Conformationally Restricted Homotryptamines. 2. Indole Cyclopropylmethylamines as Selective Serotonin Reuptake Inhibitors

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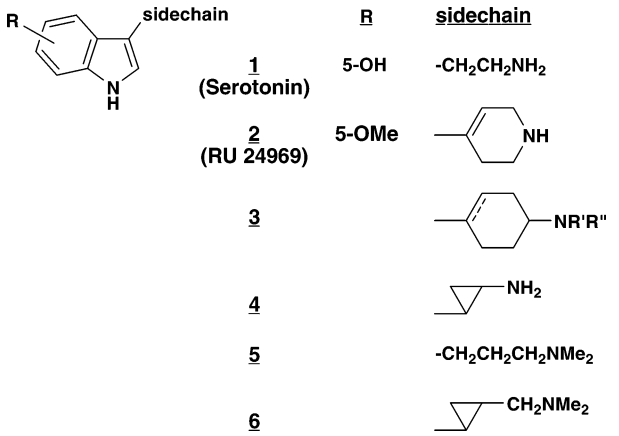
A series of indole cyclopropylmethylamines were found to be potent serotonin reuptake inhibitors. Nitrile substituents at the 5 and 7 positions of the indole ring gave high affinity for hSERT, and the preferred cyclopropane stereochemistry was determined to be (1*S*,2*S*)-*trans*. The *cis*-cyclopropanes had 20- to 30-fold less affinity than the *trans*, and the preferred *cis* stereochemistry was (1*R*,2*S*)-*cis*. Substitution of the indole N-1 position with methyl or ethyl groups gave a 10- to 30-fold decrease in affinity for hSERT, suggesting either a hydrogen-bonding interaction or limited steric tolerance in the region of the indole nitrogen. Compound (+)-**12a** demonstrated potent hSERT binding (K_i = 0.18 nM) in vitro and was more than 1000-fold less potent at hDAT, hNET, 5-HT_{1A}, and 5-HT_6. In vivo, (+)-**12a** produced robust, dose-dependent increases in extracellular serotonin in rat frontal cortex typical of a selective serotonin reuptake inhibitor. The maximal response produced by (+)-**12a** was similar to that of fluoxetine but at an approximately 10-fold lower dose.

Introduction

One key target for psychoactive drugs is the serotonergic (5-HT) system, where the human serotonin transporter (hSERT) is one of the major regulators of synaptic 5-HT levels. The selective serotonin reuptake inhibitors (SSRIs) are effective antidepressants and are relatively safe despite some recognized drawbacks.[1] Although SSRIs are prescribed most often for depressive disorders, they are increasingly being used to treat a variety of anxiety disorders, as well as being used as off-label treatments for a broad list of other disorders.[2] More recent SSRI research has focused on compounds with additional properties that may result in a more rapid onset of antidepressant action, e.g., SERT inhibition combined with 5-HT_{1A} or 5-HT_{1B} antagonism.[3]

Most binding studies of SERT inhibitors are consistent with one hSERT binding site. A proposed 3D QSAR model[4] with a single binding site has been derived from a diverse set of compounds including SSRIs, tricyclic antidepressants, and other compounds such as venlafaxine and trazodone. In contrast, site-directed mutagenesis studies suggest multiple binding sites are present on SERT. A 3D model[5] of SERT based on mutagenesis studies suggest there are at least three ligand binding sites that bind imipramine, citalopram, and paroxetine at different sites. Some SSRIs interact with a low-affinity, allosteric binding site that modulates the primary SERT binding site. The *R*-citalopram and *S*-citalopram have different activities at the allosteric binding site,[6] and this has been proposed as an advantage for *S*-citalopram.[7]

The conformational restriction of serotonergic ligands is a well-precedented way to improve binding of these agents. One of the earliest semirigid analogues of serotonin (**1**) replaced the aminoethylene side chain with a tetrahydropyridyl side chain to give **2** (RU 24969).[8] The further extension of the side chain to aminocyclohexenyl and aminocyclohexyl (**3**) gave compounds with 5-HT_{1A} activity,[9] SSRI activity,[10] or both.[11] Aminocyclopropane analogues (**4**) of serotonin also were investigated, with the conclusion that this was a good strategy only for the tryptamines that exhibited 5-HT_{2C} binding rather than 5-HT_{1A} or 5-HT_{2A} activity.[12]



We have previously reported a facile one-pot synthesis of *N*,*N*-dimethylhomotryptamines[13] (**5**) and their affinity[14] for hSERT. This initial pharmacological report identified *N*,*N*-dimethylhomotryptamine as a basic scaffold for potent SSRI activity. We now report a series of conformationally restricted homotryptamines using the cyclopropylmethylamine side chain (**6**) as new potent SSRIs.

Synthesis

The racemic *trans*-cyclopropanes were prepared from the appropriately substituted indoles (**7a**−**h**, Scheme 1)

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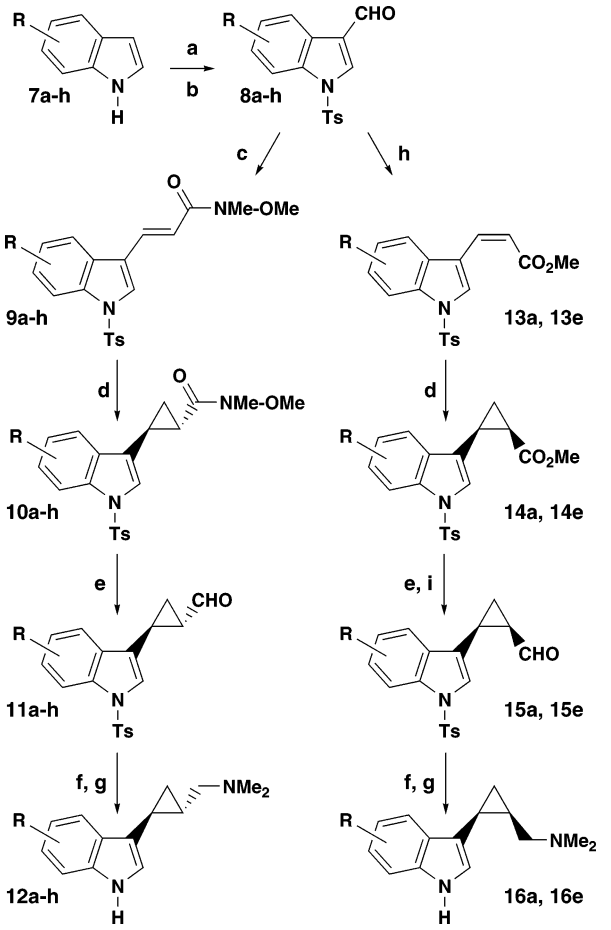
Scheme 1. Synthesis of Racemic *trans*- and *cis*-Cyclopropanes[a]

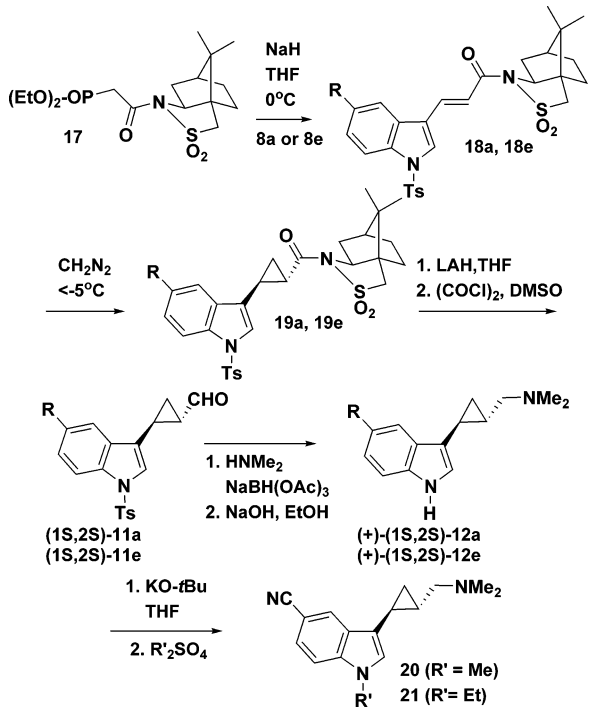


[a] (a) $POCl_3$, DMF; (b) TsCl, NEt_3; (c) NaH, (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate, THF; (d) CH_2N_2, $Pd(OAc)_2$; (e) LAH, THF; (f) Me_2NH, $NaBH(OAc)_3$; (g) NaOH, H_2O/EtOH; (h) NaH, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF; (i) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N.

by modification of published methods.[15] Indoles (**7a**−**h**) that were not commercially available were prepared by the published methods.[16] Formylation[17] of **7a**−**h** under Vilsmeier−Haack conditions with subsequent tosylation of the indole N-1 position provided aldehydes **8a**−**h** in good yields. Subsequent Horner−Wadsworth−Emmons olefination of **8a**−**h** with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate[18] gave the corresponding *trans* Weinreb amides **9a**−**h**, which were cyclopropanated with diazomethane and palladium acetate to give the *trans*-cyclopropyl Weinreb amides **10a**−**h**. Reduction of the Weinreb amides with LAH, reductive amination of the resulting aldehydes **11a**−**h**, and hydrolysis of the *N*-tosyl group gave the racemic *trans*-cyclopropanes **12a**−**h**.

The racemic *cis*-cyclopropanes **16a** and **16e** were prepared from **8a** and **8e** in a manner similar to the procedure for *trans*-cyclopropanes. A *cis*-selective Still−Gennari modified Horner−Wadsworth−Emmons olefination[19] provided a 3:1 *cis*/*trans* mixture, from which the *cis* olefins (**13a** and **13e**) could be obtained pure by silica gel chromatography. Cyclopropanation of **13a** and **13e** with diazomethane and palladium acetate regioselectively produced the *cis*-cyclopropanes (**14a** and **14e**). Careful reduction of the ester with LAH gave the corresponding alcohols, which were oxidized under

Scheme 2. Enantioselective Synthesis of *trans*-Cyclopropanes



Swern conditions to provide aldehydes **15a** and **15e**. Reductive amination and hydrolysis of the indole N-1 tosyl group then provided the desired *cis*-cyclopropanes **16a** and **16e**.

The chiral *trans*-cyclopropanes were prepared by a modification of published methods.[12c,20] Horner−Wadsworth−Emmons olefination of **8a** and **8e** using the chiral phosphonate **17**[21] gave intermediates **18a** and **18e** bearing the (+)-camphorsultam chiral auxiliary (Scheme 2). Intermediates **18a** and **18e** were cyclopropanated with diazomethane and palladium acetate to stereoselectively produce the (1*S*,2*S*)-*trans*-cyclopropanes (**19a** and **19e**). Similar to the racemic synthesis, amides (**19a** and **19e**) were reduced to the corresponding alcohols and then oxidized to the aldehydes (1*S*,2*S*)-**11a** and -**11e**, which were then carried on to the *trans*-cyclopropanes, [(+)-**12a** and **-12e**]. The (1*R*,2*R*)-*trans*-cyclopropanes were prepared in a similar manner using the (−)-camphorsultam chiral auxiliary. The (1*S*,2*S*)-stereochemistry of **19a** and (+)-**12a** were confirmed by X-ray crystallography (Figures 1 and 2). To investigate the effects of indole N-1 substituents on SERT inhibition, (+)-**12a** was alkylated with dimethyl sulfate and diethyl sulfate to give the indole N-1 methyl and ethyl derivatives **20** and **21**, respectively.

