Synthesis and Ligand Binding of Tropane Ring Analogues of Paroxetine

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(3*S*,4*R*)-4-(4-Fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine [(3*S*,9*R*)-**3**, paroxetine] is a selective serotonin reuptake inhibitor (SSRI) used as an antidepressant in humans. In previous studies, we reported that certain (1*R*)-3*β*-(substituted phenyl)nortropane-2*β*-carboxylic acid methyl esters (**2a**) exhibited high affinity and reasonable selectivity for the serotonin transporter (5-HTT). The major structural differences between **2a** and (3*S*,4*R*)-**3** are that **2a** possesses a different absolute stereochemistry and has an ethylene bridge not present in **3**. In addition, **2a** possesses a carbomethoxy substituent adjacent to the aryl ring, whereas (3*S*,4*R*)-**3** contains a [3,4-(methylenedioxy)phenoxy]methyl group. In this study, we present the synthesis and biological evaluations of six of the possible eight isomers of 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane (**4**). The data for inhibition of [^{3}H]paroxetine binding show that (1*R*)-2*β*,3α-**4c**, which has the same stereochemistry as paroxetine, has the highest affinity at the 5-HTT. Strikingly, the most potent compounds for inhibition of [^{3}H]WIN-35,428 binding were not the (1*R*)-2*β*,3*β*-isomers but rather (1*R*)-2*β*,3α-**4c** and (1*S*)-2*β*,3α-**4f**. Conformational analyses show that these isomers exist in a flattened boat conformation with pseudoequatorial substituents. Thus, the binding data show that this conformation is recognized by the DAT-associated binding site and also suggest that this conformation of paroxetine is recognized by the 5-HTT-associated binding site.

Much research has been devoted to gaining an understanding of the pharmacological action of cocaine (**1**).[1,2] Considerable evidence suggests that the reinforcing or addicting properties of cocaine are due to its ability to inhibit dopamine uptake in the limbic brain area.[3−7] Similar to dopamine, the reuptake of previously released serotonin plays the major role in regulating the synaptic availability of serotonin and thus serotonergic neurotransmission. Numerous neurochemical and behavioral outcomes are known to result from the treatment of animals with serotonin uptake inhibitors. For example, neuroendocrine, anticonvulsant, and analgesic effects, as well as changes in food intake and alcohol consumption, are observed.[8] In addition, evidence suggests that inhibition of serotonin reuptake modulates the reinforcing properties of cocaine.[9−13] Even though the importance of the serotonin transporter in mediating the neurochemical and behavioral actions of cocaine is now recognized, the molecular mechanism of action and regulation of this transporter are not well understood.

We, and others, have reported that certain (1*R*)-3*β*-(substituted phenyl)nortropanes possessing 2*β*-carboxylic acid ester groups (**2a**)[14] and 2*β*-ketone groups (**2b**)[15] exhibit high potency at, and reasonable selectivity for, the serotonin transporter relative to the dopamine and norepinephrine transporters. These compounds share structural features with the 4-(4-fluorophenyl)-3-[[3,4-(methylenedioxy)phenoxy]methyl]piperidine (**3**) class of serotonin uptake inhibitors. The serotonin uptake inhibitor paroxetine, which is (3*S*,4*R*)-**3**, has proven to be an effective antidepressant in humans.[8] Both classes of compounds, **2** and **3**, contain a piperidine ring with an aryl moiety in a similar position. The major structural differences between **2a** and (3*S*,4*R*)-**3** are that (a) in **2a** the substituent *β* to the amino group is a carbomethoxy group whereas the analogous position in **3** is occupied by a [3,4-(methylenedioxy)phenoxy]methyl group, (b) the substituents in **2a** are cis to each other while they are in trans orientation in (3*S*,4*R*)-**3**, and (c) in the nortropane **2a** the positions α to the amino group are ethylene bridged. To gain a better understanding of the important structural features required by the nortropane class of compounds for good affinity and selectivity at serotonin transporters, we have prepared and evaluated the transporter binding properties of six of the possible eight isomers of 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane (**4**).

Synthesis

Scheme 1 outlines the general synthesis used to prepare the nortropane analogues **4**. Lithium aluminum hydride reduction of the appropriate 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl ester isomer **5** gives the 2-(hydroxymethyl)tropane **6**. Treatment of **6** with methanesulfonyl chloride afforded the 2-hydroxymethyl mesylate which, when heated in a tetrahydro-

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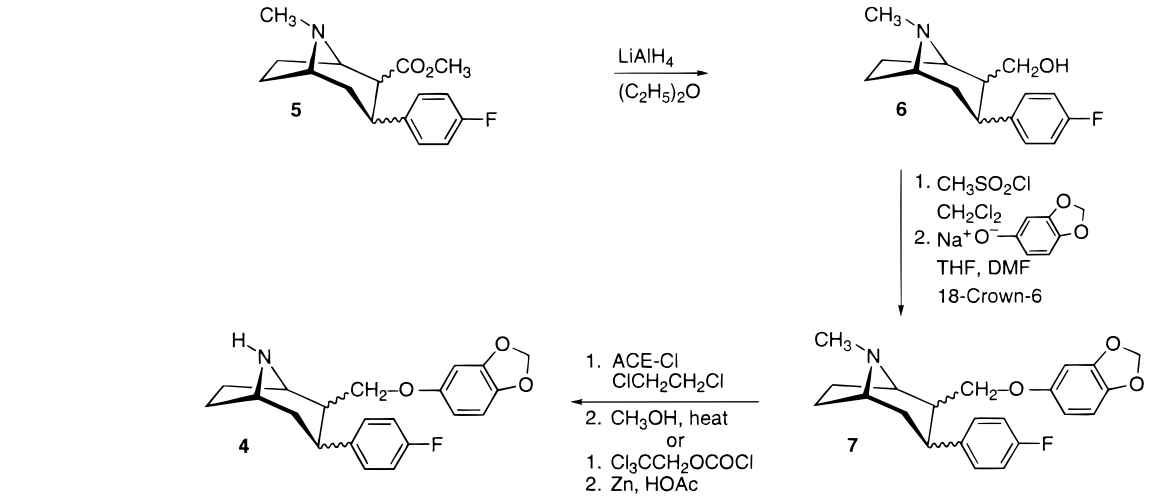
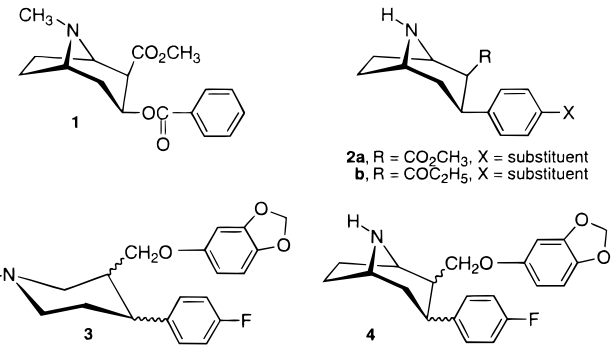
Scheme 1





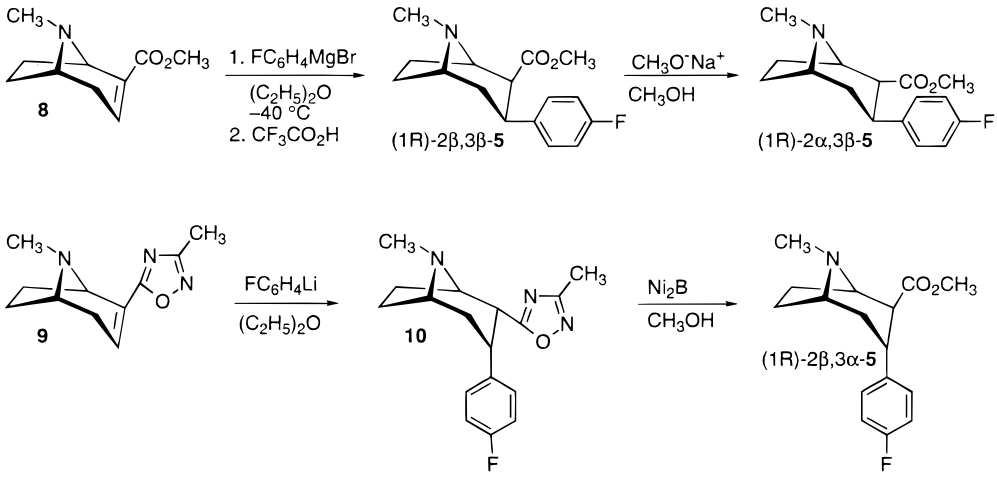
furan:DMF (5:1) mixture containing 18-crown-6 with the sodium salt of sesamol, yields 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]tropane **7**. N-Demethylation using 1-chloroethyl chloroformate (ACE-Cl) in ethylene dichloride followed by treatment with methanol, or using trichloroethyl chloroformate followed by treatment with zinc, affords the nortropane analogues **4**.

The synthesis used to prepare three of the 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl esters (**5**) (possessing the (1*R*)-configuration) is shown in Scheme 2. The addition of (*p*-fluorophenyl)magnesium bromide to anhydroecgonine methyl ester (**8**), which was derived from (−)-cocaine as previously reported, gives (1*R*)-2β,3β-**5**.[16] Isomerization of (1*R*)-2β,3β-**5** with sodium methoxide in methanol affords (1*R*)-2α,3β-**5**. The addition of (*p*-fluorophenyl)lithium to the α,β-unsaturated 1,2,4-oxadiazole **9** gives the cis-addition product **10**. Subjection of **10** to reduction with nickel boride in methanol results in conversion of the oxadiazole to a methyl ester and effects complete isomerization at the 2-position to give (1*R*)-2β,3α-**5**.[17] We had hoped to prepare (1*R*)-2α,3α-**5** by appropriate modification of this reductive opening of the oxadiazole ring to the 2β-methyl ester. However, all attempts to effect this conversion resulted in isomerization of the 2α group to the 2β-isomer.

