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Synthesis of 8-thiabicyclo[3.2.1]octanes and their binding affinity for the dopamine and serotonin transporters

Duy-Phong Pham-Huu,[a] Jeffrey R. Deschamps,[b] Shanghao Liu,[a] Bertha K. Madras[c] and Peter C. Meltzer[a,*]

[a]*Organix Inc., 240 Salem Street, Woburn, MA 01801, USA*
[b]*Naval Research Laboratory, Washington D.C. 20375, USA*
[c]*Harvard Medical School and New England Regional Primate Research Center, Southborough, MA 01772, USA*

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Abstract—Cocaine is a potent stimulant of the central nervous system. Its reinforcing and stimulant properties have been associated with inhibition of the dopamine transporter (DAT) on presynaptic neurons. In the search for medications for cocaine abuse, we have prepared 2-carbomethoxy-3-aryl-8-thiabicyclo[3.2.1]octane analogues of cocaine. We report that this class of compounds provides potent and selective inhibitors of the DAT and SERT. The selectivity resulted from reduced activity at the SERT. The 3β-(3,4-dichlorophenyl) analogue inhibits the DAT and SERT with a potency of IC_{50} = 5.7 nM and 8.0 nM, respectively. The 3-(3,4-dichlorophenyl)-2,3-unsaturated analogue inhibits the DAT potently (IC_{50} = 4.5 nM) and selectively (>800-fold vs SERT). Biological enantioselectivity of DAT inhibition was limited for both the 3-aryl-2,3-unsaturated and the 3α-aryl analogues (2-fold), but more robust (>10-fold) for the 3β-aryl analogues. The (1*R*)-configuration provided the eutomers.

1. Introduction

Cocaine abuse continues to present a societal problem of monumental proportions. The search for suitable medications has not yet yielded a clinically proven candidate, and physicians presented with addicted patients do not yet have the tools with which to deal with this challenging problem.

Cocaine is a potent stimulant of the central nervous system. Its reinforcing and stimulant properties have been primarily associated with its ability to inhibit the dopamine transporter (DAT) on presynaptic neurons in the striatum.[1–3] While the DAT has been considered a prime target of cocaine, and therefore of potential medications designed to inhibit the activity of cocaine, the serotonin transporter (SERT) may also play a substantial role in the pharmacological activity of cocaine.[4–6] Inhibition of the monoamine uptake systems by cocaine effectively incapacitates the system that removes excess dopamine from the synapse. This, in turn, results in an increase of the synaptic dopamine concentration, with the consequence of increased activation of postsynaptic dopamine receptors. This hyperstimulation of postsynaptic receptors is responsible for cocaine's stimulant activity. The reinforcing and addictive properties of cocaine are thought to be related to its pharmacokinetic profile. The addict gains almost immediate effect (<15 s) with short duration of action (10–15 min), and only the lack of continuous availability of drug appears to terminate the addict's binge. Therefore, in the search for a safe replacement therapeutic agent, many researchers have focused their efforts on the design of compounds that bind with selectivity to the DAT and manifest slow onset of action and long duration of action.[7]

The focus of much attention in the design of prospective medications for cocaine abuse has been the class of bicyclo[3.2.1]octanes.[8–23] This focus has its historic origins in the structure of cocaine itself (Fig. 1) as well as the metabolically more stable lead tropane, WIN 35,428, a 3β-aryl-2β-carbomethoxy-8-azabicyclo[3.2.1]octane analogue of cocaine disclosed by Clarke et al. in 1973.[24]

Until 1997 when we presented evidence[14] that the 8-aza functionality within the bicyclo[3.2.1]octane (tropane) series is not a prerequisite for potent inhibition of

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* Corresponding author. Tel.: +1 781 932 4142; fax: +1 781 933 6695; e-mail: meltzer@organixinc.com

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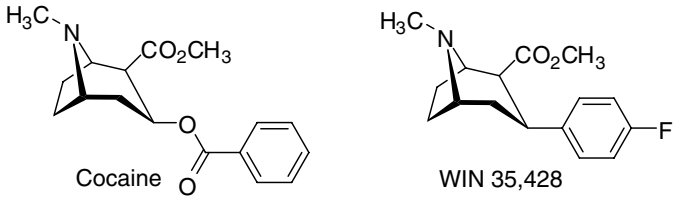


Figure 1. Cocaine and WIN35,428 are the lead compounds.

monoamine uptake systems, it was assumed that the presence of an amine nitrogen was essential for binding to these systems.[25,26] We later demonstrated that the topological properties of tropane-like ligands (bicyclo[3.2.1]octanes) that bind to monoamine uptake systems were possibly more important than the presence, or absence, of specific functionality.[14] Indeed, 8-oxabicyclo[3.2.1]octanes (8-oxatropanes)[14] and 8-carbabicyclo[3.2.1]octanes (8-carbatropanes)[27] also manifested substantial binding potency at the DAT as well as selectivity versus SERT inhibition.

The concept of replacement of an amine nitrogen by an ether oxygen or a methylene carbon was then extended to methylphenidate where we showed that, once again, binding potency was maintained in methylphenidate analogues that are topologically similar, but functionally different.[28]

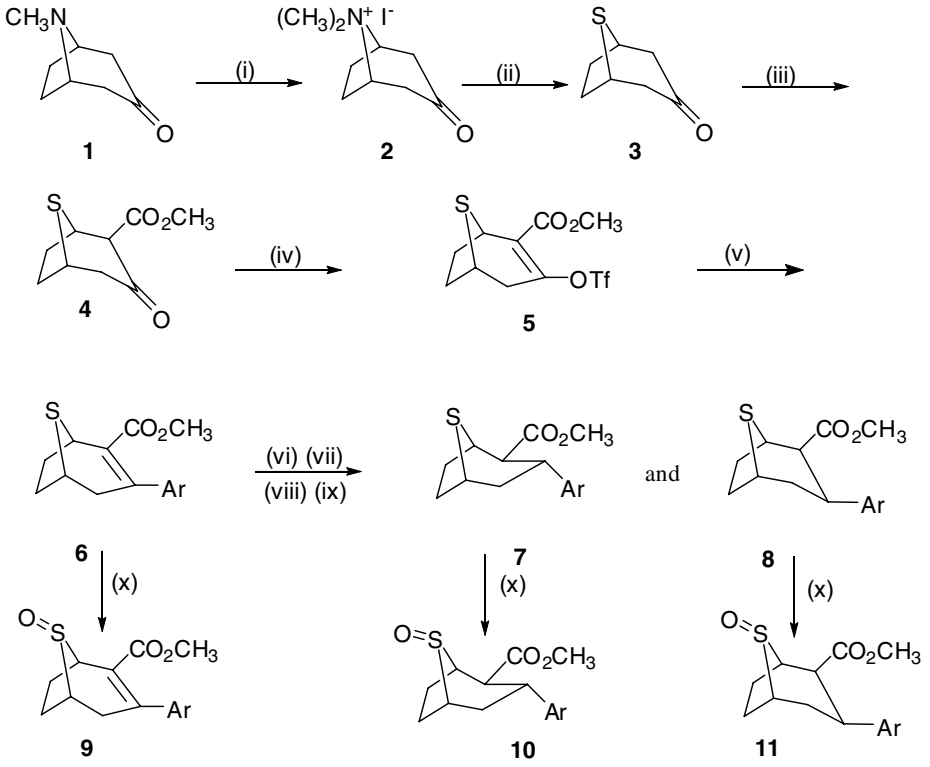
In this report, we again explore the functional role of the 8-heteroatom in the bicyclo[3.2.1]octane skeletal nucleus. We were particularly interested in the effect of a sulfur for nitrogen exchange because sulfur is similar to oxygen in that it has two lone pairs of electrons. However, it does not favor hydrogen bonding and therefore has some attributes that are more similar to the 8-methylene group of our 8-carbatropanes[29] with respect to interaction with a biological macromolecule. This exchange of S for N has been reported for unrelated D_2 ligands previously.[30–34] However, although the resultant thia compounds manifested potency, their potency was much reduced compared with their aza counterparts. Majewski et al. have explored enolate chemistry of 8-thiabicyclo[3.2.1]octane-3-one and have used enantioselective deprotonation to prepare 2-substituted-8-thiabicyclo[3.2.1]octane-3-ones as an entry to sulfur analogues of tropanes.[35,36] However, no 3-aryl-8-thiabicyclo[3.2.1]octanes were reported.

We have previously published a preliminary report concerning 3-aryl-2-carbomethoxy-8-thiabicyclo[3.2.1]oct-2-enes.[37] We now report the synthesis and biological evaluation of a family of 2-carbomethoxy-8-thiabicyclo[3.2.1]octanes and oct-2-enes that provide examples of compounds that are potent inhibitors of the DAT while manifesting substantial selectivity versus inhibition of the SERT.

2. Chemistry

The general approach that we have adopted for the synthesis of bicyclo[3.2.1]octanes has pivoted around an enol triflate that is then subjected to palladium catalyzed Suzuki coupling with a suitably substituted arylboronic acid.[14,37] In this synthesis of 8-thia analogues, this seminal intermediate is **5** (Scheme 1). Thus, tropinone **1** was quaternized with methyl iodide to obtain the dimethylammonium iodide intermediate **2** in 90% yield. Treatment with sodium sulfide, as described by Parr et al.,[38] then provided the 3-ketobicyclooctane **3** in 78% yield. Introduction of the 2-carbomethoxy group was effected[14,36] with methylcyanoformate, and the keto ester **4** was obtained in 69% yield. It is important to note that the racemic ketoester **4** exists in an equilibrium mixture of three tautomeric forms: the 2α-carbomethoxy keto ester, the 2β-carbomethoxy keto ester, and the enol ester. This tautomerism is of no stereochemical significance since all centers are lost in the ensuing conversion to the enol triflate **5**. However the existence of the three tautomers complicates the ^{1}H NMR spectrum of **4** significantly. Introduction of the triflate was effected with *N*-phenyltriflimide and sodium bis(trimethylsilyl)amide in 75% yield. ^{1}H NMR of the triflate **5** is unequivocal. The H_1 proton at δ 4.39 appears as a double doublet (J = 0.9, 3.6 Hz), while the $H_{4\beta}$ proton at δ 2.99 appears as a double double doublet [J = 2.1 ($H_{4\beta}$–$H_{6\beta}$), 4.3 ($H_{4\beta}$–H_5), 18.6 Hz ($H_{4\beta}$–$H_{4\alpha}$)].

Suzuki coupling of the appropriately substituted boronic acids with enol triflate **5** under palladium tetrakis triphenylphosphine catalysis provided the products **6** (74–96%). Samarium iodide reduction[14,39] then provided the saturated compounds as a mixture of **7** and **8** in 60–90% yields. In general, a 4:1 ratio of the 3α-aryl (**7**) to 3β-aryl (**8**) analogues was obtained from this samarium iodide reduction. Compounds **7** and **8** were initially separated by laborious sequential column chromatography in order to obtain the pure 3α-aryl (**7f,g,i,j**) and 3β-aryl (**8f,g,i,j**) esters in 30–40% and 20–35% yields, respectively. Subsequently, a two-step procedure was utilized to obtain configurationally pure 3α-aryl and 3β-aryl compounds for those compound mixtures that could not be purified effectively by column chromatography. Thus the mixed esters **7** and **8**, obtained directly from the samarium iodide reduction, were de-esterified (50–76% yield) under nonhydrolytic conditions with aluminum trichloride and dimethyl sulfide under an argon atmosphere[40,41] to provide their carboxylic acids (50–80% yields). The acids were separated by flash column chromatography and then re-esterified with trimethylsilyldiazomethane to obtain pure **7** and **8** (77–94% yields). The combined yields via the two step procedure were similar to those of the direct chromatographic separation of the samarium iodide products (see **7** and **8 f,g,i,j**), and were in the range of 35–51% for the 3α-aryl



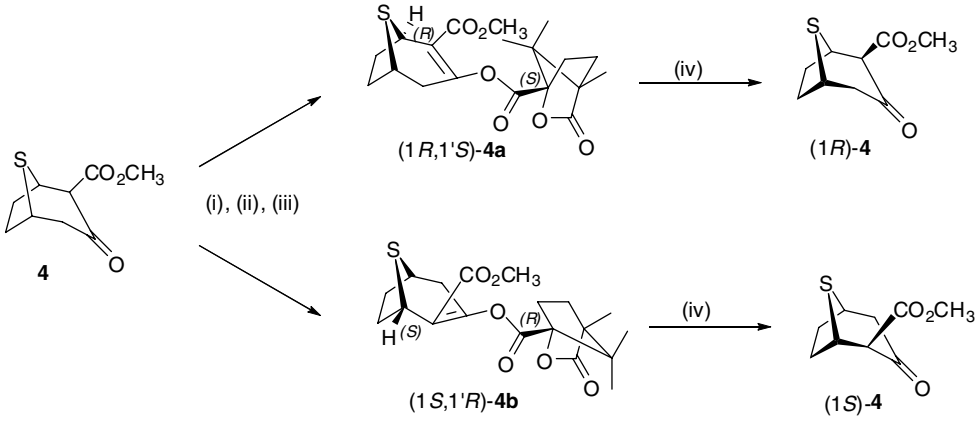
Scheme 1. Synthesis of 8-thiabicyclo[3.2.1]octanes and 8-thiabicyclo[3.2.1]octenes. Reagents and conditions: (i) CH_3I, 90%; (ii) Na_2S, 78%; (iii) LDA, $NCCOOCH_3$, 69%; (iv) $NaN(TMS)_2$, $PhN(Tf)_2$, 75%; (v) $ArB(OH)_2$, $Pd(PPh_3)$, LiCl, Na_2CO_3, 74–96%; (vi) SmI_2, THF, MeOH, −60 °C, 60–90%; (vii) $AlCl_3$, $(CH_3)_2S$, 50–80%; (viii) column chromatography; (ix) $TMSCHN_2$, 77–94%; (x) KO_2, TMSCl, CH_3CN, 49–94%.

