Synthesis, Radiosynthesis, and Biological Evaluation of Carbon-11 Labeled 2β-Carbomethoxy-3β-(3′-((Z)-2-haloethenyl)phenyl)nortropanes: Candidate Radioligands for in Vivo Imaging of the Serotonin Transporter with Positron Emission Tomography

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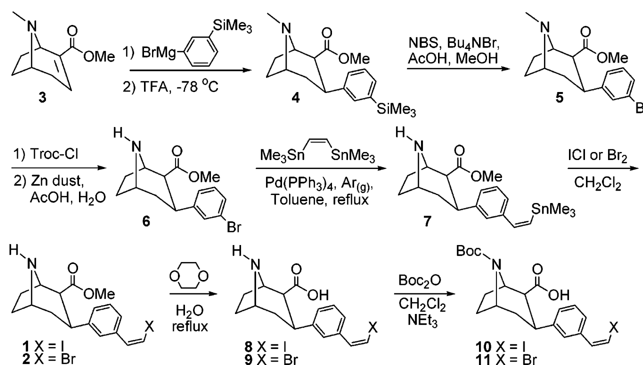
2β-Carbomethoxy-3β-(3′-((*Z*)-2-iodoethenyl)phenyl)nortropane (*m*ZIENT, **1**) and 2β-carbomethoxy-3β-(3′-((*Z*)-2-bromoethenyl)phenyl)nortropane (*m*ZBrENT, **2**) were synthesized and evaluated for binding to the human serotonin, dopamine, and norepinephrine transporters (SERT, DAT, and NET, respectively) using transfected cells. Both **1** and **2** have a high affinity for the SERT ($K_i = 0.2$ nM) and are ∼160 times more selective for the SERT than the DAT. Compound **2** has a significantly higher affinity for the NET than **1**, and this may be a result of the different size and electronegativity of the halogen atoms. MicroPET imaging in nonhuman primates with [11C]**1** and [11C]**2** demonstrated that both tracers behave similarly in vivo with high uptake being observed in the SERT-rich brain regions and peak uptake being achieved in about 55 min postinjection. Chase studies with citalopram and methylphenidate demonstrated that this uptake is the result of preferential binding to the SERT.

Introduction

The human serotonin transporter (SERT) is a 630 amino acid transmembrane protein in the brain and peripheral organs.[1,2] Within the central nervous system (CNS), the SERT is localized on the presynaptic terminals of serotonergic neurons and functions to terminate neurotransmission by removing serotonin from the synapse. Serotonergic neurons originate primarily in the median and dorsal raphe nuclei of the brainstem and innervate discrete areas that include the hypothalamus, thalamus, striatum, and cerebral cortex.[3−6] The SERT can therefore serve as a specific marker for serotonergic neuronal anatomy and integrity. Dysregulation of serotonin neurotransmission has been implicated in the pathophysiology of major depression, and a reduction in SERT density has been observed postmortem in the tissues of depressed patients and suicide victims.[7−10] The ability to image CNS SERT in vivo using positron emission tomography (PET)[11−13] may provide insight into the pathophysiology of depression by enabling the SERT density of specific brain regions to be measured, thereby indicating which regions of the brain have SERT density altered by the disease as well as allow for improved diagnostic techniques and monitoring of antidepressant therapy.[14−16]

As part of ongoing research in our laboratories to develop SERT-specific tropane and nortropane PET and single-photon-emission computed tomography (SPECT) imaging agents for human diagnostic applications, we have been exploring the incorporation of unsaturated groups or heterocycles in the 4′-position of the 3β-phenyl ring.[17−19] The *cis*-vinyl iodide group, when placed at the *para*-position of the 3β-phenyl ring of a nortropane, has been shown to impart a high SERT affinity and selectivity as well as to provide good kinetics for in vivo imaging of the SERT with PET.[20] To further investigate this pharmacophore we have moved the *cis*-vinyl halide group to the *meta*-position of the 3β-phenyl ring. We report here the synthesis, radiosynthesis, and biological evaluation of 2β-carbomethoxy-3β-(3′-((*Z*)-2-iodoethenyl)phenyl)nortropane (*m*ZIENT, **1**)[21] and 2β-carbomethoxy-3β-(3′-((*Z*)-2-bromoethenyl)phenyl)nortropane (*m*ZBrENT, **2**)[22] along with the microPET imaging of [11C]-**1** and [11C]**2** in nonhuman primates.

Scheme 1



Chemistry

Conjugate addition of 3-trimethylsilylphenylmagnesium bromide to anhydroecgonine methyl ester (**3**) afforded the *m*-trimethylsilylphenyl tropane **4**[23] (Scheme 1). Bromination of **4** afforded the *m*-bromophenyl tropane **5** which was reacted with Troc-Cl[24] followed by Zn/AcOH to give the *m*-bromophenyl nortropane **6**. Palladium catalyzed coupling of **6** with (*Z*)-1,2-bis(trimethylstannyl)ethene[25,26] afforded the vinyl-tin nortropane **7** as a *cis*:*trans* mixture (with *cis* being the predominant isomer) along with 3β-phenyl nortropane (nor-WIN 35,065-2) as a side-product. Purification by radial chromatography on silica afforded fractions enriched in the *cis* isomer, but complete separation of the two isomers was not obtained. Halodestannylation of **7** afforded **1** or **2** in varying *cis*:*trans* ratios which depended partly on the *cis*:*trans* ratio of starting material **7**.[25] The *cis*:*trans* isomers were separated by semipreparative HPLC to afford isomerically pure **1** or **2** for binding assays and spectroscopic

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Scheme 2

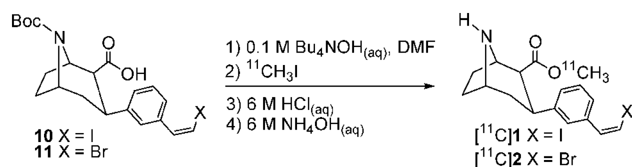

Table 1. Results of in Vitro Competition Binding Assays with Transfected Human Monoamine Transporters

	$K_i \pm$ SEM (nM)			SERT selectivity	
compd	SERT	DAT	NET	DAT/SERT	NET/SERT
1	0.2 ± 0.0^b	29.9 ± 3.1^c	102.2 ± 5.0^a	~150	~511
2	0.2 ± 0.0^a	32.6 ± 0.7^a	31.7 ± 5.2^b	~163	~159

[a] $n = 2$. [b] $n = 3$. [c] $n = 4$.

analysis. (The X-ray crystal structure of **1**[27] is reported in the Supporting Information.) Vinylhalide nortropanes **1** and **2** were hydrolyzed in refluxing 1,4-dioxane/H_2O[28] to afford the nortropane acids **8** and **9** which were *N*-Boc protected to give the radiolabeling precursors **10** and **11**. In some instances, the isomeric mixture was carried through to the end of the synthesis and radiolabeling as the isomers could be separated during semipreparative HPLC purification of the radiolabeled compound.

