hydrochloride salt: mp 210 °C (dec); $[\alpha]_D^{20}$ +23.53° (c 0.26, CH_3OH); Anal. Calcd for $C_{17}H_{21}Br_2N{\cdot}HCl{\cdot}0.25H_2O$: C, 46.39; H, 5.15; N, 3.18. Found: C, 46.21; H, 5.36; N, 3.11.

5.4. 3β-(4-Chlorophenyl)-2β-(2,2-dibromovinyl)tropane (7b) and 3β-(4-chlorophenyl)-2α-(2,2-dibromovinyl)tropane (8b)

The procedure for **7a** and **8a** was followed using 5.30 g (0.02 mol) of **5b** to give 4.53 g (54%) of 2β-isomer **7b** and 0.12 g (1.4%) of 2α-isomer **8b**. Compound **7b:** white solid; mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 7.30–7.20 (m, 2H), 7.10–7.03 (m, 2H), 6.70 (d, J = 9.5 Hz, 1H), 3.32–3.26 (m, 1H), 3.18–3.10 (m, 1H), 3.07 (ddd, J = 12.9, 5.6, 5.4 Hz, 1H), 2.62 (ddd, J = 5.6, 3.3, 9.5 Hz, 1H), 2.22 (s, 3H), 2.20–2.02 (m, 3H), 1.80–1.57 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 140.5, 139.2, 132.0, 129.3, 128.2, 88.2, 65.9, 62.1, 51.3, 42.1, 36.0, 35.0, 26.6, 25.2; MS (ESI) m/z 420.3 (M+1). The free base was converted to the hydrochloride salt: mp 235 °C (dec); $[\alpha]_D^{20}$ −34.9° (c 0.22, CH_3OH); Anal. Calcd for $C_{16}H_{18}Br_2ClN{\cdot}HCl$: C, 42.14; H, 4.20; N, 3.07. Found: C, 42.27; H, 4.21; N, 3.14.

Compound **8b:** oil; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.07 (d, J = 9.4 Hz, 1H), 3.30–3.16 (m, 2H), 3.00 (ddd, J = 11.9, 2.4, 9.4 Hz, 1H), 2.61 (ddd, J = 11.9, 12.2, 5.4 Hz, 1H), 2.39 (s, 3H), 2.20–1.94 (m, 2H), 1.85 (ddd, J = 12.2, 12.6, 2.4 Hz, 1H), 1.77–1.53 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.7, 139.4, 132.4, 129.3, 128.8, 90.4, 64.5, 61.4, 50.1, 40.3, 40.1, 39.6, 26.3, 23.7; MS (ESI) m/z 420.5 (M+1). The free base was converted to the hydrochloride salt: mp 140 °C (fusion); $[\alpha]_D^{20}$ +26.1° (c 0.23, CH_3OH); Anal. Calcd for $C_{16}H_{18}Br_2ClN{\cdot}HCl$: C, 42.14; H, 4.20; N, 3.07. Found: C, 42.27; H, 3.97; N, 3.02.

5.5. 3β-(4-Methylphenyl)-2β-ethynyltropane (9a)

To a stirred solution of **7a** (400 mg, 1.00 mmol) in anhydrous THF (10 mL) at −78 °C under nitrogen was added BuLi (1.6 M solution, 1.31 mL, 2.10 mmol). After stirring at −78 °C for 1 h, the reaction mixture was warmed to room temperature and the stirring was continued for another 1 h. The reaction mixture was quenched by addition of saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted