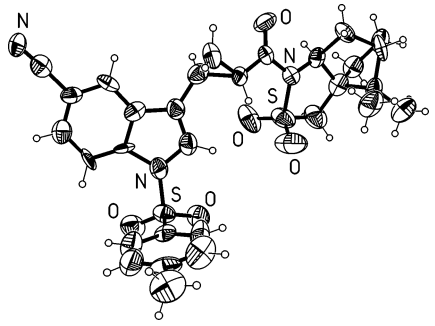


Figure 1. ORTEP drawing of **19a**.

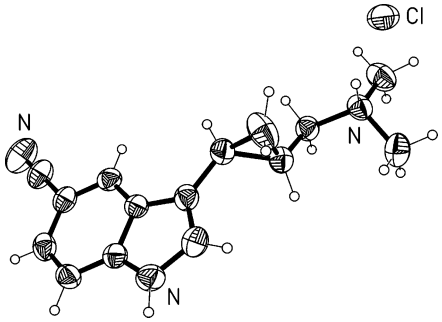


Figure 2. ORTEP drawing of (+)-(1*S*,2*S*)-**12a**·HCl.

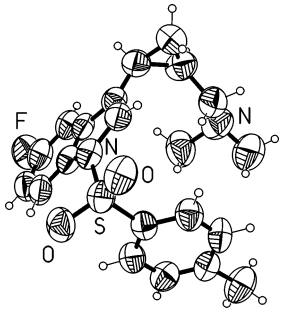


Figure 3. ORTEP drawing of **22**.

The enantiomers of both the *trans*- and *cis*-cyclopropanes (**12a**, **12e**, **16a**, and **16e**) could also be separated analytically and preparatively by chiral HPLC. The enantiomers of **12a** and **12e** were separated on a Chiralcel AD column HPLC using EtOH/hexane as the eluent, with the (1*R*,2*R*)-enantiomer eluting before the (1*S*,2*S*)-enantiomer. In both cases, the separated materials were identical to the corresponding material that was stereoselectively synthesized. The *cis*-cyclopropanes (**16a** and **16e**) were similarly separated into their enantiomers using the same column, with the (+)-enantiomer eluting before the (−)-enantiomer. The absolute stereochemistry of (−)-**16e** was determined to be (1*R*,2*S*) by X-ray crystallography (Figure 3) of the indole N-1 tosyl derivative (**22**). The stereochemistry of the enantiomers of **16a** was assigned by analogy to those of **16e** based on the order of elution from the chiral column and sign of optical rotation.

Results and Discussion

Our previous communication[14] identified *N*,*N*-dimethylhomotryptamines (**5a** and **5e**, Table 1) as potent serotonin reuptake inhibitors. In the current *trans*-cyclopropylmethylamine series, the 5-cyano and 5-fluoro compounds (**12a** and **12e**) were more active at hSERT than the prototypical homotryptamines (**5a** and **5e**). Moving a substituent around the indole ring showed that the 7-cyano compound (**12b**) was equipotent with the 5-cyano analogue (**12a**). However, the 7-fluoro compound (**12f**) was less active than the 5-fluoro analogue (**12e**). The 6-substituted compounds (**12c** and **12d**) and 4-substituted compounds (**12g** and **12h**) were less active than the 5-substituted analogues (**12a** and **12e**). The *cis*-cyclopropylmethylamines (**16a** and **16e**) were less active than either the *trans*-cyclopropanes (**12a** and **12e**) or the homotryptamines (**5a** and **5e**).

To define the stereochemical requirements for hSERT inhibition, the binding of the enantiomers of the *trans*-cyclopropanes (**12a** and **12e**) and the *cis*-cyclopropanes (**16a** and **16e**) was investigated. In the *trans*-cyclopropanes, the (1*S*,2*S*)-enantiomers [(+)-**12a** and -**12e**] were significantly (>50-fold) more active than the (1*R*,2*R*)-enantiomers [(−)-**12a** and -**12e**]. In the *cis*-cyclopropanes, the (1*R*,2*S*)-enantiomers [(−)-**16a** and -**16e**] were only slightly more active than the corresponding (1*S*,2*R*)-enantiomers [(+)-**16a** and -**16e**]. Thus, the more active enantiomers of the *cis*- and *trans*-cyclopropanes retained the (*S*)-stereochemistry adjacent to the indole but differ in the stereochemistry at the cyclopropane carbon that bore the dimethylaminomethyl group.

The importance of the indole N-1 H to hSERT binding was also investigated. The indole N-1 methyl and ethyl analogues **20** and **21** demonstrated a 10- to 30-fold decrease in affinity for hSERT relative to (+)-**12a**. Thus, hydrogen bonding of hSERT to the indole N-1 hydrogen

Table 1. hSERT, hDAT, and hNET Binding of Indole Cyclopropylmethylamines

compd	R	R′	*cis*/*trans*	±	hSERT K_i (nM)	*n*	hDAT K_i (nM)	hNET K_i (nM)
fluoxetine					0.72 ± 0.05	24	1900 ($n = 2$)	440 ($n = 2$)
paroxetine					0.04 ± 0.003	18	400 ($n = 2$)	90 ($n = 2$)
5a	5-CN	H			2 ± 0.4	3	*a*	*a*
5e	5-F	H			4 ± 0.3	3	*a*	*a*
12a	5-CN	H	*trans*	±	0.56 ± 0.15	13	*a*	*a*
12b	7-CN	H	*trans*	±	0.58 ± 0.11	3	*a*	*a*
12c	6-CN	H	*trans*	±	7.4 ± 1.8	3	*a*	*a*
12d	4-CN	H	*trans*	±	230, 420	2	nt[b]	nt[b]
12e	5-F	H	*trans*	±	2.1 ± 0.4	7	*a*	*a*
12f	7-F	H	*trans*	±	10 ± 2.4	3	*a*	*a*
12g	6-F	H	*trans*	±	38 ± 6.1	3	*a*	*a*
12h	4-F	H	*trans*	±	59 ± 17	3	*a*	*a*
16a	5-CN	H	*cis*	±	7.1 ± 2.1	3	*a*	*a*
16e	5-F	H	*cis*	±	24 ± 5.9	3	*a*	*a*
(+)-**12a**	5-CN	H	*trans*	1*S*,2*S*	0.18 ± 0.02	12	2100 ($n = 2$)	4600 ($n = 2$)
(−)-**12a**	5-CN	H	*trans*	1*R*,2*R*	8.9 ± 1.7	5	*a*	*a*
(+)-**12e**	5-F	H	*trans*	1*S*,2*S*	0.68 ± 0.11	11	*a*	*a*
(−)-**12e**	5-F	H	*trans*	1*R*,2*R*	41 ± 2.7	4	*a*	*a*
(−)-**16a**	5-CN	H	*cis*	1*R*,2*S*	5.7 ± 1.9	3	*a*	*a*
(+)-**16a**	5-CN	H	*cis*	1*S*,2*R*	17 ± 2.6	3	*a*	*a*
(−)-**16e**	5-F	H	*cis*	1*R*,2*S*	14 ± 1.9	4	*a*	*a*
(+)-**16e**	5-F	H	*cis*	1*S*,2*R*	100 ± 1.4	3	nt[b]	nt[b]
20	5-CN	Me	*trans*	1*S*,2*S*	6.5 ± 4.3	4	*a*	*a*
21	5-CN	Et	*trans*	1*S*,2*S*	1.8 ± 1.1	4	*a*	*a*

[a] Less than 50% inhibition at 1 μM. [b] nt: not tested.

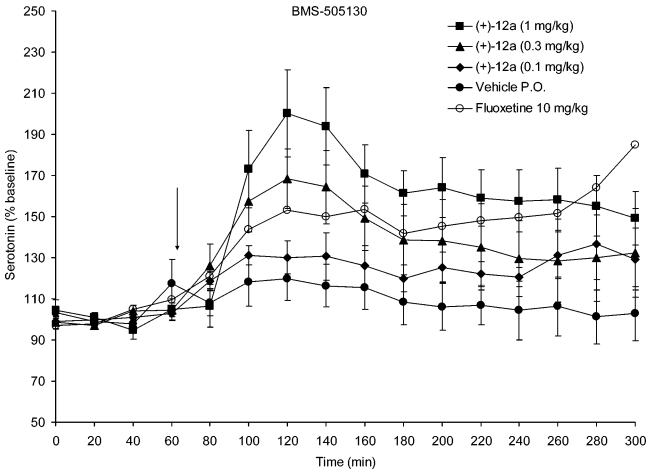


Figure 4. Effects of (+)-**12a** on extracellular serotonin levels in the frontal cortex of rats measured by microdialysis. Data points represent mean ± SEM of five to six rats per group, and the black arrow indicates the time of compound administration. Dosing was via oral gavage in a volume of 1 L/kg to rats fasted overnight.

may play a role in the binding of these indole SSRIs, or there may be limited steric tolerance in this region.

The selectivity of (+)-**12a** for hSERT versus other receptors and transporters was also evaluated. Since it is well established that the increase in synaptic 5-HT caused by SSRIs is limited by feedback mechanisms mediated by 5-HT_{1A} and 5-HT_{1B} autoreceptors,[22] it was of added importance to test (+)-**12a** for binding at a variety of serotonergic receptors. Compound (+)-**12a** demonstrated only modest binding at the 5-HT_{1A} (K_i = 410 ± 10 nM) and at 5-HT_6 (K_i = 270 ± 40 nM) receptors, while there was no significant binding (<32% inhibition at 1 μM) at the 5-HT_{1B}, 5-HT_{2A}, 5-HT_3, 5-HT_{5A}, and 5-HT_7 receptors. In addition, (+)-**12a** did not bind significantly to the human dopamine transporter (hDAT) or the human norepinephrine transporter (hNET) (K_i = 2.1 and 4.6 μM, respectively).[23] Since (+)-**12a** demonstrated greater than 1000-fold more potent binding for hSERT than for hDAT, hNET, 5-HT_{1A}, and 5-HT_{1B}, it seems unlikely that these latter interactions would exert significant pharmacological effects. Thus (+)-**12a** demonstrated a high selectivity for hSERT.