Radiochemistry

The radiosynthesis of [^{11}C]**1** and [^{11}C]**2** is shown in Scheme 2. *N*-Boc acid **10** or **11** was dissolved in DMF, deprotonated with 0.1 M Bu_4NOH(aq), placed in a septum-capped 3 mL V-vial, and cooled to 0 °C. The carboxylate salt was *O*-methylated by bubbling $^{11}CH_3I$ through the cold DMF solution, the *N*-Boc group was cleaved under acidic conditions, the solution was neutralized, and the mixture purified by semipreparative HPLC. The desired HPLC fractions were combined, and the product was isolated by solid phase extraction according to a previously reported procedure.[29] The octanol/water partition coefficients[30] of [^{11}C]**1** and [^{11}C]**2** were measured according to a previously reported procedure[31] and found to be [^{11}C]**1** $\log P_{7.4} = 1.49 \pm 0.08$ and [^{11}C]**2** $\log P_{7.4} = 1.43 \pm 0.01$ (each value is the average of 12 trials ± the standard deviation).

In Vitro Competition Binding Assays

Nortropanes **1** and **2** were screened for binding to human monoamine transporters using in vitro competition binding assays with transfected human SERT, dopamine transporter (DAT), or norepinephrine transporter (NET) according to a previously reported procedure.[17,32] The binding affinities for each transporter were determined using [^{3}H]-citalopram (SERT), [^{125}I]-RTI-55 (DAT), or [^{3}H]-nisoxetine (NET). The data in Table 1 indicate that **1** and **2** bind to the SERT with the same affinity and also to the DAT with the same affinity, but they have different affinities for the NET. Nortropanes **1** and **2** each have a high selectivity for the SERT over the DAT, and **1** also has a very high selectivity for the SERT over the NET. Because **1** and **2** have the same affinity for the SERT and also the same affinity for the DAT, the size and electronegativity of the halogen atom presumably does not significantly influence the binding of **1** and **2** to these two monoamine transporters but this may account for the different NET affinities. We did not screen *trans*-**1** or *trans*-**2** because it has been previously shown[18,25] that *trans*-isomers have a reduced SERT affinity and an increased DAT affinity.

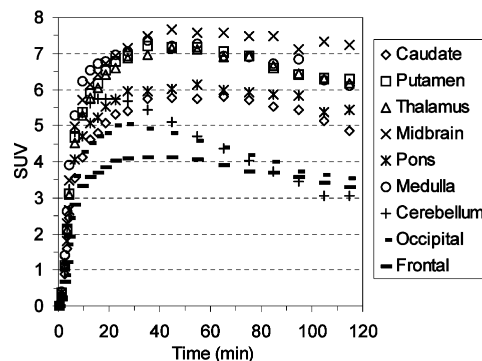

Figure 1. MicroPET baseline study TACs for the brain regions of a cynomolgus monkey after injection of [^{11}C]**1**.

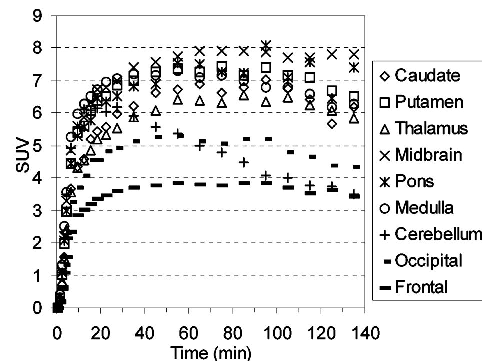

Figure 2. MicroPET baseline study TACs for the brain regions of a cynomolgus monkey after injection of [^{11}C]**2**.

In Vivo Nonhuman Primate MicroPET Imaging

The in vivo regional brain uptake of [^{11}C]**1** and [^{11}C]**2** was determined in anesthetized cynomolgus monkeys using a Concorde microPET P4 according to a previously reported procedure.[17] Two baseline studies were initially performed with each compound to determine the extent of uptake of [^{11}C]**1** (Figures 1 and S1) and [^{11}C]**2** (Figures 2 and S2) in the SERT-rich regions of the brain. Figure 1 shows the time−activity curves (TACs) for the brain regions of a cynomolgus monkey after injection of [^{11}C]**1**. The data indicate a high uptake in the SERT-rich brain regions with peak uptake achieved 45−55 min postinjection (Table S1). The amount of radioactivity in the cerebellum, an area with low SERT concentration,[33] reaches peak uptake after about 25 min and then washes out fairly rapidly. In the second baseline study performed with [^{11}C]**1** (Figure S1), peak uptake is achieved 55−65 min postinjection with high uptake also observed in the SERT-rich brain regions. In contrast to [^{11}C]**1**, the *para*-substituted *cis*-vinyl iodide isomer ([^{11}C]*p*ZIENT)[20] does not reach peak uptake until 75 min postinjection and there is a minimal washout of radioactivity from the cerebellum. Therefore, placement of the *cis*-vinyl iodide group in the *meta*-position of the 3β-phenyl ring results in a tracer that reaches peak uptake faster than the *para*-substituted isomer along with a reduced accumulation of radioactivity in the cerebellum. Figure 2 shows the TACs for the brain regions of a cynomolgus monkey after injection of [^{11}C]**2**. High uptake is observed in the SERT-rich brain regions with peak uptake achieved at 55−65 min postinjection (Table S2) and washout from the cerebellum beginning after about 25 min. Similar results were observed with the second baseline study performed with [^{11}C]**2** (Figure S2). (For comparison, the baseline study with [^{11}C]**1** in Figure 1 and the baseline study with [^{11}C]**2** in Figure S2 were performed in the same monkey.) The microPET images for the baseline studies with [^{11}C]**1** and

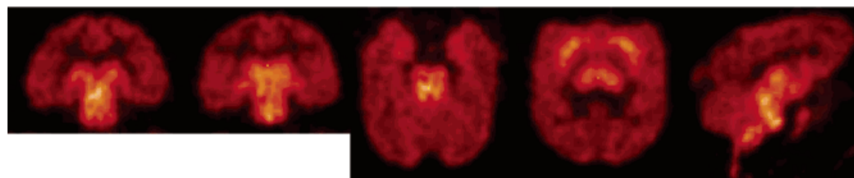

Figure 3. MicroPET images obtained by injection of [^{11}C]**1** into a cynomolgus monkey.

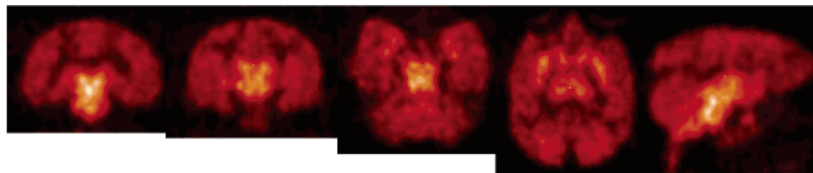

Figure 4. MicroPET images obtained by injection of [^{11}C]**2** into a cynomolgus monkey.

