Synthesis and Transporter Binding Properties of 2,3-Diphenyltropane Stereoisomers. Comparison to 3β-Phenyltropane-2β-carboxylic Acid Esters

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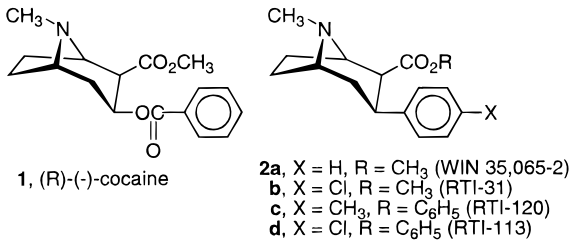
2β,3β-Diphenyl-(**5**), 2α,3α-diphenyl-(**6**), and 2α,3β-diphenyltropane (**3**) as well as 2,3-diphenyltrop-2-ene (**4**) were prepared in racemic form and assayed for inhibition of radioligand binding at the dopamine (DA), serotonin (5-HT), and norepinephrine (NE) transporters. Among all three transporters, compounds **4**−**6** bound the DA transporter with the highest affinity. The 2β,3β-diphenyltropane (**5**) bound the DA transporter with an IC_{50} value (28 nM) almost identical to that of 3β-phenyltropane-2β-carboxylic acid methyl ester (WIN 35,065-2) and has much greater selectivity relative to binding to the serotonin transporter. A comparison of the radioligand data from this study to radioligand data obtained on other WIN 35,065-2 analogs suggests that hydrophobicity of the C-2 substituent of some analogs of the WIN 35,065-2 class may be an important contributing factor to binding at the DA transporter.

Because of its powerful reinforcing properties, (*R*)-(−)-cocaine (**1**) has great abuse potential, and the level of its abuse has reached epidemic proportions in the recent years. While cocaine inhibits the presynaptic uptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE), evidence suggests that cocaine binding to the dopamine transporter and consequently the inhibition of dopamine uptake may be responsible for the reinforcing and locomotor properties of cocaine.[1−5] These findings have prompted extensive studies aimed at a better understanding of cocaine's mechanism of action and the structural requirements of the cocaine binding site on the dopamine transporter.

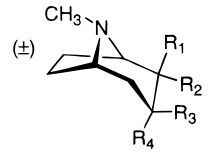
Extensive structure−activity relationship (SAR) studies of cocaine (**1**) and the WIN 35,065-2 (**2a**) classes of compounds have identified structural features required for potency and selectivity for inhibition of radioligand binding at the dopamine transporter which include an aromatic ring at the 3-position, the tropane nitrogen, and the N-substituent.[6−11] However, the requirements for the 2-substituent have been less well-defined. Recent studies have shown that the 2β-carbomethoxy group found in cocaine (**1**) and WIN 35,065-2 analogs (**2**) can be replaced by ketones,[12] heterocycles,[13,14] amides,[15] alkyl groups,[16,17] and olefins[18] and still retain high potency for the dopamine transporter.

In the present study, we investigate the effect of replacement of the 2β-carbomethoxy group of WIN-35,-065-2 with a phenyl group on dopamine transporter binding. Various stereoisomers of (±)-2,3-diphenyltropanes (**3**−**6**) were synthesized and evaluated in competitive binding assays to determine their affinities for the DA, 5-HT, and NE transporters.



1, (R)-(-)-cocaine

2a, X = H, R = CH_3 (WIN 35,065-2)
b, X = Cl, R = CH_3 (RTI-31)
c, X = CH_3, R = C_6H_5 (RTI-120)
d, X = Cl, R = C_6H_5 (RTI-113)



	R_1	R_2	R_3	R_4
3	-OH	-PH	-Ph	-H
4 (2-tropene)	—	-Ph	-Ph	—
5	-Ph	-H	-Ph	-H
6	-H	-Ph	-H	-Ph

Chemistry

The target compounds were synthesized as racemates from intermediate (±)-**7**, which was prepared in five steps from 3-tropinone via a reported synthesis.[19,20] Treatment of (±)-**7** with phenylmagnesium bromide produced intermediates **8** (Scheme 1). Reduction of the ethoxycarbonyl group in compound **8** with lithium aluminum hydride yielded target compound **3**. Alternatively, intermediate **8** was dehydrated to produce the tropene **9**, which was found to readily undergo a photochemical reaction, presumably cyclizing to form a phenanthrene derivative. However, compound **9** could be reduced to target compound **4** or hydrogenated before lithium aluminum hydride reduction to generate compounds **10** and **11**. Thus, the routes in Scheme 1 resulted in the synthesis of 2α,3β-diphenyl (**3**), 2β,3β-diphenyl (**5**), and 2α,3α-diphenyltropanes (**6**) as well as 2,3-diphenyltrop-2-ene (**4**). Attempts to prepare 2β,3α-diphenyltropane were unsuccessful.

