Nucleophilic substitution reactions on indole nucleus: Formation of (3a,8a-cis)-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-b]indoles having a substituent at the 3a-position

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journal or publication title	Heterocycles
volume	95
number	2
page range	844-861
year	2017-12-13
URL	http://doi.org/10.24517/00049644

doi: 10.3987/COM-16-S(S)53

HETEROCYCLES, Vol. , No. , , pp. -. © The Japan Institute of Heterocyclic Chemistry
Received, , Accepted, , Published online, .
DOI: 10.3987/COM- (Please do not delete.)

NUCLEOPHILIC SUBSTITUTION REACTIONS ON INDOLE NUCLEUS: FORMATION OF (3a,8a-*cis*)-1,2,3,3a,8,8a-HEXAHYDROPYRROLO-[2,3-*b*]INDOLES HAVING A SUBSTITUENT AT THE 3a-POSITION[1,#]

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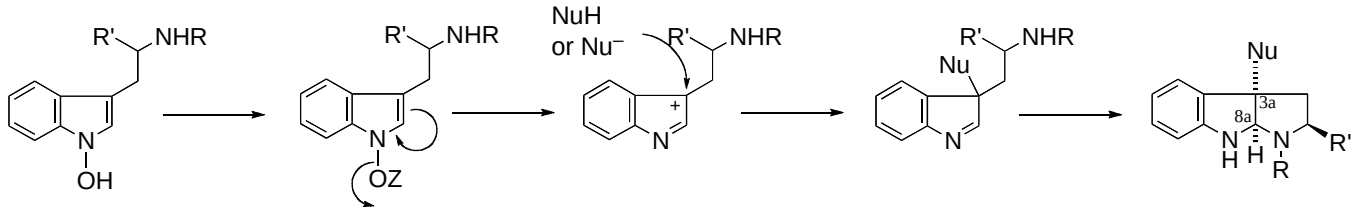
Abstract – Various nucleophiles, such as indole, 1,2,3-trimethoxybenzene, anisole, phenol, and pyrrole, reacted with 1-hydroxy-*N*b-trifluoroacetyltryptamine under the presence of mesyl chloride to give novel series of (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles having a substituent at the 3a-position. Their structures and by-products were strictly determined.

INTRODUCTION

We have opened the door to the chemistry of 1-hydroxyindole and 1-hydroxytryptophan derivatives,[3] and demonstrated that these compounds generally undergo nucleophilic substitution reaction,[4] which was thus far rarely observed in indole chemistry.[4]

In our 1-hydroxyindole hypothesis,[5] we assume the 1-hydroxy group of the general formula (**A**) in Scheme 1 departs, after being transformed to a good leaving group (**B**), leaving a resonance stabilized indolyl cation[6] (**C**). It would be possible to trap it with suitable nucleophiles to give imine[6] (**D**).



R,R',Z = an appropriate substituent

Scheme 1

NuH or Nu⁻ = nucleophiles

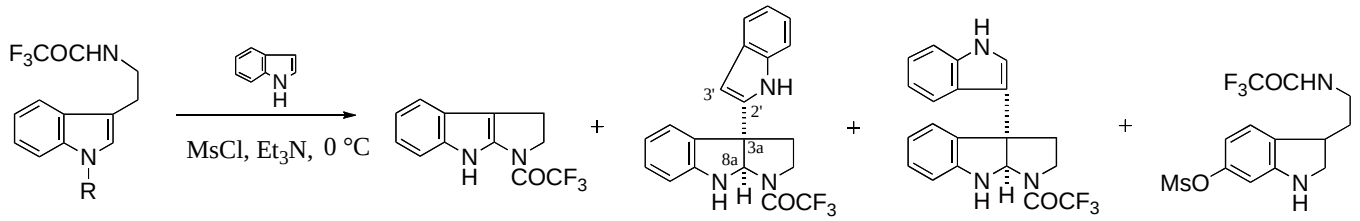
Dedicated to the 70th birthday of Professor Dr. Masakatsu Shibasaki

Subsequent cyclization of *N*b-nitrogen on the side chain results in providing simple and novel methodology for the preparation of (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles (**E**) having an employed nucleophile at the 3a-position. According to the idea, we first employed indole as a nucleophile and reported the result as the previous communication.[7] This is its full report together with the results of additionally examined nucleophiles such as 1,2,3-trimethoxybenzene, anisole, phenol, and pyrrole.

