JOC The Journal of Organic Chemistry

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Sequential Electrophilic Trifluoromethanesulfanylation–Cyclization of Tryptamine Derivatives: Synthesis of C(3)-Trifluoromethanesulfanylated Hexahydropyrrolo[2,3-*b*]indoles

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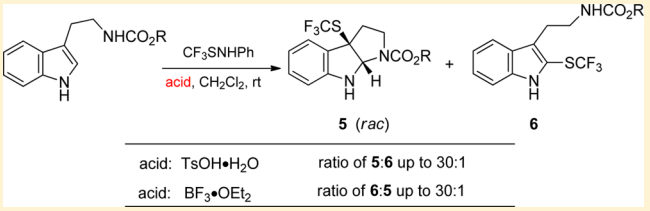
Supporting Information

ABSTRACT: A practical and efficient synthesis of C(3)-trifluoromethanesulfanylated hexahydropyrrolo[2,3-*b*]indoles **5** from tryptamine derivatives was described. The features of this synthesis included electrophilic activation of C(3) of tryptamine derivatives with "CF_3S^+" and cascade ring cyclization by carbamate nucleophile attacking at C(2). Surprisingly, when Lewis acid ($BF_3{\cdot}OEt_2$) was used as activator instead of proton acid ($TsOH{\cdot}H_2O$) for the electrophilic trifluoromethanesulfanylation of tryptamine derivatives, the uncyclized product **6** was formed preferentially. This sequential trifluoromethanesulfanylation–cyclization protocol was used to synthesize several pyrrolidinoindolinic alkaloid analogues. The cytotoxicity activities of these trifluoromethanesulfanylated alkaloid analogues were evaluated against three cancer cell lines (K562, HeLa, L929).



INTRODUCTION

Natural products containing a hexahydropyrrolo[2,3-*b*]indole (HPI) unit usually exhibit interesting biological activities, such as miotic, anticancer, anticholinergic and neuroprotective properties.[1] The C(3) substituted pyrrolidinoindolines, as exemplified by (−)-physostigmine **1** and (−)-phenserine **2**, have been found to be clinically useful for treating glaucoma and relieving symptoms of Alzheimer's disease.[2] Besides the C(3) carbon-centered group substituted pyrrolidinoindolines, the C(3) nitrogen and oxygen-substituted ones also received a significant amount of attention from synthetic and medicinal chemistry communities (Figure 1).[3] To gain diverse substitutions at C(3) position, the thio-substituted pyrrolidinoindolines are appealing targets for drug modification and total synthesis efforts. However, the rapid and efficient approaches to construct C(3) thio-substituted pyrrolidinoindolines remain limited.[4] The CF_3S moiety possesses an extremely large Hansch lipophilicity parameter (π = 1.44).[5] Consequently compounds bearing CF_3S group are potentially important targets in the pharmaceutical and agrochemical fields.[6] We anticipate that if the CF_3S group can be incorporated into the C(3) site of hexahydropyrrolo[2,3-*b*]indole, this novel structural motif could be attractive and valuable for the development of biologically active compounds.

A variety of processes for the incorporation of the CF_3S group into diverse organic molecules have been developed.[7]

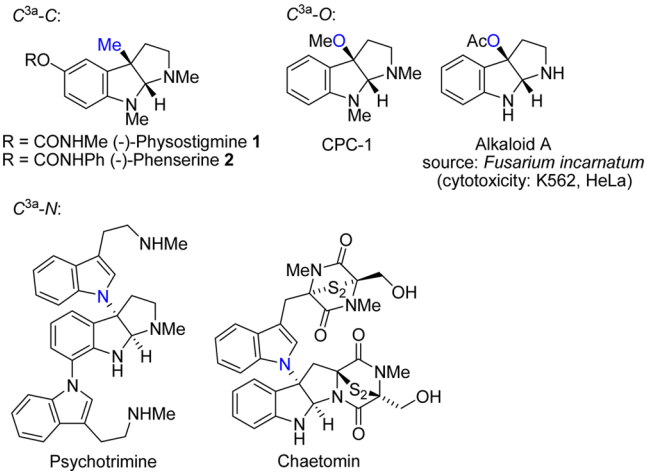


Figure 1. Various substitutions at C(3) position of hexahydropyrrolo-[2,3-*b*]indole.

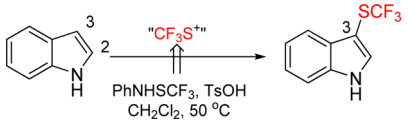
Trifluoromethanesulfanylation in an electrophilic fashion has emerged as powerful synthetic tools in this arena. Recently, Billard and Langlois report the trifluoromethanesulfanylation of

Received: June 27, 2012
Published: August 13, 2012

   dx.doi.org/10.1021/jo3013385 | *J. Org. Chem.* 2012, 77, 7538–7547

electron-rich (hetero)arenes like indoles using trifluoromethanesulfanylamides as easy-to-handle equivalents of the trifluoromethanesulfanyl cation (Scheme 1).[8−10] Inspired by this work,

Scheme 1. Electrophilic Trifluoromethanesulfanylation of Indole



we anticipate that the C(3)-trifluoromethanesulfanylated hexahydropyrrolo[2,3-*b*]indoles could be formed through electrophilic activation of the electron-rich C(3) position of indole with the trifluoromethanesulfanyl cation equivalent ("CF_3S^+") and subsequent cyclization onto the resulting C(2) iminium ion by the side chain nitrogen (Scheme 2, biomimetic approach). It was noteworthy that the efficiencies of accesses to C(3)-substituted hexahydropyrrolo[2,3-*b*]indoles via biomimetic approach[11] were limited, as this reaction profile was highly sensitive to the nature of the electrophiles and the indole substrates.[12] Herein, we describe a practical and efficient construction of C(3)-trifluoromethanesulfanylated hexahydropyrrolo[2,3-*b*]indoles by electrophilic activation of C(3) of tryptamine derivatives with "CF_3S^+" and cascade ring cyclization by carbamate nucleophile attacking at C(2).

RESULTS AND DISCUSSION

Chemistry. We began our synthesis of C(3)-trifluoromethanesulfanylated hexahydropyrrolo[2,3-*b*]indoles with tryptamine derivative **4a** as a model substrate (Table 1). Trifluoromethanesulfanylamide **3** was chosen for the formation of "CF_3S^+" equivalent.[8] Initially, treatment of compound **4a** with **3** using *p*-toluenesulfonic acid (TsOH) as acid activator at elevated temperature (50 °C) gave nearly 1:1 mixture of the desired product **5a** and uncyclized compound **6a** in 95% yield (Table 1, entry 1). But compounds **5a** and **6a** could not be separated by column chromatography. To our delight, the ratio of **5a**:**6a** was greatly improved to 20:1 when the reaction was conducted at room temperature (entry 2). It was found that **5a** was converted into **6a** completely upon treatment with TsOH at 50 °C for 12 h. This result indicated that reaction temperature played key role in the formation of **5a**. (+)-Camphorsulfonic acid (CSA) and methanesulfonic acid (MsOH) were also proven to be the efficient activator for the formation of the desired cyclic product **5a** preferentially (entries 3−4). However, carboxylic acids HOAc and CF_3CO_2H were poor activators for this reaction. There was no reaction in the presence of HOAc (entry 5). When CF_3CO_2H was used as acid activator, the yield and ratio of **5a**:**6a** were decreased (entry 6). Interestingly, the uncyclized compound **6a** was formed as the single product in the presence of the Lewis acid $BF_3{\cdot}OEt_2$ (entry 7). The formation of the uncyclized compound **6a** was probably due to the strong interaction[13] between $BF_3{\cdot}OEt_2$ and the side chain nitrogen. This interaction resulted in the inhibition of subsequent cyclization onto the at C(2) position of thiiranium ion **4a**′[14,15] by the side chain nitrogen. Thereby, the reaction proceeded in Path II instead of Path I to provide C(2)-trifluoromethanesulfanylated product **6a** preferentially (Scheme 3).

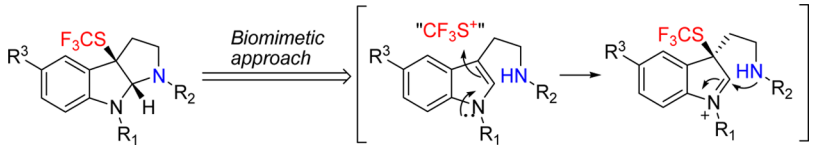
With the optimum reaction conditions determined (Table 1, entry 2), the scope of this cascade electrophilic activation/cyclization process was investigated with respect to both the attached nucleophile and the substitution pattern of the indole structural core. First, a wide variety of nucleophiles at the side chain were examined (Table 2). When tryptamine **4b** was taken as substrate for this sequential trifluoromethanesulfanylation−cyclization, its conversion was less than 10% (entry 1). For acetyl, tosyl protected tryptamine and side chain prolonged substrates (**4c**, **4d** and **4e**), the uncyclized products **6c**, **6d** and **6e** were formed respectively in priority instead of cyclized products (entries 2−4). In the cases of substrates (**4f** and **4g**) in which the center of nucleophile in the side chain was carbon or oxygen, there was no formation of the cyclized products (entries 5−6). These results showed that the nucleophile was very critical in this sequential trifluoromethanesulfanylation−cyclization process.

