The Discovery of an Unusually Selective and Novel Cocaine Analog: Difluoropine. Synthesis and Inhibition of Binding at Cocaine Recognition Sites

Peter C. Meltzer,*,† Anna. Y. Liang,† and Bertha. K. Madras‡

Organix Inc., 65 Cummings Park, Woburn, Massachusetts 01801, and Department of Psychiatry, Harvard Medical School and New England Regional Primate Center, Southborough, Massachusetts 01772

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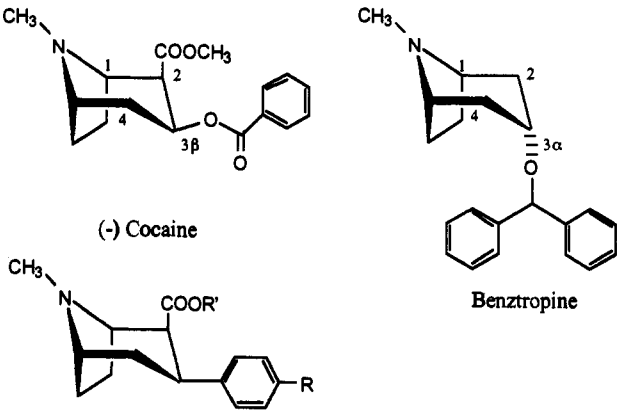
Cocaine is a stimulant drug with a high abuse liability. Although it inhibits several monamine transporters in the mammalian brain, its primary mechanism of action has been ascribed to its inhibition of the dopamine transporter. The synthesis, characterization, and receptor binding properties of all eight isomers of a unique tropane analog, 2-carbomethoxy-3-[bis(4-fluorophenyl)-methoxy]tropane is described. In addition, we report that the *S*-enantiomer, (*S*)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane, Difluoropine, is a potent (IC_{50} 10.9 nM) and selective (324 [DA/5HT]) ligand for the dopamine transporter.

Introduction

Cocaine is one of the most addictive drugs of abuse. Consequently a considerable effort has been expended in the study of its mechanisms of action. It is known that (−)-cocaine is a powerful reinforcer and stimulant that binds to specific recognition sites associated with monoamine transporters[1–6] in the mammalian brain. Its primary mechanism of action has been ascribed to its ability to inhibit the dopamine transporter.[3,7–10]

The topology of the cocaine binding site on the dopamine transporter has been mapped, and structure–activity relationship (SAR) studies of cocaine analogs have been aided considerably by the synthesis of a series of 3β-(aryltropanyl)-2β-(carboxylic acid methyl ester) analogs. Among the more potent of these congeners at [^{3}H]cocaine binding sites in striatum[3,4] is (1*R*)-3β-(4-fluorophenyl)-tropane-2β-carboxylic acid methyl ester, (also known as WIN 35,428 or CFT),[5,6,11,12] originally reported by Clarke[13] in 1973. This finding led to the development of its radiolabeled form and recognition that it was a highly selective probe for the dopamine transporter in primate brain.[5,6,14] It is also noteworthy that WIN 35,428 and congeners have been proposed by Kaufman and Madras[14] as potential tools for the presymptomatic diagnosis of Parkinson's diseased striatum since depletion of [^{3}H]WIN 35,428 binding in human Parkinson's diseased brains parallels dopamine depletion.[14,15] These results with [^{3}H]-WIN 35,428 led to the synthesis of other tropane analogs, some of which are among the most potent inhibitors of binding sites in striatum. These analogs include (1*R*)-3β-(3,4-dichlorophenyl)tropane-2β-carboxylic acid methyl ester (O-401),[16] (1*R*)-RTI 55,[17] and (1*R*)-RTI 121[18] (Figure 1). Detailed SAR of the binding of these agents and their effects on dopamine transporter function has only now begun to emerge,[16,19–22] and some of the earlier concepts are undergoing revision to incorporate the new data.

Although this series provided important structure–activity information, there is yet a considerable need for the design and synthesis of compounds that bind with high affinity and selectivity to the dopamine uptake mechanism, but in addition differ sufficiently *topologically* from the current tropane family. Such compounds may reveal the possible existence of multiple binding domains or an allosteric site that gives hope for the eventual discovery of a cocaine antagonist at the dopamine transporter.[23]



	R	R'
WIN 35,428	F	CH_3
O-401	3,4-Cl_2	CH_3
RTI 55	I	CH_3
RTI 121	I	$CH(CH_3)_2$

Figure 1.

In light of the results which we now report, it is important to note that the natural isomer, (1*R*)-(−)-cocaine, is considerably more potent than the unnatural isomer, (1*S*)-(+)-cocaine. It has about 200-fold higher affinity at the dopamine transporter than does the inactive enantiomer.[3,4,7,11,12] This stereoselective binding[3,4,7,24,25] has been evident throughout the cocaine and tropane analog series, and, indeed, only the *R*-enantiomers have been shown to be active in a wide variety of biological and neurochemical measures.[3,4,7,11–13,26] Parallel stereoselective behavioral effects have also been observed. In primates and rodents, the stimulating and reinforcing properties of the (−)-enantiomer of cocaine or its phenyltropane analogs were considerably greater than for the (+)-enantiomers.[3,9,26,27] Recently, Wang et al.[28] have demonstrated a parallel effect with RTI 55 (β-CIT) in as much as the *R*-isomer was about 14 000 times more potent than the *S*-isomer. Consequently most researchers have concentrated on the preparation

† Organix Inc.
‡ Harvard Medical School and New England Regional Primate Center.
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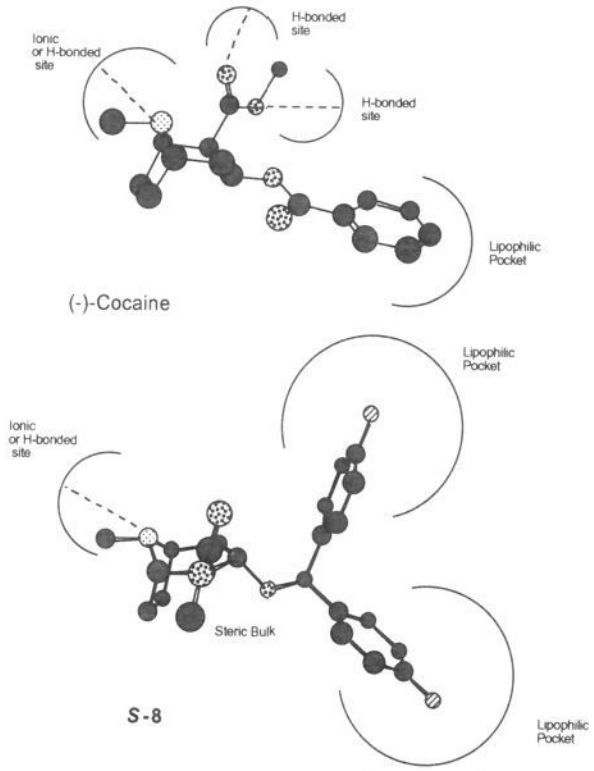


Figure 2. Schematic representation of the possible interaction of cocaine and ***S*-8** at the binding site on the dopamine transporter. The representation of the interaction of cocaine is taken, with permission, from Carroll et al. *J. Med. Chem.* **1992**, *35*, 969–981.

and pharmacological evaluation of enantiomerically pure compounds of the *R*-configuration.

The results which we now report are in stark contrast to this and show that, in certain instances, *none* of the currently accepted criteria for binding at this transporter are necessary.

The currently accepted[19,20] molecular requirements for binding of cocaine and its analogs at the dopamine transporter include the following: the *R*-configuration of the tropane, a 2β-substituent, and an aromatic ring at C-3, preferably in the 3β-orientation (see Figure 2). In congruence with these three requirements, it has since been shown that a variety of esters at the 2β-position can provide active compounds,[18,29] although esters are not an absolute requirement. In that regard, Davies[21] has reported the introduction of ketones at this site, while Kozikowski has successfully tested the limits of hydrogen-bonding requirements at this site by the introduction of unsaturated alkyl groups.[22] These results suggest that no hydrogen bonding moiety (such as an ester) is required here for binding, although Carroll[30] has offered an alternate explanation in which he proposed that an electrostatic contribution in the region of the 2β-substituent may be a requirement for activity. This contention has since been negated by the finding that a saturated alkyl group in the 2β-position maintains binding potency.[31] The active (–)-cocaine series, including all the tropane analogs of WIN 35,428, are of the *R*-configuration. Indeed, no tropanes in the *S*-configuration series have been found to date to display any high-affinity binding.

