Structure−Activity Relationship Comparison of (*S*)-2*β*-Substituted 3α-(Bis[4-fluorophenyl]methoxy)tropanes and (*R*)-2*β*-Substituted 3*β*-(3,4-Dichlorophenyl)tropanes at the Dopamine Transporter

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Extensive structure−activity relationships at the dopamine transporter (DAT) have been developed around two classes of tropane-based ligands. Opposing stereoselectivity and divergent structural requirements for optimal DAT binding suggest that these tropane-based DAT inhibitors may not access identical binding domains. To further investigate this hypothesis, a series of (*S*)-2*β*-carboalkoxy-3α-(bis[4-fluorophenyl]methoxy)tropanes (**11a**−**f**, **13**−**16**) and their identically (*R*)-2*β*-substituted 3*β*-(3,4-dichlorophenyl)tropanes (**3**, **5a**−**d**) were prepared and evaluated for binding at the DAT and for inhibition of [^{3}H]dopamine uptake in rat brain. These studies showed that most of the identically 2-carboalkoxy-substituted analogues, within the two classes of compounds, bind with high affinity to DAT (K_i = 5.5−100 nM), albeit with opposite stereochemistry. However, the larger azido- (**15**) and isothiocyanato- (**16**) (*S*)-2*β*-carbophenylethoxy-3α-(bis[4-fluorophenyl]methoxy)tropanes demonstrated a significant decrease in DAT binding potency (IC_{50} = 210 and 537 nM, respectively), suggesting that the DAT does not tolerate 2-position steric bulk in the benztropine class, as it does with the 2-substituted 3-aryltropanes. In addition, binding affinities at the serotonin transporter, norepinephrine transporter, and muscarinic receptors were evaluated and compared for compounds **2**, **3**, **11a**−**e**, and **13**. Together, the binding profiles across these systems demonstrated significant differences between these two classes of tropane-based ligands, which may be exploited toward the discovery of a cocaine-abuse pharmacotherapeutic.

Cocaine is a highly addictive central nervous system stimulant (for recent reviews, see refs 1−3). Although the identification of mechanism(s) associated with cocaine addiction remains uncertain, its psychostimulant and reinforcing effects are associated with its inhibition of dopamine reuptake into dopaminergic neurons via the dopamine transporter (DAT).[4−7]

Extensive structure−activity relationship (SAR) studies of cocaine analogues at the DAT have led to the discovery of a potent class of DAT inhibitors wherein the 3-benzoyl ester was replaced with various aryl ring systems to give more potent 2-carbomethoxy-3-aryltropane analogues (for a review, see ref 8). The most potent DAT inhibitors in this class of analogues, as well as cocaine, must possess a 2-substituent, and the *R*-configuration is generally required.[3,8] Although the enantiomeric requirement for an *R*-2*β*-substituent is stringent, a wide variety of chemical moieties with differing steric and electronic properties are well tolerated. Many of these compounds have demonstrated utility as radioligands and irreversible and fluorescent probes.[9−12]

In another class of tropane-based DAT ligands, based on 3α-(diphenylmethoxy)tropane (benztropine), a substituent in the 2-position is not necessary for high-affinity DAT binding. For example, compound **2** (AHN 1-055) binds with high affinity to DAT (K_i = 11.8 nM).[13] Meltzer and colleagues synthesized all eight isomers of 2-carbomethoxy-3α-(bis[4-fluorophenyl]methoxy)tropane and discovered that the *S*-enantiomer, *S*-(+)-difluoropine, demonstrated considerably higher affinity for the DAT than any of the other seven isomers.[14]

Numerous 3-aryltropane analogues have been evaluated in animal models of cocaine abuse and with few exceptions are generally potent psychomotor stimulants with reinforcing effects that mimic those of cocaine.[4,15−17] These behaviors have been attributed primarily to their interactions at the DAT and subsequent inhibition of dopamine uptake. Nevertheless, recently there have been reported exceptions.[18]

In contrast, the benztropine analogues, with few exceptions, do not demonstrate cocaine-like behavioral profiles despite being potent dopamine uptake inhibitors both in vitro and in vivo.[3,19] Because the DAT tolerates significant modification of the 2-substituent in the 3-aryltropane class of compounds, it was of interest to determine what 2-substitutions in the benztropine class would be permitted. Thus, a SAR comparison of a series of 2-substituted *S*-(+)-2*β*-carboalkoxy-3α-(bis[4-fluorophenyl]methoxy)tropanes with the identically substituted *R*-(−)-2*β*-carboalkoxy-3*β*-(3,4-dichlorophenyl)tropanes was undertaken (Figure 1).

It has been previously demonstrated that the 3*β*-(3,4-dichlorophenyl)tropane pharmacophore binds optimally to the DAT, and thus, this compound (**3**) was chosen as the parent ligand for the 3-aryltropane series[20,21] from

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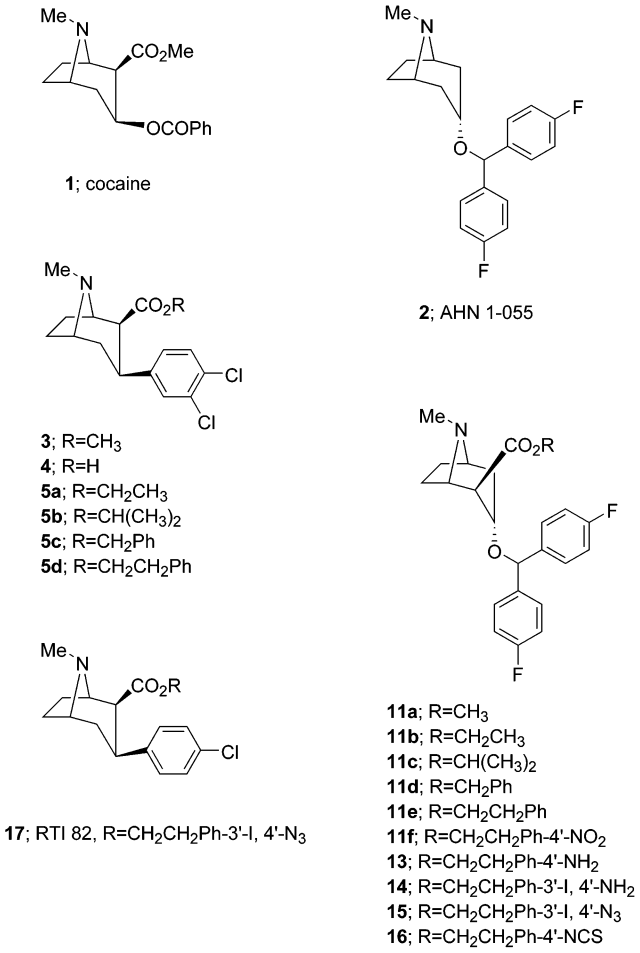


Figure 1. Chemical structures of cocaine (**1**), the parent compounds **2** and **3**, and the target compounds.

which compounds **5a**−**d** were derived. As previously communicated, an enantioselective synthesis of the *S*-(+)-2*β*-carboalkoxy-3α-(bis[4-fluorophenyl]methoxy)-tropanes[22] was further elaborated upon to give >99% enantiomeric excess (ee) products (**11a**−**f**, **13**, **14**). Evaluation of these novel compounds for DAT binding and inhibition of dopamine uptake (DAUI) was investigated. Further, how this chemical modification affected binding profiles at the other monoamine transporters and muscarinic receptors was also examined. In addition, in an attempt to prepare novel irreversible ligands for the DAT, *S*-2*β*-carboethoxyphenylisothiocyanato- and azido-substituted analogues (**15**, **16**) of the 3α-(bis-[4-fluorophenyl]methoxy)tropane series were also prepared.