Table 2. Comparison of the Ratio of Uptake of [^{11}C]**1** and [^{11}C]**2** in Specific Brain Regions to Cerebellum Uptake at 65, 85, and 105 min Postinjection for the Baseline Studies Shown in Figures 1 and 2

brain region	65 min		85 min		105 min	
	[^{11}C]**1**	[^{11}C]**2**	[^{11}C]**1**	[^{11}C]**2**	[^{11}C]**1**	[^{11}C]**2**
caudate	1.3	1.4	1.5	1.5	1.7	1.7
putamen	1.6	1.5	1.8	1.6	2.1	1.8
thalamus	1.6	1.3	1.8	1.5	2.1	1.6
midbrain	1.7	1.6	2.0	1.8	2.4	1.9
pons	1.4	1.5	1.6	1.6	1.8	1.8
medulla	1.6	1.4	1.8	1.6	2.1	1.7
frontal	1.0	1.0	1.1	1.2	1.2	1.2
occipital	0.9	0.8	1.0	0.9	1.1	0.9

[^{11}C]**2** (Figures 1 and 2) are shown in Figures 3 and 4, respectively.

Table 2 compares the ratios of uptake of [^{11}C]**1** and [^{11}C]**2** in the SERT-rich regions of the brain to cerebellum uptake[33] after 65, 85, and 105 min postinjection for the baseline TACs shown in Figures 1 and 2 (Table S3 compares the uptake ratios for the studies shown in Figures S1 and S2.) From these data it can be seen that the ratio of uptake continues to increase throughout the course of the study for both tracers and that at all three time points the uptake ratios are similar in all regions of interest. Both **1** and **2** have similar binding affinities to the SERT (Table 1), both [^{11}C]**1** and [^{11}C]**2** have similar $\log P_{7.4}$ values (see above), and these baseline studies demonstrate that both [^{11}C]**1** and [^{11}C]**2** also have similar in vivo characteristics. Therefore, it appears that the choice of iodine or bromine as the vinyl halide atom does not significantly affect the properties of this nortropane (other than binding to the NET).

In an effort to demonstrate that the observed uptake in the baseline studies with [^{11}C]**1** and [^{11}C]**2** is the result of preferential binding to the SERT, chase studies were performed with the SERT-selective ligand (*R/S*)-citalopram·HBr (1.5 mg/kg) at 60 min postinjection (30 s infusion) of [^{11}C]**1** and [^{11}C]**2** (Figures 5 and 6, respectively). These TACs demonstrate that [^{11}C]**1** and [^{11}C]**2** can both be displaced from brain regions with high SERT density and that the uptake in these regions is therefore the result of preferential binding to the SERT. Unfortunately, the short half-life of ^{11}C (20.4 min) did not allow for data collection to continue until the radioactivity in these regions decreased to the levels observed in the cerebellum.

As was shown in Table 1, **1** and **2** are ~160 times more selective for the SERT than the DAT. To verify that the uptake of [^{11}C]**1** and [^{11}C]**2** in the caudate and putamen is the result of binding to the SERT and not the DAT, chase studies were performed with the DAT ligand methylphenidate·HCl at 60 min (30 s infusion) postinjection of [^{11}C]**1** and [^{11}C]**2** (Figures 7 and 8, respectively). No significant displacement is evident in these two chase studies. The minor washout of radioactivity in the caudate and putamen is similar to that observed in the baseline studies, verifying that the uptake in these regions is the result of preferential SERT binding.

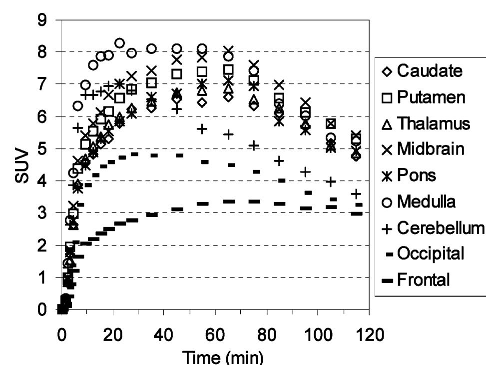

Figure 5. Time–activity curves showing the results of injection of (*R/S*)-citalopram·HBr (1.5 mg/kg) in a cynomolgus monkey at 60 min (30 s infusion) postinjection of [^{11}C]**1**.

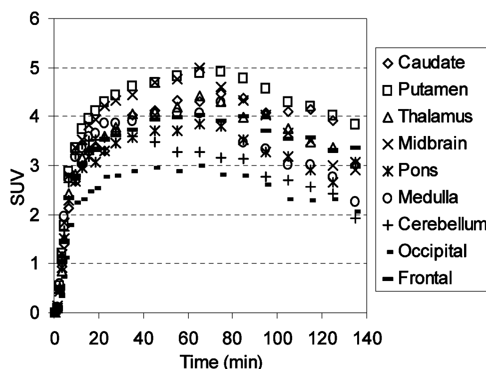

Figure 6. Time–activity curves showing the results of injection of (*R/S*)-citalopram·HBr (1.5 mg/kg) in a cynomolgus monkey at 60 min (30 s infusion) postinjection of [^{11}C]**2**.

The binding data in Table 1 indicate that **1** is ~511 times more selective for the SERT than the NET, whereas **2** is only ~159 times more selective for the SERT than the NET. Chase studies were performed with the NET ligand (±)-reboxetine·mesylate to determine if [^{11}C]**1** or [^{11}C]**2** bind to the NET in any appreciable fashion (Figures 9 and 10, respectively). For these studies the chase compound was administered 60 min postinjection of the tracer with a 2 min infusion time. From the TACs in Figures 9 and 10 it can be seen that there is displacement of the tracer from all the areas of the brain that show uptake. Reboxetine has a high affinity for the NET but

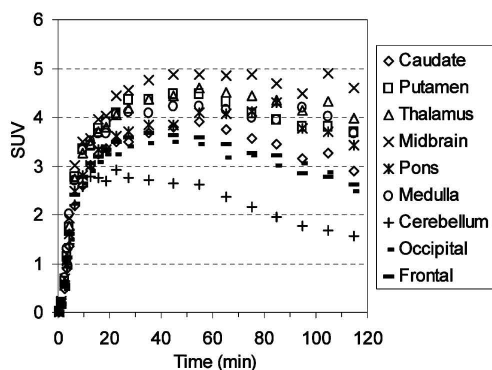

Figure 7. Time−activity curves showing the results of injection of methylphenidate•HCl (0.3 mg/kg) in a cynomolgus monkey at 60 min (30 s infusion) postinjection of [^{11}C]**1**.