Guided by our desire to seek topologically different tropanes, we focused our attention on a series of benztropine analogs. Benztropine sulfonate (Cogentin or 3α-(diphenylmethoxy)-1αH,5αH-tropanemethanesulfonate[32] was synthesized[33] in 1952 and subsequently demonstrated to be useful as an anticholinergic drug in the treatment of Parkinsonism. This compound has served as our lead in the study now reported.

Benztropine (Figure 1) is a 3α-(diphenylmethoxy)-tropane analog of cocaine. It is unsubstituted in the C-2 position and therefore not optically active. Benztropine has an IC_{50} for inhibition of [^{3}H]CFT binding of 0.312 μM,[34] and we attributed this weak binding to the absence of the 2β-carbomethoxy group present in cocaine and its analogs. It should be noted that cocaine and WIN 35,428 both have the C-3 substituent in the β-configuration while benztropine has a 3α-(diphenylmethoxy) group. Introduction of functionality at the C-2 position of the benztropine confers optical isomerism and generates eight stereoisomers.

We now report a striking finding that *the S-enantiomer, (S)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)-methoxy]tropane, **S*-8, is considerably more potent than the R-enantiomers in our series of benztropines.* Compound ***S*-8** (also known as Difluoropine or O-620) not only binds potently, but its selectivity for the dopamine transporter exceeds that of any other molecule in our hands (see Table 3).

We now describe the synthesis, characterization, and receptor-binding properties of the eight isomers of 2-carbomethoxy-3-[bis(4-fluorophenyl)methoxy]tropane.

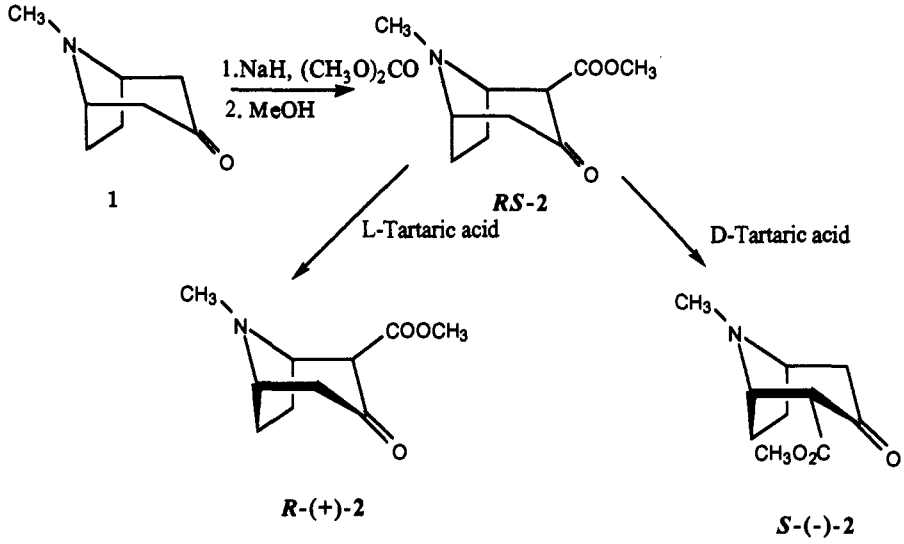
Chemistry

2-Carbomethoxy-3-(diphenylmethoxy)-1αH,5αH-tropane (2-carbomethoxybenztropine) exists in eight stereoisomeric forms. Any synthesis of these eight compounds must therefore take into account the preparation of four diastereomers and the resolution of the enantiomeric pairs. A synthesis of the eight stereoisomeric forms of cocaine has been reported by Carroll,[35] and this work has guided our synthesis. Since our goal has not been to achieve an optimum synthetic pathway to each of the isomers but rather to obtain sufficient material in hand for pharmacological studies, we elected to approach the synthesis of these compounds in a simultaneous manner without regard to optimization of yields. The series was therefore prepared by total synthesis from 3-tropinone as presented in Schemes 1–3. The β-configured *R*-compound, ***R*-9**, could also be obtained from ecgonine methyl ester which is readily available from naturally occurring (–)-cocaine.[16]

As shown in Scheme 1, commercially available 3-tropinone (**1**) was reacted with dimethyl carbonate[36,37] to provide (±)-2-carbomethoxy-3-tropinone, ***RS*-2**, in 68% yield. Resolution was then effected by fractional crystallization[35] of the bitartrates formed from (–)-tartaric acid to obtain (*S*)-(–)-2-carbomethoxy-3-tropinone, ***S*-2** (30%), and (+)-tartaric acid to obtain the (*R*)-(+)-2-carbomethoxy-3-tropinone, ***R*-2** (30%). This resolution was sufficiently critical so as to warrant an additional checking experiment. Therefore, the other enantiomer in each case was also obtained by treatment of the mother liquors from each initial crystallization with base to obtain the free bases and subsequent formation of the diastereomeric bitartrate salts with the alternate tartaric acid. Recrystallization then provided the alternate enantiomers. These proved identical with those obtained via the first method.

The enantiomeric purity of each of these resolved precursors was of critical importance to our further studies since their optical purity dictates the eventual enantio-

Scheme 1



meric purity of each of the eight final compounds. Consequently, we developed an HPLC method for the estimation of enantiomeric excess. The enantiomeric purity of ***R*-2** and ***S*-2** was measured by chiral HPLC. A base-line separation was obtained when a co-injection, or the unresolved racemic mixture, of ***S*-2** or ***R*-2** was applied to a Chiralcel OC column. Each individual racemate was shown to be entirely pure of the other when injected individually. The enantiomeric excess of each isomer was therefore >99% with retention times of 9 min (***R*-2**) and 12 min (***S*-2**). The optical rotations of ***R*-2** and ***S*-2** were measured in order to confirm the configuration of each compound. The rotation for ***S*-2** was −18.5°, while ***R*-2** gave a rotation of +18.6°. The values compared well with those reported by Findlay[38] (***S*-2**, −18.3°; ***R*-2**, +18.3°). We could not obtain Carroll's values[35] (***S*-2**, −25.7°; ***R*-2**, +25.4°) even after repeated crystallization. However, since the signs and absolute values of our ***R*-2** and ***S*-2** compared well with the literature values, it is clear that our ***R*-2** and ***S*-2** assignments are correct.

Reduction of each of the resolved enantiomerically pure tropinones ***R*-2** and ***S*-2** to provide six 2-carbomethoxy-3-hydroxy compounds, (***R*)-** and (***S*)-3, 4**, and **5** (Schemes 2 and 3) was effected with sodium borohydride in methanol at low temperature (−30 °C). Careful column chromatography allowed the three compounds obtained in each case to be separated. Isolated yields of 3.5% (***R*-3**), 17% (***R*-4**), 66% (***R*-5**) and 1.3% (***S*-3**), 19% (***S*-4**), 70% (***S*-5**) were obtained, respectively.

Epimerization at C-2 of ***S*-** and ***R*-5** to obtain the desired β-carbomethoxy epimers was then carried out, with concurrent hydrolysis, upon reflux with water. The methyl esters were then reintroduced, without epimerization, by means of methanol and HCl, to obtain the target intermediates ***R*-** and ***S*-6**[35] in 48% and 55% yields, respectively.

NMR spectra of the eight tropanols thus obtained were measured and the resonance positions and multiplicities for each compound proved identical with those reported by Carroll.[37] It should be noted that only four distinct spectra are obtained for the eight compounds since each enantiomeric pair is spectrally identical (see Table 2). Melting points for our compounds compared favorably with those reported in the literature, where available.