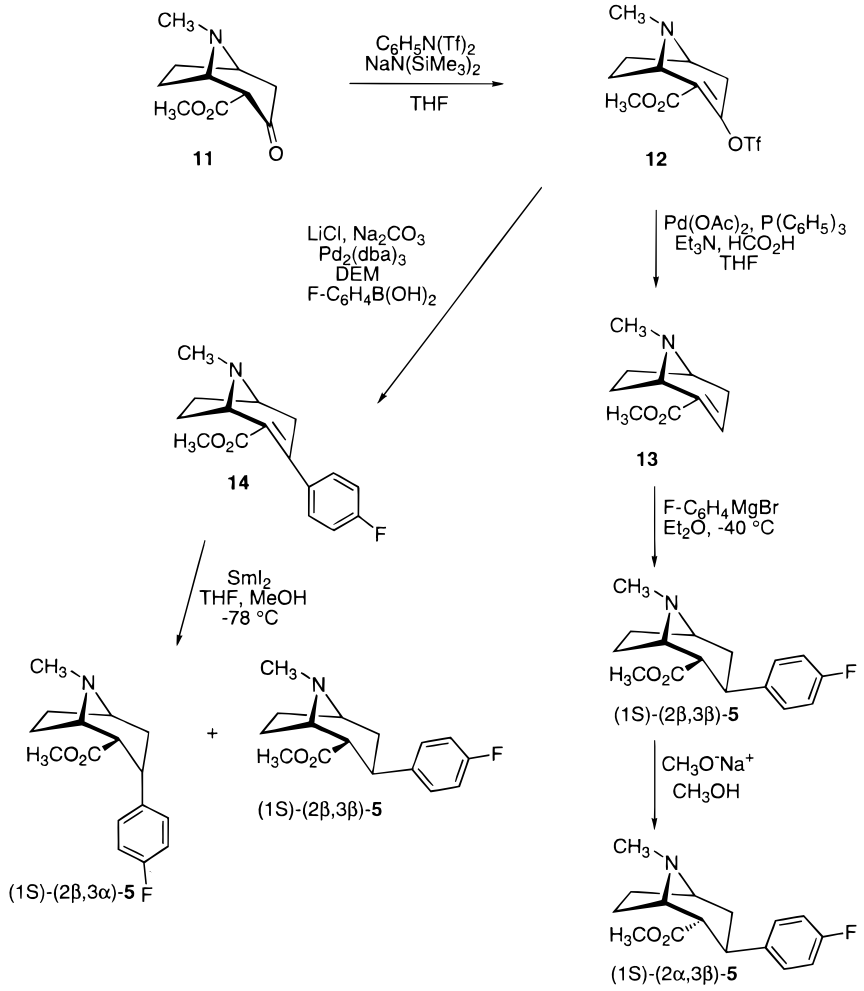
Three of the (1*S*) isomers of 3-(4-fluorophenyl)tropane-2-carboxylic acid methyl esters were prepared by routes given in Scheme 3. The synthesis of **12**−**14**, (1*S*)-2β,3α-**5**, and (1*S*)-2β,3β-**5** is analogous to that presented in a preliminary communication for the synthesis of the corresponding (1*R*) analogues.[18] The addition of *N*-phenyltrifluoromethanesulfonimide to a tetrahydrofuran solution of (1*S*)-2-carbomethoxy-3-tropinone (**11**)[19] containing sodium bis(trimethylsilyl)amide yielded triflate **12**. This triflate was utilized in two ways. Treatment of **12** with triethylamine, formic acid, triphenylphosphine, and palladium catalyst gave (1*S*)-anhydroecgonine methyl ester (**13**).[18] The (1*S*)-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester [(1*S*)-2β,3β-5] was synthesized as described previously for (1*R*)-2β,3β-**5**.[16] Treatment of (1*S*)-2β,3β-**5** with sodium methoxide in methanol afforded (1*S*)-2α,3β-**5**. Reaction of **12** with (4-fluorophenyl)boronic acid in refluxing diethoxymethane using tris(dibenzilideneacetone)dipalladium(0) as catalyst, followed by chromatographic purification, gave the (4-fluorophenyl)tropene **14**.[18] Reduction of **14** with samarium (II) iodide at −78 °C using methanol as the proton source, followed by quenching with trifluoroacetic acid at 0 °C, gave a mixture of (1*S*)-3α-(4-fluorophenyl)-2β-carboxylic acid methyl ester [(1*S*)-2β,3α-**5**] as the major product and (1*S*)-3β-(4-fluorophenyl)-2β-carboxylic acid methyl ester [(1*S*)-2β,3β-**5**], which were separated by column chromatography.

Specific structural and stereochemical assignments were made for the compounds (1*R*)-**7** and (1*R*)-**4** using 1D ^{1}H and ^{13}C NMR spectra and 2D COSY,[20,21] NOESY,[22] and HQMC[23] spectra. Thus, the presence of a large (10.6 Hz) coupling in the pattern of H3 in the ^{1}H NMR spectrum of (1*R*)-2β,3β-**7a** requires H3 to be axial, showing that the aryl substituent at C3 must occupy the equatorial (β) position. Similarly, the magnitude of $J_{2,3}$ (5.8 Hz), which is characteristic of axial−equatorial coupling, taken together with the axial nature of H3, mandates that H2 must be equatorial, confirming the β-position of the C2 substituent. The observed NOESY interaction between H3 and H6 further confirms the axial configuration of H3 and requires that (1*R*)-2β,3β-**7a** be in the chair conformation. Similar arguments confirm the structural assignment of 2β,3β-**4a**. The observation of two large coupling constants (J = 12.0 Hz) for H3, which are both (COSY) associated with H2 and H4β, characterize the structure of 2α,3β-**7b**. The observed NOESY interactions of H2 with H4β and of H3 with H6 provide further evidence for the 2α,3β-sterochemistry and show that the compound is

Scheme 2

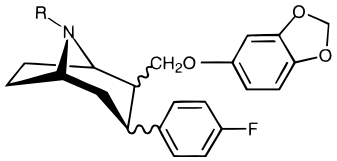


Scheme 3



in the chair conformation. The structure of the *N*-nor analogue 2α,3*β*-**4b** is deduced from similar considerations. The compound 2*β*,3α-**7c** also exhibits two large couplings and one smaller coupling for H3. The large couplings (J = 10.8 and 10.3 Hz) are associated with H2 and H4α, respectively, while the smaller coupling (J = 8.3 Hz) is associated with H4*β*. In addition, the NOESY spectrum shows an interaction between H2 and H4α. These observations cannot be reconciled with a chair conformation for this compound. Since the structures of the 3*β* isomers are definite, this isomer must possess a 3α substituent, i.e., H3 must be equatorial. However, the two large coupling constants between H3 and its geminal neighbors are inconsistent with dihedral angles of ~60°, which are associated with equatorial−equatorial or equatorial−axial protons in a chair conformation. Therefore, the preferred conformation for this compound must be boatlike. This observation is supported by molecular modeling where the global energy minimum conformation was found to be a

Table 1. Comparison of Transporter Binding Potencies of the Isomers of **4** and **7**



	stereochemistry			IC_{50} (nM)[a]				
compd	R	2	3	5-HT [^{3}H]Paroxetine	DA [^{3}H]WIN 35,428	NE [^{3}H]Nisoxetine	DA/5-HT ratio[b]	NE/5-HT ratio[b]
paroxetine				0.28 ± 0.02	623 ± 25	535 ± 15	2230	1910
(1*R*)-**7a**	CH_3	*β*	*β*	294 ± 18	308 ± 20	5300 ± 450	1.0	18
(1*R*)-**4a**	H	*β*	*β*	480 ± 21	835 ± 90	37400 ± 1400	1.7	78
(1*R*)-**7b**	CH_3	α	*β*	52.9 ± 3.6	172 ± 8.8	26600 ± 1200	3.3	500
(1*R*)-**4b**	H	α	*β*	90 ± 3.4	142 ± 13	2500 ± 250	1.6	28
(1*R*)-**7c**	CH_3	*β*	α	422 ± 16	3.01 ± 0.2	123 ± 9.5	0.007	0.29
(1*R*)-**4c**	H	*β*	α	5.62 ± 0.2	3.86 ± 0.2	14.4 ± 1.3	0.7	2.6
(1*S*)-**7d**	CH_3	*β*	*β*	88.1 ± 2.8	1050 ± 45	27600 ± 1100	12	310
(1*S*)-**4d**	H	*β*	*β*	424 ± 15	1210 ± 33	17300 ± 1800	2.9	41
(1*S*)-**7e**	CH_3	α	*β*	447 ± 47	1500 ± 74	2,916 ± 1950	32	640
(1*S*)-**4e**	H	α	*β*	55.8 ± 5.73	27.6 ± 2.4	1690 ± 150	0.49	30
(1*S*)-**7f**	CH_3	*β*	α	178 ± 13	298 ± 17	12400 ± 720	1.7	70
(1*S*)-**4f**	H	*β*	α	19 ± 1.8	407 ± 33	1990 ± 176	21	100

[a] Data are mean ± standard error of three or four experiments with triplicate values at each concentration. [b] DA/5-HT and NE/5-HT are ratios of IC_{50} values.

flattened boat. This conformation is preferred over the lowest energy chair conformation by >3 kcal/mol. The similarity of the NMR parameters of the *N*-nor analogue 2*β*,3α-**4** indicates that it exists in a similar conformation.