Since these molecules bind with high affinity and selectivity to hSERT in vitro, it was of interest to determine if these compounds could produce functional changes in serotonin levels in vivo. In microdialysis studies in rats in vivo, (+)-**12a** produced robust, dose-dependent increases in extracellular serotonin in the frontal cortex (Figure 4). Doses of 1 and 0.3 mg/kg po produced effects that were significantly greater than vehicle, while the effects of 0.1 mg/kg were not statistically significant. The maximal effect of (+)-**12a** was comparable to that of fluoxetine. However, the dose of (+)-**12a** (1 mg/kg po) necessary to produce the maximal response was approximately 10-fold lower than with fluoxetine (10 mg/kg). Thus, (+)-**12a** produced potent and robust effects on extracellular serotonin levels in vivo, consistent with an earlier report.[23]

Compounds **12a**,**e** and **16a**,**e** share pharmacophoric features (e.g., basic amine and substituted aromatic ring) with other SSRIs such as sertraline and *S*-citalopram. However, **12a**,**e** and **16a**,**e** lack the second phenyl ring of the latter compounds and feature an indole N-1 hydrogen as an additional site for a potential hydrogen-bonding interaction. A computational study of (+)-**12a**, (−)-**16e**, *S*-citalopram, and sertraline ((1*S*,4*S*)-stereochemistry) was performed (Figure 5) to evaluate the possibility that (+)-**12a** and (−)-**16e** might bind to SERT in an analogous fashion to other known inhibitors. The overall method used, including the use of an

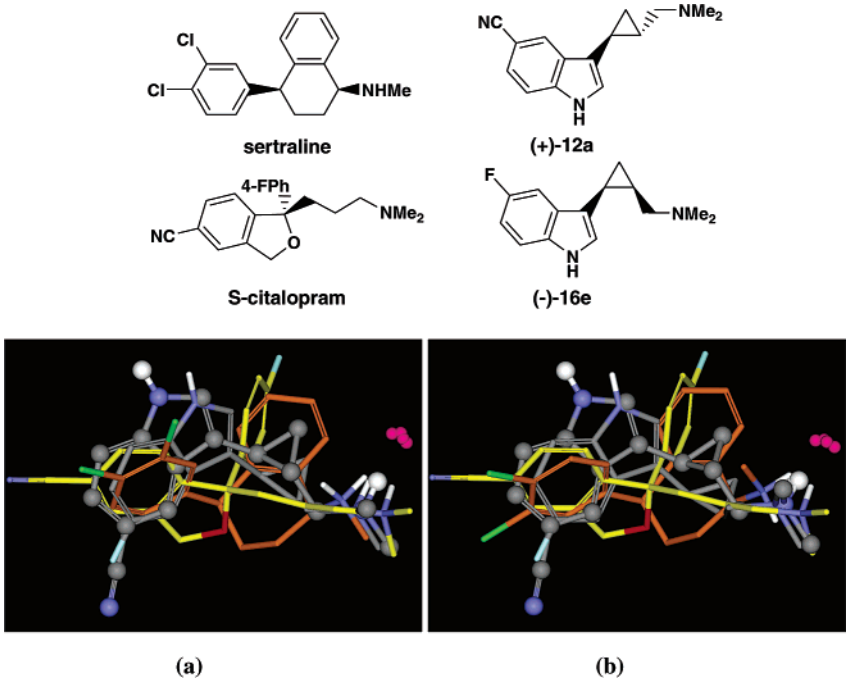


Figure 5. (a, b) Models showing overlays of low-energy conformations of sertraline ((1*S*,4*S*)-stereochemistry, orange carbon atoms), *S*-citalopram (yellow carbon atoms), (−)-**16e** (gray carbon atoms, stick representation), and (+)-**12a** (gray carbon atoms, ball-and-stick representation). Pink spheres are acceptor site points used in fitting procedure. Nonpolar hydrogen atoms are omitted for clarity. The artwork was generated with DS ViewerPro 5.0 (Accelrys, Inc., San Diego, CA, 2002).

acceptor site point located 2.8 Å from the basic nitrogen atom in these compounds, is very similar to that previously employed in a pharmacophore model for SERT ligands.[24] For each molecule, the conformers shown in Figure 5 may or may not be representative of its bioactive conformation. However, Figure 5 does show good correspondence between the positions of the basic nitrogen atoms, the substituted aromatic rings, the ring substituents, and the acceptor site points for all four compounds. Furthermore, the energies of the conformers shown are all predicted to be relatively low using a high level of DFT with an implicit solvation model. This suggests that the four compounds have the ability to interact with hSERT in a similar manner.

Conclusions

The present work investigated a series of indole cyclopropylmethylamines as conformationally restricted homotryptamines with SSRI activity and determined the preferred stereochemistry for binding of these molecules to hSERT. Nitrile substituents at the 5 and 7 positions of the indole ring gave high affinity for hSERT, and the preferred cyclopropane stereochemistry was determined to be (1*S*,2*S*)-*trans*. The *cis*-cyclopropanes had 20- to 30-fold less affinity than the *trans*, and the preferred *cis*-stereochemistry was (1*R*,2*S*)-*cis*. Substitution of the indole N-1 position with methyl or ethyl groups gave a 10- to 30-fold decrease in affinity for hSERT, suggesting either a hydrogen-bonding interaction or limited steric tolerance in the region of the indole nitrogen. Compound (+)-**12a** (BMS-505130) demonstrated very potent hSERT binding (K_i = 0.18 nM) in vitro and was more than 1000-fold less potent at hDAT, hNET, 5-HT_{1A}, and 5-HT_6. In vivo, (+)-**12a** produced robust, dose-dependent increases in extracellular serotonin in rat frontal cortex typical of an SSRI, and (+)-**12a** was approximately 10-fold more potent than fluoxetine.

These conformationally restricted homotryptamines are distinguished from other SSRIs, which have two separated phenyl rings. In contrast, these homotryptamines possess only one fused aromatic ring and also feature an indole N-1 hydrogen that may provide a site for an additional hydrogen-bonding interaction with hSERT. The present studies add to the understanding of the SAR of the homotryptamine SSRIs and the stereochemistry requirements of hSERT. Efforts aimed at achieving even more potent homotryptamine SSRIs will be reported in due course.

Experimental Section

Chemistry. NMRs were recorded on Brüker Avance spectrometers. Elemental analyses were performed at Robertson Microlit Laboratories, Madison, NJ, and were within ±0.4 of the calculated values. Exact mass determinations were made using a Micromass LCT unit, and all samples were determined using a TOF ESI (+) source. ORTEP drawings of the X-ray crystal structures for **19a**, (+)-**12a**·HCl, and **22** are given in Figures 1−3 with ellipsoids drawn at the 50% probability level and H atoms arbitrarily scaled. Full crystallographic data for these compounds have been deposited at the Cambridge Crystallographic Data Center (CCDC reference numbers 268270, 268271, and 268272). Copies of the data can be obtained free of charge via the Internet at http://www.ccdc.cam.ac.uk.

Pharmacology. The binding affinities of these homotryptamine analogues for hSERT, the human dopamine transporter (hDAT), and the human norepinephrine transporter (hNET) were determined using literature methods.[14,23] Compounds with significant hSERT binding (K_i < 100 nM) were investigated for hDAT and hNET binding, and the results are given as percent inhibition of radioligand binding at 1 μM. Percent inhibition at both hNET and hDAT was found to be <50% at 1 μM for all active compounds (hSERT K_i < 100 nM) listed in Table 1. For (+)-**12a**, K_i values were determined for hNET and hDAT inhibition.

Binding studies for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_{5A}, 5-HT_6, and 5-HT_7 serotonergic receptors were performed on (+)-**12a** at Cerep, Celle L'Evescalult, France, with the results expressed as percent inhibition of radioligand binding at 1 μM. Further receptor binding studies for 5-HT_{1A} and 5-HT_6[25] were performed on (+)-**12a** within our labs to generate K_i values for these receptors. In vivo microdialysis and 5-HT_{1A} binding studies were performed by published methodology.[26]

Computational Procedures. Initial conformational searches were done for the N-protonated forms of (+)-**12a**, (−)-**16e**, *S*-citalopram, and sertraline ((1*S*,4*S*)-stereochemistry) using MacroModel 8.6 (Schrödinger, LLC, Portland, OR, 2004).[27] Each search was carried out using the torsional sampling (MCMM) option. Default settings were used except for the number of steps, which was set to 2500. Conformers were minimized using the Polak−Ribiere conjugate gradient (PRCG) algorithm,[28] OPLS2001 force field,[29] and GB/SA water solvation model,[30] with the maximum number of steps set to 10 000. A gradient convergence criterion of 0.05 was employed. For each molecule, all unique conformers were then subjected to density functional theory (DFT) geometry optimization at the RB3LYP/6-31+G* level including a self-consistent reaction field (SCRF) water solvation model.[31,32] DFT calculations were performed with Jaguar 5.5 (Schrödinger, LLC, Portland, OR, 2003). Fine grid density and ultrafine accuracy level settings were used. For the four molecules, each unique conformer within 2.0 kcal/mol of the lowest energy conformer identified was kept for further analysis. There were 18, 6, 10, and 9 conformers retained for (+)-**12a**, (−)-**16e**, citalopram, and sertraline, respectively.

Pairwise rms fitting of each conformer of sertraline to all conformers of (+)-**12a**, (−)-**16e**, and *S*-citalopram was performed using SYBYL 6.9.2 (Tripos Inc., 1699 South Hanley Road, St. Louis, MO, 63144) and a SYBYL Programming Language (SPL) script written in-house that employs the "FIT" function. Comparison of sertraline conformers to those of *S*-citalopram was done using four points per molecule corresponding to the centroids of both aromatic rings, the basic nitrogen atom, and an acceptor site point located 2.8 Å from the basic nitrogen atom along the N−H bond. The cyanophenyl ring of *S*-citalopram was assumed to correspond to the dichlorophenyl ring in sertraline in the fitting procedure. Three points per conformer were used in the fitting of sertraline to (+)-**12a** and (−)-**16e**. These correspond to the centroids of the substituted phenyl rings (the dichlorophenyl ring in sertraline), the basic nitrogen atom, and an acceptor site point located 2.8 Å from the basic nitrogen atom along the N−H bond. Each pairwise combination of a sertraline conformer with a conformer of one of the other three compounds in which the rms fit was less than or equal to 1.0 was retained for further analysis. Models were generated from all remaining combinations of sertraline/citalopram, sertraline/(+)-**12a**, and sertraline/(−)-**16e** conformers. Each model was scored on the basis of the total relative energies of the conformers included in the model. Figure 5 shows the first and second best scoring (lowest overall energy) models. Only the conformation of sertraline differs between the two models. The DFT energies of the conformers of sertraline in Figure 5 are 1.3 and 1.4 kcal/mol above the global minimum, respectively. The conformer of *S*-citalopram shown in Figure 5 is 0.5 kcal/mol above the global minimum. For both (+)-**12a** and (−)-**16e**, the conformers shown are the lowest energy conformers found in the study.

3-Formyl-1-(4-toluenesulfonyl)-1*H*-indole-5-carbonitrile, 8a. $POCl_3$ (10.9 mL, 117 mmol) was added dropwise over

30 min to anhydrous DMF (50 mL) that was maintained at 10−20 °C. The resulting mixture was stirred for 30 min and then chilled to 0 °C. A solution of 5-cyanoindole (15 g, 106 mmol) in anhydrous DMF (30 mL) was added over 10 min. The ice bath was removed, and the solution was warmed to room temperature. After 2 h, a very thick paste resulted. The off-white paste was carefully quenched with ice chips. An aqueous solution of NaOH (2.12 g/100 mL H_2O) was added. After a mild exotherm, a clear yellow solution resulted. The solution was poured into H_2O (400 mL), and a fine solid was immediately precipitated. The mixture was filtered through a 600 mL glass fritted funnel of medium porosity. The yellow filtrate was diluted with an equal volume of H_2O and left to stand for 16 h. The yellow precipitate was collected and dried in vacuo to give (5-cyanoindol-3-yl)carboxaldehyde (13.6 g, 75%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.58 (1H, br s), 10.00 (1H, s), 8.51 (1H, d, J = 3.1 Hz), 8.46 (1H, d, J = 0.6 Hz), 7.22 (1H, dd, J = 8.6, 0.5 Hz), 7.64 (1H, dd, J = 8.5, 1.6 Hz); MS *m/e* 171 $(M + H)^+$.

p-Tosyl chloride (15.2 g, 79.5 mmol) was added to a solution of (5-cyanoindol-3-yl)carboxaldehyde (13.5 g, 79.5 mmol) and triethylamine (12.2 mL, 87.5 mmol) in CH_2Cl_2 (250 mL). The mixture was stirred for 24 h at room temperature. The solid precipitate was collected, washed with EtOH, and dried in vacuo to give **8a** (16.85 g, 65%): mp 243 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (1H, s), 9.07 (1H, s), 8.49 (1H, d, J = 1.1 Hz), 8.16 (1H, dd, J = 8.6, 0.3 Hz), 8.06 (2H, d, J = 8.5 Hz), 7.87 (1H, dd, J = 8.7, 1.7), 7.48 (2H, d, J = 8.1 Hz), 2.36 (3H, s); MS *m/e* 325 $(M + H)^+$. Anal. ($C_{17}H_{12}N_2O_3S$) C, H, N.