Although benztropine itself is prepared by the action of diphenyldiazomethane on tropine,[33] we found it more convenient to react each of compounds **3–6** with the appropriate benzhydrol in order to obtain the eight desired benztropine analogs, (***R*)-** and (***S*)-7–10**. Thus, in each case the alcohol was reacted with 4,4′-difluorobenzhydrol under conditions of azeotropic distillation in the presence of catalytic *p*-toluenesulfonic acid. Yields above 80% could be obtained for this reaction, once optimized.

As an additional confirmation of configuration, (*R*)-2β-carbomethoxy-3β-[bis(4-fluorophenyl)methoxy]tropane, ***R*-9**, could also be prepared by reaction of 4,4′-difluorobenzhydrol with ecgonine methyl ester. Ecgonine methyl ester was prepared in quantitative yield from (−)-cocaine by sequential hydrolysis and Fischer esterification with methanolic HCl.[16] Resolution was not required in this instance since all stereochemistry is controlled by the starting material: (−)-cocaine.

Since the biological data which we have uncovered are in stark contrast to what may be predicted from the data reported in the literature for the WIN 35,428 tropane analogs, it is essential that each of the eight benztropine analogs be fully characterized and their configurations established beyond doubt. It should be noted that the enantiomeric purity of the critical precursors, ***R*-2** and ***S*-2**, had already been established and no epimerization at C-1 is possible during the course of the subsequent chemistry. Therefore, the *R*- and *S*-configurations, respectively, must, per force, be maintained throughout.

Each of the four enantiomeric pairs has identical spectral features although opposite optical rotations. Configurational assignments were therefore made on each of the four pairs. Confirmation of enantiomeric purity was obtained from measurement of optical rotation. In this regard, the rotations measured for each of the enantiomeric pairs were generally equal and opposite within experimental error (Table 1). Notably, ***R*-** and ***S*-7** displayed opposite signs to all other enantiomeric pairs.

Chiral HPLC separation of enantiomers was confirmed for ***S*-8** and ***R*-8**, the most important compounds in this study. Elution of a mixture of ***R*-** and ***S*-8** with hexane/2-propanol (298:2 + 0.1% diethylamine) gave two base line separated peaks at t_R 8.8 and t_R 7.8 min, respectively. Elution of each individual compound showed the same retention times and purity of each enantiomer was >99%.

The similarities between the NMR data reported by Carroll et al.[35] for their four cocaine isomers and the four

Scheme 2. *S*-Enantiomers

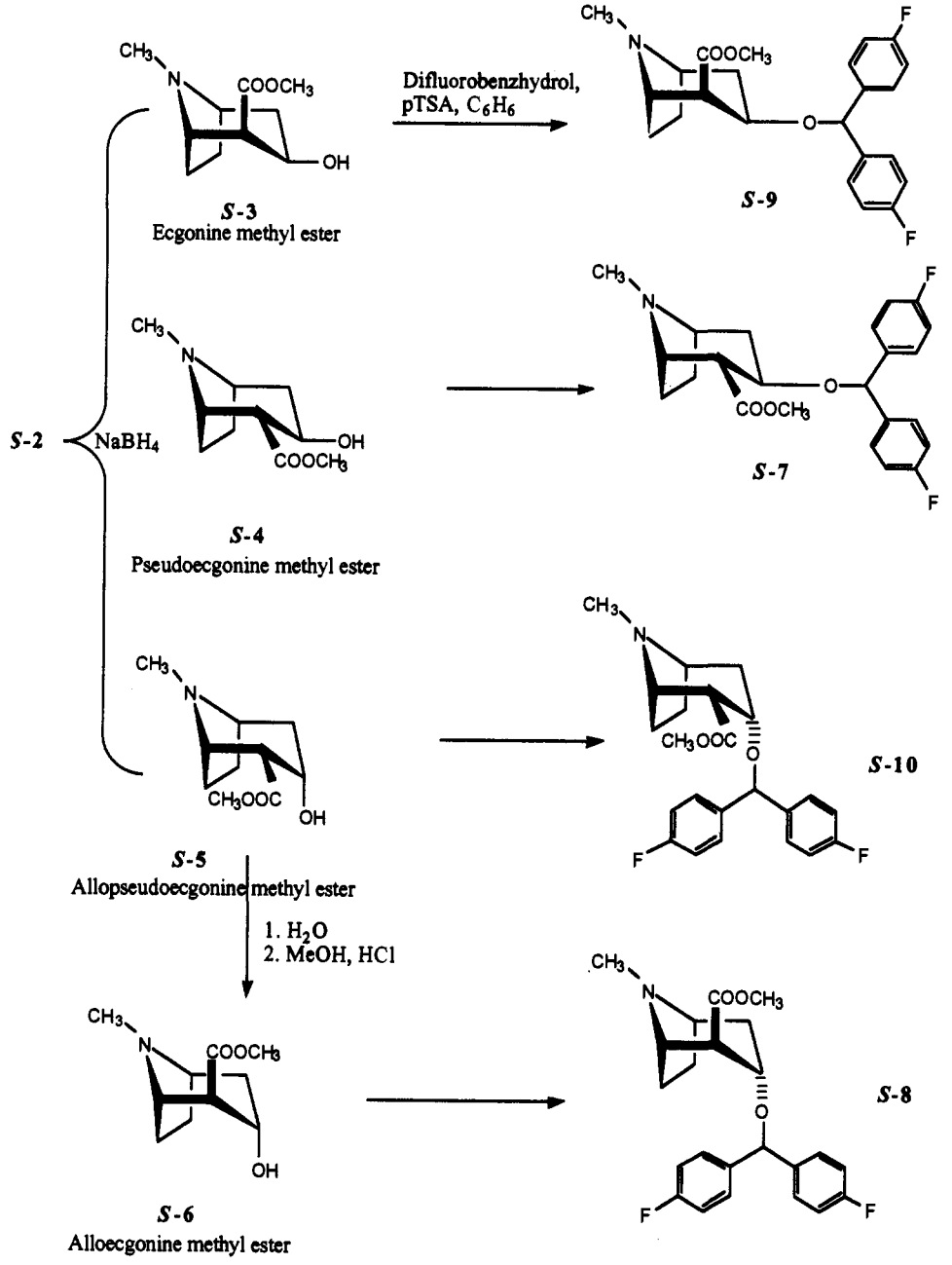


Table 1. Physical Data for the Eight Benztropine Analogs

compd	$[\alpha]_D$, deg	R_f (EtOAc + NH_4OH) (5% MeOH/EtOAc + NH_4OH)	mp, °C
***R*-7**	+31.6	0.47 (0.67)	193–195
***R*-8**	−18.9	0.57 (0.72)	132–133
***R*-9**	−36.8	0.59 (0.74)	89–90
***R*-10**	−29	0.15 (0.42)	118–120
***S*-7**	−30.2	0.47 (0.67)	202–203
***S*-8**	+21.6	0.57 (0.72)	131–132
***S*-9**	+36.1	0.59 (0.74)	76–77
***S*-10**	+19	0.15 (0.42)	128–130

pairs of 2-carbomethoxybenztropine isomers which we report here are striking (see Table 2). Indeed, for the diagnostic protons (H_1, H_2, H_{4ax}, and H_5) the spectra obtained are almost superimposable. For H_3, although the resonance positions for the benztropine analogs lie upfield of those of the cocaine (benzoyl ester), the patterns of multiplicity are identical, thus implying very similar coupling constants. It can be inferred, therefore, that, as for cocaine, the chair is the preferred conformation of the tropane ring in this series. A careful analysis of our data confirms, *a priori*, the configurational assignments especially of the most interesting compound in this series, ***S*-8**.

Some outstanding features of the NMR spectra are presented below. The trans diaxial relationship of the substituents at C-2 and C-3 in ***S*-8** results in a dihedral angle of about 90° between both H_3 and H_2 as well as H_3 and H_{4eq}. Consequently the coupling constant between these protons is close to $J = 0$ Hz. However, the angle between H_3 and H_{4ax} is about 40° with a resultant theoretical coupling constant of 5.3 Hz (calculated from the Karplus equation).[39] In fact, a doublet is observed at δ 4.00 ($J = 5.37$ Hz) for H_3 in ***S*-8**. In contrast, multiplets are observed for H_3 in all three other configurations.