(**7**) and 11–18% for the 3β-aryl (**8**) compounds. However, the two-step procedure allowed facile separation of **7** and **8**, whereas the direct column chromatography of compounds obtained from samarium iodide reduction did not.

Oxidation of **6**, **7**, and **8** was carried out with potassium superoxide and trimethylsilyl chloride in acetonitrile to provide **9a**, **10a**–**f**, and **11a**,**b** in 49–94% yields. The sulfoxide **10f** was crystallized from ethyl acetate/heptane to obtain monoclinic crystals, and the *exo* orientation of the oxygen was established by X-ray crystallography.

Since biological enantioselectivity had already been demonstrated for the 8-oxabicyclooctanes[14] as well as for 8-azatropanes,[16] it was important to explore biological selectivity in this new class of 8-thiabicyclooctanes. The 3,4-dichlorophenyl analogues were selected for determination of biological enantioselectivity because the racemic 3,4-dichlorophenyl substituted **6f**, **7f**, and **8f** manifested substantial potency at the dopamine transporter. Intermediate ketoester **4** served as the springboard for resolution (Scheme 2).

Thus the enolate of **4** obtained by treatment with sodium bis(trimethylsilyl)amide in THF was functionalized



Scheme 2. Resolution of keto ester reagents and conditions. Reagents: (i) $NaN(TMS)_2$; (ii) (1*R*) or (1*S*)-camphanyl chloride; (iii) recrystallization from THF/hexanes, 64%; (iv) $NaOCH_3$, MeOH, 90%.

with (1*S*)-camphanyl chloride to provide the (1*R*,1′*S*)-camphanyl enol ester **4a**. Crystallization from THF/hexanes provided a pure diastereomer. The absolute stereochemistry of the ester derived from (1*S*)-camphanyl chloride was established as (1*R*,1′*S*)-**4a** by X-ray crystallography. (1*R*,1′*S*)-**4a** was then hydrolyzed with sodium methoxide in methanol to provide enantiomerically pure intermediate keto ester (1*R*)-**4**. Enantiomer (1*S*)-**4** was obtained similarly by the use of the (1*R*)-camphanyl chloride. The enantiomeric excess of (1*R*)-**4** and (1*S*)-**4** was established by ^{1}H NMR. The methyl resonances for the camphanyl methyl group of the esters (1*R*,1′*S*)-**4a** and (1*S*,1′*S*)-**4a** (or (1*S*,1′*S*)-**4b** and (1*S*,1′*R*)-**4b**) were baseline differentiated for the diastereomeric pairs (δ = 0.970 and 0.928 ppm) and could therefore be quantitated within the experimental error of NMR integration. Diastereomeric excess (de) was thus calculated as 97% for the (1*R*,1′*S*)-**4a** and 88% for (1*S*,1′*R*)-**4b**. This optical purity of (1*R*,1′*S*)-**4a** and (1*S*,1′*R*)-**4b** then governed the optical purity of the keto esters (1*R*)-**4** and (1*S*)-**4** generated upon ester hydrolysis (Scheme 2), as well as the purity of all subsequent products in the synthetic sequence (Scheme 1) since there were no transformations that could effect ring opening and closing thus altering the chirality at the bridgehead. Subsequent conversion of (1*R*)-**4** and (1*S*)-**4** was effected, as for racemic **4** above, to provide the 2,3-enes (1*R*)-**6f** and (1*S*)-**6f**. Samarium iodide reduction then gave the 3α-(3,4-dichlorophenyl) compounds (1*R*)-**7f** and (1*S*)-**7f** and the 3β-(3,4-dichlorophenyl) compounds (1*R*)-**8f** and (1*S*)-**8f**.

3. Biology

The affinities (IC_{50}) of the 8-thia-2-carbomethoxybicyclo[3.2.1]octane(ene)s for the dopamine (DAT) and serotonin (SERT) transporters were determined in competition studies using [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428) to label the dopamine transporter and [^{3}H]citalopram to label the serotonin transporter.[20,42,43] Studies were conducted in cynomolgous or rhesus monkey striata since these compounds are part of an ongoing investigation of structure–activity relationships at the dopamine transporter in these tissues, and meaningful comparisons with an extensive database and in vivo imaging data can be made. Competition studies were conducted with a fixed concentration of 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. Binding constants are presented in Tables 1 and 2.

4. Discussion

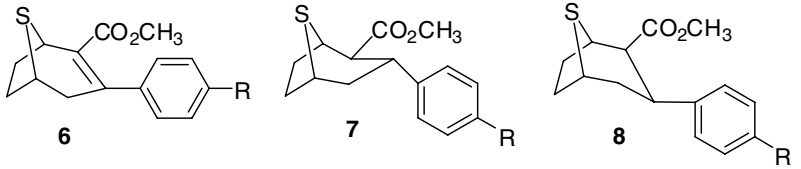
The affinities (IC_{50}) for the dopamine (DAT) and serotonin (SERT) transporters determined in competition studies using [^{3}H]WIN 35,428 to label the dopamine transporter and [^{3}H]citalopram to label the serotonin transporter are presented for a family of racemic 3-aryl-2-carbomethoxy-8-thiabicyclo[3.2.1]-octane(ene)s (Table 1). The most potent DAT and SERT inhibitors among these compounds possessed 3,4-dichloro substitution at the 3-aryl ring. These 3,4-dichlorophenyl analogues were obtained enantiomerically pure and their binding data, in comparison with data from the (1*R*)- and (1*S*)-8-oxa-,[14] (1*R*)- and (1*S*)-8-aza-,[9] 7β-hydroxy-(1*R*)- and (1*S*)-8-aza-,[20] and racemic 8-carba-[29] bicyclo[3.2.1]octane(ene)s, are presented in Table 2.

Among this class of 8-thia compounds, inhibitory potency at the DAT was not markedly different between the 2,3-enes **6**, the 3α-aryl **7**, (boat configured) and 3β-aryl **8** (chair configured) compounds. This was especially true for the more potent compounds (Table 1): 4-Cl (IC_{50} for **6c**, **7c**, **8c**: 13 nM, 11 nM, 9.6 nM, respectively), 4-Br (IC_{50} for **6d**, **7d**, **8d**: 9.1 nM, 6 nM, 6 nM, respectively), 4-I (IC_{50} for **6e**, **7e**, **8e**: 6.7 nM, 9 nM, 14 nM, respectively), 3,4-Cl_2 (IC_{50} for **6f**, **7f**, **8f**: 4.5 nM, 6.9 nM, 5.7 nM, respectively) and 3-(2-naphthyl) (IC_{50} for **6h**, **7h**, **8h**: 8 nM, 8 nM, 16 nM, respectively). However, inhibitory potency at the SERT, and therefore selectivity for the DAT, was quite different among these three classes. Thus the 3β-aryl analogues **8** were most potent at the SERT followed by the 3α-aryl compounds **7**. The unsaturated analogues **6** were the least potent inhibitors of the SERT, and were therefore the most selective for the DAT. Therefore the selectivity exhibited by 8-thia-2,3-unsaturated 3α-aryl and 3β-aryl compounds did not derive from enhanced activity at DAT, but rather from reduced activity at SERT. This DAT selectivity as a consequence of diminishing inhibitory potency at SERT was also evident in other 8-heterobicyclo[3.2.1]octanes. Thus in a comparison of 3,4-dichlorophenyl substituted tropanes (Table 2), SERT inhibition for the racemic 8-oxatropane analogues ranged from an IC_{50} = 6 μM (*R*/*S*-**12**) to IC_{50} = 64.5 nM (*R*/*S*-**13**) to the SERT potent *R*/*S*-**14a** with IC_{50} = 6.5 nM. This relative selectivity was also evident in the 8-carbatropane series with the 2,3-unsaturated *R*/*S*-**21** manifesting SERT IC_{50} = 5.1 μM, 3α-aryl *R*/*S*-**22** IC_{50} = 166 nM, and the least DAT selective 3β-aryl *R*/*S*-**23** with a SERT IC_{50} = 33 nM.

It is quite interesting that for the most potent DAT inhibitors, the differences between the DAT inhibitory potencies are less marked within this class of 8-thiatropane analogues, than they are for 8-aza or 8-oxatopane analogues. Therefore, SAR interpretations are less robust for these 8-thiatropane analogues. However, the relative binding potencies at the DAT of the 3-aryl-4-substituted analogues: 4-H, 4-F, 4-Cl, 4-Br, 4-I, 4-(2-naphthyl), and 3,4-dichlorophenyl in the three classes of 2,3-ene, (**6**), 3α-aryl (**7**), and 3β-aryl, (**8**) appear similar to that evidenced in all other 8-heterobicyclo[3.2.1]octanes explored.[14,20,27,29,37] Therefore, the structure–activity relationships (SAR) of the 2-carbomethoxy-3-arylbicyclo[3.2.1]octane(ene)s are consistent, thus supporting the hypothesis that these 8-hetero-tropanes likely bind in very similar, if not identical, domains on the DAT.

It is noteworthy that exchange of either the 3- or 4-chloro substituent in **6f** for a 3-fluoro (**6i**) or a 4-fluoro (**6j**)

Table 1. Inhibition of [^{3}H]WIN 35,428 binding to the dopamine transporter (DAT) and [^{3}H]citalopram binding to the serotonin transporter (SERT) in rhesus (*Macaca mulatta*) or cynomolgus monkey (*Macaca fascicularis*) caudate-putamen for **6**–**11**[a,b]



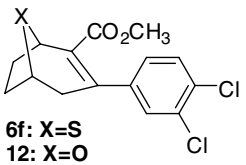
Compound	Compound #	R 8-S	IC_{50} (nM)		SERT/DAT[b]	Compound	Compound #	IC_{50} (nM)		SERT/DAT[b]	Compound	Compound #	IC_{50} (nM)		SERT/DAT[b]
			DAT	SERT				DAT	SERT				DAT	SERT	
	WIN35,428[c]		11	160											
	(−)-Cocaine[c]		96	270											
6a	O-2682	H	910	>10 μM	>11	**7a**	O-3767	140	>8 μM	>57	**8a**	O-3808	117	>3 μM	>29
6b	O-2643	F	220	>30 μM	>127	**7b**	O-3856	59	>11 μM	>186	**8b**	O-3876	38	494	13
6c	O-2683	Cl	13	>10 μM	>770	**7c**	O-3768	11	1 μM	91	**8c**	O-3806	9.6	33	3.4
6d	O-2752	Br	9.1	>25 μM	>2,747	**7d**	O-2878	6.0	342	57	**8d**	O-3807	6.0	14	2.3
6e	O-2838	I	6.7	>8 μM	>1,300	**7e**	O-2859	9.0	70	8	**8e**	O-3878	14	10	0.7
6f	O-2642	3,4-Cl_2	4.5	>3 μM	>800	**7f**	O-2751	6.9	99	14	**8f**	O-2793	5.7	8.0	1.5
6g	O-2890	3,4-F_2	75	>10 μM	>133	**7g**	O-2891	11.3	1 μM	88	**8g**	O-2940	32	235	7
6h	O-2795	2-Naphthyl	8.0	>1 μM	>163	**7h**	O-2876	8.0	36	4.5	**8h**	O-3877	16	13	0.8
6i	O-3244	4-Cl–3-F	10	> 50 μM	>5,000	**7i**	O-3325	7.0	702	100	**8i**	O-3387	6.0	17	3
6j	O-2837	3-Cl–4-F	7.6	>6 μM	>789	**7j**	O-2879	7.1	480	68	**8j**	O-2858	6.7	370	55
		8-S═O													
9a	O-2938	H	6 μM	>10 μM	>1.6	**10a**	O-2915	1 μM	100 μM	100					
		Br				**10b**	O-3384	14	>24 μM	>1,714					
		3,4-Cl_2				**10c**	O-3243	7.8	>3 μM	>346	**11a**	O-3264	5.3	120	23
		3-Cl–4-F				**10d**	O-2939	23	>31 μM	>1,348					
		4-Cl–3-F				**10e**	O-3388	17	>14 μM	>824	**11b**	O-3385	14	>4 μM	>286
		3,4-F_2				**10f**	O-2916	89	>69 μM	>775					

[a] These compounds are racemic. Each value is the mean of two or more independent experiments each conducted in different brains and in triplicate. Errors generally do not exceed 10% between replicate experiments.

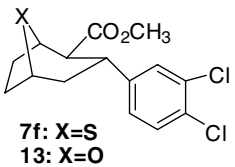
[b] Preference for DAT inhibition over SERT inhibition.