with EtOAc (3× 30 mL). The combined organic phases were washed with brine (3× 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography on silica gel (12 g Isco prepacked column) using 0 → 5% ether in hexanes with 5% TEA afforded **9a** (130 mg, 54%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.22–7.08 (m, 4H), 3.38–3.28 (m, 2H), 2.97 (ddd, J = 12.9, 5.4, 5.4 Hz, 1H), 2.73–2.67 (m, 1H), 2.40–2.00 (m, 10H), 1.76–1.51 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 139.4, 136.0, 128.8, 128.1, 84.8, 71.6, 66.7, 61.9, 42.3, 41.6, 35.9, 35.1, 26.1, 25.2, 21.2; MS (ESI) m/z 240.4 (M+1). The free base was converted to the hydrochloride salt: mp 210 °C (dec); $[\alpha]_D^{20}$ −114.2° (c 0.28, CH_3OH); Anal. Calcd for $C_{17}H_{21}N{\cdot}HCl{\cdot}0.25H_2O$: C, 72.84; H, 8.09; N, 5.00. Found: C, 72.66; H, 8.08; N, 4.99.

5.6. 3β-(4-Chlorophenyl)-2β-ethynyltropane (9b)

The procedure for **9a** was followed using 650 mg (1.55 mmol) of **7b** to give 260 mg (65%) of **9b** as a white solid: mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 7.32–7.18 (m, 4H), 3.40–3.30 (m, 2H), 2.98 (ddd, J = 12.9, 5.4, 5.4 Hz, 1H), 2.72–2.65 (m, 1H), 2.33 (s, 3H), 2.30–2.00 (m, 4H), 1.78–1.53 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.0, 132.3, 129.7, 128.2, 84.4, 71.9, 66.6, 61.8, 42.3, 41.5, 35.9, 35.1, 26.1, 25.2; MS (ESI) m/z 260.4 (M+1). The free base was converted to the hydrochloride salt: mp 145 °C (fusion); $[\alpha]_D^{20}$ −106.3° (c 0.26, CH_3OH); Anal. Calcd for $C_{16}H_{18}ClN{\cdot}HCl{\cdot}1.25H_2O$: C, 60.29; H, 6.80; N, 4.39. Found: C, 60.37; H, 6.89; N, 4.27.

5.7. 3β-(4-Methylphenyl)-2β-(phenylethynyl)tropane (10a)

To a stirred mixture of **9a** (40.0 mg, 0.17 mmol), CuI (3.18 mg, 0.017 mmol), and $Pd(PPh_3)_4$ (6.00 mg, 0.005 mmol) in 1:1 mixture of benzene–TEA (5 mL) at room temperature under nitrogen was added iodobenzene (0.075 mL, 0.67 mmol). The reaction mixture was stirred at 40 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL), washed with NH_4Cl (10 mL), brine (3 × 30 mL), and concentrated under reduced pressure. The resultant residue was partitioned between ether (10 mL) and 6 N HCl (10 mL). The aqueous layer was separated, basified to pH 11 with NH_4OH and extracted with EtOAc (3× 30 mL). The combined EtOAc extracts were washed with brine (3× 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography on silica gel (12 g Isco prepacked column) using 2% TEA in hexanes afforded **10a** (45.0 mg, 86%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.34–7.08 (m, 9H), 3.47–3.40 (m, 1H), 3.39–3.30 (m, 1H), 3.06 (ddd, J = 12.9, 5.4, 5.4 Hz, 1H), 2.93–2.87 (m, 1H), 2.42–2.03 (m, 9H), 1.80–1.54 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 139.8, 136.1, 131.8, 128.8, 128.5, 128.0, 127.3, 124.6, 91.2, 83.9, 66.6, 61.9, 42.5, 42.1, 36.8, 35.3, 26.5, 25.4, 21.2; MS (ESI) m/z 316.5 (M+1). The free base was converted to the hydrochloride salt: mp 228 °C (dec); $[\alpha]_D^{20}$ −229.0° (c 0.25, CH_3OH); Anal. Calcd for $C_{23}H_{25}N{\cdot}HCl{\cdot}0.25H_2O$: C, 77.51; H, 7.49; N, 3.93. Found: C, 77.30; H, 7.45; N, 3.92.