Ligand Binding Studies

IC_{50} values at the DA, NE, and 5HT transporters represent inhibition of 0.5 nM [^{3}H]WIN 35,428, 0.5 nM [^{3}H]nisoxetine, and 0.2 nM [^{3}H]paroxetine binding, respectively, and were determined as previously described.[24] The IC_{50} values for paroxetine, the six nortropane analogues **4**, and six *N*-methyl analogues **7** are listed in Table 1.

Discussion

Cocaine (**1**) is an inhibitor of the neuronal transport of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) at roughly similar concentrations, i.e., with K_i's between 220 and 310 nM.[25] Biochemical binding studies indicate slight DA selectivity.[26,27] In recent years, structure−activity relationship studies of cocaine analogues for binding at monoamine transporters, particularly at the dopamine transporter, have been explored,[26−32] and some structural modifications that result in selectivity for the dopamine transporter over the norepinephrine and serotonin transporters have been reported.[33−35] In the introduction section, we pointed out that serotonergic activity may affect the reinforcing effects of cocaine. Since the in vitro potency of cocaine (**1**) to inhibit serotonin reuptake is essentially identical with its potency to inhibit dopamine reuptake, some of the pharmacological properties of cocaine might be due to its inhibition of reuptake of serotonin. Even though the importance of the serotonin transporter in mediating the neurochemical and behavioral actions of cocaine is now recognized, the biochemical mechanism of action and regulation of this transporter is not well understood.

The nortropane derivatives **4** were designed to be similar to known serotonin uptake inhibitors **3**. Both classes of compounds contain a piperidine ring with a 4-fluorophenyl group and a [3,4-(methylenedioxy)phenoxy]methyl moiety in similar positions on the ring. The eight possible isomers of **4** are listed in Figure 1. The major structural difference between **3** and **4** is the presence of an ethylene bridge, not present in **3**, which leads to reduced conformational heterogeneity. For example, whereas the piperidine ring in the (3*S*,4*R*)-isomer of **3**, which is paroxetine, may interconvert between the chair conformations C_{aa} and C_{ee}, and the boat conformation B_{ee} and B_{aa}, the piperidine ring in the analogous isomer of **4** can only interconvert between the chair and boat conformations (see Figure 2) but not between two chair conformations. In the series of analogues **3**, the potency of paroxetine, i.e., the *trans*-(+)-3*S*,4*R* isomer, exceeds that of the other isomers by factors of 60−160.[36] This isomer may exist in either a diequatorial (C_{ee}) or a diaxial (C_{aa}) chair conformation, as well as in boat conformations B_{aa} and B_{ee}, all of which are interconvertible. The chair conformations C_{aa} and C_{ee} are mimicked by the isomers (1*R*)-2*β*,3α-**4c** and (1*S*)-2α,3*β*-**4e**, respectively, each of which can adopt a boat conformation, but which are not interconvertible. Therefore, it would be expected that, if conformation C_{ee} were responsible for the high potency of paroxetine, (1*S*)-2α,3*β*-**4e** would possess high potency to inhibit [^{3}H]-paroxetine binding. Conversely, if conformation C_{aa} were the potent form of paroxetine, (1*R*)-2*β*,3α-**4c** would exhibit high potency. However, since the chair conformation of (1*R*)-2*β*,3α-**4c** possesses two axial substituents, the chair may not be the energy minimum conformation for this compound. Thus, we had found that although the chair is the preferred conformation of allococaine, the (2α,3α)-diaxial isomer of cocaine, boat

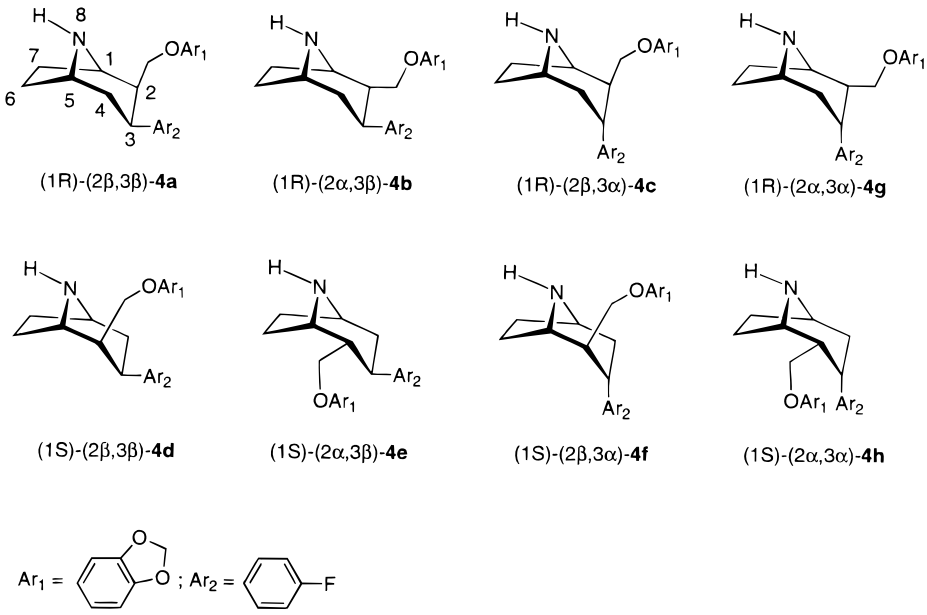


Figure 1. Isomers of **4**.

conformations were preferred for diaxial analogues of 3-aryltropane-2-carboxylates.[17,37]

Binding affinities at the 5-HT transporter, determined by inhibition of [^{3}H]paroxetine binding (Table 1), show that the diequatorial isomers, (1*R*)-2α,3*β*-**4b** and (1*S*)-2α,3*β*-**4e**, are substantially less potent than the diaxial isomers, (1*R*)-2*β*,3α-**4c** and (1*S*)-2*β*,3α-**4f**, demonstrating that conformation C_{ee}, which may well be the low-energy conformation of paroxetine, is not well accommodated by the receptor at the 5-HT transporter. The most potent of the isomers is (1*R*)-2*β*,3α-**4c**, suggesting that its conformation best mimics the conformation of paroxetine which is recognized by the receptor. Since the preferred conformation of the piperidine ring of (1*R*)-2*β*,3α-**4c** is a substantially flattened boat, it appears that a relatively flat conformation may be required for paroxetine to bind the receptor at the 5-HT transporter. Such a conformation could resemble both the (1*R*)- and the (1*S*)-isomers of 2*β*,3α-**4c**, and indeed, the potency of (1*R*)-2*β*,3α-**4c** is only 3.4 times greater than that of the (1*S*)-isomer. The more than 1 order of magnitude lower potency of (1*R*)-2*β*,3α-**4c** (IC_{50} = 5.62 nM) relative to paroxetine (IC_{50} = 0.28 nM) may be due to steric inhibition of binding by the ethylene bridge in (1*R*)-2*β*,3α-**4c**.

The fact that several 3*β*-(para-substituted phenyl)-tropane-2*β*-carboxylic acid methyl esters, which possess the natural (1*R*)-cocaine stereochemistry, have high afffinity at the 5-HT site[38] suggested that (1*R*)-2*β*,3*β*-**4a** (i.e., an analogue of the cis isomer of paroxetine) might also possesss high affinity at the 5-HT transporter. Additionally, it had been shown that N-demethylation of 3*β*-(*p*-fluorophenyl)-2*β*-carbomethoxytropane (WIN 35,428) to give the *N*-nor analogue (RTI-142) resulted in increased affinity at the DA, 5-HT, and NE transporters.[39] The data in the Table indicate that these observations do not generalize to this set of compounds. In other words, N-demethylation leads to increased potency at 5-HT transporters only for the isomers which preferentially exist in a boat conformation; the effect on potency at DA and NE transporters appears to be random. In addition, it was surprising to note that both (1*R*)-2*β*,3*β*-**4a** and (1*S*)-2*β*,3*β*-**4d** had low affinity for all three transporters. The low affinity of (1*R*)-2*β*,3*β*-**7a** and its *N*-nor analogue (1*R*)-2*β*,3*β*-**4a** at the DAT relative to the (1*R*)-2*β*,3α-isomers is particularly striking. Thus, since the ratio of potencies to inhibit radioligand binding at the DAT for cocaine, which has the (1*R*)-2*β*,3*β* configuration, to allococaine, which has (1*R*)-2*β*,3α configuration, is 59,[40] it might have been expected that the potency of the (1*R*)-2*β*,3*β*-**7a** and (1*R*)-2*β*,3*β*-**4a** would exceed that of their (1*R*)-2*β*,3α-isomers. Instead, the ratio is 0.01 for (1*R*)-2*β*,3*β*-**7a** to (1*R*)-2*β*,3α-**7c** and 0.005 for (1*R*)-2*β*,3*β*-**4a** to (1*R*)-2*β*,3α-**4c**. This unexpected result may be attributable to the flattened boat conformation of (1*R*)-2*β*,3α-**7c** and (1*R*)-2*β*,3α-**4c**. A less striking but similar situation had been observed for the isomeric 3-phenyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)tropanes, where the potency of the 2*β*,3α isomer, which exists in a boat conformation, was only slightly lower (1.48) than that of the 2*β*,3*β* isomer, which exists in a chair conformation.[37]