RESULTS AND DISCUSSION

I. Reaction of 1-hydroxy-*N*b-trifluoroacetyltryptamine (2) with indole

*N*b-Trifluoroacetyltryptamine (**1**, Scheme 2) was converted to 1-hydroxy-*N*b-trifluoroacetyltryptamine (**2**) by our 1-hydroxyindole synthetic method.[3] Then, **2** was reacted with mesyl chloride (MsCl) in 1,2-dichloroethane in the presence of indole (3 mol eq) and trimethylamine (Et_3N) at 0 °C (Table 1, Entry 3). As expected, smooth reaction occurred to provide 1,2,3,8-tetrahydro-1-trifluoroacetylpyrrolo[2,3-*b*]-indole[8,9] (**3**), (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-(indol-2-yl)- (**4**), -3a-(indol-3-yl)-1-trifluoro-acetylpyrrolo[2,3-*b*]indole (**5**), and 6-mesyloxy-*N*b-trifluoroacetyltryptamine[8,9] (**6**), in 13, 5, 11, and 3%



1: R=H, **2**: R=OH **3** **4** **5** **6**

Scheme 2

yields, respectively.

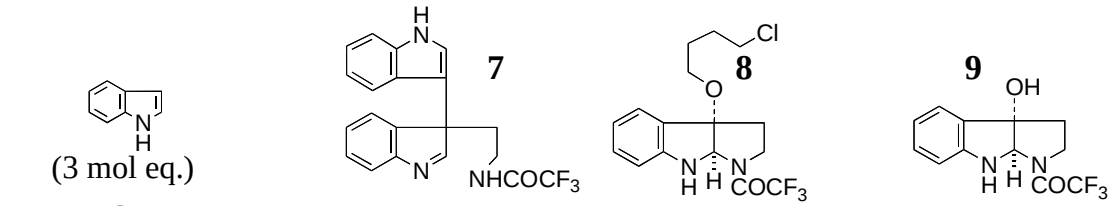
With an attempt to improve the product yield of nucleophilic reaction and examine solvent effect, 1,2-dichloroethane was changed to benzene, $CHCl_3$, THF, DMF, MeCN, MeNHCHO, and EtOAc. The product and their distribution ratio variably changed and their results are summarized in Table 1.

When the reaction was carried out in $CHCl_3$ (Entry 2), the yield of **5** was improved to 21% together with the formations of **3**, **4**, and **6** in the respective yields of 14, 5, and 4%. Under similar reaction conditions, the use of excess indole (10 mol eq., Entry 8) further raised the yield of **5** up to 30% in addition to the concomitant formations of **3**, **4**, and **6** in 4, 7, and 1% yields, respectively.

In the case of THF as the solvent, various products were formed (Entry 4). Thus, the reaction of **2** with MsCl in THF in the presence of indole (3 mol eq) and Et_3N at 0 °C gave **3**, **4**, **5**, **6,** 3*H*-3-(indol-3-yl)-*N*b-trifluoroacetyltryptamine (**7**), and (3a,8a-*cis*)-3a-(4-chlorobutoxy)-1,2,3,3a,8,8a-hexahydro-1-tri-fluoroacetylpyrrolo[2,3-*b*]indole[9] (**8**), in 28, 6, 15, 5, 4, and 6% yields, respectively. From the results shown in Table 1, we found that solvent polarity has no effect for the preferred product formation, though

MeNHCHO produced (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-hydroxy-1-trifluoroacetylpyrrolo[2,3-*b*]indole (**9**) as a major product (Entry 7).

