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Synthesis, structural identification, and ligand binding of tropane ring analogs of paroxetine and an unexpected aza-bicyclo[3.2.2]nonane rearrangement product

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Abstract—The structural requirements for high affinity at the serotonin transporter (5-HTT) have been investigated through the preparation of rigid paroxetine analogs. Tropane-derived analogs (**4a**–**i**) of paroxetine (**2**) were designed and synthesized as potential inhibitors of serotonin reuptake based on the structural and biological similarity between the two compound classes. Overall, the affinity of tropane-derived analogs at the 5-HTT was found to be at least an order of magnitude lower than that of paroxetine and ranged from 2–400 nM. The reduced affinity at the 5-HTT may be attributed to the inability of the rigid tropane-derived analogs to adopt conformations favored by the 5-HTT. Within the series of tropane analogs, the 2β,3β- and 2β,3α-isomers, **4a** and **4d**, were the most potent at the DAT and NET and are also significantly more potent than paroxetine (**2**) suggesting that their reduced conformational flexibility maximizes residence time in conformations favored by these transporters. Examination of the previously published preparation and structural assignment of **4a** by additional NMR and X-ray crystallographic data has established that nucleophilic addition to the intermediate 2β-methanesulfonyloxymethyl-3β-(4-fluorophenyl)tropane unexpectedly provided the aza-bicyclo[3.2.2]nonane derivative **10a**.

1. Introduction

In order to understand the biochemical mechanism related to its addictive properties, the molecular site where cocaine (**1**) interacts to produce its physiological effects had to first be identified. In our 1992 perspective paper,[1] we summarized the information that strongly suggested the dopamine transporter (DAT) as the cocaine receptor responsible for its abuse. Over the past several years numerous studies have supported the hypothesis implicating the DAT as a key target for cocaine abuse.[2–5] However, it is well known that cocaine also influences serotonin (5-HT) neurotransmission by interacting at the serotonin transporter (5-HTT) as well. Thus, the 5-HTT may also be involved in some way, perhaps via modulation of cocaine's action.[6,7]

Paroxetine (**2**) is a selective 5-HTT reuptake inhibitor with demonstrated antidepressant activity in humans.[8] Since the 3β-phenylnortropane **3** also possesses high affinity for the 5-HTT and shares some structural features with paroxetine,[9] we carried out an investigation of rigid tropane-derived paroxetine analogs **4a**–**i**[10] (see Table 2 for structures) to gain a better understanding of the structural requirements necessary for high affinity at the 5-HTT.

During a subsequent investigation of 3β-phenyltropanes similar to those we had reported,[10] Ogier et al. noted that a key intermediate, 2β-methanesulfonyloxymethyl-

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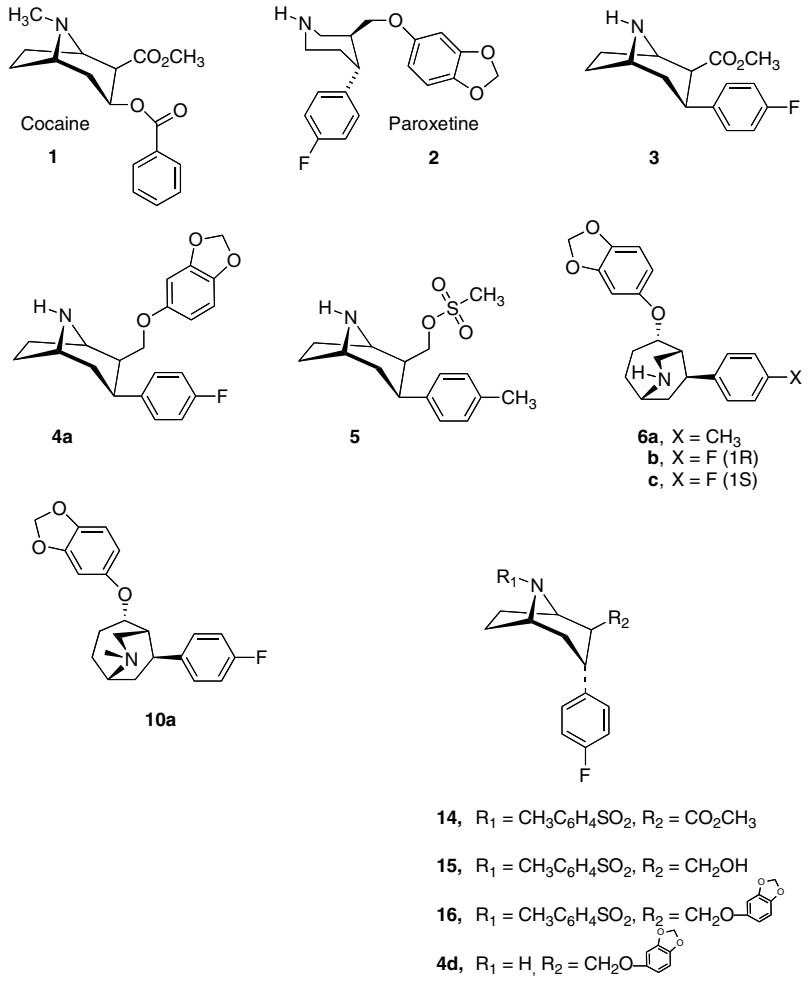
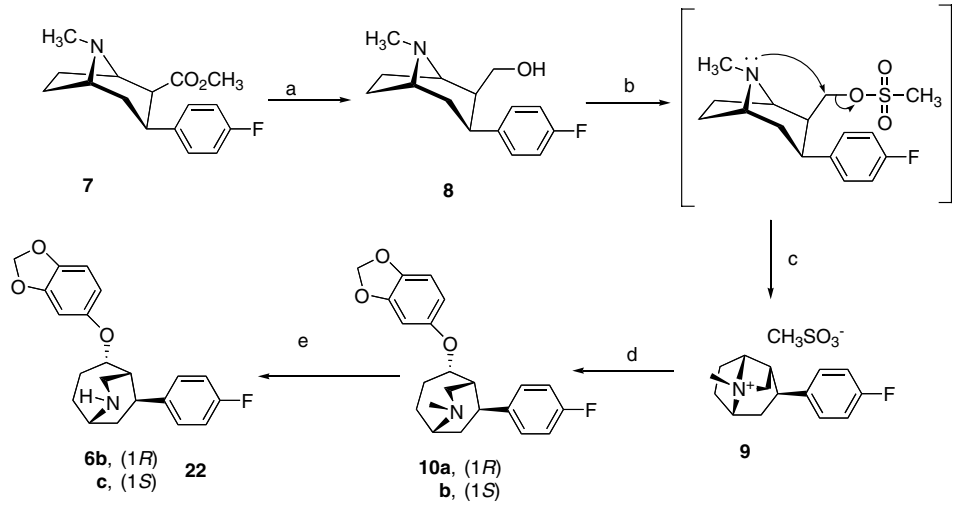


3β-(4-methylphenyl)tropane **5**, could not be isolated since it had undergone an unanticipated intermolecular nucleophilic addition to provide the rearranged product **6a**.[11] This information prompted us to reinvestigate the structures of the similar compounds that we had previously reported.[10] Through X-ray crystallographic and additional NMR analysis, we discovered that the compound we previously reported as **4a** has the structure **6b**. In addition, we reinvestigated the previously reported structural assignments of the 2β,3α tropane derivatives and have determined that these compounds did not undergo rearrangement.[10]