[c] Data from Ref. 9.

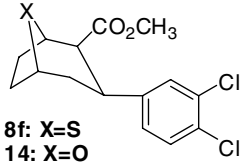
Table 2. Inhibition of [^{3}H]WIN 35,428 binding to the dopamine transporter (DAT) and [^{3}H]citalopram binding to the serotonin transporter (SERT) in rhesus (*Macaca mulatta*) or cynomolgus monkey (*Macaca fascicularis*) caudate-putamen[a,c]



6f: X=S
12: X=O
15: X=NCH$_3$, 7β-OH
18: X=NCH$_3$
21: X=CH$_2$



7f: X=S
13: X=O
16: X=NCH$_3$, 7β-OH
19: X=NCH$_3$
22: X=CH$_2$



8f: X=S
14: X=O
17: X=NCH$_3$, 7β-OH
20: X=NCH$_3$
23: X=CH$_2$

Compound	Enantiomer	Compound #	IC$_{50}$ (nM)		SERT/DAT[b]	Compound	Compound #	IC$_{50}$ (nM)		SERT/DAT[b]	Compound	Compound #	IC$_{50}$ (nM)		SERT/DAT[b]
			DAT	SERT				DAT	SERT				DAT	SERT	
	X = S														
6f	(1*R*/1*S*)	O-2642	4.5	3600	800	**7f**	O-2751	6.9	99	14	**8f**	O-2793	5.7	8.0	1.4
6f	(1*R*)	O-3513	2.5	2600	1,040	**7f**	O-3635	4.9	39	8	**8f**	O-3516	2.0	3.0	1.5
6f	(1*S*)	O-3514	5.0	4000	800	**7f**	O-3636	10	139	14	**8f**	O-3520	22	90	4
Bioenant[d]			2.0	1.5				2.0	3.6				11	30	
	X = O														
12a	(1*R*/1*S*)	O-1014	10	6000	600	**13a**	O-913	3.1	64.5	21	**14a**	O-914	3.3	6.5	2
12b	(1*R*)	O-1059	4.6	2120	460	**13b**	O-1066	2.3	31.0	13	**14b**	O-1072	3.3	4.7	1.4
12c	(1S)	O-1108	58	46,700	805	**13c**	O-1113	56	2860	51	**14c**	O-1114	47	58	1.2
Bioenant[d]			12.6	22				24	92				14	12	
	7β-OH X = NCH$_3$														
15a	(1*R*)	O-1677	265	1590	6	**16a**	O-1676	482	5300	11	**17a**	O-1675	2,690	139	0.05
15b	(1*S*)	O-1923	7.4	5370	730	**16b**	O-1924	0.76	1220	1,610	**17b**	O-1945	0.3	15	50
Bioenant[d]			35.8	3.3				634	4.3				897	9.3	
	X = NCH$_3$														
18a	(1*R*)	O-1109	1.2	867	723	**19a**	O-1157	0.4	27	68	**20a**	O-401	1.1	2.5	2.2
18b	(1*S*)	O-1120	490	1900	4	**19b**	NA				**20b**	NA			
Bioenant[d]			408	2.2											
	X = CH$_2$														
21	(1*R*/1*S*)	O-1231	7.1	5160	727	**22**	O-1442	13	166	13	**23**	O-1414	9.6	33	3.4

[a] Each value is the mean of two or more independent experiments each conducted in different brains and in triplicate.
[b] Preference for DAT inhibition over SERT inhibition.
[c] Where X = NCH$_3$, data taken from Ref. 9; where X = NCH$_3$ and 7-OH, data are taken from Ref. 20; where X = O, data are from Ref. 14; where X = CH$_2$, data are for the racemic compounds only and are taken from Ref. 27. NA, not available
[d] Biological enantioselectivity 'Bioenant' is given as the ratio of IC$_{50}$ distomer/IC$_{50}$ eutomer.

had very little impact on DAT inhibitory potency. In contrast, introduction of two fluorines (**6g**, **7g**, and **8g**) reduced DAT potency most for the 2,3-ene **6g** (17-fold) followed by the 3β-difluorophenyl analogue **8g** (6-fold). The least affected analogue was the 3α-difluorophenyl analogue **7g** (2-fold). SERT inhibitory potency was also much reduced for the 3,4-difluorophenyl compounds.

Oxidation of the 8-S to provide the 8-sulfoxides proved interesting. In the case of the inherently weak inhibitor (**6a**: 4-H), potency was essentially absent for both the 2,3-ene **9a** as well as for the 3α-aryl compound **10a**. When halogens were present in the aromatic ring, DAT potency was evident (IC_{50} DAT = 5.3–89 nM), however all analogues tested were inactive at SERT with the exception of the 3,4-dichlorophenyl compound **11a** that possessed the SERT-favoring 3β-aryl (chair) configuration (IC_{50} = 120 nM). Again, the 3,4-dichlorophenyl compounds proved interesting. Here the 3α-boat **10c** retained similar DAT inhibitory potency (IC_{50} = 7.8 nM) as the unoxidized **7f** (DAT IC_{50} = 6.9 nM). However all potency was absent for the sulfoxide **10c** at the SERT (IC_{50} = >3 μM). Thus the DAT selectivity manifested by the sulfoxide **10c** was considerably greater (>346-fold) than that manifested by the thioether **7f** (14-fold). This enhancement of selectivity by reduction of SERT potency was also evident in the 3β-chair configured compounds. Thus the thioether **8f** showed almost no DAT versus SERT selectivity (1.5-fold), whereas the sulfoxide **11a** was about 23-fold DAT selective. It was not unexpected that bulk at the 8-position can reduce SERT potency because, in the class of 8-azatropanes, Carroll et al. have demonstrated that the nitrogen unsubstituted 8-NH analogues were more potent SERT inhibitors than were their 8-NCH_3 counterparts.[44,45]

5. Stereospecific binding

Biological enantioselectivity for inhibition of monoamine uptake systems has been demonstrated for 8-aza and 8-oxa tropanes.[16,19,20] We selected the 3,4-dichlorophenyl analogues to explore biological enantioselectivity of these 8-thia compounds. Table 2 presents comparative data for the enantiomers of the analogous 3,4-dichlorophenyl-sustituted 8-oxa- (**12**–**14**),[14] 7β-hydroxy-8-aza- (**15**–**17**),[20] and 8-aza- (**18**–**20**)[9] bicyclo[3.2.1]octane(ene)s. It was evident that biological enantioselectivity of DAT inhibition was limited in the 8-thia series. The (1*R*)-configuration provided the more active enantiomers in the 2,3-ene (**6f**-1*R*; 2-fold over 1*S*), 3α-aryl (**7f**-1*R*; 2-fold over 1*S*), and 3β-aryl (**8f**-1*R*, 11-fold over 1*S*) analogues. Notwithstanding, the 1*S* isomers in this series remained potent DAT inhibitors (IC_{50} = 5–22 nM). Biological enantioselectivity was much more pronounced in the 8-oxa series where again the 1*R* isomers were the eutomers. However, there was over an order of magnitude decrease in potency manifested by the 1*S* enantiomers in the 8-oxa series. The presence of a nitrogen in the 8-position resulted in compounds that possessed the greatest biological enantioselectivity. Data from our laboratories for the 2,3-ene showed that the 1*R*-**18a** was about 400-fold selective for DAT over the 1*S*-**18b**. The 8-aza bridge hydroxylated (7β-OH) compounds (**15**–**17**) manifested greatest DAT selectivity, with the 2,3-ene eutomer **15a** about 35-fold selective, followed by the 3α-aryl eutomer **16a** with 635-fold selectivity, and then the 3β-aryl eutomers in which the 1*R* isomer was effectively inactive at DAT (1*R*/1*S* ~9000-fold). [Note that the stereochemical designator (*R* vs *S*) in the 7β-hydroxy series is reversed as a consequence of naming rules and the presence of an oxygen functionality adjacent to the chiral center. The relative absolute structure of the 7β-hydroxy 1*S*-compounds is the same as that within the 1*R* series of 8-hetero analogues lacking a bridge hydroxyl group.] Therefore 3,4-dichlorophenyl-8-thiabicyclo[3.2.1]octanes are less biologically enantioselective than are their 8-oxa or 8-aza[10,20,46] counterparts. The biological availability of these compounds may rest, at least partially, on their lipophilicities. In that regard, it is promising that the clog *P* values for the 8-thia, 8-aza, and 8-oxa analogues range from 2.7 to 4.5. Therefore, any of these compounds can meet lipophilicity requirements for biological availability.

6. Conclusion

The functional role of the 8-thia in the bicyclo[3.2.1]octane skeletal nucleus is the focus of this report. In this class, inhibitory potency at the dopamine transporter was not markedly different between the 2,3-enes **6**, the 3α-aryl **7**, and 3β-aryl **8** compounds. For example, the 3,4-dichlorophenyl compounds manifested IC_{50} values for the 2,3-ene **6f**, the 3α-aryl **7f**, and the 3β-aryl **8f** of 4.5 nM, 6.9 nM, 5.7 nM, respectively. In contrast, the selectivity exhibited by 8-thia-2,3-unsaturated, 3α-aryl, and 3β-aryl compounds for inhibition of both the dopamine and serotonin transporters derived specifically from reduced activity at the SERT. The unsaturated analogues **6** were the least potent inhibitors of the SERT and therefore most selective for the DAT. The 3α-(3,4-dichlorophenyl)-8-sulfoxide **10c** retained DAT inhibitory potency (IC_{50} = 7.8 nM), however all SERT potency was absent. Biological enantioselectivity of DAT inhibition was limited in the 8-thia series. The (1*R*)-configuration provided the eutomers in the 2,3-ene (**6f**-1*R*; 2-fold over 1*S*), 3α-aryl (**7f**-1*R*; 2-fold over 1*S*), and 3β-aryl (**8f**-1*R*, 11-fold over 1*S*) series. In general, molecular topology appeared to be more important for SERT binding than it was for DAT inhibition. This may imply that the SERT offers a more rigid binding site than does the DAT and that there is only one binding site on the SERT for tropane-like ligands. In contrast, there are either multiple binding sites on the DAT, or it is more accommodating than the SERT.

7. Supplementary information

Atomic coordinates for (1*R*,1′*S*)-**4a** (deposition number 617590) and **10f** (deposition number 617808) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK [fax: +44(0) 1223 336033; e-mail: deposit@ccdec.cam.ac.uk.]

8. Experimental

NMR spectra were recorded on a Jeol 300 NMR spectrometer with tetramethylsilane (TMS) as internal standard and $CDCl_3$ as solvent. Melting points are uncorrected and were measured on a Mel-Temp melting point apparatus. Optical rotations were measured with a JASCO DIP 320 polarimeter at the sodium D line at room temperature. Room temperature (*t*) is 22 °C ± 1 °C. Thin layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was accomplished with iodine vapor, UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 μM (Silica gel). All reactions were conducted under an atmosphere of dry nitrogen. Yields have not been optimized. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. HPLC and MS data were obtained on an Agilent 1100 LC/MSD system. A Beckman 1801 Scintillation Counter was used for scintillation spectrometry. 0.1% Bovine serum albumin and (−)-cocaine were purchased from Sigma Chemicals. ([^{3}H]WIN35,428, 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 Perkin Elmer (Boston, MA). (−)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse. Fluoxetine was donated by E. Lilly & Co.

8.1. 2-Carbomethoxy-8-thiabicyclo[3.2.1]octan-3-one (4)

A solution of 8-thiatropinone **3**[38] (15.5 g, 109 mmol) in THF (300 mL) was stirred at −78 °C under nitrogen, then LDA (2 M, 60 mL) was added dropwise. After stirring for 2 h, methyl cyanoformate (10.4 mL, 131 mmol) was added. The reaction was quenched after 1 h with saturated aqueous $NaHCO_3$ (100 mL) and allowed to warm to room temperature. Water was added and the mixture was extracted with ether (3× 100 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$, brine and dried (Na_2SO_4). The solvents were removed on a rotary evaporator and the residue was purified by flash chromatography (5% EtOAc/hexanes) to afford 15.0 g (69%) of **4**, which was comprised of three tautomers: the 2α-carbomethoxy keto ester, the 2β-carbomethoxy keto ester, and the enol ester. Since these compounds could not be separated, characterization was conducted on the triflate derivative **5**.