With the proper nitrogen nucleophile determined, the substitution patterns of the indole structural core went into examination (Table 3). The reaction tolerated various carbamate functions on the side chain nitrogen (entries 1−3), but the lower ratio of **5i**:**6i** was observed for Troc-protected form (entry 2). Substitutions at the 5 or 6 position of the indole substrate impacted the regioselectivity and/or reactivity. In comparison with electron-withdrawing substituent (fluorine in **4m**), the electron-donating groups (methyl and methoxyl) are beneficial for the higher ratio of cyclized products formation (entries 4−6, 10−11). In addition, the R^2 groups on the indole nitrogen atom were also examined. The ratio of **5n**:**6n** was decreased to 1:1 when the indole N^a atom was masked by methyl group (entry 7). The N^a-allyl indole gave the same result besides keeping the double bond of the ally group intact (entry 8).[9] However, N^a-acetyl indole did not afford the electrophilic trifluoromethanesulfanylation product due to the attenuated electron-density of C(3) position (entry 9).

To illustrate the synthetic utility of this methodology and explore the biological properties of the newly found structural motif, we undertook the synthesis of trifluoromethanesulfanylated analogues **7** in which the trifluoromethanesulfanyl group mimics the acetoxyl function of alkaloid **A**[16] (Scheme 4). The analogues **7** can be easily obtained from intermediates **5j**, **5q** and **5r** by Fmoc deprotection (Scheme 4).

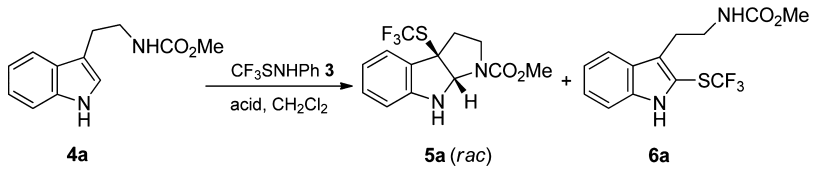
Other analogues bearing methyl at N^a or N^b atom could also be synthesized from intermediates **5j** and **5r** (Scheme 5). The indole N^a atoms in **5j** and **5r** were methylated through reductive methylation by using formaldehyde, HOAc, and

Scheme 2. Biomimetic Approach



dx.doi.org/10.1021/jo3013385 | J. Org. Chem. 2012, 77, 7538−7547

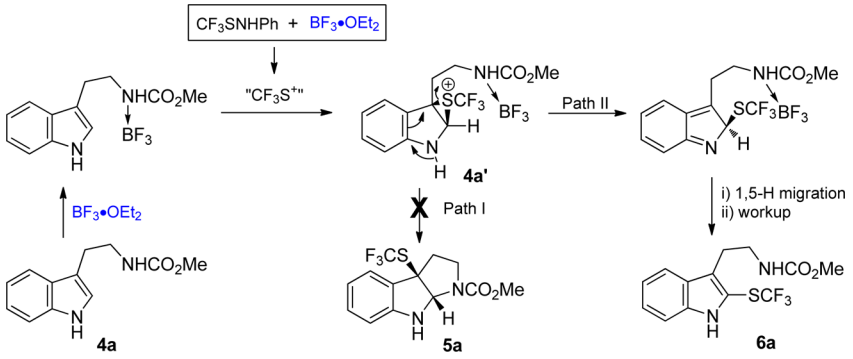
Table 1. Optimization of the Sequential Trifluoromethanesulfanylation−Cyclization of Tryptamine Derivative 4a[a]



entry	acid	temp (°C)	time (h)	ratio (**5a**:**6a**)[b]	isolated yield (%)
1	TsOH	50	12	1:1	95
2	**TsOH**	**rt**	**12**	**>20:1**	**96**
3	(+)-CSA	rt	12	>20:1	94[c]
4	MsOH	rt	12	9:1	95
5	HOAc	rt	24	NR	NR
6	CF_3CO_2H	rt	24	5.5:1	33[d]
7[e]	$BF_3{\cdot}OEt_2$	rt	48	nearly only **6a**	97

[a]All the reactions were run on 0.2 mmol scale in CH_2Cl_2 (2 mL), CF_3SNHPh (1.2 equiv), acid (2.5 equiv). [b]The ratio of **5a**:**6a** was determined by ^{19}F NMR of the crude product. [c]Nearly racemic product **5a** was afforded (*ee* < 5%). [d]1/3 $PhNHSCF_3$ was consumed. [e]5 equiv of $BF_3{\cdot}OEt_2$ were added in two portions at 24 h intervals.

Scheme 3. Pathway for Formation of 6a



sodium cyanoborohydride, repectively. Then deprotection of Fmoc group on N^b atoms in **8j** and **8r** were conducted under the treatment of piperidine. Finally, compounds **10j** and **10r** were obtained by a second reductive methylation at N^b atom. Compound **10j** could be interpreted as the trifluoromethanesulfanylated analogue of alkaloid CPC-1,[17] in which the methoxyl group was replaced by trifluoromethanesulfanyl (Scheme 5).

Biological Evaluation. The antiproliferative activities of the trifluoromethanesulfanylated analogues were evaluated against three cancer cell lines: K562 (human myelogenous leukemia), HeLa, and L929 (mouse fibroblast cell), which were grown in vitro (cell lines were provided from the American Type Culture Collection, ATCC, M anassas, VA). Taxol was used as positive control. The IC_{50} values (μM) were summarized in Table 4. Compounds **10j** and **10r** were not evaluated against cancer cell lines, as they were unstable.

Compounds **8j**, **5a**, **5j** and **5h** showed no or negligible inhibition toward all three cell lines: K562, HeLa, and L929 (Table 4, entries 8−11). Compound **5i** displayed moderate inhibition to K562, HeLa, L929 with IC_{50} values of 21.4, 14.5, and 55.2 μM, respectively (entry 12). Compound **7q** presented higher potency than **7j** and alkaloid **A** for L929 cell line (entries 1−3). Compounds **7r** and **8r** bearing CH_3O group on the fused aryl group ($R^3 = OCH_3$) were found to be the most potent in inhibiting K562 cancer cell growth than the other compounds with IC_{50} values of 4.7 and 6.4, μM respectively (entries 4, 7). Furthermore, **7r** showed good inhibition toward HeLa cancer cell (entry 4), and **8r** exhibited better selectivity than **7r** for inhibition against K562 cancer cell (entry 7). Overall, the bioassay data indicated that the introduction of trifluoromethanesulfanyl group at C(3) position of hexahydropyrrolo[2,3-*b*]indoles renders us a novel framework for pursuing new anticancer agents.

■ CONCLUSION

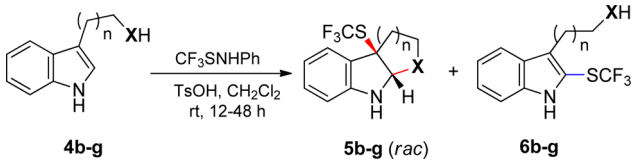
In conclusion, we have demonstrated a practical and efficient approach to synthesize the C(3)-trifluoromethanesulfanylated hexahydropyrrolo[2,3-*b*]indoles. This methodology highlights the electrophilic activation at C(3) site with "CF_3S^+" and a carbamate nucleophile attacking the generated iminium ion. The application of this chemistry for the concise synthesis of several trifluoromethanesulfanylated alkaloid analogues was also described. Further investigations of the scope and enantioinduction of this sequential trifluoromethanesulfanylation−cyclization are underway, and the results will be reported in due course.