The structures and stereochemical assignments for the compounds were determined using ^{1}H, ^{13}C NMR, 2D COSY,[21,22] NOESY,[23] and HMQC[24] spectral analysis. The stereochemical assignments for compounds **3**, **5**, and **6** were established using vicinal coupling constants obtained from ^{1}H NMR spectra supplemented with through-space interactions obtained from 2D NOESY

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Scheme 1

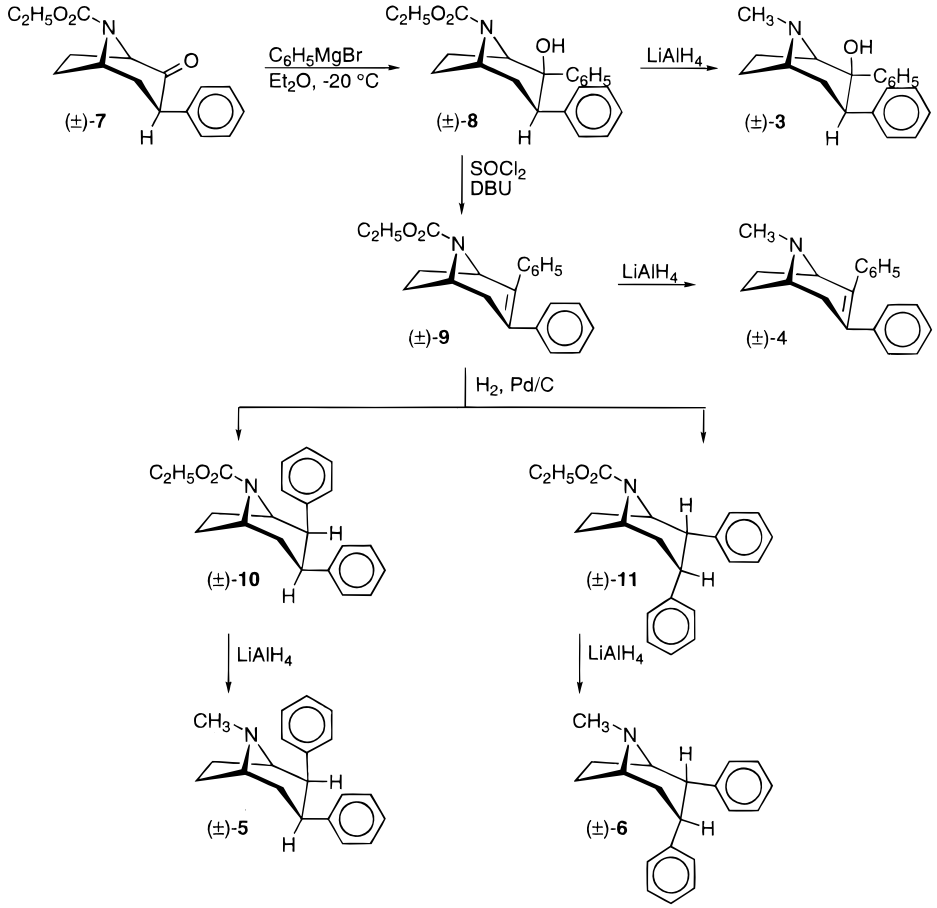
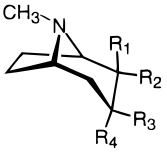


Table 1. Binding Affinities of **3**−**6** at the DA, 5-HT, and NE Transporters

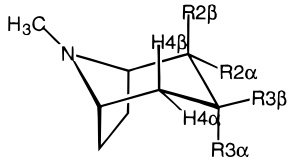


						IC$_{50}$ (nM)	
compd	R_1	R_2	R_3	R_4	DA	5-HT	NE
cocaine (**1**)[a]					89 ± 4.8	1050 ± 89	3300 ± 290
2a[a]	CO_2CH_3	H	Ph	H	23 ± 5	1960 ± 61	920 ± 73
(±)-**3**	OH	Ph	Ph	H	2860 ± 290	37200 ± 2410	>175000
(±)-**4** (2-tropene)		Ph	Ph		550 ± 43	47800 ± 4910	21400 ± 1630
(±)-**5**	Ph	H	Ph	H	28 ± 1.9	34700 ± 3950	2670 ± 6270
(±)-**6**	H	Ph	H	Ph	1270 ± 120	18600 ± 1880	2770 ± 280

[a] The IC$_{50}$ values are from ref 15.