1.1. Synthesis

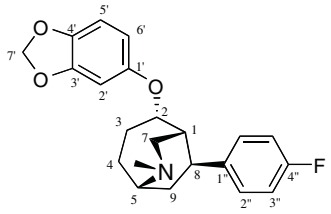
The previously published reaction sequence[10] describing the synthesis of **4a** has been modified to show the formation of the rearranged product **6b** (Scheme 1). Although the addition of methanesulfonyl chloride to **8** in triethylamine provided an intermediate mesylate, which could be isolated, it rapidly underwent intramolecular nucleophilic addition to form 1-methyl-4-(4-fluorophenyl)-1-azonium-tricyclo[4.3.0.0^{3,9}]nonane mesylate **9**. Ring opening of **9** occurred at the C-9 position with the sodium salt of sesamol at reflux and provided the rearranged aza-bicyclo[3.2.2]nonane **10a** in 44% yield. The structure of **10a** was confirmed by ^{1}H NMR analysis (see Table 1). *N*-Demethylation of **10a** with 1-chloroethyl chloroformate in 1,2-dichloroethane at reflux provided the *N*-nor analog **6b** in 62% yield. The structure was established by single-crystal X-ray analysis (Fig. 1). Compound **10b** possessing the (1*S*) configuration was prepared from (1*S*)-2β-hydroxymethyl-3β-(4-fluorophenyl)tropane following a route similar to that described for **10a**. Demethylation of **10b** with trichloroethylformate and zinc dust provided the *N*-nor analog **6c** in 26% yield. For simplicity, only the structures of the (1*R*) isomers are shown in Scheme 1. The (1*S*) isomers (**6c**, **10b**, and **17**) are detailed in the Experimental section.

The paroxetine analog **4a** was prepared in a manner analogous to that described by Ogier et al.[11] as outlined in Scheme 2. *N*-Demethylation of **7** with 1-chloroethyl chloroformate was followed by formation of the tosylamide **11** using *p*-toluenesulfonyl chloride in triethylamine at 0 °C. This protection step prevents nucleophilic attack of the tropane nitrogen at C-9. Lithium aluminum hydride reduction of resulting 2β-carbomethoxy-3β-(4-fluorophenyl)-8-(4-toluenesulfonyl)tropane **11** provided the hydroxymethyl derivative **12** in 96% yield. Treatment of alcohol **12** with trifluoromethanesulfonic anhydride provided the intermediate mesylate, which was treated with the sodium salt of sesamol to afford the desired tropane analog **13** in 58% yield. The *p*-toluenesulfonyl protecting group was removed with



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C; (b) (1) methanesulfonyl chloride, TEA, 0 °C; (c) toluene, 1 h reflux; (d) Na, sesamol, THF, reflux; (e) (1) 1-chloroethyl chloroformate, 1,2-dichloroethane, 24 h reflux; (2) MeOH, 24 h reflux.

Table 1. NMR assignments for **10a** obtained in d_6-benzene



Assignment	Carbon (δ)	Proton (δ)	HMBC correlations
4	22.29	1.14, 1.52	H3,H9,H5
3	27.14	1.70, 1.91	H4,H1,H5
9	32.65	1.82, 2.06	H4,H1,H8,H5
8	34.44	3.35	H7,H2,H1,H9
1	42.89	2.09	H7,H3,H8,H9
NMe	43.08	2.14	H7,H5
7	50.24	1.94, 2.82	NMe,H2,H8,H5
5	55.39	2.69	NMe,H7,H4,H3,H8
2	83.83	4.01	H7,H4,H3,H1,H8
6′	100.12	6.59	H5′,H2′
7′	101.15	5.30	—
5′	108.43	6.27	—
2′	108.87	6.59	H6′
3″	115.17	6.83	H3″,H2″
2″	129.89	7.35	H3″,H2″
4′	142.38	—	H7′,H6′
1″	143.87	—	H3″,H3,
3′	148.96	—	H7′,H5′
1′	153.43	—	H5′,H2′
4″	161.73	—	H3″,H2″

5% sodium amalgam and disodium hydrogen phosphate in methanol at reflux to provide the paroxetine analog **4a** in 78% yield. The structure of **4a** was confirmed by ^{1}H NMR spectral analysis (Table 2) and single-crystal X-ray analysis (Fig. 2).

In order to confirm the previous structural assignment[10] of the 2β,3α paroxetine analogs **4b–e**, a representative compound **4d**, was resynthesized according to the method of Ogier et al.[11] as shown for **4a** (Scheme 2). The corresponding intermediates, **14–16**, were fully characterized. The ^{1}H NMR spectrum of the product was consistent with the spectrum of **4d**.[10] The structure of **4d** was further confirmed by single-crystal X-ray analysis (Fig. 3).

1.2. Biology

The binding affinities of the compounds at the DAT, 5-HTT, and the norepinephrine transporter (NET) were determined via competition binding assays using the previously reported procedures.[12] The final concentration of radioligands in the assays were 0.5 nM [^{3}H]WIN35,428 for the DAT, 0.2 nM [^{3}H]paroxetine for the 5-HTT, and 0.5 nM [^{3}H]nisoxetine for the NET. The binding data for (1*R*) **10a**, (1*S*) **10b**, (1*R*) **6b**, and (1*S*) **6c**, along with data for previously reported compounds for comparison, are given in Table 3.

2. Results and discussion

Tropane ring analogs of paroxetine (**2**) were designed as potential inhibitors of serotonin reuptake based on the structural similarity and known biological activity among the two classes of compounds. Although 3-(4-fluorophenyl)tropanes (**4**) and paroxetine are structurally similar, they possess distinct differences in conformational flexibility. Importantly, the difference between paroxetine and the tropane/paroxetine hybrid structures (**4a–i**) is the presence of an ethylene bridge, which imparts increased steric bulk and reduces conformational heterogeneity. Paroxetine is a flexible molecule capable of existing in solution as an interconverting population of the conformers, C*aa*, B*ee*, C*ee*, and B*aa* (Fig. 4). The tropane/paroxetine hybrid structures can adopt analogous conformations, however, the chair form analogous to *Caa* (2β,3α) can only convert to the boat form analogous to B*ee* and the chair form analogous to C*ee* (2α,3β) can only convert to the boat form analogous to*aa*. Interconversion of C*aa* and C*ee* (and B*ee*/B*aa*) in