Chemistry

The *R*-(−)-2*β*-carboalkoxy-3*β*-(3,4-dichlorophenyl)tropanes were prepared from **3**.[12] Deesterification in 6 N aqueous HCl gave the carboxylic acid intermediate **4**, which was first converted to the acid chloride and then esterified with the corresponding alcohols to generate compounds **5a**−**d**.

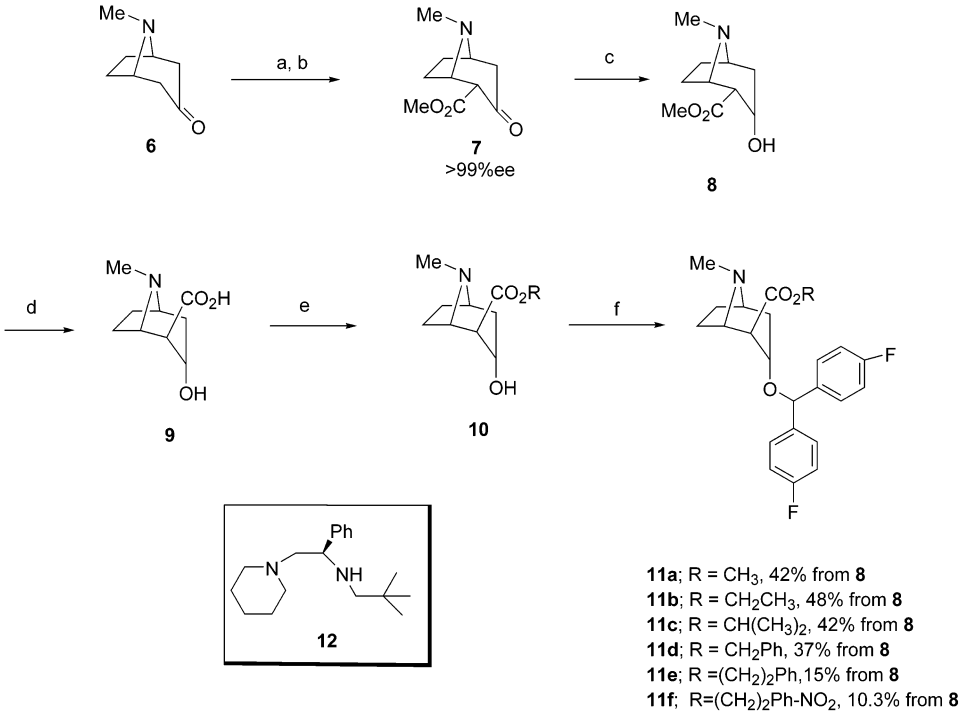
The enantioselective synthesis of the common intermediate **8** for the *S*-(+)-2*β*-carboalkoxy-3α-[bis(4-difluorophenyl)methoxy]tropanes (**11a**−**f**) was achieved through the asymmetric deprotonation strategy of Majewski and Lazny,[23] as depicted in Scheme 1 and previously communicated for compounds **11a**−**d**.[22] Conversion to the carboxylic acid intermediate **9** was followed by esterification in the appropriate alcohol, under acidic conditions to give the esters **10a**−**f**. The final products **11a**−**f** were obtained using a standard procedure.[14] Full experimental details for these compounds are included in the Experimental Section and were not previously described.

Synthesis of the potential irreversible ligands **15** and **16** is depicted in Scheme 2. Compound **11f** was reduced to amine **13** by catalytic hydrogenation (10% Pd/C). By use of a modification of procedures previously described,[24] compound **13** was reacted with ICl to give intermediate **14**, which was first treated with $NaNO_2$ under acidic conditions and then reacted with NaN_3 to give the iodoazido product **15**. Compound **13** was converted to **16** by treatment with $CSCl_2$.

Structure−Activity Relationships

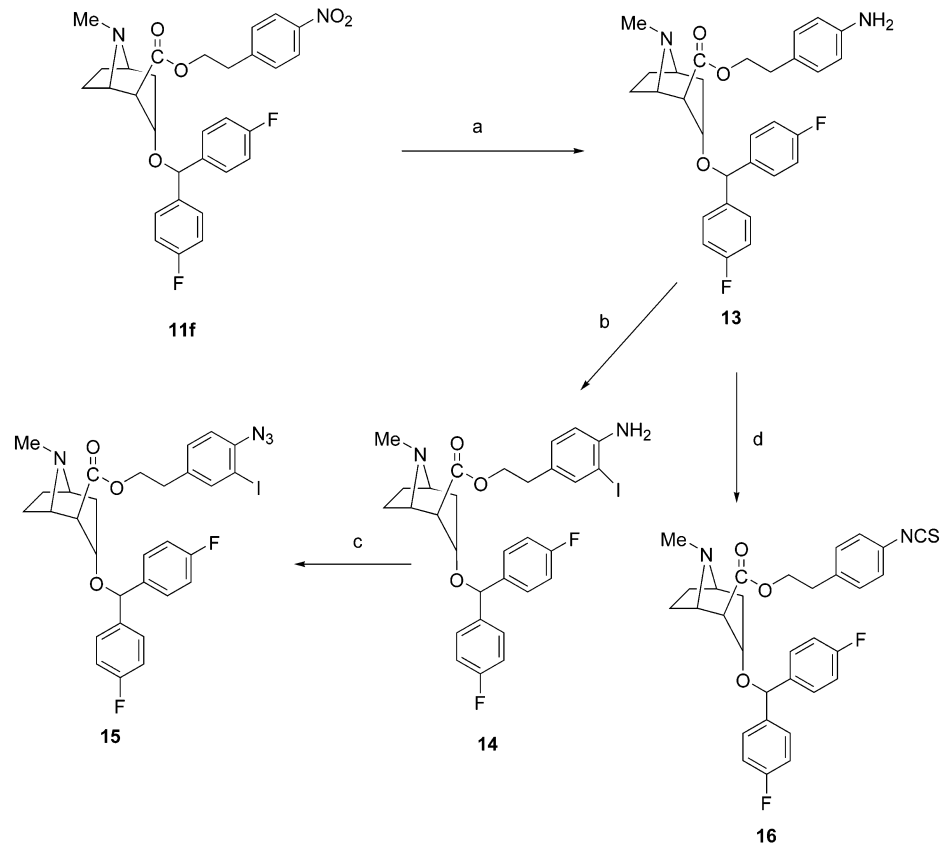
Binding affinities of all novel compounds were evaluated in radiolabeled ligand displacement assays for DAT in rat brain. The methods for the binding assays have been previously described in detail.[25] Inhibition of [^{3}H]-dopamine uptake in rat synaptosomes was also evaluated using a previously reported procedure.[26] The results of these studies are in Table 1. Most of the compounds in both series demonstrated high binding affinity at the DAT, although the *S*-(+)-2*β*-carboalkoxy-3α-[bis(4-difluorophenyl)methoxy]tropane compounds were consistently and slightly less potent than the identically substituted 3,4-dichlorophenyltropanes (e.g., **3**, DAT K_i = 6.30 nM vs **11a**, DAT K_i = 13.4 nM). When the steric bulk of the 2-position ester in both series was increased, DAT binding affinities decreased only slightly. For the *S*-(+)-2*β*-carboethoxyphenyl analogue (**11e**, K_i = 36.7 nM), nitro substitution at the 4-position of the terminal phenyl ring resulted in a ∼2.5-fold decrease in binding affinity to the DAT (**11f**, K_i = 97.7 nM). Whereas reduction of the nitro group to the amine (**13**, K_i = 36.7 nM) resulted in a ∼2.5-fold increase in binding affinity, the addition of the 3′-iodo substituent (**14**, K_i = 42.3 nM) did not appreciably alter binding affinity at the DAT. However, conversion of the amine to the azide or isothiocyanate gave rise to dramatic decreases in DAT binding potencies in the 3α-(bis[4-fluorophenyl]-methoxy)tropane series (**15**, IC_{50} = 210 nM and **16**, IC_{50} = 537 nM). In contrast, the 4′-azido-substituted **17** (RTI 82), binds with high potency to the DAT (IC_{50} = 14.5 nM). Indeed, it is predicted that the 3,4-dichloro-substituted analogue of **17** would have even higher binding potency at the DAT. These results suggest that the DAT tolerates more steric bulk in the 2-position of the 3,4-dichlorophenyltropanes than is tolerated with the 3α-(bis[4-fluorophenyl]methoxy)tropanes. In fact, the small differences in binding affinities of the smaller 2-carboalkoxy analogues (**11a**−**e**) compared to those of the unsubstituted compound **2** may suggest that these substituents have insignificant interactions at the DAT. However, when the substituent is sterically bulky and perhaps electronically unfavorable, DAT binding affinities decrease because of detrimental interactions. Nevertheless, despite its reduced binding potency, compound **15** will be further investigated for wash-resistant binding and may still be a useful photoaffinity label for the DAT.