Also, H_2 in ***S*-8** appears as a singlet, thus reflecting both the dihedral angles between H_1, H_3, and H_2 as about 90° ($J = 0$ Hz). In all other isomers, the H_2 proton resonates as either a multiplet (***R*-9** m; ***R*-7** dd; $J = 2.8$, 10.2 Hz) or a very broad singlet (***S*-10** bs).

Scheme 3. *R*-Enantioners

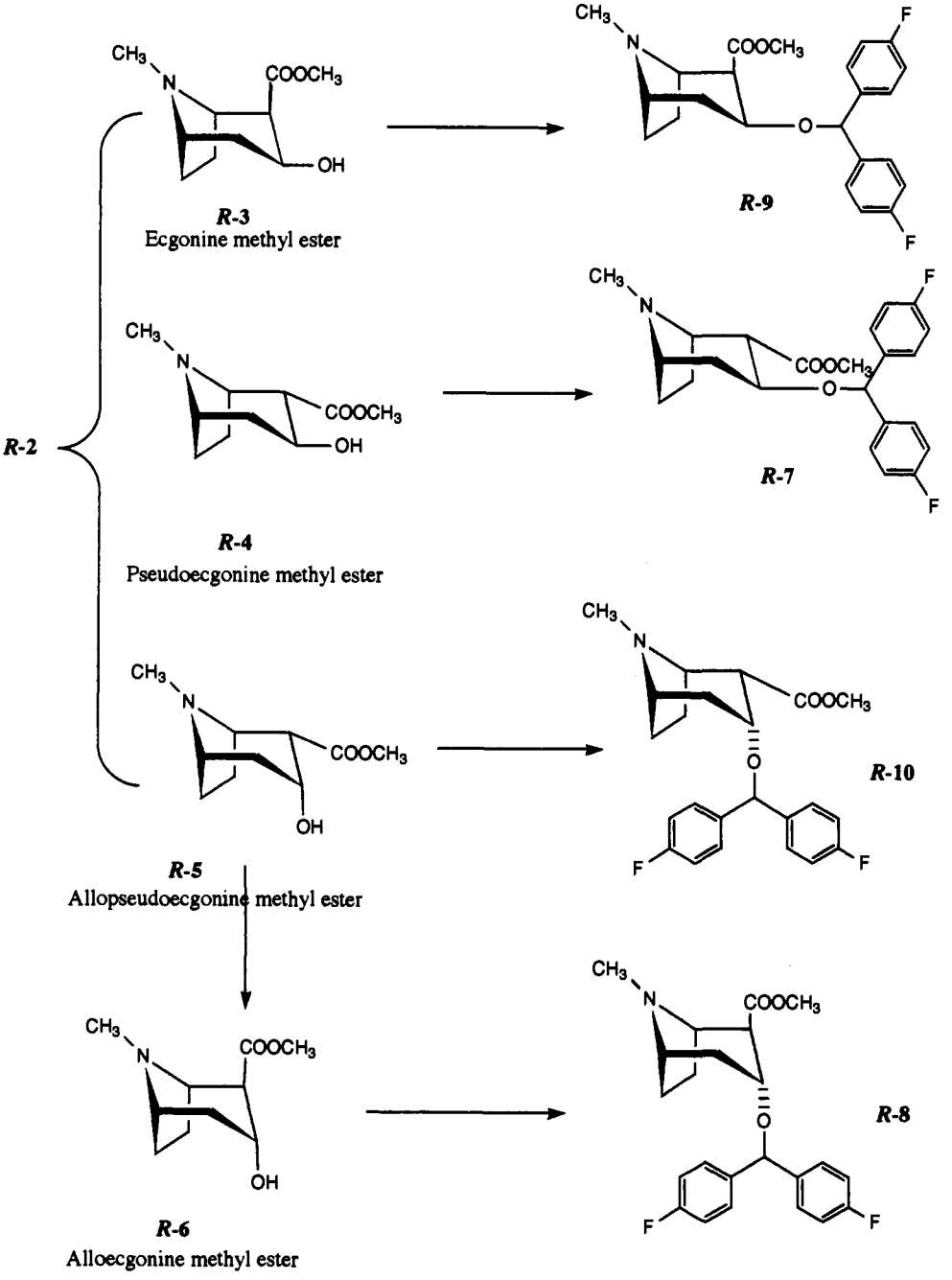


Table 2. Resonance Positions[a] for Eight Benztropine Analogs and Precursor Alcohols

compd	H_1	H_2	H_3	H_{4ax}	H_{4eq}	H_5	NCH_3	OCH_3	OCH	arom
***S*-7/*R*-7**	3.34	3.00	4.03	1.93?	1.81?	3.16	2.41	3.66	5.52	7.0–7.27
***S*-8/*R*-8**	3.59	2.73	4.00	2.00	−2.15	3.11	2.20	3.69	5.36	7.0–7.26
***S*-9/*R*-9**	3.39	2.76	3.58	2.31	2.00	3.19	2.15	3.68	5.38	7.0–7.26
***S*-10/*R*-10**	3.39	2.98	4.05	2.53	2.17	3.04	2.29	3.49	5.36	7.0–7.27
***S*-3/*R*-3**	3.58	2.76	3.80	1.5–2.20		3.14	2.19	3.76		
***S*-4/*R*-4**	3.46	2.71	4.13	1.5–2.20		3.21	2.40	3.75		
***S*-5/*R*-5**	3.42	2.90	4.27	1.5–2.20		3.11	2.32	3.75		
***S*-6/*R*-6**	3.57	2.63	4.37	1.5–2.20		3.10	2.19	3.72		

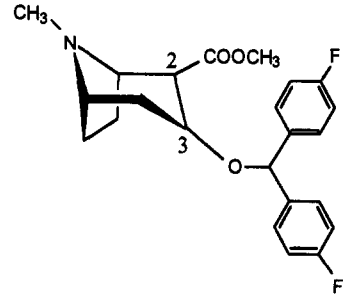
[a] ^{1}H-NMR (400 MHz, $CDCl_3$) with TMS as internal standard. See Carroll (*J. Org. Chem.* 1982, *47*, 13–19) for comparative resonance positions of the eight cocaine isomers.

Also for H_{4ax} in ***S*-10**, a septet is seen reflecting one small, one medium, and one large coupling constant while in ***S*-9** an apparent doublet of triplets (formally a ddd) is seen as expected for a combination of two large coupling constants and one small. Examination of a Dreiding model of ***S*-10** shows the dihedral relationship of the H_{4ax} proton with the H_3, H_5, and gem proton (H_{4eq}) to be entirely consistent with this observed coupling.