3-Formyl-1-(4-toluenesulfonyl)-1*H*-indole-7-carbonitrile, 8b. 8b was prepared from 7-cyanoindole in a manner similar to **8a** (32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.61 (m, 1H), 8.53 (s, 1H), 7.99 (d, J = 8.52 Hz, 2H), 7.73 (m, 1H), 7.45 (m, 1H), 7.37 (d, J = 8.04 Hz, 1H), 2.43 (s, 3H); MS (ESI) *m/e* 325.15 $(M + H)^+$.

3-Formyl-1-(4-toluenesulfonyl)-1*H*-indole-6-carbonitrile, 8c. 8c was prepared from (6-cyanoindol-3-yl)carboxaldehyde[33] in a manner similar to **8a** (88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.1 (1H, s), 9.14 (1H, s), 8.46 (1H, s), 8.27 (1H, d, J = 8.2 Hz), 8.16 (2H, d, J = 8.4 Hz), 7.81 (1H, dd, J = 8.2, 1.3 Hz), 7.48 (2H, d, J = 8.2 Hz), 2.36 (3H, s); MS *m/e* 323 $(M - H)^-$.

3-Formyl-1-(4-toluenesulfonyl)-1*H*-indole-4-carbonitrile, 8d. 8d was prepared from 3-formyl-1*H*-indole-4-carbonitrile[34] in a manner similar to **8a** (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.46 (s, 1H), 8.28 (dd, J = 0.88, 8.52 Hz, 1H), 7.83−7.86 (m, 2H), 7.73 (dd, J = 0.84, 7.60 Hz, 1H), 7.49 (dd, J = 7.68, 8.44 Hz, 1H), 7.33 (d, J = 8.04 Hz, 2H), 2.40 (s, 3H); MS (ESI) *m/e* 325.15 $(M + H)^+$.

[7-Fluoro-1-(4-toluenesulfonyl)indol-3-yl]carboxaldehyde, 8f. 8f was prepared from 7-fluoroindole in a manner similar to **8a** (79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (1H, s), 8.43 (1H, s), 8.08 (1H, dd, J = 0.6, 5.5 Hz), 7.89 (2H, dd, J = 0.5 Hz, 5.7 Hz), 7.33 (2H, d, J = 6.0 Hz), 7.27 (1H, m), 7.07 (1H, m), 2.42 (3H, s); MS *m/e* 318.20 $(M + H)^+$.

[6-Fluoro-1-(4-toluenesulfonyl)indol-3-yl]carboxaldehyde, 8g. 8g was prepared from (6-fluoroindol-3-yl)carboxaldehyde[35] in a manner similar to **8a** (60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.26 (1H, d, J = 2.1 Hz), 8.20 (2H, m), 7.85 (2H, d, 8.4 Hz), 7.66 (1H, dd, J = 7.1, 2.3 Hz), 7.34 (2H, d, J = 8.20 Hz), 7.12 (1H, m), 2.40 (3H, s); MS *m/e* 318.20 $(M + H)^+$.

[4-Fluoro-1-(4-toluenesulfonyl)indol-3-yl]carboxaldehyde, 8h. 8h was prepared from (4-fluoroindol-3-yl)carboxaldehyde[36] in a manner similar to **8a** (57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (1H, s), 8.29 (1H, s), 7.82 (3H, m), 7.33 (3H, m), 7.07 (2H, dd, J = 8.2, 1.9 Hz), 2.39 (3H, s); MS *m/e* 318.16 $(M + H)^+$.

***trans*-3-[5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methyl-acrylamide, 9a.** A solution of diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (12.81 mL, 14.85 g, 62.1 mmol) in anhydrous THF (50 mL) was added to a stirred suspension of oil-free NaH (1.49 g, 62.1 mmol) in anhydrous THF (900 mL) maintained at 0 °C. The mixture was warmed to room temperature and was stirred for 2 h. After the mixture was cooled to 0 °C, **8a** (16.8 g, 51.8 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with aqueous HCl (0.1 N), and the mixture was poured into H_2O (250 mL). After it was made acidic with HCl (1.0 N), the aqueous portion was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. The filtrate was concentrated in vacuo. The crude product was purified by recrystallization from EtOAc to give **9a** (19.1 g total; 12.5 g first crop, 6.58 g second crop; 91%) as a white solid: mp 177−178 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (1H, s), 8.47 (1H, s), 8.14 (1H, d, J = 8.7 Hz), 7.98 (2H, d, J = 8.4 Hz), 7.81 (1H, dd, J = 8.7, 1.4 Hz), 7.72 (1H, d, J = 16.0 Hz), 7.44 (2H, d, J = 8.2 Hz), 7.21 (1H, d, J = 16.0 Hz), 3.77 (3H, s), 3.24 (3H, s), 2.34 (3H, s); MS *m/e* 410 $(M + H)^+$. Anal. ($C_{21}H_{19}N_3O_4S$) C, H, N.

***trans*-3-[7-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methylacrylamide, 9b. 9b** was prepared from **8b** in a manner similar to **9a** (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.06 (dd, J = 1.16, 8.04 Hz, 1H), 7.95 (d, J = 8.48 Hz, 2H), 7.85 (dd, J = 0.56, 16.00 Hz, 1H), 7.70 (dd, J = 1.00, 7.56 Hz, 1H), 7.39 (t, J = 7.84 Hz, 1H), 7.34 (d, J = 8.08 Hz, 2H), 7.12 (d, J = 15.97 Hz, 1H), 3.82 (s, 3H), 3.34 (s, 3H), 2.41 (s, 3H); MS (ESI) *m/e* 410.13 $(M + H)^+$.

***trans*-3-[6-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methylacrylamide, 9c. 9c** was prepared from **8c** in a manner similar to **9a** (77%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.77 (1H, s), 8.42 (1H, m), 8.07 (3H, dd, J = 8.5, 2.4 Hz), 7.73 (2H, m), 7.45 (2H, d, J = 8.2 Hz), 7.20 (1H, d, J = 16 Hz), 3.77 (3H, s), 3.23 (3H, s), 2.34 (3H, s); MS *m/e* 408 $(M - H)^-$. Anal. ($C_{21}H_{19}N_3O_4S$) C, H, N.

***trans*-3-[4-Cyano-1-(4-toluenesulfonyl)-1H-indol-3-yl]-*N*-methoxy-*N*-methylacrylamide, 9d. 9d** was prepared from **8d** in a manner similar to **9a** (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.28 (m, 2H), 8.03 (s, 1H), 7.79 (dd, J = 1.68, 6.76 Hz, 2H), 7.63 (dd, J = 0.88, 7.56 Hz, 1H), 7.41 (dd, J = 7.72, 8.32 Hz, 1H), 7.29 (d, J = 8.04 Hz, 2H), 7.07 (d, J = 15.73 Hz, 1H), 3.80 (s, 3H), 3.32 (s, 3H), 2.38 (s, 3H); MS (ESI) *m/e* 410.14 $(M + H)^+$.

***trans*-3-[5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methylacrylamide, 9e. 9e** was prepared from **8e** in a manner similar to **9a** (88%): mp 199−200 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (1H, s), 7.99 (1H, m), 7.93 (2H, d, J = 8.4 Hz), 7.68 (2H, m), 7.42 (2H, d, J = 8.1 Hz), 7.28 (1H, t, J = 9.2 Hz), 7.12 (1H, d, J = 16 Hz), 3.77 (3H, s), 3.22 (3H, s), 2.33 (3H, s); MS *m/e* 403 $(M + H)^+$. Anal. ($C_{20}H_{19}FN_2O_4S$) C, H, N.

***trans*-3-[7-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methylacrylamide, 9f. 9f** was prepared from **8f** in a manner similar to **9a** (53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, s), 7.84 (3H, m), 7.57 (1H, d, J = 7.5 Hz), 7.29 (2H, d, J = 6.1 Hz), 7.23 (1H, m), 7.10 (1H, d, J = 16.0 Hz), 7.02 (1H, m), 3.80 (3H, s), 3.33 (3H, s), 2.39 (3H, s); MS *m/e* 403.07 $(M + H)^+$.

***trans*-3-[6-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methylacrylamide, 9g. 9g** was prepared from **8g** in a manner similar to **9a** (48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−7.68 (6H, m), 7.28 (1H, s), 7.04 (2H), 3.79 (3H, s), 3.32 (3H, s), 2.37 (3H, s); MS *m/e* 403.09 $(M + H)^+$.

***trans*-3-[4-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methylacrylamide, 9h. 9h** was prepared from **8h** in a manner similar to **9a** (59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (1H, s), 7.78 (2H, m), 7.28 (3H, m), 7.15 (1H, d, J = 15.9 Hz), 6.96 (1H, m), 3.78 (3H, s), 3.31 (3H, s), 2.36 (3H, s); MS *m/e* 403.11 $(M + H)^+$.

***trans*-2-[5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10a.** The following procedure was carried out behind a safety shield using plastic-coated glassware free of scratches and ground glass joints. 1-Methyl-3-nitro-1-nitrosoguanidine (14.4 g, 98 mmol) was carefully added portionwise over 30 min to an Erlenmeyer flask containing a swirled mixture of aqueous NaOH (100 mL, 5 N) and diethyl ether (250 mL) at 0°C. After

vigorous bubbling had ceased, the organic layer (containing diazomethane) was decanted into a chilled (0 °C) Erlenmeyer flask containing KOH chips (20 g). The mixture was swirled for 10 min, and the yellow solution was decanted into a dropping funnel. The solution of diazomethane was added over 30 min to an open flask containing a stirred mixture of **9a** (8.0 g, 19.6 mmol) and palladium acetate (132 mg, 0.58 mmol) in CH_2Cl_2 (200 mL) maintained at 0 °C. After the mixture was stirred for 1 h, a second batch of freshly prepared diazomethane (98 mmol) in ~250 mL of diethyl ether was added over 30 min. After the mixture was stirred for 1 h, the reaction was quenched with AcOH (4 mL) and the mixture was poured into an aqueous saturated solution of $NaHCO_3$ (250 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was triturated with EtOAc (150 mL) and cooled with vigorous stirring to 0 °C for 1 h. The product was collected by vacuum filtration and rinsed with cold EtOAc (25 mL). The white solid was dried under vacuum to afford 4.46 g (54%) of **10a**. An analytical sample was obtained by recrystallization from EtOAc/hexane: mp 174−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (1H, d, J = 1.1 Hz), 8.07 (1H, d, J = 8.6 Hz), 7.91 (2H, d, J = 8.4 Hz), 7.86 (1H, s), 7.75 (1H, dd, J = 8.6, 1.5 Hz), 7.40 (2H, d, J = 8.2 Hz), 3.64 (3H, s), 3.16 (3H, s), 2.43 (2H, m), 2.33 (3H, s), 1.43 (2H, m); MS *m/e* 424 $(M + H)^+$. Anal. ($C_{22}H_{21}N_3O_4S$) C, H, N.

***trans*-2-[7-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10b. 10b** was prepared from **9b** in a manner similar to **10a** (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.92 (m, 3H), 7.65 (dd, J = 1.08, 7.56 Hz, 1H), 7.55 (d, J = 0.96 Hz, 1H), 7.26−7.34 (m, 3H), 3.73 (s, 3H), 3.27 (s, 3H), 2.52 (m, 1H), 2.39 (s, 3H), 1.63−1.66 (m, 2H), 1.2−1.33 (m, 1H); MS (ESI) *m/e* 424.15 $(M + H)^+$.