Scheme 1[a]



[a] Reagents and conditions: (a) (1) n-BuLi, **12**, THF, (2) $NCCO_2Me$, 77%; (b) resolution with D-tartaric acid, 80%; (c) H_2 (50 psi), PtO_2, EtOH, 86%; (d) H_2O, reflux; (e) ROH, HCl; (g) room temp or heating; (f) 4,4′-difluorobenzhydrol, *p*-TSA, benzene, reflux, 10.3−47.5% yield from compound **8**.

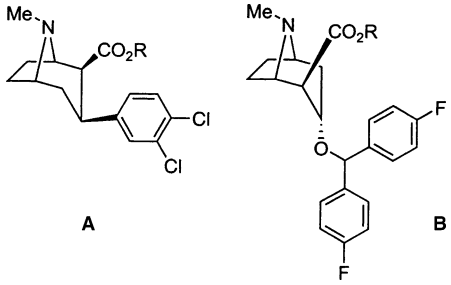
Scheme 2[a]



[a] Reagents and conditions: (a) H_2 (40 psi), Pd/C (10%), MeOH, 1 h, 70%; (b) ICl, HOAc, 49%; (c) (1) $NaNO_2$, $HOAc/H_2O$, 0 °C, (2) NaN_3, 0 °C, 63%; (d) $CSCl_2$, $CHCl_3/H_2O$, 0 °C, 81%.

Figure 2 provides a Molcad surface comparison of compounds **15** and **17** to provide a depiction of these two molecules in three-dimensional space. On the basis of their SAR, a large binding pocket on DAT appears to be available for the 3-aryltropanes but is more limited for the benztropine analogues. Coupled with opposite

Table 1. DAT Binding and Dopamine Uptake Inhibition Data for Novel 2-Substituted Tropanes



compd	structure	R	[^{3}H]WIN 35,428 DAT, K_i [a,b] ± SEM (nM)	[^{3}H]DAUI, IC_{50} [b] ± SEM (nM)
3	A	CH_3	6.30 ± 0.7	1.4 ± 0.2
5a	A	CH_2CH_3	5.54 ± 0.2	1.9 ± 0.2
5b	A	$CH(CH_3)_2$	17.9 ± 1.6	2.7 ± 0.4
5c	A	CH_2Ph	34.7 ± 3.1	19 ± 2.8
5d	A	CH_2CH_2Ph	10.9 ± 0.5	3.2 ± 0.4
17, RTI 82[c]	A	CH_2CH_2Ph-3′-I,4′N_3	14.5 ± 0.94[d,e]	NT
11a	B	CH_3	13.4 ± 0.9	1.5 ± 0.2[f]
11b	B	CH_2CH_3	16.4 ± 2.0	1.8 ± 0.2[f]
11c	B	$CH(CH_3)_2$	30.3 ± 2.0	6.2 ± 0.3[f]
11d	B	CH_2Ph	48.4 ± 6.1	2.2 ± 0.3[f]
11e	B	CH_2CH_2Ph	36.7 ± 4.2	2.6 ± 018
11f	B	CH_2CH_2Ph-4′NO_2	97.7 ± 14	3.3 ± 0.30
13	B	CH_2CH_2Ph-4′NH_2	36.7 ± 2.0	8.0 ± 0.63
14	B	CH_2CH_2Ph-3′-I,4′NH_2	42.3 ± 4.0	NT
15	B	CH_2CH_2Ph-3′-I,4′N_3	210 ± 29[d]	NT
16	B	CH_2CH_2Ph-4′NCS	537 ± 37[d]	NT
1, cocaine			285 ± 27	236 ± 21
2, AHN 1-055			11.8 ± 1.3[g]	13.8 ± 1.7

[a] Each K_i value represents data from at least three independent experiments, each performed in triplicate. *K*i values were analyzed by PRISM. [b] A detailed description of DAT binding and DAUI assay methods have been previously published.[25,26] [c] **17** does not have a 3′-Cl group but is included for comparison. [d] IC_{50} value. [e] Data from ref 24. [f] Data from ref 22. [g] Data from ref 13.

stereoselectivity requirements at the 2-position, these results provide further evidence that these two classes of tropane-based DAT inhibitors bind at different domains on the DAT.

Compounds **11a**−**e** and **13** were evaluated for binding affinities at the serotonin transporter (SERT), norepinephrine transporter (NET), and muscarinic receptors and compared to the parent ligands **2** and **3** (Table 2). In general, none of these analogues demonstrated high binding affinities to the NET or SERT as did compound **3**. Likewise, none of the compounds showed high-affinity binding to muscarinic receptors, compared to **2**, demonstrating that the 2-substituent serves to diminish muscarinic receptor interactions in this class of compounds. Thus, good DAT selectivity over SERT, NET, and muscarinic receptors was observed with the *S*-(+)-2*β*-carboalkoxy-3α-(bis[4-fluorophenyl]methoxy)-tropanes. In a comparison of compounds **2** and **11a**, addition of the 2-methyl ester increases binding affinity at the SERT and NET by 5- and 2-fold, respectively. However, this addition significantly reduces muscarinic receptor binding by 12-fold. Increasing steric bulk further decreases binding affinities at the SERT, NET, and muscarinic receptors, with compound **11c** demonstrating the highest overall DAT selectivity (i.e., SERT/DAT = 400, NET/DAT = 20, M_1/DAT = 90). Interestingly, when the 2-substituent gets very large, as in compounds **11e** and **13**, muscarinic receptor binding begins to improve. In contrast, compound **3** binds with high affinities to the SERT and NET but with very low affinity to muscarinic receptors. These data clearly demonstrate that these classes of tropane-based ligands have widely differing SARs at these three proteins, as with the DAT.

In addition to DAT binding affinities, potency for inhibiting [^{3}H]dopamine uptake (DAUI) in vitro was assessed (Table 1). Both series of compounds also showed high potency in inhibiting [^{3}H]dopamine uptake, and these IC_{50} values were generally similar across identically 2-substituted tropanes. Interestingly, in general, the 2-carboalkoxy-substituted 3α-(bis[4-fluorophenyl]methoxy)tropanes were more potent in inhibiting dopamine uptake than in binding to the transporter (e.g., **11d**, K_i = 48.4 nM and IC_{50} for DAUI = 2.2 nM). This is in contrast to the parent compound **2**, which showed similar values for binding affinity to the DAT (K_i = 11.8 nM) and potency for inhibition of dopamine uptake (IC_{50} = 13.8 nM). Disparity in potency in various functional assays compared to binding constants may be related to assay conditions and might not be reflected in vivo. However, these differences appear to be related to compound structure, with the 2-substituted benztropine analogues showing these differences more profoundly than the 3-aryltropanes, which were studied under identical conditions. Further, the differences between values for in vitro DAT binding vs DAUI have not been previously encountered with the benztropine analogues lacking a 2-position substituent (e.g., **2**). The possibility that they may be reflected in different in vivo profiles is certainly intriguing and will be investigated further.