Biology

The affinities of the eight benztropine analogs and (−)-cocaine for the dopamine and serotonin transporters were

Table 3. Inhibition of [^{3}H]-3β-(4-Fluorophenyl)tropane-2β-carboxylic Acid Methyl Ester Binding to the Dopamine Transporter (DA) and [^{3}H]Citalopram Binding to the Serotonin Transporter (5HT) by Benztropine Analogs in Cynomolgus Monkey Caudate-Putamen[a]



compd	configuration		IC_{50}, nM		selectivity 5HT/DA
	C_2	C_3	DA	5HT	
***S*-7**	α	β	8900 ± 1520	4087*	0.5
***S*-8**	β	α	10.9 ± 1.2	3530 ± 78	324
***S*-9**	β	β	3380 ± 780	1830 ± 135	0.5
***S*-10**	α	α	1750 ± 369	4930 ± 253	2.8
***R*-7**	α	β	21900 ± 605	5500 ± 2914	0.25
***R*-8**	β	α	2040 ± 283	1980 ± 406	1.0
***R*-9**	β	β	11700 ± 836	1460 ± 255	0.10
***R*-10**	α	α	3840 ± 239	9150 ± 147	2.4
benztropine	–	α	312 ± 1.1	24100 ± 14800	77
WIN 35,428	β	β	12.9 ± 1.1	160 ± 20	12
RTI 55	β	β	1.08 ± 0.06	2.53 ± 0.02	2

[a] Each radioligand was incubated with tissue (4 mg/mL original wet tissue weight) and 7–14 concentrations of a cocaine congener as described in the Experimental Section. Nonspecific binding of [^{3}H]WIN 35,428 was measured with 30 μM (–)-cocaine and of [^{3}H]citalopram with 1 μM fluoxetine. IC_{50} values were computed by the EBDA computer program and are the means (±SD) of 2–7 independent experiments, each conducted in triplicate. *n = 1.

determined in competition studies using [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428) to label elements of the dopamine transporter and [^{3}H]citalopram to label the serotonin transporter (Table 3). The studies were conducted in cynomolgus monkey striatum for two reasons. First, cynomolgus monkeys were planned to be used as subjects for future PET imaging studies. Second, as these compounds may be suitable for monitoring Parkinson's disease, it is necessary to determine the DA/5HT transporter selectivities in the brain region, striatum, that undergoes the most severe depletion of dopamine nerve terminals.

Competition studies were conducted with nonsaturating concentrations of the radioligand and a range of concentrations of the test drug. All drugs inhibited [^{3}H]WIN 35,428 and [^{3}H]citalopram binding in a concentration-dependent manner.

Of the eight possible enantiomers in this series, only one, ***S*-8**, bound to [^{3}H]WIN 35,428 labeled sites on the dopamine transporter in the low nanomolar range (IC_{50} 10.9 nM). This observation corresponds well with similar findings in the series of eight cocaine isomers in that only (–)-cocaine showed appreciable binding while the other isomers were relatively inactive.[35] Furthermore, the binding exhibited by ***S*-8** was characterized by high selectivity for the dopamine transporter over the 5HT transporter, a selectivity that is one of the highest of any compound studied in our hands. This high-affinity binding was not conferred on any other isomer in this series, either *R* or *S*. All the other enantiomers also were relatively nonselective for the dopamine transporter over the 5HT transporter. Indeed, for two of the compounds, ***R*-7** and ***R*-9**, an increased affinity for the 5HT transporter was observed. Among the least potent of the compounds was ***R*-9**, the direct analog of WIN 35,428. It is clear from this series that ***S*-8** (O-620 or Difluoropine) has a unique fit and conformation for the dopamine transporter.

Discussion

The most striking result reported here is that, as might be expected for a stereoselective binding site, only one of the eight isomers of the 2-carbomethoxybenztropines shows significant binding to the dopamine transporter (***S*-8**, IC_{50} 10.9 nM). Furthermore, this compound displays a selectivity (324:1) for the dopamine transporter over serotonin binding that exceeds, in our hands, that displayed by any other tropane analog including WIN 35,428 or RTI 55.

The current model used to describe the interaction of a tropane ligand with its receptor, the dopamine uptake receptor, cannot account for the results presented here and requires careful reinterpretation of notions of receptor ligand interaction in this field. As we now report, the *only isomer* that displayed substantial binding to the dopamine uptake receptor is of the form that possesses none of the structural features commonly associated with high-affinity phenyltropane binding, while the isomers which do possess "appropriate" structural features (for example: (*R*)-2β-3β) displayed little binding to that transporter. There are at least two possibilities that may account for our observations.

First, the benztropine analogs which we now report and the tropane analogs reported earlier by ourselves and others bind differently to this receptor, or bind at different sites.

In this regard, a concept which is increasingly accepted[2,8,23,24,40–42] and which has guided much of the work reported here involves the idea that binding for dopamine and for the tropane analogs may not be identical.[23] Therefore, it may be possible to discover an antagonist of cocaine which does not block uptake of dopamine. Such antagonists have been suggested by Rothman.[43,44]

Second, the tropanes and benztropines may bind at the same general site on the dopamine transporter but differ in how they fit that site. If this is the case, one may speculate as follows.

Upon examination of an energy-minimized[45] or Dreiding model of *S*-8, it is evident that the tropane is in a chair conformation as borne out by the NMR coupling constants presented earlier. The 2-carbomethoxy group can then provide a steric barrier to the diphenylmethoxy system, and one of the rings in the diphenyl system is consequently pushed away from the 2-site, while the remaining ring (which lies face-to-face with the first at an angle of about 109°) fills the positional requirement of 3-substitution, that is, perpendicular and level to the plane of the tropane ring (Figure 2).

In the *S*-series, the other phenyl ring is "pushed" topologically into the domain of the 2β-carbomethoxy group of, for instance, WIN 35,428. Carroll has reported[18,29] that the phenyl ester of his WIN analogs show substantial binding, and our model corroborates this finding in that in *S*-8, one phenyl ring appears to lie topologically where the phenyl ester of Carroll's molecule resides. Thus meeting the requirement of filling a proposed lipophilic pocket on the receptor rather than a hydrogen bonding site. Consequently, the 2β-carbomethoxy group in the *S*-series of these benztropine analogs may satisfy nothing more than a steric function, namely to *push the phenyl ring into the correct position for binding.*

This also suggests that the 2β-carbomethoxy in (*R*)-cocaine or the other active WIN analogs serves only to provide some lipophilicity to engage a lipophilic pocket of the receptor and invites the synthesis and biological evaluation of compounds with less polar, or nonpolar, 2β-substituents of varying steric bulk (e.g., phenalkyl groups).

The similarity between compounds in the GBR series and the benztropine analogs reported here is interesting.[46] Most notable is the common diphenylmethoxy functionality. It is intriguing to speculate how these two classes of compounds may bind at the same site. Specifically, we have recently reported[47] that the two nitrogen atoms in the piperidine ring of the GBR series effect binding differently and that the nitrogen distal to the diphenylmethoxy substituent is responsible for the binding potency exhibited by those compounds. A superimposition of Dreiding models of both *S*-8 and GBR 12935 shows a good fit between the diphenylmethoxy substituents of each compound as well as the tropane nitrogen and the distal nitrogen of GBR 12935.

Conclusions

In this report we have described the synthesis and biological evaluation of the eight isomers of 2-carbomethoxy-3-[bis(4-fluorophenyl)methoxy]tropane. A striking discovery is reported in that, in strong contrast to the known biology of all other cocaine or tropane analogs, an *S*-enantiomer, namely *(S)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane*, has been found to be a potent and selective inhibitor of the dopamine uptake transport mechanism. These results provide some evidence for the notion that either multiple binding sites exist or that binding of this benztropine analog does not fit the cocaine binding domain in the same way as does cocaine. Such an interpretation lends hope for the discovery of a cocaine antagonist which displays reduced influence on the uptake of dopamine itself. Such compounds may have clinical implications.

Experimental Section

NMR spectra were recorded on either a Bruker 100, a Varian XL 400, or a Bruker 300 NMR spectrometer. TMS was used as internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Optical rotations were measured at the sodium D line at 21 °C using a JASCO DIP 320 polarimeter (1-dm cell). Thin-layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was accomplished with either iodine vapor, UV exposure, or treatment with phosphomolybdic acid (PMA). Preparative TLC was carried out on Analtech uniplates silica gel GF 2000 microns. Flash chromatography was carried out on Baker silica gel 40 mM. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. A Beckman 1801 scintillation counter was used for scintillation spectrometry. 0.1% bovine serum albumin and (−)-cocaine were purchased from Sigma Chemicals.

[^{3}H]WIN 35,428 ([^{3}H]CFT, 2β-carbomethoxy-3β-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 79.4–87.0 Ci/mmol) and [^{3}H]-citalopram (86.8 Ci/mmol) were purchased from DuPont-New England Nuclear (Boston, MA). (*R*)-(−)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse [NIDA]. Fluoxetine was donated by E. Lilly & Co. HPLC analyses were carried out on a Waters 510 system with detection at 254 nm on a Chiralcel OC column (flow rate 1 mL/min).