5.8. 3β-(4-Chlorophenyl)-2β-(phenylethynyl)tropane (10b)

The procedure for **10a** was followed using 78.0 mg (0.30 mmol) of **9b** and 0.13 mL (1.20 mmol) of iodobenzene to give 70.0 mg (70%) of **10b** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 5H), 7.20 (m, 4H), 3.50–3.40 (m, 1H), 3.39–3.30 (m, 1H), 3.07 (ddd, J = 12.9, 5.4, 5.4 Hz, 1H), 2.92–2.84 (m, 1H), 2.37 (s, 3H), 2.35–2.05 (m, 3H), 1.78–1.53 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 141.5, 132.4, 131.8, 130.0, 128.2, 127.5, 124.2, 90.6, 84.2, 66.5, 61.8, 42.3, 42.0, 36.6, 35.1, 26.5, 25.4; MS (ESI) m/z 336.5 (M+1). The free base was converted to the hydrochloride salt: mp 234 °C (dec); $[\alpha]_D^{20}$ −228.1° (c 0.21, CH_3OH); Anal. Calcd for $C_{22}H_{22}ClN{\cdot}HCl{\cdot}0.5H_2O$: C, 69.29; H, 6.34; N, 3.67. Found: C, 69.65; H, 6.12; N, 3.73.

5.9. 3β-(4-Chlorophenyl)-2β-(4-nitrophenylethynyl)tropane (10c)

The procedure for **10a** was followed using 78.0 mg (0.30 mmol) of **9b** and 299 mg (1.20 mmol) of 1-iodo-4-nitrobenzene to give 110 mg (96%) of **10c** as a white solid: mp 62–64 °C; ^{1}H NMR ($CDCl_3$) δ 8.12–8.02 (m, 2H), 7.40–7.23 (m, 6H), 3.50–3.41 (m, 1H), 3.40–3.30 (m, 1H), 3.12 (ddd, J = 12.6, 5.4, 5.4 Hz, 1H), 2.98–2.90 (m, 1H), 2.36 (s, 3H), 2.32–2.05 (m, 3H), 1.80–1.54 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 146.6, 141.1, 132.5, 132.4, 131.3, 129.7, 128.3, 123.4, 97.0, 82.7, 66.3, 61.8, 42.7, 42.1, 36.3, 35.1, 26.3, 25.3; MS (ESI) m/z 381.6 (M+1). The free base was converted to the hydrochloride salt: mp 115–117 °C; $[\alpha]_D^{20}$ −265.3° (c 0.23, CH_3OH); Anal. Calcd for $C_{22}H_{21}ClN_2O_2{\cdot}HCl{\cdot}0.25H_2O$: C, 62.64; H, 5.38; N, 6.64. Found: C, 62.44; H, 5.31; N, 6.49.

5.10. 3β-(4-Chlorophenyl)-2β-(4-aminophenylethynyl)tropane (10d)

The procedure for **10a** was followed using 78.0 mg (0.30 mmol) of **9b** and 263 mg (1.20 mmol) of 4-iodoaniline to give 65.0 mg (62%) of **10d** as a white solid: mp 188–190 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (s, 4H), 7.01 (d, J = 6.0 Hz, 2H), 6.50 (d, J = 6.0 Hz, 2H), 3.64 (br s, 2H), 3.45–3.38 (m, 1H), 3.38–3.30 (m, 1H), 3.02 (ddd, J = 12.6, 5.4, 5.4 Hz, 1H), 2.88–2.81 (m, 1H), 2.37 (s, 3H), 2.32–2.03 (m, 3H), 1.80–1.53 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 146.0, 141.6, 132.9, 132.2, 130.0, 128.2, 114.7, 113.9, 87.9, 84.5, 66.6, 61.8, 42.2, 42.0, 36.7, 35.1, 26.5, 25.4; MS (ESI) m/z 351.3 (M+1). The free base was converted to the hydrochloride salt: mp 240 °C (dec); $[\alpha]_D^{20}$ −199.2° (c 0.26, CH_3OH); Anal. Calcd for $C_{22}H_{23}ClN_2{\cdot}2HCl{\cdot}1.25\ H_2O$: C, 59.20; H, 6.21; N, 6.28. Found: C, 59.57; H, 6.11; N, 6.05.

