Synthesis and Transporter Binding Properties of 3β-[4′-(Phenylalkyl, -phenylalkenyl, and -phenylalkynl)phenyl]tropane-2β-carboxylic Acid Methyl Esters: Evidence of a Remote Phenyl Binding Domain on the Dopamine Transporter

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A series of 4′-substituted 3β-phenyltropane-2β-carboxylic acid methyl esters were synthesized and evaluated for binding at the dopamine transporter (DAT) in order to better define the pharmacophore for the cocaine binding site on the DAT. Results from the study of 3β-[(4′-phenylalkyl)phenyl]tropane-2β-carboxylic acid methyl esters (**5a**−**c** and **6a**,**b**) revealed strong evidence of a previously unknown remote binding domain. The 3β-[(4′-phenylethyl)phenyl]-tropane-2β-carboxylic acid methyl ester (**5a**), which has a two methylene linker between the 3β-phenyl group and the remote phenyl group, has an IC_{50} value of 5.14 nM at the DAT. The 3β-[4′-(benzyl)phenyl] and 3β-[4′-(phenylpropyl)phenyl] analogues **6b** and **5b**, respectively, are 102- and 68-fold less potent than **5a** at the DAT. Compound **5a** also has good affinity for the serotonin and norepinephrine transporters (K_i = 21 and 6.5 nM, respectively) and is thus a nonselective monoamine uptake inhibitor. Electrostatic effects make a significant contribution to the DAT binding affinity of the 3β-[(4′-phenylalkenyl)phenyl]tropane-2β-carboxylic methyl esters (**6c**, **7a**,**b**, and **8**) and 3β-[(4′-phenylalkynl)phenyl]tropane-2β-carboxylic acid methyl esters (**4a**−**e**). However, the results from the DAT binding on these compounds suggest that there may be another binding domain even further remote from the 4′-position on the 3β-phenyl group. In both cases, steric barriers have to be overcome before potent binding to the DAT is observed. 3β-(4′(3-Phenyl-1-propynyl)phenyl)tropane-2β-carboxylic acid methyl ester (**4b**), with an IC_{50} value of 1.82 nM, was the most potent compound studied. This compound possessed K_i values of 1.19 and 16.5 nM for the serotonin and norepinephrine transporter and is thus a nonselective monoamine uptake inhibitor.

Introduction

Studies directed toward gaining a better understanding of the pharmacology of cocaine (**1**) (Chart 1) are necessary for the development of therapeutic agents for combating addiction.[1,2] Cocaine binds to a specific recognition site on the dopamine transporter (DAT), blocking the reuptake of dopamine into the presynaptic neurons resulting in the accumulation of excess dopamine in the synaptic gap.[3] Characterization of this recognition site through structure−activity relationship (SAR) studies has provided insight into the role of the DAT in the pharmacological properties of cocaine.[4] These studies are an integral part of the design of medications that might be useful for treating cocaine abuse. The present study was undertaken to further explore the SAR of 4′-substituents on the 3β-phenyl ring of the 3-phenyltropane (**2a**) class of monoamine uptake inhibitors.

In contrast to cocaine (**1**), which has a 3β-benzoyloxy substituent, the 3-phenyltropane (**2a**) class of DAT uptake inhibitors has an aromatic ring attached directly to the 3-position on the tropane ring system.[4] In general, the 3-phenyltropane class of DAT uptake inhibitors has higher affinity for the DAT than the cocaine (**1**) class.[4] Previous SAR studies directed at the 3-phenyltropane class of compounds have shown that the affinity and selectivity of compounds for the DAT relative to the serotonin and norepinephrine transporters (5-HTT and NET) are dependent on the substituents and substitution pattern on the aromatic ring connected to the 3β-position of the tropane ring.[5] Early studies reported from this laboratory showed that RTI-32 (**2b**) containing a 4′-methyl aromatic substituent binds with good affinity and moderate selectivity to the DAT.[6] Later studies showed that RTI-83 (**2c**) and RTI-282 (**2d**), which contain a larger ethyl and propyl group in the 4′-position, caused significant loss in binding affinity at the DAT.[5,7] More recently, we reported that RTI-359 (**2e**), RTI-360 (**2f**), and RTI-281 (**2g**), which contain a 4′-vinyl, 4′-ethynyl, and 4′-propynyl group, respectively, retain high potency for the DAT.[5] The present study was undertaken to further characterize the SAR of substituents on the 3β-phenyl ring. Specifically, we present the synthesis and monoamine transporter binding properties of a series of 4′-substituent analogues **3** where M is a linker group between the 4′-position of the 3β-phenyl group and a second phenyl group attached to the terminal end of the linker group. Compounds were investigated where M varied in size, length, and degree

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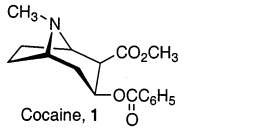
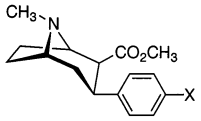
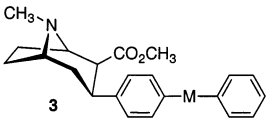
Chart 1



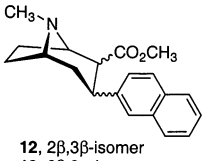
Cocaine, **1**



2a, WIN 35,065-2, X = H
2b, X = CH_3
2c, X = C_2H_5
2d, X = C_3H_7
2e, X = HC≡C-
2f, X = HC≡C-
2g, X = CH_3C≡C-
2h, X = t-CH_3CH=C-

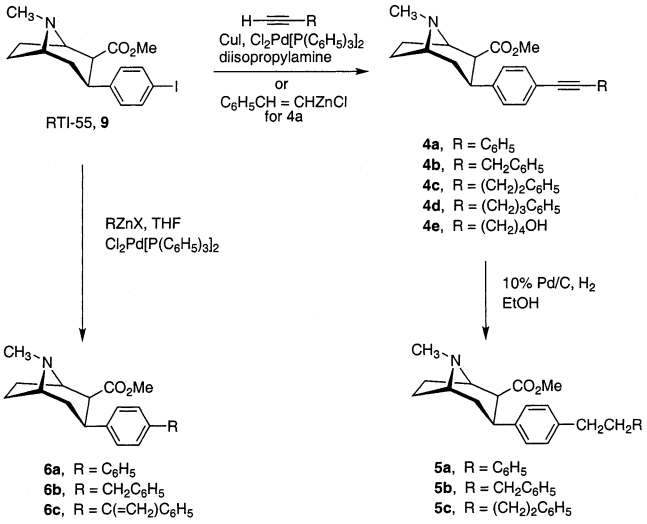


3



12, 2β,3β-isomer
13, 2β,3α-isomer

Scheme 1

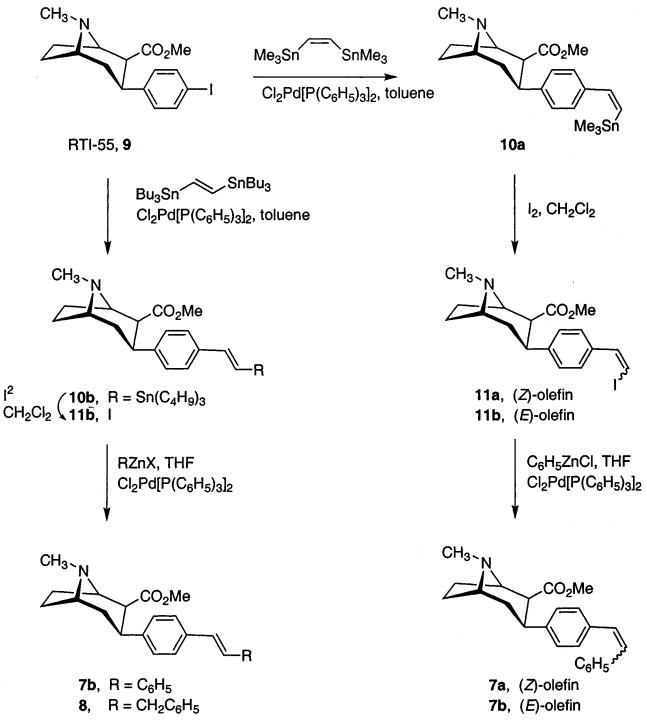


of unsaturation (see structures **4a**−**e**, **5a**−**c**, **6a**−**c**, **7a**,**b**, and **8** in Schemes 1 and 2).