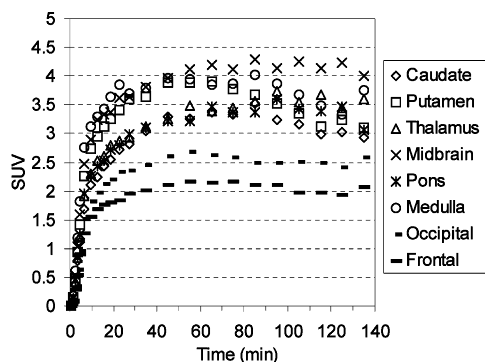

Figure 8. Time−activity curves showing the results of injection of methylphenidate•HCl (0.3 mg/kg) in a cynomolgus monkey at 60 min (30 s infusion) postinjection of [^{11}C]**2**.

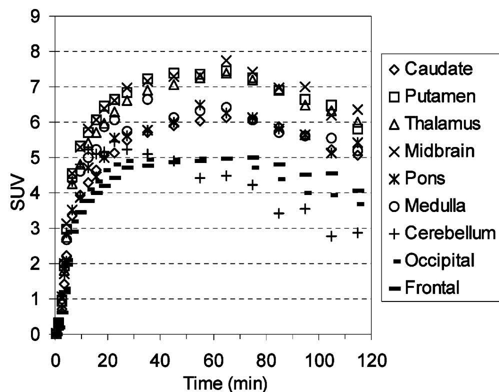

Figure 9. Time−activity curves showing the results of injection of (±)-reboxetine•mesylate (1.0 mg/kg) in a cynomolgus monkey at 60 min (2 min infusion) postinjection of [^{11}C]**1**.

also an appreciable affinity for the SERT,[18,34] and this is presumably the cause of the observed displacement.

Summary

*m*ZIENT **1** and *m*ZBrENT **2** were synthesized from *m*-bromophenyl nortropane **6** and evaluated for binding to the SERT, DAT, and NET. Both **1** and **2** have a high, and equal, affinity for the SERT. Affinity for the DAT was also found to be nearly equal for **1** and **2**, but affinity for the NET was found to be quite different with **1** being less potent than **2**. This difference is believed to be derived from the different size and electronegativity of the two halogen atoms. Radiolabeling and microPET imaging evaluation of [^{11}C]**1** and [^{11}C]**2** demonstrated that both tracers behave similarly in vivo with high uptake in the SERT-rich regions of the brain. In baseline studies with each tracer, peak uptake was achieved after about 55 min with washout from the cerebellum beginning after about 25 min. Both tracers therefore exhibit better imaging kinetics than the *para*-substituted analogue [^{11}C]*p*ZIENT. [20] Both [^{11}C]**1** and [^{11}C]**2** could be displaced with the SERT ligand (*R/S*)-citalopram•HBr but not with the DAT ligand methylphenidate•HCl. In chase studies with (±)-reboxetine•mesylate both [^{11}C]**1** and [^{11}C]**2** were displaced from all the brain regions that showed uptake, but this is believed to be a result of the affinity reboxetine has for the SERT. In conclusion, both [^{11}C]**1** and [^{11}C]**2** have very similar microPET imaging properties and both **1** and **2** have very similar binding affinities at the SERT and DAT with the only significant difference between the two being the binding affinity at the NET. Therefore, both tracers are good candidates for imaging the SERT in humans with PET when labeled with ^{11}C. Additionally, these two tracers have the potential to be adapted for SPECT imaging with [^{123}I]**1** or PET imaging with [^{76}Br]**2**.[35]

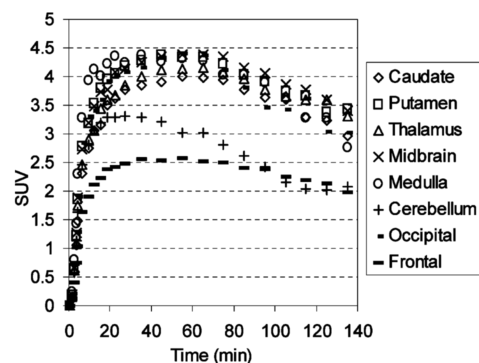

Figure 10. Time−activity curves showing the results of injection of (±)-reboxetine•mesylate (1.0 mg/kg) in a cynomolgus monkey at 60 min (2 min infusion) postinjection of [^{11}C]**2**.

Experimental Section

1-Bromo-3-trimethylsilyl Benzene. 1,3-Dibromobenzene (25.66 g, 108.8 mmol) was dissolved in EtOEt (100 mL) under Ar and cooled to −54 °C (dry ice/ CH_3CN). *n*-BuLi (1.6 M hexanes, 67 mL, 107 mmol) was added dropwise over a period of 19 min, the reaction mixture was stirred for 45 min, and then Me_3SiCl (15.5 mL, 123 mmol) was added dropwise over a period of 10 min. The reaction mixture was warmed to room temperature, stirred at room temperature for 1 h, and filtered through Celite. The solvent was removed from the filtrate to give a faint yellow oil that was purified by flash column chromatography (210 g silica, hexane) to afford 23.92 g (96%) of a colorless oil: TLC R_f = 0.55 (silica, hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (m, 1 H), 7.47 (dm, 1 H, J = 7.8 Hz), 7.42 (dm, 1 H, J = 7.2 Hz), 7.22 (dd, 1 H, J = 7.2 Hz, J = 7.8 Hz), 0.27 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.93, 136.16, 131.95, 131.85, 129.76, 123.09, −1.05.

2β-Carbomethoxy-3β-(3′-(trimethylsilyl)phenyl)tropane (4). Mg^0 (2.72 g, 112 mmol, 3.1 equiv) was placed in a 250 mL three-neck flask and stirred violently under Ar for 30 min followed by addition of anhydrous EtOEt (13 mL) and DIBAL[36] (1.0 M toluene, 1.58 mL) and stirring for 10 min. I_2 (76 mg, 0.30 mmol) was dissolved in anhydrous EtOEt (1 mL) and added to the flask. 1-Bromo-3-trimethylsilylbenzene (25.60 g, 112 mmol, 3.1 equiv) was dissolved in anhydrous EtOEt (86 mL), placed in an addition funnel, and added dropwise to the flask over a period of 20 min (self-refluxing started after 2 min and continued throughout the addition). The reaction mixture was heated at reflux under Ar for 30 min, cooled to room temperature, transferred under Ar pressure to a 500 mL three-neck flask, diluted with anhydrous CH_2Cl_2 (40 mL), and cooled to −43 °C (CH_3CN/dry ice). Anhydroecgonine methyl ester (**3**) (6.61 g, 36.47 mmol) was dissolved in anhydrous CH_2Cl_2 (60 mL), placed in an addition funnel, and added dropwise