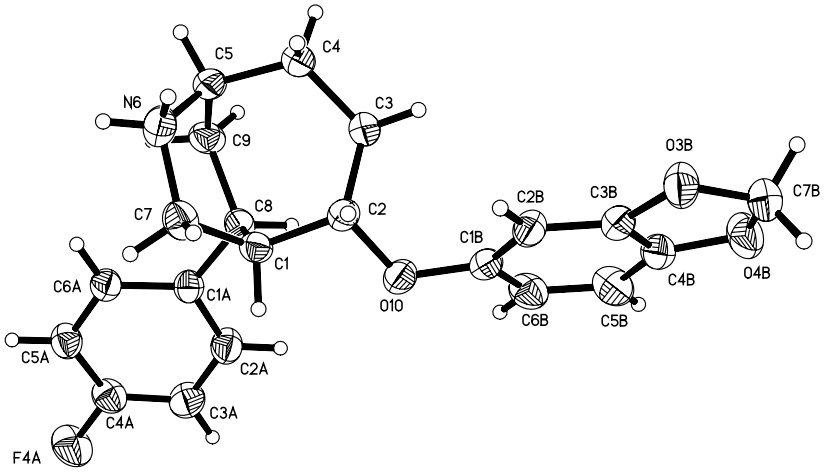
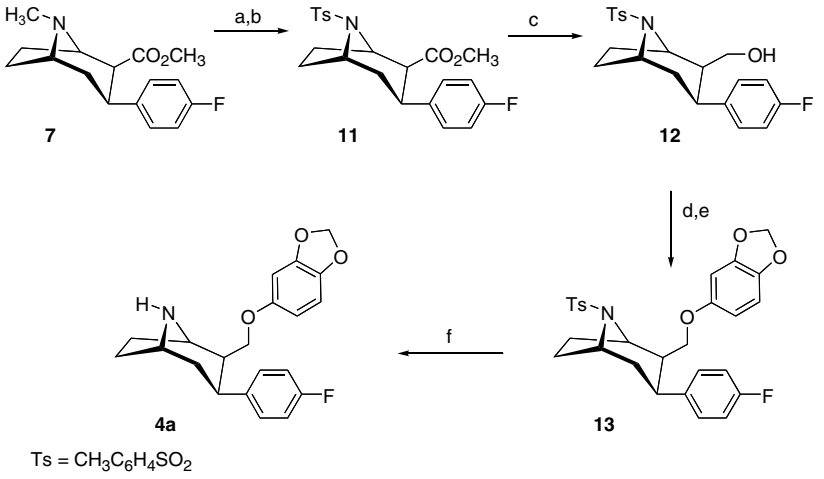


Figure 1. Structure of compound **6b** as determined by X-ray diffraction. Thermal ellipsoids are shown at the 30% probability level, hydrogen atoms are shown as circles of an arbitrary radius.

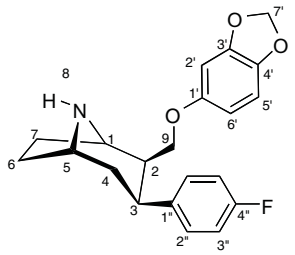


Scheme 2. Reagents and conditions: (a) (1) 1-chloroethyl chloroformate, 1,2-dichloroethane, reflux; (2) MeOH reflux; (b) *p*-toluenesulfonyl chloride, triethylamine; (c) $LiAlH_4$, THF, rt; (d) trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2; (e) Na, sesamol, THF; (f) 5% Na/Hg amalgam, Na_2HPO_4, MeOH.

the tropane analogs is impossible due to the ethylene bridge. NMR analysis indicates that in solution a flattened boat conformation is preferred for **4d** (2β,3α) and that **4i** (2α,3β) exists predominately as a chair.[10] Confirmation of the NMR data was obtained through single crystal X-ray analysis, which demonstrated that **4d** exists in the boat conformation (Fig. 3). Therefore, compound **4d** represents a rigid analog of the B*ee* conformation of paroxetine and compound **4i** represents the C*ee* paroxetine conformation. Radioligand binding studies showed that when compared to paroxetine, **4d**, has a 20-fold reduced affinity for the 5-HTT and 156- and 38-fold enhancement of affinity for the DAT and the NET, respectively. The affinities of **4i** at the 5-HTT and NET are reduced by 170- and 3-fold, respectively, compared to paroxetine; however, affinity for the DAT is enhanced 22-fold. The striking difference in the affinity profiles between **4d**,**i**, and paroxetine may be attributable to increased steric bulk introduced by the ethylene bridge, or may imply that the active conformation of paroxetine at the 5-HTT is not mimicked by either **4d** or **4i**. Unfortunately, the remaining two conformers of paroxetine are not mimicked in tropane-paroxetine hybrid structures.

In an attempt to further elucidate the effects of stereochemistry on the binding affinity of rigid paroxetine-like structures, tropane analogs **4e** and **4h** were prepared to represent the mirror images of paroxetine conformations *Bee* and *Cee*, respectively. This change in stereochemistry, had only a modest effect at 5-HTT, but significantly reduced affinity at DAT and NET (Table 3). Radioligand binding studies of the 2β,3β-isomer **4a**, revealed relatively high affinity at the 5-HTT (K_i = 0.2 nM), DAT (3 nM), and NET (K_i = 4.0 nM). Since several (1*R*)-3β-(*para*-substituted-phenyl)tropane-2β-carboxylic acid esters possess high affinity at the 5-HTT;[13] this observation is not surprising. However, the relatively small differences between the affinity of **4a** (2β,3β) and **4d** (2β,3α) at all three transporters is striking; it suggests that stereochemistry at C-3 is irrelevant in this case. Indeed, an overlay of the X-ray struc-

Table 2. NMR assignments for **4a** obtained in $CDCl_3$



Assignment	Carbon (δ)	Proton (δ)	HMBC correlations
6	28.93	1.79, 1.86	H4,H7,
7	30.16	1.86, 2.00	H6,H4,H5
4	33.98	1.59, 2.12	H3,H6
3	35.10	3.24	H4,H5,H9,H2″
2	44.91	2.06	H9,H9,H3,H4
5	54.70	3.68	H4,H6,
1	56.68	3.81	H9,H9
9	67.67	3.41, 3.97	H3,H1
2′	97.93	6.31	H6′
7′	100.96	5.85	—
5′	105.70	6.11	—
6′	107.76	6.60	—
3″	115.11	6.99	H6″
2″	128.66	7.13	H3″,H2″
1″	138.30	—	H3″,H2″
3′	141.40	—	H5′
4′	148.03	—	H2′
1′	154.35	—	H5′
4″	161.34	—	H2″

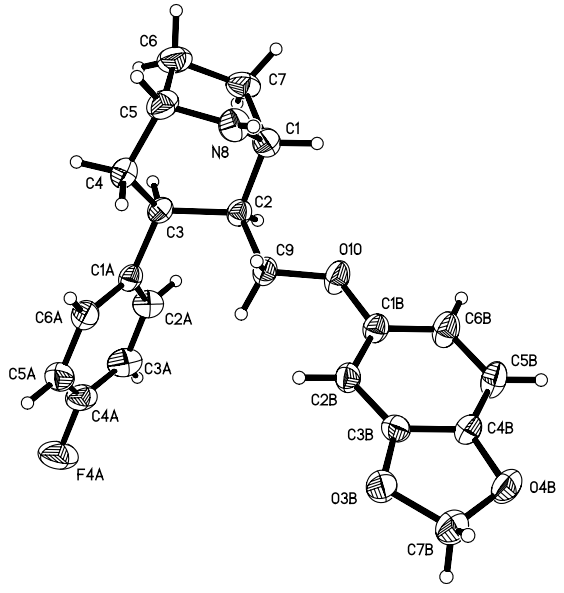


Figure 2. Structure of compound **4a** as determined by X-ray diffraction. Thermal ellipsoids are shown at the 30% probability level, hydrogen atoms are shown as circles of an arbitrary radius.

tures of **4a** and **4d** (Fig. 5) demonstrates that the orientation of the aromatic rings is remarkably similar despite the difference in stereochemistry at C-3. This is of particular interest since the side-chains of **4a** and **4d** are flexible and could potentially interact with the transporters in a similar manner.