spectra. Analysis of the dihedral angles in substitituted 3-phenyltropanes in the chair conformation have shown that a 1,2 diaxial relationship between two protons produces a dihedral angle of approximately 180° and therefore, using the Karplus relationship,[25] gives a large vicinal coupling constant, whereas a 1,2 axial− equatorial relationship produces a dihedral angle of around 45° and, therefore, gave a medium vicinal coupling constant.[13] The large diaxial coupling constant (J^3= 12.5 Hz) between H3 and H4β (Table 2) of compound **3** showed that this compound possessed a 3β-phenyl group. Since H4β is axial, H3 must also be axial, and the 3-phenyl is equatorial. The 2-position is disubstituted; thus, information cannot be gained from analysis of coupling constants. However, the NOESY spectrum of compound **3** reveals an interaction between the 2-phenyl and H7. This shows that the 2-phenyl group is equatorial. In compound **5** the large diaxial coupling constant (J^3 = 13.0 Hz) between H3 and H4β shows that H3 is axial. Since H3 is axial, the medium coupling

Table 2. NMR Characteristics of **3**, **5**, and **6**



compd	R2β	R2α	R3β	R3α	J_{23} (Hz)	$J_{34\beta}$ (Hz)	characteristic NOE interactions
(±)-**3**	OH	Ph	Ph	H		12.5	H7-Ph2α
(±)-**5**	Ph	H	Ph	H	6.6	13.0	H3α-H6, H2α-H7
(±)-**6**	H	Ph	H	Ph	8.0	8.0	H2-H4β, H2β-NMe

constant ($J^3 = 6.6$ Hz) between H3 and H2, characteristic of an axial−equatorial relationship, fixes H2 as equatorial. Further confirmation of this stereochemistry was obtained from the NOESY spectrum which shows an interaction between H2α and H7and between H3α and H6. These interactions also validate the assumption of the chair conformer. In compound **6** the medium coupling constant ($J^3 = 8.0$ Hz) reveals an axial−equatorial relationship between H3 and H4β. Therefore, H3 must be equatorial. Neither the coupling of H2 to H3 nor to H1 is diagnostic of the stereochemistry of H2. However, the NOESY spectrum of **6** shows an interaction between H2 and H4β which is possible only if H2 is axial. This interaction also eliminates the possibility of the boat conformation in compound **6**.

Biology

The binding affinities of the compounds for dopamine, serotonin, and norepinephrine transporters were determined via competitive binding assays using previously reported procedures.[14] The radioligands used were 0.5 nM [^{3}H]WIN35,428 for the DA transporter, 0.2 nM [^{3}H]-paroxetine for the 5-HT transporter, and 0.5 nM [^{3}H]-nisoxetine for the NE transporter.

The binding affinities of compounds **1**, **2a**, and **3**−**6** are listed in Table 1. The 2β,3β-diphenyl isomer **5** with an IC_{50} value of 28 nM was the most potent at the DA transporter. Moreover, this compound is highly selective for the DA transporter relative to the serotonin transporter. The 2α,3β-diphenyl isomer **3** and the 2α,3α-diphenyl isomer **6** were found to have poor affinity for the cocaine binding site on the DA transporter, with IC_{50} values of 2.9 and 1.3 μM, respectively.

Discussion

The presently reported results provide additional information that a 2β-carbomethoxy group is not necessary for high-affinity binding at the cocaine binding site on the DA transporter. Furthermore, the present results indicate that a phenyl ring can substitute for the 2β-carbomethoxy group in WIN 35,065-2 without loss in binding affinity. The high potency of the 2β,3β isomer relative to the 2α,3β and 2α,3α isomers is also consistent with other cocaine analogues bearing substituents at both C-2 and C-3 positions of the other tropane systems.[6−18]

In view of the racemic nature of the compounds reported in this study, it can be concluded that (±)-**5** and (R)-**2a** bind the DA transporter with equal affinity. However, **5** exhibits much greater selectivity for the DA transporter over the 5-HT and at least equal selectivity over the NE transporters relative to **2a**. This is consistent with previous studies which found that 3β-(4′-methylphenyl)- and 3β-(4′-chlorophenyl)tropane-2β-carboxylic acids phenyl esters (**2c** and **2d**, respectively) retained DA transporter binding affinity similar to their corresponding methyl esters while showing significantly improved DA transporter selectivity.[15] These results suggest that an aromatic ring C-2 substituent may be an important contributing factor to binding at the DA transporter. Aryl substitution at the 2-position places the aromatic group two carbons away from the basic tropane nitrogen. The resulting nitrogen atom-to-phenyl ring distance (measured from the centroid of the phenyl ring) can be calculated using molecular modeling techniques to range from 4.2 Å (β epimer) to 5.1 Å (α epimer). These 2-phenyl derivatives therefore mimic the spatial arrangement seen in calculated low-energy conformations of dopamine (3.3−5.1 Å) and in 5-HT and NE pharmacophore geometries (ca. 5.1 Å).[26,27]