(*RS*)-(±)-2-Carbomethoxy-3-tropinone (*RS*-2). 3-Tropinone, 1 (20.59 g, 0.148 mol), in cyclohexane (140 mL) was added dropwise to a mixture of NaH (60% dispersion, 11.83 g, 0.296 mol), dimethyl carbonate (27.4 mL, 0.325 mol), and cyclohexane (60 mL) at gentle reflux. MeOH (0.5 mL) was added at the end of addition. The reaction mixture was heated at reflux until effervescence ceased. Water (250 mL) was added after the reaction mixture was cooled to room temperature. The layers were separated, and the cyclohexane layer was extracted with additional water (2 × 100 mL). The combined aqueous layers were saturated with NH_4Cl (120 g) and extracted with CH_2Cl_2 (8 × 100 mL). The dried (K_2CO_3) extracts were concentrated to dryness to afford 23.1 g (79%) of *RS*-2 as a yellow oil which crystallized upon standing. The material was purified by flash chromatography (10% $iPrNH_2$, 30% Et_2O/hexane) to afford 20 g (68%) of *RS*-2: mp 102–103 °C (lit.[38] mp 103.5–104.6 °C); R_f 0.65 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions).

Resolution of (*RS*)-(±)-2-Carbomethoxy-3-tropinone (*RS*-2). (*R*)-(+)-2-Carbomethoxy-3-tropinone (*R*-2). L-Tartaric acid (9.0 g, 0.06 mol) was added to (*RS*)-(±)-2-carbomethoxy-3-tropinone, *RS*-2 (11.61 g, 0.059 mol), in EtOH (100 mL). EtOH was removed in vacuo after all the tartaric acid had dissolved. The residue was recrystallized once from a 10:1 acetone/water (440 mL) mixture (19.68 g of material obtained) and once from MeOH (100 mL) to afford 6.21 g of (*R*)-(+)-2-carbomethoxy-3-tropinone bitartrate as a white crystalline solid. The salt was dissolved in saturated Na_2CO_3 (50 mL), and the free base generated was extracted with CH_2Cl_2 (2 × 100 mL). The dried (K_2CO_3) extracts were concentrated to afford 3.56 g (30%) of (*R*)-(+)-2-carbomethoxy-3-tropinone, *R*-(+)-2, as a white solid: mp 104–106 °C (lit.[38] mp 108.5–109.5 °C); R_f 0.65 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.5–2.4 (m, 7H), 2.32 (s, 3H), 2.75 (m, 1H), 3.32 (t, 1H), 3.75 (s, 3H); $[\alpha]^{21}_D$ +18.6° (*c* = 1, MeOH) [lit.[35] $[\alpha]^{25}_D$ +25.4° (*c* = 1, MeOH)]; $[\alpha]^{20}_D$ +18.3° (*c* = 1, MeOH)[38]; analytical HPLC (Chiralcel OC column) eluting with hexane/2-propanol (9:1) t_R 9 min, >99%.

(*S*)-(−)-2-Carbomethoxy-3-tropinone (*S*-2). The filtrates from above were concentrated to dryness. The residue obtained was dissolved in saturated Na_2CO_3 (50 mL), and the free base generated was extracted with CH_2Cl_2 (100 mL). The dried (K_2CO_3) organic extract was concentrated to dryness. The residue (2.37 g, 0.012 mol) and D-tartaric acid (2.6 g, 0.017 mol) were dissolved in EtOH. EtOH was then removed in vacuo, and the residue was recrystallized once from a 10:1 acetone/water (110 mL) mixture (3.7 g obtained) and once from MeOH (20 mL) to afford 2.15 g (11%) of (*S*)-2-carbomethoxy-3-tropinone (−)-bitartrate. The free base, *S*-(−)-2, was generated as above (1.1 g, 10%): mp 104–105 °C (lit.[38] mp 108.5–109.5 °C); R_f 0.65 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H-NMR as for *R*-2 above; $[\alpha]^{21}_D$ −18.5° (*c* = 1, MeOH) [lit.[35] $[\alpha]^{25}_D$ −25.7° (c = 1, MeOH); $[\alpha]^{21}_D$ −18.3° (*c* = 1, MeOH);[38] analytical HPLC

(Chiralcel OC column) eluting with hexane/2-propanol (9:1) t_R 12 min, >99%.

Alternate Procedure: Resolution of (*RS*)-(±)-2-Carbomethoxy-3-tropinone (*RS*-2) To Obtain (*S*)-(−)-2-Carbomethoxy-3-tropinone (*S*-2). D-Tartaric acid (57.16 g, 0.38 mol) was added to (*RS*)-(±)-2-carbomethoxy-3-tropinone, ***RS*-2** (75 g, 0.38 mol), in EtOH (500 mL). EtOH was removed in vacuo after all the tartaric acid had dissolved. The residue was recrystallized once from a 10:1 acetone/water (440 mL) mixture (129.7 g of material obtained) and once from MeOH (500 mL) to afford 39.9 g of (*S*)-(+)-2-carbomethoxy-3-tropinone bitartrate as a white crystalline solid.

The salt was dissolved in saturated Na_2CO_3 (150 mL,) and the free base generated was extracted with CH_2Cl_2 (2 × 100 mL). The dried (K_2CO_3) extracts were concentrated to afford 22.6 g (30%) of (*S*)-(−)-2-carbomethoxy-3-tropinone, ***S*-(−)-2**, as a white solid: mp 103–105 °C (lit.[38] mp 108.5–109.5 °C); R_f 0.65 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H-NMR as for ***R*-2** above; $[\alpha]^{21}_D$ −18.1° (*c* = 1, MeOH) [lit.[35] $[\alpha]^{25}_D$ −25.7° (*c* = 1, MeOH); $[\alpha]^{21}_D$ −18.3° (*c* = 1, MeOH);[38] analytical HPLC (Chiralcel OC column) eluting with hexane/2-propanol (9:1) t_R 12 min, >99%.

(*R*)-Ecgonine Methyl Ester (*R*-3), (*R*)-Pseudoecgonine Methyl Ester (*R*-4), and (*R*)-Allopseudoecgonine Methyl Ester (*R*-5). Sodium borohydride (1.55 g, 0.041 mol) was added to a solution of (*R*)-2-carbomethoxy-3-tropinone, ***R*-2** (3.4 g, 0.017 mol), in MeOH (300 mL) at −78 °C. The reaction mixture was left in the freezer (−30 °C) overnight. Concentrated HCl (8 mL) was added carefully, and the solution was concentrated to dryness. The residue was dissolved in water (100 mL), basified with NH_4OH, saturated with NaCl, and extracted with CH_2Cl_2 (3 × 100 mL). The dried (K_2CO_3) extracts were concentrated to dryness (3.1 g). The residue was chromatographed over silica gel (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1) to afford the following compounds.

(*R*)-Ecgonine methyl ester, ***R*-3** (120 mg, 3.5%): yellow oil; R_f 0.69 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H-NMR see Table 2.

(*R*)-Pseudoecgonine methyl ester, ***R*-4** (590 mg, 17%): white solid; mp 115-117 °C (lit.[48] mp 114–116 °C); R_f 0.33 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H-NMR see Table 2.

(*R*)-Allopseudoecgonine methyl ester, ***R*-5** (2.25 g, 66%): pale yellow solid; mp 60–62 °C (lit.[48] mp 78–79 °C); R_f 0.25 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H-NMR see Table 2.

(*R*)-Alloecgonine Methyl Ester (*R*-6). (*R*)-Allopseudoecgonine methyl ester, ***R*-5** (1.68 g, 8.4 mmol), and water (25 mL) were combined and heated at reflux for 18 h. Water was removed. Methanolic HCl (100 mL) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness. The residue was dissolved in water (100 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (150 mL). The dried (K_2CO_3) extract was concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 5% MeOH in EtOAc) to afford (*R*)-alloecgonine methyl ester, ***R*-6** (0.80 g, 48%), as a light brown solid: mp 63–65 °C: R_f 0.54 (5% MeOH/EtOAc + NH_4OH), anhydroecgonine methyl ester (45 mg) and starting material, ***R*-5** (350 mg, 21%).