8.2. Resolution of 4. (1*R*)-2-Carbomethoxy-8-thiabicyclo[3.2.1]octan-3-one (1*R*-4)

Racemic keto ester **4** (8.0 g, 40 mmol) was dissolved in THF (150 mL) and cooled to −78 °C. A solution of sodium bis(trimethylsilyl)amide (1 M in THF, 44 mL, 44 mmol) was added under nitrogen over a period of 30 min. After stirring for 1 h, (1*S*)-camphanyl chloride (8.68 g, 40 mmol) was added in one portion and the resulting mixture was stirred for 1 h. The cooling bath was removed and a saturated solution of $NaHCO_3$ was added. The reaction mixture was allowed to warm to room temperature, ether was added and the organic phase separated. The aqueous phase was extracted with ether and the combined extracts were washed with saturated aq $NaHCO_3$, brine and dried (Na_2SO_4). Organic solvents were removed under reduced pressure. The crude product was recrystallized from ether/hexanes to provide the camphanyl ester (9.78 g) as a 10:1 mixture of the 1*R*,1′*S*: 1*S*,1′*S* isomers. The camphanyl ester was then recrystallized repeatedly from THF/hexanes and monitored by ^{1}H NMR. Recrystallization was terminated when the ratio of diastereomer (1*R*,1′*S*-**4a**) to diastereomer (1*S*,1′*S*-**4a**) was >100:1 (ee = 98%) as evidenced by the methyl resonances at δ 0.970 and δ 0.928. X-ray structural analysis confirmed the structure as (1*R*,1′*S*-**4a**). Lithium hydroxide (0.68 g, 16.2 mmol) was added to the camphanyl ester (1*R*,1′*S*-**4a**) (4.14 g, 10.9 mmol) in THF/H_2O (40:10 mL) at 0 °C. After 1 h the solution was neutralized with 1 N HCl; ether (200 mL) was added and the organic phase separated. The aqueous phase was extracted with ether and the combined extracts were washed with brine, dried (Na_2SO_4), and solvent was evaporated in vacuo. The residue was recrystallized from ethyl acetate/hexanes. Purification by flash column chromatography (5% ethyl acetate/hexanes) provided the desired enantiomer (1*R*)-**4** (1.72 g, 79%). All other spectral data were identical to those for racemic **4**. Anal. ($C_{15}H_{14}O_2SCl_2$) C, H, S, Cl.

8.3. (1*S*)-2-Carbomethoxy-8-thiabicyclo[3.2.1]octan-3-one (1*S*-4)

Racemic keto ester **4** was treated as described above for (1*R*-**4**) with sodium bis(trimethylsilyl)amide followed by (1*R*)-camphanyl chloride to provide the camphanyl ester. The camphanyl ester was recrystallized repeatedly from THF/hexanes and monitored by ^{1}H NMR. Recrystallization was terminated when the ratio of diastereomer (1*S*,1′*R*-**4b**) to diastereomer (1*S*,1′*S*-**4b**) was >100:1 (ee = 98%) as evidenced by the methyl resonances at δ0.970 and δ 0.928. Lithium hydroxide was added to the camphanyl ester (1*S*,1′*R*-**4b**) in THF/H_2O (40:10 mL) at 0 °C. After 1 h the solution was neutralized with 1 N HCl; ether was added, and the organic phase separated. The aqueous phase was extracted with ether and the combined extracts were washed with brine, dried (Na_2SO_4), and solvent was evaporated in vacuo. The residue was recrystallized from ethyl acetate/hexanes. Purification by flash column chromatography (5% ethyl acetate/hexanes) provided the desired enantiomer (1*S*)-**4**. All other spectral data were identical to those for racemic **4**. Anal. ($C_{15}H_{14}O_2SCl_2$) C, H, S, Cl.

8.4. 2-Carbomethoxy-3[(trifluoromethanesulfonyl)oxy]-8-thiabicyclo[3.2.1]-2-octene (5)

Sodium bis(trimethylsilyl)amide (1.0 M in THF, 67 mL) was added drop wise at −78 °C under nitrogen to a solution of **4** (10.1 g, 50.5 mmol) in anhydrous THF (200 mL). After stirring for 1 h at −78 °C, *N*-phenyltrifluoromethanesulfonimide (19.9 g, 55.6 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 (200 mL). The organic phase was washed with H_2O (2×

100 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was removed on a rotary evaporator and the residue was purified by flash chromatography (5% EtOAc/hexanes) to give 12.6 g (75%) of **5** as a pale yellow oil: ^{1}H NMR: δ 4.39 (dd, J = 0.9, 3.6 Hz, 1H), 3.94 (m, 1H), 3.84 (s, 3H), 2.99 (ddd, J = 2.1, 4.3, 18.6 Hz, 1H), 2.53–2.42 (m, 2H), 2.36–2.14 (m, 2H), 1.95 (m, 1H).

8.5. General procedure for synthesis of 2-carbomethoxy-3-aryl-8-thiabicyclo[3.2.1]-2-octenes. 2-Carbomethoxy-3-phenyl-8-thiabicyclo[3.2.1]-2-octene (6a)

$Pd(PPh_3)_4$ (0.31 g, 0.27 mmol), LiCl (0.76 g, 18 mmol), and Na_2CO_3 (2 M solution, 9 mL) were added to a solution of **5** (3.0 g, 9.0 mmol) in diethoxymethane (30 mL). The mixture was stirred vigorously and phenylboronic acid (1.32 g, 10.8 mmol) was added. The resulting mixture was heated at reflux for 3 h and cooled to room temperature, filtered through celite, and washed with ether. Water was added and the mixture was basified to pH 10 with NH_4OH. The aqueous phase was extracted with chloroform (2× 30 mL). The chloroform and ether layers were combined, dried (Na_2SO_4), and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford 2.17 g (92%) of **6a** as a white solid: mp 81–82 °C; R_f 0.25 (5% EtOAc/hexanes). ^{1}H NMR: δ 7.32–7.25 (m, 3H), 7.06 (dd, J = 8.0, 1.9 Hz, 2 H), 4.30 (d, J = 5.1 Hz, 1H), 3.89 (m, 1H), 3.44 (s, 3H), 2.95 (ddd, J = 2.1, 4.4, 18.9 Hz, 1H), 2.54–2.43 (m, 2H), 2.37–2.16 (m, 2H), 2.01 (m, 1H);. MS (CI, *m*/*z*): 261 [(M+H)$^+$]. Anal. ($C_{15}H_{16}O_2S$) C, H, S.

8.6. 2-Carbomethoxy-3-(4-fluorophenyl)-8-thiabicyclo-[3.2.1]-2-octene (6b)

Compound **6b** was prepared from **5** with 4-fluorophenylboronic acid as described for **6a**. Compound **6b** was obtained (94%) as white solid: mp 60–61 °C; R_f 0.28 (5% EtOAc/hexanes). ^{1}H NMR: δ 7.06–6.94 (m, 4H), 4.30 (d, J = 5.3 Hz, 1H), 3.89 (m, 1H), 3.47 (s, 3H), 2.91 (ddd, J = 2.0, 4.2, 19.0 Hz, 1H), 2.51–2.40 (m, 2H), 2.32–2.12 (m, 2H), 2.01 (m, 1H); MS (CI, *m*/*z*): 279 [(M+H)$^+$]. Anal. ($C_{15}H_{15}O_2SF$) C, H, S, F.

8.7. 2-Carbomethoxy-3-(4-chlorophenyl)-8-thiabicyclo-[3.2.1]-2-octene (6c)

Compound **6c** was prepared from **5** with 4-chlorophenylboronic acid as described for **6a**. Compound **6c** was obtained (93%) as white solid: mp 47–48 °C; R_f 0.25 (5% EtOAc/hexanes). ^{1}H NMR: δ 7.27 (d, J = 8.2 Hz, 2H), 7.01 (d, 2H), 4.31 (d, J = 5.2 Hz, 1H), 3.89 (m, 1H), 3.48 (s, 3H), 2.91 (ddd, J = 1.9, 4.2, 19.0 Hz, 1H), 2.50 (m, 1H), 2.42 (dd, J = 2.2, 19.0, 1H), 2.34–2.17 (m, 2H), 2.01 (m, 1H); MS (CI, *m*/*z*): 295 [M$^+$]. Anal. ($C_{15}H_{15}O_2SCl$) C, H, S, Cl.

8.8. 2-Carbomethoxy-3-(4-bromophenyl)-8-thiabicyclo-[3.2.1]-2-octene (6d)

Compound **6d** was prepared from **5** with 4-bromophenylboronic acid as described for **6a**. Compound **6d** was obtained (85%) as white solid: mp 70–71 °C; R_f 0.20 (5% EtOAc/hexanes). ^{1}H NMR: δ 7.42 (d, J = 8.5 Hz, 2H), 6.94 (d, 2H), 4.31 (d, J = 5.2 Hz, 1H), 3.89 (m, 1H), 3.49 (s, 3H), 2.91 (ddd, J = 1.9, 4.2, 19.2 Hz, 1H), 2.48 (m, 1H), 2.41 (dd, J = 2.2, 19.2, 1H), 2.33–2.17 (m, 2H), 1.99 (m, 1H); MS (CI, *m*/*z*): 339, 341 [M$^+$]. Anal. ($C_{15}H_{15}O_2SBr$) C, H, S, Br.

8.9. 2-Carbomethoxy-3-(4-iodophenyl)-8-thiabicyclo-[3.2.1]-2-octene (6e)

Compound **6e** was prepared from **5** with 4-iodophenylboronic acid as described for **6a**. Compound **6e** was obtained (74%) as white solid: mp 111–112 °C; R_f 0.31 (10% EtOAc/hexanes). ^{1}H NMR: δ 7.63 (d, J = 8.5 Hz, 2H), 6.82 (d, 2H), 4.31 (d, J = 5.3 Hz, 1H), 3.89 (m, 1H), 3.49 (s, 3H), 2.89 (ddd, J = 1.9, 4.1, 19.2 Hz, 1H), 2.48 (m, 1H), 2.40 (dd, J = 2.3, 19.1, 1H), 2.33–2.15 (m, 2H), 2.01 (m, 1H); MS (CI, *m*/*z*): 387 [(M+H)$^+$]. Anal. ($C_{15}H_{15}O_2SI$) C, H, S, I.

8.10. 2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]-2-octene (6f)

Compound **6f** was prepared from **5** with 3,4-dichlorophenylboronic acid as described for **6a**. Compound **6f** was obtained (96%) as white solid: mp 94–95 °C; R_f 0.27 (10% EtOAc/hexanes). ^{1}H NMR: δ 7.37 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 6.90 (dd, 1H), 4.32 (d, J = 5.0 Hz, 1H), 3.89 (m, 1H), 3.52 (s, 3H), 2.90 (ddd, J = 1.9, 4.1, 19.2 Hz, 1H), 2.50–2.15 (m, 4H), 2.02 (m, 1H); MS (CI, *m*/*z*): 329 [M$^+$]. Anal. ($C_{15}H_{14}O_2SCl_2$) C, H, S, Cl.

8.10.1. (1*R*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]-2-octene 1*R*-6f).

$[\alpha]_D^{21}$ −52° (*c* 0.25, MeOH). All other spectral data were identical to those for racemic **6f**. Anal. ($C_{15}H_{14}O_2SCl_2$) C, H, S, Cl.

8.10.2. (1*S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]-2-octene (1*S*-6f).

$[\alpha]_D^{21}$ +51° (*c* 0.25, MeOH). All other spectral data were identical to those for racemic **6f**. Anal. ($C_{15}H_{14}O_2SCl_2$) C, H, S, Cl.

8.11. 2-Carbomethoxy-3-(3,4-difluorophenyl)-8-thiabicyclo[3.2.1]-2-octene (6g)

Compound **6g** was prepared from **5** with 3,4-difluorophenylboronic acid as described for **6a**. Compound **6g** was obtained (89%) as an oil: R_f 0.19 (5% EtOAc/hexanes). ^{1}H NMR: δ 7.09 (dt, J = 8.2 Hz, 10.2 Hz, 1 H), 6.90 (ddd, J = 2.1 Hz, 7.4 Hz, 11.0 Hz, 1H), 6.78 (m, 1H), 4.31 (d, J = 5.2 Hz, 1H), 3.89 (m, 1H), 3.51 (s, 3H), 2.89 (ddd, J = 1.9, 4.1, 19.2 Hz, 1H), 2.49?2.12 (m, 4H), 1.98 (m, 1H); MS (CI, *m*/*z*): 295 [M$^+$]. Anal. ($C_{15}H_{14}O_2SF_2$) C, H, S, F.

8.12. 2-Carbomethoxy-3-(2-naphthyl)-8-thiabicyclo-[3.2.1]-2-octene (6h)

Compound **6h** was prepared from **5** with 2-naphthylboronic acid as described for **6a**. A clear viscous oil was obtained (93%): R_f 0.27 (10% EtOAc/hexanes).

^{1}H NMR δ 7.82–7.76 (m, 3H), 7.54 (d, J = 1.7, 1H), 7.48–7.42 (m, 2H), 7.20 (dd, J = 1.7, 8.4 Hz, 1H), 4.36 (d, J = 4.9 Hz, 1H), 3.94 (m, 1H), 3.40 (s, 3H), 3.03 (ddd, J = 1.9, 4.4, 19.3 Hz, 1H), 2.60–2.50 (m, 2H), 2.41–2.23 (m, 2H), 2.05 (m, 1H); MS (CI, *m/z*): 311 [(M+H)$^+$]. Anal. ($C_{19}H_{18}O_2S$) C, H, S.

8.13. 2-Carbomethoxy-3-(4-chloro-3-fluorophenyl)-8-thiabicyclo[3.2.1]-2-octene (6i)

Compound **6i** was prepared from **5** with 4-chloro-3-fluorophenylboronic acid as described for **6a**. Compound **6i** was obtained (89%) as an oil; R_f 0.35 (10% EtOAc/hexanes). ^{1}H NMR: δ 7.31 (t, J = 7.9 Hz, 1H), 6.87 (dd, J = 2.1 Hz, 9.9 Hz, 1H), 6.78 (dd, 1H), 4.31 (d, J = 5.2 Hz, 1H), 3.89 (m, 1H), 3.53 (s, 3H), 2.91 (ddd, J = 1.9, 4.1, 19.2 Hz, 1H), 2.49–2.14 (m, 4H), 2.02 (m, 1H); MS (CI, *m/z*): 313 [M$^+$]. Anal. ($C_{15}H_{14}O_2SFCl$) C, H, S, F, Cl.