Conclusions

Six of the possible eight stereoisomers of 3-(4-fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]-nortropane (**4**) have been prepared as analogues of paroxetine. Ligand binding data show that (1*R*)-2*β*,3α-**4c**, which is one of the isomers that has the same relative stereochemistry as paroxetine, has the highest affinity for the 5-HT transporter. Since this isomer exists in a flattened boat conformation with pseudo-equatorial substituents, it appears that a flattened boat conformation of paroxetine is recognized by the binding site at the 5-HT transporter. The order of magnitude lower potency of (1*S*)-2α,3*β*-**4e**, which is the other isomer that has the same relative stereochemistry as paroxetine, confirms that a chair conformation with two equatorial substituents is not recognized by the 5-HT transporter-associated receptor. The good affinity of (1*R*)-2*β*,3α-**4c** and (1*R*)-2*β*,3α-**7c** at the DA transporter suggests that tropane analogues which exist in a flat-

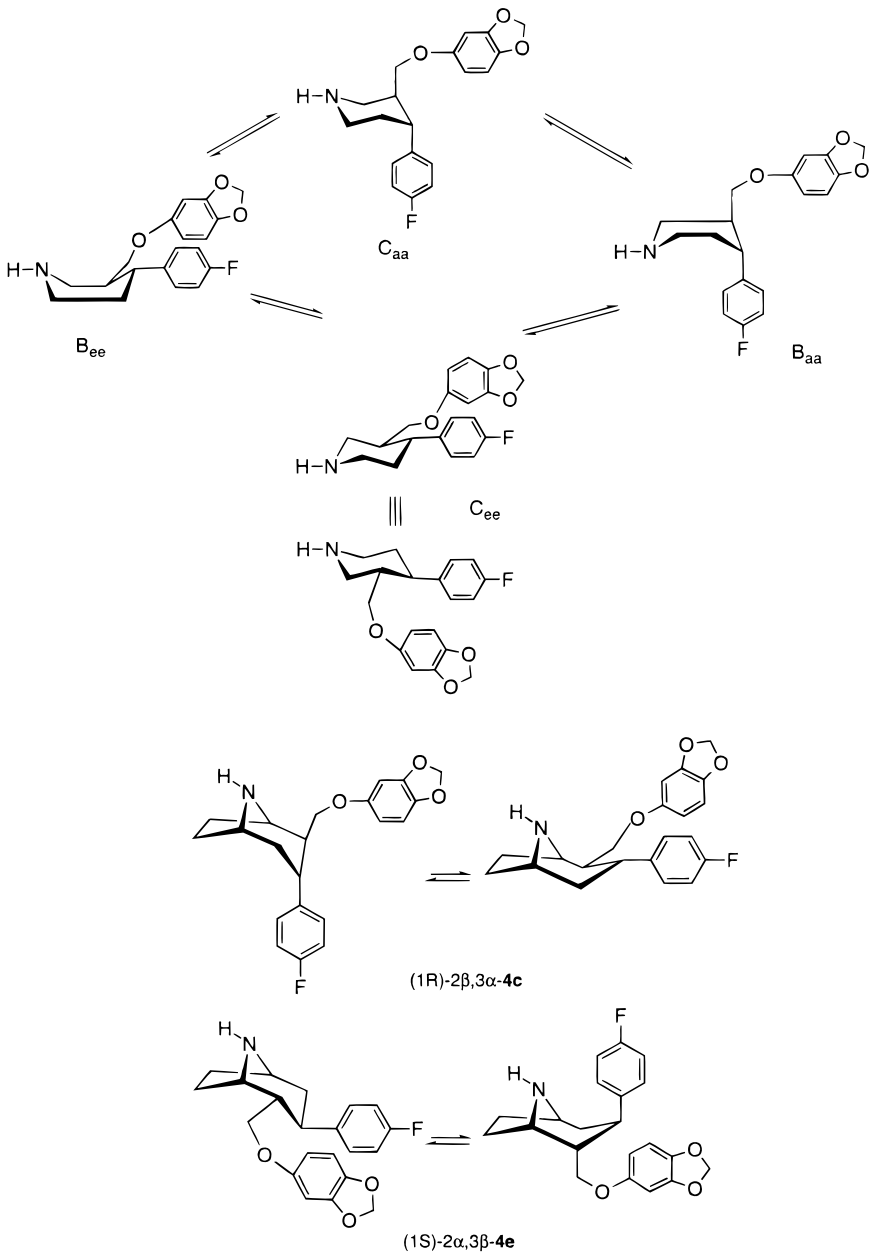


Figure 2. Chair and boat conformations.

tened boat conformation with pseudoequatorial substituents are well recognized by the DAT-associated binding site.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary tube apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). Thin-layer chromatography was carried out on Whatman silica gel 60 TLC plates, and flash chromatography was conducted on silica gel 60 (230−400 mesh). Visualization was accomplished under UV or in an iodine chamber. Microanalyses were carried out by Atlantic Microlab, Inc. Tropinone was purchased from Lancaster Synthesis, Inc., and samarium iodide was from Fluka Chemical Corp. All other chemicals were purchased from Aldrich Chemical Co, Inc. THF and ether were freshly distilled from sodium benzophenone. All other reagents were used without further purification.

Nuclear Magnetic Resonance Studies. Routine NMR spectra were obtained on a Bruker AM-250 spectrometer. COSY, NOESY, and HMQC spectra were recorded on a Bruker AMX-500 spectrometer operating at 500.13 MHz for ^{1}H using a Bruker 5 mm inverse detect broadband probe. The double quantum filtered phase sensitive COSY[20,21] and NOESY[22] were acquired as 1024 × 512 data points with a spectral width of 4800 Hz in both dimensions. The data were apodized with a squared sine function and zero filled to 2K × 2K data points prior to Fourier transformation. NOESY spectra were obtained with a 1200 ms mixing time and a recycle delay of 4 s. Heteronuclear multiple quantum correlation (HMQC)[23] spectra were acquired as 1024 × 256 data points with a spectral width of 4800 Hz in F2 and 24 375 Hz in F1. An average coupling constant of 145 Hz was used to optimize $1/2J_{CH}$ delays. The data were apodized with a squared sine function and zero filled to 2048 × 512 data points prior to Fourier transformation.

Molecular Modeling Studies. Molecular modeling was performed on a SGI O2 using Sybyl 6.3[41] and Spartan.[42] Minimum energy structures were obtained using the simulated annealing module in Sybyl. For each structure, 50 cycles were calculated with a simulated temperature of 500 K for 500 fs and then annealed to 200 K for 500 fs with an exponential ramping function. The overall boat or chair conformation was maintained during the annealing procedure by placing a

penalty function on the N−C3 torsional angle with an equilibrium value of 0° for the boat conformation and 65° for the chair conformation. The lowest energy structures for each conformation were transferred to Spartan where the structures were further optimized using MM3; then the heats of formation were obtained from semiempirical (AM1) quantum mechanics calculations.

General Synthesis of 3-(4-Fluorophenyl)-2-(hydroxymethyl)tropane (6). A solution of **5** (3.0 mmol) in 10 mL of Et_2O was added dropwise to a cooled slurry (0 °C) of lithium aluminum hydride (5.0 mmol) in 20 mL of anhydrous Et_2O. The reaction mixture was stirred at room temperature for 2 h and then cooled to 0 °C and quenched with NH_4Cl (∼3 mL). Water was added, and the layers were separated. The aqueous layer was extracted with Et_2O. The organic layers were combined, and the solvent was removed to afford a white solid which was recrystallized from hexanes or EtOAc. Results from each isomer are described in the following experiments.

(1*R*)-3*β*-(4-Fluorophenyl)-2*β*-(hydroxymethyl)tropane [(1*R*)-2*β*,3*β*-6]. Recrystallization from hexanes gave 0.745 g (83%) of white solid: mp 75−78 °C; $[\alpha]^{25}_D$ −59.8° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 1H), 1.58−1.67 (m, 1H), 1.72 (s, 1H), 1.75 (s, 1H), 2.16 (m, 2H), 2.28 (s, 3H), 2.50 (m, 1H), 3.07 (m, 1H), 3.35 (m, 2H), 3.46 (m, 1H), 3.75 (m, 1H), 7.01 (m, 2H), 7.32 (m, 2H). Anal. ($C_{15}H_{20}FNO$) C, H, N.

(1*R*)-3*β*-(4-Fluorophenyl)-2α-(hydroxymethyl)tropane [(1*R*)-2α,3*β*-6]. Recrystallization from EtOAc gave 0.494 g (79%) of white solid: mp 174−176 °C; $[\alpha]_D$ +26.3° (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.54−1.62 (m, 2H), 1.70−2.22 (m, 6H), 2.27−2.35 (m, 1H), 2.35 (s, 3H), 3.20−3.41 (m, 4H), 6.96 (m, 2H), 7.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 162.33 (d), 139.21, 128.77, 128.64, 115.08, 114.74, 62.41, 61.43, 48.58, 40.84, 40.59, 37.19, 25.48, 21.26. Anal. ($C_{15}H_{20}FNO$) C, H, N. The alcohol was converted to the D-tartrate salt. Recrystallization from MeOH/Et_2O gave a white hygroscopic powder: mp 89 °C (fusion); ^{1}H NMR (CD_3OD) δ 1.88−2.39 (m, 7H), 2.72 (m, 1H), 2.87 (s, 3H), 3.25 (dd, 2H), 3.96 (m, 1H), 4.07 (m, 1H), 7.05 (m, 2H), 7.31 (m, 2H); $[\alpha]^{25}_D$ +3.5° (*c* 0.20, CH_3OH). Anal. ($C_{19}H_{26}FNO_7$) C, H, N.