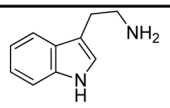
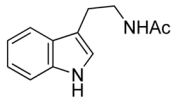
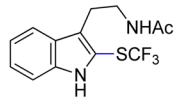
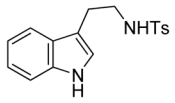
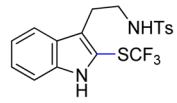
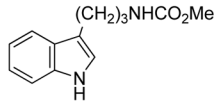
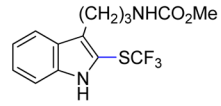
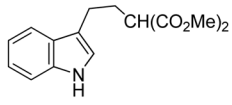
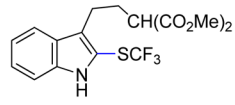
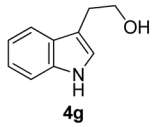
■ EXPERIMENTAL SECTION

Chemistry. *N-[(Trifluoromethyl)thio]aniline (**3**).* A flame-dried double-necked vessel was successively charged, under nitrogen, with diisopropylethylamine (7 mL, 40 mmol) and anhydrous dichloromethane (80 mL). The resulting mixture was cooled to −20 °C before addition of diethylaminosulfurtrifluoride (5.5 mL, 44 mmol), followed by the addition of trimethylsilyltrifluoromethane (5.9 mL, 40 mmol) in 20 min intervals. After stirring under at −20 °C for 1 h, aniline (1 equiv) was added at 0 °C. The reaction mixture was stirred at room

dx.doi.org/10.1021/jo3013385 | J. Org. Chem. 2012, 77, 7538−7547

Table 2. Investigation of the Nucleophiles[a]



Entry	Substrate	Time (h)	Result
1	 **4b**	24	Conversion < 10%
2	 **4c**	24	 **6c**, 82%
3	 **4d**	30	 **6d**, 70%
4	 **4e**	20	 **6e**, 94%
5	 **4f**	18	 **6f**, 73%
6	 **4g**	24	complex

[a]All reactions were run on 0.2 mmol scale in CH_2Cl_2 (2 mL), CF_3SNHPh (1.2 equiv), TsOH (2.5 equiv).

temperature overnight. The reaction mixture was washed with distilled water. The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by distillation under reduced pressure to afford the corresponding sulfanylamide **3** as yellow oil (5.25 g, Yield 68%): bp 46 °C/20 Pa; ^{1}H NMR (300 MHz, $CDCl_3$) 7.28 (t, J = 7.5 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 5.08 (NH); ^{19}F NMR (282 MHz, $CDCl_3$) −52.5 (s, 3F).

General Procedure for the Protic Acid Catalyzed Eletrophilic Trifluoromethananesulfanylation of Tryptamine Derivatives with N-[(Trifluoromethyl)thio]aniline ***3***. To a solution of compound **3** (0.24 mmol) in dichloromethane (2 mL) were added tryptamine derivative (0.2 mmol) and then TsOH (0.5 mmol). The reaction mixture was stirred at room temperature for 12−36 h until the substrate disappeared by TLC detecting. Then, the organic phase was washed with saturated $NaHCO_3$ solution and then dried over sodium sulfate. After removing the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 5:1) to afford the corresponding product.

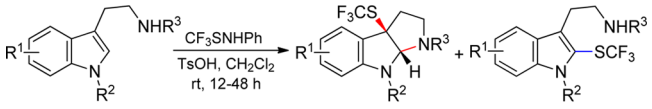
*N-(2-(2-(Trifluoromethylthio)-1H-indol-3-yl)ethyl)acetamide (**6c**).* White solid: mp 133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.29 (t, J = 6.3 Hz, 1H), 7.12 (t, J = 6.9 Hz, 1H), 5.80 (s, 1H), 3.58 (q, J = 6.3 Hz, 2H), 3.14 (t, J = 6.6 Hz, 2H), 1.92 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −43.2 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 170.4, 137.7, 128.4 (q, J = 312.7 Hz), 127.2, 124.9, 124.0, 120.4, 119.9, 113.8, 111.5, 39.9, 24.9, 23.2; IR (KBr) υ_{max} 3404, 3266, 2923, 1704, 1654, 1535, 1133, 1109, 745 cm^{-1}; MS (ESI) m/z 303 (M + H)$^+$, 325 (M + Na)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{13}H_{14}N_2OF_3S$ 303.0779, found 303.0773.

*4-Methyl-N-(2-(2-(trifluoromethylthio)-1H-indol-3-yl)ethyl)-benzenesulfonamide (**6d**).* White solid: mp 143 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.8 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.25 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 6.60 (t, J = 6.0 Hz, 1H), 3.24−3.19 (m, 2H), 3.14−3.10 (m, 2H), 2.37 (s, 3H); ^{19}F NMR (282 MHz, acetone-d_6) −39.0 (s, 3F); ^{13}C NMR (100.7 MHz, acetone-d_6) δ 142.8, 138.3, 138.1, 129.5, 128.8 (q, J = 310.5 Hz), 127.0, 126.9, 124.4, 123.1, 119.9, 119.6, 113.2, 111.7, 43.5, 25.4, 20.4; IR (KBr) υ_{max} 3335, 3058, 2924, 1699, 1445, 1323, 1158, 1110, 746, 663 cm^{-1}; MS (ESI) m/z 415 (M + H)$^+$, 432 (M + NH$_4$)$^+$, 437 (M + Na)$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{18}H_{17}N_2O_2F_3S_2Na$ 437.0581, found 437.0576.

*Methyl 3-(2-(trifluoromethylthio)-1H-indol-3-yl)propylcarbamate (**6e**).* White solid: mp 100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s,

dx.doi.org/10.1021/jo3013385 | J. Org. Chem. 2012, 77, 7538−7547

Table 3. Exploration of the Substitution Patterns in the Indole Structural Core[a]



4h-4r 5h-5r (*rac*) 6h-6r

entry	4h–4r	R^1	R^2	R^3	time (h)	ratio (5:6)[b]	isolated yield[h] (%)
1	**4h**	H	H	Cbz	30	10:1	83[c]
2	**4i**	H	H	Troc	36	5.5:1	81[d]
3	**4j**	H	H	Fmoc	12	10:1	95[c] (82[e])
4	**4k**	5-Me	H	Moc	12	24:1	96[c]
5	**4l**	5-MeO	H	Moc	10	37:1	94[c]
6	**4m**	6-F	H	Moc	24	4:1	92[f]
7	**4n**	H	Me	Moc	24	1:1	52[g]
8	**4o**	H	Allyl	Moc	18	1:1	81[d]
9	**4p**	H	Ac	Moc	24		NR
10	**4q**	5-Me	H	Fmoc	12	20:1	87[c]
11	**4r**	5-MeO	H	Fmoc	12	18:1	95[c]

[a]All the reactions were run on 0.2 mmol scale in CH_2Cl_2 (2 mL), CF_3SNHPh (1.2 equiv), TsOH (2.5 equiv). [b]The ratio of **5**:**6** was determined by ^{19}F NMR of the crude product. [c]After flash chromatgrapy, the ratio of **5**:**6** became greater than 20:1 (determined by ^{19}F NMR). [d]After flash chromatgrapy, the cyclized product and uncyclized product can be separated and characterized. [e]After recrystallization, the ratio of **5j**:**6j** became greater than 100:1 (determined by ^{19}F NMR). [f]After flash chromatgrapy, **5m** and **6m** were obtained as a mixture in the ratio of 4:1. [g]After flash chromatgrapy, only pure **5n** was obtained. [h]Isolated yield of a mixture of **5** and **6**.

1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 6.9 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 4.87 (s, 1H), 3.68 (s, 3H), 3.24 (d, *J* = 5.7 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 1.94–1.84 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −43.4 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 157.3, 137.7, 128.5 (q, *J* = 312.5 Hz), 127.0, 126.4, 124.6, 120.1, 119.8, 113.0, 111.5, 52.1, 40.8, 30.5, 22.0; IR (KBr) υ_{max} 3403, 3298, 2944, 2860, 1709, 1526, 1262, 1110, 745 cm^{-1}; MS (ESI) *m*/*z* 333 (M + H)$^+$, 355 (M + Na)$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ Calcd for $C_{14}H_{15}N_2O_2F_3SNa$ 355.0704, found 355.0699.

Dimethyl 2-(2-(2-(trifluoromethylthio)-1H-indol-3-yl)ethyl)-malonate (**6f**). Light yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 6H), 3.47 (t, *J* = 7.2 Hz, 1H), 3.00 (t, *J* = 8.0 Hz, 2H), 2.33 (q, *J* = 7.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −42.6 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 169.7, 137.6, 128.5 (q, *J* = 312.3 Hz), 127.0, 125.8, 124.8, 120.3, 120.0, 113.4, 111.4, 52.6, 51.3, 29.4, 22.6; IR (KBr) υ_{max} 3367, 2954, 1731, 1434, 1344, 1132, 1109, 746 cm^{-1}; MS (ESI) *m*/*z* 376 (M + H)$^+$, 393 (M + NH_4)$^+$, 398 (M + Na)$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ Calcd for $C_{16}H_{16}F_3O_4NSNa$ 398.0650, found 398.0644.