8.14. 2-Carbomethoxy-3-(3-chloro-4-fluorophenyl)-8-thiabicyclo[3.2.1]-2-octene (6j)

Compound **6j** was prepared from **5** with 3-chloro-4-fluorophenylboronic acid as described for **6a**. Compound **6j** was obtained (90%) as a white solid: mp 76–77 °C; R_f 0.33 (10% EtOAc/hexanes). ^{1}H NMR δ 7.11 (dd, J = 2.2 Hz, 7.1 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.93 (ddd, 1H), 4.31 (d, J = 5.5 Hz, 1H), 3.90 (m, 1H), 3.51 (s, 3H), 2.91 (ddd, J = 1.9, 4.3, 19.2 Hz, 1H), 2.50–2.14 (m, 4H), 2.01 (m, 1H); MS (CI, *m/z*): 313 [M$^+$]. Anal. ($C_{15}H_{14}O_2SFCl$) C, H, S, F, Cl.

8.15. General procedure for synthesis of 3α-aryl- and 3β-aryl bicyclo[3.2.1]octanes

8.15.1. 2β-Carbomethoxy-3α-phenyl-8-thiabicyclo[3.2.1]-octane (7a) and 2β-carbomethoxy-3β-phenyl-8-thiabicyclo[3.2.1]octane (8a). Compound **6a** (520 mg, 2 mmol) was dissolved in a mixture of THF (30 mL) and isopropyl alcohol (10 mL). To the stirred solution at −60 °C under a nitrogen atmosphere, SmI_2 (80 mL, 0.1M in THF) was added dropwise. The mixture was stirred at −60 °C for 3 h. Water was added (10 mL) and the reaction mixture was allowed to warm to room temperature. A saturated solution of $NaHCO_3$ (120 mL) was added. The mixture was stirred for 1 h, then filtered and washed with ether (2× 100 mL). The organic phase was washed with brine (100 mL) and dried (Na_2SO_4). The solvents were removed on a rotary evaporator and the residue was purified by gravity column chromatography (10% EtOAc/hexanes) providing a mixture of 460 mg of the two isomers **7a** and **8a** in a ratio 5:1 (^{1}H NMR), which was used in the next reaction without further separation.

Note: The two reduced isomers (3α-aryl and 3β-aryl) could not be readily separated either by flash or by gravity column chromatography. Therefore a two-step procedure was utilized to obtain configurationally pure 3α-aryl- and 3β-aryl compounds. The mixed esters **7/8** were de-esterified, separated, and re-esterified to obtain pure **7** and **8**, as detailed below.

8.16. General procedure for de-esterification

8.16.1. 2β-Carboxy-3α-phenyl-8-thiabicyclo[3.2.1]-octanes and 2β-carboxy-3β-phenyl-8-thiabicyclo[3.2.1]octane. To $AlCl_3$ (798 mg, 6 mmol) powder was added dropwise dimethyl sulfide (6 ml)[41] at 0 °C under an argon atmosphere. The solution was stirred for 10 min and allowed to warm to room temperature. A solution of compounds **7a** and **8a** in CH_2Cl_2 (5 ml) was added slowly. The reaction was monitored by TLC every hour (For TLC: $AlCl_3$ was quenched by methanol). When the reaction was complete, the reaction mixture was poured into water, to which 1 M HCl solution was added. The reaction mixture was extracted with CH_2Cl_2 (2× 100 ml). The combined organic phase was washed with brine, dried (Na_2SO_4), and filtered. The solvents were removed on a rotary evaporator to give a solid. The crude products were purified and separated by flash chromatography using 3% MeOH in $CHCl_3$ to give the carboxylic acid of **7a** (307 mg, 62%) and the carboxylic acid of **8a** (67 mg, 14%). These carboxylic acids were characterized by ^{1}H NMR: and converted to their methyl esters as described below.

8.16.2. 2β-Carboxy-3α-phenyl-8-thiabicyclo[3.2.1]octane. Yield 62%. ^{1}H NMR: δ 7.32–7.15 (m, 5 H); 3.79 (d, J = 6.3 Hz, 1H); 3.66 (dd, J = 5.3 Hz, 8.5 Hz, 1H); 3.26 (dt, J = 7.5 Hz, 11.5 Hz, 1H); 2.53 (d, J = 11.3 Hz, 1H); 2.45–1.89 (m, 5H), 1.34 (t, J = 13.4 Hz, 1H).

8.16.3. 2β-Carboxy-3β-phenyl-8-thiabicyclo[3.2.1]octane. Yield 14%. ^{1}H NMR: δ 7.35–7.15 (m, 5H); 3.97 (t, J = 4.8 Hz, 1H); 3.74 (t, J = 4.7 Hz, 1H); 3.21–3.12 (m, 2H); 2.70 (t, J = 12.9 Hz, 1H); 2.27–1.94 (m, 5H).

8.16.4. 2β-Carboxy-3α-(4-fluorophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 57%. ^{1}H NMR: δ 7.15 (dd, J = 5.4 Hz, J = 8.5 Hz, 2H); 6.95 (t, J = 8.5 Hz, 2H); 3.78 (d, J = 6.3 Hz, 1H); 3.66 (dd, J = 5.5 Hz, 9.1 Hz, 1H); 3.25 (dt, J = 7.2, 11.8 Hz, 1H); 2.46 (d, J = 11.3 Hz, 1H); 2.43–1.85(m, 5H), 1.29 (t, J = 13.2 Hz, 1H).

8.16.5. 2β-Carboxy-3β-(4-fluorophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 17%. ^{1}H NMR: δ 7.21 (dd, J = 5.4 Hz, J = 8.6 Hz, 2H); 6.96 (t, J = 8.6 Hz, 2H); 3.97 (t, J = 4.7 Hz, 1H); 3.73 (m, 1H); 3.17–3.06 (m, 2H); 2.66 (t, J = 12.6 Hz, 1H); 2.32–1.91 (m, 5H).

8.16.6. 2β-Carboxy-3α-(4-chlorophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 56%. ^{1}H NMR: δ 7.21 (dd, J = 5.2 Hz, J = 8.5 Hz, 2H); 7.13 (t, J = 8.5 Hz, 2H); 3.74 (d, J = 6.2 Hz, 1H); 3.69 (dd, J = 5.5 Hz, 9.0 Hz, 1H); 3.30 (dt, J = 7.1, 11.5 Hz, 1H); 2.45 (d, J = 11.4 Hz, 1H); 2.42–1.89 (m, 5H), 1.31 (t, J = 13.2 Hz, 1H).

8.16.7. 2β-Carboxy-3β-(4-chlorophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 15%. ^{1}H NMR: δ 7.28–7.12 (m, 4H); 3.99 (t, J = 4.9 Hz, 1H); 3.75 (m, 1H); 3.18–3.06 (m, 2H); 2.72 (t, J = 12.7 Hz, 1H); 2.32–1.91 (m, 5H).

8.16.8. 2β-Carboxy-3α-(4-bromophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 42%. ^{1}H NMR: δ 7.38 (d, J = 8.5 Hz, 2H); 7.06 (d, 2H); 3.79 (d, J = 6.3 Hz, 1H);

3.67 (dd, J = 5.5 Hz, 9.0 Hz, 1H); 3.27 (dt, J = 7.1, 11.5 Hz, 1H); 2.45 (d, J = 11.1 Hz, 1H); 2.40–1.85 (m, 5H), 1.28 (t, J = 13.2 Hz, 1H).

8.16.9. 2β-Carboxy-3β-(4-bromophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 22%. ^{1}H NMR: δ 7.32 (d, J = 8.5 Hz, 2H); 7.00 (d, 2H); 3.90 (t, J = 5.1 Hz, 1H); 3.64 (t, J = 4.4 Hz, 1H); 3.06 (t, J = 4.7 Hz, 1H); 2.96 (dt, J = 4.7 Hz, 12.9 Hz, 1H); 2.57 (t, J = 12.9 Hz, 1H); 2.32–1.84 (m, 5H).

8.16.10. 2β-Carboxy-3α-(4-iodophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 37%. ^{1}H NMR: δ 7.58 (d, J = 8.5 Hz, 2H); 6.94 (d, 2H); 3.75 (d, J = 6.2 Hz, 1H); 3.68 (dd, J = 5.5 Hz, 9.1 Hz, 1H); 3.27 (dt, J = 7.1, 11.4 Hz, 1H); 2.45 (d, J = 11.4 Hz, 1H); 2.40–1.85 (m, 5H), 1.32 (t, J = 13.1 Hz, 1H).

8.16.11. 2β-Carboxy-3β-(4-iodophenyl)-8-thiabicyclo-[3.2.1]octane. Yield 13%. ^{1}H NMR: δ 7.57 (d, J = 7.7 Hz, 2H); 6.95 (d, 2H); 3.95 (t, J = 4.7 Hz, 1H); 3.71 (m, 1H); 3.11 (t, J = 4.6 Hz, H); 3.01 (dt, J = 4.7 Hz, 12.6 Hz, 1H); 2.62 (t, J = 12.9 Hz, 1H); 2.32–1.84 (m, 5H).

8.16.12. 2β-Carboxy-3α-(2-naphthyl)-8-thiabicyclo[3.2.1]-octane. Yield 54%. ^{1}H NMR: δ 7.79–7.72 (m, 3H), 7.61 (s, 1H), 7.47–7.38 (m, 2H), 7.31 (dd, J = 1.7 Hz, 8.5 Hz, 1H); 3.80 (d, J = 6.3 Hz, 1H), 3.69 (dd, J = 5.2 Hz, 9.0 Hz, 1H), 3.44 (dt, J = 7.1 Hz, 11.5 Hz, 1H), 2.65 (d, J = 11.1 Hz, 1H); 2.47–1.91 (m, 5H), 1.43 (t, J = 12.9 Hz, 1H).

8.16.13. 2β-Carboxy-3β-(2-naphthyl)-8-thiabicyclo[3.2.1]-octane. Yield 17%. ^{1}H NMR: δ 7.79–7.72 (m, 3H), 7.65 (s, 1H), 7.47–7.35 (m, 3H), 4.00 (m, 1H), 3.78 (m, 1H), 3.33–3.24 (m, 2H), 2.82 (t, J = 12.8 Hz, 1H); 2.36–2.01 (m, 5H).

8.16.14. General procedure for esterification of 2β-carboxy-3-aryl-8-thiabicyclo[3.2.1]octane to provide 7 and 8. 2β-Carbomethoxy-3β-phenyl-8-thiabicyclo[3.2.1]-octane (8a). 2β-Carboxy-3β-phenyl-8-thiabicyclo[3.2.1]-octane (150 mg, 0.6 mmol) was dissolved in THF (15 mL) and 0.5 M HCl in methanol (5 mL). To the stirred solution was added dropwise a 2 M solution of $TMSCHN_2$ (1.2 mL, 2.4 mmol) at 0 °C. After the addition was complete, the mixture was stirred for 4 h at room temperature, then concentrated. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to provide compound **8a** (124 mg, 80%) as white solid: mp 95–96 °C; R_f 0.25 (10% EtOAc/hexanes). ^{1}H NMR: δ 7.32–7.15 (m, 5H); 3.97 (t, J = 4.8 Hz, 1H); 3.74 (t, J = 4.7 Hz, 1H); 3.50 (s, 3H); 3.20 (t, J = 4.7 Hz, 1H); 3.12 (m, 1H); 2.76 (t, J = 12.6 Hz, 1H); 2.27–1.91 (m, 5H); MS (CI, m/z): 263 [$(M+H)^+$]. Anal. ($C_{15}H_{18}O_2S$) C, H, S.

8.16.15. 2β-Carbomethoxy-3α-phenyl-8-thiabicyclo[3.2.1]-octane (7a). Compound **7a** was prepared from 2β-carboxy-3α-phenyl-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **7a** was obtained (77%) as white solid: mp 49–50 °C; R_f 0.26 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.32–7.15 (m, 5H); 3.73 (d, J = 6.3 Hz, 1H); 3.67 (dd, J = 5.5 Hz, 9.1 Hz, 1H); 3.52 (s, 3H); 3.32 (dt, J = 7.4 Hz, 11.5 Hz, 1H); 2.51 (d, J = 11.4 Hz, 1H); 2.45–1.89 (m, 5H), 1.37 (t, J = 12.7 Hz, 1H); MS (CI, m/z): 263 [$(M+H)^+$]. Anal. ($C_{15}H_{18}O_2S$) C, H, S.