to the Grignard solution over a period of 15 min. The reaction mixture was stirred at −43 °C under Ar for 3 h, cooled to −78 °C, and quenched by dropwise addition of TFA (28.6 mL, 0.37 mol, 10.2 equiv) in anhydrous CH_2Cl_2 (75 mL) over a period of 3.5 min (temperature rose to −35 °C). The reaction mixture was warmed to room temperature and the solvent removed to give an orange oil that was dissolved in CH_2Cl_2 (100 mL) followed by addition of H_2O (100 mL). The mixture was cooled to 0 °C, the aqueous layer was basified to pH 10 with concentrated NH_4OH(aq), the mixture was filtered, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL × 2), the combined CH_2Cl_2 layers were dried over $MgSO_4$, and the solvent was removed to give an orange oil that was vacuum flash chromatographed on silica (13 cm high × 4 cm i.d.; eluted with CH_2Cl_2 (200 mL), hexane/EtOAc/NEt_3 v/v/v 90:8:2 (100 mL), 75:20:5 (400 mL)) to afford 7.90 g (65%) of a faint yellow oil: TLC R_f = 0.34 (silica, 75:20:5 v/v/v hexane/EtOAc/NEt_3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 1 H), 7.32 (m, 1 H), 7.31 (m, 1 H), 7.27 (s, 1 H), 3.55 (m, 1 H), 3.48 (s, 3 H), 3.37 (m, 1 H), 3.01 (dt, 1 H, J = 5.4 Hz, J = 13.2 Hz), 2.91 (m, 1 H), 2.61 (td, 1 H, J = 3.0 Hz, J = 12.6 Hz), 2.23 (s, 3 H), 2.19 (m, 1 H), 2.10 (m, 1 H), 1.75 (m, 1 H), 1.70 (m, 1 H), 1.62 (m, 1 H), 0.24 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.46, 142.18, 139.80, 132.50, 131.07, 128.25, 127.53, 65.59, 62.48, 53.09, 51.27, 42.17, 34.33, 34.12, 26.16, 25.36, −0.89; HRMS (APCI) $[MH]^+$ Calcd for $C_{19}H_{30}NO_2Si$: 332.2040, Found: 332.2039.

2β-Carbomethoxy-3β-(3′-bromophenyl)tropane (5). 2β-Carbomethoxy-3β-(3′-(trimethylsilyl)phenyl)tropane (**4**) (1.02 g, 3.08 mmol) was dissolved in MeOH (20 mL) followed by addition of AcOH (40 mL), then NBS (1.74 g, 9.78 mmol, 3.2 equiv), and then n-Bu_4NBr (3.01 g, 9.34 mmol, 3.0 equiv). (**Caution**: addition of NBS last may result in an explosive release of gas!). The solution was stirred at 77 °C under Ar for 20 h, cooled to room temperature, diluted with CH_2Cl_2 (150 mL) and H_2O (150 mL), and cooled to 0 °C. The aqueous phase was basified to pH 11 with concentrated NH_4OH(aq), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL × 2). The combined CH_2Cl_2 layers were dried over $MgSO_4$, and the solvent was removed to give a yellow oil that was purified by vacuum flash chromatography on silica (11.5 cm high × 4 cm i.d.) eluted with CH_2Cl_2 (200 mL) and then 75:20:5 v/v/v hexane/EtOAc/NEt_3 to afford 0.66 g (63%) of a viscous, colorless syrup: TLC R_f = 0.27 (silica, 75:20:5 v/v/v hexane/EtOAc/NEt_3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 1 H), 7.28 (d, 1 H, J = 7.8 Hz), 7.20 (d, 1 H, J = 7.8 Hz), 7.14 (dd, 1 H, J = 7.8 Hz), 3.57 (m, 1 H), 3.52 (s, 3 H), 3.36 (m, 1 H), 2.97 (dt, 1 H, J = 5.4 Hz, J = 12.6 Hz), 2.90 (m, 1 H), 2.53 (td, 1 H, J = 3.0 Hz, J = 12.6 Hz), 2.22 (s, 3 H), 2.19 (m, 1 H), 2.10 (m, 1 H), 1.69 (m, 2 H), 1.60 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.13, 145.90, 130.74, 129.71, 129.12, 126.12, 122.35, 65.48, 62.35, 52.83, 51.44, 42.14, 34.12, 33.82, 26.06, 25.39; HRMS (APCI) $[MH^+]$ Calcd for $C_{16}H_{21}O_2N^{79}Br$: 338.0750, Found: 338.0752; Calcd for $C_{16}H_{21}O_2N^{81}Br$: 340.0734, Found: 340.0732.

2β-Carbomethoxy-3β-(3′-bromophenyl)nortropane (6). 2β-Carbomethoxy-3β-(3′-bromophenyl)tropane (**5**) (0.61 g, 1.80 mmol), 2,2,2-trichloroethyl chloroformate (2.5 mL, 18.2 mmol, 10.1 equiv), Na_2CO_3(s) (0.11 g, 1.04 mmol, 0.6 equiv), and toluene (12 mL) were stirred at reflux under Ar for 21 h, cooled, poured onto dry silica (33 mm high × 43 mm i.d.), and eluted under vacuum with CH_2Cl_2 (75 mL) and then 75:20:5 v/v/v/hexane/EtOAc/NEt_3 (150 mL). The solvent was removed to give a colorless residue that was dried under vacuum (0.94 g). To the residue were added Zn dust (1.24 g), AcOH (25 mL), and H_2O (0.7 mL), and the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered, the filtrate was diluted with CH_2Cl_2 (75 mL) and H_2O (75 mL), and the mixture was cooled to 0 °C. The aqueous phase was basified to pH 11 with concentrated NH_4OH(aq), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL × 2). The combined CH_2Cl_2 layers were dried over $MgSO_4$, and the solvent was removed to give a colorless oil. The oil was dissolved in CH_2Cl_2, poured onto dry silica (38 mm high × 43 mm i.d.), and eluted under vacuum: CH_2Cl_2 (100 mL), then hexane/EtOAc/NEt_3 v/v/v 75:20:5 (100 mL), 50:45:5 (300 mL), 20:75:5 (300 mL). The solvent was removed to give 0.46 g (79%) of a colorless residue: TLC R_f = 0.19 (silica, 20:75:5 v/v/v hexane/EtOAc/NEt_3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (s, 1 H), 7.32 (m, 1 H), 7.14 (m, 2 H), 3.73 (m, 1 H), 3.71 (m, 1 H), 3.42 (s, 3 H), 3.21 (dt, 1 H, J = 6.0 Hz, J = 12.6 Hz), 2.73 (m, 1 H), 2.37 (td, 1 H, J = 12.6 Hz, J = 3.0 Hz), 2.12 (m, 1 H), 2.01 (m, 1 H), 1.75 (m, 1 H), 1.65 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.79, 144.94, 130.77, 130.01, 129.85, 126.19, 122.61, 56.54, 53.78, 51.44, 51.09, 35.73, 33.75, 29.22, 27.83; HRMS (APCI) $[MH]^+$ Calcd for $C_{15}H_{19}O_2N^{79}Br$: 324.0594, Found: 324.0594; Calcd for $C_{15}H_{19}O_2N^{81}Br$: 326.0578, Found: 326.0574.