Table 1. Solvent effect on the product formation and distribution



Entry	Solvent (ε)	Yield (%) of **3**	**4**	**5**	**6**	**7**	**8**	**9**
1	benzene (2)	18	0	4	0	4	0	0
2	$CHCl_3$ (4.8)	14	5	21	4	0	0	0
3	$ClCH_2CH_2Cl$ (25)	13	5	11	3	0	0	0
4	THF (30)	28	6	15	5	4	6	0
5	DMF (37)	30	1	7	2	0	0	0
6	MeCN (38)*	10	1	8	0	0	0	0
7	MeNHCHO (182)	2	1	4	0	0	0	20
	2 → Indole (10 mol eq.), MsCl, Et_3N → Entries 8—10							
8	$CHCl_3$ (4.8)	4	7	30	1	0	0	0
9	$ClCH_2CH_2Cl$ (25)	8	5	18	2	0	0	0
10	EtOAc (30)	6	7	25	3	0	0	0

* **1** was obtained in 6% yield.

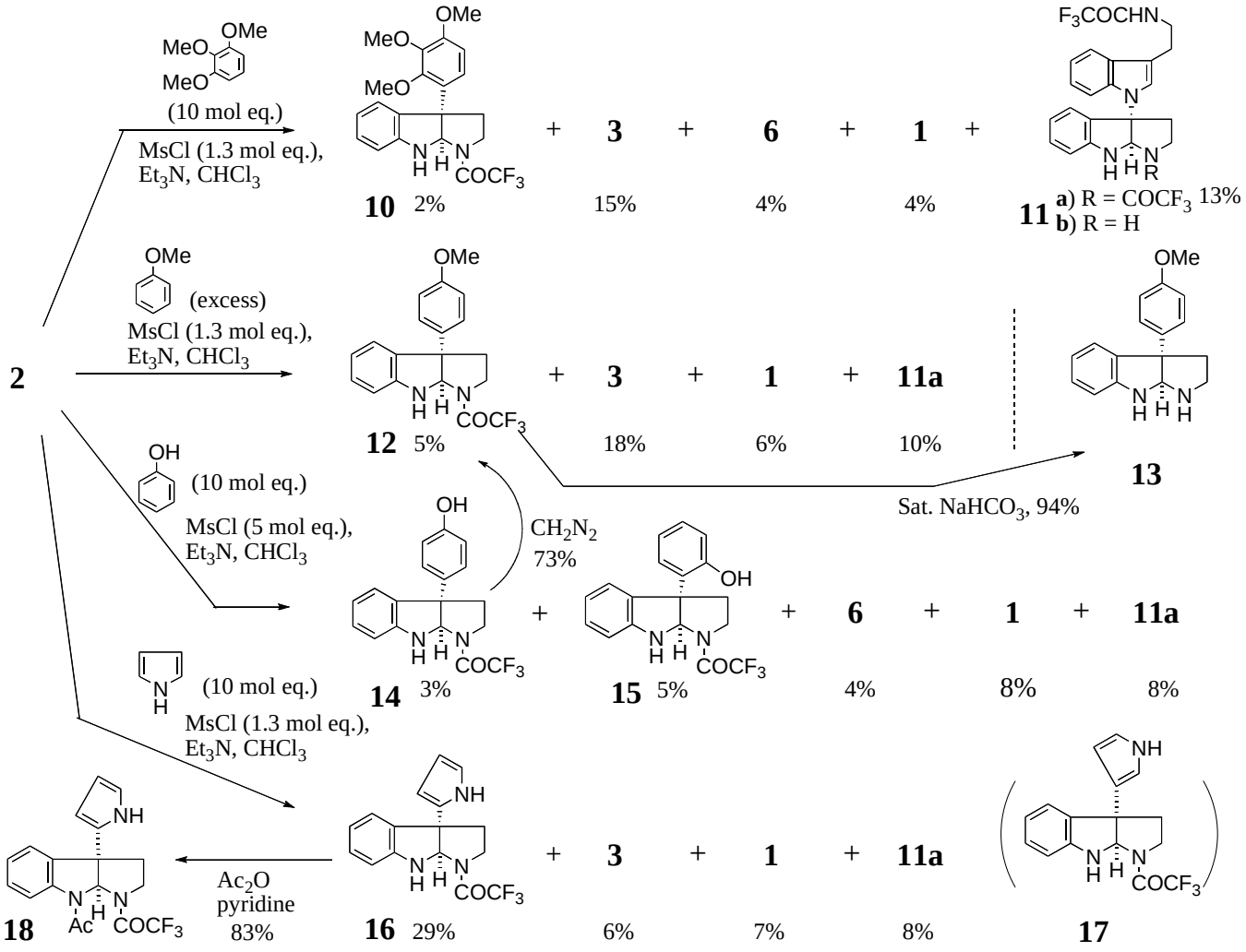
II. Reaction of 1-hydroxy-*N*b-trifluoroacetyltryptamine (2) with nucleophiles