***trans*-2-[6-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10c. 10c** was prepared from **9c** in a manner similar to **10a** (64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (1H, d, J = 1.0 Hz), 7.98 (3H, m), 7.83 (1H, m), 7.67 (1H, dd, J = 8.2, 1.3 Hz), 7.41 (2H, d, J = 8.1 Hz), 3.63 (3H, s), 3.15 (3H, s), 2.40 (2H, m), 2.33 (3H, s), 1.45 (2H, m); MS *m/e* 422 $(M - H)^-$. Anal. ($C_{22}H_{21}N_3O_4S$) C, H, N.

***trans*-2-[4-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10d. 10d** was prepared from **9d** in a manner similar to **10a** (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 0.40, 7.96 Hz, 1H), 7.76 (d, J = 8.40 Hz, 2H), 7.57 (dd, J = 0.44, 7.56 Hz, 1H), 7.44 (d, J = 1.24 Hz, 1H), 7.37 (t, J = 8.08 Hz, 1H), 3.73 (s, 3H), 3.27 (s, 3H), 2.72−2.74 (m, 1H), 2.36−2.38 (m, 4H), 1.68−1.72 (m, 1H), 1.30−1.35 (m, 1H); MS (ESI) *m/e* 424.16 $(M + H)^+$.

***trans*-2-[5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10e. 10e** was prepared from **9d** in a manner similar to **10a** (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, m), 7.72 (2H, d, J = 8.4 Hz), 7.30 (1H, s), 7.23 (3H, m), 7.04 (1H, t, J = 9.0 Hz), 3.71 (3H, s), 3.26 (3H, s), 2.40 (2H, m), 2.34 (3H, s), 1.59 (1H, m), 1.25 (1H, m); MS *m/e* 417 $(M + H)^+$.

***trans*-2-[7-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10f. 10f** was prepared from **9d** in a manner similar to **10a** (87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 7.7 Hz), 7.47 (1H, d, J = 0.9 Hz), 7.38 (1H, dd, J = 7.9, 0.8 Hz), 7.27 (2H, m), 7.09 (1H, m), 6.89 (1H, m), 3.73 (3H, s), 3.27 (3H, s), 2.41 (2H, m), 2.39 (3H, s), 1.60 (1H, m), 1.31 (1H, m); MS *m/e* 417.09 $(M + H)^+$.

***trans*-2-[6-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10g. 10g** was prepared from **9g** in a manner similar to **10a** (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−7.66 (4H, m), 7.50 (1H, dd, J = 5.2, 8.6 Hz), 7.23 (2H, m), 6.99 (1H, m), 3.70 (3H, s), 3.25 (3H, s), 2.44 (2H, m), 2.35 (3H, s), 1.58 (m, 1H), 1.25 (1H, m); MS *m/e* 417.09 $(M + H)^+$.

***trans*-2-[4-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cycloprop-1-yl-*N*-methoxy-*N*-methylcarboxamide, 10h. 10h** was prepared from **9h** in a manner similar to **10a** (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (3H, m), 7.23 (4H, m), 6.89 (1H, dd, J = 8.0, 10.0 Hz), 3.70 (3H, s), 3.26 (3H, s), 2.47 (2H, m), 2.36 (3H, s), 1.60 (1H, m), 1.29 (1H, m); MS *m/e* 417.11 $(M + H)^+$.

***trans*-2-[5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11a.** Powdered LAH (1.79 g, 47.3 mmol) was carefully added portionwise to a stirred solution of **10a** (4.0 g, 9.45 mmol) in anhydrous THF (250 mL) at −40 °C. The resulting mixture was stirred at −40 °C for 2 h. The reaction was quenched with EtOAc (25 mL), and the mixture was warmed to room temperature. After 30 min, H_2O (1.79 mL) was added followed by a solution of aqueous NaOH (15% w/v, 3.58 mL). After the mixture was stirred for 30 min at room temperature, the aluminum salts were removed by vacuum filtration. The salts were rinsed with EtOAc (100 mL), and the combined filtrates were concentrated in vacuo. The crude material was purified by silica gel chromatography using hexane/EtOAc (4:1 to 3:1) as the eluent to give **11a** (2.86 g, 74%) as a white solid. An analytical sample was obtained by recrystallization from EtOAc/hexane: mp 165−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (1H, d, J = 5.5 Hz), 8.32 (1H, d, J = 1.1 Hz), 8.06 (1H, d, J = 8.6 Hz), 7.90 (2H, d, J = 8.6 Hz), 7.89 (1H, s), 7.75 (1H, dd, J = 8.6, 1.5 Hz), 7.40 (2H, d, J = 8.2 Hz), 2.77 (1H, m), 2.33 (3H, s), 2.13 (1H, m), 1.74 (2H, m); MS *m/e* 363 $(M - H)^-$. Anal. ($C_{20}H_{16}N_2O_3S$) C, H, N.

***trans*-2-[7-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11b. 11b** was prepared from **10b** in a manner similar to **11a** (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, J = 4.12 Hz, 1H), 7.91 (d, J = 8.44 Hz, 2H), 7.82 (dd, J = 1.20, 7.92 Hz, 1H), 7.68 (dd, J = 1.04, 7.60 Hz, 1H), 7.60 (d, J = 1.04 Hz, 1H), 7.30−7.35 (m, 3H), 2.62 (m, 1H), 2.40 (s, 3H), 2.17−2.20 (m, 1H), 1.75−1.80 (m, 1H), 1.51−1.55 (m, 1H).

***trans*-2-[6-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11c. 11c** was prepared from **10c** in a manner similar to **11a** (37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (1H, d, J = 5.5 Hz), 8.33 (1H, d, J = 1.0 Hz), 7.99 (3H, m), 7.88 (1H, d, J = 8.1 Hz), 7.69 (1H, dd, J = 8.2, 1.4 Hz), 7.41 (2H, d, J = 8.0 Hz), 2.76 (1H, m), 2.33 (3H, s), 2.14 (1H, m), 1.70 (2H, m); MS *m/e* 363 $(M - H)^-$. Anal. ($C_{20}H_{16}N_2O_3S$) C, H, N.

***trans*-2-[4-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11d. 11d** was prepared from **10d** in a manner similar to **11a** (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, J = 4.92 Hz, 1H), 8.21 (dd, J = 0.88, 8.48 Hz, 1H), 7.74 (dd, J = 1.76, 6.68 Hz, 2H), 7.59 (dd, J = 0.88, 7.56 Hz, 1H), 7.45 (d, J = 1.20 Hz, 1H), 7.39 (dd, J = 7.80, 8.32 Hz, 1H), 7.26−7.28 (m, 2H), 2.90−2.91 (m, 1H), 2.38 (s, 3H), 2.09−2.12 (m, 1H), 1.78−1.80 (m, 1H), 1.47−1.52 (m, 1H).

***trans*-2-[5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11e. 11e** was prepared from **10e** in a manner similar to **11a** (76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (1H, d, J = 5.6 Hz), 7.90 (1H, m), 7.84 (2H, d, J = 8.4 Hz), 7.75 (1H, s), 7.51 (1H, dd, J = 9.1, 2.6 Hz), 7.38 (2H, d, J = 8.1 Hz), 7.20 (1H, t, J = 9.2 Hz), 2.69 (1H, m), 2.32 (3H, s), 2.09 (1H, m), 1.68 (2H, m); MS *m/e* 358 $(M + H)^+$. Anal. ($C_{19}H_{16}FNO_3S$) C, H, N.

***trans*-2-[7-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11f. 11f** was prepared from **10f** in a manner similar to **11a** (52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (1H, d, J = 4.3 Hz), 7.81 (2H, d, J = 7.6 Hz), 7.51 (1H, d, J = 0.9 Hz), 7.29 (4H, m), 7.16 (1H, m), 6.98 (1H, dd, J = 7.8, 12 Hz), 2.61 (1H, m), 2.37 (3H, s), 2.16 (1H, m), 1.76 (1H, m), 1.53 (1H, m); MS *m/e* 358.07 $(M + H)^+$.

***trans*-2-[6-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11g. 11g** was prepared from **10g** in a manner similar to **11a** (59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (1H, d, J = 4.4 Hz), 7.75 (2H, d, J = 8.4 Hz), 7.69 (1H, dd, J = 2.3, 9.7 Hz), 7.44 (1H, dd, J = 8.7, 5.2 Hz), 7.27 (3H, m), 6.99 (1H, m), 2.56 (1H, m), 2.37 (3H, s), 2.13 (1H, m), 1.72 (1H, m), 1.48 (1H, m); MS *m/e* 358.08 $(M + H)^+$.

***trans*-2-[4-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-cyclopropanecarboxaldehyde, 11h. 11h** was prepared from **10h** in a manner similar to **11a** (59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (1H, d, J = 4.7 Hz), 7.74 (3H, m), 7.24 (4H, m), 6.92 (1H, m), 2.78 (1H, m), 2.36 (3H, s), 2.10 (1H, m), 1.73 (1H, m), 1.47 (1H, m); MS *m/e* 358.10 $(M + H)^+$.

***trans*-2-(5-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12a.** A mixture of **11a** (2.0 g, 5.49 mmol), dimethylamine (8.2 mL, 16.5 mmol, 2.0 M/THF), and anhydrous EtOH (70 mL) was heated to 80 °C with stirring until all solids were dissolved (20 min). The reaction vessel was removed from the heating source, and $NaBH(OAc)_3$ was added. After the mixture was stirred for 30 min, the reaction vessel was placed in an ice bath and the reaction was quenched with aqueous HCl (40 mL, 1 N). The resulting mixture was stirred for 20 min and then poured into a saturated aqueous solution of $NaHCO_3$ (100 mL) and brine (50 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The solid residue was dried under vacuum for 24 h, and the crude product was taken on without purification. A sample of *trans*-2-[5-cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-1-(*N*,*N*-dimethylaminomethyl)cyclopropane was purified by silica gel chromatography for analytical purposes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (1H, d, J = 1.0 Hz), 8.06 (1H, d, J = 8.6 Hz), 7.89 (2H, d, J = 8.4 Hz), 7.74 (1H, dd, J = 8.6, 1.6 Hz), 7.67 (1H, s), 7.39 (2H, d, J = 8.1 Hz), 2.32 (5 H, m), 2.21 (6 H, s), 1.83 (1H, m), 1.21 (1H, m), 1.07 (1H, m), 0.80 (1H, m); MS *m/e* 394 $(M + H)^+$.

Water (5 mL) and an aqueous solution of NaOH (2 mL, 10 N) were sequentially added to a flask charged with a solution of the crude *trans*-2-[5-cyano-1-(*p*-toluenesulfonyl)indol-3-yl]-1-(*N*,*N*-dimethylaminomethyl)cyclopropane dissolved in anhydrous EtOH (60 mL). The resulting mixture was heated at 70 °C for 45 min. After the mixture was cooled to room temperature, the reaction was quenched with aqueous HCl (21 mL, 1 N) and the mixture was then poured into a mixture of saturated aqueous $NaHCO_3$ (100 mL) and brine (50 mL). The aqueous layer was extracted with 10% MeOH/EtOAc (4 × 100 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by chromatography using silica gel pretreated with 2% triethylamine in chloroform/MeOH (9:1). The column was eluted using a step gradient of a ternary solvent mixture (chloroform/MeOH/NH_4OH (2 M in MeOH); 90/10/0, 85/15/1, 80/20/1, 80/20/2) to give **12a** (1.2 g, 98%) as an off-white solid foam after drying under vacuum. Recrystallization from EtOH/H_2O provided **12a** (934 mg total (583 mg first crop, 351 mg second crop), 77%): mp 120−121 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (1H, br s), 8.09 (1H, s), 7.47 (1H, d, J = 8.4 Hz), 7.40 (1H, dd, J = 8.4, 1.5 Hz), 7.23 (1H, d, J = 2.0 Hz), 2.37 (2H, m), 2.21 (6 H, s), 1.80 (1H, m), 1.09 (1H, m), 0.91 (1H, m), 0.73 (1H, m). Anal. ($C_{15}H_{17}N_3$) C, H, N.