Chemistry

The 3-phenyltropane analogues, **4a**−**e**, **5a**−**c**, **6a**−**c**, **7a**,**b**, and **8** (see Schemes 1 and 2), were all derived from **9** (RTI-55) via Stille or Sonogashira type coupling reactions.[8−10] Compounds **4a**−**e** were synthesized by the Sonogashira coupling of RTI-55 (**9**) with phenylacetylene, 1-phenylpropyne, 1-phenylbutyne, and 1-phenylpentyne, respectively (Scheme 1). Compound **4a** was also unexpectedly obtained when **9** was coupled with (*E*)-β-styrenylzinc chloride in tetrahydrofuran (THF) using bis(triphenylphosphine)palladium(II)chloride. The (*E*)-β-styrenylzinc chloride was made in situ from (*E*)-β-iodostyrene by lithiation with *n*-butyllithium followed by the addition of zinc chloride. We are unsure whether the zinc reagent formed improperly or if elimination of the stilbene intermediate occurred in the presence of palladium. Acetylenes **4a**−**c** were then converted to the 4′-phenylalkyl analogues **5a**−**c** by reduction with hydrogen in methanol using 10% palladium on carbon as catalyst. Stille coupling of RTI-55 (**9**) with phenylzinc chloride and benzyl- and 1-phenylethenylzinc bromide yielded compounds **6a**−**c** (Scheme 1).

Scheme 2

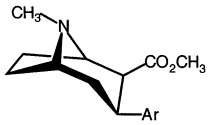


The synthesis of the stilbene analogues **7a**,**b** was less straightforward. Attempts to selectively reduce acetylene **4a** to an olefin were unsuccessful, regardless of the reduction conditions. The reduction always proceeded to the fully saturated analogue **5c** even when using Lindlar's catalyst. Direct coupling of **9** with (*E*)-β-tributylstannylstyrene under several conditions using different catalysts failed, commonly resulting in decomposition of the tropane ring.

Fortunately, RTI-55 (**9**) coupled to (*Z*)-1,2-bistrimethylstannylethylene and (*E*)-1,2-bistributylstannylethylene forming the (*Z*)- and (*E*)-stannylolefins, **10a**,**b**, which proved to be useful intermediates for the preparation of **7a**,**b** and **8** (Scheme 2). Initially, the reaction mixture resulting from the synthesis of **10a** was acidified with 1 M hydrochloric acid in order to extract organic byproducts. This resulted in protonolysis of the stannane **10a** and the isolation of RTI-359 (**2e**). However, we found that treatment of the crude (*Z*)-stannylolefin **10a** with iodine in methylene chloride afforded a 50:50 mixture of (*Z*)/(*E*) iodoolefins, **11a**,**b**. Coupling the mixture with phenylzinc chloride provided the desired stilbenes, **7a**,**b**, which were separated via high-performance liquid chromatography (HPLC).

Stannane **10b** was converted to stilbene **7b** by first reaction with iodine, forming only (*E*)-iodoolefin **11b** followed by coupling with phenylzinc chloride. (*E*)-

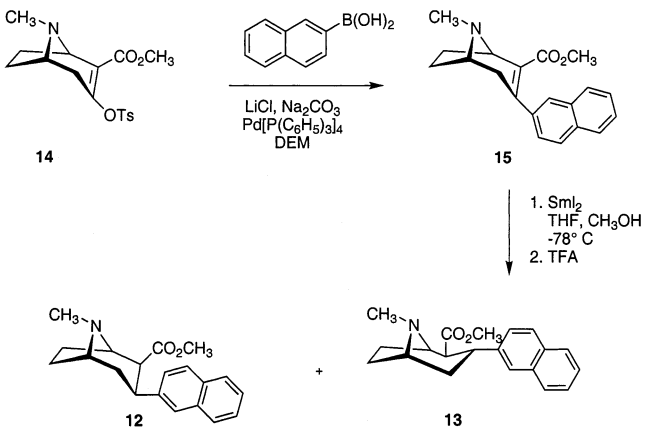
Table 1. 3β-Phenyltropane 2β-Carboxylic Acid Methyl Ester Analogues



compd	Ar	IC$_{50}$, nM (K_i, nM) DAT [^{3}H]WIN 35,428	5-HTT [^{3}H]paroxetine	NET [^{3}H]nisoxetine
WIN 35,065-2 (**2a**)[a]	C_6H_5	23 ± 5	1960 ± 61 (178 ± 5.5)	920 ± 73 (55 ± 44)
2b[a]	C_6H_4(4′-CH_3)	1.71 ± 0.31	240 ± 27 (21.8 ± 2.5)	60 ± 0.53 (36 ± 0.03)
2c[b]	C_6H_4(4′-C_2H_5)	55 ± 2.1	28.4 ± 3.8 (2.58 ± 3.5)	3910 ± 381 (2360 ± 230)
2d[b]	C_6H_4(4′-C_3H_7)	68.5 ± 7	70.4 ± 4 (6.40 ± 0.36)	3921 ± 130 (2360 ± 78)
2e[b]	C_6H_4(4′-CH=CH_2)	1.24 ± 0.2	9.5 ± 0.8 (0.86 ± 0.01)	78 ± 4.1 (47 ± 2.5)
2f[b]	C_6H_4(4′-C≡CH)	1.2 ± 0.1	4.4 ± 0.4 (0.40 ± 0.04)	83.2± 2.8 (50.1 ± 1.7)
2g[b]	C_6H_4(4′-C≡CCH_3)	2.37 ± 0.2	15.7 ± 1.5 (1.43 ± 0.14)	820 ± 46 (494 ± 28)
2h[b]	C_6H_4(4′-CH=$CHCH_3$)	5.29 ± 0.5	11.4 ± 0.28 (1.04 ± 0.03)	1590 ± 93 (958 ± 56)
12	2′-naphthyl	0.51 ± 0.03	0.80 ± 0.06 (0.07 ± 01)	21.1 ± 1.0 (12.7 ± 0.60)
13[c]	2′-naphthyl	1.1 ± 0.09	11.4 ± 1.3 (1.05 ± 0.12)	70.2 ± 6.3 (42.3 ± 3.8)
15[d]	2′-naphthyl	5.17 ± 0.23	345 ± 37 (31.4 ± 3.4)	372 ± 21 (224 ± 13)

[a] Taken from ref 6. [b] Taken from ref 5. [c] This is the 2β,3α-isomer. [d] This is 3-(2′-naphthyl)tropene-2-carboxylic acid methyl ester.

Scheme 3



Iodoolefin **11b** was also coupled to benzylzinc chloride in a similar fashion forming **8**.

The olefin stereochemistry of styrenes **7a,b** was verified by ^{1}H NMR analysis. The olefin protons were observed as singlets in deuteriochloroform but nonsinglets in d_6 benzene. Unfortunately, the peaks were buried within the aromatic region of the ^{1}H NMR spectrum making coupling constant analysis difficult. Instead, the stereochemistry of the two analogues could be correlated with the ^{1}H shifts of the known (*Z*)- and (*E*)-stilbene olefin singlets. The (*Z*)- and (*E*)-stilbene olefin singlets appear at 6.56 and 7.08 ppm, respectively. The resonances for the olefin protons of **7a**,**b** come at 6.53 and 7.06 ppm, respectively, and are clearly correlated.