We next examined aromatic electron rich nucleophiles. When 1,2,3-trimethoxybenzene (10 mol eq.) was employed in the reaction of **2** with MsCl in $CHCl_3$ in the presence of Et_3N (Scheme 3), (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetyl-3a-(2,3,4-trimethoxyphenyl)pyrrolo[2,3-*b*]indole (**10**), **3**, **6**, **1**, and (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetyl-3a-[3-(*N*b-trifluoroacetyl)aminoethylindol-1-yl]pyrrolo[2,3-*b*]indole (**11a**) were formed in 2, 15, 4, 4, and 13% yields, respectively. Further treatment of **11a** with $NaHCO_3$ afforded **11b** in 67% yield.

Under similar reaction conditions with anisole as a nucleophile, (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-(4-methoxyphenyl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (**12**), **3**, **1**, and **11a** were isolated in the

respective yields of 5, 18, 6, and 10%. **12** was easily converted to (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-(4-methoxyphenyl) pyrrolo[2,3-*b*]indole (**13**) in 94% yield by the treatment with aq. $NaHCO_3$.

In the case of employing phenol as a nucleophile, (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-(4-hydroxyphenyl)- (**14**) and -3a-(2-hydroxyphenyl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (**15**) were produced in addition to **6**, **1**, and **11a** in 3, 5, 4, 8, and 8% yields, respectively. The compound **14** was derived to **12** in 73% yield by the reaction with CH_2N_2.