***trans*-2-(7-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12b. 12b** was prepared from **11b** in a manner similar to **12a** (56%) as a pale-yellow solid that was recrystallized from ethyl/hexane as off-white needles: mp 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (brd s, 1H), 7.92 (d, J = 7.96 Hz, 1H), 7.50 (dd, J = 0.84, 7.44 Hz, 1H), 7.15 (dd, J = 7.56, 7.92 Hz, 1H), 6.99 (d, J = 1.56 Hz, 1H), 2.51 (m, 1H), 2.35−2.40 (m, 7H), 1.78 (m, 1H), 1.26 (m, 1H), 0.90 (m, 1H), 0.84 (m, 1H).

***trans*-2-(6-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12c. 12c** was prepared from **11c** in a manner similar to **12a** (66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.4 (1H, br s), 7.80 (1H, s), 7.74 (1H, d, J = 8.5 Hz), 7.32 (2H, m), 2.39 (1H, m), 2.20 (7H, s), 1.76 (1H, m), 1.05 (1H, m), 0.90 (1H, m), 0.74 (1H, m). Anal. ($C_{15}H_{17}N_3 \cdot 0.14H_2O$) C, H, N.

***trans*-2-(4-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12d. 12d** was prepared from **11d** in a manner similar to **12a** (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (brd s, 1H), 7.54 (dd, J = 0.80, 8.20 Hz, 1H), 7.48 (dd, J = 0.76, 7.36 Hz, 1H), 7.20 (t, J = 7.84 Hz, 1H), 7.01 (dd, J = 0.68, 2.32 Hz, 1H), 2.62 (m, 1H), 2.41 (m, 1H), 2.37 (s, 6H), 2.13 (m, 1H), 1.24 (m, 1H), 0.88 (m, 2H).

***trans*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12e. 12e** was prepared from **11e** in a manner similar to **12a** (68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.8 (1H, br s), 7.29 (2H, m), 7.09 (1H, s), 6.90 (1H, t, J = 9.2 Hz), 2.39 (1H, m), 2.19 (7 H, m), 1.69 (1H, m), 1.06 (1H, m), 0.85 (1H, m), 0.68 (1H, m).

***trans*-2-(7-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12f. 12f** was prepared from **11f** in a manner similar to **12a** (43%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.33 (s, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.97 (m, 1H), 6.92 (m, 1H), 3.20 (br, 2H), 2.84 (s, 6H), 2.07 (m, 1H), 1.34 (m, 1H), 1.12 (m, 1H), and 0.99 (m, 1H).

***trans*-2-(6-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12g. 12g** was prepared from **11g** in a manner similar to **12a** (33%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 7.61 (dd, J = 12.5, 3.0 Hz, 1H), 7.10 (m, 1H), 7.07 (d, J = 2.5 Hz, 1H), 6.88 (m, 1H), 3.05 (m, 2H), 3.00 (s, 6H), 2.02 (m, 1H), 1.20 (m, 1H), 1.02 (m, 1H), 0.95 (m, 1H).

***trans*-2-(4-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12h. 12h** was prepared from **11h** in a manner similar to **12a** (67%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 2.5 Hz, 1H), 7.03 (m, 1H), 6.73 (dd, J = 19.0, 7.5 Hz, 1H), 3.17 (m, 1H), 3.12 (m, 1H), 2.81 (s, 6H), 2.14 (m, 1H), 1.32 (m, 1H), 1.04 (m, 1H), 0.99 (m, 1H).

Methyl *cis*-3-[5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]acrylate, 13a. A solution of bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl)phosphonate (470 μL, 2.2 mmol) in anhydrous THF (5 mL) was added to a stirred suspension of oil-free sodium hydride (89 mg, 2.2 mmol) in anhydrous THF (25 mL) maintained at 0 °C. The mixture was warmed to room temperature and was stirred for 1.5 h. After the mixture was cooled to 0 °C, **8a** (600 mg, 1.85 mmol) was added. The resulting mixture was stirred at room temperature for 5 h. The solvent was evaporated, and the residue was taken up in brine (20 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried with anhydrous magnesium sulfate, and the solvent was removed in vacuo. The product was purified by silica gel chromatography using EtOAc/hexane (15%) as the eluent to give **13a** (192 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (1H, s), 8.10 (1H, d, J = 8.3 Hz), 7.92 (1H, d, J = 1.0 Hz), 7.86 (2H, d, J = 8.4 Hz), 7.59 (1H, dd, J = 8.6, 1.5 Hz), 7.29 (2H, d, J = 8.1 Hz), 6.98 (1H, d, J = 13.0 Hz), 6.08 (1H, d, J = 12.6 Hz), 3.80 (3H, s), 2.37 (3H, s); MS *m/e* 395.1 $(M + H)^+$.

Methyl *cis*-3-(5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl)acrylate, 13e. 13e was prepared from **8b** in a manner similar to **13a** (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H) 7.94 (dd, J = 4.40, 9.04 Hz, 1H), 7.84 (dd, J = 1.68, 6.68 Hz, 2H), 7.21−7.26 (m, 2H), 7.06 (dt, J = 6.44, 9.00 Hz, 1H), 6.93 (dd, J = 0.64, 12.60 Hz, 1H), 6.00 (d, J = 12.60 Hz, 1H), 3.80 (s, 3H), 2.35 (s, 3H); MS (ESI) *m/e* 374.10 $(M + H)^+$.

Methyl *cis*-2-(5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl)cyclopropanecarboxylate, 14a. The following procedure was carried out behind a safety shield using plastic-coated glassware free of scratches and ground glass joints. 1-Methyl-3-nitro-1-nitrosoguanidine (850 mg, 5.8 mmol) was carefully added portionwise over 10 min to an Erlenmeyer flask containing a swirled mixture of aqueous NaOH (100 mL, 5 N) and diethyl ether (50 mL) at 0 °C. After vigorous bubbling had ceased, the organic layer (containing diazomethane) was decanted into a chilled (0 °C) Erlenmeyer flask containing KOH chips (2 g). The mixture was swirled for 10 min, and the yellow solution was decanted into a dropping funnel. The solution of diazomethane was added over 10 min to an open flask containing a stirred mixture of **13a** (220 mg, 0.58 mmol) and palladium acetate (7 mg, 0.029 mmol) in CH_2Cl_2 (50 mL) maintained at 0 °C. After the mixture was stirred for 30 min, the reaction was quenched with AcOH (2 mL) and poured into

aqueous NaOH (0.5 N, 40 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. The product was purified by silica gel chromatography using EtOAc/hexane (15%) as the eluent to give **14a** (187 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, J = 8.7 Hz), 7.89 (1H, s), 7.73 (2H, d, J = 6.7 Hz), 7.52 (2H, m), 7.24 (2H, d, J = 8.0 Hz), 3.34 (3H, s), 2.38 (1H, m), 2.34 (3H, s), 2.22 (1H, m), 1.61 (1H, m), 1.25 (1H, m); MS *m/e* 473.2 $(M + H)^+$.

Methyl *cis*-2-(5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl)cyclopropanecarboxylate, 14e. 14e was prepared from **13e** in a manner similar to **14a** (73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 4.36, 9.04 Hz, 1H), 7.70 (dd, J = 1.76, 6.64 Hz, 2H), 7.42 (d, J = 1.04 Hz, 1H), 7.17−7.21 (m, 3H), 6.98 (dt, J = 2.56, 9.04 Hz, 1H), 3.32 (s, 3H), 2.32−2.36 (m, 4H), 2.15−2.19 (m, 1H), 1.58−1.63 (m, 1H), 1.41−1.45 (m, 1H); MS (ESI) *m/e* 410 $(M + Na)^+$.

***cis*-2-[5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl)-cyclopropanecarboxaldehyde, 15a.** Powdered LAH (120 mg, 3.16 mmol) was carefully added to a stirred solution of **14a** (185 mg, 0.47 mmol) in anhydrous THF (10 mL) at −30 °C. The resulting mixture was stirred at −20 °C for 1.5 h. The reaction was quenched with EtOAc (5 mL), and the mixture was warmed to room temperature. After 10 min, H_2O (120 μL) was added and after 5 min followed by a solution of aqueous NaOH (1 N, 360 μL). After a further 5 min, H_2O (120 μL) was added and the solution was stirred 20 min. The aluminum salts were removed by vacuum filtration. The salts were rinsed with EtOAc (100 mL), and the combined filtrates were concentrated in vacuo. The crude material was purified by silica gel chromatography using EtOAc/hexane (45%) to give *cis*-2-[5-cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]cyclopropanemethanol (131 mg, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1H, d, J = 8.6 Hz), 7.99 (1H, d, J = 1.0 Hz), 7.74 (2H, d, J = 6.8 Hz), 7.57 (1H, dd, J = 8.6, 1.6 Hz), 7.44 (1H, d, J = 1.3 Hz), 7.26 (2H, d, J = 8.2 Hz), 3.50 (1H, m), 3.16 (1H, m), 2.36 (3H, s), 2.05 (1H, m), 1.60 (1H, m), 1.19 (1H, m), 0.99 (1H, t, J = 5.5 Hz), 0.72 (1H, q, J = 5.6 Hz); MS *m/e* 349 $(M - OH)^+$.

To a −78 °C solution of oxalyl chloride (52 μL, 0.60 mmol) in CH_2Cl_2 (20 mL) was added DMSO (50 μL, 0.70 mmol) dropwise. After the mixture was stirred for 10 min, a solution of *cis*-2-[5-cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]cyclopropanemethanol (129 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After the mixture was stirred for 20 min at −78 °C, triethylamine (294 μL, 2.10 mmol) was added dropwise. The mixture was stirred for 5 min at −78 °C and then warmed to room temperature. The mixture was washed with H_2O (2 × 5 mL) and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give **15a**, which was taken on without purification.

***cis*-2-(5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl)-cyclopropanecarboxaldehyde, 15e. 15e** was prepared from **14b** in a manner similar to **15a** via the intermediate *cis*-(2-(5-fluoro-1-tosyl-1*H*-indol-3-yl)cyclopropyl)methanol (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 4.36, 9.04 Hz, 1H), 7.70 (dd, J = 1.68, 6.68 Hz, 2H), 7.32 (d, J = 1.16 Hz, 1H), 7.21−7.28 (m, 3H), 7.04 (dt, J = 2.52, 9.00 Hz, 1H), 3.45−3.47 (m, 1H), 3.13 (t, J = 9.80 Hz, 1H), 2.34 (s, 3H), 1.98−2.05 (m, 1H), 1.54−1.60 (m, 1H), 1.11−1.16 (m, 1H), 0.92−0.95 (m, 1H), 0.70 (dd, J = 5.64, 11.00 Hz, 1H); MS (ESI) *m/e* 342.14 $(M - OH)^+$. Subsequent Swern oxidation gave **15e**, which was taken on without purification.

***cis*-2-(5-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 16a. 16a** was prepared from **15a** in a manner similar to **12a** (75% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (1H, br s), 8.07 (1H, s), 7.41 (2H, apparent q, J = 8.0 Hz), 7.03 (1H, s), 2.37 (1H, dd, J = 12.6, 4.7 Hz), 2.18 (6 H, s), 1.97 (1H, m), 1.69 (1H, dd, J = 12.6, 8.6 Hz), 1.34 (1H, m), 1.22 (1H, m), 0.71 (1H, q, J = 5.0 Hz).