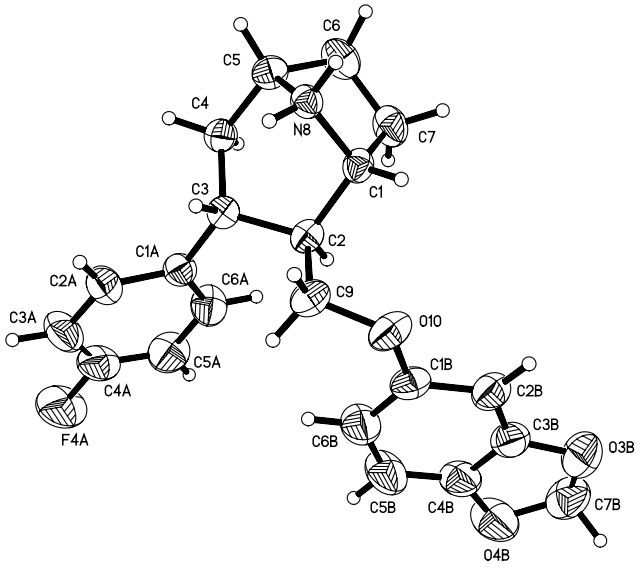


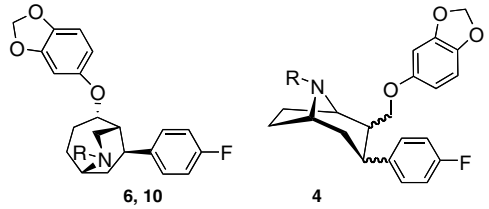
Figure 3. Structure of compound **4d** as determined by X-ray diffraction. Thermal ellipsoids are shown at the 30% probability level, hydrogen atoms are shown as circles of an arbitrary radius.

Taken together these results suggest that tropane/paroxetine hybrid structures **4a**–**i** interact differently than paroxetine at monoamine transporters. The reduced conformational flexibility of **4a** and **4d** may contribute to the high affinity of these analogs by maximizing their residence in conformations favored for these transporters. The greater flexibility of paroxetine permits conformational heterogeneity therefore allowing paroxetine to adopt a conformation favored by the 5-HTT, which cannot be achieved by the structurally-rigid tropane ring analogs **4a** and **4d**.

Compounds **10a**, **10b**, **6a**, and **6c** were prepared as a result of an unexpected intermolecular nucleophilic addition and subsequent ring opening with sesamol. The affinity and selectivity of these compounds is not particularly noteworthy with the exception of (1*S*) **10b**. Compound **10b** possesses moderate affinity for the 5-HTT and displays selectivity for the 5-HTT (11- and 119-fold relative to the DAT and NET). Although these compounds were prepared inadvertently, some interesting biological data may be gleaned from further study of this novel ring system.

The previously reported attempt to synthesize **4a** resulted in the isolation of the rearranged product **10a** instead of the expected intermediate *N*-methyl derivative of **4a**. Furthermore, we incorrectly identified **10a** as the expected tropane. Our incorrect identification was made based on the similarity of the proton and carbon NMR spectra between the isolated product **10a** and the anticipated structure *N*-methyl **4a**. Specifically, the carbon resonance at 50.24 ppm had been attributed to the alkoxy methylene carbon C-9 in structure **4a** (Table 2) instead of the methylene C-7 of **10a** (Table 1). On this basis the chemical shifts and proton coupling patterns determined via a COSY spectrum were self-consistent and therefore further supported the incorrect assignment. Subsequently, we have employed a more detailed

Table 3. Comparison of transporter binding affinity for isomers of **10**, **6**, and **4**



Compd	R	Stereochemistry		IC_{50}, nM (K_i, nM)[a]		
		2	3	5-HTT	DAT	NET
				[^{3}H]Paroxetine	[^{3}H]WIN 35,428	[^{3}H]Nisoxetine
Paroxetine[b]				0.3 ± 0.02 (0.03 ± 0.001)	623 ± 25	535 ± 15 (322 ± 9.0)
(1*R*)-**10a**	CH_3			294 ± 18 (27 ± 1.6)	308 ± 20	5300 ± 450 (3200 ± 270)
(1*S*)-**10b**	CH_3			88 ± 3 (8 ± 0.3)	1050 ± 45	27,600 ± 1100 (16,600 ± 660)
(1*R*)-**6b**	H			480 ± 21 (44 ± 1.9)	835 ± 90	37,400 ± 1400 (22,500 ± 840)
(1*S*)-**6c**	H			424 ± 15 (39 ± 1.4)	1210 ± 33	17,300 ± 1800 (10,400 ± 1080)
(1*R*)-**4a**	H	β	β	2 ± 0.7 (0.2 ± 0.06)	3 ± 0.6	6 ± 0.3 (4 ± 0.2)
(1*R*)-**4b**[b]	CH_3	β	α	422 ± 16 (38 ± 1.5)	3 ± 0.2	123 ± 9.5 (74 ± 5.7)
(1*S*)-**4c**[b]	CH_3	β	α	178 ± 13 (16 ± 1.2)	298 ± 17	12,400 ± 720 (7500 ± 430)
(1*R*)-**4d**[b]	H	β	α	6 ± 0.2 (0.5 ± 0.02)	4 ± 0.2	14 ± 1.3 (8.4 ± 0.78)
(1*S*)-**4e**[b]	H	β	α	19 ± 1.8 (1.7 ± 0.2)	407 ± 33	1990 ± 176 (1200 ± 106)
(1*R*)-**4f**[b]	CH_3	α	β	53 ± 3.6 (4.8 ± 0.3)	172 ± 8.8	26,600 ± 1200 (16,000 ± 720)
(1*S*)-**4g**[b]	CH_3	α	β	447 ± 47 (41 ± 4.3)	1500 ± 74	2916 ± 1950 (1750 ± 1170)
(1*R*)-**4h**[b]	H	α	β	90 ± 3.4 (8.2 ± 0.3)	142 ± 13	2500 ± 250 (1500 ± 150)
(1*S*)-**4i**[b]	H	α	β	56 ± 5.6 (5.1 ± 0.5)	28 ± 2.4	1690 ± 150 (1020 ± 90)

[a] Data are mean ± standard error of three or four experiments with triplicate values at each concentration.
[b] IC_{50} values were obtained from previous studies.[10]

analysis using gradient enhanced COSY, HSQC, and HMBC NMR spectra for structural assignment. The complete proton and carbon assignments of **10a** are presented in Table 1. Stereochemical assignments were made using a ROESY NMR spectrum. The relative stereochemistry is identified by observation of a through space correlation between H-2 and one of the H-7 protons and between the aromatic proton H-2″and the other H-7 proton. This sets the stereochemistry of both H-2 and the 4-fluorophenyl group as *syn* to the azamethylene bridge.