In summary, identically 2*β*-carboalkoxy-substituted *R*-(−)-3*β*-(3,4-dichlorophenyl)tropanes and *S*-(+)-3α-(bis-[4-fluorophenyl]methoxy)tropanes were synthesized.

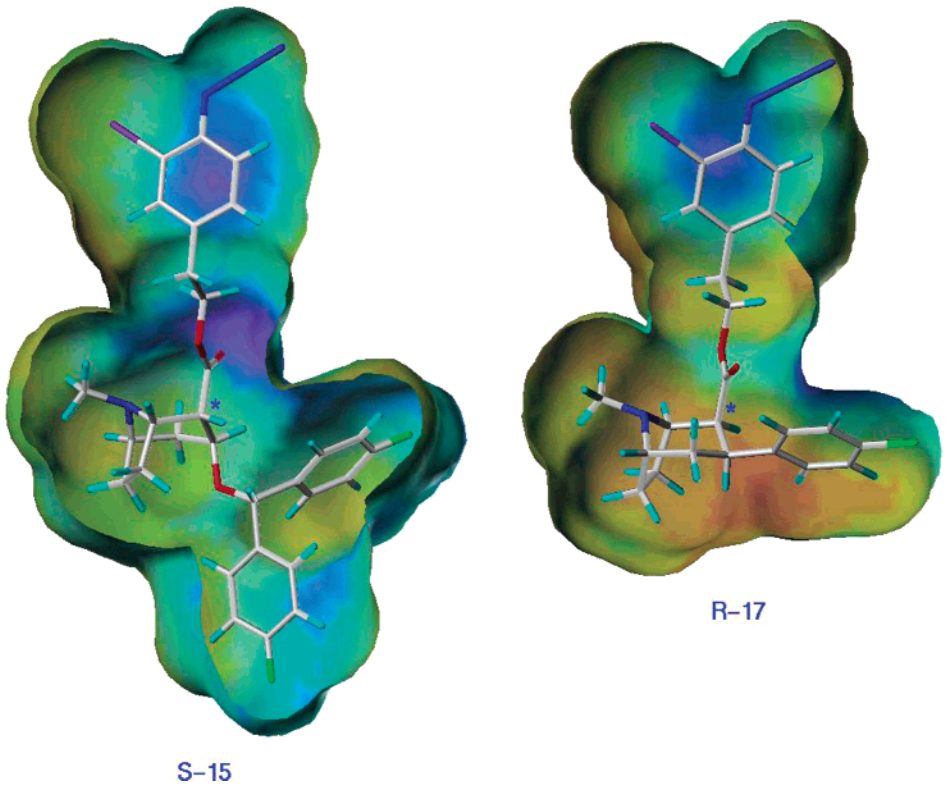


Figure 2. Molcad surface analyses of **15** and **17** demonstrate steric bulk in the 2-position of these molecules. Compound **17** is well tolerated at the DAT (IC_{50} = 14.5 nM), whereas **15** binds with significantly lower potency (IC_{50} = 210 nM).

Table 2. Binding Results at the SERT, NET, and Muscarinic M_1 Receptors

compd	[^{3}H]citalopram SERT K_i [a] ± SEM (nM)	[^{3}H]nisoxetine NET K_i [a] ± SEM (nM)	[^{3}H]pirenzepine M_1 K_i [a] ± SEM (nM)
(+)-**11a**	690 ± 58[b]	269 ± 39[b]	133 ± 4.2[b]
(+)-**11b**	1850 ± 270[b]	629 ± 31[b]	1890 ± 130[b]
(+)-**11c**	12000 ± 1280[b]	642 ± 13[b]	2680 ± 140[b]
(+)-**11d**	2040 ± 300[b]	2230 ± 200[b]	4380 ± 530[b]
(+)-**11e**	3160 ± 461	1030 ± 85	354 ± 52
13	1500 ± 210	1340 ± 120	263 ± 5.6
2, AHN 1-055	3260 ±110[b]	610±81[b]	11.6 ± 0.9[b]
3	1.46 ± 0.2	15.8 ± 1.6	3140 ± 260

[a] Each K_i value represents data from at least three independent experiments, each performed in triplicate. K_i values were analyzed by PRISM. A detailed description of SERT, NET, and muscarinic receptor binding assay methods have been previously published.[25] [b] Data from ref 22.

Binding evaluation revealed that both series of compounds were highly potent DAT ligands that inhibited dopamine uptake with high and equivalent potencies. The exceptions were the potential irreversible ligands **15** and **16** that, unlike **17**, were significantly less potent than the other analogues in this series. Comparison of the SAR suggests that the two series of ligands likely bind at different domains on the DAT protein. These differences may be exploited toward developing tools with which to map the topology of the DAT. Significantly different binding profiles at SERT, NET, and muscarinic receptors suggest that these tropane-based molecules do not interact at these proteins in a similar manner either. Furthermore, it is of considerable interest to further investigate the differences in dopamine uptake inhibition between the unsubstituted benztropine analogues and their 2-substituted counterparts and to compare these to cocaine and the 3-aryltropanes in vivo. Currently, behavioral evaluation of **11a**−**c** in animal models of cocaine abuse is underway. Exploring the behavioral outcomes of structurally similar but distinct DAT inhibitors that exhibit significantly different binding profiles at SERT and NET may provide clues toward an optimal behavioral profile for potential cocaine-abuse medication.

Experimental Methods

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Billerica, MA) AC-300 instrument. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$ or CD_3OD). Proton and carbon chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (Me_4Si, 0.00 ppm), which was used as an internal standard. To maximize the signal-to-noise ratio, all spectra for the ^{1}H NMR analysis of the enantiomeric excess value (% ee) were recorded on samples (0.10−0.15 M) in the presence of ca. 15 mg of *S*-(+)-2,2,2-trifluoro-1-(9-antranyl)-ethanol [*S*-(+)-TFAE]. The enantiomeric analyses were conducted on the chiral HPLC column "Klassix Chiral-A", 250 mm × 4.6 mm i.d., 10 μm (flow rate of 1 mL/min). Mass spectra were recorded on a Hewlett-Packard (Palo Alto, CA) 5973 mass-selective ion detector in the electron-impact mode with sample introduction via an HP-6890 series gas chromatograph fitted with an HP-1 (cross-linked methyl silicone gum) 25 m × 0.2 mm i.d., 50 μm film thickness. Ultrapure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line temperatures were 250 and 280 °C, respectively. The initial oven temperature was 100 °C, held for 3.0 min, programmed to 295 °C at 15.0 °C/min, and maintained at 295 °C for 10−23 min. Infrared spectra were recorded as a neat film on KBr plates with a Perkin-Elmer Spectrum RX I FT-IR system. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within ±0.4% of the calculated values. All flash column chromatog-

raphy was performed using the flash-grade silica gel (Aldrich, 230−400 mesh, 60A). All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis, Inc. unless otherwise indicated and used without further purification.