8.16.16. 2β-Carbomethoxy-3α-(4-fluorophenyl)-8-thiabicyclo[3.2.1]octane (7b). Compound **7b** was prepared from 2β-carboxy-3α-(4-fluorophenyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **7b** was obtained (90%) as a syrup; R_f 0.26 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.15 (dd, J = 5.4 Hz, J = 8.5 Hz, 2H); 6.95 (t, J = 8.5 Hz, 2H); 3.71 (d, J = 6.0 Hz, 1H); 3.67 (m, 1H); 3.53 (s, 3H); 3.31 (dt, J = 7.1, 11.6 Hz, 1H); 2.44 (d, J = 11.3 Hz, 1H); 2.40–1.87 (m, 5H), 1.31 (t, J = 12.6 Hz, 1H); MS (CI, m/z): 281 [$(M+H)^+$]. Anal. ($C_{19}H_{17}O_2SF$) C, H, S, F.

8.16.17. 2β-Carbomethoxy-3β-(4-fluorophenyl)-8-thiabicyclo[3.2.1]octane (8b). Compound **8b** was prepared from 2β-carboxy-3β-(4-fluorophenyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **8b** was obtained (90%) as white solid: mp 114–115 °C; R_f 0.27 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.21 (dd, J = 5.4 Hz, J = 8.6 Hz, 2H); 6.96 (t, J = 8.6 Hz, 2H); 3.96 (t, J = 4.8 Hz, 1H); 3.73 (m, 1H); 3.51 (s, 3H); 3.14 (t, J = 4.8 Hz, 1H); 3.06 (m, 1H); 2.72 (t, J = 12.7 Hz, 1H); 2.32–1.91 (m, 5H); MS (CI, m/z): 281 [$(M+H)^+$]. Anal. ($C_{19}H_{17}O_2SF$) C, H, S, F.

8.16.18. 2β-Carbomethoxy-3α-(4-chlorophenyl)-8-thiabicyclo[3.2.1]octane (7c). Compound **7c** was prepared from 2β-carboxy-3α-(4-chlorophenyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **7c** was obtained (89%) as white solid: mp 69–70°C; R_f 0.26 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.22 (dd, J = 5.4 Hz, J = 8.5 Hz, 2H); 7.12 (t, J = 8.5 Hz, 2H); 3.72 (d, J = 6.3 Hz, 1H); 3.67 (dd, J = 5.5 Hz, 9.1 Hz, 1H); 3.54 (s, 3H); 3.31 (dt, J = 7.1, 11.6 Hz, 1H); 2.44 (d, J = 11.3 Hz, 1H); 2.40–1.85 (m, 5H), 1.30 (t, J = 13.1 Hz, 1H); MS (CI, m/z): 297 [$(M+H)^+$]. Anal. ($C_{15}H_{17}O_2SCl$) C, H, S, Cl.

8.16.19. 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-thiabicyclo[3.2.1]octane (8c). Compound **8c** was prepared from 2β-carboxy-3β-(4-chlorophenyl)-8-thiabicyclo-[3.2.1]octane as described for **8a**. Compound **8c** was obtained (87%) as white solid: mp 100–101 °C; R_f 0.25 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.28–7.12 (m, 4H); 3.97 (t, J = 5.0 Hz, 1H); 3.73 (m, 1H); 3.51 (s, 3H); 3.15 (t, J = 4.7 Hz, 1H); 3.06 (m, 1H); 2.72 (t, J = 12.7 Hz, 1H); 2.32–1.91 (m, 5H); MS (CI, m/z): 297 [$(M+H)^+$]. Anal. ($C_{15}H_{17}O_2SCl$) C, H, S, Cl.

8.16.20. 2β-Carbomethoxy-3α-(4-bromophenyl)-8-thiabicyclo[3.2.1]octane (7d). Compound **7d** was prepared from 2β-carboxy-3α-(4-bromophenyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **7d** was obtained (89%) as white solid: mp 106–107 °C; R_f 0.32 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.38 (d, J = 8.5 Hz, 2H); 7.06 (d, 2H); 3.72 (d, J = 6.1 Hz, 1H); 3.67 (dd,

J = 5.6 Hz, 9.1 Hz, 1H); 3.54 (s, 3H); 3.30 (dt, J = 7.1, 11.6 Hz, 1H); 2.45 (d, J = 11.3 Hz, 1H); 2.40–1.85 (m, 5H), 1.30 (t, J = 13.2 Hz, 1H); MS (CI, *m/z*): 341, 343 [(M+H)$^+$]. Anal. ($C_{15}H_{17}O_2SBr$) C, H, S, Br.

8.16.21. 2β-Carbomethoxy-3β-(4-bromophenyl)-8-thiabicyclo[3.2.1]octane (8d). Compound **8d** was prepared from 2β-carboxy-3β-(4-bromophenyl)-8-thiabicyclo-[3.2.1]octane as described for **8a**. Compound **8d** was obtained (84%) as white solid: mp 141–143 °C; R_f 0.31 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.39 (d, J = 8.5 Hz, 2H); 7.11 (d, 2H); 3.96 (t, J = 4.9 Hz, 1H); 3.73 (m, 1H); 3.51 (s, 3H); 3.15 (t, J = 4.7 Hz, 1H); 3.05 (dt, J = 4.9 Hz, 12.9 Hz, 1H); 2.71 (t, J = 12.9 Hz, 1H); 2.32–1.91 (m, 5H); MS (CI, *m/z*): 341, 343 [(M+H)$^+$]. Anal. ($C_{15}H_{17}O_2SBr$) C, H, S, Br.

8.16.22. 2β-Carbomethoxy-3α-(4-iodophenyl)-8-thiabicyclo[3.2.1]octane (7e). Compound **7e** was prepared from 2β-carboxy-3α-(4-iodophenyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **7e** was obtained (94%) as white solid: mp 137–138 °C; R_f 0.29 (10% EtOAc/hexanes); ^{1}H NMRδ 7.57 (d, J = 8.5 Hz, 2H); 6.94 (d, 2H); 3.72 (d, J = 6.3 Hz, 1H); 3.66 (dd, J = 5.6 Hz, 9.1 Hz, 1H); 3.54 (s, 3H); 3.28 (dt, J = 7.1, 11.6 Hz, 1H); 2.45 (d, J = 11.3 Hz, 1H); 2.40–1.85 (m, 5H), 1.29 (t, J = 13.2 Hz, 1H); MS (CI, *m/z*): 389 [(M+H)$^+$]. Anal. ($C_{15}H_{17}O_2SI$) C, H, S, I.

8.16.23. 2β-Carbomethoxy-3β-(4-iodophenyl)-8-thiabicyclo[3.2.1]octane (8e). Compound **8e** was prepared from 2β-carboxy-3β-(4-iodophenyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **8e** was obtained (93%) as white solid: mp 167–168 °C; R_f 0.28 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.59 (d, J = 8.3 Hz, 2H); 7.00 (d, 2H); 3.96 (t, J = 4.8 Hz, 1H); 3.73 (m, 1H); 3.52 (s, 3H); 3.14 (t, J = 4.7 Hz, 1H); 3.04 (m, 1H); 2.70 (t, J = 13.0 Hz, 1H); 2.31–1.91 (m, 5H); MS (CI, *m/z*): 389 [(M+H)$^+$]. Anal. ($C_{15}H_{17}O_2SI$) C, H, S, I.

8.16.24. 2β-Carbomethoxy-3α-(2-naphthyl)-8-thiabicyclo[3.2.1]octane (7h). Compound **7h** was prepared from 2β-carboxy-3α-(2-naphthyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **7h** was obtained (91%) as white solid: mp 122–123 °C; R_f 0.29 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.82–7.74 (m, 3H), 7.64 (d, 1H), 7.47–7.41 (m, 2H), 7.32 (dd, J = 1.7 Hz, 8.5 Hz, 1H); 3.76 (d, J = 6.1 Hz, 1H), 3.70 (dd, J = 5.8 Hz, 9.1 Hz, 1H), 3.57–3.46 (m, 4H), 2.65 (d, J = 11.3 Hz, 1H); 2.50–1.91 (m, 5H), 1.47 (t, J = 12.4 Hz, 1H); MS (CI, *m/z*): 313 [(M+H)$^+$]. Anal. ($C_{19}H_{20}O_2S$) C, H, S.

8.16.25. 2β-Carbomethoxy-3β-(2-naphthyl)-8-thiabicyclo[3.2.1]octane (8h). Compound **8h** was prepared from 2β-carboxy-3β-(2-naphthyl)-8-thiabicyclo[3.2.1]octane as described for **8a**. Compound **8h** was obtained (85%) as white solid: mp 111–112 °C; R_f 0.29 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.79–7.74 (m, 3H), 7.68 (s, 1H), 7.48–7.37 (m, 3H), 4.01 (m, 1H), 3.79 (m, 1H), 3.45 (s, 3H), 3.33–3.24 (m, 2H), 2.90 (t, J = 12.5 Hz, 1H); 2.33–2.04 (m, 5H); MS (CI, *m/z*): 313 [(M+H)$^+$]. Anal. ($C_{19}H_{20}O_2S$) C, H, S.

8.17. General procedure for synthesis of octanes 7f, g, i, j, and 8f, g, i, j

8.17.1. 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]octanes (7f) and 2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]octanes (8f). Compound **6f** (659 mg, 2 mmol) was dissolved in a mixture of THF (30 mL) and isopropyl alcohol (10 mL). SmI_2 (0.1 M, 80 mL) was added dropwise to the stirred solution at −60 °C under a nitrogen atmosphere. The mixture was stirred at −60 °C for 3 h, after which water was added (10 mL) and the reaction mixture was allowed to warm to room temperature. A saturated solution of $NaHCO_3$ (120 mL) was added. The mixture was stirred for 1 h, then filtered and washed with ether (2× 100 mL). The organic phase was washed with brine (100 mL) and dried (Na_2SO_4). The solvents were removed on a rotary evaporator and the residue was purified by flash column chromatography (10% EtOAc/hexanes) to give a mixture of 2β,3α and 2β,3β isomers in a ratio 1:1 (554 mg). The mixture was repeatedly recrystallized from heptane to provide pure **6f** (82 mg). The combined mother liquors were concentrated and subjected to gravity chromatography (10% EtOAc in hexanes). Fractions were collected and monitored by TLC and GC. The first fraction was pure 2β,3α compound **7f** (97 mg). The second fraction (116 mg) was a mixture of 2β,3α and 2β,3β isomers, which was enriched with the 2β,3α isomer. The third fraction (242 mg) was a mixture of 2β,3α and 2β,3β isomers, which was enriched with 2β,3β isomer. The third fraction was concentrated and recrystallized twice from heptane to give pure 2β,3β isomer **8f** (120 mg). The mother liquors and the second fraction were combined and purified by gravity column chromatography (10% EtOAc/hexanes) followed by recrystallization of the enriched mixture of two isomers to give another portion of pure **7f** (108 mg) and **8f** (32 mg). Compound **7f** was obtained (205 mg, 31%) as white solid: mp 99–100 °C; R_f 0.28 (10% EtOAc/hexanes); ^{1}H NMR δ 7.32 (d, J = 8.2 Hz, 1H); 7.27 (d, J = 2.1 Hz, 1H); 7.04 (dd, 1H); 3.73 (d, J = 6.3 Hz, 1H); 3.66 (dd, J = 5.8 Hz, 8.8 Hz, 1H); 3.56 (s, 3H); 3.31 (dt, J = 7.3, 11.7 Hz, 1H); 2.43 (d, J = 11.5 Hz, 1H); 2.40–1.88 (m, 5H), 1.29 (t, J = 12.8 Hz, 1H); MS (CI, *m/z*): *m/z* 331, 333 [(M+H)$^+$]. Anal. ($C_{15}H_{16}O_2SCl_2$) C, H, S, Cl. Compound **8f** was obtained (234 mg, 35%) as white solid: mp 131–132 °C; R_f 0.28 (10% EtOAc/hexanes; ^{1}H NMR: δ 7.35–7.26 (m, 2H); 7.10 (dd, J = 1.9 Hz, 8.3 Hz, 1H); 3.98 (t, J = 4.9 Hz, 1H); 3.73 (m, 1H); 3.54 (s, 3H); 3.15 (t, J = 4.6 Hz, 1H); 3.05 (dt, J= 4.7 Hz, 11.3 Hz, 1H); 2.68 (t, J = 12.7 Hz, 1H); 2.28–1.91 (m, 5H); MS (CI, *m/z*): 331, 333 [(M+H)$^+$]. Anal. ($C_{15}H_{16}O_2SCl_2$) C, H, S, Cl.

8.17.2. (1*R*)-2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]octanes (1*R*-7f) and (1*R*)-2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]octanes (1*R*-8f). Compound (1*R*-**7f**): $[\alpha]_D^{21}$ −101° (*c* 0.25, MeOH). All other spectral data were identical to those reported for racemic **7f**. Anal. ($C_{15}H_{16}O_2SCl_2$) C, H, S, Cl.

Compound (1*R*-**8f**): $[\alpha]_D^{21}$ −105° (*c* 0.25, MeOH). All other spectral data were identical to those reported for racemic **8f**. Anal. ($C_{15}H_{16}O_2SCl_2$) C, H, S, Cl.

8.17.3. (1*S*)-2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]octanes (1*S*-7f) and (1*S*)-2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-thiabicyclo[3.2.1]octanes (1*S*-8f). Compound (1*S*-**7f**): $[\alpha]_D^{21}$ +95° (*c* 0.25, MeOH). All other spectral data were identical to those reported for racemic **7f**. Anal. ($C_{15}H_{16}O_2SCl_2$) C, H, S, Cl.