The structure of **4a** was also determined by gradient enhanced COSY, HSQC, HMBC, and ROESY NMR spectra (Table 2). The protons of the sesamoyl and 4-fluorophenyl group were identified by the characteristic 1,3,5-trisubstitiution and 1,4-disubstitution coupling patterns, respectively, with the latter being modified by fluorine–proton coupling interactions. H-3 was identified by the long-range proton–carbon correlations between H-3 and the carbons of the 4-fluorophenyl group observed in a gradient HMBC experiment. Carbon C-9 was identified as the methylene carbon with a chemical shift of 67.67 ppm, which is reasonable for an oxymethylene carbon. A gradient COSY spectrum shows a vicinal coupling of both H-9 protons to a methine proton, which in turn is coupled, to H-3 thus identifying the methine proton as H-2. Likewise a coupling between H-2 and a methine proton at 3.81 ppm identifies the methine resonance as H-1. A long-range proton–carbon correlation between H-3 and a methylene carbon identified C-4. The protons on C-4 show a vicinal coupling to a methine proton identified as H-5. Their mutual proton couplings and their proximity to either H-5 or H-1 assigned the remaining low field protons as H-6 and H-7, respectively. The methylene protons at 5.85 ppm were assigned to the methylenedioxy moiety C-7′ based on the characteristic chemical shift. The complete assignment of the proton and carbon spectra of **4a** is presented in Table 2. The stereochemistry was identified by the observation of a correlation in the ROESY spectrum between H-9 and H-4β. This interaction is possible only if C-9 and H4β are diaxial. Furthermore, an interaction between H-2″ and both H-9 and H-4β indicates that the fluorophenyl group is equatorial. An axial C-9 and equatorial 4-fluorophenyl group is consistent with the expected 2β,3β tropane.

3. Conclusion

Tropane ring analogs **4a**–**i** of paroxetine (**2**) were prepared in order to gain a better understanding of the conformational requirements for high affinity and selectivity at the 5-HTT. Ligand binding inhibition data demonstrate that tropane-derived analogs of paroxetine (**4a**–**i**) interact with the 5-HTT in a manner distinct from paroxetine. Paroxetine displays higher affinity and selectivity than the two most potent tropane analogs **4a** (2β,3β) and **4d** (2β,3α). Both **4a** and **4d** have a nonselective profile with respect to the 5-HTT, NET, and DAT and possess moderate affinity at all three transporters. These

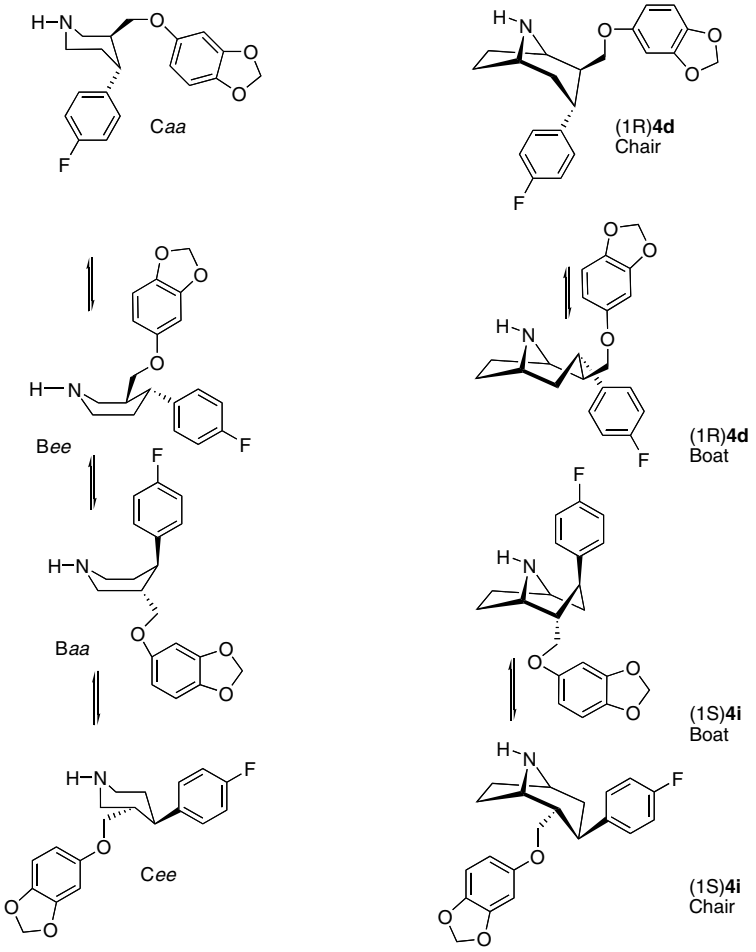


Figure 4. Potential conformations of paroxetine **2** and the analogous tropanes **4d** and **4i**. B and C indicate boat and chair conformations while *aa* and *ee* are axial–axial and equatorial–equatorial.

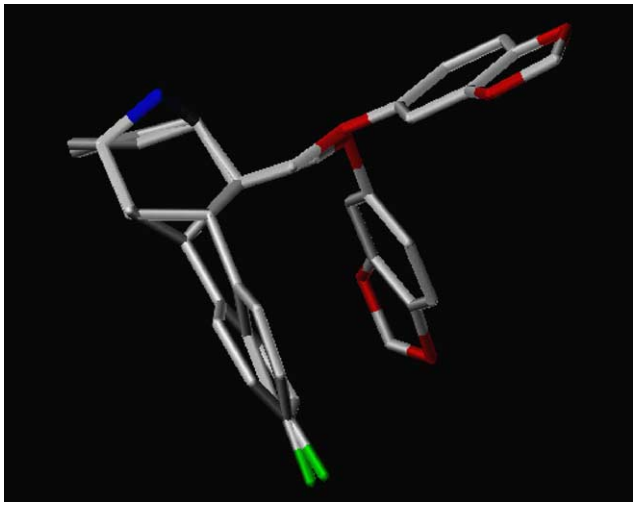


Figure 5. A superimposition of the X-ray crystal structures of **4a** and **4d**.

results suggest that greater flexibility of paroxetine permits conformational heterogeneity therefore allowing paroxetine to obtain a conformation favored by the 5-HTT, which cannot be achieved by the structurally-rigid tropane ring analogs **4a** and **4d**.

4. Experimental

Melting points were determined using a Thomas Hoover melting point apparatus and were uncorrected. Magnetic resonances (^{1}H NMR and ^{13}C NMR) were obtained with a Bruker AMX 500 MHz and a Bruker Avance DPX 300 MHz spectrometer using tetramethylsilane as an internal standard. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol lII polarimeter (1 dm cell). Thin layer chromatography (TLC) was carried out using Whatman and Merck silica gel 60 TLC plates. Medium pressure column chromatography was performed using silica gel 60, 0.040–0.063 mm (230–400 mesh), EM Science. All chemicals were purchased from Aldrich Chemical Co., Inc. and were used without further purification. Elemental analysis was conducted by Atlantic Microlab, Norcross, GA. Results were within ±0.4% of the critical values

4.1. (1*R*)-2β-[(3,4-Methylenedioxy)phenoxy]methyl-3β-(4-fluorophenyl)nortropane tartrate (4a)

(1*R*)-2β-[(3,4-Methylenedioxy)phenoxy]methyl-3β-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane **13** (0.5 g, 0.98 mmol) was added to a suspension of Na_2HPO_4