A possible explanation for the wide range of substituents that can be accommodated at the C-2 position of the tropanes is the existence of several different binding modes for the C-2 group. While the β-orientation of the C-2 group is required, C-2 substituents may be capable of interacting with the DA transporter binding site via an electrostatic/hydrogen-bonding or hydrophobic process depending on the nature of the C-2 group. Moreover, the results obtained with cocaine analogues bearing aromatic heterocycles at the C-2 position[13,14] suggest that the electrostatic interactions predominate over hydrophobic interactions when both types of interactions are possible for the 2β-substituent. For cocaine analogues bearing 2β-heterocycles, a high correlation was found between molecular electrostatic potential (not hydrophobicity) and binding potency.[13] The QSAR developed for the 2β-heterocycles also strongly suggested that the role of the 2-substituents involved electrostatic forces *other* than hydrogen bonding. Consistent with this are these new 2β-phenyl analogs which lack hydrogen-bonding functionality at the 2-position but retain significant binding potency.

Preparation of **5** in optically pure form via either resolution or stereoselective synthesis and substitutions of the 2- and 3-phenyl rings should improve both binding affinity and selectivity for the dopamine transporter. Since 4′-substitution of the 3β-phenyl ring of WIN 35,065-2 analogs significantly enhances the biological activity of cocaine analogues;[6−18] similar changes to **5** would be expected to enhance potency. For example, since changing the 3β-phenyl group of **2a** to a 4′-chlorophenyl **2b** resulted in a 23-fold increase in potency,[7] similar changes in the optical isomer of **5** would be expected to provide analogs with greater potency at the DAT. Also, in direct analogy to modifications that have been performed on the 3β-phenyl group, similar modifications of the 2β-phenyl ring will be undertaken to study the effect of altering the electrostatic and steric properties of this substituent and thereafter allow the development of an expanded QSAR correlating the structural variation and binding potency of the various 2β-heterocyclic and 2β-aryl-substituted analogs.

Experimental Section

Elemental analyses were conducted by Atlantic Microlab, Inc. in Norcross, GA. [^{3}H]-3β-(*p*-Fluorophenyl)tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428) and [^{3}H]-paroxetine were purchased from DuPont-New England Nuclear (Boston, MA). [^{3}H]Nisoxetine was purchased from American Radiolabeled Chemicals, Inc. (St. Louis, MO). When anhydrous conditions were required, solvents were distilled and dried by standard techniques immediately prior to use. All air- and moisture-sensitive reactions were conducted under a prepurified nitrogen atmosphere in oven-dried glassware at 115 °C. Routine NMR spectra were obtained on a Bruker AM-250 spectrometer. COSY, NOESY, and HMQC spectra were recorded on a Bruker AMX-500 spectrometer operating at 500.13 MHz for ^{1}H using a Bruker 5 mm inverse detect broadband probe. The double quantum filtered phase-sensitive COSY[21,22] and NOESY[28] were acquired as 1024 × 512 data points with a spectral width of 4800 Hz in both dimensions. The data were apodized with a squared sine function and zero filled to 2K × 2K data points prior to Fourier transformation.

NOESY spectra were obtained with a 1200 ms mixing time and a recycle delay of 4 s. Heteronuclear multiple quantum correlation (HMQC)[24] spectra were acquired as 1024 × 256 data points with a spectral width of 4800 Hz in F2 and 24375 Hz in F1. An average coupling constant of 145 Hz was used to optimize $1/J_{CH}$ delays. The data were apodized with a squared sine function and zero filled to 2048 × 512 data points prior to Fourier transformation.