(*R*)-(+)-2α-Carbomethoxy-3β-[bis(4-fluorophenyl)-methoxy]tropane (*R*-7). (*R*)-Pseudoecgonine methyl ester, ***R*-4** (220 mg, 1.1 mmol), 4,4′-difluorobenzhydrol (442 mg, 2.0 mmol), *p*-toluenesulfonic acid monohydrate (384 mg, 2.0 mmol), and benzene (40 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser were heated at reflux for 6 h. 4,4′-Difluorobenzhydrol (440 mg, 2.0 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) were added, and the reaction mixture was heated at reflux for another 16 h. Benzene was removed. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 10% MeOH in EtOAc) to afford (*R*)-(+)-2α-carbomethoxy-3β-[bis-(4-fluorophenyl)methoxy]tropane, ***R*-7** (439 mg, 99%), as a pale yellow viscous oil which was treated with ethereal HCl to afford 421 mg (87%) of the HCl salt as a white solid: mp 197–199 °C; R_f 0.67 (5% MeOH/EtOAc + NH_4OH); ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.35 (m, 2H), 1.56 (m, 1H), 1.78 (m, 1H), 1.81 (m, 1H), 1.93 (m, 1H), 2.41 (s, 3H, NCH_3), 3.00 (dd, 1H, *H*-2), 3.16 (m, 1H, *H*-5), 3.34 (bs, 1H, *H*-1), 3.66 (s, 3H, OCH_3), 4.03 (m, 1H, *H*-3), 5.52 (s, 1H, OC*H*), 7.00 (m, 4H, Ar*H*), 7.20 (dd, 2H, Ar*H*), 7.27 (dd, 2H, Ar*H*); $[\alpha]^{21}_D$ +31.6° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$·HCl) C, H, N, Cl.

(*R*)-(−)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-tropane (*R*-8). (*R*)-Alloecgonine methyl ester, ***R*-8** (173 mg, 0.87 mmol), 4,4′-difluorobenzhydrol (382 mg, 1.74 mmol), *p*-toluenesulfonic acid monohydrate (200 mg, 1.04 mmol), and benzene (50 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser were heated at reflux for 18 h. 4,4′-Difluorobenzhydrol (320 mg, 1.45 mmol) and *p*-toluenesulfonic acid monohydrate (70 mg, 0.36 mmol) were added, and the reaction mixture was heated at reflux for a further 5 h. Benzene was removed in vacuo. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 2% MeOH in EtOAc) to afford (*R*)-(−)-2β-carbomethoxy-3α-[bis-(4-fluorophenyl)methoxy]tropane, ***R*-8** (283 mg, 81%), as a white solid: mp 132–133 °C; R_f 0.72 (5% MeOH/EtOAc + NH_4OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.80 (d, 1H), 2.00–2.15 (m, 5H), 2.20 (s, 3H, NCH_3), 2.73 (s, 1H, *H*-2), 3.11 (bs, 1H, *H*-5), 3.59 (d, 1H, *H*-1), 3.69 (s, 3H, OCH_3), 4.00 (d, 1H, *H*-3), 5.36 (s, 1H, OC*H*), 7.00 (m, 4H, Ar*H*), 7.26 (dd, 4H, Ar*H*); analytical HPLC (Chiralcel OC column) eluting with hexane/2-propanol (98:2 + 0.1% DEA) t_R = 8.8 min; $[\alpha]^{21}_D$ −18.9° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$) C, H, N.

(*R*)-(−)-2β-Carbomethoxy-3β-[bis(4-fluorophenyl)methoxy]-tropane (*R*-9). (*R*)-Ecgonine methyl ester (from natural (*R*)-(−)-cocaine), ***R*-3** (200 mg, 1.0 mmol), 4,4′-difluorobenzhydrol (442 mg, 2.0 mmol), *p*-toluenesulfonic acid monohydrate (384 mg, 2.0 mmol), and benzene (40 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser were heated at reflux for 6 h. 4,4′-Difluorobenzhydrol (400 mg, 1.8 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) were added, and the reaction mixture was heated at reflux for another 16 h. Benzene was removed. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness. The residue was chromatographed over silica gel (EtOAc/hexane, 1:1, EtOAc, 10% MeOH/EtOAc) to afford (*R*)-(−)-2β-carbomethoxy-3β-[bis(4-fluorophenyl)methoxy]tropane, ***R*-9** (248 mg, 62%), as a pale yellow solid: mp 89–90 °C; R_f 0.74 (5% MeOH/EtOAc + NH_4OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.24–1.31 (m, 2H), 1.64 (m, 2H) 2.0 (m, 1H, H-4_{eq}), 2.15 (s, 3H, NCH_3), 2.31 (ddd, 1H, H-4_{ax}), 2.76 (m, 1H, *H*-2), 3.19 (bs, 1H, *H*-5), 3.39 (bs, 1H, *H*-1), 3.58 (ddd, 1H, *H*-3), 3.68 (s, 3H, OCH_3), 5.38 (s, 1H, OC*H*), 6.98 (dd, 4H, Ar*H*), 7.19 (dd, 2H, Ar*H*) 7.26 (dd, 2H, arom-*H*); $[\alpha]^{21}_D$ −36.8° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$) C, H, N.

(*R*)-(−)-2α-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-tropane (*R*-10). (*R*)-Allopseudoecgonine methyl ester, ***R*-5** (330 mg, 1.7 mmol), 4,4′-difluorobenzhydrol (774 mg, 3.5 mmol), *p*-toluenesulfonic acid monohydrate (405 mg, 2.1 mmol), and benzene (50 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser were heated at reflux for 18 h. 4,4′-Difluorobenzhydrol (400 mg, 1.8 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) were added, and the reaction mixture was heated at reflux for another 5 h. Benzene was removed in vacuo. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 2% MeOH in EtOAc) to afford (*R*)-(−)-2α-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane, ***R*-10** (554 mg, 83%), as a pale yellow viscous oil: R_f 0.42 (5% MeOH/EtOAc + NH_4OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.73 (m, 24), 1.90 (m, 2H), 2.12 (m, 1H, H-4_{eq}), 2.29 (s, 3H, NCH_3), 2.53 (sept, 1H, H-4_{ax}), 2.98 (bs, 1H, *H*-2), 3.04 (m, 1H, *H*-5), 3.39 (m, 1H, *H*-1), 3.49 (s, 3H, OCH_3), 4.05 (bs, 1H, *H*-3), 5.36 (s, 1H, OC*H*), 7.00 (dd, 4H, Ar*H*), 7.16 (dd, 2H, Ar*H*), 7.27 (dd, 2H, Ar*H*); HCl salt mp 118–120 °C; $[\alpha]^{21}_D$ −29.0° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$·HCl·H_2O) C, H, N, Cl.

(*S*)-Ecgonine Methyl Ester (*S*-3), (*S*)-Pseudoecgonine Methyl Ester (*S*-4), and (*S*)-Allopseudoecgonine Methyl Ester (*S*-5). Sodium borohydride (0.5 g, 13.2 mmol) was added to a solution of (*S*)-2-carbomethoxy-3-tropinone, ***S*-2** (1.09 g, 5.5 mmol), in MeOH (100 mL) at −78 °C. The reaction mixture was left in the freezer (−30 °C) overnight. Concentrated HCl (3 mL) was added carefully, and the solution was concentrated to dryness. The residue was dissolved in water (30 mL), basified with NH_4OH, saturated with NaCl, and extracted with CH_2Cl_2 (3 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness (1.06 g). The residue was chromatographed over silica gel (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1) to afford the following compounds.

(*S*)-Ecgonine methyl ester, ***S*-3**: yellow oil (15 mg, 1.3%); R_f 0.69 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H NMR identical to ***R*-3** (see Table 2).

(*S*)-Pseudoecgonine methyl ester, ***S*-4** (214 mg, 19%): off-white solid; mp 105–107 °C (lit.[8] mp 114–115 °C); R_f 0.33 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H NMR identical to ***R*-4** (see Table 2).