(0.69 g, 4.9 mmol) and 5% Na/Hg amalgam (10 g, 50 mmol) in anhydrous MeOH (35 mL). The reaction was heated at reflux for 3 h and allowed to cool to room temperature. Water (100 mL) and NH_4OH (100 mL) were added, and the mixture was extracted with CH_2Cl_2 (3×100 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a tan solid. The solid was purified using medium pressure column chromatography ($CHCl_3$/MeOH/NH_4OH, 9:0.9:0.1) to provide a tan solid (0.27 g, 78%). Mp 122–123 °C. The tartrate salt was prepared by adding D(−)-tartaric acid to the amine in 2-propanol. The suspension was heated until the salt dissolved, cooled, and the solid precipitate **4a** was collected. Mp 183–185 °C; $[\alpha]_D^{22}$ −10.3 (*c* 0.46, MeOH). ^{1}H NMR (CD_3OD): δ 1.88 (m, 1H), 2.11–2.33 (m, 5H) 2.63 (dd, J = 13.8, 13.8 Hz, 1H), 3.53–3.67 (m, 2H), 3.80 (dd, J = 3.3, 10 Hz, 1H), 4.25 (m, 1H), 4.3 (m, 3H), 5.8 (s, 2H, O–CH_2–O), 6.29 (dd, J = 2.4, 8.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 7.03 (m, 2H, Ar–H), 7.31 (m, 2H, Ar–H). Anal. Calcd for $C_{29}H_{28}FNO_9$: C, 59.40; H, 5.58; N, 2.77. Found: C, 59.03; H, 5.58; N. 2.70.

4.2. (1*R*)-2β-[(3,4-Methylenedioxy)phenoxy]methyl-3α-(4-fluorophenyl)nortropane tartrate (4d).

The title compound was prepared in a manner analogous to **4a**. The resulting oil was purified using medium pressure column chromatography ($CHCl_3$/MeOH/NH_4OH, 90:9:1) to provide a colorless oil (0.22 g, 63%). The tartrate salt was prepared by the addition of 1.1 equiv of D(−)-tartaric acid to the amine in 2-propanol. The suspension was heated until the solid dissolved, cooled, and the salt precipitated with anhydrous Et_2O. The solid was collected and recrystallized from EtOH/Et_2O to provide **4d** as a white solid. Mp 177–179 °C. $[\alpha]_D^{22}$ −82.12 (*c* 0.47, MeOH). ^{1}H NMR (CD_3OD): δ 1.58–1.67 (m, 1H), 1.89–2.24 (m, 5H), 2.45–2.50 (m, 1H), 2.83–2.89 (m, 1H), 3.54–3.69 (m, 2H), 5.77 (s, 2H), 6.18–6.21 (dd, J = 2.4, 8.4 Hz, 1H), 6.40–6.41 (d, J = 2.4 Hz, 1H), 6.94–7.0 (m, 2H), 7.21–7.26 (m, 2H).

4.3. (1*R*,2*S*,5*S*,8*S*)-2-[(3,4-Methylenedioxy)phenoxy]-8-(4-fluorophenyl)-6-aza-bicyclo[3.2.2]nonane tartrate (6b)

1-Chloroethyl chloroformate (0.62 g, 4.63 mmol) was added under N_2 to a suspension of 1,8-bis(dimethylamino)naphthalene (0.02 g, 0.09 mmol) and **10a** (0.14 g, 0.68 mmol) in CH_2Cl_2 (10 mL). The suspension was heated at reflux for 24 h and was concentrated under reduced pressure to provide a red oil. The oil was dissolved in MeOH (10 mL) and heated at reflux for 24 h. The solvent was removed under reduced pressure, and the reaction was made basic with NH_4OH. The biphasic mixture was then extracted with CH_2Cl_2 (3×75 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide an orange oil. The oil was purified using medium pressure column chromatography (50% 9:1, Et_2O/Et_3N; 50% 8:1.8:0.2, $CHCl_3$/MeOH/NH_4OH) to provide a pink oil (0.08 g, 61.9%). The oil was converted to a tartrate salt using D(−)-tartaric acid in EtOAc. The solid was collected and recrystallized from EtOH/Et_2O to provide **6b** as a white powder. Mp 183–184 °C. $[\alpha]_D^{22}$ +10.6 (*c* 0.36, MeOH). ^{1}H NMR (CD_3OD): δ 1.98–2.37 (m, 7H), 3.24–3.42 (m, 2H), 3.72 (m, 1H), 3.87 (s, 1H), 4.42 (s, 2H), 4.55 (s, 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). Anal. Calcd for $C_{29}H_{28}FNO_9$: C, 59.40; H, 5.58; N, 2.77. Found: C, 59.27; H, 5.63; N, 2.70.

4.4. (1*S*,2*R*,5*R*,8*R*)-2-[(3,4-Methylenedioxy)phenoxy]-8-(4-fluorophenyl)-6-aza-bicyclo[3.2.2]nonane tartrate (6c)

Trichloroethyl chloroformate (0.08 g, 3.77 mmol) was added under N_2 to a suspension of potassium carbonate (0.05 g, 0.36 mmol) and **10b** (0.39 g, 1.07 mmol) in toluene (10 mL). The suspension was heated at reflux for 24 h, and H_2O (50 mL) and $CHCl_3$ (100 mL) were added. The biphasic mixture was extracted with $CHCl_3$ (3×100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The oil was then dissolved in glacial acetic acid (6 mL), and Zn dust (1.0 g) was added in small portions. The slurry was then allowed to stir at room temperature for 12 h. Water (50 mL) and $CHCl_3$ (100 mL) were added, and the reaction was filtered through Celite. The biphasic mixture was made basic with NH_4OH and extracted with $CHCl_3$ (3×100 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated under reduced pressure to provide an oil. The oil was purified using medium pressure column chromatography (50% 9:1, Et_2O/Et_3N; 50% 8:1.8:0.2, $CHCl_3$/MeOH/NH_4OH) to provide an oil (0.12 g, 26%). The oil was converted to a tartrate salt using L(+)-tartaric acid in EtOH. The solid was collected and recrystallized from EtOH/Et_2O to provide **6c** as a tan powder. Mp 180–184 °C. $[\alpha]_D^{22}$ −10.3 (*c* 0.30, MeOH). ^{1}H NMR (CD_3OD): δ 1.98–2.37 (m, 7H), 3.24–3.42 (m, 2H), 3.72 (m, 1H), 3.87 (s, 1H), 4.42 (s, 2H), 4.55 (s, 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). Anal. Calcd for $C_{29}H_{28}FNO_9$: C, 59.40; H, 5.58; N, 2.77. Found: C, 59.22; H, 5.61; N. 2.74.

4.5. (1*R*)-2β-Hydroxymethyl-3β-(4-fluorophenyl)tropane (8)

(1*R*)-2β-Carbomethoxy-3β-(4-fluorophenyl)tropane **7**[10] (1.01 g, 3.61 mmol) in Et_2O (10 mL) was added under N_2 in a dropwise manner to an ice-cold solution of $LiAlH_4$ (0.19 g, 5.01 mmol) in Et_2O (20 mL). The suspension was allowed to warm to room temperature while stirring was continued (3 h). The suspension was cooled to 0 °C, and saturated NH_4Cl (≈3 mL) was added. The suspension was allowed to warm to room temperature, water was added, and the suspension was extracted with Et_2O (3×100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a white solid. The solid was recrystallized from hexane to provide **8** (0.56 g, 62%) as a white solid. Mp 75–78 °C. ^{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).