Scheme 3

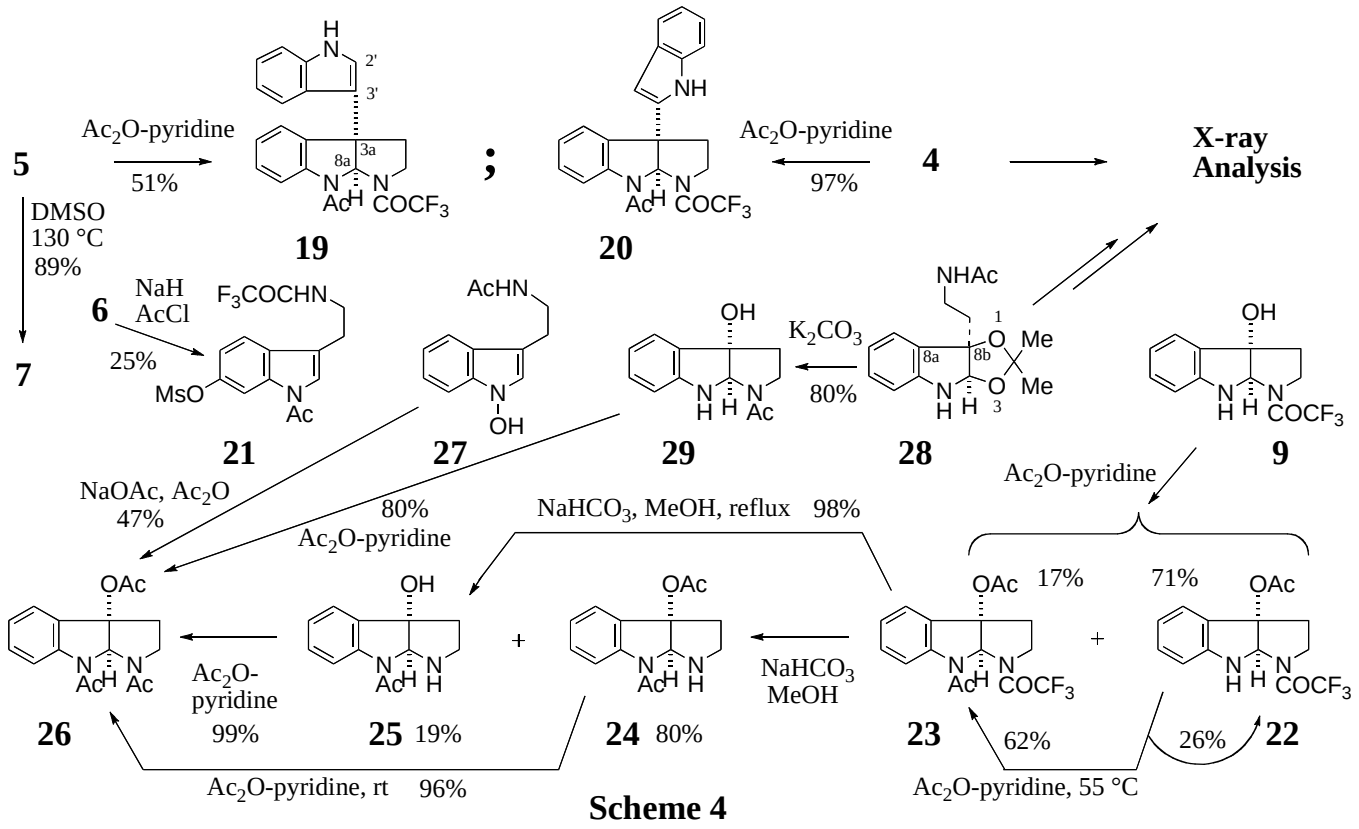
Since pyrrole is a good nucleophile, expected product, (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-(pyrrol-2-yl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (**16**), was obtained in rather better yield (29%) compared to the above products (**10**–**12**, **14**, **15**) together with **3**, **1**, and **11a** in 6, 7, and 8% yields, respectively. Formation of the other expected isomer, pyrrol-3-yl isomer (**17**), was not detected at all. Treatment of **16** with Ac_2O-pyridine afforded (3a,8a-*cis*)-8-acetyl-1,2,3,3a,8,8a-hexahydro-3a-(pyrrol-2-yl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (**18**) in 83% yield.

III. Structural determination of products (Scheme 4)

Structures of various products reported in the above sections were determined spectroscopically. In cases where spectroscopically more than two structures were possible candidates, the product was led to suitable derivative which could prove its structure.

The high resolution MS and other spectral data of **4** and **5** show the presence of an extra indole moiety in both molecules. In the ^{1}H-NMR spectra, **4** and **5** show characteristic C-(8a) proton signal at δ5.63 and 5.92, respectively, proving the presence of hexahydropyrrolo[2,3-*b*]indole skeleton. In addition, **5** has a long-range coupled doublet proton (*J*=2.5 Hz) at δ6.93 and is assigned to be C(2')-proton, which is unusually shielded compared to the usual indole C(2)-proton.[10,11] In the spectrum of **4**, a double doublets proton (*J*=2.2 and 0.7 Hz) resonates at δ6.48, which is attributed to the C(3')-proton. The structures of **4** and **5** were further confirmed by treating them with Ac_2O and pyridine to provide the acetyl derivatives (**20** and **19**) in the respective yields of 97 and 51% (Scheme 4). From these data, **4** and **5** were deduced to be indol-2-yl and indol-3-yl isomers, respectively.

Repeated recrystallization of **4** formed suitable prisms for X-ray single crystallographic analysis and the structure was determined unequivocally as shown in Figure 1. Since the indol-2-yl structure of **4** is established, then it determines that the other isomer (**5**) is the indol-3-yl isomer. The preferred formation of **5** to **4** is in accord with the well-known positional order 3>2 for the reactivity of unsubstituted indole.