(*S*)-Allopseudoecgonine methyl ester, ***S*-5** (768 mg, 70%): off-white solid; mp 75.5–77.5 °C (lit.[8] mp 79–80 °C); R_f 0.25 (CH_2Cl_2/$CHCl_3$/MeOH/NH_4OH, 100:40:9:1, two elutions); ^{1}H NMR identical to ***R*-5** (see Table 2).

(*S*)-Alloecgonine Methyl Ester (*S*-6). (*S*)-Allopseudoecgonine methyl ester, ***S*-5** (0.43 g, 2.16 mmol), and water (10 mL) were combined and heated at reflux for 18 h. Water was removed in vacuo. Methanolic HCl (25 mL) was added, and the mixture stirred at room temperature overnight. The reaction mixture was concentrated to dryness. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (50 mL). The dried (K_2CO_3) extract was concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 5% MeOH in EtOAc) to afford (*S*)-alloecgonine methyl ester, ***S*-6** (235 mg, 55%): mp 76.5–77.5 °C; R_f 0.54 (5% MeOH/EtOAc + NH_4OH); ^{1}H NMR identical to ***R*-6** (see Table 2) and starting material, ***S*-5** (135 mg, 31%).

(*S*)-(−)-2α-Carbomethoxy-3β-[bis(4-fluorophenyl)methoxy]tropane (*S*-7). (*S*)-Pseudoecgonine methyl ester, ***S*-4** (94 mg, 0.47 mmol), 4,4′-difluorobenzhydrol (208 mg, 0.94 mmol), *p*-toluenesulfonic acid monohydrate (181 mg, 0.94 mmol), and benzene (40 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser were heated at reflux for 22 h. Benzene was removed. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 5% MeOH in EtOAc) to afford (*S*)-(−)-2α-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane, ***S*-7** (162 mg, 86%), as a pale yellow viscous oil: R_f 0.67 (5% MeOH/EtOAc + NH_4OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.35 (m, 2H), 1.56 (m, 1H), 1.78 (m, 1H), 1.81 (m, 1H), 1.93 (m, 1H), 2.41 (s, 3H, NC*H*$_3$), 3.00 (dd, 1H, *H*-2), 3.16 (m, 1H, *H*-5), 3.34 (bs, 1H, *H*-1), 3.66 (s, 3H, OC*H*$_3$), 4.03 (m, 1H, *H*-3), 5.52 (s, 1H, OC*H*), 7.00 (m, 4H, Ar*H*), 7.20 (dd, 2H, Ar*H*), 7.27 (dd, 2H, Ar*H*); HCl salt mp 202–203 °C; $[\alpha]^{21}_D$ −30.2° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$·HCl·0.2 H_2O) C, H, N, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane (*S*-8). (*S*)-Alloecgonine methyl ester, ***S*-6** (900 mg, 4.5 mmol), 4,4′-difluorobenzhydrol (1.99 g, 9.0 mmol), *p*-toluenesulfonic acid monohydrate (1.3 g, 6.8 mmol), and benzene (50 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser was heated at reflux for 18 h. An additional amount of 4,4′-difluorobenzhydrol (1.0 g, 4.5 mmol) and *p*-toluenesulfonic acid monohydrate (200 mg, 1.0 mmol) was added and reflux continued for 5 h. Benzene was removed in vacuo. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness. The residue was chromatographed over silica gel (2% NH_4OH, 2% MeOH in EtOAc, 5% MeOH, 3% NH_4OH in EtOAc) to afford (*S*)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane, ***S*-8** (1.14 g, 63%), as an off white solid: mp 131–132 °C; R_f 0.72 (5% MeOH/EtOAc + NH_4OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.80 (d, 1H), 2.00–2.15 (m, 5H), 2.20 (s, 3H, NC*H*$_3$), 2.73 (s, 1H, *H*-2), 3.11 (bs, 1H, *H*-5), 3.59 (d, 1H, *H*-1), 3.69 (s, 3H, OC*H*$_3$), 4.00 (d, 1H, *H*-3), 5.36 (s, 1H, OC*H*), 7.00 (m, 4H, Ar*H*), 7.26 (dd, 4H, Ar*H*); analytical HPLC (Chiralcel OC column) eluting with hexane/2-propanol, 98:2, + 0.1% DEA) t_R = 7.8 min; $[\alpha]^{21}_D$ +21.6° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$) C, H, N.

(*S*)-(+)-2β-Carbomethoxy-3β-[bis(4-fluorophenyl)methoxy]tropane (*S*-9). (*S*)-Ecgonine methyl ester, ***S*-5** (62 mg, 0.31 mmol), 4,4′-difluorobenzhydrol (137 mg, 0.62 mmol), *p*-toluenesulfonic acid monohydrate (119.6 g, 0.62 mmol), and benzene (50 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser were heated at reflux for 18 h. 4,4′-Difluorobenzhydrol (137 mg, 0.62 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol) were added, and the reaction mixture was heated at reflux for another 5 h. Benzene was removed in vacuo. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) organic extracts were concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 2% MeOH in EtOAc) to afford (*S*)-(+)-2β-carbomethoxy-3β-[bis(4-fluorophenyl)methoxy]tropane, ***S*-9** (58 mg, 46%), as an off-white solid: mp 76–77 °C; R_f 0.56 (10% Et_3N/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.24–1.31 (m, 2H), 1.64 (m, 2H) 2.0 (m, H, *H*-4$_{eq}$), 2.15 (s, 3H, N-C*H*$_3$), 2.31 (ddd, 1H, *H*-4$_{ax}$), 2.76 (m, 1H, *H*-2), 3.19 (bs, 1H, *H*-5), 3.39 (bs, 1H, *H*-1), 3.58 (ddd, 1H, *H*-3), 3.68 (s, 3H, OC*H*$_3$), 5.38 (s, 1H, OC*H*), 6.98 (dd, 4H, arom-*H*), 7.19 (dd, 2H, arom-*H*) 7.26 (dd, 2H, arom-*H*); $[\alpha]_D$ +36.1° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$) C, H, N.

(*S*)-(+)-2α-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane (*S*-10). (*S*)-Allopseudoecgonine methyl ester, ***S*-5** (204 mg, 1.02 mmol), 4,4′-difluorobenzhydrol (451 mg, 2.04 mmol), *p*-toluenesulfonic acid monohydrate (244 mg, 1.22 mmol), and benzene (50 mL) in a 100-mL round-bottom flask fitted with a Dean–Stark trap and condenser were heated at reflux for 18 h. 4,4′-Difluorobenzhydrol (450 mg, 2.04 mmol) was added, and the reaction mixture was heated at reflux for a further 8 h. Benzene was removed in vacuo. The residue was dissolved in water (10 mL), basified with NH_4OH, and extracted with CH_2Cl_2 (2 × 50 mL). The dried (K_2CO_3) extracts were concentrated to dryness. The residue was chromatographed over silica gel (3% NH_4OH, 2% MeOH in EtOAc) to afford (*S*)-(+)-2α-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane, ***S*-10** (234 mg, 57%), as a pale yellow viscous oil: R_f 0.39 (5% MeOH/EtOAc + NH_4OH); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.73 (m, 2H), 1.90 (m, 2H), 2.12 (m, 1H, *H*-4$_{eq}$), 2.29 (s, 3H, NC*H*$_3$), 2.53 (sept, 1H, *H*-4$_{ax}$), 2.98 (bs, 1H, *H*-2), 3.04 (m, 1H, *H*-5), 3.39 (m, 1H, *H*-1), 3.49 (s, 3H, OC*H*$_3$), 4.05 (bs, 1H, *H*-3), 5.36 (s, 1H, OC*H*), 7.00 (dd, 4H, Ar*H*), 7.16 (dd, 2H, Ar*H*), 7.27 (dd, 2H, Ar*H*); HCl salt mp 128–130 °C; $[\alpha]^{21}_D$ +19.0° (*c* = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$·HCl·0.5 H_2O) C, H, N, Cl.

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