(±)-8-(Ethoxycarbonyl)-2α-phenyl-3β-phenylnortropan-2β-ol (8). With stirring at −20 °C (salt−ice), 3.0 M PhMgBr in Et_2O (1.9 mL, 5.8 mmol) was added dropwise over 4 min to a solution of (±)-**7**[19,20] (1.06 g, 3.87 mmol) in dry Et_2O (20 mL), and the mixture was stirred at −20 °C under Ar. After 15 min, more cold Et_2O (5 mL) was added to rinse down the flask walls. After 1 h, the mixture was quenched with Et_2O (30 mL) and H_2O and was stirred at room temperature for 30 min. The mixture was then partitioned between Et_2O (150 mL) and H_2O (50 mL), and the organic fraction was washed with brine before it was dried (Na_2SO_4), filtered through Celite, and evaporated. The crude product was purified by flash column eluting with hexane/30% Et_2O to yield 0.85 g of **8** (63%): ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 3H, CH_3), 1.74−1.82 (m, 2H, H7 and H4α), 1.86−1.91 (m, 1H, H6), 1.97−2.08 (m, 2H, H7 and H6), 2.35−2.40 (ddd, J = 3.0, 13.0, 13.0 Hz, 1H, H4β), 3.20 (br s, 1H, OH), 3.61 (dd, J = 12.5 and 5.5 Hz, 1H, H3α), 4.24 (q, J = 7.0 Hz, 2H, OCH_2), 4.27 (m, 1H, H1), 4.50 (br s, 1H, H5), 7.10 (tt, J = 7.0 and 1.0 Hz, 1H, H4″), 7.20 (m, 3H, H3″, H5″, and H4′), 7.27 (t, J = 8.0 Hz, 2H, H3′ and H5′), 7.39 (d, J = 8.0 Hz, 2H, H2″ and H6″), 7.53 (dd, J = 8.0 and 1.0 Hz, 2H, H2′ and H6′); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 24.8 (C7), 27.0 (C6), 36.9 (C4), 41.1 (C3), 53.6 (C5), 61.5 (OCH_2), 65.5 (C1), 78.9 (C2, observed only when spectrum was recorded in a mixture of CD_3OD and $CDCl_3$), 126.4 (C4″), 126.9 (C2′ and C6′), 127.0 (C4′), 127.89 and 127.92 (C3′, C5′ and C3″, C5″), 130.1 (C2″, C6″), 140.3 and 143.0 (C1′ and C1′), 156.1 (CO); MS (EI) m/z 351.20. Anal. ($C_{22}H_{25}NO_3$) C, H, N.

(±)-2α,3β-Diphenyltropan-2-ol (3). With stirring at room temperature under Ar, a solution of **8** (0.1129 g, 0.321 mmol) in dry Et_2O (3 × 1 mL) was added to a 1.0 M solution of LAH in Et_2O (0.96 mL, 0.96 mmol), and the mixture was heated to reflux with stirring under N_2. After 2 h, the mixture was diluted with Et_2O (8 mL) and quenched with a few drops of saturated $NaHCO_3$. The mixture was filtered through Celite, and the filter cake was washed thoroughly with Et_2O. The combined filtrate was washed with saturated $NaHCO_3$ and brine before it was dried (Na_2SO_4), filtered through Celite, and evaporated. The crude product was purified by radial PLC on 1 mm silica gel plates eluting with $CHCl_3$/2.5% MeOH/0.25% NH_4OH. The free base was converted to the HCl salt with 1.0 M HCl in Et_2O to yield 0.075 g of **3**·HCl (70%): mp (HCl salt) >250 °C dec; ^{1}H NMR ($CDCl_3$, free base) δ 1.65−2.20 (complex, 6H, 3 CH_2), 2.29 (s, 3H, NCH_3), 2.89 (m, 1H, CH), 3.16 (m, 1H, CH), 3.30 (dd, J = 12.5 and 5.3 Hz, 1H, CH), 5.44 (br s, 1H, OH), 6.90−7.20 (m, 6H, aromatic), 7.41 (d, J = 7.0 Hz, 2H, aromatic), 7.49 (d, J = 7 Hz, 2H, aromatic); ^{13}C NMR ($CDCl_3$, free base) δ 21.78, 24.87, 39.44, 40.47, 41.55, 61.26, 75.81, 76.29, 125.93, 126.53, 126.88, 127.77 (overlap of two carbon peaks), 130.17, 141.88, 143.57; MS (EI) m/z 293.25. Anal. ($C_{20}H_{23}NO$·HCl·0.75H_2O) C, H, N.

(±)-8-(Ethoxycarbonyl)-2,3-diphenyl-nortrop-2-ene (9). With stirring at 0 °C under N_2, $SOCl_2$ (0.79 mL, 10.8 mmol) was added to a mixture of **8** (0.76 g, 2.17 mmol) and DBU (3.2 mL, 21.7 mmol) in dry CH_2Cl_2 (40 mL), and the mixture was stirred at 0 °C under N_2. After 1.5 h, more DBU (3.2 mL, 21.7 mmol) and $SOCl_2$ (0.79 mL, 10.8 mmol) were added with stirring at 0 °C under N_2. After 1 h, the mixture was quenched with H_2O (10 mL) and was then partitioned between Et_2O (500 mL) and H_2O. The organic fraction was washed repeatedly with H_2O until the organic fraction was nearly colorless. The organic fraction was then washed with brine before it was dried (Na_2SO_4), filtered through Celite, and evaporated. The crude product was purified by flash column, eluting with hexane/10% Et_2O to yield 0.63 g of **9** (87%): ^{1}H NMR ($CDCl_3$, free base) δ 1.31 (br s, 3H, CH_3), 1.82−3.10 (br m, 6H, 3 CH_2), 4.21 (q, J = 7.0 Hz, 2H, OCH_2), 4.52 (br s, 1H, CH), 4.72 (br s, 1H, CH), 6.90−7.20 (m, 10H, aromatic); ^{13}C NMR ($CDCl_3$, free base) δ 14.87, 30.59 (d), 33.81 (d), 38.77 (d), 52.95, 58.62, 61.08, 126.46, 126.63, 127.79, 128.02, 128.96, 129.49, 130.74 (d), 139.84, 140.83, 141.45 (d), 154.93; MS (EI) m/z 333.40. Anal. ($C_{22}H_{23}NO_2$) C, H, N.