Scheme 4

The structure of **6** was proved as reported in the previous paper[9] by converting it to 1-acetyl-6-mesyloxy-*N*b-trifluoroacetyltryptamine (**21**) in 25% yield by the treatment with NaH-AcCl. The compound (**7**) has a ring opened structure of **5**. It was proved by isolating **7** in 89% yield when **5** was heated in DMSO at 130 °C.

To establish the structure of **9**, it was converted to the common compound for structural determination by series of reactions. First, **9** was led to (3a,8a-*cis*)-3a-acetoxy- (**22**) and -8-acetyl-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetylpyrrolo[2,3-*b*]indole (**23**) in 71 and 17% yields, respectively, by the reaction with Ac_2O-pyridine at rt. Treatment of **22** with Ac_2O-pyridine at 55 °C afforded **23** in 62% yield together with 26% yield of recovery. Hydrolysis of trifluoroacetyl group of **23** with aq. $NaHCO_3$ at rt provided (3a,8a-*cis*)-3a-acetoxy-8-acety-1,2,3,3a,8,8a-hexahydro- (**24**) and (3a,8a-*cis*)-8-acety-1,2,3,3a,8,8a-hexahydro-3a-hydroxypyrrolo[2,3-*b*]indole (**25**) in 80 and 19% yields, respectively. At the reflux conditions **23** gave 98% yield of **25**. Treatment of both **24** and **25** with Ac_2O-pyridine at rt furnished (3a,8a-*cis*)-3a-acetoxy-1,8-diacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**26**) in the respective yields of 99 and 96%.

On the other hand, **26** was obtained from **27**[3,4] by the treatment with Ac_2O-NaOAc. Aside from this, **26** was produced by the treatment with Ac_2O-pyridine in 80% yield from (3a,8a-*cis*)-1-acetyl-1,2,3,3a,8,8a-hexahydro-3a-hydroxypyrrolo[2,3-*b*]indole (**29**), which was derived in 80% yield from 8b-(2-acetyl-aminoethyl)-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*b*]indole (**28**) by the treatment with K_2CO_3. Since the structure of a derivative of **28** is determined by X-ray single crystallographic analysis as reported in our previous paper,[12] the structure of common compound (**26**) is established.

In conclusion, 1-hydroxy-*N*b-trifluoroacetyltryptamine is a suitable starting material for obtaining novel type of (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indoles carrying aromatic and/or heteroaromatic substituent at the 3a position. Among this family members are core structures of Leptosins A–F,[13] which are cytotoxic substances against P-388 lymphocytic leukemia cell line comparable to that of mytomycin C. Therefore, we expect that compounds shown in this paper would have a useful biological activity.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra with a Shimadzu IR-420, a Shimadzu IR-460, and a Horiba FT-720 spectrophotometer and proton nuclear magnetic resonance (^{1}H-NMR) spectra with a JEOL JNM-GSX 500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study. The solution of diazomethane (CH_2N_2) in diethylether (Et_2O) was prepared as follows: a solution of potassium hydroxide (KOH) (5.50 g, 98.0

mmol) in H_2O (8.0 mL) was placed in a 500 mL round bottom flask and cooled in an ice bath. The 95% EtOH (25 mL), Et_2O (60.0 mL), and *p*-tolylsulfonylmethylnitrosoamide (21.5 g, 100 mmol) were added and the whole was slowly distilled to give the Et_2O solution including about 3 g of CH_2N_2. Anhydrous *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), and $CHCl_3$ were prepared by distillation over calcium hydride, sodium, and calcium chloride, respectively.