The synthetic results provide additional evidence for the structural assignments. Conversion of (*E*)-stannane **10b** to (*E*)-iodoolefin **11a** occurred with >99% retention of stereochemistry while the conversion of less thermodynamically stable (*Z*)-stannane **10a** to (*Z*)-iodoolefin **11a** occurred with only a 50% retention of stereochemistry. One would not expect the (*Z*)-stannane to fully retain its stereochemistry and the (*E*)-stannane to partially isomerize.

To gain information about the steric effect on DAT affinity, 3β-(2′-naphthyl)tropane-2β-carboxylic acid methyl ester (**12**) was prepared by the route shown in Scheme 3. Treatment of the triflate **14**[11] with 2-naphthylboronic acid in refluxing diethoxymethane (DEM) using tetrakis(triphenylphosphine)palladium(0) as catalyst gave tropene **15**. Reduction of **15** with samarium iodide at −78 °C using methanol as the proton source followed by quenching with trifluoroacetic acid gave the desired **12** along with the 2β,3α-isomer **13**, which were separated by column chromatography. A comparison of the ^{1}H NMR spectrum of **13** to other previously reported 2β,3α-analogues[12] suggests that this compound exists largely in the boat conformation as shown in Scheme 3.

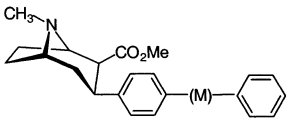
Biology

The binding affinities of the compounds at the DAT, 5-HTT, and NET were determined via competition binding assays using the previously reported procedures.[13] The final concentration of radioligands in the assays was 0.5 nM [^{3}H]WIN35,428 for the DAT, 0.2 nM [^{3}H]paroxetine for the 5-HTT, and 0.5 nM [^{3}H]nisoxetine for the NET.

Results and Discussion

The results of the binding studies are summarized in Tables 1 and 2 along with the results for **2a** (WIN 35,-065-2) and other previously reported compounds for comparison. The original paper from our laboratory concerning the SAR of the 3-phenyltropane class of dopamine uptake inhibitors was directed toward explaining the effect of adding substituents to the 3β-aromatic ring of the lead compound WIN 35,065-2.[4] The studies showed that substitution of the 4′-position with both electron-donating and electron-releasing groups led to compounds with high affinity for the DAT.[14] Quantitative SAR (QSAR) and comparative molecular field analysis (CoMFA) models were initially reported for 12 4′-substituted analogues[14] and then for 25 4′-substituted and 3′,4′-disubstituted WIN 35,065-2 analogues.[4,7,14] The classical QSAR models suggested that distribution properties (hydrophobicity) were important contributors to binding at the DAT. The CoMFA models showed that some steric bulk extending from below and above the 4′-position contributes to enhanced potency, although excessive bulk led to reduced potency. In addition, the model suggests that electrostatic forces account for approximately one-quarter of the binding affinity and thus may make a significant contribution to potency.

Table 2. 3β-Phenyltropane 2β-Carboxylic Acid Methyl Ester Analogues with Linkers



		IC_{50}, nM (K_i, nM)		
Cmpd	M	DAT [^{3}H]WIN 35,428	5-HTT [^{3}H]Paroxetine	NET [^{3}H]Nisoxetine
(4a)	—C≡C—	3.7 ± 0.16	46.8 ± 5.8 (4.3 ± 0.53)	347 ± 25 (209 ± 15)
(4b)	—C≡C—CH_2	1.82 ± 0.42	13.1 ± 1.7 (1.19 ± 0.42)	27.4 ± 2.6 (16.5 ± 1.6)
(4c)	—C≡C—$(CH_2)_2$	6.28 ± 1.25	2180 ± 345 (198 ± 31)	1470 ± 109 (885 ± 66)
(4d)	—C≡C-$(CH_2)_3$—	300 ± 37	1340 ± 232 (122 ± 21)	4450 ± 637 (2680 ± 384)
(4e)	a	57 ± 4	828 ± 29 (75 ± 2.6)	9500± 812 (5720 ± 489)
(6a)	—	15.6 ± 0.6	95.8 ± 36 (8.7 ± 3.3)	1480 ± 269 (892 ± 162)
(6b)	—CH_2—	526 ± 65	7240 ± 390 (658 ± 35)	6670 ± 377 (606 ± 277)
(6c)	$\overset{CH_2}{\overset{\|\|}{C}}$	474 ± 133	2710 ± 800 (246 ± 73)	7060 ± 1760 (4260 ± 1060)
(5a)	—$(CH_2)_2$—	5.14 ± 0.63	234 ± 26 (21.3 ± 2.4)	10.8 ± 0.3 (6.50 ± 0.20)
(5b)	—$(CH_2)_3$—	351 ± 52	1243 ± 381 (113 ± 35)	14,200 ± 1800 (8500 ± 1100)
(5c)	—$(CH_2)_4$—	228 ± 21	4824 ± 170 (439 ± 16)	2310 ± 293 (1390 ± 177)
(7b)	—CH=CH-(trans)	3.09 ± 0.75	335 ± 150 (30.5 ± 13.6)	1960 ± 383 (1180 ± 231)
(7a)	—CH=CH-(cis)	11.7 ± 1.12	ND	ND
(8)	—CH=CH-CH_2	15.8 ± 1.31	781 ± 258 (71 ± 24)	1250 ± 100 (759 ± 60)

[a] Compound **4e** has a $-C\equiv C-(CH_2)_4OH$ substituent at the 4-position.

Later studies demonstrated that a large, bulky substituent at the 4-position of the aromatic ring of 3-phenyltropane analogues hinders binding to the DAT.[4,5,7] As shown in Table 1, RTI-83 (**2c**) and RTI-282 (**2d**), which have a 4′-ethyl and a 4′-propyl substituent, respectively, were reported to have IC_{50} values of 55 and 69 nM. Yet their sizes were only slightly larger than the 4′-methyl analogue RTI-32 (**2b**), which had an IC_{50} value of 1.71 nM. Thus, exchanging one of the hydrogens on the 4′-methyl group of RTI-32 with a methyl or ethyl group to give RTI-83 and RTI-282 resulted in a 32- and 40-fold loss in binding potency, respectively. These results suggest that as the substituent increases in size, the potency decreases. However, in contrast, **2e** (RTI-359) and **2f** (RTI-360), which have a two carbon vinyl and acetylenic group conjugated to the tropane phenyl group, show IC_{50} values of 1.24 and 1.2 nM, respectively.[5] Compounds RTI-282 (**2d**), RTI-281 (**2g**), and RTI-296 (**2h**), which possess linearly oriented three carbon atom 4′-substituents, show increased binding affinity at the DAT as the degree of unsaturation increases with the propyl, propenyl, and propynyl analogues, **2d**,**h**,**g**, showing IC_{50} values of 65.8, 5.29, and 2.37 nM, respectively.

Table 2 lists the monoamine transporter binding properties of a number of compounds where M represents linkers of different types between the 4′-position on the tropane 3β-aryl ring to a second aromatic ring or in the case of **4e** a hydroxyl group. Several points are evident from the binding data. Comparing the acetylene analogues **4a**−**e** shows that adding one methylene to the acetylenic moiety of **4a** to give analogue **4b** results in only a small increase of binding affinity, 1.82 vs 3.7 nM. Whereas, adding two methylenes to give **4c** results in a small decrease in binding affinity. However, adding three additional methylene groups to **4a** to give analogue **4d** decreases binding affinity 2 orders of magnitude to an IC_{50} value of 300 nM. Interestingly, replacing the terminal phenyl group in **4a** with a hydroxybutyl group to give **4e**, a more polar substituent further removed from the acetylene moiety, causes an order of magnitude decrease in binding affinity (IC_{50} = 57 nM).