4.6. (3*R*,4*S*,6*S*,9*R*)-1-Methyl-4-(4-fluorophenyl)-1-azonium-tricyclo[4.3.0.0^{3,9}]nonane mesylate (9)

Methanesulfonyl chloride (0.30 g, 2.6 mmol) was added dropwise at 0 °C under N_2 to a solution of triethylamine (0.22 g, 2.16 mmol) and **8** (0.46 g, 1.86 mmol) in CH_2Cl_2 (15 mL). The reaction was allowed to stir at 0 °C for 0.5 h and then at room temperature for 3 h. Water and CH_2Cl_2 were added, and the suspension was made basic (pH 10) with NH_4OH. The CH_2Cl_2 was removed, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a colorless oil. Toluene (100 mL) was added, and the suspension was heated at reflux for 1 h. The toluene was removed under reduced pressure to provide **9** (0.58 g, 95%) as a white semisolid, which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 2.09 (m, 1H), 2.30 (m, 3H), 2.57 (m, 1H), 2.78 (s, 3H), 2.93 (m, 2H), 3.28 (s, 3H), 3.37 (m, 1H), 4.45 (m, 1H), 4.56 (m, 1H), 4.69 (m, 1H), 5.35 (m, 1H), 7.02 (m, 2H), 7.22 (m, 2H).

4.7. (1*R*,2*S*,5*S*,8*S*)-2-[(3,4-Methylenedioxy)phenoxy]-8-(4-fluorophenyl)-6-methyl-6-aza-bicyclo[3.2.2]nonane tartrate (10a)

Sesamol (0.56 g, 4.08 mmol) in anhydrous THF (10 mL) was added under N_2 at 0 °C to a suspension of NaH (60% dispersion, 0.17 g, 4.30 mmol, washed 2 × 10 mL with hexanes) in anhydrous THF (10 mL). The reaction was allowed to warm to room temperature over 1 h. (3*R*,4*S*, 6*S*,9*R*) 1-Methyl-4-(4-fluorophenyl)-1-azonium-tricyclo[4.3.0.0^{3,9}]nonane mesylate **9** (0.58 g, 2.6 mmol) in THF (10 mL) was added at 0 °C in a dropwise manner over 10 min. The reaction was allowed to warm to room temperature and was heated at reflux for 3 h. Water (100 mL) and concentrated NH_4OH were added until the aqueous layer was basic (pH ≈ 10), and the biphasic mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a yellow oil. The oil was purified using medium pressure column chromatography (30% 9:1 Et_2O/EtN, 70% hexane) to provide an oil (0.33 g, 44%). The oil was converted to a tartrate salt with D(−)-tartaric acid in EtOAc. The resulting solid was collected and recrystallized from 2-propanol/Et_2O to provide **10a** as a white powder. Mp 97 °C (fusion). $[\alpha]_D^{25}$ +11.8 (*c* 0.27, MeOH). ^{1}H NMR (CD_3OD): δ 2.0–2.43 (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).

4.8. (1*S*,2*R*,5*R*,8*R*)-1-[(3,4-Methylenedioxy)phenoxy]-8-(4-fluorophenyl)-6-methyl-6-aza-bicyclo[3.2.2]nonane tartrate (10b)

Sesamol (1.4 g, 10.2 mmol) in anhydrous THF (10 mL) was added under N_2 at 0 °C to a suspension of NaH (60% dispersion, 0.41 g, 10.2 mmol, washed 2 × 10 mL with hexanes) in anhydrous THF (10 mL). The reaction was allowed to warm to room temperature over 1 h. (3*S*,4*R*,6*R*,9*S*)-1-Methyl-4-(4-fluorophenyl)-1-azonium-tricyclo[4.3.0.0^{3,9}]nonane mesylate **17** (1.66 g, 7.6 mmol) in THF (20 mL) was added at 0 °C in a dropwise manner over 10 min. The reaction was allowed to warm to room temperature and was heated at reflux for 3 h. Water (100 mL) and concentrated NH_4OH were added until the aqueous layer was basic (pH ≈ 10), and the biphasic mixture was extracted with CH_2Cl_2 (3 × 150 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a yellow oil. The oil was purified using medium pressure column chromatography (30% 9:1 Et_2O/EtN, 70% hexane) to provide an oil (1.02 g, 69%). The oil was converted to a tartrate salt with D(−)-tartaric acid in EtOAc. The resulting solid was collected and recrystallized from 2-propanol/Et_2O to provide **10b** as a white powder. Mp 90 °C (fusion). $[\alpha]_D^{25}$ −26.8 (*c* 0.63, MeOH). ^{1}H NMR (CD_3OD): δ 2.0–2.43 (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).

4.9. (1*R*)-2β-Carbomethoxy-3β-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane (11)

Tosylchloride (4 g, 20.9 mmol) was added under N_2 to a solution of (1*R*)-2β-carbomethoxy-3β-(4-fluorophenyl)nortropane[9] (5 g, 19 mmol) in triethylamine (150 mL) at −10 °C. The reaction was allowed to stir for 10 h before water (200 mL) and CH_2Cl_2 (150 mL) were added. The mixture was then extracted with CH_2Cl_2 (3 × 150 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a white solid. The solid was then recrystallized from MeOH/toluene to provide **11** (6.27 g, 79%) as a white solid. Mp 195–197 °C. ^{1}H NMR ($CDCl_3$): δ 1.6–2.1(m, 5H) 2.42 (s, 3H, Ar–CH_3), 2.67 (ddd, *J* = 3, 9.6, 9.6 Hz, 1H), 2.92 (m, 1H), 3.1 (m, 1H), 3.35 (s, 3H, OCH_3), 4.45 (m, 1H), 4.59 (m, 1H), 6.93 (m, 2H, Ar–H), 7.17 (m, 2H, Ar–H), 7.28 (d, *J* = 9 Hz, 2H, Ar–H), 7.77 (d, *J* = 9 Hz, 2H, Ar–H).

4.10. (1*R*)-2β-Hydroxymethyl-3β-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane (12)

(1*R*)-2β-Carbomethoxy-3β-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane **11** (6.0 g, 14.37 mmol) in anhydrous THF (50 mL) was added under N_2 to a suspension of $LiAlH_4$ (1.64 g, 43.11 mmol) in anhydrous THF (300 mL) at 0 °C. The reaction was allowed to stir at room temperature for 1 h. Water (1.65 mL) and 10% NaOH (1.65 mL) were cautiously added followed by Celite (2 g). The slurry was then filtered through a sintered glass filter, and the filtrate was concentrated under reduced pressure to provide a white solid. The solid was recrystallized from toluene/ethanol to provide **12** (5.4 g, 96%) as a white solid. Mp 154–156 °C. ^{1}H NMR ($CDCl_3$): δ 1.4–1.7 (m, 5H) 2.01 (m, 1H), 2.34 (ddd, *J* = 3, 10.2, 10.2 Hz, 1H), 2.44 (s, 3H, Ar-CH_3), 3.03 (m, 1H), 3.16 (m, 1H), 3.81 (m, 1H) 4.45 (m, 2H), 6.98 (m, 2H, Ar–H), 7.09 (m, 2H, Ar–H), 7.32 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.77 (d, *J* = 8.5 Hz, 2H, Ar–H).