(1*R*)-3α-(4-Fluorophenyl)-2*β*-(hydroxymethyl)tropane [(1*R*)-2*β*,3α-6]. Recrystallization from hexanes gave 0.681 g (64%, two steps from oxadiazole **10**) of white solid: mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 1.43−1.56 (m, 2H), 1.74 (m, 1H), 1.84 (m, 1H), 2.01−2.13 (m, 2H), 2.23 (s, 3H), 2.46 (m, 1H), 2.95 (m, 1 H), 3.24 (m, 2H), 3.64 (m, 1H), 3.83 (m, 1H), 6.96 (m, 2H), 7.24 (m, 2H); ^{13}C NMR δ ($CDCl_3$) 163.27 (d), 142.79, 128.66, 128.54, 115.09, 114.75, 69.11, 65.21, 60.27, 49.62, 40.88, 37.82, 35.53, 26.95, 26.53; $[\alpha]_D$ −41.9° (*c* 0.31, $CHCl_3$). Anal. ($C_{15}H_{20}FNO$) C, H, N. The product was converted to the D-tartrate salt. Recrystallization from $(CH_3)_2CHOH/Et_2O$ gave a hygroscopic off-white solid: mp 79 °C (fusion); ^{1}H NMR (CD_3OD) δ 1.86 (m, 1H), 2.02−2.13 (m, 3H), 2.30−2.72 (m, 3H), 2.78 (s, 3H), 3.01 (m, 1H), 3.51 (m, 2H), 3.88 (m, 1H), 7.06 (m, 2H), 7.35 (m, 2H); $[\alpha]^{25}_D$ −24.0° (*c* 0.48, CH_3OH). Anal. ($C_{19}H_{26}FNO_7$·0.5 H_2O) C, H, N.

(1*S*)-3*β*-(4-Fluorophenyl)-2*β*-(hydroxymethyl)tropane [(1*S*)-2*β*,3*β*-6]. Recrystallization from hexanes gave 1.18 g (70%) of white solid: mp 77−79 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 1H), 1.67−1.58 (m, 1H), 1.72 (s, 1H), 1.75 (s, 1H), 2.16 (m, 2H), 2.28 (s, 3H), 2.50 (m, 1H), 3.07 (m, 2H), 3.35 (m, 2H), 3.46 (m, 1H), 3.75 (m, 1H), 7.01 (m, 2H), 7.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.42, 138.41, 129.86, 129.73, 115.13, 114.80, 68.56, 65.21, 61.96, 45.49, 41.19, 37.32, 36.19, 26.29, 25.18. $[\alpha]_D$ +58.9° (*c* 0.54, $CHCl_3$). Anal. ($C_{15}H_{20}FNO$) C, H, N.

(1*S*)-3*β*-(4-Fluorophenyl)-2α-(hydroxymethyl)tropane [(1*S*)-2α,3*β*-6]. Recrystallization from EtOAc gave 0.88 g (66%) of white solid: mp 173−175 °C; ^{1}H NMR ($CDCl_3$) δ 1.54−1.62 (m, 2H), 1.70−2.22 (m, 6H), 2.27−2.35 (m, 1H), 2.36 (s, 3H), 3.20−3.41 (m, 4H), 6.96 (m, 2H), 7.18 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.42 (d), 139.69, 129.22, 129.09, 115.44, 115.11, 62.71, 62.15, 61.90, 49.28, 41.20, 41.00, 37.53, 25.84, 21.62; $[\alpha]_D$ −24.7° (*c* 0.51, $CHCl_3$). Anal. ($C_{15}H_{20}FNO$) C, H, N.

(1*S*)-3α-(4-Fluorophenyl)-2*β*-(hydroxymethyl)tropane [(1*S*)-2*β*,3α-6]. Recrystallization from Et_2O/hexanes gave 0.540 g (72%) of white solid: mp 83−85 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 2H), 1.74 (m, 2H), 2.05 (m, 2H), 2.23 (s, 3H), 2.47 (m, 1H), 2.94 (m, 2 H), 3.23 (m, 2H), 3.65 (m, 1H), 3.85 (m, 1H), 6.96 (m, 2H), 7.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 160.99 (d), 141.98, 128.63, 128.57, 114.93, 114.77, 68.69, 64.94, 60.16, 49.88, 40.83, 38.01, 35.49, 27.07, 26.62; $[\alpha]_D$ +38.6° (*c* 0.29, $CHCl_3$). Anal. ($C_{15}H_{20}FNO$·0.5H_2O) C, H, N.

Procedure for the General Synthesis of 3-(4-Fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]-tropane (7). A solution of the appropriate isomer of **6** (2.0 mmol) in 15 mL of CH_2Cl_2 was cooled to 0 °C, and methanesulfonyl chloride (2.5 mmol) was added. Et_3N (2.0 mmol) was then added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature. After 3 h, CH_2Cl_2 and water were added. The reaction was basified to pH 10 with NH_4OH, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with 1 N NaOH, water, NH_4Cl solution, water, and NaCl solution, and dried over Na_2SO_4. The solvent was removed to give a colorless, slightly cloudy oil which was used without further purification.

Sodium hydride (60% dispersion, 4.0 mmol) was washed twice with hexanes under nitrogen gas. Anhydrous THF (10 mL) was added, and the slurry was cooled to 0 °C. A solution of sesamol (4.0 mmol) in 10 mL of THF was added dropwise. Eventually the mixture cleared and became yellow. The alkoxide was warmed to room temperature and refluxed for 45 min. The mesylate and 18-crown-6 ether (∼5 mg) were dissolved in 10 mL of a mixture of THF and 2 mL of DMF and added dropwise over 10 min. The reaction was warmed to room temperature after the addition was complete, refluxed for 3 h, and then stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C and quenched with water. THF was removed under reduced pressure, water and NH_4OH were added, and the aqueous layer (pH 10) was extracted with CH_2Cl_2. The organic layers were combined, washed with 1 N NaOH, water, and NaCl solution, and dried over $MgSO_4$. The solvent was removed to give a light yellow oil which was purified by flash chromatography on silica gel, eluting with Et_2O/Et_3N/hexanes (27:3:70).

(1*R*)-3*β*-(4-Fluorophenyl)-2*β*-[[3,4-(methylenedioxy)-phenoxy]methyl]tropane [(1*R*)-2*β*,3*β*-7a]. Purification by flash chromatography gave 0.33 g (44%) of the pure product as an oil: ^{1}H NMR (C_6D_6) δ 1.59 (m, 1H), 1.81 (m, 2H), 2.09 (m, 2H), 2.14 (m, 1H), 2.20 (ddd, 1H, *J* = 14.3, 5.8, 5.8 Hz), 2.38 (ddd, 1H, *J* = 11.6, 1.6, 1.6 Hz), 2.40 (s, 3H), 2.98 (dd, 1H, *J* = 11.6, 6.2 Hz), 3.01 (ddd, 1H, *J* = 6.2, 6.2, 1.6 Hz), 3.42 (dd, 1H, *J* = 10.6, 5.8 Hz), 4.31 (ddd, 1H, *J* = 9.7, 1.8, 1.8 Hz), 5.89 (s, 2H), 6.32 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.48 (d, 1H, *J* = 2.3 Hz), 6.66 (d, 1H, *J* = 8.6 Hz), 6.95 (dd, 2H, *J* = 8.8, 8.8 Hz), 7.39 (dd, 2H, *J* = 8.8, 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 163.06, 159.20, 152.75, 148.28, 143.23, 141.82, 129.45, 129.33, 115.12, 114.78, 108.57, 108.09, 101.15, 99.90, 83.74, 55.25, 50.49, 54.52, 42.89, 33.96, 31.96, 26.98, 23.38. The D-tartrate salt recrystallized from 2-propanol/ethyl ether yielded a white powder which had mp 97 °C (fusion): ^{1}H NMR (CD_3OD) δ 2.00−2.43 (m, 7H), 2.95 (s, 3H), 3.48 (m, 2H), 3.68 (m, 2H), 4.61 (m, 1H), 5.86 (s, 2H), 6.39 (dd, 1H), 6.49 (d, 1H), 6.68 (dd, 1H), 7.03 (m, 2H), 7.36 (m, 2H); $[\alpha]^{25}_D$ +11.8° (*c* 0.27, CH_3OH). Anal. ($C_{26}H_{30}FNO_9$) C, H, N.

3*β*-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)-phenoxy]methyl]tropane [(1*R*)-2α,3*β*-7b]. Fractions were pooled to give 0.34 g (51%) of the product as a colorless oil: ^{1}H NMR (C_6D_6) δ 1.37 (ddd, 1H, *J* = 12.0, 9.6, 4.8 Hz), 1.44 (ddd, 1H, *J* = 12.0, 5.7, 3.0 Hz), 1.71 (m, 1H), 1.77 (m, 1H), 1.87 (ddd, 1H, *J* = 12.0, 6.4, 6.4 Hz), 1.94 (ddd, 1H, *J* = 12.0, 12.0, 3.4 Hz), 2.20 (s, 3H), 2.31(ddd, 1H, *J* = 12.0, 12.0, 5.7 Hz), 2.65 (ddd, 1H, *J* = 12.0, 9.6, 3.5 Hz), 3.00 (dd, 1H, *J* = 6.4, 6.4, 3.0 Hz), 3.40 (dd, 1H, *J* = 9.6, 9.6 Hz), 3.49 (dd, 1H, *J* = 9.6, 3.5 Hz), 3.52 (dd, 1H, *J* = 6.7, 3.0 Hz), 5.33 (s, 2H), 6.12 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.49 (d, 1H, *J* = 2.5 Hz), 6.56 (d, 1H, *J* = 8.5 Hz), 6.79 (dd, 2H, *J* = 8.7, 8.7 Hz), 6.94 (dd, 2H, *J* = 8.7, 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 154.45, 148.30, 144.66, 139.53, 129.33, 129.20, 115.73, 115.40, 107.98, 105.68,

101.23, 98.14, 70.84, 68.91, 63.28, 62.01, 46.23, 41.55, 41.23, 37.54, 26.10, 22.07. The compound was converted to the D-tartrate salt. Recrystallization from EtOH/Et_2O gave a hygroscopic off-white powder: mp 105 °C (fusion); ^{1}H NMR (CD_3OD) δ 1.95 (m, 1H), 2.13−2.46 (m, 5H), 2.77−3.00 (m, 2H), 2.89 (s, 3H), 3.46−3.70 (m, 2H) 3.99 (m, 1H), 4.14 (m, 1H), 4.43 (s, 2H), 5.84 (s, 2H), 6.15 (dd, 1H), 6.35 (d, 1H), 6.62 (d, 1H), 7.06 (m, 2H), 7.35 (m, 2H); $[\alpha]^{25}_D$ +32.8° (c 0.29, CH_3OH). Anal. ($C_{26}H_{30}FNO_9$) C, H, N.