A comparison of compounds **7a**,**b** possessing an olefinic linker reveals that the (*E*)-isomer **7b** with an IC_{50} value of 3.09 nM is about four times as potent as the (*Z*)-isomer **7a**, which has an IC_{50} value of 11.7 nM. Lengthening the olefinic group of **7b** by one methylene to give compound **8** resulted in a 5-fold decrease in affinity. These results fall within the length constraints observed for the acetylenes. Compound **6c** with a one carbon linker possessing an exo-methylene group gave an IC_{50} value of 474 nM.

Compounds **5a**−**c** and **6b** contain a second phenyl group linked by methylene spacers of increasing length. The biphenyl analogue **6a** with no spacer has an IC_{50} value of 15.6 nM. Analogues **6b** and **5b**,**c** which possess one, three, and four methylenes between the two phenyl rings, all showed very low affinity for the DAT: IC_{50} values of 228−526 nM. Surprisingly, compound **5a**, which contains a two methylene linker connecting the remote phenyl group to the tropane phenyl ring, binds to the DAT with an IC_{50} value of 5.14 nM. These results, particularly the 102-fold increase in binding affinity in going from the one methylene linker analogue **6b** to the two methylene linker analogue **5a**, suggest that a remote binding site exists in the DAT binding domain extended out approximately two carbons from the tropane 3β-phenyl ring. This spatial region is somewhat confined and apparently ends abruptly as evidenced by

the dramatic loss of binding affinity of **5b**,**c**, which possesses one and two additional methylene groups between the phenyl groups. This suggestion of a remote DAT binding domain is supported by comparing the binding affinities of **5a** and **6b** to those of **2c** (RTI-83) and **2b** (RTI-32). Thus, replacement of one of the methyl hydrogens of **2b** with a phenyl group to give **6b** results in a 300-fold loss of affinity (1.71 vs 526 nM); whereas, replacement of one of the methyl hydrogens of **2c** with a phenyl group to give **5a** results in a 11-fold increase in affinity (55 vs 5.14 nM).

Compounds **4a**−**d**, **7a**,**b**, and **8** possess an acetylenic and olefinic group, respectively, conjugated to the 4′-phenyl on the tropane ring. The analogues **4a**−**c**, **7a**,**b**, and **8** have IC_{50} values at the DAT of 1.82−15.8 nM. The relatively high DAT binding affinity of these analogues could be due to electronic contribution from the conjugated acetylenic and olefinic group or to interaction with remote binding sites or both. Regardless of the reason for the high DAT binding affinity, a comparison of **4c** ($IC_{50} = 6.28$) to **4d** ($IC_{50} = 300$) shows that the extension of the linker of **4c** by one methylene group to give **4d** results in a 48-fold loss in binding affinity. Thus, there appears to be a steric barrier to binding if the linker M is longer than five carbon atoms. Compounds **6b**,**c** both of which have a one carbon linker between the two phenyl rings, show very low affinity for the DAT.

The binding data listed in Table 2 for the acetylenic compound, **4a**, and the olefinic, **7a**,**b**, all of which have two carbon linkers, also indicate that a moderate steric barrier exists adjacent to the tropane phenyl ring, which limits the binding affinity of compounds. The binding affinity is ordered as follows: alkyne (**4a**) = (*E*)-alkene (**7b**) > (*Z*)-alkene (**7a**). This steric barrier is also evident in **6b**,**c** both of which possess a one carbon linker between the two phenyl groups. Support for this notion may also be found by the observation that a large, flat 3*β*-(2′ naphthyl) group binds with high potency to the DAT, as shown by the IC_{50} value of 0.51 nM for compound **12**. It is interesting to note that the 3α-(2′-naphthyl)tropane **13** with a IC_{50} value of 1.1 nM is highly potent at the DAT. Even the 2-tropene analogue **15** with an IC_{50} value of 5.17 nM has reasonable affinity for the DAT. Because Davis et al.[15,16] reported that 3*β*-(2-naphthyl)2-*β*-acetyltropane also possessed high affinity for the DAT, the increase in affinity is not dependent on the 2*β*-ester group.

Previous studies have shown that the size and type of 2*β*-group has very little effect on the binding affinity of 3*β*-phenyl-2*β*-substituted tropane analogues.[4] These results suggest that there is a large open domain extending out from the C2 position on the tropane ring, which has little effect on binding to the DAT. The present studies on the 3*β*-(4′-substituted phenyl)-2*β*-carboxylic acid methyl ester analogues show that there are binding domains extending out from the 4′-position on the 3*β*-phenyl ring. However, in contrast to the 2*β*-position, these binding domains are highly specific.

Examination of the 5-HTT binding affinity data in Table 2 shows that **4a**,**b** and **6a** with K_i values of 4.3, 1.19, and 8.7 nM, respectively, possess high affinity for the 5-HTT. Other analogues show K_i values between 21.3 and 439 nM. Compounds **4b** and **5a** with K_i values of 16.5 and 6.50, respectively, were the only two analogues to show good affinity for the NET. Other analogues showed K_i values between 25 and 1800 nM. Because compounds **4b** and **5a** possess high affinity for all three transporters, they are nonselective monoamine uptake inhibitors. Compound **4a** has good affinity for both the DAT and 5-HTT with much weaker NET affinity and is thus a DAT/5HTT selective uptake inhibitor.

In summary, we provide evidence of a previously unknown remote cavity or binding domain on the DAT. Regions close to the 4-position of the 3*β*-phenyl group are also bounded by a steric barrier, which must be overcome before potent binding occurs. The exact nature of the domain and whether binding in the area affects transporter function are unknown. Additional experiments are being conducted to probe the site further and also examine whether the C2 and C3 open domains are connected.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on either a 250 MHz (Bruker AM-250) or a 300 MHz (Bruker AVANCE 300) 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. All moisture sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. HPLC separations were performed on a Rainen Rabbit-HP instrument using a Dynamax-60A semiprep column.

THF was distilled just prior to its use (sodium benzophenone ketyl) or was purchased dry from J. T. Baker (dispensed from a Ultralow Water cylinder). Anhydrous methylene chloride, toluene, and ethyl acetate were purchased from Aldrich Chemical Co. Triethylamine and diisopropylamine were distilled from CaH_2 and stored.

3*β*-(4′-Phenylethynylphenyl)tropane-2*β*-carboxylic Acid Methyl Ester (4a). To a solution of 0.302 g (0.783 mmol) of 3*β*-(4′-iodophenyl)tropane-2*β*-carboxylic acid methyl ester (**9**, RTI-55) in 8 mL of degassed diisopropylamine under nitrogen was added 55 mg (0.078 mmol) of bis(triphenylphosphine)-palladium(II)chloride and 15 mg (0.078 mmol) of copper(I) iodide. To this yellow slurry was added 0.084 g (0.823 mmol) of phenylacetylene. The solution darkened almost immediately and was stirred for 8 h. The reaction was quenched with saturated aqueous ammonium chloride. To this mixture were added ether and a small amount of ammonium hydroxide and stirred overnight. The aqueous layer turned blue, and the copper salts disappeared. The free base was extracted from the aqueous layer with methylene chloride. The combined organic layers were concentrated in vacuo. The product was partially purified by dissolving the crude product in diethyl ether, adding 1 M HCl until acidic, and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting with methylene chloride. The combined organic layers were concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel, eluting with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine to give 0.255 g (91%) of **4a**. ^{1}H NMR ($CDCl_3$): δ 1.71 (m, 3H), 2.15 (m, 2H), 2.25 (s, 3H), 2.58 (dt, 1H, J = 2.7, 12.2 Hz), 2.92 (bs, 1H), 3.0 (m, 1H), 3.36 (bs, 1H),

3.49 (s, 3H), 3.57 (bs, 1H) 7.2−7.58 (m, 9H). The free base was converted to the (D)-tartrate salt: $[\alpha]_D^{24}$ −109.1° (*c* 0.05, CH_3OH). Anal. ($C_{28}H_{31}NO_8 \cdot 1.5H_2O$) C, H, N.