4.11. (1*R*)-2β-[(3,4-Methylenedioxy)phenoxy]methyl-3β-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane (13)

Trifluoromethanesulfonic anhydride (2.17 g, 7.70 mmol) was added dropwise at −78 °C under N_2 to a solution of **12** (2.0 g, 5.13 mmol) in pyridine (0.49 g, 6.16 mmol) and CH_2Cl_2 (50 mL). The reaction was allowed to stir at −78 °C for 1 h and then warmed to room temperature. Water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide crude (1*R*)-2β-trifluoromethanesulfonyloxymethyl-3β-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane as a white solid. The desired compound was used in the next step without further purification.

Sodium (0.14 g, 6.20 mmol) was added under N_2 to a solution of sesamol (0.79 g, 5.64 mmol) in anhydrous THF (35 mL). The reaction was allowed to stir at room temperature until all of the sodium had dissolved (about 2 h). The sodium sesamol solution was then added under N_2 to a solution of (1*R*)-2β-trifluoromethanesulfonyloxymethyl-3β-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane (2.68 g, 5.13 mmol) in CH_2Cl_2 (15 mL). The solution was allowed to stir at room temperature for 12 h. Water (100 mL) and 10% NaOH (20 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to provide a white solid. The solid was recrystallized from MeOH/toluene to provide **13** (1.56 g, 58%) as a white solid. mp 173–175 °C. ^{1}H NMR ($CDCl_3$): δ 1.7–2.1(m, 5H) 2.20 (m, 2H), 2.30 (s, 3H, Ar–CH_3), 3.2 (dd, *J* = 4, 9 Hz, 1H), 3.27 (m, 1H), 3.69 (dd, *J* = 12.6, 12.6 Hz, 1H), 4.47 (m, 1H), 4.57 (m, 1H), 5.87 (s, 2H, O–CH_2–O), 5.96 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.12 (d, *J* = 2.7 Hz, 1H), 6.27 (d, *J* = 12 Hz, 1H), 7.01 (m, 2H, Ar–H), 7.09 (m, 4H, Ar–H), 7.68 (d, J = 8.4 Hz, 2H, Ar–H).

4.12. (1*R*)-2β-Carbomethoxy-3α-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane (14)

The title compound was prepared in a manner analogous to that of **11**. The resulting solid was recrystallized from toluene to provide **14** as a white solid (0.70 g, 68%). Mp 187–189 °C. ^{1}H NMR ($CDCl_3$): δ 1.04–1.70 (m, 4H), 1.95–1.98 (m, 1H), 2.43 (s, 3H), 2.47–2.57 (m, 2H), 3.19–3.28 (dd, *J* = 9.9, 17 Hz, 1H), 4.33–4.38 (dd, *J* = 7.2, 15 Hz, 1H), 4.43–4.46 (d, *J* = 7.2 Hz, 1H), 6.90–6.98 (m, 2H), 7.10–7.15 (m, 2H), 7.29–7.32 (d, *J* = 8.4 Hz, 2H), 7.78–7.80 (d, *J* = 8.2 Hz).

4.13. (1*R*)-2β-Hydroxymethyl-3α-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane (15)

The title compound was prepared in a manner analogous to that of **12**. The resulting solid was recrystallized from toluene to provide **15** as a white solid (0.56 g, 90%). Mp 165–167 °C. ^{1}H NMR ($CDCl_3$): δ 1.33–1.57 (m, 4H), 1.72–1.79 (m, 2H), 2.03 (br s, 1H), 2.43 (s, 3H), 2.46–2.66 (m, 2H), 3.51–3.53 (d, *J* = 6 Hz, 2H), 4.28–4.33 (m, 2H), 6.89–7.02 (m, 2H), 7.11–7.18 (m, 2H), 7.28–7.31 (d, *J* = 8.1 Hz, 2H), 7.74–7.77 (d, *J* = 8.1 Hz).

4.14. (1*R*)-2β-[(3,4-Methylenedioxy)phenoxy]methyl-3α-(4-fluorophenyl)-8-(4-methyl benzenesulfonyl)tropane (16)

The title compound was prepared in a manner analogous to that of **13**. The resulting solid was purified using medium pressure column chromatography (petroleum ether/acetone, 8:2). The solid was recrystallized from toluene/petroleum ether to provide **16** as a white solid (0.60 g, 77%). Mp 170–172 °C. ^{1}H NMR ($CDCl_3$): δ 1.27–1.37 (m, 1H), 1.45–1.62 (m, 3H), 1.83–1.99 (m, 2H), 2.39 (s, 3H), 2.46–2.63 (m, 2H), 3.49–3.53 (m, 1H), 3.56–3.66 (m, 1H), 4.29–4.31 (d, *J* = 7.5 Hz, 1H), 4.36–4.40 (dd, *J* = 5.7, 13 Hz, 1H), 5.89 (s, 2H), 6.12–6.15 (dd, *J* = 3, 8.4 Hz, 1H), 6.32 (d, *J* = 3 Hz, 1H), 6.64–6.70 (d, *J* = 18 Hz, 1H), 6.88–6.99 (m, 2H), 7.11–7.16 (m, 2H), 7.22–7.25 (d, *J* = 8.4 Hz, 2H), 7.73–7.76 (d, *J* = 8.1 Hz, 2H).

4.15. (3*S*,4*R*,6*R*,9*S*)-1-Methyl-4-(4-fluorophenyl)-1-azonium-tricyclo[4.3.0.0^{3,9}]nonane mesylate (17)

Methanesulfonyl chloride (0.74 g, 6.46 mmol) was added dropwise at 0 °C under N_2 to a solution of triethylamine (0.73 g, 7.2 mmol) and (1*S*)-2β-hydroxymethyl-3β-(4-fluorophenyl)tropane[10] (1.0 g, 4.02 mmol) in CH_2Cl_2 (15 mL). The reaction was allowed to stir at 0 °C for 0.5 h and then at room temperature for 3 h. Water and CH_2Cl_2 were added, and the suspension was made basic (pH 10) with NH_4OH. The CH_2Cl_2 was removed, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to provide a colorless oil. Toluene (100 mL) was added, and the suspension was heated at reflux for 1 h. The toluene was removed under reduced pressure to provide crude **17** (1.67 g) as a yellow semisolid that was used without further purification. ^{1}H NMR ($CDCl_3$): δ 2.09 (m, 1H), 2.30 (m, 3H), 2.57 (m, 1H), 2.78 (s, 3H), 2.93 (m, 2H), 3.28 (s, 3H), 3.37 (m, 1H), 4.45 (m, 1H), 4.56 (m, 1H), 4.69 (m, 1H), 5.35 (m, 1H), 7.02 (m, 2H), 7.22 (m, 2H).

Supporting information available: Crystallographic data for the structures **4a**,**d**, and **6b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 252218, 252219, and 252220, respectively. Copies can be obtained free of charge by application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: + 44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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