***cis*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 16e. 16e** was prepared from **15e** in a manner similar to **12a** (77% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.34 (d J = 2.52, 9.56 Hz, 1H), 7.24 (dd, J = 4.40, 8.84 Hz, 1H), 6.93 (m, 2H), 2.42 (m, 1H), 2.18 (s, 3H), 2.08 (m, 1H), 1.70 (dd, J = 8.72, 12.56 Hz, 1H), 1.33 (m, 1H), 1.22 (m, 1H), 0.66 (m, 1H).

(+)-*N*-[(*E*)-3-[5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-2-propenoyl]bornane-10,2-sultam, 18a. NaH (0.69 g of 60% in oil, 17.3 mmol) was washed with hexane (5 mL) and then suspended in THF (500 mL) at 0 °C. (+)-Sultam, **17** (6.8 g, 17.3 mmol), in THF (50 mL) was then added over 10 min. The mixture was stirred for 1 h at room temperature, then cooled to 0 °C before adding **8a** (4.67 mg, 14.4 mmol) in one portion. The mixture was stirred for 24 h at room temperature, and the solvent was removed in vacuo. The residue was dissolved in H_2O (100 mL) and was extracted with EtOAc (3 × 50 mL). The organic phase was dried over magnesium sulfate for 16 h. The resulting crystals were collected by filtration. The filtrate was evaporated, and the residue was recrystallized from EtOAc/hexane to give a second crop of crystals. (+)-**18a** (4.71 g, 58%) was collected as a white solid: mp 203−205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, s), 8.09 (1H, d, J = 8.8 Hz), 7.98 (1H, s), 7.81 (1H, d, J = 15.7 Hz), 7.80 (2H, d, J = 8.4 Hz), 7.62 (1H, dd, J = 8.6, 1.4 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.25 (1H, d, J = 15.6 Hz), 3.99 (1H, dd, J = 7.4, 5.2 Hz), 3.53 (2H, AB, $\Delta\nu$ = 32 Hz, J = 13.8 Hz), 2.38 (3H, s), 2.25−2.12 (2H, m), 2.01−1.87 (3H, m), 1.48−1.32 (2H, m), 11.21 (3H, s), 1.00 (3H, s); MS *m/e* 564.3 $(M + H)^+$.

(+)-*N*-[(*E*)-3-[5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]-2-propenoyl]bornane-10,2-sultam, 18e. 18e was prepared from **8e** in a manner similar to **18a** (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, J = 9.1, 4.4 Hz), 7.90 (1H,s), 7.85 (1H, d, J = 15.6 Hz), 7.76 (2H, d, J = 8.4 Hz), 7.50 (1H, dd, J = 9.0, 2.4 Hz), 7.26 (2H, d, J = 8.1 Hz), 7.21 (1H, d, J = 15.6 Hz), 7.10 (1H, td, J = 8.9, 2.4 Hz), 3.99 (1H, dd, J = 7.5, 5.1 Hz), 3.51 (2H, AB, $\Delta\nu$ = 28 Hz, J = 13.7 Hz), 2.36 (3H, s), 2.26−2.10 (2H, m), 1.97−1.87 (3 H, m), 1.49−1.32 (2H, m), 1.21 (3H, s), 1.00 (3H, s); MS *m/e* 557.3 $(M + H)^+$.

***N*-[(1*S*,2*S*)-*trans*-2-[5-Cyano-1-(4-toluenesulfonyl)indol-3-yl]cycloprop-1-yl]carbonylbornane-10,2-sultam, 19a.** The following reaction was performed behind a blast shield using glassware without ground glass joints. A solution of diazomethane in ether was prepared by slowly adding 1-methyl-3-nitro-1-nitrosoguanidine (13.3 g, 90 mmol) to a mixture of diethyl ether (200 mL) and 5 N NaOH (200 mL) at 0 °C and then decanting the ether layer. The ether layer was dried with KOH and transferred to a dropping funnel. This ethereal diazomethane solution was then added dropwise over 30 min to a solution of **18a** (5.1 g, 9.0 mmol) and palladium(II) acetate (100 mg, 0.45 mmol) in CH_2Cl_2 (200 mL) at a temperature of −10 °C. The mixture was stirred a further 20 min with the temperature maintained below −5 °C, and the reaction was then quenched by the addition of AcOH (6 mL). To the mixture 1 N NaOH (10 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried with magnesium sulfate and evaporated to dryness. The crude product was purified by chromatography on silica gel using EtOAc/hexane (20%) to give **19a** (3.23 g, 62%) as a white solid. This material was recrystallized from boiling EtOH (350 mL) to give white crystals (1.18 g). The mother liquor was evaporated and recrystallized from boiling EtOH (100 mL) to provide a second crop of **19a** (total amount 1.22 g, white solid, 46%): mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, d, J = 8.6 Hz), 7.99 (1H, d, J = 1.0 Hz), 7.75 (2H, d, J = 8.4 Hz), 7.57 (1H, d, J = 1.2 Hz), 7.54 (1H, dd, J = 8.6, 1.5 Hz), 7.25 (2H, m), 3.96 (1H, dd, J = 7.4, 5.1 Hz), 3.53 (2H, AB, $\Delta\nu$ = 18 Hz, J = 13.8 Hz), 2.57 (1H, dt, J = 7.7, 4.8 Hz), 2.45 (1H, m), 2.36 (3H, s), 2.16−2.04 (2H, m), 2.00−1.87 (3 H, m), 1.81 (1H, dt, J = 9.1, 4.3 Hz), 1.55 (3H, s), 1.50−1.32 (2H, m), 1.29 (1H, m), 1.21 (3H, s), 1.00 (3H, s); MS *m/e* 578.2 $(M + H)^+$. The crystals for X-ray crystallography were developed by slow evaporation from MeCN/*i*-PrOH/H_2O and collected.

***N*-[(1*S*,2*S*)-*trans*-2-[5-Fluoro-1-(4-toluenesulfonyl)indol-3-yl]cycloprop-1-yl]carbonylbornane-10,2-sultam, 19e. 19e** was prepared from **18e** in a manner similar to **19a** (56%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 9.1,

4.4 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.49 (s, 1H), 7.27 (m, 1H), 7.21 (d, J = 8.2 Hz, 2H), 7.01 (td, J = 9.0, 2.5 Hz, 1H), 3.94 (dd, J = 7.6, 5.0 Hz, 1H), 3.51 (AB, $\Delta\nu$ = 21.6 Hz, J = 13.8 Hz, 2H), 2.57 (m, 1H), 2.43 (m, 1H), 2.34 (s, 3H), 1.82−2.17 (m, 4H), 1.76 (p, J = 4.5 Hz, 1H), 1.23−1.60 (m, 4H), 1.22 (s, 3H), 0.99 (s, 3H).

(1*S*,2*S*)-*trans*-2-[5-Cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]cyclopropanecarboxaldehyde, (1*S*,2*S*)-11a. A solution of **19a** (2.30 g, 3.98 mmol) in THF (100 mL) was cooled to −40 °C (dry ice/MeCN). LAH (600 mg, 15.9 mmol) was added, with a further addition (600 mg) after 1 h (reaction temperature maintained at −40 °C throughout). After a total reaction time of 1.5 h, EtOAc (50 mL) was added and the mixture was warmed to room temperature. Water (1.2 mL) was added, and after 10 min 1 N NaOH (3.6 mL) was added. After another 5 min, more H_2O (1.2 mL) was added, and the mixture was stirred for a final 15 min. Magnesium sulfate was added, and the mixture was filtered through Celite and sand and rinsed with EtOAc. The filtrate was evaporated in vacuo. The crude material was partially purified on a short pad of silica by elution with EtOAc/hexane (50%) to give (1*S*,2*S*)-*trans*-2-[5-cyano-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]cyclopropanemethanol as a white solid (1.18 mg, 81%): mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, dd, J = 8.6, 0.6 Hz), 8.00 (1H, d, J = 1.5 Hz), 7.74 (2H, d, J = 8.6 Hz), 7.55 (1H, dd, J = 8.6, 1.5 Hz), 7.33 (1H, d, J = 1.0 Hz), 7.26 (2H, d, J = 8.5 Hz), 3.77 (1H, m), 3.60 (1H, m), 2.37 (3H, s), 1.77 (1H, m), 1.37 (1H, m), 0.95 (2H, t, J = 7.0 Hz); MS *m/e* 349.1 $(M - OH)^+$.

Oxalyl chloride (0.42 mL, 4.8 mmol) in CH_2Cl_2 (50 mL) at −78 °C was treated with DMSO (0.39 mL, 5.4 mmol) dropwise. After addition, the mixture was stirred for 15 min and a solution of (1*S*,2*S*)-*trans*-2-[5-cyano-1-(*p*-toluenesulfonyl)indol-3-yl]cyclopropanemethanol (1.17 g, 3.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After a further 15 min, triethylamine (2.45 mL, 17.6 mmol) was added dropwise. The mixture was stirred a further 5 min at −78 °C and was then warmed to room temperature. The mixture was washed twice with H_2O (10 mL), dried with $MgSO_4$, and evaporated to dryness to give (1*S*,2*S*)-**11a** as a yellow oil that was taken on without purification.

(1*S*,2*S*)-*trans*-2-[5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]cyclopropanecarboxaldehyde, (1*S*,2*S*)-11e. 11e was prepared from **18e** in a manner similar to (1*S*,2*S*)-**11a** via the intermediate (1*S*,2*S*)-*trans*-2-[5-fluoro-1-(*p*-toluenesulfonyl)indol-3-yl]cyclopropanemethanol (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, dd, J = 9.0, 4.4 Hz), 7.70 (2H, d, J = 8.4 Hz), 7.30−7.20 (4H, m), 7.03 (1H, td, J = 9.0, 2.6 Hz), 3.73 (1H, dd, J = 11.2, 6.4 Hz), 3.59 (1H, dd, J = 11.2, 7.2 Hz), 2.34 (3H, s), 1.72 (1H, dt, J = 9.6, 5.3 Hz), 1.34 (1H, m), 0.96−0.86 (2H, m); MS *m/e* 360.1 $(M + H)^+$. Subsequent Swern oxidation gave (1*S*,2*S*)-**11e** that was taken on without purification.

(1*S*,2*S*)-*trans*-2-(5-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (+)-12a. The crude (1*S*,2*S*)-**11a** was dissolved in hot EtOH (50 mL) and treated with dimethylamine (3.2 mL, 2 M solution in THF, 6.4 mmol). After the mixture was stirred for 5 min, $NaBH(OAc)_3$ (2.71 g, 12.8 mmol) was added in several portions over 10 min while the mixture was cooled in a 10 °C H_2O bath. After being stirred for 45 min at room temperature, the mixture was concentrated in vacuo, the residue was taken up in brine (10 mL), and 1 N NaOH was added until a solution was achieved. The sample was extracted with EtOAc (4 × 10 mL), and the organic layer was dried with magnesium sulfate and evaporated to give (+)-**12a** as a yellow oil. A solution of this material in EtOH (25 mL), H_2O (4 mL), and NaOH (2 mL, 10 N, 20 mmol) was heated to 70 °C for 1 h. The mixture was cooled to room temperature, poured into brine (100 mL), and extracted twice with EtOAc (50 mL) and three times with EtOAc/MeOH (9:1, 50 mL). The organic layer was dried with magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography using chloroform/MeOH/NH_4OH (2 M MeOH) (90:10:1) as the eluent to give (+)-**12a** as a yellow oil that solidified on standing (590 mg, 77% over three steps from alcohol): $[\alpha_D]$ +17.5° (*c* 2.92 mg/mL, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (1H, brs), 8.04 (1H, s), 7.38 (1H, dd, J = 7.2, 1.4 Hz), 7.34 (1H, dd, 7.2, 0.5 Hz), 6.96 (1H, d, J = 1.6 Hz), 2.49 (1H, dd, J = 12.4, 6.4 Hz), 2.37 (1H, dd, J = 12.4, 7.0 Hz), 2.37 (6 H, s), 1.76 (1H, m), 1.23 (1H, m), 0.90 (1H, m), 0.84 (1H, m). The free base was converted to the HCl salt, and crystals for X-ray were developed by slow evaporation from EtOH/MIBK and collected.