Note: Compound **9** readily undergoes a photochemical reaction when exposed to UV radiation.

(±)-2,3-Diphenyl-trop-2-ene (4). Compound **4** was prepared from **9** (0.11 g, 0.34 mmol) and 1.0 M LAH in Et_2O (1.01 mL, 1.01 mmol) using conditions similar to those for the preparation of **3**. The crude product was purified by flash column chromatography eluting with $CHCl_3$/5% MeOH/0.5% NH_4OH. The free base was converted to the HCl salt with 1.0 M HCl in Et_2O to yield 0.106 g of **4**·HCl (100%) after evaporation from a mixture of hexane and CH_2Cl_2: mp (HCl salt) 102 °C dec; ^{1}H NMR ($CDCl_3$, free base) δ 1.70−2.40 (complex, 5H), 2.58 (s, 3H, NCH_3), 2.78 (dd, J = 18.0 and 4.0 Hz, 1H, H4), 3.44 (m, 1H, CH), 3.65 (m, 1H, CH), 6.90−7.20 (m, 10H, aromatic); ^{13}C NMR ($CDCl_3$, free base) δ 30.35, 33.59, 36.17, 58.19, 65.21, 126.25, 127.78, 127.94, 128.88, 129.30, 130.13, 138.54, 141.22 (not all sp^2 carbons were observed due to overlap of peaks); MS (EI) m/z 275.30. Anal. ($C_{20}H_{21}N$·HCl·0.75H_2O) C, H, N.

(±)-8-(Ethoxycarbonyl)-2β,3β-diphenylnortropane (10) and (±)-8-(Ethoxycarbonyl)-2α,3α-diphenylnortropane (11). A mixture of (±)-**9** (0.06 g, 0.18 mmol) and 10% Pd/C (31 mg) in MeOH (4 mL) was hydrogenated at room temperature under 50 psi. The hydrogen pressure was raised to 50 psi as needed. After 5 days, the mixture was filtered through Celite, and the Pd/C was washed with MeOH (120 mL). The combined filtrate was evaporated to dryness to yield a mixture of (±)-**10** and (±)-**11**, which were separated by radial PLC on 1 mm silica gel plates eluting with hexane/10% Et_2O to yield the more polar (±)-**10** (37.5 mg, 62%) and the more nonpolar (±)-**11** (18.7 mg, 31%).

(±)-8-(Ethoxycarbonyl)-2β,3β-diphenylnortropane (10): ^{1}H NMR ($CDCl_3$) δ 0.84−1.25 (2 br s, 3H, CH_3), 1.82−2.67 (complex, 6H, 3 CH_2), 3.17 (br s, 1H, CH), 3.58−3.78 (complex, 3H, 1 CH and OCH_2), 4.50 (br s, 1H, CH), 4.74 (br s, 1H, CH), 6.99−7.11 (m, 10H, aromatic). Anal. ($C_{22}H_{25}NO_2$·0.25H_2O) C, H, N.

(±)-8-(Ethoxycarbonyl)-2α,3α-diphenylnortropane (11): ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3H, CH_3), 1.59−2.71 (complex, 6H, 3 CH_2), 3.52 (m, 1H, CH), 4.03 (m, 1H, CH), 4.20 (q, J = 7.0 Hz, 2H, OCH_2), 4.49 (m, 1H, CH), 4.68 (m, 1H, CH), 6.96−7.21 (m, 10H, aromatic). Anal. ($C_{22}H_{25}NO_2$) C, H, N.