General Procedure for the Preparation of *R*-(−)-2*β*-Carboalkoxy-3*β*-(3,4-dichlorophenyl)tropanes 5a−d from 3. Compound **3** (330 mg, 1 mmol)[12] was dissolved in aqueous HCl (6 N, 10 mL), and the mixture was heated to gentle reflux for 6 h. H_2O was then removed, and the residue was further dried under vacuum to give **4** as a solid that was used without further purification. To compound **4**, 5 mL of $POCl_3$ was added, and the mixture was stirred overnight at room temperature under an argon atmosphere. Excess $POCl_3$ was removed in vacuo. The residue was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. The corresponding alcohol (4 mmol, 4 equiv) was added followed by dropwise addition of Et_3N (0.7 mL, 5 mmol). The solution was warmed to room temperature and stirred for 3 h. H_2O (10 mL) was added, the mixture was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layer was dried (K_2CO_3) and concentrated. The residue was purified by flash column chromatography to give the pure products.

***R*-(−)-2*β*-Carboethoxy-3*β*-(3,4-dichlorophenyl)tropane (5a).** Compound **5a** was prepared and isolated as a white solid in 81% yield. Mp 70−71.5 °C; $[\alpha]^{25}_D$ −26.8° (*c* 1.0, CH_3OH); IR 1735, 1180 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.53−1.73 (3H, m), 2.05−2.25 (2H, m), 2.22 (3H, s, NCH_3), 2.50 (1H, m), 2.82−2.98 (2H, m, H-2, H-3), 3.35 (1H, m, H-5), 3.59 (1H, m, H-1), 3.83−3.96 (1H, m, OCH_2), 4.00−4.11 (1H, m, OCH_2), 7.11 (1H, m, Ar−H), 7.31 (2H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.5, 25.6, 26.2, 33.6, 34.4, 42.3, 52.9, 60.2, 62.4, 65.7, 127.1, 129.9, 130.1, 132.2, 144.2, 171.7 ppm; EIMS (*m*/*z*) 327 (M^+). Anal. ($C_{17}H_{21}NCl_2O_2$·2HCl) C, H, N.

***R*-(−)-2*β*-Carbo-2-propoxy-3*β*-(3,4-dichlorophenyl)tropane (5b).** Compound **5b** was prepared and isolated as a white solid in 79% yield. Mp 88−90 °C; $[\alpha]^{24}_D$ −24.6° (*c* 1.0, CH_3OH); IR 1727, 1185 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (6H, d, J = 6.2 Hz, $CH(CH_3)_2$), 1.53−1.73 (3H, m), 2.05−2.25 (2H, m), 2.21 (3H, s, NCH_3), 2.51 (1H, m), 2.81 (1H, m, H-3), 2.90 (1H, m, H-2), 3.34 (1H, m, H-5), 3.58 (1H, m, H-1), 4.91 (1H, m, OCH), 7.79 (1H, m, Ar−H), 7.30−7.36 (2H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.0, 22.2, 25.6, 26.1, 42.3, 52.9, 62.4, 65.7, 67.3, 127.1, 129.8, 130.1, 132.2, 144.4, 171.2 ppm. Anal. ($C_{18}H_{23}NCl_2O_2$·HCl·0.5H_2O) C, H, N.

***R*-(−)-2*β*-Carbobenzoxy-3*β*-(3,4-dichlorophenyl)tropane (5c).** Compound **5c** was prepared and isolated as a colorless oil in 72% yield. $[\alpha]^{24}_D$ −23.4° (*c* 1.02, CH_3OH); IR 1744, 1170 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53−1.73 (3H, m), 2.05−2.25 (2H, m), 2.19 (3H, s, NCH_3), 2.52 (1H, m), 2.87−2.98 (2H, m, H-2, H-3), 3.36 (1H, m, H-5), 3.59 (1H, m, H-1), 4.86 (1H, d, J = 12.4 Hz, OCH_2Ph), 5.10 (1H, d, J = 12.4 Hz, OCH_2Ph), 7.07 (1H, m, Ar−H), 7.17 (2H, m, Ar−H), 7.25−7.36 (5H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 25.6, 26.2, 33.6, 34.3, 42.6, 46.6, 53.0, 62.5, 65.6, 66.1, 127.1, 128.3, 128.8, 129.8, 130.2, 132.3, 136.5, 144.0, 171.5 ppm. Anal. ($C_{22}H_{23}NCl_2O_2$·HCl·1.5H_2O) C, H, N.

***R*-(−)-2*β*-Carbophenylethoxy-3*β*-(3,4-dichlorophenyl)-tropane (5d).** Compound **5d** was prepared and isolated as a white solid in 74% yield. Mp 87−89 °C; $[\alpha]^{24}_D$ −24.1° (*c* 0.85, CH_3OH); IR 1734, 1166 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50−1.70 (3H, m), 2.00−2.23 (2H, m), 2.11 (3H, s, NCH_3), 2.46 (1H, m), 2.79−2.97 (4H, m, CH_2Ph, H-2, H-3), 3.32 (1H, m, H-5), 3.47 (1H, m, H-1), 4.04−4.29 (2H, m, OCH_2), 7.07 (1H, m, Ar−H), 7.10−7.32 (7H, m, 2 Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 25.6, 26.2, 33.6, 34.2, 35.3, 42.2, 52.9, 62.5, 64.7, 65.6, 126.8, 127.1, 128.8, 129.2, 129.9, 130.2, 132.3, 138.4, 144.1, 171.6 ppm. Anal. ($C_{23}H_{25}NCl_2O_2$) C, H, N.

(−)-2α-Carbomethoxytropinone (7). n-BuLi (10 M in hexane, 4.36 mL, 43.6 mmol) was added dropwise to a solution of chiral amine **12**[27] (11.95 g, 43.6 mmol) in dry THF (120 mL) at 0 °C, and the mixture was stirred for 45 min. LiCl (0.5 M in THF, 36 mL, 18 mmol) was added, and the solution was stirred for an additional 15 min. After the mixture was cooled to −78 °C, a solution of tropinone (5.06 g, 36.3 mmol) in THF (36 mL) was added dropwise and the resulting mixture was stirred for 2.5 h at −78 °C. Methyl cyanoformate (4.32 mL, 54.5 mmol) was then added quickly to the solution, and the mixture was stirred at −78 °C for 30 min followed by quenching with $AgNO_3$ (6.5 g, 36 mmol) in THF (36 mL), H_2O (9 mL), and HOAc (9 mL). Immediately after warming to room temperature, the mixture was treated with NH_4OH (to dissolve the Ag salts), diluted with H_2O, and extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried over anhydrous $MgSO_4$, the solvents were removed in vacuo, and the residue was purified by flash column chromatography (hexanes/EtOAc/Et_3N, 3:1:0.5, followed by $CHCl_3$/MeOH/NH_4OH, 95:5:1) to give 5.5 g (77%) of **7** as a white solid: 92% ee by ^1H NMR with *S*-(+)-TFAE. Mp 102−104 °C. D-Tartaric acid (15 g, 10 mmol) was added to the hot solution of **7** (10 g, 5.08 mmol) in EtOH (150 mL). EtOH was removed in vacuo after all the tartaric acid was dissolved. The residue was recrystallized once from a 10:1 acetone/H_2O mixture and then from MeOH to afford 20.7 g of (−)-2α-carbomethoxytropinone bitartrate as a colorless crystalline solid. The salt was dissolved in saturated Na_2CO_3 (50 mL), and the free base was extracted with $CHCl_3$ (3 × 25 mL). The dried (K_2CO_3) extracts were concentrated to afford 8.03 g (80%) of **7** as a white solid: >99% ee by ^1H NMR with *S*-(+)-TFAE. Mp 107−108 °C; lit.[28] sublimed mp 108.6−109.6 °C; $[\alpha]^{27}_D$ −22.8° (*c* 1.0, MeOH); lit.[28] $[\alpha]^{20}_D$ −18.3° (*c* 1, MeOH).