(1*S*-**8f**): $[\alpha]_D^{21}$ +103° (*c* 0.25, MeOH). All other spectral data were identical to those reported for racemic **8f**. Anal. ($C_{15}H_{16}O_2SCl_2$) C, H, S, Cl.

8.17.4. 2β-Carbomethoxy-3α-(3,4-difluorophenyl)-8-thiabicyclo[3.2.1]octanes (7g). Compound **7g** was prepared from **6g** as described for **7f**. Compound **7g** was obtained (43%) as white solid: mp 102–103 °C; R_f 0.29 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.11–6.92 (m, 3H); 3.72 (d, *J* = 6.3 Hz, 1H); 3.67 (dd, *J* = 5.6 Hz, 9.0 Hz, 1H); 3.56 (s, 3H); 3.30 (dt, *J* = 7.2, 11.5 Hz, 1H); 2.41 (d, *J* = 11.3 Hz, 1H); 2.40–1.85 (m, 5H), 1.28 (t, *J* = 13.2 Hz, 1H); MS (CI, *m*/*z*): 299 [(M+H)$^+$]. Anal. ($C_{15}H_{16}O_2SF_2$) C, H, S, F.

8.17.5. 2β-Carbomethoxy-3β-(3,4-difluorophenyl)-8-thiabicyclo[3.2.1]octanes (8g). Compound **8g** was prepared from **6g** as described for **8f**. Compound **8g** was obtained (19%) as white solid: mp 102–103 °C; R_f 0.27 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.14–6.92 (m, 3H); 3.97 (t, *J* = 4.9 Hz, 1H); 3.72 (m, 1H); 3.53 (s, 3H); 3.14 (t, *J* = 4.6 Hz, 1H); 3.02 (dt, *J* = 4.7 Hz, 11.2 Hz, 1H); 2.67 (t, *J* = 12.9 Hz, 1H); 2.29–1.92 (m, 5H); MS (CI, *m*/*z*): 299 [(M+H)$^+$]. Anal. ($C_{15}H_{16}O_2SF_2$) C, H, S, F.

8.17.6. 2β-Carbomethoxy-3α-(4-chloro-3- fluorophenyl)-8-thiabicyclo[3.2.1]octanes (7i). Compound **7i** was prepared from **6i** as described for **7f**. Compound **7i** was obtained (38%) as white solid: mp 85–87 °C; R_f 0.37 (10% EtOAc/hexanes); ^{1}H NMR δ 7.27 (m, 1H); 6.96 (m, 2H); 3.73 (d, *J* = 6.0 Hz, 1H); 3.66 (dd, *J* = 5.4 Hz, 9.1 Hz, 1H); 3.57 (s, 3H); 3.31 (dt, *J* = 7.1, 11.6 Hz, 1H); 2.43 (d, *J* = 11.1 Hz, 1H); 2.40–1.87 (m, 5H), 1.28 (t, *J* = 13.3 Hz, 1H); MS (CI, *m*/*z*): 315 [(M+H)$^+$]. Anal. ($C_{15}H_{16}O_2SFCl$) C, H, S, F, Cl.

8.17.7. 2β-Carbomethoxy-3β-(4-chloro-3- fluorophenyl)-8-thiabicyclo[3.2.1]octanes (8i). Compound **8i** was prepared from **6i** as described for **8f**. Compound **8i** was obtained (27%) as white solid: mp 97–98 °C; R_f 0.37 (10% EtOAc/hexanes); ^{1}H NMR δ 7.28 (dd, *J* = 8.2 Hz, 10.6 Hz, 1H); 7.03 (dd, *J* = 1.9 Hz, 10.6 Hz, 1H); 6.96 (dd, *J* = 1.9 Hz, 8.2 Hz, 1H); 3.98 (t, *J* = 4.9 Hz, 1H); 3.73 (m, 1H); 3.53 (s, 3H); 3.16 (t, *J* = 4.8 Hz, 1H); 3.04 (dt, *J* = 4.8 Hz, 12.9 Hz, 1H); 2.67 (t, *J* = 12.9 Hz, 1H); 2.28–1.94 (m, 5H); MS (CI, *m*/*z*): 315 [M$^+$]. Anal. ($C_{15}H_{16}O_2SFCl$) C, H, S, F, Cl.

8.17.8. 2β-Carbomethoxy-3α-(3-chloro-4- fluorophenyl)-8-thiabicyclo[3.2.1]octanes (7j). Compound **7j** was prepared from **6j** as described for **7f**. Compound **7j** was obtained (34%) as white solid: mp 88–89 °C; R_f 0.28 (10% EtOAc/hexanes); ^{1}H NMR δ 7.21 (dd, *J* = 2.2 Hz, 7.4 Hz, 1H); 7.04 (m, 2H); 3.72 (d, *J* = 6.3 Hz, 1H); 3.66 (dd, *J* = 5.5 Hz, 9.1 Hz, 1H); 3.56 (s, 3H); 3.30 (dt, *J* = 7.1, 11.7 Hz, 1H); 2.42 (d, *J* = 11.6 Hz, 1H); 2.40–1.88 (m, 5H), 1.28 (t, *J* = 13.2 Hz, 1H); MS (CI, *m*/*z*): 315 [(M+H)$^+$]. Anal. ($C_{15}H_{16}O_2SFCl$) C, H, S, F, Cl.

8.17.9. 2β-Carbomethoxy-3β-(3-chloro-4- fluorophenyl)-8-thiabicyclo[3.2.1]octanes (8j). Compound **8j** was prepared from **6j** as described for **8f**. Compound **8j** was obtained (23%) as white solid: mp 130–131 °C; R_f 0.28 (10% EtOAc/hexanes); ^{1}H NMR: δ 7.26 (m, 1H); 7.16–7.02 (m, 2H); 3.97 (t, *J* = 5.2 Hz, 1H); 3.72 (m, 1H); 3.54 (s, 3H); 3.13 (t, *J* = 4.6 Hz, 1H); 3.03 (dt, *J* = 4.7 Hz, 11.3 Hz, 1H); 2.68 (t, *J* = 12.9 Hz, 1H); 2.28–1.91 (m, 5H); MS (CI, *m*/*z*): 315 [M$^+$]. Anal. ($C_{15}H_{16}O_2SFCl$) C, H, S, F, Cl.

8.18. General procedure for the oxidation of 8-thiabicyclo[3.2.1]octan(ene)s to 8-oxo-8-thiabicyclo[3.2.1]-octan(ene)s, 9a, 10a–f, 11a,b

8.18.1. 2-Carbomethoxy-3-phenyl-8-oxo-8-thiabicyclo-[3.2.1]oct-2-ene (9a). A mixture of compound **6a** (447 mg, 1.72 mmol), KO_2 (244 mg, 3.43 mmol) in dry acetonitrile (5 mL) was stirred at 0 °C and a solution of trimethylsilyl chloride (373 mg, 3.43 mmol) in acetonitrile (15 mL) was added dropwise to the solution with vigorous stirring under an argon atmosphere. After stirring for 4 h at 0 °C, the reaction was quenched by addition of 0.2 M HCl (30 mL) and then extracted with ethyl acetate (2× 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (2–5% CH_3OH in $CHCl_3$) and recrystallized from heptane/EtOAc (1:1) to give the product **9a** as a solid (268 mg, 56%); mp 151–152 °C, R_f 0.20 (2% CH_3OH in $CHCl_3$); ^{1}H NMR: δ 7.31 (m, 3H); 7.05 (m, 2H); 4.30 (d, *J* = 4 Hz, 1H); 3.659 (m, 1H); 3.45 (s, 3H); 3.10 (dd, 1H); 2.64–2.81 (m, 4H); 2.17 (m, 1H); MS (CI, *m*/*z*): 277 [M$^+$]. Anal. ($C_{15}H_{16}O_3S$) C, H, S.

8.18.2. 2β-Carbomethoxy-3α-phenyl-8-oxo-8-thiabicyclo[3.2.1]octane (10a). Compound **10a** was prepared from **7a** as described for **9a**. Compound **10a** was obtained (59%) as white solid after flash chromatography with $CHCl_3$/MeOH (50:1): mp 140–142 °C; R_f 0.20 (2% CH_3OH in $CHCl_3$); ^{1}H NMR: δ 7.14–7.29 (m, 5H); 3.71 (d, *J* = 6 Hz, 1H); 3.63 (m, 1H); 3.57 (s, 3H); 3.35 (m, 1H); 3.00 (d, *J* = 10.8 Hz, 1H); 2.79 (m, 2H); 2.61 (m, 1H); 2.05 (m, 2H); 1.93 (t, 1H); MS (CI, *m*/*z*): 279 [(M+H)$^+$]. Anal. ($C_{15}H_{18}O_3S$) C, H, S.

8.18.3. 2β-Carbomethoxy-3α-(4-bromophenyl)-8-oxo-8-thiabicyclo[3.2.1]octane (10b). Compound **10b** was prepared from **7b** as described for **9a**. Compound **10b** was obtained (49%) as white solid: mp 122–123 °C; R_f 0.23 (2% CH_3OH in $CHCl_3$); ^{1}H NMR: δ 7.41 (d, 2H); 7.02 (d, 2H); 3.69 (d, *J* = 6 Hz, 1H); 3.59 (m, 1H); 3.59 (s, 3H); 3.33 (m, 1H); 2.93 (d, *J* = 12 Hz, 1H); 2.81 (m, 2H); 2.60 (m, 1H); 2.09 (m, 2H); 1.85 (t, *J* = 13.5 Hz, 1H); MS (CI, *m*/*z*): 357 [M$^+$], 359. Anal. ($C_{15}H_{17}O_3SBr$) C, H, S, F, Br.

8.18.4. 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-oxo-8-thiabicyclo[3.2.1]octane (10c). Compound **10c** was prepared from **7f** as described for **9a**. Compound **10c** was obtained as white solid (94%): mp 140–142 °C; R_f 0.17 (2% CH_3OH in $CHCl_3$); ^1H NMR: δ 7.35 (d, 1H); 7.24 (d, 1H); 7.00 (dd, 1H); 3.70 (d, $J = 6$ Hz, 1H); 3.69 (m, 1H); 3.62 (s, 3H); 3.32 (m, 1H); 2.92 (d, $J = 9.6$ Hz, 1H); 2.89 (m, 2H); 2.61 (m, 1H); 2.07 (m, 2H); 1.85 (t, 1H); MS (CI, *m/z*): 347 [$(M+H)^+$], 349, 351. Anal. ($C_{15}H_{16}O_3SCl_2$) C, H, S, Cl.

8.18.5. 2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-oxo-8-thiabicyclo[3.2.1]octane (11a). Compound **11a** was prepared from **8f** as described for **9a**. Compound **11a** was obtained as white solid (57%): mp 142–143 °C; R_f 0.14 (2% CH_3OH in $CHCl_3$); ^1H NMR: δ 7.34 (d, 1H); 7.30 (d, 1H), 7.06 (dd, 1H); 3.87 (m, 1H); 3.76 (t, 1H); 3.54 (s, 3H); 3.21 (m, 1H); 3.05 (m, 1H); 2.67–2.76 (m, 3H); 2.16 (m, 2H); 2.13 (m, 1H); MS (CI, *m/z*): 347 [M^+]. 349; Anal. ($C_{15}H_{16}O_3SCl_2$) C, H, S, F, Cl.

8.18.6. 2β-Carbomethoxy-3α-(3-chloro-4- fluorophenyl)-8-oxo-8-thiabicyclo[3.2.1]octane (10d). Compound **10d** was prepared from **7j** as described for **9a**. Compound **10d** was obtained as white solid (91%): mp 150–152 °C; R_f 0.27 (2% CH_3OH in $CHCl_3$); ^1H NMR: δ 7.18 (dd, 1H); 7.02 (m, 2H); 3.69 (d, $J = 6$ Hz, 1H); 3.63 (m, 1H); 3.59 (s, 3H); 3.33 (m, 1H); 2.91 (d, $J = 12$ Hz, 1H); 2.87 (m, 2H); 2.60 (m, 1H); 2.08 (m, 2H); 1.84 (ddd, 1H); MS (CI, *m/z*): 331 [M^+], 333. Anal. ($C_{15}H_{16}O_3SClF$) C, H, S, F, Br.

8.18.7. 2β-Carbomethoxy-3α-(4-chloro-3- fluorophenyl)-8-oxo-8-thiabicyclo[3.2.1]octane (10e). Compound **10e** was prepared from **7i** as described for **9a**. Compound **10e** was obtained (64%) as white solid: mp 151–152 °C; R_f 0.16 (2% CH_3OH in $CHCl_3$); ^1H NMR: δ 7.30 (m, 1H); 6.91 (m, 2H); 3.69 (d, $J = 6$ Hz, 1H); 3.61 (m, 1H); 3.60 (s, 3H); 3.33 (m, 1H); 2.92 (d, $J = 12$ Hz, 1H); 2.81 (m, 2H); 2.61 (m, 1H); 2.06 (m, 2H); 1.84 (t, $J = 13.5$ Hz, 1H); MS (CI, *m/z*): 331 [M^+], 333. Anal. ($C_{15}H_{16}O_3SClF$) C, H, S, F, Cl.