(±)-2β,3β-Diphenyltropane (5). Compound **5** was prepared from (±)-**10** (0.22 g, 0.65 mmol) and 1.0 M LAH in Et_2O (1.9 mL) using conditions similar to those for the preparation of **4**. The crude product was purified by radial PLC on 2 mm silica gel plates eluting with $CHCl_3$/2.5% MeOH/0.25% NH_4OH. The product fractions were dried (Na_2SO_4), filtered through Celite, and evaporated. Once concentrated, the product solution was filtered through a cotton-plugged pipet and evaporated to yield 0.16 g (90%) of (±)-**5**, which was converted to the HCl salt with 1.0 M HCl in Et_2O: mp (HCl salt) 140 °C dec; ^{1}H NMR (free base, $CDCl_3$) δ 1.65 (ddd, J = 13.0, 4.0, 4.0 Hz, 1H, H4α), 1.75−1.83 (m, 2H, H6 and H7), 2.13 (m, 1H, H6), 2.24 (s, 3H, NCH_3), 2.28 (m, 1H, H7), 2.39 (ddd, J = 13.0, 13.0, 2.6 Hz, 1H, H4β), 2.88 (dd, J = 6.6, 2.4 Hz, 1H, H2), 3.31 (ddd, J = 13.0, 6.6, 4.0 Hz, 1H, H3), 3.35 (m, 1H, H1), 3.40 (m, 1H, H5), 6.84−7.40 (complex, 10H, aromatic); ^{13}C NMR (free base, $CDCl_3$) δ 25.0 (C6), 27.3 (C7), 35.2 (C4), 37.4 (C3), 42.0 (NCH_3), 53.2 (C2), 61.9 (C5), 67.7 (C1), 125.4 (aromatic), 125.5 (aromatic), 127.0 (aromatic), 127.5 (aromatic), 128.0 (aromatic), 130.6 (aromatic), 142.8 (aromatic), 143.2 (aromatic). Anal. ($C_{20}H_{23}N$·HCl·0.5H_2O) C, H, N.

(±)-2α,3α-Diphenyltropane (6). Compound **6** was prepared from (±)-**11** (0.093 g, 0.28 mmol) and 1.0 M LAH in Et_2O (0.83 mL) using conditions similar to those for the preparation of **3**. The crude product was purified by radial PLC on 1 mm silica gel plates eluting with $CHCl_3$/5% MeOH/0.5% NH_4OH. The product fractions were dried (Na_2SO_4), filtered through Celite, and evaporated. Once concentrated, the product solution was filtered through a cotton-plugged pipet and evaporated to yield 60.9 mg (79%) of (±)-**6**, which was converted to

the HCl salt with 1.0 M HCl in Et_2O: mp (HCl salt) 249−250 °C; ^{1}H NMR (free base, $CDCl_3$) δ 1.45 (m, 1H, H6), 1.79−1.94 (m, 2H, H7), 2.03 (m, 1H, H6), 2.09 (ddd, J = 14.1, 6.2, 2.5 Hz, 1H, H4α), 2.35 (s, 3H, NCH_3), 2.64 (ddd, J = 14.1, 8.0, 8.0 Hz, 1H, H4β), 3.30 (m, 1H, H5), 3.55 (m, 1H, H1), 3.81 (ddd, J = 8.0, 8.0, 6.2 Hz, 1H, H3), 3.98 (dd, J = 8.0, 5.0 Hz, 1H, H2), 6.92−7.17 (complex, 10H, aromatic); ^{13}C NMR (free base, $CDCl_3$) δ 22.57 (C7), 27.23 (C6), 36.87 (C3), 37.11 (C4), 40.70 (NCH_3), 49.39 (C2), 60.45 (C5), 64.28 (C1), 124.8 (aromatic), 125.5 (aromatic), 127.2 (aromatic), 127.9 (aromatic), 128.3 (aromatic), 128.4 (aromatic), 142.7 (aromatic), 144.0 (aromatic). Anal. ($C_{20}H_{23}N\cdot HCl\cdot 0.5H_2O$) C, H, N.