(*Z*)-1,2-Bis(trimethylstannyl)ethene. Purified acetylene (passed successively through a −78 °C cold trap, concentrated H_2SO_4(aq), NaOH(s), $CaCl_2$(s), and then Drierite) was bubbled through a solution of hexamethylditin (2.52 g, 7.69 mmol), $Pd(PPh_3)_4$ (0.89 g, 0.77 mmol), and 1,4-dioxane (20 mL, purged with Ar for 45 min prior to use) at 65 °C for 4 h. The solution was cooled to room temperature, stirred at room temperature for 20 min, and filtered. The filtrate was poured onto silica gel (14 cm high × 4 cm i.d.) that had been pretreated with 10% NEt_3/hexane (100 mL) and then 1% NEt_3/hexane (100 mL). The product was eluted under vacuum with 1% NEt_3/hexane (200 mL), and the solvent was removed to give a dark orange oil that was briefly dried under vacuum (2.48 g, 91%). TLC R_f = 0.66 (1% NEt_3/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2 H), 0.17 (t, 18 H, $^2J_{SnH}$ = 26.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.17, −8.10.

2β-Carbomethoxy-3β-(3′-((*Z*)-2-trimethylstannylethenyl)-phenyl)nortropane (7). 2β-Carbomethoxy-3β-(3′-bromophenyl)-nortropane (**6**) (0.25 g, 0.77 mmol), $Pd(PPh_3)_4$ (89 mg, 0.77×10^{-4} mol, 0.1 equiv), (*Z*)-1,2-bis(trimethylstannyl)ethene (1.00 g, 2.83 mmol, 3.7 equiv), and Ar-purged toluene (25 mL) were stirred at reflux under Ar for 18 h, cooled to room temperature, and poured onto silica (43 mm h × 43 mm i.d.) that had been pretreated with 10% NEt_3/hexane (100 mL). Elution under vacuum with CH_2Cl_2 (100 mL), then hexane/EtOAc/NEt_3 v/v/v 75:20:5 (100 mL), 50:45:5 (200 mL), 20:75:5 (500 mL) gave a crude brown oil that was ∼76:24 *cis/trans* by integration of the vinyl proton NMR resonances. Purification by radial chromatography (2 mm silica; hexane/EtOAc/NEt_3 v/v/v 90:8:2 (1 L), 85:12:3 (100 mL), 80:14:6 (100 mL)) afforded 56 mg (17%) of a yellow oil that was ∼92:8 *cis/trans*, 71 mg (21%) of a yellow oil that was ∼88:12 *cis/trans*, and 68 mg (20%) of a yellow oil that was ∼73:27 *cis/trans*. TLC R_f = 0.21 (silica, 20:75:5 v/v/v hexane/EtOAc/NEt_3); *cis*-**7**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (td, 1 H, $^3J_{HH}$ = 13.2 Hz, $^3J_{SnH}$ = 73.1 Hz), 7.23 (dd, 1 H, J = 7.8 Hz), 7.10 (m, 2 H), 7.06 (s, 1 H), 6.19 (td, 1 H, $^3J_{HH}$ = 13.2 Hz, $^2J_{SnH}$ = 32.0 Hz), 3.78 (m, 1 H), 3.74 (m, 1 H), 3.37 (s, 3 H), 3.25 (dt, 1 H, J = 5.4 Hz, J = 13.2 Hz), 2.74 (m, 1 H), 2.44 (td, 1 H, J = 2.6 Hz, J = 12.9 Hz), 2.17 (m, 1 H), 2.07 (m, 1 H), 1.77 (m, 1 H), 1.71 (m, 1 H), 1.65 (m, 1 H), 0.07 (s, 9 H, $^2J_{SnH}$ = 27.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.03, 147.51,142.42, 141.24, 133.78, 128.32, 127.00, 126.40, 125.57, 56.52, 53.82, 51.30, 36.06, 33.98, 29.31, 27.86, −7.88. *cis/trans*-**7**: HRMS (ESI) $[MH]^+$ Calcd for $C_{20}H_{30}O_2N^{120}Sn$: 436.1293, Found:436.1290; Calcd for $C_{20}H_{30}O_2N^{118}Sn$: 434.1287, Found: 434.1284.

2β-Carbomethoxy-3β-(3′-((*Z*)-2-iodoethenyl)phenyl)nortropane (*m*ZIENT, 1). 2β-Carbomethoxy-3β-(3′-((*Z*)-2-trimethylstannylethenyl)phenyl)nortropane (**7**) (∼75:25 *cis*/*trans*, 0.17 g, 0.39 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C under Ar. ICl (1 M CH_2Cl_2, 0.75 mL, 1.9 equiv) was added dropwise until a faint red color persisted, the reaction mixture was stirred at 0 °C under Ar for 10 min, and the reaction was quenched by addition of $Na_2S_2O_3$(aq) (0.60 g in 10 mL of H_2O). The reaction mixture was stirred at room temperature for 10 min and diluted with CH_2Cl_2 (25 mL) and H_2O (25 mL), and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2), the combined CH_2Cl_2 layers were dried over $MgSO_4$, and the solvent was removed to give a yellow foam (0.18 g). Purification by radial chromatography (2 mm silica, elution:hexane (15 mL), hexane/EtOAc/NEt_3 v/v/v 95:4:1 (100 mL), 90:8:2 (200 mL), 75:20:5 (800

mL), 50:45:5 (50 mL)) afforded 0.11 g of a faint, yellow syrup that was ∼81:19 *cis*/*trans* by integration of the ^{1}H NMR vinyl resonances. The isomers were separated by semipreparative HPLC (Waters XTerra Prep RP$_{18}$ 5μm, 19 × 100 mm, 60:40:0.1 v/v/v MeOH/H$_2$O/NEt$_3$, 9 mL/min, *cis* t_R = 17−21 min (range for ∼10 mg/injection); *trans* t_R = 25−30 min (range for ∼10 mg/injection)) to afford 64 mg (41%) of **1** as an off-white crystalline solid: TLC R_f = 0.14 (silica, 20:75:5 v/v/v hexane/EtOAc/NEt$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.46 (d, 1 H, J = 8.4 Hz), 7.44 (s, 1 H), 7.30 (dd, 2 H, J = 7.8 Hz), 7.18 (d, 1 H, J = 7.8 Hz), 6.56 (d, 1 H, J = 8.4 Hz), 3.75 (m, 1 H), 3.72 (dd, 1 H, J = 2.4 Hz, J = 6.9 Hz), 3.38 (s, 3 H), 3.28 (dt, 1 H, J = 5.4 Hz, J = 13.2 Hz), 2.79 (m, 1 H), 2.45 (td, 1 H, J = 3.0 Hz, J = 12.9 Hz), 2.12 (m, 1 H), 2.02 (m, 1 H), 1.78 (m, 1 H), 1.69 (m, 1 H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.97, 142.53, 138.83, 136.82, 128.29, 127.59, 126.74, 79.49, 56.57, 53.86, 51.38, 51.31, 35.76, 33.79, 29.32, 27.89; HRMS (APCI) [MH]$^+$ Calcd for C$_{17}$H$_{21}$O$_2$N^{127}I: 398.0612, Found: 398.0611.