(3a,8a)-Methyl 3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5a**). White solid: mp 112 °C; ^1H NMR (300 MHz, $CDCl_3$) (ca. 3:2 mixture of rotamers, both reported) δ 7.53 (d, *J* = 4.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 8.1 Hz, 1H), 5.90 (s, 0.6H), 5.87 (s, 0.4H), 4.83 (br, 1H), 4.15–4.06 (m, 1H), 4.07 (s, 1.2H), 3.99 (s, 1.8H), 3.37 (q, *J* = 9.3 Hz, 1H), 2.90–2.80 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 3:2 mixture of rotamers, both reported) −37.0 (s, 1.8F), −37.1 (s, 1.2F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.1, 154.3, 149.1, 148.8, 130.6, 129.6 (q, *J* = 309.0 Hz), 125.6, 124.5, 124.4, 119.9, 119.7, 110.2, 110.1, 81.2, 80.9, 63.6, 62.5, 52.9, 52.6, 45.0, 44.8, 36.8, 36.7; IR (KBr) υ_{max} 3354, 2955, 2884, 1697, 1609, 1452, 1386, 1110, 747 cm^{-1}; MS (ESI) *m*/*z* 319 (M + H)$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{13}H_{14}N_2O_2F_3S$ 319.0728, found 319.0723. Anal. Calcd for $C_{13}H_{13}F_3N_2O_2S$: C, 49.05; H, 4.12; N, 8.80. Found: C, 49.31; H, 4.34; N, 8.85.

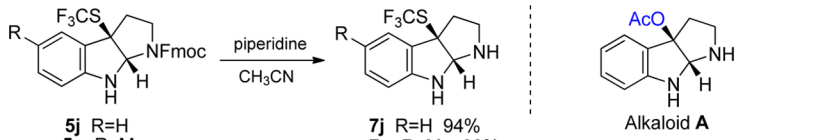
(3a,8a)-Benzyl 3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5h**). Clear oil: ^1H NMR (400 MHz, $CDCl_3$) (ca. 3:2 mixture of rotamers, both reported) δ 7.41–7.32 (m, 5H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18–7.13 (m, 1H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 0.6H), 6.57 (d, *J* = 8.0 Hz, 0.4H), 5.65 (s, 0.6H), 5.63 (s, 0.4H), 5.27–5.17 (m, 0.8H), 5.20–5.08 (m, 1.2H), 4.90 (br, 1H), 3.86 (t, *J* = 8.8 Hz, 0.4H), 3.80–3.75 (m, 0.6H), 3.16–3.08 (m, 1H), 2.62–2.55 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 3:2 mixture of ratamers, both reported) δ −37.7 (s), −37.8 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 154.5, 153.7, 149.1, 148.8, 136.2, 136.1, 130.6, 129.6 (q, *J* = 310.5 Hz), 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 125.7, 125.5, 124.5, 124.4, 120.0, 119.7, 110.3, 110.1, 81.3, 80.9, 67.5, 67.2, 63.5, 62.6, 45.1, 44.9, 36.8, 36.6; IR (KBr) υ_{max} 3363, 3033, 2952, 2880, 1698, 1417, 1117, 740 cm^{-1}; MS (ESI) *m*/*z* 395 (M + H)$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{19}H_{18}N_2O_2F_3S$ 395.1041, found 395.1036.

(3a,8a)-2,2,2-Trichloroethyl 3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5i**). Clear oil: ^1H NMR (400 MHz, $CDCl_3$) (ca. 3:2 mixture of rotamers, both reported) δ 7.26 (d, *J* = 6.4 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.86–6.82 (m, 1H), 6.68–6.65 (m, 1H), 5.71 (s, 0.6H), 5.69 (s, 0.4H), 5.32 (br, 0.4H), 5.16 (br, 0.6H), 5.00 (d, *J* = 12.4 Hz, 0.6H), 4.82 (d, *J* = 12.0 Hz, 0.4H), 4.70 (s, 0.6H), 4.67 (s, 0.4H), 3.92–3.85 (m, 1H), 3.26–3.14 (m, 1H), 2.67–2.63 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 1.1:1 mixture of rotamers, both reported) δ −36.9 (s), −37.0 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 152.8, 151.8, 148.9, 148.6, 130.8, 130.7, 129.6 (q, *J* = 311.1 Hz), 125.5, 125.2, 124.5, 124.4, 120.1, 119.9, 110.2, 110.1, 95.5, 95.3, 81.5, 81.0, 74.9, 74.9, 63.4, 62.6, 45.4, 45.0, 36.7, 36.2; IR (KBr) υ_{max} 3422, 3381, 2953, 2886, 1716, 1609, 1416, 1110, 747 cm^{-1}; MS (ESI) *m*/*z* 437 (M + H)$^+$, 459 (M + Na)$^+$; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{14}H_{13}N_2O_2F_3SCl_3$ 434.9715, found 434.9710.

2,2,2-Trichloroethyl 2-(2-(trifluoromethylthio)-1H-indol-3-yl)-ethylcarbamate (**6i**). White solid: mp 105 °C; ^1H NMR (400 MHz, $CDCl_3$) (ca. 9:1 mixture of rotamers, both reported) δ 8.54 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 5.14 (s, 0.9 H), 4.91 (s, 0.1 H), 4.77 (0.3 H), 4.73 (s, 1.7 H), 3.55 (q, *J* = 6.8 Hz, 2H), 3.17 (t, *J* = 7.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 9:1 mixture of ratamers, both reported) δ −42.3 (s), −42.4 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 154.6, 137.6, 128.4 (q, *J* = 312.3 Hz), 127.1, 125.0, 123.7, 120.6, 120.0, 114.0, 111.4, 95.5, 74.9, 74.5, 42.1, 41.6, 25.9, 25.3. IR (KBr) υ_{max} 3401, 3323, 2950, 1723, 1519, 1110, 815, 746, 727 cm^{-1}; MS (ESI) *m*/*z* 437 (M + H)$^+$, 459 (M + Na)$^+$; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ Calcd for $C_{14}H_{12}N_2O_2F_3SCl_3Na$ 456.9535, found 456.9529.

(3a,8a)-(9H-Fluoren-9-yl)methyl 3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5j**).

Scheme 4. Synthesis of Trifluoromethanesulfanylated Analogues 7 of Alkaloid A



5j R=H
5q R=Me
5r R=MeO

7j R=H 94%
7q R=Me 90%
7r R=MeO 86%

Alkaloid **A**
cytotoxicity: K562, HeLa, L929

dx.doi.org/10.1021/jo3013385 | *J. Org. Chem.* 2012, 77, 7538–7547

Scheme 5. Synthesis of other Analogues Bearing Methyl at N[a] or N[b]

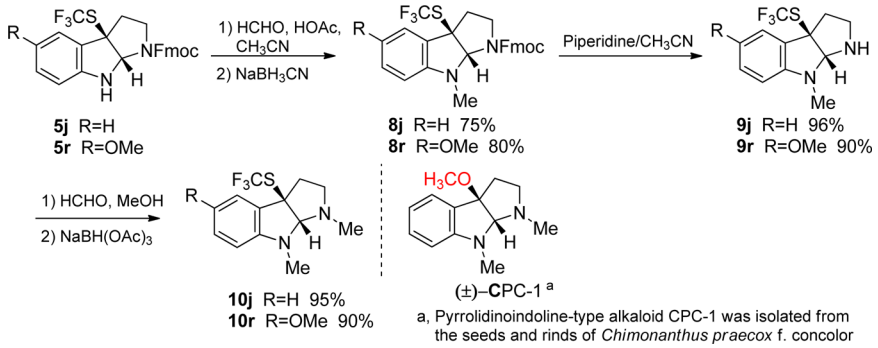
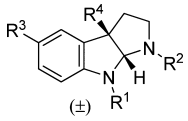


Table 4. Structures of Trifluoromethanesulfanylated Pyrrolidinoindolines and Their in Vitro Inhibition against Cancer Cell Lines



						IC_{50} (μM)[a]		
entry	compound	R^1	R^2	R^3	R^4	K562	HeLa	L929
1	**A**	H	H	H	OAc	28.9[b]	66.1[b]	61.9[b]
2	**7j**	H	H	H	SCF_3	>100	>100	87.5
3	**7q**	H	H	Me	SCF_3	>100	>100	20.9
4	**7r**	H	H	OMe	SCF_3	4.7	10.0	>100
5	**9r**	Me	H	OMe	SCF_3	57.9	>100	>100
6	**9j**	Me	H	H	SCF_3	68.4	21.6	>100
7	**8r**	Me	Fmoc	OMe	SCF_3	6.4	>100	>100
8	**8j**	Me	Fmoc	H	SCF_3	>100	>100	>100
9	**5a**	H	Moc	H	SCF_3	>100	>100	>100
10	**5j**	H	Fmoc	H	SCF_3	>100	>100	>100
11	**5h**	H	Cbz	H	SCF_3	>100	>100	>100
12	**5i**	H	Troc	H	SCF_3	21.4	14.5	55.2
13	Taxol[c]					1.7	1.1	31.2

[a] IC_{50} is the concentration of drug that inhibits the cell growth by 50% relative to the control. [b] IC_{50} values of alkaloid **A** was reported in ref 16. [c] Taxol was used as a positive control standard.