3*β*-(4′-(3-Phenyl-1-propynyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (4b). The procedure for **4a** was followed using 0.462 g (1.2 mmol) of **9** (RTI-55), 0.153 g (1.3 mmol) of 3-phenyl-1-propyne, and a catalytic amount of bis(triphenylphosphine)palladium(II)chloride and of copper(I)-iodide to give 0.342 g (76%) of **4b**. ^{1}H NMR ($CDCl_3$): δ 1.61 (m 3H), 1.87 (m 2H), 2.14 (s, 3H), 2.49 (t, 1H. J = 12.5 Hz), 2.83 (bs, 1H), 2.89 (dd, 1H, J = 5.3, 12.5 Hz), 3.28 (bs, 1H), 3.41 (s, 3H), 3.48 (bs, 1H), 3.74 (s, 2H), 7.08−7.34 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 25.1, 25.7, 25.9, 33.6, 33.7, 41.8, 51.2, 52.6, 62.2, 65.2, 82.8, 86.9, 121.0, 126.6, 127.2 (2C), 127.9 (2C), 128.5 (2C), 131.3 (2C), 136.8, 142.9, 172.0. The free base was converted to the hydrochloride salt; mp 85−87 °C; $[\alpha]_D^{20}$ −103° (*c* 0.50, CH_3OH). Anal. ($C_{25}H_{28}ClNO_2 \cdot 2.5H_2O$) C, H, N.

3*β*-(4′-(4-Phenyl-1-butynyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (4c). The procedure for **4a** was followed using 0.250 g (0.65 mmol) of **9** (RTI-55), 0.088 g (0.68 mmol) of 4-phenyl-1-butyne, 45 mg (0.065 mmol) of bis(triphenylphosphine)palladium(II)chloride, and 12 mg (0.065 mmol) of copper iodide to give 0.253 g (100%) of **4c**. ^{1}H NMR ($CDCl_3$): δ 1.73 (m, 3H), 2.06 (m, 2H), 2.20 (s, 3H), 2.55 (dt, 1H, J = 2.7, 12.5 Hz), 2.66 (t, 2H, J = 7.4 Hz), 2.89 (t, 2H, 7.4 Hz), 2.86−2.97 (m, 2H), 3.33 (bs, 1H), 3.47 (s, 3H), 3.54 (bs, 1H), 7.13−7.32 (m, 9H). The free base was converted to the (D)-tartrate salt; mp 82−84 °C; $[\alpha]_D^{24}$ −87.4° (*c* 0.175, MeOH). Anal. ($C_{30}H_{35}NO_8 \cdot 0.25H_2O$) C, H, N.

3*β*-(4′-(5-Phenyl-1-pentynyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (4d). The procedure for **4a** was followed using 0.378 g (0.98 mmol) of **9** (RTI-55), 0.141 g (1.18 mmol) of 5-phenyl-1-pentyne, and a catalytic amount of bis(triphenylphosphine)palladium(II)chloride and of copper(I)-iodide to give 0.191 g (48%) of **4d** as a solid. ^{1}H NMR ($CDCl_3$): δ 1.64−1.71 (m, 3H), 1.90 (q, 2H, J = 7.2 Hz), 2.0−2.3 (m, 2H), 2.22 (s, 3H), 2.34 (t, 2H, J = 6.9 Hz), 2.56 (dt, 1H, J = 2.7, 12.3 Hz), 2.79 (t, 2H, J = 7.5 Hz), 2.89 (m 1H), 2.98 (dt, 1H, J = 5.1, 12.6 Hz), 3.36 (bs, 1H), 3.48 (s, 3H), 3.55 (bs, 1H), 7.17 (d, 2H, J = 8.4 Hz), 7.20−7.33 (m 5H), 7.32 (d, 2H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$): δ 17.8, 18.0, 24.1, 24.9, 28.7, 29.4, 30.4, 32.6, 32.8, 33.8, 40.1, 50.1, 51.2, 61.2, 64.3, 80.2, 88.1, 120.3, 124.8, 126.2 (2C), 127.3 (2C), 127.5 (2C), 130.1 (2C), 140.7, 141.7, 171.0; mp 106−108 °C; $[\alpha]_D^{24}$ −41.0° (*c* 0.20, MeOH). Anal. ($C_{27}H_{31}NO_2$) C, H, N.

3*β*-(4′-(6′-Hydroxy-1-hexynyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (4e). To a solution of 1.18 g (3.0 mmol) of **9** (RTI-55) in 3.0 mL of degassed triethylamine under nitrogen was added a catalytic amount of bis(triphenylphosphine)palladium(II)chloride and of copper(I)iodide. To this yellow slurry was added 0.72 g (3.7 mmol) of 1-tributylsiloxy-5-pentyn-1-ol dissolved in degassed triethylamine. The solution darkened almost immediately and was stirred for 48 h. The reaction was quenched with saturated aqueous ammonium chloride. To this mixture were added ether and a small amount of ammonium hydroxide and stirred overnight. The aqueous layer turned blue, and the copper salts disappeared. The free base was extracted from the aqueous layer with methylene chloride. The combined organic layers were concentrated in vacuo.

The crude product was dissolved in 8 mL of THF. To this mixture was added 3.3 mL (3.3 mmol) of 1.0 M tetrabutylammonium fluoride. The mixture was stirred for 2 h and was complete. To this mixture was added water, and the aqueous layer was extracted three times with ether. The combined organic extracts were dried over sodium sulfate and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel and was partially dissolved in methylene chloride in order for the crude mixture to be applied to the column. Elution with ethyl acetate−hexane (50:50) with the addition of 5% triethylamine afforded 0.78 g (72%) of **4e**. ^{1}H NMR ($CDCl_3$): δ 1.71 (m 7H), 2.17 (m, 2H), 2.21 (s, 3H), 2.44 (m, 2H), 2.54 (t, 1H, 12.4 Hz), 2.90 (bs, 1H), 2.97 (dd, 1H, J = 5.0, 12.4 Hz), 3.36 (bs, 1H), 3.48 (s, 3H), 3.55 (bs, 1H), 3.70 (bs, 2H), 7.16 (d, 2H, J = 10.4 Hz), 7.29 (d, 2H, J = 10.5 Hz). The free base was converted to the hydrochloride salt; $[\alpha]_D^{24}$ −85.4° (*c* 0.12, CH_3OH). Anal. ($C_{22}H_{30}NClO_3 \cdot 0.5H_2O$) C, H, N.