3α-(4-Fluorophenyl)-2*β*-[[(3,4-(methylenedioxy)phenoxy]methyl]tropane [(1*R*)-2*β*,3α-7c]. Fractions were pooled to give 0.312 g (42%) of the product as a light yellow oil: ^{1}H NMR (C_6D_6) δ 1.25 (dd, 1H, J = 13.2, 10.8 Hz), 1.50 (ddd, 1H, J = 12.5, 9.5, 3.4 Hz), 1.59 (ddd, 1H, J = 17.0, 12.1, 4.9 Hz), 1.87 (ddd, 1H, J = 10.8, 10.8, 3.5 Hz), 2.13 (ddd, 1H, J = 17.0, 12.1, 5.8 Hz), 2.29 (m, 4H), 2.46 (ddd, 1H, J = 13.2, 8.6, 8.3 Hz), 2.62 (ddd, 1H, J = 10.8, 10.3, 8.3 Hz), 3.29 (m, 2H), 3.59 (dd, 1H, J = 10.8, 3.5 Hz), 3.75 (dd, 1H, J = 10.8, 10.8 Hz), 5.87 (s, 2H), 6.18 (dd, 1H, J = 8.5, 2.5 Hz), 6.38 (d, 1H, J = 2.5 Hz), 6.63 (d, 1H, J = 8.5 Hz), 6.96 (dd, 2H, J = 8.6, 8.6 Hz), 7.16 (dd, 2H, J = 8.6, 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 163.29, 159.39, 154.48, 148.111, 141.39, 140.73, 140.68, 129.47, 129.28, 115.32, 114.99, 107.85, 105.53, 101.05, 97.98, 71.33, 62.73, 59.48, 50.89, 41.45, 41.11, 36.12, 29.43, 28.48. The product was converted to the D-tartrate salt. Recrystallization from EtOH/Et_2O gave a hygroscopic off-white solid: mp 84 °C (fusion); ^{1}H NMR (CD_3OD) δ 1.82 (m, 1H), 2.07−2.19 (m, 2H), 2.30−2.76 (m, 4H), 2.82 (s, 3H), 3.02−3.15 (m, 1H), 3.76 (m, 2H), 3.96 (m, 2H), 5.87 (s, 2H), 6.30 (dd, 1H), 6.51 (d, 1H), 6.65 (d, 1H), 7.07 (m, 2H), 7.35 (m, 2H); $[\alpha]^{25}_D$ −48.3° (*c* 0.29, CH_3OH). Anal. ($C_{26}H_{30}FNO_9$·0.5H_2O) C, H, N.

(1*S*)-3*β*-(4-Fluorophenyl)-2*β*-[[3,4-(methylenedioxy)phenoxy]methyl]tropane [(1*S*)-2*β*,3*β*-7d]. Fractions were pooled to give 1.02 g (69%) of the pure product. ^{1}H and ^{13}C NMR are identical with the (1*R*)-enantiomer. The product was converted to the D-tartrate salt. Recrystallization from 2-propanol/ethyl ether yielded a white powder: mp 90 °C (fusion); ^{1}H and ^{13}C NMR are identical with those of the (1*R*)-enantiomer; $[\alpha]_D$ −26.8° (*c* 0.63, CH_3OH). Anal. ($C_{26}H_{30}FNO_9$) C, H, N.

(1*S*)-3*β*-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)phenoxy]methyl]tropane [(1*S*)-2α,3*β*-7e]. Fractions were pooled to give 0.76 g (64%) of the product as a slightly yellow oil. ^{1}H and ^{13}C NMR are identical with those of the (1*R*)-enantiomer. The compound was converted to the D-tartrate salt. Recrystallization from MeOH/Et_2O gave a hygroscopic off-white powder: mp 95 °C (fusion); ^{1}H and ^{13}C NMR are identical with the (1*R*)-enantiomer; $[\alpha]^{25}_D$ −50.8° (*c* 0.50, CH_3OH). Anal. ($C_{26}H_{30}FNO_9$) C, H, N.

(1*S*)-3α-(4-Fluorophenyl)-2*β*-[[3,4-(methylenedioxy)phenoxy]methyl]tropane [(1*S*)-2*β*,3α-7f]. Fractions were pooled to give 0.24 g (32%) of the product as a light yellow oil. ^{1}H and ^{13}C NMR are identical with those the (1*R*)-enantiomer. The product was converted to the D-tartrate salt. Recrystallization from MeOH/Et_2O gave a hygroscopic white solid: mp 56 °C dec. ^{1}H and ^{13}C NMR are identical with the those of (1*R*)-enantiomer, $[\alpha]^{25}_D$ +38.2° (*c* 0.33, CH_3OH). Anal. ($C_{26}H_{30}FNO_9$·0.25H_2O) C, H, N.

General Procedure for Demethylation of 3-(4-Fluorophenyl)-2-[[3,4-(methylenedioxy)phenoxy]methyl]tropane (7). Method A. The appropriate isomer of **7** (1.0 mmol) was dissolved in 15 mL of dichloroethane under nitrogen gas. Proton Sponge [1,8-bis(dimethylamino)naphthalene, 0.14 mmol; Aldrich] was added, and the solution was stirred for 0.5 h at room temperature. ACE-Cl (6.0 mmol) was added, and the reaction mixture was refluxed for 24 h. The reaction mixture was cooled and the solvent removed under reduced pressure. MeOH (10 mL) was added, and the reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure to afford a dark orange/red oil. Water was added, and the reaction mixture was basified with NH_4OH. The aqueous layer was extracted with CH_2Cl_2. The solvent was removed under reduced pressure, and the product was purified by flash chromatography

Method B. The appropriate isomer of **7** (1.0 mmol) was dissolved in 10 mL of toluene under nitrogen gas. Potassium carbonate (0.4 mmol) was added, and the solution was refluxed for 0.5 h. Trichloroethyl chloroformate (3.8 mmol) was added, and the reaction was refluxed for 24 h. Additional chloroformate was added, and the reaction was refluxed for 24 h. Water and $CHCl_3$ were added, and the reaction mixture was basified with NH_4OH. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4. The solvent was removed to afford a brown oil. The carbamate was dissolved in glacial acetic acid (6.0 mL), and Zn dust (1.00 g) was added in small portions. The mixture was stirred for 12 h at room temperature. Water and $CHCl_3$ were added, and the reaction was filtered through Celite. After basifying with NH_4OH and extracting with $CHCl_3$, the organic layers were dried over K_2CO_3. The product was purified by flash chromatography on silica gel, first eluting with Et_2O/Et_3N (9:1) followed by $CHCl_3$/CH_3OH/NH_4OH (90:9:1).

3*β*-(4-Fluorophenyl)-2*β*-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane [(1*R*)-2*β*,3*β*-4a]. Method A. Purification afforded 0.083 g (62%) of the product as a pink oil: ^{1}H NMR (C_5D_5N) δ 1.67 (dd, 1H, J = 12.0, 3.5 Hz), 1.91 (m, 2H), 2.05 (ddd, 1H, J = 13.9, 10.9, 1.9 Hz), 2.15 (m, 3H), 2.93 (dd, 1H, J = 12.3, 1.9 Hz), 3.28 (dd, 1H, J = 12.3, 5.5 Hz), 3.32 (m, 1H), 3.60 (dd, 1H, J = 10.6, 6.2 Hz), 4.55 (ddd, 1H, J = 9.5, 5.5, 1.9 Hz), 5.93 (s, 2H), 6.58 (dd, 1H, J = 8.4, 2.4 Hz), 6.86 (d, 1H, J = 8.4 Hz), 6.87 (d, 1H, J = 2.4 Hz), 7.06 (dd, 2H, J = 8.7, 8.7 Hz), 7.49 (dd, 2H, J = 8.7, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 163.18, 159.29, 152.51, 148.34, 142.14, 141.93, 129.11, 128.99, 115.40, 115.06, 108.42, 108.10, 1010.18, 99.82, 83.05, 47.72, 46.21, 42.18, 39.84, 33.54, 31.31, 27.02. The product was converted to the D-tartrate salt. Recrystallization from EtOH/Et_2O gave a white hygroscopic powder: mp 183−185 °C dec; ^{1}H NMR (CD_3OD) δ 1.98−2.37 (m, 7H), 3.24−3.42 (m, 2H), 3.72 (m, 1H), 3.87 (br s, 1H), 4.42 (s, 2H), 4.55 (bs, 1H), 5.7 (s, 2H), 6.39 (dd, 1H), 6.58 (d, 1H), 6.68 (d, 1H), 7.05 (m, 2H), 7.33 (m, 2H); $[\alpha]^{23}_D$ +10.6° (*c* 0.36, CH_3OH). Anal. ($C_{25}H_{28}FNO_9$) C, H, N.