***N*-(*t*-Butoxycarbonyl)-3*β*-(3′-((*Z*)-2-iodoethenyl)phenyl)nortropane-2*β*-carboxylic Acid (10).** 2β-Carbomethoxy-3β-(3′-((*Z*)-2-iodoethenyl)phenyl)nortropane (**1**) (33 mg, 8.31 × 10^{-5} mol), 1,4-dioxane (2 mL), and H$_2$O (2.5 mL) were stirred at reflux under Ar for 21 h, and then the solvent was removed to give a white foam that was purified by preparative-TLC (silica, 20:75:5 v/v/v hexane/EtOAc/NEt$_3$). The component with R_f = 0.2 was isolated and dried under vacuum to afford 8 mg (24% recovery) of **1**. The component with R_f = 0 was isolated and dried under vacuum to afford 18 mg of **8** as a white foam that was combined with di-*tert*-butyl dicarbonate (13 mg, 5.96 × 10^{-5} mol), NEt$_3$ (12 μL, 8.6 × 10^{-5} mol), and CH$_2$Cl$_2$ (2 mL), and the mixture was stirred at room temperature under Ar for 1 h. The solvent was removed to give a colorless oil that was purified by preparative-TLC (silica, 2.5% MeOH/CH$_2$Cl$_2$ × 2) to afford 12 mg (39%—calculated based on the recovery of unreacted **1**) of a colorless residue: TLC R$_f$ = 0.42 (silica, 5% MeOH/CH$_2$Cl$_2$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.52 (s, 1 H), 7.42 (d, 1 H, J = 7.8 Hz), 7.28 (m, 2 H), 7.23 (d, 1 H, J = 7.8 Hz), 6.54 (d, 1 H, J = 8.4 Hz), 4.77 (br s, 1 H), 4.45 (br s, 1 H), 3.21 (m, 1 H) 2.83 (br s, 1 H), 2.75 (apparent t, 1 H, J = 11.7 Hz), 2.15 (m, 1 H), 2.01 (m, 1 H), 1.81 (m, 1 H), 1.70 (m, 1 H), 1.62 (m, 1 H), 1.26 (br s, 9 H); HRMS (APCI) [MH − C$_4$H$_8$]$^+$ Calcd for C$_{17}$H$_{19}$O$_4$NI: 428.0359, Found: 428.0351; HRMS (ESI) [M − H]$^-$ Calcd for C$_{21}$H$_{25}$O$_4$N^{127}I: 482.0823, Found: 482.0817.

2*β*-Carbomethoxy-3*β*-(3′-((*Z*)-2-bromoethenyl)phenyl)nortropane (*m*ZBrENT, 2). 2β-Carbomethoxy-3β-(3′-((*Z*)-2-trimethylstannylethenyl)phenyl)nortropane (**7**) (∼95:5 *cis*/*trans*, 48 mg, 0.11 mmol) was dissolved in CH$_2$Cl$_2$ (4 mL) and cooled to 0 °C under Ar. Br$_2$ (57 mg, 0.36 mmol) was dissolved in CH$_2$Cl$_2$ (1 mL) to give a 0.36 M solution that was added dropwise to the cold solution of **7** until a light yellow color persisted (not all of the solution was added). The reaction mixture was stirred at 0 °C under Ar for 12 min and then quenched by addition of Na$_2$S$_2$O$_3$(aq) (4 mL, 94 mM, 0.38 mmol). The reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL) and H$_2$O (10 mL), the layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (5 mL × 2). The combined CH$_2$Cl$_2$ layers were dried over MgSO$_4$, and the solvent was removed to give a white foam that was purified by preparative-TLC (20:75:5 v/v/v hexane/EtOAc/NEt$_3$) to afford 28 mg (73%) of a faint yellow residue that was ∼97:3 *cis*/*trans* by integration of the ^{1}H NMR vinyl resonances. The isomers were separated by semipreparative HPLC (Waters XTerra Prep RP$_{18}$ 5 μm, 19 × 100 mm, 60:40:0.1 v/v/v MeOH/H$_2$O/NEt$_3$, 9 mL/min, *cis* t_R = 15.3 min) to provide samples for binding assays and spectroscopic analysis. TLC R_f = 0.20 (20:75:5 v/v/v hexane/EtOAc/NEt$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.54 (d, 1 H, J = 7.8 Hz), 7.48 (s, 1 H), 7.30 (dd, 1 H, J = 7.8 Hz), 7.16 (d, 1 H, J = 7.8 Hz), 7.05 (d, 1 H, J = 8.4 Hz), 6.43 (d, 1 H, J = 7.8 Hz), 3.83 (m, 1 H), 3.79 (m, 1 H), 3.38 (s, 3 H), 3.28 (dt, 1 H, J = 6.0 Hz, J = 12.6 Hz), 2.79 (m, 1 H), 2.46 (td, 1 H, J = 2.4 Hz, J = 13.2 Hz), 2.19 (m, 1 H), 2.10 (m, 1 H), 1.80 (m, 1 H), 1.71 (m, 2 H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 173.94, 142.07, 135.11, 132.53, 128.40, 128.19, 127.52, 127.48, 106.63, 56.46, 53.93, 51.52, 50.98, 35.72, 33.46, 28.94, 27.57; HRMS (APCI) [MH]$^+$ Calcd for C$_{17}$H$_{21}$O$_2$N^{79}Br: 350.0750, Found: 350.0748; Calcd for C$_{17}$H$_{21}$O$_2$N^{81}Br: 352.0729, Found: 352.0727.