3*β*-(4′-(2-Phenylethyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (5a). A solution of 0.255 g (0.71 mmol) of **4a** in 4 mL of methanol was added to a slurry of a catalytic amount of 10% palladium on carbon (fire hazard) in enough methanol to cover the active catalyst. The gauge assembly on a Parr hydrogenation apparatus was fitted on top, and the tube was pressurized with 60 psi hydrogen gas. To ensure maximum hydrogen content, the slurry was then evacuated using an aspirator and then repressurized with hydrogen gas. This procedure was repeated twice. The slurry was stirred for 0.5 h. The tube was vented, and the slurry was filtered through a plug of Celite to remove the palladium on carbon and washed with methylene chloride. The remaining solution was concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel. The oil was eluted with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine to give 0.252 g (98%) of **5a**. ^{1}H NMR ($CDCl_3$): δ 1.67 (m, 4H), 2.12 (m, 2H), 2.21 (s, 3H), 2.58 (t, 1H, J = 12.2 Hz), 2.84 (s, 4H), 2.93 (m, 1H), 3.35 (bs, 1H), 3.48 (s, 3H), 3.52 (bs, 1H), 7.09 (d, 2H, J = 8.1 Hz), 7.19 (d, 5H, J = 8.7 Hz), 7.26 (d, 2H, J = 8.2 Hz). The free base was converted to the tosylate salt; mp 117−119 °C; $[\alpha]_D^{24}$ −73.6° (*c* 0.250, MeOH). Anal. ($C_{31}H_{37}NO_5S$) C, H, N.

3*β*-(4′-(3-Phenylpropyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (5b). The procedure for **5a** was followed using 0.202 g (0.5 mmol) of **4b** to give 0.120 g (60%) of **5b**. ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 3H), 1.92 (p, 2H, J = 7.8 Hz), 2.17 (m, 2H), 2.24 (s, 3H), 2.61 (q, 8.8 Hz), 2.61 (m, 1H), 2.89 (m, 1H), 2.98 (dt, 1H, J = 5.2, 12.6 Hz), 3.37 (bs, 1H), 3.48 (s, 3H), 3.56 (bs, 1H), 7.08 (d, 2H, J = 8.2 Hz), 7.17 (d, 5H, J = 8.4 Hz), 7.3 (m, 2H). The free base was converted to the hydrochloride salt; mp 132−136 °C; $[\alpha]_D^{24}$ −94.6° (*c* 0.35, MeOH). Anal. ($C_{25}H_{32}NClO_2 \cdot 0.75H_2O$) C, H, N.

3*β*-(4′-(4-Phenylbutyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (5c). The procedure for **5a** was followed using 0.695 g (0.18 mmol) of **4c** to give 0.75 g (100%) of **5c**. ^{1}H NMR ($CDCl_3$): δ 1.63 (m, 7H), 2.07 (m, 2H), 2.29 (s, 3H), 2.88 (bs, 1H), 2.97 (dt, 1H, J = 5.3, 12.8 Hz), 3.35 (bs, 1H), 3.48 (s, 3H), 3.55 (bs, 1H), 7.11 (d, 2H, J = 8.1), 7.11−7.29 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 25.1, 25.9, 31.0, 31.2, 33.4, 34.1, 35.4, 35.8, 42.0, 51.1, 52.8, 62.3, 65.4, 125.6, 127.2 (2C), 128.0 (2C), 128.2 (2C), 128.4 (2C), 139.9, 140.2, 142.6, 172.2. The free base was converted to the (D)-tartrate salt; mp 97−99 °C; $[\alpha]_D^{24}$ −83.1° (*c* 0.160, MeOH). Anal. ($C_{30}H_{39}NO_8 \cdot 1H_2O$) C, H, N.

3*β*-(4′-Biphenyl)tropane-2*β*-carboxylic Acid Methyl Ester (6a). To a solution of 0.200 g (0.519 mmol) of **9** (RTI-55) in 2.3 mL of dry degassed THF under nitrogen was added phenylzinc chloride, made by reacting 0.164 mL (1.55 mmol) of bromobenzene with 0.62 mL (1.55 mmol) of 2.5 M *n*-butyllithium in THF and 3.1 mL (1.55 mmol) of 0.5 M zinc chloride in THF, followed by a catalytic amount of bis(triphenylphosphine)palladium(II)chloride. The reaction darkened immediately and was stirred overnight. To this mixture was added water that formed a precipitate of zinc salts. The solids were filtered leaving a biphasic mixture. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded 0.078 g (45%) of **6a**. ^{1}H NMR ($CDCl_3$): δ 1.60−1.73 (m, 3H), 2.05−2.23 (m, 2H), 2.24 (s, 3H), 2.64 (dt, 1H, J = 2.7, 12.6 Hz), 2.96 (m, 1H), 3.05 (dt, 1H, J = 5.1, 12.6 Hz), 3.38 (bs, 1H), 3.52 (s, 3H), 3.59 (bs, 1H), 7.26−7.34 (m, 4H), 7.41 (t, 1H, J = 7.5 Hz), 7.51 (d, 2H, J =

8.1 Hz), 7.57 (d, 2H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$): δ 25.6, 26.3, 33.9, 34.5, 42.4, 51.5, 53.2, 62.7, 65.7, 127.0 (2C), 127.3, 127.4 (2C), 127.6 (2C), 128.1 (2C), 129.0, 139.0, 141.4, 142.6, 172.6. The free base was converted to the (D)-tartrate salt; mp 120−121 °C; $[\alpha]_D^{24}$ −98.0° (*c* 0.150, MeOH). Anal. ($C_{26}H_{31}NO_8 \cdot 0.25H_2O$) C, H, N.

3β-(4′-Benzylphenyl)tropane-2β-carboxylic Acid Methyl Ester (6b). To a solution of 0.289 g (0.75 mmol) of **9** (RTI-55) in 7.5 mL of dry degassed THF under nitrogen was added 3.0 mL (1.5 mmol) of 0.5 M benzylzinc chloride in THF, followed by a catalytic amount of bis(triphenylphosphine)-palladium(II)chloride. The reaction darkened immediately and was stirred overnight. To this mixture was added water that formed a precipitate of zinc salts. The solids were filtered leaving a biphasic mixture. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded 0.258 g (99%) of **6b**. ^{1}H NMR ($CDCl_3$): δ 1.67 (m, 3H), 2.13 (m, 2H), 2.21 (s, 3H), 2.58 (t, 1H, J = 10.4 Hz), 2.87 (m, 1H), 2.96 (dt, 1H, J = 5.3, 12.5 Hz), 3.34 (bs, 1H), 3.48 (s, 3H), 3.54 (bs, 1H), 3.91 (s, 2H), 7.07 (d, 2H, J = 8.0 Hz), 7.16 (m, 5H), 7.24 (d, 2H, 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 25.6, 26.4, 33.9, 34.5, 41.9, 42.4, 51.5, 53.2, 62.8, 65.8, 126.4, 127.9 (2C), 128.8 (2C), 128.9 (2C), 129.4 (2C), 138.9, 141.2, 141.7, 172.6. The free base was converted to the (D)-tartrate salt; mp 146−148 °C; $[\alpha]_D^{24}$ −84.2° (*c* 0.09, MeOH). Anal. ($C_{27}H_{33}NO_8 \cdot 0.25H_2O$) C, H, N.

3β-(4′-(1-Phenyl-1-ethenyl)phenyl)tropane-2β-carboxylic Acid Methyl Ester (6c). To a solution of 0.360 g (0.93 mmol) of **9** (RTI-55) in 9.3 mL of degassed dry THF under nitrogen was added 3.7 mL (1.87 mmol) of 0.5 M 1-styrenylzinc chloride in THF, followed by a catalytic amount of bis-(triphenylphosphine)palladium(II)chloride. The reaction darkened immediately and was stirred overnight. To this mixture was added water that formed a precipitate of zinc salts. The solids were filtered leaving a biphasic mixture. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded 0.288 g (85%) of **6c**. ^{1}H NMR ($CDCl_3$): δ 1.6−1.76 (m, 3H), 2.0−2.23 (m, 2H), 2.23 (s, 3H), 2.61 (dt, 1H, J = 2.7, 12.6 Hz), 2.92 (m, 1H), 3.02 (dt, 1H, J = 5.1, 12.9 Hz), 3.38 (bs, 1H), 3.52 (s, 3H), 3.57 (bs, 1H), 5.38 (s, 1H), 5.44 (s, 1H), 7.21 (d, 2H, J = 8.7 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 25.6, 26.3, 34.0, 34.4, 42.4, 51.5, 53.2, 62.7, 64.1, 65.8, 114.2, 127.5 (2C), 128.0, 128.2 (2C), 128.5 (2C), 128.7 (2C), 139.2, 142.1, 143.1, 150.3, 172.6. The free base was converted to the tosylate salt; mp 203−205 °C; $[\alpha]_D^{24}$ −84.7° (*c* 0.08, MeOH). Anal. ($C_{31}H_{35}NO_5S$) C, H, N.