(1*R*)-3*β*-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane [(1*R*)-2α,3*β*-4b]. Method A. Fractions were pooled to afford 0.19 g (55%) of pink oil: ^{1}H NMR (C_5D_5N) δ 1.68 (m, 3H), 1.78 (m, 1H), 1.87 (ddd, 1H, J = 12.6, 12.6, 2.2 Hz), 1.97 (m, 1H), 2.58 (m, 1H), 2.73 (ddd, 1H, J = 11.9, 11.9, 5.5 Hz), 3.58 (ddd, 1H, J = 6.6, 3.2, 3.2 Hz), 3.69 (s, 1H), 3.71 (d, 1H, J = 1.9 Hz), 3.96 (dd, 1H, J = 6.4, 2.2 Hz), 5.90 (s, 2H), 6.32 (dd, 1H, J = 8.3, 2.5 Hz), 6.62 (d, 1H, J = 2.5 Hz), 6.78 (d, 1H, J = 8.3 Hz), 7.11 (dd, 2H, J = 8.7, 8.7 Hz), 7.32 (dd, 2H, J = 8.7, 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 163.96, 159.66, 154.13, 148.14, 141.57, 138.91, 129.10, 128.98, 115.66, 115.33, 107.81, 105.44, 101.08, 97.91, 68.57, 56.35, 55.16 46.48, 46.21, 41.24, 37.89, 28.98, 24.99. The product was converted to the D-tartrate salt. Recrystallization from MeOH/Et_2O gave a hygroscopic light yellow powder: mp 140 °C (fusion); ^{1}H NMR (CD_3OD) δ 1.88−2.45 (m, 6H), 2.66 (m, 1H), 3.00 (m, 1H), 3.53−3.70 (m, 2H), 4.13 (m, 1H), 4.28 (m, 1H), 4.42 (s, 2H), 5.84 (s, 2H), 6.14 (dd, 1H), 6.34 (d, 1H), 6.60 (d, 1H), 7.06 (m, 2H), 7.33 (m, 2H); $[\alpha]^{25}_D$ +36.0° (*c* 0.30, CH_3OH). Anal. ($C_{25}H_{28}FNO_9$·0.5H_2O) C, H, N.

(1*R*)-3α-(4-Fluorophenyl)-2*β*-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane [(1*R*)-2*β*,3α-4c]. Method A. Fractions were pooled to afford 0.069 g (55%) of yellow oil: ^{1}H NMR (C_5D_5N) δ 1.51 (m, 1H), 1.65 (m, 2H), 1.92 (m, 2H), 2.23 (ddd, 1H, J = 13.8, 9.1, 7.4 Hz), 2.80 (ddd, 1H, J = 11.1, 11.1, 7.4 Hz), 3.52 (m, 2H), 3.71 (d, 1H, J = 3.3 Hz), 3.75 (dd, 1H, J = 9.1, 3.7 Hz), 3.91 (dd, 1H, J = 9.1, 9.1 Hz), 5.85 (s, 2H), 6.35 (dd, 1H, J = 8.4, 2.3 Hz), 6.65 (d, 1H, J = 2.4 Hz), 6.77 (d, 1H, J = 8.5 Hz), 7.09 (dd, 1H, J = 8.6 Hz), 7.25 (dd, 1H, J = 8.4, 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 163.61, 154.52, 148.07, 141.62, 140.39, 129.47, 115.37, 115.03, 107.87, 105.60, 101.08, 98.03, 71.11, 55.25, 51.96, 49.84, 39.12, 35.92, 34.33, 32.30. The product was converted to the D-tartrate salt. Recrystallization from 2-propanol/Et_2O gave a hygroscopic white crystalline solid: mp 174 °C dec; ^{1}H NMR (CD_3OD) δ 1.72 (m, 1H),

2.01−2.24 (m, 5H), 2.58 (m, 1H), 2.94 (m, 1H), 3.69 (m, 2H), 4.11 (m, 2H), 5.86 (s, 1H), 62.8 (dd, 1H), 6.50 (d, 1H), 6.65 (d, 1H), 7.06 (m, 2H), 7.33 (m, 2H); $[\alpha]^{23}_D$ −79.7° (*c* 0.32, CH_3OH). Anal. ($C_{25}H_{28}FNO_9$) C, H, N.

(1*S*)-3*β*-(4-Fluorophenyl)-2*β*-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane [(1*S*)-2*β*,3*β*-4d]. Method B. Flash chromatography gave 0.098 g (26%) of the product. Another fraction contained 0.118 g of the *N*-methyl starting material. ^1H and ^{13}C NMR are identical with the (1*R*)-enantiomer. The product was converted to the L-tartrate salt. Recrystallization from EtOH/Et_2O gave a light tan hygroscopic powder: mp 180−184 °C dec; ^1H and ^{13}C NMR are identical with those of the (1*R*)-enantiomer; $[\alpha]^{25}_D$ −10.3° (*c* 0.30, CH_3OH). Anal. ($C_{25}H_{28}FNO_9$) C, H, N.

(1*S*)-3*β*-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane [(1*S*)-2α,3*β*-4e]. Method A. Fractions were pooled to afford 0.135 g (40%) of pink oil. ^1H and ^{13}C NMR are identical with those of the (1*R*)-enantiomer. The product was converted to the d-tartrate salt. Recrystallization from MeOH/Et_2O gave a hygroscopic tan powder: mp 170 °C (fusion); ^1H and ^{13}C NMR are identical with those of the (1*R*)-enantiomer: $[\alpha]^{25}_D$ −52.4° (*c* 0.50, CH_3OH). Anal. ($C_{25}H_{28}FNO_9 \cdot 0.25H_2O$) C, H, N.

(1*S*)-3α-(4-Fluorophenyl)-2*β*-[[3,4-(methylenedioxy)phenoxy]methyl]nortropane [(1*S*)-2*β*,3α-4f]. Method B. Flash chromatography afforded 0.095 g (55%) of the product as a brown oil. ^1H and ^{13}C NMR are identical with those of the (1*R*)-enantiomer. The product was converted to the L-tartaric acid salt. Recrystallization from EtOH/Et_2O gave a light tan hygroscopic powder: mp 163−166 °C dec; ^1H and ^{13}C NMR are identical with those of the (1*R*)-enantiomer; $[\alpha]^{25}_D$ +76.3° (*c* 0.27, CH_3OH). Anal. ($C_{25}H_{28}FNO_9 \cdot 0.5H_2O$) C, H, N.

(1*R*)-3α-(4-Fluorophenyl)-2α-(3-methyl-1,2,4-oxadiazol-5-yl)tropane (10). To a cooled solution (−78 °C) of bromofluorobenzene (0.64 g, 3.66 mmol) in 10 mL of anhydrous Et_2O was added *t*-BuLi (1.0 M in pentane, 6.0 mL, 6.00 mmol) dropwise. After the mixture was stirred for 20 min at −78 °C, a solution of **9** (0.31 g, 1.51 mmol) in 20 mL of Et_2O was added slowly. The reaction was stirred at −78 °C for 2 h and then at −40 °C for 1 h. The reaction was treated with ethereal TFA over 5 min, allowed to warm to 0 °C, and diluted with ether. The mixture was basified with dilute NH_4OH and the layers were separated. After the organic layer was dried over Na_2SO_4, the solvent was removed to give 0.44 g of oil. Flash chromatography [EtOAc/Et_3N/hexanes (27:3:70)] gave 0.28 g of product as a white solid. Recrystallization from hexanes afforded 0.158 g (35%) of white crystals: mp 101−103 °C; ^1H NMR ($CDCl_3$) *δ* 1.52−1.67 (m, 2H), 1.83−2.15 (m, 3H), 2.25 (s, 3H), 2.32 (s, 3H), 2.47 (m, 1H), 3.35 (m, 1H), 3.56 (m, 1H), 3.65 (m, 1H), 4.18 (m, 1H), 6.84 (m, 2H), 7.06 (m, 2H); ^{13}C NMR ($CDCl_3$) *δ* 179.41, 166.49, 137.41, 129.28, 129.16, 114.89, 114.55, 62.24, 59.63, 44.31, 40.48, 35.33, 34.69, 28.39, 23.10, 11.49; $[\alpha]^{23}_D$ +52.0° (*c* 0.60, $CHCl_3$). Anal. ($C_{17}H_{20}FNO_3$) C, H, N.

(1*R*)-3α-(4-Fluorophenyl)-2*β*-carbomethoxytropane [(*R*)-2*β*,3α-5]. To a solution of nickel acetate (5.33 g, 21.43 mmol) in 50 mL of MeOH was added slowly a slurry of $NaBH_4$ (0.801 g, 21.43 mmol) in 25 mL of MeOH. A solution of the oxadiazolyltropane **10** (1.29 g, 4.28 mmol) and HCl (12 N, 1.78 mL, 21.43 mmol) in 50 mL of MeOH was added slowly to the black slurry. The reaction mixture was stirred at room temperature for 2 h and then refluxed for 3 h. The reaction mixture was cooled and then Et_2O and saturated $NaHCO_3$ were added. The reaction was basified with NH_4OH to pH 10. The layers were separated, and the blue aqueous layer was extracted with Et_2O several times. The solvent was removed to afford 1.03 g of clear oil: ^1H NMR (C_6D_6) *δ* 1.03−1.18 (m, 2H), 1.27−1.33 (m, 1H), 1.70−192 (m, 2H), 2.02 (s, 3H), 2.25 (m, 1H), 2.38 (m, 1H), 2.88 (m, 1H), 3.25 (s, 3H), 3.31 (m, 1H), 3.55−3.66 (m, 1H), 6.77 (m, 2H), 6.91 (m, 2H). The ester was characterized as the D-tartrate salt:[17] $[\alpha]^{24}_D$ −34.4° (*c* 0.54, CH_3OH); mp 65 °C. Anal. ($C_{20}H_{26}FNO_8 \cdot 0.5H_2O$) C, H, N.