***N*-(*t*-Butoxycarbonyl)-3*β*-(3′-((*Z*)-2-bromoethenyl)phenyl)nortropane-2*β*-carboxylic Acid (11).** 2β-Carbomethoxy-3β-(3′-((*Z*)-2-bromoethenyl)phenyl)nortropane (**2**, ∼94:6 *cis*/*trans*) (25 mg, 7.14 × 10^{-5} mol), 1,4-dioxane (1.5 mL), and H$_2$O (1.5 mL) were stirred at reflux under Ar for 22 h. The solvent was reduced in volume and then removed azeotropically with EtOH to give a yellow residue that was purified by preparative-TLC (silica, 20:75:5 v/v/v hexane/EtOAc/NEt$_3$). The component with R_f = 0.2 was isolated and dried under vacuum to afford 9 mg (36% recovery) of **2**. The component with R_f = 0 was isolated and dried under vacuum to afford 17 mg of **9** as an off-white foam that was combined with di-*tert*-butyl dicarbonate (25 mg, 1.15 × 10^{-4} mol), NEt$_3$ (10 μL, 7.2 × 10^{-5} mol), and CH$_2$Cl$_2$ (2 mL), and the mixture was stirred at room temperature under Ar for 20 min. The solvent was removed to give a faint yellow residue that was purified by preparative-TLC (silica, 4% MeOH/CH$_2$Cl$_2$) to afford 12 mg (60%—calculated based on the recovery of unreacted **2**) of a white foam that was ∼91:9 *cis*/*trans* by integration of the ^{1}H NMR vinyl resonances: TLC R_f = 0.14 (4% MeOH/CH$_2$Cl$_2$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.53 (m, 2 H), 7.27 (m, 1 H), 7.22 (m, 1 H), 7.04 (d, 1 H, J = 7.8 Hz), 6.41 (d, 1 H, J = 7.8 Hz), 4.72 (br s, 1 H), 4.49 (br s, 1 H), 3.23 (m, 1 H), 2.86 (br s, 1 H), 2.75 (apparent t, 1 H, J = 12.3 Hz), 2.14 (m, 1 H), 2.02 (m, 1 H), 1.83 (m, 1 H), 1.72 (m, 1 H), 1.65 (m, 1 H), 1.33 (s, 9 H); HRMS (ESI) [MH]$^+$ Calcd for C$_{21}$H$_{27}$O$_4$N^{79}Br: 436.1118, Found: 436.1119.

^{11}CH$_3$I. ^{11}CO$_2$(g) was produced with a Siemens 11 MeV RDS 112 cyclotron by employing the ^{14}N(p,α)^{11}C reaction. The ^{11}CO$_2$(g) was then converted to ^{11}CH$_3$I(g) with a GE MicroLab MeI system.

2*β*-Carbo[^{11}C]methoxy-3*β*-(3′-((*Z*)-2-iodoethenyl)phenyl)nortropane ([^{11}C]1). *N*-(*t*-Butoxycarbonyl)-3β-(3′-((*Z*)-2-iodoethenyl)phenyl)nortropane-2β-carboxylic acid (**10**) (∼0.6 mg, 1.2 μmol) was dissolved in DMF (0.3 mL) followed by addition of 0.1 M Bu$_4$NOH(aq) (12 μL, 1 equiv). The solution was placed in a sealed conical vial and cooled to 0 °C, and ^{11}CH$_3$I was bubbled through the solution at 0 °C. The solution was heated at 90 °C for 7 min, 6 M HCl(aq) (∼0.15 mL, 725 equiv) was added, and the solution was heated at 90 °C for 10 min, cooled to 0 °C, and neutralized by addition of 6 M NH$_4$OH(aq) (∼0.15 mL, 725 equiv). The solution was diluted with HPLC solvent and purified by semipreparative HPLC (Waters XTerra Prep RP$_{18}$ 5 μm, 19 × 100 mm + guard cartridge 19 × 10 mm; 60:40:0.1 v/v/v MeOH/ H$_2$O/NEt$_3$; 9.2 mL/min; t_R (range) = 10−17 min). The desired fractions were combined, diluted 1:2 v/v with H$_2$O, and loaded onto a C$_{18}$ Sep-Pak. The Sep-Pak was washed with 0.9% NaCl(aq) (20 mL) and then EtOH (0.5 mL). The product was eluted from the Sep-Pak with EtOH (1.5 mL) and collected in a sealed sterile vial containing 0.9% NaCl(aq) (3.5 mL). This solution was passed successively through a 1 μm filter and then a 0.2 μm filter (Acrodisc PTFE) under Ar-pressure and collected in a sealed sterile dose vial containing 0.9% NaCl(aq) (10 mL). The total synthesis time was 80 min from EOB with an average radiochemical yield of 23% (decay corrected from end of ^{11}CH$_3$I synthesis). The product was then analyzed by analytical HPLC (Waters Nova-Pak C$_{18}$ 3.9 × 150 mm, 75:25:0.1 v/v/v MeOH/H$_2$O/NEt$_3$, 1 mL/min, t_R = 5.5 min) to determine the radiochemical purity (avg > 98%) and the specific activity (range = 188−930, avg = 560 mCi/μmol) at the time of injection.

2*β*-Carbo[^{11}C]methoxy-3*β*-(3′-((*Z*)-2-bromoethenyl)phenyl)nortropane ([^{11}C]2). *N*-(*t*-Butoxycarbonyl)-3β-(3′-((*Z*)-2-bromoethenyl)phenyl)nortropane-2β-carboxylic acid (**11**) (∼91:9 *cis*/*trans*) (∼0.6 mg, 1.4 μmol) was dissolved in DMF (0.3 mL) followed by addition of 0.1 M Bu$_4$NOH(aq) (12 μL, 0.9 equiv). The solution was placed in a sealed conical vial, cooled to 0 °C, and ^{11}CH$_3$I was bubbled through the solution at 0 °C. The solution was heated at 90 °C for 7 min, 6 M HCl(aq) (∼0.15 mL, 643 equiv) was added, and the solution was heated at 90 °C for 10 min, cooled to 0 °C, and neutralized by addition of 6 M NH$_4$OH(aq) (∼0.15 mL, 643

equiv). The solution was diluted with HPLC solvent and purified by semipreparative HPLC (Waters XTerra Prep RP_{18} 5 μm, 19 × 100 mm + guard cartridge 19 × 10 mm; 60:40:0.1 v/v/v MeOH/H_2O/NEt_3; 9.2 mL/min; t_R (range) = 8−15 min). The desired fractions were combined, diluted 1:2 v/v with H_2O, and loaded onto a C_{18} Sep-Pak. The Sep-Pak was washed with 0.9% NaCl(aq) (20 mL) and then EtOH (0.5 mL). The product was eluted from the Sep-Pak with EtOH (1.5 mL) and collected in a sealed sterile vial containing 0.9% NaCl(aq) (3.5 mL). This solution was passed successively through a 1 μm filter and then a 0.2 μm filter (Acrodisc PTFE) under Ar-pressure and collected in a sealed sterile dose vial containing 0.9% NaCl(aq) (10 mL). The total synthesis time was 75 min from EOB with an average radiochemical yield of 25% (decay corrected from end of $^{11}CH_3I$ synthesis). The product was then analyzed by analytical HPLC (Waters Nova-Pak C_{18} 3.9 × 150 mm, 75:25:0.1 v/v/v MeOH/H_2O/NEt_3, 1 mL/min, t_R = 5.5 min) to determine the radiochemical purity (avg 96%) and the specific activity (range = 195−347, avg = 266 mCi/μmol) at the time of injection.

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Supporting Information Available: Additional microPET data, elemental analysis data, and ^{1}H NMR spectra of the samples of **1** and **2** that were used for the in vitro competition binding assays, X-ray crystal structure of **1**, crystal packing analysis, crystallographic experimental details, and crystallography data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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