(*Z*)- and (*E*)-3β-(4′-(2-Phenyl-1-ethenyl)phenyl)tropane-2β-carboxylic Acid Methyl Ester (7a,b). To a solution of 0.584 g (1.5 mmol) of **9** (RTI-55) in 15 mL of degassed toluene were added 0.804 g (2.3 mmol) of (*Z*)-1,2-bistrimethylstannylethylene and a catalytic amount of bis(triphenylphosphine)-palladium(II)chloride. The mixture was heated to reflux. After 15 min, the solution became black, and the reaction was complete. The cooled slurry was filtered through Celite to remove the palladium. The solution was concentrated in vacuo forming (*Z*)-stannane **10a**.

The yellow oil was immediately dissolved in 7 mL of dry methylene chloride, and 0.944 g (3.72 mmol) of iodine was added to the solution. A dark precipitate formed. The slurry was stirred until the iodine disappeared and then worked up as before. The solution was concentrated in vacuo to remove excess solvent. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded a 50:50 mixture of the (*Z*)- and (*E*)-iodides **11a**,**b.** The two iodides could not be separated on silica gel; thus, they were used without further purification in the next reaction.

To a solution of the iodides in 4 mL of degassed THF under nitrogen was added phenylzinc chloride, made by first reacting 1.55 mL (2.48 mmol) of 1.6 M phenyllithium in THF and 4.97 mL (2.48 mmol) of 0.5 M zinc chloride in THF, followed by a catalytic amount of bis(triphenylphosphine)palladium(II)-chloride. The reaction darkened immediately and was stirred overnight. To this mixture was added water that formed a precipitate of zinc salts. The solids were filtered leaving a biphasic mixture. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was first purified by flash chromatography on silica gel to remove any byproducts. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded a 50:50 mixture of **7a**,**b**. The two isomers were purified by HPLC using a normal phase semiprep HPLC column, eluting with hexanes−ethyl acetate (70:30) with 2% triethylamine at 15 mL/min.

(*Z*)-3β-(4′-(2-Phenyl-1-ethenyl)phenyl)tropane-2β-carboxylic Acid Methyl Ester (7a). ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 3H), 2.1 (m, 2H), 2.21 (s, 3H), 2.55 (t, 1H, J = 7.3 Hz), 2.89 (bs, 1H), 2.97 (dt, 1H, J = 5.2, 12.4 Hz), 3.36 (bs, 1H), 3.49 (s, 3H), 3.52 (bs, 1H), 6.53 (s, 2H), 7.09 (dd, 4H, J = 7.3, 8.3 Hz), 7.26 (m, 5H). The free base was converted to the hydrochloride salt; mp 101−103 °C; $[\alpha]_D^{24}$ −136.4° (*c* 0.05, MeOH). Anal. ($C_{24}H_{28}NClO_2 \cdot 1.5H_2O$) C, H, N.

(*E*)-3β-(4′-(2-Phenyl-1-ethenyl)phenyl)tropane-2β-carboxylic Acid Methyl Ester (7b). ^{1}H NMR ($CDCl_3$): δ 1.60−1.73 (m, 3H), 2.05−2.23 (m, 2H), 2.23 (s, 3H), 2.61 (dt, 1H, J = 2.7, 12.3 HZ), 2.92 (m, 1H), 3.02 (dt, 1H, J = 5.1, 12.6 Hz), 3.38 (bs, 1H), 3.50 (s, 3H), 3.57 (bs, 1H), 7.06 (s, 2H), 7.22−7.30 (m, 4H), 7.35 (t, 1H, J = 7.2 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 25.6, 26.3, 34.0, 34.4, 42.4, 51.5, 53.2, 62.7, 65.7, 126.5 (2C), 126.8 (2C), 127.8, 128.0 (2C), 128.3, 129.0 (3C), 135.3, 137.9, 143.1, 172.5. The free base was converted to the tosylate salt; mp 182−184 °C; $[\alpha]_D^{24}$ −97.6° (*c* 0.08, MeOH). Anal. ($C_{31}H_{35}NO_8S \cdot 0.25H_2O$) C, H, N.

(*E*)-3β-(4′-(2-Phenyl-1-ethenyl)phenyl)tropane-2β-carboxylic Acid Methyl Ester (7b). A more direct synthesis of **7b** is as follows. To a solution of 0.5 g (1.3 mmol) of **9** (RTI-55) in 5 mL of degassed toluene were added 0.943 g (1.56 mmol) of (*E*)-1,2-bistributylstannylethylene and a catalytic amount of bis(triphenylphosphine)palladium(II)chloride. The mixture was heated to reflux. After 45 min, the solution became black and the reaction was complete. The cooled slurry was filtered through Celite to remove the palladium. The solution was concentrated in vacuo forming (*E*)-stannane **10b**.

The yellow oil was immediately dissolved in 6.5 mL of dry methylene chloride, and 0.987 g (3.9 mmol) of iodine was added to the solution. A dark precipitate formed. The slurry was stirred for 1 h and then worked up as before. The solution was concentrated in vacuo to remove excess solvent. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded 0.226 g (42%) of (*E*)-iodide **11b**, which was used without further purification in the coupling reaction.

To a solution of 0.111 g (0.27 mmol) of **11b** in 2 mL of dry degassed THF under nitrogen was added phenylzinc chloride, made as described above by first reacting 0.299 mL (0.54 mmol) of 1.8 M phenyllithium in THF and 1.08 mL (0.54 mmol) of 0.5 M zinc chloride in THF, followed by a catalytic amount of bis(triphenylphosphine)palladium(II)chloride. The reaction darkened immediately and was stirred overnight. To this mixture was added water that formed a precipitate of zinc salts. The solids were filtered leaving a biphasic mixture. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was first purified by flash chromatography on silica gel to remove any byproducts. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded 0.048 g (49%) of **7b**.

(*E*)-3*β*-(4′-(3-Phenyl-1-propenyl)phenyl)tropane-2*β*-carboxylic Acid Methyl Ester (8). To a solution of 0.115 g (0.28 mmol) of the **11b** prepared above for **7b** in 2 mL of dry degassed THF under nitrogen was added 1.08 mL (0.56 mmol) of 0.5 M benzylzinc chloride in THF, followed by a catalytic amount of bis(triphenylphosphine)palladium(II)chloride. The reaction darkened immediately and was stirred overnight. To this mixture was added water that formed a precipitate of zinc salts. The solids were filtered leaving a biphasic mixture. The product was partially purified by adding 1 M HCl until acidic and extracting the aqueous layer with diethyl ether. The remaining aqueous layer was cooled to 0 °C by adding ice and then basified by the addition of ammonium hydroxide with stirring until cloudiness persisted. The free base was extracted from the aqueous layer by first stirring at room temperature with methylene chloride for 1 h and then extracting as normal. The combined organic layers were concentrated in vacuo. The resulting yellow oil was first purified by flash chromatography on silica gel to remove any byproducts. Elution with ethyl acetate−hexane (75:25) with the addition of 2% triethylamine afforded 0.081 g (77%) of **8**. ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 3H), 2.22 (m, 2H), 2.21 (s, 3H), 2.58 (t, 1H, J = 12.2 Hz), 2.88 (bs, 1H), 2.96 (dd, 1H, J = 5.9, 12.5 Hz), 3.35 (bs, 1H), 3.47 (s, 3H), 3.49 (m, 3H), 6.28 (dt, 1H, J = 6.7, 15.7 Hz), 6.40 (d, 1H, J = 15.9 Hz), 7.16 (m, 9H). The free base was converted to hydrochloride salt; mp 116−118 °C; $[\alpha]_D^{24}$ −110.5° (*c* 0.09, MeOH). Anal. ($C_{25}H_{30}NClO_2 \cdot 2H_2O$) C, H, N.