Yellow solid: mp 143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 55:45 mixture of rotamers, both reported) δ 7.87−7.10 (m, 10H), 6.84 (d, J = 7.2 Hz, 0.45H), 6.76 (t, J = 6.8 Hz, 0.55H), 6.67 (d, J = 7.6 Hz, 0.45H), 6.37 (d, J = 8.0 Hz, 0.55H), 5.65 (s, 0.45H), 5.32 (s, 0.45H), 5.04 (s, 0.55H), 4.77 (dd, J = 6.0 Hz, 4.8 Hz, 0.45H), 4.68 (dd, J = 6.0 Hz, 4.8 Hz, 0.55H), 4.49−4.40 (m, 1H), 4.31 (t, J = 3.6 Hz, 0.45H), 4.23 (t, J = 6.8 Hz, 0.55H), 3.86 (s, 0.55H), 3.77−3.73 (m, 0.45H), 3.68 (t, J = 9.2 Hz, 0.55H), 3.18−3.11 (m, 0.45H), 3.00−2.94 (m, 0.55H), 2.67−2.64 (m, 1H), 2.50−2.37 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 1:1.2 mixture of ratamers, both reported) −36.8 (s), −37.1 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 154.5, 153.5, 149.1, 148.6, 143.9, 143.8, 143.7, 141.7, 141.3, 141.3, 130.6, 130.4, 129.6 (q, J = 309.7 Hz), 127.9, 127.8, 127.4, 127.3, 127.1, 125.6, 125.3, 125.0, 124.9, 124.6, 124.4, 124.4, 124.3, 110.3, 109.6, 98.7, 81.3, 80.7, 67.4, 66.4, 63.1, 62.5, 47.3, 47.2, 44.9, 44.7, 36.8, 36.5; IR (KBr) υ_{max} 3419, 3364, 3063, 2953, 2892, 1701, 1608, 1420, 1109, 740 cm^{-1}; MS (ESI) m/z 483 (M + H)$^+$, 505 (M + Na)$^+$, 521 (M + K)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{26}H_{22}N_2O_2F_3S$ 483.1354, found 483.1349.

*(3a,8a)-Methyl 5-methyl-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5k**).* Clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 3:2 mixture of rotamers, both reported) δ 7.04 (s, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 7.6 Hz, 1H), 5.61 (s, 0.6H), 5.58 (s, 0.4H), 4.80 (br, 1H), 3.86−3.80 (m, 0.4H), 3.79 (s, 1.2H), 3.74−3.68 (m, 0.6H), 3.70 (s, 1.8H), 3.08 (q, J = 7.6 Hz, 1H), 2.60−2.53 (m, 2H), 2.27 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 4:3 mixture of rotamers, both reported) δ −36.9 (s), −37.1 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.1, 154.4, 146.9, 146.6, 132.8 (q, J = 305.1 Hz), 131.2, 129.5, 129.2, 128.1, 125.8, 124.8, 124.7, 110.3, 110.1, 81.5, 81.1, 63.7, 62.7, 52.8, 52.5, 45.0, 44.8, 36.6, 20.8; IR (KBr) υ_{max} 3358, 2957, 1704, 1619, 1497, 1452, 1385, 1113, 773 cm^{-1}; MS (ESI) m/z 333 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{14}H_{16}N_2O_2F_3S$ 333.0885, found 333.0879.

*(3a,8a)-Methyl 5-methoxy-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5l**).* Light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) (ca. 3:2 mixture of rotamers, both reported) δ 6.83 (s, 0.4H), 6.82 (s, 0.6H), 6.77 (d, J = 8.7 Hz, 0.6H), 6.75 (d, J = 8.7 Hz, 0.4H), 6.62 (s, 0.6H), 6.59 (s, 0.4H), 5.62 (s, 0.6H), 5.60 (s, 0.4H), 4.58 (br, 1H), 3.87−3.80 (m, 1H), 3.83 (s, 1.2H), 3.76 (s, 3H), 3.71 (s, 1.8H), 3.15−3.06 (m, 1H), 2.60−2.50 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 3:2 mixture of rotamers, both reported) δ −36.8 (s), −37.0 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ155.1, 154.4, 154.3, 154.1, 143.0, 142.7, 131.4 (q, J = 310.9 Hz), 131.1, 128.1, 127.1, 116.5, 116.4, 111.4, 111.3, 110.2, 110.1, 82.0, 81.6, 64.0, 62.9, 56.0, 52.8, 52.5, 44.9, 44.8, 36.7, 36.6; IR (KBr) υ_{max} 3356, 2952, 1701, 1495, 1452, 1384, 1201, 1112 cm^{-1}; MS (ESI) m/z 349 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{14}H_{16}F_3N_2O_3S$ 349.0834, found 349.0828.

*(3a,8a)-Methyl 6-fluoro-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5m**) and Methyl 2-(6-fluoro-2-(trifluoromethylthio)-1H-indol-3-yl)ethylcarbamate (**6m**).* After purification by flash chromatography on silica gel

dx.doi.org/10.1021/jo3013385 | J. Org. Chem. 2012, 77, 7538−7547

(petroleum ether:ethyl acetate = 4:1), compounds **5m** and **6m** are obtained as a mixture. Clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 4:1 mixture of two compounds, both reported) δ 8.80 (s, 0.2H), 7.63 (t, J = 6.4 Hz, 0.2H), 7.16 (t, J = 5.6 Hz, 0.8H), 7.05 (d, J = 9.2 Hz, 0.2H), 6.94 (t, J = 6.8 Hz, 0.2H), 6.48 (q, J = 7.6 Hz, 0.8H), 6.33 (d, J = 9.2 Hz, 0.8H), 5.64 (s, 0.5H), 5.63 (s, 0.3H), 5.46 (br, 0.5H), 5.03 (br, 0.3H), 4.86 (s, 0.2H), 3.80 (s, 0.9H), 3.72 (s, 1.5H), 3.68 (s, 0.6H), 3.14−3.07 (q, J = 10.8 Hz, 1.2H), 3.49−3.44 (m, 0.4H), 2.59−2.47 (m, 1.6H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 4:1 mixture of two compounds, both reported) δ −36.7 (s, 1.7F), −36.9 (s, 1.3F), −42.4 (s, 0.72F), −109.9 (m, 0.4F), −110.0 (m, 0.6F), −115.8 (s, 0.24F); ^{13}C NMR (100.7 MHz, $CDCl_3$) (ca. 4:1 mixture of two compounds, both reported) δ 166.1, 163.6, 162.6, 160.2, 157.1, 155.1, 154.2, 150.7 (d, J = 12.4 Hz), 150.4 (d, J = 12.4 Hz), 137.7, 137.6, 129.5 (q, J = 310.1 Hz), 125.7, 125.5, 125.4, 123.9, 122.7 (q, J = 326.3 Hz), 121.2, 109.9, 109.6, 106.7, 106.5, 106.4, 106.2, 97.8, 97.7, 97.6, 97.4, 81.9, 81.6, 62.9, 61.9, 52.9, 52.6, 52.1, 44.9, 44.7, 41.3, 37.0, 36.8, 29.7, 25.4; IR (KBr) υ_{max} 3346, 2959, 1697, 1619, 1454, 1393, 1142, 1112, 775 cm^{-1}; MS (ESI) m/z 337 (M + H)$^+$, 359 (M + Na)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{13}H_{13}N_2O_2F_4S$ 337.0634, found 337.0628.

*(3a,8a)-Methyl 8-methyl-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5n**).* Clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) (ca. 55:45 mixture of rotamers, both reported) δ 7.21−7.17 (m, 2H), 6.74 (t, J = 7.5 Hz, 1H), 6.43 (d, J = 8.1 Hz, 1H), 5.79 (s, 0.55H), 5.70 (s, 0.45H), 4.03−3.86 (m, 1H), 3.80 (s, 1.2 H), 3.75 (s, 1.8H), 3.07 (s, 1.8H), 2.98 (s, 1.2H), 3.06−3.00 (m, 1H), 2.43 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca.1:1 mixture of rotamers, both reported) δ −37.0 (s), −37.1 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.7, 154.9, 150.9, 131.0, 130.6, 129.7 (q, J = 310.4 Hz), 127.9, 124.3, 118.3, 118.1, 106.9, 106.8, 87.9, 87.5, 63.1, 62.0, 52.7, 44.6, 38.7, 38.3, 33.5, 32.9, 31.6, 29.0, 22.6, 18.7, 14.1, 11.4; IR (KBr) υ_{max} 2954, 2884, 1709, 1607, 1447, 1386, 1113, 745 cm^{-1}; MS (ESI) m/z 333 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{14}H_{16}F_3N_2O_2S$ 333.0885, found 333.0879.