***S*-(+)-Allopseudoecgonine Methyl Ester (8).** Compound **7** (1.97 g, 10 mmol) was dissolved in absolute EtOH (80 mL) and reduced by hydrogenation over PtO_2 catalyst (80 mg) at 50 psi for 4 days. The catalyst was removed using suction filtration through Celite, and the solvent was removed under vacuum. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 90:10:1) to afford 1.71 g (86%) of **8** as a colorless solid. Mp 74−76 °C; lit.[29] mp 79−80 °C; $[\alpha]^{24}_D$ +35.9° (*c* 1, $CHCl_3$); lit.[29] $[\alpha]^{20}_D$ +37.7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.81−2.10 (6H, m), 2.32 (3H, s, NCH_3), 2.91 (1H, t, J = 3.6 Hz, H-2), 3.11 (1H, m, H-5), 3.35 (1H, m, H-1), 3.46 (1H, br, OH), 3.75 (3H, s, OCH_3), 4.27 (1H, m, H-3) ppm; ^{13}C NMR ($CDCl_3$) δ 24.7, 26.1, 37.8, 40.4, 50.5, 52.2, 60.2, 62.1, 65.0, 174.5 ppm; EIMS (*m*/*z*) 199 (M^+).

***S*-(+)-Alloecgonine (9).** Compound **8** (498 mg, 2.5 mmol) was suspended in H_2O (20 mL), and the mixture was stirred at reflux for 18 h. H_2O was removed in vacuo, and the residue was further dried to give **9** as a colorless solid. The crude product was used in the next step without further purification.

***S*-(+)-Alloecgonine Methyl Ester (10a).** Compound **9** was dissolved in MeOH (15 mL) and acidified with HCl gas for 10 min at 0 °C. The reaction mixture was stirred at room temperature overnight. MeOH was removed in vacuo, and the residue was dissolved in H_2O (20 mL), neutralized with NH_4OH to pH 9, and extracted with $CHCl_3$ (3 × 15 mL). The combined extract was dried (K_2CO_3) and concentrated to dryness. The residue was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:5:1) to afford **10a** (293 mg, 59%) as a light-brown solid. Mp. 74−76 °C; lit.[21] mp 76.5−77.5 °C; $[\alpha]^{24}_D$ +3.0° (*c* 1.0, MeOH); IR 3244, 1749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55−2.20 (6H, m), 2.18 (3H, s, NCH_3), 2.62 (1H, m, H-2), 3.08 (1H, br, H-5), 3.57 (1H, m, H-1), 3.71 (3H, s, OCH_3), 4.39 (1H, m, H-3) ppm; EIMS (*m*/*z*) 199 (M^+).

***S*-(+)-Alloecgonine Ethyl Ester (10b).** Compound **10b** was prepared by dissolving **9** in EtOH and acidifying with HCl gas, as described for **10a**, giving an oil in 62% yield. $[\alpha]^{26}_D$ +4.0° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.0 Hz, CH_3), 1.60−2.20 (6H, m), 2.18 (3H, s, NCH_3), 2.61 (1H, m, H-2), 3.10 (1H, m, H-5), 3.58 (1H, m, H-1), 4.07−4.25 (2H, m, OCH_2), 4.34 (1H, d, J = 5.2 Hz, H-3) ppm; EIMS (*m*/*z*) 213 (M^+).

***S*-(+)-Alloecgonine Isopropyl Ester (10c).** Compound **10c** was prepared by dissolving **9** in 2-propanol and acidifying with HCl gas, as described for **10a**, giving an oil in 53% yield. $[\alpha]^{25}_D$ +1.2° (*c* 1.0, MeOH); IR 3506 (br), 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, d, J = 4 Hz, CH_3), 1.25 (3H, d, J = 4 Hz, CH_3), 1.57−2.26 (6H, m), 2.18 (3H, s, NCH_3), 2.57 (1H, m, H-2), 3.10 (1H, br, H-5), 3.56 (1H, m, H-1), 4.36 (1H, d, J = 5.1 Hz,

H-3), 5.07 (1H, m, OCH) ppm; ^{13}C NMR ($CDCl_3$) δ 21.7, 24.5, 25.3, 39.2, 41.6, 54.2, 60.7, 63.0, 64.8, 67.3, 172.1 ppm; EIMS (*m*/*z*) 227 (M^+).

***S*-(+)-Alloecgonine Benzyl Ester (10d).** Compound **10d** was prepared by suspending **9** in benzyl alcohol and acidifying with HCl gas, as described for **10a.** The reaction mixture was stirred at 50 °C (oil-bath temperature) overnight. The benzyl alcohol was removed through a short silica gel column, and the residue was dissolved in H_2O (20 mL), neutralized with NH_4OH to pH 9, and extracted with $CHCl_3$ (3 × 15 mL). The combined extract was dried (K_2CO_3) and concentrated to dryness. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:5:1) to afford **10d** (340 mg, 49.5%) as an oil. $[\alpha]^{25}_D$ +5.8° (*c* 1.0, MeOH); IR 3394, 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60−2.17 (6H, m), 2.17 (3H, s, NCH_3), 2.68 (1H, m, H-2), 3.10 (1H, m, H-5), 3.61 (1H, m, H-1), 4.41 (1H, d, *J* = 5.2 Hz, H-3), 5.10 (1H, d, *J* = 12.5 Hz, OCH_2), 5.22 (1H, d, *J* = 12.5 Hz, OCH_2), 7.26−7.40 (5H, m, Ar−H) ppm; EIMS *m*/*z* 275 (M^+).

***S*-(+)-Alloecgonine Phenylethyl Ester (10e).** Compound **10e** was prepared by suspending **9** in phenylethyl alcohol and acidifying with HCl gas, as described for **10d**, giving an oil in 21.5% yield. $[\alpha]^{25}_D$ +6.3° (*c* 1.0, CH_3OH); IR 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5−2.2 (6H, m), 2.10 (3H, s, NCH_3), 2.60 (1H, m, H-2), 2.96 (2H, t, *J* = 6.9 Hz, CH_2Ph), 3.08 (1H, m, H-5), 3.49 (1H, m, H-1), 4.27−4.41 (3H, m, OCH_2, H-3), 7.18−7.31 (5H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 25.0, 25.8, 35.4, 39.7, 42.0, 54.7, 61.2, 63.5, 65.4, 126.9, 128.8, 129.3, 138.4, 173.1 ppm; EIMS (*m*/*z*) 289 (M^+).

***S*-(+)-Alloecgonine (4-Nitrophenyl)ethyl Ester (10f).** 4-Nitrophenylethyl alcohol (50 g) was melted by heating and acidified with HCl gas for 10 min. The solution was cooled to 60 °C (oil-bath temperature). To the solution was added **9**. The reaction mixture was stirred at that temperature overnight. The 4-nitrophenylethyl alcohol was removed through a short silica gel column, and the residue was dissolved in H_2O (20 mL), neutralized with NH_4OH to pH 9, and extracted with $CHCl_3$ (3 × 15 mL). The combined extract was dried (K_2CO_3) and concentrated to dryness. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:5:1) to afford **10f** (113 mg, 13.5%) as a dark oil. $[\alpha]^{24}_D$ +7.2° (*c* 1.05, MeOH); IR 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60−2.18 (6H, m), 2.08 (3H, s, NCH_3), 2.61 (1H, m, H-2), 3.03−3.15 (3H, m, H-5, CH_2Ph), 3.42 (1H, m, H-1), 4.30−4.44 (3H, m, H-3, OCH_2), 7.42 (2H, d, *J* = 8.6 Hz, Ar−H), 8.18 (2H, d, *J* = 8.6 Hz, Ar−H) ppm.