3-(2′-Naphthyl)tropene-2-carboxylic Acid Methyl Ester (15). To a round bottom flask were added the triflate **14** (2.026 g, 616 mmol). LiCl (0.503 g, 12.0 mmol), Pd-$[P(C_6H_5)_3]_4$ (0.203 g), Na_2CO_3 (2.0 M solution in H_2O, 6.0 mL, 12.0 mmol), and diethoxymethane (15 mL). The mixture was stirred vigorously, and 2′-naphthyl boronic acid (1.234 g, 7.18 mmol) was added. After 2 h reflux, the reaction mixture was filtered through Celite. Et_2O and H_2O were added, and the mixture was basified to pH 10 with NH_4OH. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The organic layers were combined and dried over Na_2SO_4. Solvent was removed to afford 2.39 g of yellow oil. Purification by flash chromatography SiO_2 using Et_2O/Et_3N/hexane (45:5:50) as eluent gave 1.37 g (72%) of the tropene as a slightly yellow oil, which solidified upon standing. Recrystallization from Et_2O/hexane gave light yellow crystals; mp 98−100 °C; $[\alpha]_D^{22}$ −75.6° (*c* 0.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.78 (m, 3H), 7.60 (s, 1H), 7.45 (m. 2H), 7.25 (m, 1H), 3.91 (m, 1H), 3.42 (s, 3H), 3.38 (m, 1H), 2.83 (m, 1H), 2.49 (s, 3H), 1.99−2.32 (m, 4H), 1.69 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 168.50, 143.63, 138.78, 133.15, 132.66, 130.96, 127.99, 127.68, 127.50, 126.14, 125.95, 125.62, 125.24, 60.42, 57.49, 51.36, 37.57, 36.07, 34.36, 30.28. Anal. ($C_{20}H_{21}NO_2$) C, H, N. The free base was converted to the (D)-tartaric acid salt. Recrystallization from 2-propanol/Et_2O gave a hygroscopic white powder; mp 48 °C (dec); $[\alpha]_D^{22}$ −30.8° (*c* 0.26, CH_3OH). ^{1}H NMR (CD_3OD): δ 7.86 (m, 3H), 7.72 (s, 1H), 7.49 (m, 2H), 7.30 (m, 1H), 4.64 (m, 1H), 4.07 (m, 1H), 3.50 (s, 3H), 3.25 (m, 1H), 2.94 (s, 3H), 2.75 (m, 1H), 2.41−2.60 (m, 3H), 2.12 (m, 1H). Anal. ($C_{24}H_{27}NO_8 \cdot 0.5H_2O$) C, H, N.

3*β*(2-Naphthyl)tropane-2*β*-carboxylic Acid Methyl Ester (12) and 3α-(2-Naphthyl)tropane-2*β*-carboxylic Acid Methyl Ester (13). The tropene **15** (1.00 g, 3.26 mmol) was dissolved in 5 mL of anhydrous MeOH under Ar. After it was cooled to −78 °C, the SmI_2 solution (0.1 M in THF, 130.0 mL, 13.0 mmol) was added dropwise via syringe. The mixture was stirred at −78 °C and monitored by TLC. After 1.0 h, the reaction was quenched by the dropwise addition of a solution of TFA (3.0 mL) in Et_2O at −78 °C. After it was warmed to 0 °C, water was added. The mixture was basified to pH 11 with NH_4OH and filtered through Celite. Et_2O and saturated $Na_2S_2O_3$ were added, and the layers were separated. The aqueous layer was extracted with $CHCl_3$. The organic layers were combined and dried over Na_2SO_4. Solvent was removed to afford an oil. Purification via flash chromatography using 2.5% EtOH/$CHCl_3$ and Et_2O/Et_3N/hexane (9:1:30) as eluent gave the desired 2*β*,3α and 2*β*,3*β* isomers **13** and **12**, respectively.

The tropane **13** was isolated in 19.1% yield as an oil. ^{1}H NMR ($CDCl_3$): δ 7.76 (m, 3H), 7.66 (m, 1H), 7.33−7.47 (m, 3H), 3.56 (s, 3H), 3.54 (m, 1H), 3.40 (m, 1H), 3.31 (m, 1H), 2.67 (dd, 1H), 2.52 (m, 1H), 2.28 (s, 3H), 2.11−2.25 (m, 2H), 1.48−1.64 (m, 3H). ^{13}C NMR ($CDCl_3$): 175.20, 141.65, 133.42, 132.18, 127.94, 127.68, 127.52, 126.36, 125.88, 125.35, 63.26, 59.66, 56.05, 51.78, 41.11, 38.88, 36.22, 28.84.

The tropane **13** was characterized as its (D)-tartaric acid salt; mp 55 °C (dec); $[\alpha]_D$ −60.0° (*c* 0.28, CH_3OH). ^{1}H NMR (CD_3OD): δ 7.85 (m, 4H), 7.44−7.56 (m, 3H), 4.19 (m, 1H), 3.97 (m, 1H), 3.67 (s, 3H), 3.62 (m, 1H), 3.47 (m, 1H), 2.84 (s, 3H), 2.67 (m, 1H), 2.31−2.43 (m, 3H), 2.04 (m, 2H). Anal. ($C_{24}H_{29}NO_8 \cdot 0.5H_2O$) C, H, N. The tropane **12** was isolated in 19.4% yield as an oil. ^{1}H NMR ($CDCl_3$): δ 7.75 (m, 4H), 7.41 (m, 3H), 3.58 (m, 1H), 3.44 (s, 3H), 3.40 (m, 1H), 3.14 (m, 1H), 3.03 (m, 1H), 2.72 (m, 1H), 2.31 (s, 3H), 2.10−2.29 (m, 2H), 1.65−1.84 (m, 3H). ^{13}C NMR ($CDCl_3$): 172.14, 140.80, 133.37, 127.81, 127.47, 127.33, 125.90, 125.84, 125.69, 125.16, 65.42, 62.33, 52.84, 51.16, 42.04, 34.19, 33.93, 26.00, 25.26. Anal. ($C_{24}H_{29}NO_8 \cdot 0.5H_2O$) C, H, N.

The tropane **12** was characterized as its (D)-tartaric acid salt; mp 106 °C (dec); $[\alpha]_D$ −85.4° (*c* 0.26, CH_3OH). ^{1}H NMR (CD_3OD): δ 7.83 (m, 3H), 7.70 (s, 1H), 7.38−7.49 (m, 3H), 4.18 (m, 1H), 4.11 (m, 1H), 3.75 (m, 1H), 3.30 (m, 1H), 2.96 (s, 3H), 2.95 (m, 1H), 2.26−2.55 (m, 4H), 2.08 (m, 1H). Anal. ($C_{24}H_{29}NO_8 \cdot 0.5H_2O$) C, H, N.

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