(1*S*)-2-Carbomethoxy-3-[[(trifluoromethyl)sulfonyl]oxy]tropene (12). Carbomethoxytropinone[19,40,43] (6.01 g, 30.5 mmol) was dissolved in 150 mL of anhydrous THF under N_2. After the mixture was cooled to −78 °C, bis(trimethylsilyl)amide (1.0 M solution in THF, 40.0 mL, 40.0 mmol) was added dropwise by an addition funnel. The mixture was stirred at −78 °C for 0.5 h. The triflimide (13.03 g, 36.5 mmol) was dissolved in 100 mL of anhydrous THF and added dropwise. The reaction was stirred for 10 min at −78 °C, then warmed to 0 °C, and stirred for 2 h. The reaction vessel was fitted with a drying tube and allowed to remain at 5 °C for 36 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2. After the mixture was dried over Na_2SO_4, solvent was removed from the solution to afford 11.77 g of brown oil. Purification by flash chromatography (hexane/EtOAc, 3:2) gave 8.07 g (80%) of triflate **12** as a golden oil: ^1H NMR ($CDCl_3$) *δ* 1.60 (m, 1H), 2.00 (m, 2H), 2.20 (m, 2H), 2.40 (s, 3H), 2.85 (m, 1H), 3.43 (m, 1H), 3.82 (s, 3 H), 3.93 (d, 1H); ^{13}C NMR ($CDCl_3$) *δ* 163.79, 149.10, 125.19, 118.21 (q), 60.08, 57.40, 52.05, 34.86, 34.66, 33.03, 29.96; $[\alpha]^{23}_D$ −7.8° (*c* 1.0, $CHCl_3$). Anal. ($C_{11}H_{14}F_3O_5S$) C, H, N.

(1*S*)-Anhydroecognine Methyl Ester (13). The triflate **12** (11.36 g, 34.5 mmol) was dissolved in 250 mL of anhydrous THF under N_2. Next, $Pd(OAc)_2$ (0.177 g, 0.788 mmol), PPh_3 (0.461 g, 1.76 mmol), and Et_3N (14.4 mL, 10.45 g, 103.3 mmol) were added. The reaction was stirred for 5 min, HCO_2H (2.60 mL, 3.17 g, 68.9 mmol) was added dropwise, and the mixture was refluxed for 1 h. After to room temperature, water was added. The reaction was extracted with $CHCl_3$ and dried over Na_2SO_4. Purification by flash chromatography (Et_2O/Et_3N/hexane, 9:1:10) gave 5.43 g (87%; 75%, 2 steps from **11**) of **13**: ^1H NMR ($CDCl_3$) *δ* 1.49 (m, 1H), 1.86 (m, 2H), 2.14 (m, 2H), 2.34 (s, 3H), 2.62 (m, 1H), 3.24 (m, 1H), 3.74 (s, 3H), 3.79 (m, 1H), 6.82 (m, 1H); $[\alpha]^{25}_D$ +35.5° (*c* 1.0, $CHCl_3$) [lit.[43] $[\alpha]^{25}_D$ +38.3° (*c* 1.0, CH_3OH)].

(1*S*)-3*β*-(4-Fluorophenyl)tropane-2*β*-carboxylic Acid Methyl Ester [(1*S*)-2*β*,3*β*-5]. The synthesis of this compound has been described previously.[43] The fractions were pooled to give 4.22 g (51%) of product as a white solid: mp 92−93 °C (lit.[43] mp 94−96 °C). A second fraction (1.48 g) contained the α-isomer: ^1H NMR ($CDCl_3$) *δ* 7.22 (m, 2H), 6.95 (m, 2H), 3.57 (m, 1H), 3.50 (s, 3H), 3.36 (m, 1H), 2.95 (m, 1H), 2.86 (m, 1H), 2.57 (m, 1H), 2.22 (s, 3H), 2.15 (m, 2H), 1.57−1.75 (m, 3H); $[\alpha]^{25}_D$ +49.2° (*c* 0.52, CH_3OH) [lit.[43] for the naphthalene-1,5-disulfonate $[\alpha]^{24}_D$ +84.5° (*c* 1.0, H_2O)].

(1*S*)-3*β*-(4-Fluorophenyl)tropane-2α-carboxylic Acid Methyl Ester [(1*S*)-2α,3*β*-5]. A white solid was obtained which was recrystallized to give white crystals: mp 68−70 °C (lit.[43] mp 71.5−73.5 °C); ^1H NMR ($CDCl_3$) *δ* 1.56−2.15 (m, 6H), 2.40 (s, 3H), 3.00−3.14 (m, 2H), 3.23 (m, 1H), 3.41 (m, 1H), 3.50 (s, 3H), 6.97 (m, 2H), 7.21 (m, 2H); ^{13}C NMR ($CDCl_3$) *δ* 173.30, 161.40 (d), 139.38, 129.19, 129.07, 115.30, 114.97, 63.62, 61.12, 51.49, 51.42, 39.65, 38.76, 36.14, 26.40, 23.20; $[\alpha]^{23}_D$ −14.5° (*c* 0.55, CH_3OH) [lit.[43] $[\alpha]^{24}_D$ −1.2° (*c* 5.0, $CHCl_3$)].

(1*S*)-2-Carbomethoxy-3-(4-fluorophenyl)tropene (14). To a round-bottom flask was added the triflate **12** (1.51 g, 4.59 mmol), LiCl (0.402 g, 9.57 mmol), tris(dibenzilideneacetone)-dipalladium(0) (0.170 g), Na_2CO_3 (2.0 M soln in H_2O, 4.5 mL, 9.0 mmol), and diethoxymethane (10 mL). The mixture was stirred vigorously, and (*p*-fluorophenyl)boronic acid (0.852 g, 6.08 mmol) was added. The reaction was refluxed and monitiored by TLC (Et_2O/Et_3N, 9:1). After 1 h, the reaction 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. The solvent was removed from the dried solution to afford a dark yellow oil. Purification of the residue by flash chromatography (silica gel, Et_2O/Et_3N/hexane, 9:1:10) afforded 1.09 g (86%) of the tropene as a yellow oil which solidified upon standing: mp 56−58 °C; ^1H NMR ($CDCl_3$) *δ* 7.13−6.97 (m, 4H), 3.85 (d, 1H), 3.50 (s, 3H), 3.35 (m, 1H), 2.74 (m, 1H), 2.44 (s, 3H), 1.94−2.24 (m, 4H), 1.64 (m, 1H); ^{13}C NMR ($CDCl_3$) *δ* 168.21, 162.12 (d), 142.77, 137.15, 131.02, 128.52, 128.40,

115.15, 114.81, 60.35, 57.45, 51.36, 37.82, 36.14, 34.21, 30.13; $[\alpha]^{23}_D$ +61.7° (c 0.86, $CHCl_3$). Anal. ($C_{16}H_{18}FNO_2$) C, H, N.

(1*S*)-3α-(4-Fluorophenyl)tropane-2*β*-carboxylic Acid Methyl Ester [(1*S*)-2*β*,3α-5]. Tropene **14** (0.93 g, 3.38 mmol) was dissolved in 5 mL of anhydrous MeOH under argon. After the solution was heated to 40 °C, the SmI_2 solution (0.1 M in THF, 140 mL, 14.0 mmol) was added dropwise via syringe. The mixture was stirred at 40 °C and monitored by TLC [Et_2O/Et_3N (9:1)]. After 1.0 h, the reaction was quenched by the dropwise addition of a 10% HCl solution. Water and Et_2O were added, and 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 from the dried solution to afford a yellow oil. Purification of the residue by flash chromatography (2.5% EtOH/$CHCl_3$ and Et_2O/Et_3N/hexane, 9:1:10) gave the desired 2*β*,3α isomer (45%) along with 14% of the 2*β*,3*β* isomer: ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 2H), 6.93 (m, 2H), 3.58 (s, 3H), 3.28 (m, 3H), 2.42 (m, 2H), 2.38 (s, 3H), 2.19 (m, 2H), 1.47−1.64 (m, 2H), 1.31 (m, 1H); ^{1}H NMR (C_6D_6) δ 6.91 (m, 2H), 6.77 (m, 2H), 3.59 (m, 1H), 3.31 (m, 1H), 3.25 (s, 3H), 2.88 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 2.01 (s, 3H), 1.73−1.92 (m, 2H), 1.28 (m, 1H), 1.03−1.17 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.34, 161.62 (d), 139.91, 129.43, 129.31, 115.49, 115.16, 63.38, 59.66, 57.03, 52.01, 41.29, 39.72, 35.99, 29.38, 29.26.

The compound was characterized as the L-tartaric acid salt: mp 90−95 °C (fusion); ^{1}H NMR (CD_3OD) δ 1.81 (m, 1H), 2.11 (m, 2H), 2.51 (m, 1H), 2.63 (m, 1H), 2.70 (m, 1H), 2.81 (s, 3H), 3.45 (m, 2H), 3.95 (m, 2H), 4.47 (s, 3H), 7.05 (m, 2H), 7.48 (m, 2H); $[\alpha]^{24}_D$ +47.8° (c 0.27, CH_3OH). Anal. ($C_{20}H_{26}FNO_8 \cdot H_2O$) C, H, N.

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