5.11. 3β-(4-Chlorophenyl)-2β-[1-(2-piperidin-1-yl)ethyl-1H-[1,2,3]triazol-4-yl]tropane (11)

To a stirred suspension of **9b** (130 mg, 0.50 mmol) and 1-(2-azidoethyl)-piperidine (77.1 mg, 0.50 mmol) in 1:1 mixture of tBuOH-H_2O (4 mL) at room temperature under nitrogen was added a freshly prepared 1 M sodium ascorbate solution (0.50 mL, 0.50 mmol) followed by 0.3 M $CuSO_4$ solution (0.167 mL, 0.05 mmol). After stir-

ring for 10 h, the reaction mixture was diluted with EtOAc (50 mL), washed with brine (3× 30 mL) and dried (Na_2SO_4). The solvent was concentrated under reduced pressure. Flash column chromatography on silica gel (12 g Isco prepacked column) using 0 → 10% ether in hexanes with 5% TEA afforded **11** (135 mg, 65%) as a white solid: mp 250 °C (dec); ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.02–6.92 (m, 2H), 6.83–6.73 (m, 2H), 4.37–4.16 (m, 2H), 3.34–3.09 (m, 4H), 2.60 (t, J = 6.0 Hz, 2H), 2.40–2.21 (m, 4H), 2.20–1.92 (m, 6H), 1.80–1.30 (m, 9H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 147.4, 141.2, 131.6, 129.1, 128.0, 124.1, 66.8, 61.8, 58.6, 54.5, 47.7, 45.7, 42.2, 35.6, 35.0, 26.3, 26.2, 25.2, 24.3; MS (EI) m/z 414.2 (M^+). The free base was converted to the hydrochloride salt: mp 145 °C (fusion); $[\alpha]_D^{20}$ −66.0° (c 0.24, CH_3OH); Anal. Calcd for $C_{23}H_{32}ClN_5 \cdot 2HCl \cdot 1.5H_2O$: C, 53.75; H, 7.26; N, 13.63. Found: C, 54.13; H, 7.21; N, 13.27.

5.12. 3β-(4-Chlorophenyl)-2β-(1-benzyl-1H-[1,2,3]triazol-4-yl)tropane (12)

The procedure for **11** was followed using 130 mg (0.50 mmol) of **9b** and 0.066 mL (0.50 mmol) of benzylazide to give 155 mg (79%) of **12** as a white solid: 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 1H), 7.40–7.27 (m, 3H), 7.10–6.95 (m, 4H), 6.77 (d, J = 8.4 Hz, 2H), 5.55 (d, J = 15.0 Hz, 1H), 5.31 (d, J = 15.0 Hz, 1H), 3.46–3.40 (m, 1H), 3.32–3.18 (m, 3H), 2.30–1.93 (m, 6H), 1.88–1.53 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 148.3, 141.1, 135.9, 131.7, 129.0, 128.9, 128.4, 128.1, 127.3, 123.6, 66.7, 61.8, 53.7, 46.0, 42.2, 35.4, 34.9, 26.3, 25.2; MS (EI) m/z 393.2 (M^+). The free base was converted to the hydrochloride salt: mp 118 °C (fusion); $[\alpha]_D^{20}$ −110.9° (c 0.23, CH_3OH); Anal. Calcd for $C_{23}H_{25}ClN_4 \cdot HCl \cdot 0.75H_2O$: C, 62.37; H, 6.26; N, 12.65. Found: C, 62.44; H, 6.29; N, 12.53.

Acknowledgment

This research was supported by the National Institute on Drug Abuse, Grant No. DA05477.

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