***S*-(+)-2β-Carbomethoxy-3α-(bis[4-fluorophenyl]methoxy)tropane (11a).** Compound **10a** (200 mg, 1 mmol), 4,4′-difluorobenzhydrol (440 mg, 2 mmol), *p*-toluenesulfonic acid monohydrate (285 mg, 1.5 mmol), and benzene (12 mL) were placed in a 50 mL round-bottom flask fitted with a Dean−Stark trap and condenser. The reaction mixture was heated at reflux for 18 h. Additional 4,4′-difluorobenzhydrol (220 mg, 1 mmol) and *p*-toluenesulfonic acid monohydrate (24 mg, 0.13 mmol) were added, and the reaction mixture was heated at reflux for another 6 h. The solvent was removed in vacuo, and the residue was dissolved in H_2O (30 mL), neutralized with NH_4OH to pH 9, and extracted with $CHCl_3$ (3 × 15 mL). The extracts were combined, dried (K_2CO_3), and concentrated to dryness. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 98:2:1) to afford 290 mg (72%) of **11a** as a white solid. Mp: 126.5−127.5 °C; lit.[21] mp 132−133 °C; $[\alpha]^{26}_D$ +19.6° (*c* 1.0, MeOH); lit. [21] $[\alpha]^{21}_D$ +21.6° (*c* 1, MeOH); analytic HPLC (Klassix Chiral-A column) eluting with hexane/2-PrOH/triethylamine (97.5:2.5:0.5) t_R = 9.27 min, >99% ee; IR 1730, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65−2.17 (6H, m), 2.17 (3H, s, NCH_3), 2.72 (1H, m, H-2), 3.09 (1H, m, H-5), 3.56 (1H, m, H-1), 3.68 (3H, s, OCH_3), 3.96 (1H, d, *J* = 4.8 Hz, H-3), 5.35 (s, 1H, O*CH*Ph_2), 6.74−7.05 (4H, m, Ar−H), 7.20−7.32 (4H, m, Ar−H) ppm; EIMS (*m*/*z*) 401 (M^+). Anal. ($C_{23}H_{25}NF_2O_3$) C, H, N.

***S*-(+)-2β-Carboethoxy-3α-(bis[4-fluorophenyl]methoxy)tropane (11b).** Compound **11b** was prepared from **10b** as described for **11a** in 76.5% yield. Mp: 60−61 °C; $[\alpha]^{26}_D$ +20.5° (*c* 1.0, MeOH); analytic HPLC (Klassix Chiral-A column) eluting with hexane/2-PrOH/triethylamine (100:1:1) t_R = 6.6 min, >99% ee; IR 1726, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, *J* = 7.0 Hz), CH_2CH_3), 1.70−2.10 (6H, m), 2.18 (3H, s, NCH_3), 2.68 (1H, s, H-2), 3.08 (1H, m, H-5), 3.58 (1H, m, H-1), 3.98 (1H, d, *J* = 5.2 Hz, H-3), 4.0−4.2 (2H, m, OCH_2), 5.34 (1H, s, $OCHPh_2$), 6.95−7.05 (4H, m, Ar−H), 7.20−7.30 (4H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.2, 24.6, 25.2, 36.2, 41.8, 60.4, 61.0, 63.2, 70.2, 80.3, 115.2, 115.4, 128.4, 138.4, 160.5, 163.7, 172.5 ppm; EIMS (*m*/*z*) 415(M^+). Anal. ($C_{24}H_{27}NF_2O_3$) C, H, N.

***S*-(+)-2β-Carbo-2-propoxy-3α-(bis[4-fluorophenyl]-methoxy)tropane (11c).** Compound **11c** was prepared from **10c** as described for **11a** in 78% yield. $[\alpha]^{26}_D$ +20.2° (*c* 1.03, MeOH); analytic HPLC (Klassix Chiral-A column) eluting with hexane/2-PrOH/triethylamine (100:1.5:1) t_R = 7.4 min, >99% ee; IR 1726, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, d, *J* = 5.8 Hz, $CHCH_3$), 1.23 (3H, d, *J* = 5.6 Hz, $CHCH_3$), 1.75−2.17 (6H, m), 2.20 (3H, s, NCH_3), 2.66 (1H, m), 3.10 (1H, m), 3.57 (1H, m), 3.98 (1H, d, *J* = 5.1 Hz), 5.06 (1H, m, $OCH(CH_3)_2$), 5.36 (1H, s, O*CH*Ph_2), 6.97−7.04 (4H, m, Ar−H), 7.24−7.31 (4H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.2, 25.0, 25.6, 36.5, 42.1, 52.3, 61.4, 63.6, 67.9, 70.6, 80.7, 115.5, 115.8, 128.8, 172.3 ppm; EIMS (*m*/*z*) 429 (M^+). Anal. ($C_{25}H_{29}NF_2O_3$) C, H, N.

***S*-(+)-2β-Carbobenzoxy-3α-(bis[4-fluorophenyl]methoxy)tropane (11d).** Compound **11d** was prepared from **10d** as described for **11a** in 74.5% yield. $[\alpha]^{26}_D$ +12.6° (*c* 1.05, MeOH); IR 1733, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75−2.17 (6H, m), 2.17 (3H, s, NCH_3), 2.75 (1H, m, H-2), 3.09 (1H, m, H-5), 3.60 (1H, m, H-1), 4.02 (1H, d, *J* = 4.8 Hz, H-3), 5.03 (1H, d, *J* = 12.5 Hz, OCH_2), 5.19 (1H, d, *J* = 12.5 Hz, OCH_2), 5.34 (1H, s, $OCHPh_2$), 6.93−7.04 (4H, m, Ar−H), 7.21−7.39 (9H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 25.0, 25.6, 36.6, 42.1, 52.3, 61.4, 63.5, 66.6, 70.5, 80.7, 115.5, 115.8, 128.4, 129.0, 136.5, 138.6, 160.8, 164.1, 172.6 ppm; EIMS (*m*/*z*) 477 (M^+). Anal. ($C_{29}H_{29}NF_2O_3$) C, H, N.

***S*-(+)-2β-Carbophenylethoxy-3α-(bis[4-fluorophenyl]-methoxy)tropane (11e).** Compound **11e** was prepared from **10e** as described for **11a** in 70% yield. $[\alpha]^{25}_D$ +5.7° (*c* 1, CH_3OH); IR 1731, 1506 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6−2.1 (6H, m), 2.09 (3H, s, NCH_3), 2.67 (1H, m, H-2), 2.91 (2H, t, *J* = 6.8 Hz, CH_2Ph), 3.06 (1H, m. H-5), 3.49 (1H, m, H-1), 3.95 (1H, d, *J* = 4.9 Hz, H-3), 4.21−4.37 (2H, m, OCH_2), 5.31(1H, s, O*CH*Ph_2), 6.94−7.00 (4H, m, Ar−H), 7.13−7.30 (9H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 25.0, 25.6, 35.4, 36.5, 42.0, 61.3, 63.5, 65.4, 70.6, 80.7, 115.5, 115.8, 126.9, 128.8, 129.2, 138.4, 138.7, 160.8, 164.1, 172.8 ppm; EIMS (*m*/*z*) 491 (M^+). Anal. ($C_{30}H_{31}NF_2O_3$) C, H, N.

***S*-(+)-2β-Carbo(4-nitrophenyl)ethoxy-3α-(bis[4-fluorophenyl]methoxy)tropane (11f).** Compound **11f** was prepared from **10f** as described for **11a** in 76% yield as a dark oil. $[\alpha]^{26}_D$ +12.5° (*c* 1, CH_3OH); IR 1733, 1507 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62−2.12 (6H, m), 2.07 (3H, s, NCH_3), 2.68 (1H, m, H-2), 2.95−3.10 (3H, m, H-5, CH_2Ph), 3.45 (1H, m, H-1), 3.93 (1H, d *J* = 4.9 Hz, H-3), 4.25−4.42 (2H, m, OCH_2), 5.31 (1H, s, O*CH*Ph_2), 6.92−7.03 (4H, m, Ar−H), 7.20−7.28 (4H, m, Ar−H), 7.36 (2H, d, *J* = 8.6 Hz, Ar−H), 8.15 (2H, d, *J* = 8.6 Hz, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.5, 25.2, 34.9, 36.0, 41.8, 51.9, 61.0, 63.3, 63.9, 70.0, 80.4, 115.2, 115.5, 123.7, 128.3, 129.8, 138.3, 145.9, 146.8, 160.4, 163.7, 172.3 ppm. Anal. ($C_{30}H_{30}N_2F_2O_5$) C, H, N.