(1*S*,2*S*)-*trans*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (+)-12e. 12e was prepared from (1*S*,2*S*)-**11e** in a manner similar to (1*S*,2*S*)-**12a** via the intermediate (1*S*,2*S*)-*trans*-1-(*N*,*N*-dimethylaminomethyl)-2-[5-fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl]cyclopropane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, dd, J = 9.0, 4.4 Hz), 7.73 (2H, d, J = 8.4 Hz), 7.32−7.27 (2H, m), 7.23 (2H, d, J = 8.1 Hz), 7.06 (1H, td, J = 9.1, 2.5 Hz), 3.16 (1H, dd, J = 11.1, 6.5 Hz), 2.96 (1H, dd, J = 11.2, 7.3 Hz), 2.82 (3H, s), 2.08 (6 H, s), 2.03 (1H, m), 1.44 (1H, m), 1.18 (2H, t, J = 7.2 Hz); MS *m/e* 387.4 $(M + H)^+$. Subsequent hydrolysis of the indole N-1 tosyl group gave (1*S*,2*S*)-**12e** as a clear oil that solidified on standing (71% over four steps from the sultam): mp 88−90 °C; $[\alpha_D]$ +51.4° (*c* 2.45 mg/mL, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, brs), 7.33 (1H, dd, J = 9.6, 2.5 Hz), 7.24 (1H, dd, J = 8.8, 4.4 Hz), 6.98−6.88 (2H, m), 2.45 (1H, dd, J = 11.0, 6.5 Hz), 2.37 (1H, dd, J = 11.1, 6.8 Hz), 2.35 (6 H, s), 1.68 (1H, m), 1.21 (1H, m), 0.87 (1H, m), 0.76 (1H, m). The crystals for X-ray crystallography were developed by slow evaporation from EtOH/hexane and collected.

Preparative Chiral HPLC Resolution of *trans*-2-(5-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12a. The enantiomers were separated on a Chiralpak AD column, 50 mm × 500 mm with 20 μm packing, using 5% EtOH/hexane (0.15% diethylamine added in hexane as modifier) as the eluent, with a flow rate of 60 mL/min for 75 min and the UV detector at 280 nm.

(1*R*,2*R*)-*trans*-2-(5-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (−)-**12a**, eluted at 29.9 min: 100% purity with >99% ee; $[\alpha_D]^{22}$ −17.0° (*c* 2.59 mg/mL, EtOH). This material was converted to the maleate salt: >97% purity (reverse-phase HPLC), >99.5% purity with >99% ee (Chiralpak AD 4.6 mm × 250 mm, 10% MeOH, 90% hexane (0.15% diethylamine), 1.0 mL/min, t_R =7.30 min); $[\alpha_D]^{22}$ +3.2° (*c* 2.54 mg/mL, EtOH) and $[\alpha_D]^{22}$ −9.9° (*c* 3.33 mg/mL, H_2O). Anal. Calcd for $C_{15}H_{17}N_3 \cdot C_4H_4O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 63.31; H, 5.94; N, 11.34. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 9.65 (br, 1H), 9.35 (br, 1H), 8.18 (d, 1H, J = 0.6 Hz), 7.44 (dd, 2H, J = 15.9, 8.4 Hz), 7.32 (d, 1H, J = 0.6 Hz), 3.21 (dq, 2H, J = 57.0, 7.1, 33.2, 7.1 Hz), 2.84 (s, 6 H), 2.10 (q, 1H, J = 4.2 Hz), 1.18 (m, 1H), 1.15 (m, 1H), 1.02 (m, 1H).

(1*S*,2*S*)-*trans*-2-(5-Cyano-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylamino-methyl)cyclopropane, (+)-**12a**, eluted at 49.0 min and was identical to material enantioselectively synthesized.

Preparative Chiral HPLC Resolution of *trans*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 12e. The enantiomers were separated on a Chiralpak AD column, 50 mm × 500 mm with 20 μm packing, using 5% EtOH/hexane (0.15% diethylamine added in hexane as modifier) as the eluent, with a flow rate of 60 mL/min for 75 min and the UV detector at 280 nm. The injection load was 80 mg in 6.5 mL of EtOH/hexane (4:5).

(1*R*,2*R*)-*trans*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (−)-**12e**, eluted at 47.6 min: 96% purity with >99% ee (Chiralpak AD, 4.6 mm × 250 mm, 5% MeOH, 95% hexane (0.15% diethylamine), 0.5 mL/min, t_R = 21.57 min). The compound was characterized as the maleate salt: $[\alpha_D]^{22}$ −51.1° (*c* 4.64 mg/mL, EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (1H, br s), 9.35 (1H, br s), 7.36 (1H, dd, J = 10.0, 2.4 Hz), 7.32 (1H, dd, J = 8.8, 4.6 Hz), 7.19 (1H, d, J = 2.3 Hz), 6.92 (1H, td, J_t = 9.3, J_d = 2.5 Hz), 3.19 (m, 2H), 2.83 (s, 6H), 2.00 (m, 1H), 1.26 (m, 1H), 1.09 (m, 1H), 0.92 (m, 1H). Anal. ($C_{14}H_{17}FN_2 \cdot C_4H_4O_4$) C, H, N.

(1*S*,2*S*)-*trans*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (+)-**12e**, eluted at 60.8 min and was identical to material that was enantioselectively synthesized.

Preparative Chiral HPLC Resolution of *cis*-2-[5-Cyano-1*H*-indol-3-yl]-1-(*N*,*N*-dimethylaminomethyl)-cyclopropane, 16a. The enantiomers were separated on a Chiralpak AD column, 21 mm × 250 mm with 20 μm packing, using 10% EtOH/hexane (0.15% diethylamine added in hexane as modifier) as the eluent, with a flow rate of 20 mL/min for 45 min and the UV detector at 241 nm. The injection load was 18 mg in 1 mL of 1:3 EtOH/hexane.

(1*S*,2*R*)-*cis*-2-[5-Cyano-1*H*-indol-3-yl]-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (+)-**16a**, eluted at 21.02 min with >97% purity with >99% ee (Chiralpak AD 4.6 mm × 250 mm, 10% MeOH, 90% hexane (containing 0.15% diethylamine), 1.0 mL/min, t_R = 8.02 min, sign of rotation determined by laser polarimetry).

(1*R*,2*S*)-*cis*-2-[5-Cyano-1*H*-indol-3-yl]-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (−)-**16a**, eluted at 34.84 min with >98% purity with >99% ee (Chiralpak AD 4.6 mm × 250 mm, 10% MeOH, 90% hexane (containing 0.15% diethylamine), 1.0 mL/min, t_R = 10.91 min, sign of rotation determined by laser polarimetry).

Preparative Chiral HPLC Resolution of *cis*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 16e. The enantiomers were separated using the same method as for **16a** but using 5% EtOH/hexane as the eluent.

(1*S*,2*R*)-*cis*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (+)-**16e**, eluted at 23.47 min with >94% purity with >99% ee (Chiralpak AD 4.6 mm × 250 mm, 5% MeOH, 95% hexane (0.15% diethylamine), 10.5 mL/min, t_R = 20.18 min, sign of rotation determined by laser polarimetry).

(1*R*,2*S*)-*cis*-2-(5-Fluoro-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, (−)-**16e**, eluted at 39.08 min with >96% purity with >99% ee (Chiralpak AD 4.6 mm × 250 mm, 5% MeOH, 95% hexane (0.15% diethylamine), 0.5 mL/min, t_R = 30.97 min, sign of rotation determined by laser polarimetry).

(1*S*,2*S*)-*trans*-2-[5-Cyano-1-methyl-1*H*-indol-3-yl]-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 20. A solution of (+)-**12a** (90 mg, 0.38 mmol) in THF (5 mL) was treated with potassium *tert*-butoxide (46 mg, 0.41 mmol) and stirred for 1 h at room temperature. Dimethyl sulfate (52 mg, 0.41 mmol) was added, and the mixture was stirred for 3 h. The THF was removed in vacuo, and the remaining aqueous suspension was extracted with EtOAc (4 × 5 mL). The organic layer was dried with magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using chloroform/NH_4OH (2 M in MeOH) (97:3) to give **20** (62 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, d, J = 1.2 Hz), 7.42 (1H, dd, J = 8.8, 1.2 Hz), 7.28 (1H, d, J = 8.4 Hz), 6.84 (1H, s), 3.73 (3H, s), 2.44 (1H, dd, J = 13.2, 6.8 Hz), 2.34 (1H, dd, J = 13.1, 6.8 Hz), 2.33 (6 H, s), 1.75 (1H, m), 1.21 (1H, m), 0.90 (1H, m), 0.84 (1H, m).

(1*S*,2*S*)-*trans*-2-[5-Cyano-1-ethyl-1*H*-indol-3-yl]-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 21. 21 was prepared from (+)-**12a** using diethyl sulfate in a manner similar to **20** (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (1H, d, J = 1.5 Hz), 7.40 (1H, dd, J = 8.8, 1.6 Hz), 7.31 (1H, d, J = 8.4 Hz), 6.90 (1H, s), 4.10 (2H, q, J = 7.2 Hz), 2.44 (1H, dd, J = 12.9, 6.5 Hz), 2.34 (1H, dd, J = 13.0, 6.8 Hz), 2.33 (6 H, s), 1.74 (1H, m), 1.23 (1H, m), 0.88 (1H, m), 0.81 (1H, m).

(1*R*,2*S*)-*cis*-2-(5-Fluoro-1-(4-toluenesulfonyl)-1*H*-indol-3-yl)-1-(*N*,*N*-dimethylaminomethyl)cyclopropane, 22. To a solution of (−)-**16e** (25 mg, 0.11 mmol) in DMF (2 mL) at 0 °C was added dropwise a solution of sodium bis(trimethylsilyl)-amide (0.20 mL, 0.6 M in toluene, 0.12 mmol). After the mixture was stirred 15 min at 0 °C, *p*-tosyl chloride (31 mg, 0.16 mmol) was added and the mixture was stirred a further 30 min. The mixture was poured into brine (20 mL) and extracted with EtOAc (4 × 5 mL). The combined organic phases were dried with magnesium sulfate and evaporated to dryness. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (containing 2 M NH_4OH) (4:96) as the eluent to give **22** as a white solid (36 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.6, 4.5 Hz, 1H), 7.68 (d, J = 8.5, 2H), 7.18−7.25 (m, 4H), 7.02 (td, J = 9.1, 2.8 Hz, 1H), 2.32 (s, 3H), 2.25 (m, 1H), 2.12 (s, 6H), 1.94 (q, J = 7.2 Hz, 1H), 1.65 (m, 1H), 1.36 (m, 1H), 1.20 (m, 1H), 0.69 (m, 1H). The crystals for X-ray crystallography were developed by slow evaporation from EtOAc/hexane and collected.

Supporting Information Available: Results from HRMS, HPLC, and elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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