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References

(1) Fischman, M. W.; Schuster, C. R. Cocaine self administration in humans. *Fed. Proc.* **1988**, *41*, 241−246.
(2) Johanson, C. E.; Fischman, M. W. The pharmacology of cocaine related to its abuse. *Pharmacol. Rev.* **1989**, *41*, 3−52.
(3) Koob, G. F.; Bloom, F. E. Cellular and molecular mechanisms of drug dependence. *Science* **1988**, *242*, 715−723.
(4) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219−1223.
(5) Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 150−155.
(6) Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, and QSAR (CoMFA and classical) study of 3β-(3′-substituted phenyl)-, 3β-(4′-substituted phenyl)-, and 3β-(3′,4′-disubstituted phenyl)tropane-2β-carboxylic acid methyl esters. *J. Med. Chem.* **1994**, *37*, 2865−2873.
(7) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: Biochemical characterization and structure-activity relationships for the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 969−981.
(8) Boja, J. W.; Kuhar, M. J.; Kopajtic, T.; Yang, E.; Abraham, P.; Lewin, A. H.; Carroll, F. I. Secondary amine analogues of 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid esters and *N*-norcocaine exhibit enhanced affinity for serotonin and norepinephrine transporters. *J. Med. Chem.* **1994**, *37*, 1220−1223.
(9) Kozikowski, A. P.; Saiah, M. K. E.; Bergmann, J. S.; Johnson, K. M. Structure−activity relationship studies of *N*-sulfonyl analogs of cocaine: role of ionic interaction in cocaine binding. *J. Med. Chem.* **1994**, *37*, 3440−3442.
(10) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. The discovery of an unusually selective and novel cocaine analog: Difluoropine. Synthesis and Inhibition of binding at cocaine recognition sites. *J. Med. Chem.* **1994**, *37*, 2001−2010.
(11) Newman, A. H.; Allen, A. C.; Izenwasser, S.; Katz, J. L. Novel 3α-(diphenylmethoxy)tropane analogs: Potent dopamine uptake inhibitors without cocaine-like behavioral profiles. *J. Med. Chem.* **1994**, *37*, 2258−2261.
(12) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliat, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of 2β-Acyl-3β-aryl-8-azabicyclo[3.2.1]octanes and their binding affinities at dopamine and serotonin transport sites in rat striatum and frontal cortex. *J. Med. Chem.* **1994**, *37*, 1262−1268.
(13) Kotian, P.; Mascarella, S. W.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. Synthesis, ligand binding, and quantitative structure−activity relationship study of 3β-(4′-substituted phenyl)-2β-(heterocyclic)tropanes: Evidence for an electrostatic interaction at the 2β-position. *J. Med. Chem.* **1996**, *39*, 2753−2763.
(14) Carroll, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J.W.; Kuhar, M. J. 3-Aryl-2-(3′-substituted-1′,2′,4′-oxadiazol-5′-yl)tropane analogues of cocaine: Affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. *J. Med. Chem.* **1993**, *36*, 2886−2890.
(15) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine and 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid ester and amide analogues. New high-affinity and selective compounds for the dopamine transporter. *J. Med. Chem.* **1995**, *38*, 379−388.
(16) Kozikowski, A. P.; Saiah, M. K. E.; Johnson, K. M.; Bergmann, J. S. Chemistry and biology of the 2β-alkyl-3β-phenyl analogues of cocaine: Subnanomolar affinity ligands that suggest a new pharmacophore model at the C-2 position. *J. Med. Chem.* **1995**, *38*, 3086−3093.
(17) Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M.L. Synthesis, cocaine receptor affinity, and dopamine uptake inhibition of several new 2β-substituted 3β-phenyltropanes. *J. Med. Chem.* **1994**, *37*, 3875−3877.
(18) Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergmann, J. S.; Callahan, P. M.; Cunningham, K. A.; Johnson, K. M. Structure-activity relationship studies of cocaine: Replacement of the C-2 ester group by vinyl argues against H-bonding and provides an esterase-resistant, high-affinity cocaine analogue. *J. Med. Chem.* **1992**, *35*, 4764−4766.
(19) Daum, S. J.; Aceto, M. D.; Clarke, R. L. Compounds affecting the central nervous system. 3. 3β-Phenyltropan-2-ols. *J. Med. Chem.* **1973**, *16*, 667−670.
(20) Lyle, R. E.; Carle, K. R.; Ellefson, C. R.; Spicer, C. K. Orientation in the hydroboration of tetrahydropyridines and tropidines. *J. Org. Chem.* **1970**, *35*, 802−805.
(21) Shaka, A. J.; Freeman, R. Simplification of NMR spectra by filtration through multiple-quantum coherence. *J. Magn. Reson.* **1983**, *51*, 169−173.
(22) Derome, A. E.; Williamson, M. P. Rapid-pulsing artifacts in double-quantum-filtered COSY. *J. Magn. Reson.* **1990**, *88*, 177−185.
(23) Marion, D.; Wuthrich, K. Application of phase sensitive two-dimensional correlated spectroscopy (COSY) for measurements of ^{1}H-^{1}H spin-spin coupling constants in proteins. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 967−974.
(24) Bax, A.; Subramanian, S. Sensitivity-enhanced two-dimensional heteronuclear shift correlation NMR spectroscopy. *J. Magn. Reson.* **1986**, *67*, 565−569.
(25) Karplus, M. Vicinal proton coupling in nuclear magnetic resonance. *J. Am. Chem. Soc.* **1963**, *85*, 2870−2871.
(26) Timmermans, P.; Chiu, A. T.; Thoolen, M. α-Adrenergic receptors. In *Comprehensive Medicinal Chemistry*; Hansch, C., Eds.; Pergamon Press: New York, 1990; Vol. 3, p 149.
(27) Hibert, M. F.; Mir, A. K.; Fozard, J. R. Serotonin (5-HT) receptors. In *Comprehensive Medicinal Chemistry*; Hansch, C., Eds.; Pergamon Press: New York, 1990; Vol. 3, p 593.
(28) States, D. J.; Haberkorn, R. A.; Ruben, D. J. A two-dimensional nuclear Overhauser experiment with pure absorption phase in four quadrants. *J. Magn. Reson.* **1982**, *48*, 286−292.

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