8.18.8. 2β-Carbomethoxy-3β-(4-chloro-3-fluorophenyl)-8-oxo-8-thiabicyclo[3.2.1]octane (11b). Compound **11b** was prepared from **8i** as described for **9a**. Compound **11b** was obtained (18%) as white solid: mp 121–122 °C; R_f 0.13 (2% CH_3OH in $CHCl_3$); ^1H NMR: δ 7.25 (m, 1H); 7.06 (m, 2H); 3.86 (t, 1H); 3.75 (t, 1H); 3.53 (s, 3H); 3.19 (m, 1H); 3.08 (m, 1H); 2.65–2.75 (m, 3H); 2.16 (m, 2H); 2.03 (m, 1H); MS (CI, *m/z*): 331 [M^+], 333. Anal. ($C_{15}H_{16}O_3SClF$) C, H, S, F, Cl.

8.18.9. 2β-Carbomethoxy-3α-(3,4-difluorophenyl)-8-oxo-8-thiabicyclo[3.2.1]octane (10f). Compound **10f** was prepared from **7g** as described for **9a** Compound **10f** was obtained (94%) as white solid: mp 134–136 °C; R_f 0.39 (2% CH_3OH in $CHCl_3$); ^1H NMR: δ 6.87–7.09 (m, 3H); 3.69 (d, $J = 6$ Hz, 1H); 3.61 (m, 1H); 3.60 (s, 3H); 3.32 (m, 1H); 2.90 (d, $J = 11.1$ Hz, 1H); 2.86 (m, 2H); 2.60 (m, 1H); 2.07 (m, 2H); 1.83 (ddd, 1H); MS (CI, *m/z*): 315 [$(M+H)^+$]. Anal. ($C_{15}H_{16}O_3SF_2$) C, H, S, F.

8.18.10. Single-crystal X-ray analysis of 2β-carbomethoxy-3α-(3,4-difluorophenyl)-8-oxo-8-thiabicyclo[3.2.1]-octane (10f). Monoclinic crystals of the purified **10f** were obtained from ethyl acetate/heptane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection, and refinement parameters: crystal size, $0.52 \times 0.16 \times 0.16$ mm^3; cell dimensions, $a = 6.4713(3)$ Å, $b = 30.4744(14)$ Å, $c = 7.2817(3)$ Å, $\alpha = 90°$, $\beta = 90.2200\ (10)°$, $\gamma = 90°$; formula, $C_{15}H_{16}F_2SO_3$; formula weight = 314.34; volume = 1436.01 (11) $Å^3$; calculated density = 1.454 g cm^{-3}; space group = $P2(1)/c$; number of reflections = 11418 of which 3530 were considered independent ($R_{int} = 0.02717$). Refinement method was full-matrix least-squares on F^2. The final R-indices were [$I > 2\sigma$ (I)] $R1 = 0.0533$, $wR2 = 0.1465$.

8.18.11. Single-crystal X-ray analysis of (1*R*)-2-carbomethoxy-8-thiabicyclo[3.2.1]oct-2-ene-3-(1′*S*)-camphanate, (1*R*,1′*S*)-4a. Orthorhombic crystals of the purified (1*R*,1′*S*)-**4a** were obtained from methylene chloride/hexane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection, and refinement parameters: crystal size, $0.54 \times 0.24 \times 019$ mm^3; cell dimensions, $a = 6.2331(13)$ Å, $b = 6.8802(14)$ Å, $c = 43.357(10)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; formula, $C_{19}H_{24}SO_6$; formula weight = 380.44; volume = 1859.4(7) $Å^3$; calculated density = 1.359 g cm^{-3}; space group = $P21\ 21\ 21$; number of reflections = 6936 of which 3198 were considered independent ($R_{int} = 0.0297$). Refinement method was full-matrix least-squares on F^2. The final R-indices were [$I > 2\sigma$ (I)] $R1 = 0.0424$, $wR2 = 0.1041$.

8.18.12. Dopamine transporter assay. The dopamine transporter was labeled with [^{3}H]WIN35,428 ([^{3}H]CFT, 2β-carbomethoxy-3β-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 81–84 Ci/mmol, DuPont-NEN). The affinity of [^{3}H]WIN35,428 for the dopamine transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]WIN35,428 and a range of concentrations of unlabeled WIN35,428. The assay tubes received, in Tris–HCl buffer (50 mM, pH 7.4, at 0–4 °C; NaCl 100 mM), the following constituents at a final assay concentration: WIN35,428, 0.2 mL (1 pM–100 or 300 nM), [^{3}H]WIN35,428 (0.3 nM); membrane preparation 0.2 mL (4 mg original wet weight of tissue/mL). The 2 h incubation (0–4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass fiber filters presoaked in 0.1% bovine serum albumin (Sigma Chem. Co.). The filters were washed twice with 5 mL Tris–HCl buffer (50 mM), incubated overnight at 0–4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). Cpm were converted to dpm following determination of counting efficiency (>45%) of each vial by external standardization. Total binding was defined as [^{3}H]WIN35,428 bound in the

presence of ineffective concentrations of unlabeled WIN35,428 (1 or 10 pM). Non-specific binding was defined as [^{3}H]WIN35,428 bound in the presence of an excess (30 μM) of (−)-cocaine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at [^{3}H]WIN 35,428 binding sites were conducted using procedures similar to those outlined above. Stock solutions of water-soluble drugs were dissolved in water or buffer and stock solutions of other drugs were made in a range of ethanol/HCl solutions. Several of the drugs were sonicated to promote solubility. The stock solutions were diluted serially in the assay buffer and added (0.2 mL) to the assay medium as described above.

8.18.13. Serotonin transporter assay. The serotonin transporter was assayed in caudate-putamen membranes using conditions similar to those for the dopamine transporter. The affinity of [^{3}H]citalopram (spec. act.: 82 Ci/mmol, Perkin-Elmer, Boston) for the serotonin transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]citalopram and a range of concentrations of unlabeled citalopram. The assay tubes received, in Tris–HCl buffer (50 mM, pH 7.4, at 0–4 °C; NaCl 100 mM), the following constituents at a final assay concentration: citalopram, 0.2 mL (1 pM–100 or 300 nM), [^{3}H]citalopram (1 nM); membrane preparation 0.2 mL (4 mg original wet weight of tissue/ml). The 2 h incubation (0–4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass fiber filters pre-soaked in 0.1% polyethyleneimine. The filters were washed twice with 5 mL Tris–HCl buffer (50 mM), incubated overnight at 0–4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). Cpm were converted to dpm following determination of counting efficiency (>45%) of each vial by external standardization. Total binding was defined as [^{3}H]citalopram bound in the presence of ineffective concentrations of unlabeled citalopram (1 or 10 pM). Non-specific binding was defined as [^{3}H]citalopram bound in the presence of an excess (10 μM) of fluoxetine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at [^{3}H]citalopram binding sites were conducted using procedures similar to those outlined above.

8.18.14. Data analysis. Data were analyzed by the EBDA computer software programs (Elsevier-Biosoft, UK). Final estimates of IC_{50} values were computed by the EBDA program. Baseline values for the individual drugs were established from the competition curves and these generally were similar to baseline values established by 30 μM (−)-cocaine or 1 μM fluoxetine.

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References and notes

1. Kennedy, L. T.; Hanbauer, I. *J. Neurochem.* **1983**, *34*, 1137.
2. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219.
3. Kuhar, M. J.; Ritz, M. C.; Boja, J. W. *Trends Neurosci.* **1991**, *14*, 299.
4. Spealman, R. D. *Psychopharmacology* **1993**, *112*, 93.
5. Rocha, B. A.; Fumagalli, F.; Gainetdinov, R. R.; Jones, S. R.; Ator, R.; Giros, B.; Miller, G. W.; Caron, M. G. *Nat. Neurosci.* **1998**, *1*, 132.
6. Uhl, G. R.; Hall, F. S.; Sora, I. *Mol. Psychiatry* **2002**, *7*, 21.
7. Rothman, R. B.; Mele, A.; Reid, A. A.; Akunne, H. C.; Greig, N.; Thurkauf, A.; deCosta, B. R.; Rice, K. C.; Pert, A. *Pharmacol. Biochem. Behav.* **1991**, *40*, 387.
8. Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 2719.
9. Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. *J. Med. Chem.* **1993**, *36*, 855.
10. Meltzer, P. C.; Liang, A. Y.; Madras, B. K. *J. Med. Chem.* **1994**, *37*, 2001.
11. Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. *J. Med. Chem.* **1994**, *37*, 3875.
12. Kozikowski, A. P.; Saiah, M. K. E.; Bergmann, J. S.; Johnson, K. M. *J. Med. Chem.* **1994**, *37*, 3440.
13. Lomenzo, S. A.; Izenwasser, S.; Katz, J. L.; Terry, P. D.; Zhu, N.; Klein, C. L.; Trudell, M. L. *J. Med. Chem.* **1997**, *40*, 4406.
14. Meltzer, P. C.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Chen, Z.; George, C.; Madras, B. K. *J. Med. Chem.* **1997**, *40*, 2661.
15. Carroll, F. I.; Lewin, A. H.; Kuhar, M. J. *Med. Chem. Res.* **1998**, *8*, 59.
16. Meltzer, P. C.; Blundell, P.; Madras, B. K. *Med. Chem. Res.* **1998**, *8*, 12.
17. Newman, A. H. *Med. Chem. Res.* **1998**, *8*, 1.
18. Tamagnan, G.; Baldwin, R. M.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B. *Bioorg. & Med. Chem. Lett.* **2000**, *10*, 1783.
19. Singh, S. *Chem. Rev.* **2000**, *100*, 925.
20. Meltzer, P. C.; Wang, B.; Chen, Z.; Blundell, P.; Jayaraman, M.; Gonzalez, M. D.; George, C.; Madras, B. K. *J. Med. Chem.* **2001**, *44*, 2619.
21. Newman, A. H.; Kulkarni, S. S. *Med. Res. Rev.* **2002**, *22*, 429.
22. Meltzer, P. C.; Liu, S.; Blanchette, H. S.; Blundell, P.; Madras, B. K. *Bioorg. Med. Chem.* **2002**, *10*, 3583.
23. Torun, L.; Liu, S.; Madras, B. K.; Meltzer, P. C. *Tetrahedron Lett.* **2006**, *47*, 599.
24. Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. *J. Med. Chem.* **1973**, *16*, 1260.
25. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.
26. Kitayama, S.; Shimada, S.; Xu, H.; Markham, L.; Donovan, D. H.; Uhl, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *89*, 7782.
27. Meltzer, P. C.; Blundell, P.; Chen, Z.; Yong, Y.; Madras, B. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 857.
28. Meltzer, P. C.; Wang, P.; Blundell, P.; Madras, B. K. *J. Med. Chem.* **2003**, *46*, 1538.
29. Meltzer, P. C.; Blundell, P.; Yong, Y. F.; Chen, Z.; George, C.; Gonzalez, M. D.; Madras, B. K. *J. Med. Chem.* **2000**, *43*, 2982.
30. Hamada, A.; Chang, Y. A.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1984**, *27*, 675.

31. Chang, Y. A.; Ares, J.; Anderson, K.; Sabol, B.; Wallace, R. A.; Farooqui, T.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1987**, *30*, 214.
32. Harrold, M. W.; Chang, Y. A.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1987**, *30*, 1631.
33. Harrold, M. W.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller, D. D. *J. Med. Chem.* **1989**, *32*, 874.
34. Harrold, M. W.; Sriburi, A.; Matsumoto, K.; Miller, D. D.; Farooqui, T.; Uretsky, N. *J. Med. Chem.* **1993**, *36*, 3166.
35. Majewski, M.; DeCaire, M.; Nowak, P.; Wang, F. *Synlett* **2000**, 1321.
36. Majewski, M.; DeCaire, M.; Nowak, P.; Wang, F. *Can. J. Chem.* **2001**, *79*, 1792.
37. Meltzer, P. C.; Pham-Huu, D.-P.; Madras, B. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6007.
38. Parr, A. J.; Walton, N. J.; Bensalem, S.; McCabe, P. H.; Routledge, W. *Phytochemistry* **1991**, *30*, 2607.
39. Keverline, K. I.; Abraham, P.; Lewin, A. H.; Carroll, F. I. *Tetrahedron Lett.* **1995**, *36*, 3099.
40. Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett.* **1978**, *52*, 5211.
41. Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *49*, 1991.
42. Madras, B. K.; Pristupa, Z. B.; Niznik, H. B.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Meltzer, P. C. *Synapse* **1996**, *24*, 340.
43. Madras, B. K.; Fahey, M. A.; Bergman, J.; Canfield, D. R.; Spealman, R. D. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 131.
44. Boja, J. W.; Kuhar, M. J.; Kopajtic, T.; Yang, E.; Abraham, P.; Lewin, A. H.; Carroll, F. I. *J. Med. Chem.* **1994**, *37*, 1220.
45. Blough, B. E.; Abraham, P.; Lewin, A. H.; Kuhar, M. J.; Boja, J. W.; Carroll, F. I. *J. Med. Chem.* **1996**, *39*, 4027.
46. Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883.