*(3a,8a)-Methyl 8-allyl-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5o**).* Light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) (ca. 1:1 mixture of rotamers, both reported) 7.21−7.13 (m, 2H), 6.73 (t, J = 7.5 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 5.91−5.80 (m, 2H), 5.25 (d, J = 15.6 Hz, 1H), 5.16 (s, 0.5H), 5.13 (s, 0.5H), 4.11 (s, 1H), 4.03−3.97 (m, 1H), 3.90−3.84 (m, 1H), 3.76 (s, 1.5H), 3.74 (s, 1.5H), 3.08 (t, J = 9.3 Hz, 1H), 2.44 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 1:1 mixture of rotamers, both reported) −37.1 (s), −37.4(s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.4, 154.7, 149.9, 133.8, 130.5, 129.4 (q, J = 309.5 Hz), 126.2, 125.9, 124.5, 124.4, 118.3, 118.1, 116.2, 116.1, 107.2, 107.1, 98.7, 86.6, 63.3, 62.3, 52.7, 49.3, 49.1, 44.2, 39.0, 38.6; IR (KBr) υ_{max} 3080, 3054, 2956, 2886, 1711, 1606, 1448, 1116 cm^{-1}; MS (ESI) m/z 359 (M + H)$^+$, 381 (M + Na)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{16}H_{18}F_3N_2O_2S$ 359.1041, found 359.1036.

*Methyl 2-(1-allyl-2-(trifluoromethylthio)-1H-indol-3-yl)-ethylcarbamate (**6o**).* Light yellow solid: mp 90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 1H), 7.37−7.30 (m, 2H), 7.18 (t, J = 7.8 Hz, 1H), 5.90 (m, 1H), 5.15 (d, J = 10.2 Hz, 1H), 4.96 (s, 2H), 4.90 (s, 1H), 4.80 (s, 1H), 3.67 (s, 3H), 3.50 (q, J = 6.3 Hz, 2H), 3.20 (t, J = 7.2 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) −43.6 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 156.4, 144.0, 141.3, 136.4, 128.9 (q, J = 310.1 Hz), 127.7, 127.0, 125.1, 122.2, 122.1, 120.0, 119.5, 118.7, 112.9, 111.2, 66.5, 47.3, 41.3, 25.8; IR (KBr) υ_{max} 3340, 2950, 1713, 1525, 1454, 1137, 1102, 744 cm^{-1}; MS (ESI) m/z 359 (M + H)$^+$, 376 (M + NH_4)$^+$, 397 (M + K)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{16}H_{18}F_3N_2O_2S$ 359.1041, found 359.1036.

*(3a,8a)-(9H-Fluoren-9-yl)methyl 5-methyl-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5q**).* Light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 46:54 mixture of rotamers, both reported) δ 7.81 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.61−7.34 (m, 5H), 7.27 (t, J = 7.6 Hz, 1H), 7.04 (s, 0.46H), 6.97 (d, J = 8.0 Hz, 0.46H), 6.93 (s, 0.54H), 6.90 (d, J = 8.0 Hz, 0.54H), 6.56 (d, J = 8.0 Hz, 0.46H), 6.28 (d, J = 8.4 Hz, 0.54H), 5.61 (s, 0.46H), 5.16 (br, 0.5H), 5.06 (s, 0.54H), 4.74−4.62 (m, 1H), 4.46−4.36 (m, 1H), 4.28 (t, J = 4.0 Hz, 0.54H), 4.20 (t, J = 6.8 Hz, 0.46H), 3.79 (br, 0.5H), 3.74−3.65 (m, 1H), 3.16−3.09 (m, 0.46H), 2.99−2.92 (m, 0.54H), 2.60 (q, J = 4.4 Hz, 1H), 2.47−2.39 (m, 1H), 2.28 (s, 1.38H), 2.22 (s, 1.62H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 5:6 mixture of rotamers, both reported) δ −37.2 (s), −37.4 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 154.5, 153.6, 146.8, 146.4, 143.9, 143.8, 143.7, 141.6, 141.3, 141.2, 131.3, 131.1, 129.3, 129.0, 127.9, 127.8, 127.4, 127.3, 127.1, 125.8, 125.5, 125.0 (q, J = 313.7 Hz), 124.9, 124.7, 124.6, 124.4, 120.3, 120.2, 120.0, 110.4, 109.6, 81.5, 80.9, 67.4, 66.5, 63.3, 62.7, 47.3, 47.2, 44.9, 44.7, 36.6, 36.4, 20.8, 20.7; IR (KBr) υ_{max} 3412, 3355, 2952, 1701, 1497, 1419, 1200, 1114, 757, 740 cm^{-1}; MS (ESI) m/z 497 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{27}H_{24}N_2O_2F_3S$ 497.1511, found 497.1505.

*(3a,8a)-(9H-Fluoren-9-yl)methyl 5-methoxy-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**5r**).* Light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 45:55 mixture of rotamers, both reported) δ 7.79 (t, J = 8.0 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.61−7.56 (m, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.47−7.39 (m, 1H), 7.39−7.32 (m, 2H), 7.26 (t, J = 7.6 Hz, 1H), 6.82 (s, 0.45H), 6.72 (s, 0.55H), 6.76−6.68 (m, 1H), 6.58 (d, J = 8.8 Hz, 0.45H), 6.32 (d, J = 8.0 Hz, 0.55H), 5.62 (s, 0.45H), 5.07 (s, 0.55H), 4.70 (dd, J = 4.8 Hz, 4.4 Hz, 0.5H), 4.62 (dd, J = 4.8 Hz, 4.4 Hz, 0.5H), 4.45−4.36 (m, 1H), 4.26 (t, J = 4.4 Hz, 0.55H), 4.19 (t, J = 7.6 Hz, 0.45H), 3.74 (s, 1.35H), 3.70 (s, 1.65H), 3.69−3.65 (m, 1H), 3.15−3.09 (m, 0.45H), 2.96 (dt, J = 10.8 Hz, 6.0 Hz, 0.55H), 2.57 (t, J = 8.0 Hz, 1H), 2.45−2.32 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca. 1:1 mixture of rotamers, both reported) δ −36.5 (s), −36.8 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 154.5, 154.1, 153.9, 153.6, 144.0, 143.9, 143.8, 143.7, 143.0, 142.6, 141.7, 141.3, 141.2, 129.7 (q, J = 310.5 Hz), 129.6 (q, J = 310.3 Hz), 127.9, 127.8, 127.4, 127.3, 127.1, 126.8, 125.0, 124.9, 124.4, 120.2, 120.2, 120.0, 116.5, 116.4, 111.5, 110.8, 110.2, 110.0, 82.1, 81.5, 67.4, 66.5, 63.6, 63.0, 56.0, 47.3, 47.2, 44.8, 44.7, 36.8, 36.5; IR (KBr) υ_{max} 3398, 2952, 2889, 1699, 1494, 1417, 1349, 1112, 740 cm^{-1}; MS (ESI) m/z 513 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{27}H_{24}N_2O_3F_3S$ 513.1460, found 513.1454.

*General Procedure for Boron Trifluoride Etherate Mediated Eletrophilic Trifluoromethananesulfanylation of Tryptamine Derivatives with N-[(Trifluoromethyl)thio]aniline **3**.* To a solution of compound **3** (0.24 mmol) in dichloromethane (2 mL) were added the indicated indolic substrate (0.2 mmol) and then $BF_3{\cdot}OEt_2$ (0.5 mmol). The reaction mixture was stirred at room temperature for 24 h. Additional $BF_3{\cdot}OEt_2$ (0.5 mmol) was added dropwise, and the reaction was stirred for another 24 h until the indolic substrate disappeared by TLC monitoring. Then the organic phase was washed with saturated $NaHCO_3$ solution and then dried over sodium sulfate. After removing the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) to afford the corresponding uncyclized product.