***S*-(+)-2β-Carbo(4-aminophenyl)ethoxy-3α-(bis[4-fluorophenyl]methoxy)tropane (13).** Compound **11f** (233 mg, 0.43 mmol) was dissolved in a mixture of CH_3OH (5 mL) and EtOAc (5 mL) and reduced by hydrogenation over 10% Pd/C catalyst (30 mg) at 40 psi for 30 min. The catalyst was removed using suction filtration through Celite, and the solvents were removed under vacuum. The residue was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:5:1) to afford **13** (154 mg, 70%) as a gum. $[\alpha]^{25}_D$ +4.0° (*c* 1, $CHCl_3$); IR 3371, 1725, 1507 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60−1.78 (1H, m), 1.90−2.12 (5H, m), 2.12 (3H, s, NCH_3), 2.68 (1H, m, H-2), 2.80 (2H, t, *J* = 7.0 Hz, CH_2Ph), 3.06 (1H, m, H-5), 3.52 (1H, m, H-1), 3.58 (2H, br, NH_2), 3.96 (1H, d, *J* = 4.9 Hz, H-3),

4.10−4.30 (2H, m, OCH_2), 5.32 (1H, s, O*CH*Ph_2), 6.61 (2H, d, J = 8.4 Hz, Ar−H), 6.92−7.05 (6H, m, Ar−H), 7.18−7.30 (4H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.6, 25.2, 34.2, 36.2, 41.7, 51.9, 61.0, 63.1, 65.4, 70.2, 80.3, 115.4, 115.5, 127.8, 128.3, 129.8, 138.3, 138.4, 144.8, 160.4, 163.7, 172.5 ppm; EIMS (*m*/*z*) 506 (M^+). Anal. ($C_{30}H_{32}N_2F_2O_3$) C, H, N.

***S*-(+)-2β-Carbo(3-iodo-4-aminophenyl)ethoxy-3α-(bis-[4-fluorophenyl]methoxy)tropane (14).** Compound **13** (100 mg, 0.2 mmol) was dissolved in glacial HOAc (5 mL). To the solution was added extremely slowly ICl (36 mg, 0.22 mmol) in glacial HOAc (2 mL) over 2 h. The solvent was removed under vacuum. The residue was dissolved in H_2O (10 mL) and neutralized with aqueous $NaHCO_3$ solution to pH 9. The aqueous solution was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried (K_2CO_3) and concentrated. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:5:1) to give **14** (62 mg, 49%) as an oil. $[\alpha]^{24}_D$ +3.5° (*c* 1.5, $CHCl_3$); IR 3369 (br), 1725, 1506 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70−1.80 (1H, m), 1.88−2.15 (5H, m), 2.11 (3H, s, NCH_3), 2.69 (1H, mH-2), 2.75 (2H, m, CH_2Ph), 3.07 (1H, m, H-5), 3.51 (1H, m, H-1), 3.95 (1H, d, J = 4.9 Hz, H-3), 4.01 (2H, br, NH_2), 4.10−4.25 (2H, m, OCH_2), 5.32 (1H, s, O*CH*Ph_2), 6.65 (1H, d, J = J = 8.4 Hz, Ar−H), 6.90−7.05 (5H, m, Ar−H), 7.17−7.28 (4H, m, Ar−H), 7.49 (1H, s, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.6, 25.2, 33.6, 36.2, 41.7, 51.9, 61.0, 63.2, 65.1, 70.1, 80.3, 84.1, 114.6, 115.1, 115.4, 128.4, 128.5, 129.6, 129.9, 138.3, 139.1, 145.3, 160.4, 163.7, 172.4 ppm.

***S*-(+)-2β-Carbo(3-iodo-4-azidophenyl)ethoxy-3α-(bis[4-fluorophenyl]methoxy)tropane (15).** To a solution of compound **14** (40 mg, 0.06 mmol) in a mixture of acetic acid (1 mL) and H_2O (1 mL) was added $NaNO_2$ (6 mg, 0.09 mmol), and the mixture was stirred at 0 °C for 30 min. Then NaN_3 (6 mg, 0.09 mmol) was added, and the mixture was stirred for another 30 min at 0 °C. The mixture was diluted with H_2O, basified with saturated $NaHCO_3$ solution, and extracted with chloroform. The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 97:3:1) to yield 26 mg (63%) of **15** as an oil. $[\alpha]^{25}_D$ +3.1° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.74−1.80 (1H, m), 1.88−2.15 (5H, m), 2.10 (3H, s, NCH_3), 2.69 (1H, m, H-2), 2.84 (2H, m, CH_2Ph), 3.08 (1H, m, H-5), 3.48 (1H, m, H-1), 3.74 (1H, d, J = 5.0 Hz, H-3), 4.23 (2H, m, OCH_2), 5.33 (1H, s, O*CH*Ph_2), 6.95−7.06 (5H, m, Ar−H), 7.21−7.26 (5H, m, Ar−H), 7.65 (1H, s, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.6, 25.2, 33.9, 36.1, 41.7, 51.9, 61.0, 63.2, 64.5, 70.1, 80.3, 87.7, 115.2, 115.5, 118.3, 128.0, 128.4, 130.0, 136.6, 138.2, 138.4, 140.1, 140.4, 160.4, 163.7, 172.3 ppm. Anal. ($C_{30}H_{29}N_4F_2IO_3$) C, H, N.

***S*-(+)-2β-Carbo(4-isothiocyanatophenyl)ethoxy-3α-(bis-[4-fluorophenyl]methoxy)tropane (16).** Compound **13** (50 mg, 0.1 mmol) was dissolved in a mixture of $CHCl_3$ (6 mL) and aqueous $NaHCO_3$ solution (38 mg in 2.5 mL of H_2O), and the mixture was vigorously stirred. Freshly distilled $CSCl_2$ (10 μL, 0.13 mmol) was added to the solution dropwise at 0 °C. After the addition, stirring was continued for 3 h. Subsequently, the two layers were separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 97:3:1) to provide 44 mg (81%) of product **16** as an oil. Note that compound **16** is unstable at room temperature and needs to be stored at 0 °C. $[\alpha]^{25}_D$ +3.8° (*c* 1.2, $CHCl_3$); IR 2100, 1728, 1505 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60−1.80 (1H, m), 1.88−2.20 (5H, m), 2.09 (3H, s, NCH_3), 2.67 (1H, m, H-2), 2.90 (2H, m, CH_2Ph), 3.06 (1H, m, H-5), 3.46 (1H, m, H-1), 3.93 (1H, d, J = 4.77 Hz, H-3), 4.20−4.33 (2H, m, OCH_2), 5.31 (1H, s, O*CH*Ph_2), 6.90−7.03 (4H, m, Ar−H), 7.10−7.30 (7H, m, Ar−H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.6, 25.2, 34.6, 36.1, 41.7, 51.9, 61.0, 63.2, 64.4, 70.1, 80.4, 115.2, 115.5, 125.7, 128.3, 128.4, 129.6, 130.0, 137.6, 138.2, 138.4, 160.4, 163.7, 172.4 ppm.

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