*Methyl 2-(2-(trifluoromethylthio)-1H-indol-3-yl)ethylcarbamate (**6a**).* White solid: mp 120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 6.9 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 4.82 (s, 1H), 3.67 (s, 3H), 3.49 (q, J = 6.3 Hz, 2H), 3.13 (t, J = 7.2 Hz, 2H); ^{19}FNMR (282 MHz, $CDCl_3$) −42.2 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 157.2, 137.6, 128.4(q, J = 312.2 Hz), 127.1, 124.9, 124.0, 120.4, 119.9, 113.9, 111.4, 52.1, 41.3, 25.4; IR (KBr) υ_{max} 3407, 3299, 2950, 1707, 1527, 1131, 1109, 745 cm^{-1}; MS (ESI) m/z 319 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{13}H_{14}N_2O_2F_3S$ 319.0728, found 319.0723.

*Benzyl 2-(2-(trifluoromethylthio)-1H-indol-3-yl)ethylcarbamate (**6h**).* Light yellow solid: mp 117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.37−7.24 (m, 7H), 7.13 (t, J = 7.5 Hz, 1H), 5.11 (s, 2H), 4.86 (s, 1H), 3.50 (q, J = 6.6 Hz, 2H), 3.14 (t, J = 6.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) −43.3 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 156.4, 137.6, 136.5, 128.5, 128.4 (q, J = 316.2 Hz), 128.1, 127.2, 124.9, 124.0, 120.5, 120.0, 113.9, 111.4, 66.7, 41.4, 25.4. IR (KBr) υ_{max} 3413, 3299, 2950, 1704, 1519, 1131, 1109, 745 cm^{-1}; MS (ESI) m/z 395 (M + H)$^+$, 412 (M + NH_4)$^+$, 417 (M + Na)$^+$, 433 (M + K)$^+$; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{19}H_{17}N_2O_2F_3SNa$ 417.0861, found 417.0855.

dx.doi.org/10.1021/jo3013385 | J. Org. Chem. 2012, 77, 7538−7547

*(3a,8a)-3a-(Trifluoromethylthio)-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]indole (**7j**).* To a solution of compound **5j** (825 mg, 1.7 mmol) in acetomitrile (5 mL) was added piperidine (0.34 mL, 3.4 mmol). The reaction mixture was stirred at room temperature for 10 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (DCM:MeOH = 20:1) to give diamine **7j** (415 mg, Yield 94%) as clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 5.0 Hz, 1H), 7.08 (t, J = 6.9 Hz, 1H), 6.79−6.74 (m, 1H), 6.57−6.54 (m, 1H), 5.38 (s, 1H), 3.08 (t, J = 6.6 Hz, 1H), 2.79−2.70 (m, 1H), 2.50 (br, 2H), 2.34 (d, J = 12.3 Hz, 1H), 2.18−2.12 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −37.5 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 149.9, 129.8 (q, J = 309.9 Hz), 129.7, 127.8, 125.1, 119.4, 109.4, 85.7, 64.5, 44.9, 42.7; IR (KBr) υ_{max} 3395, 3257, 2967, 1608, 1484, 1312, 1115, 745 cm^{-1}; MS (ESI) m/z 261 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{11}H_{12}N_2F_3S$ 261.0673, found 261.0668.

*(3a,8a)-5-Methyl-3a-(trifluoromethylthio)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**7q**).* Using the same condition as described for compound **7j**, compound **7q** (52 mg, Yield 90%) was prepared as clear oil from compound **5q** (108 mg, 0.21 mmol), piperidine (65 μL, 0.65 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 7.5 Hz, 1H), 5.38 (s, 1H), 3.08 (dd, J = 11.4 Hz, 6.9 Hz, 1H), 2.75 (dt, J = 11.4 Hz, 4.8 Hz, 1H), 2.35 (dd, J = 12.3 Hz, 4.2 Hz, 1H), 2.19−2.04 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −38.1 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 147.7, 130.4, 129.9 (q, J = 309.9 Hz), 129.0, 128.2, 125.5, 109.7, 85.9, 64.8, 44.9, 42.6, 20.8; IR (KBr) υ_{max} 3255, 3054, 2970, 2881, 1608, 1484, 1107, 745 cm^{-1}; MS (EI) m/z 274 (M$^+$); HRMS (EI-TOF) m/z [M]$^+$ Calcd for $C_{12}H_{13}N_2F_3S$ 274.0752, found 274.0750.

*(3a,8a)-5-Methoxy-3a-(trifluoromethylthio)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**7r**).* Using the same condition as described for compound **7j**, compound **7r** (569 mg, Yield 86%) was prepared as clear oil from compound **5r** (1.17 g, 2.28 mmol), piperidine (0.45 mL, 4.57 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 5.39 (s, 1H), 3.77 (s, 3H), 3.2 (br, 2H), 3.10 (dd, J = 10.2 Hz, 7.5 Hz, 1H), 2.79 (dt, J = 10.8 Hz, 5.1 Hz, 1H), 2.36 (dd, J = 12.0 Hz, 4.5 Hz, 1H), 2.16 (dt, J = 10.8 Hz, 7.2 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −37.4 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 154.1, 143.8, 129.8 (q, J = 309.7 Hz), 129.5, 115.9, 111.0, 110.5, 86.3, 65.0, 55.9, 44.7, 42.3; IR (KBr) υ_{max} 3291(br), 2944, 2831, 1495, 1213, 1113, 1032 cm^{-1}; MS (ESI) m/z 291 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{14}F_3N_2OS$ 291.0779, found 291.0773.

*(3a,8a)-(9H-Fluoren-9-yl)methyl 8-methyl-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**8j**).* To a solution of compound **5j** (24 mg, 0.05 mmol) in acetonitrile (1 mL) were added HOAc (14 μL, 0.25 mmol) and formalin (HCHO aq, 37%) (19 μL, 0.25 mmol). The mixture was stirred at room temperature for 10 min and then cooled to 0 °C. $NaBH_3CN$ (13 mg, 0.20 mmol) was added in portions, and the reaction mixture was returned to room temperature by stirring 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted by EtOAc. The organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 10:1) on silica gel to give compound **8j** as clear oil (19 mg) in 75% yield: ^{1}H NMR (300 MHz, $CDCl_3$) (ca.1:1 mixture of rotamers, both reported) δ 7.77 (d, J = 6.9 Hz, 2H), 7.63−7.58 (m, 2H), 7.43−7.31 (m, 4H), 7.19 (d, J = 6.0 Hz, 1H), 7.12 (d, J = 6.6 Hz, 1H), 6.76−6.66 (m, 1H), 6.44 (d, J = 7.2 Hz, 0.5H), 6.30 (d, J = 7.2 Hz, 0.5H), 5.79 (s, 0.5H), 5.21 (s, 0.5H), 4.84 (d, J = 9.9 Hz, 0.5H), 4.63 (d, J = 9.9 Hz, 0.5H), 4.48 (s, 1H), 4.27 (s, 1H), 3.93 (t, J = 8.4 Hz, 0.5H), 3.81 (t, J = 9.0 Hz, 0.5H), 3.04 (s, 2.0H), 3.14−3.00 (m, 0.5H), 2.48−2.38 (m, 1H), 2.36 (s, 1.5H), 2.35−2.30 (m, 0.5H), 2.24−2.14 (m, 0.5H); ^{19}F NMR (282 MHz, $CDCl_3$) (ca.1:1 mixture of rotamers, both reported) δ −37.1 (s), −37.4 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.1, 154.3, 150.9, 150.7, 144.0, 143.9, 143.6, 141.7, 141.4, 130.6, 130.5, 129.4 (q, J = 317.3 Hz), 127.8, 127.2, 126.2, 126.0, 125.0, 124.9, 124.5, 124.3, 120.1, 118.2, 107.0, 106.7, 87.9, 87.5, 67.4, 66.8, 62.9, 62.1, 47.3, 44.7, 44.4, 38.7, 38.6, 33.5, 32.1; IR (KBr) υ_{max} 3065, 2952, 2889, 1708, 1607, 1493, 1115, 739 cm^{-1}; MS (ESI) m/z 497 (M + H)$^+$; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{27}H_{24}N_2O_2F_3S$ 497.1511, found 497.1505.

*(3a,8a)-(9H-Fluoren-9-yl)methyl 5-methoxy-8-methyl-3a-(trifluoromethylthio)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1(2H)-carboxylate (**8r**).* Using the same condition as described for compound **8j**, compound **8r** (21 mg, Yield 80%) was prepared as clear oil from compound **5r** (25.5 mg, 0.05 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) (ca. 1:1 mixture of rotamers, both reported) δ 7.72 (d, J = 6.4 Hz, 2H), 7.60−7.54 (m, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 6.81 (s, 0.5H), 6.74 (s, 0.5H), 6.75 (d, J = 8.4 Hz, 0.5H), 6.69 (d, J = 8.4 Hz, 0.5H), 6.36 (d, J = 8.4 Hz, 0.5H), 6.22 (d, J = 8.4 Hz, 0.5H), 5.75 (s, 0.5H), 5.17 (s, 0.5H), 4.81 (dd, J = 10.0 Hz, 3.6 Hz, 0.5H), 4.59 (dd, J = 10.0 Hz, 3.6 Hz, 0.5H), 4.50−4.42 (m, 1H), 4.21 (t, J = 4.8 Hz, 1H), 3.89 (t, J = 10.6 Hz, 0.5H), 3.81−3.74 (m, 0.5H), 3.71 (s, 1.5H), 3.67 (s, 1.5H), 3.10−3.04 (m, 0.5H), 3.00 (s, 1.5H), 2.93−2.86 (m, 0.5H), 2.42−2.38 (m, 0.5H), 2.33 (s, 1.5H), 2.30−2.24 (m, 1H), 2.13 (q, J = 8.8 Hz, 0.5H); ^{19}F NMR (376.4 MHz, $CDCl_3$) (ca. 1:1 mixture of rotamers, both reported) δ −37.4 (s), −37.7 (s); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.0, 154.2, 153.2, 145.4, 145.2, 144.0, 143.8, 143.8, 143.5, 141.6, 141.4, 129.5 (q, J = 310.0 Hz), 127.8, 127.5, 127.2, 127.1, 125.0, 124.9, 124.5, 120.1, 120.0, 116.0, 110.5, 108.2, 108.0, 88.8, 88.4, 67.3, 66.7, 63.0, 62.2, 56.0, 47.3, 44.7, 44.4, 38.6, 38.4, 34.7, 33.5; IR (KBr) υ_{max} 3068, 2950, 2892, 2831, 1708, 1500, 1115, 757, 740 cm^{-1}; MS (MALDI) m/z 526 (M$^+$); HRMS (MALDI-TOF) m/z [M]$^+$ Calcd for $C_{28}H_{25}N_2O_3F_3S$ 526.1538, found 526.1533.

*(3a,8a)-8-Methyl-3a-(trifluoromethylthio)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**9j**).* To a solution of compound **8j** (135 mg, 0.27 mmol) in acetomitrile (3 mL) was added piperidine (54 μL, 0.54 mmol). The reaction mixture was stirred at room temperature for 10 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 1:1) to give compound **9j** (70 mg, 96%) as clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 6.8 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.37 (d, J = 7.6 Hz, 1H), 5.14 (s, 1H), 3.12 (dd, J = 11.6 Hz, 7.2 Hz, 1H), 2.89 (s, 3H), 2.69 (dt, J = 11.2 Hz, 5.6 Hz, 1H), 2.34 (dd, J = 12.4 Hz, 5.2 Hz, 1H), 2.23 (s, 1H), 2.11−2.06 (m, 1H); ^{19}F NMR (376.4 MHz, $CDCl_3$) δ −37.7 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 151.1, 129.9, 129.7 (q, J = 309.9 Hz), 127.4, 124.8, 117.3, 105.8, 92.3, 63.1, 45.1, 43.0, 32.0; IR (KBr) υ_{max} 3331, 2938, 2877, 1607, 1496, 1115, 741 cm^{-1}; MS (MALDI) m/z 275 (M + H)$^+$; HRMS (MALDI-TOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{14}N_2F_3S$ 275.0830, found 275.0824.

*(3a,8a)-5-Methoxy-8-methyl-3a-(trifluoromethylthio)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**9r**).* Using the same condition as described for compound **9j**, compound **9r** (1.30 g, 90% yield) was prepared as clear oil from compound **8r** (2.50 g, 4.74 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 6.33 (d, J = 8.8 Hz, 1H), 5.09 (s, 1H), 3.75 (s, 3H), 3.12 (ddd, J = 11.6 Hz, 7.2 Hz, 1.6 Hz, 1H), 2.86 (s, 3H), 2.60 (br, 1H), 2.76−2.69 (m, 1H), 2.32 (ddd, J = 12.8 Hz, 5.2 Hz, 1.6 Hz, 1H), 2.12−2.04 (m, 1H); ^{19}F NMR (376.4 MHz, $CDCl_3$) δ −37.7 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 152.6, 145.7, 129.5 (q, J = 309.6 Hz), 128.8, 115.4, 111.3, 107.0, 93.2, 63.2, 56.0, 45.1, 42.7, 33.4; IR (KBr) υ_{max} 3337, 2938, 2877, 2825, 1500, 1278, 1217, 1115 cm^{-1}; MS (MALDI) m/z 304 (M$^+$); HRMS (MALDI-TOF) m/z [M]$^+$ Calcd for $C_{13}H_{15}N_2F_3SO$ 304.0857, found 304.0852.

*(3a,8a)-1,8-Dimethyl-3a-(trifluoromethylthio)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**10j**).* To a solution of compound **9j** (40 mg, 0.146 mmol) in methanol (5 mL) was added formalin (HCHO aq, 37%) (55 μL, 0.729 mmol). The mixture was stirred at 0 °C for 10 min, and then $NaBH(OAc)_3$ (155 mg, 0.729 mmol) was added in portions, and the reaction mixture was returned to room temperature by stirring 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted by EtOAc. The organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 10:1) on silica gel to give

dx.doi.org/10.1021/jo3013385 | J. Org. Chem. 2012, 77, 7538−7547

compound **10j** as a clear oil (40 mg) in 95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.15 (m, 2H), 6.76 (t, J = 7.2 Hz, 1H), 6.50 (d, J = 7.8 Hz, 1H), 4.81 (s, 1H), 3.00 (s, 3H), 2.81 (dt, J = 4.8 Hz, 3.6 Hz, 1H), 2.57 (s, 3H), 2.59−2.51 (m, 1H), 2.30−2.25 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −38.5 (s, 3F); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 152.1, 129.9, 129.3 (q, J = 310.0 Hz), 124.5, 118.2, 107.7, 96.7, 62.3, 50.9, 40.2, 37.3, 36.9; IR (KBr) υ_{max} 2964, 2931, 2866, 2796, 1606, 1490, 1111, 741 cm^{-1}; MS (EI) m/z 288 (M^+); HRMS (EI-TOF) m/z $[M]^+$ Calcd for $C_{13}H_{15}N_2F_3S$ 288.0908, found 288.0903.

*(3a,8a)-5-Methoxy-1,8-dimethyl-3a-(trifluoromethylthio)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (**10r**).* Using the same condition as described for compound **10j**, compound **10r** (47 mg, 90% yield) was prepared as clear oil from compound **9r** (50 mg, 0.164 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (d, J = 2.8 Hz, 1H), 6.74 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 6.33 (d, J = 8.8 Hz, 1H), 5.09 (s, 1H), 3.75 (s, 3H), 3.12 (ddd, J = 11.6 Hz, 7.2 Hz, 1.6 Hz, 1H), 2.86 (s, 3H), 2.60 (br, 1H), 2.76−2.69 (m, 1H), 2.32 (ddd, J = 12.8 Hz, 5.2 Hz, 1.6 Hz, 1H), 2.12−2.04 (m, 1H); ^{19}F NMR (376.4 MHz, $CDCl_3$) δ −37.3 (s, 3F). The ^{13}C NMR and MS of compound **10r** were not given because of its instability.

Biological Assay. All the cell lines were originally obtained from the American Type Culture Collection (ATCC, Manassas, VA) and were cultured in DMEM medium (HeLa) or RIPM1640 (L929, K562) with 10% FBS and supplemented with 1% P/S (penicillin/streptomycin). Cell Counting Kit-8 (CK-04) was bought from Dojindo (Kumamoto, Japan) for the Cytotoxicity Assay. All compounds tested were dissolved in DMSO to a concentration of 0.5, 5, 50 mM. The DMSO concentration is ≤0.04%. Cytotoxicity of the above compounds to the three cell lines was determined using the Cell Counting Kit-8 (CCK-8). In brief, 4 × 10^3 cells (per well) were seeded in 96-well plates and were treated for 48 h with the compounds in Table 4 at concentrations of 0, 0.5, 5, 50 μM (arranged triplicate). After 48 h of treatment, 10 μL of CCK-8 solution (Dojindo) were added to each well. Plates were incubated for an additional 2−4 h at 37 °C, after which the absorbance at 450 nm was recorded using a SpectraMax190 microplate reader (Molecular Devices, USA) to calculate the inhibition rate.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data of tryptamine derivatives **4**, and copies of ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra of all the new compounds. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

National Natural Science Foundation of China (21072028, 20832008) and National Basic Research Program of China (2012CB21600) are greatly acknowledged for funding this work.

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