Reaction of 1-hydroxy-*N*b-trifluoroacetyltryptamine (2) with indole as a nucleophile: 1,2,3,8-Tetrahydro-1-trifluoroacetylpyrrolo[2,3-*b*]indole (3), (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-(indol-2-yl)-1-trifluoroacetyl- (4), -3a-(indol-3-yl)-1-trifluoroacetyl- (5), (3a,8a-*cis*)-3a-(4-chloro-butoxy)-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetylpyrrolo[2,3-*b*]indole (8), 6-mesyloxy-*N*b-trifluo-roacetyltryptamin (6), 3*H*-3-(indol-3-yl)-*N*b-trifluoroacetyltryptamine (7) from 2 — [Table 1, Entry 4]: A solution of MsCl (232.9 mg, 1.99 mmol) in anhydrous THF (2.0 mL) was added to a solution of **2** (419.9 mg, 1.54 mmol) and indole (542.6 mg, 4.73 mmol) in anhydrous THF (14.0 mL) and Et_3N (1.6 mL, 11.5 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 successively with $CHCl_3$–hexane (1:1, v/v), $CHCl_3$, $CHCl_3$–MeOH (95:5, v/v), EtOAc–hexane (1:5, v/v), and EtOAc–hexane (1:2, v/v) to give **3** (107.7 mg, 28%), **8** (31.9 mg, 6%), **4** (31.4 mg, 6%), **5** (86.3 mg, 15%), **7** (23.4 mg, 4%), and **6** (29.4 mg, 5%) in the order of elution. **3**: mp 238.0—240.0 °C (decomp., colorless plates, recrystallized from CH_2Cl_2–hexane). IR (KBr): 3370, 1670, 1446, 1351, 1278, 1233, 1203, 1139, 1069, 746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (2H, t, *J*=7.4 Hz), 4.71 (2H, t, *J*=7.4 Hz), 7.15 (1H, dt, *J*=1.6, 6.9 Hz), 7.18 (1H, dt, *J*=1.6, 6.9 Hz), 7.36 (1H, dd, *J*=1.6, 6.9 Hz), 7.42 (1H, dd, *J*=1.6, 6.9 Hz), 9.11 (1H, br s). High resolution MS *m/z*: Calcd for $C_{12}H_9F_3N_2O$: 254.0666. Found: 254.0662. **4**: mp 223.0—225.0 °C (decomp., colorless prisms, recrystallized from $CHCl_3$). IR (KBr): 3365, 1676, 1605, 1482, 1465, 1453, 1205, 1183, 1179, 745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.60 (1/11H, dd, *J*=12.5, 5.6 Hz), 2.76 (10/11H, dd, *J*=12.5, 5.6 Hz), 2.81 (1/11H, td, *J*=12.5, 7.8 Hz), 2.93 (10/11H, td, *J*=12.5, 7.8 Hz), 3.34 (1/11H, td, *J*=12.5, 5.6 Hz), 3.45 (10/11H, td, *J*=12.5, 5.6 Hz), 4.10 (10/11H, m), 4.32 (1/11H, m), 4.54 (1/11H, s, disappeared on addition of D_2O), 5.30 (10/11H, s, disappeared on addition of D_2O), 5.63 (10/11H, s), 5.75 (1/11H, s), 6.48 (10/11H, dd, *J*=2.2, 0.7 Hz), 6.50 (1/11H, dd, *J*=2.2, 0.7 Hz), 6.76 (1/11H, d, *J*=7.6 Hz), 6.78 (10/11H, d, *J*=7.6 Hz), 6.83 (10/11H, dt, *J*=7.6, 1.0 Hz), 6.86 (1/11H, dt, *J*=7.6, 1.0 Hz), 7.07 (10/11H, dt, *J*=7.6, 1.0 Hz), 7.10 (10/11H, br d, *J*=7.6 Hz), 7.13 (10/11H, td, *J*=7.6, 1.0 Hz), 7.19 (10/11H, td, *J*=7.6, 1.0 Hz), 7.22 (10/11H, dd, *J*=7.6, 1.0 Hz), 7.07—7.24 (5/11H, m), 7.56 (10/11H, dd, *J*=7.6, 0.7 Hz), 7.58 (1/11H, dd, *J*=7.6, 0.7 Hz), 7.77 (1/11H, br s), 7.94 (10/11H, br s). High-resolution MS *m/z*: Calcd for $C_{20}H_{16}F_3N_3O$: 371.1246. Found: 371.1244.

5: colorless oil. IR (film): 3405, 1681, 1467, 1460, 1204, 1185, 1145, 744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.47—2.53 (1/6H, m), 2.64—2.70 (5/6H, m), 2.87—2.96 (1/6H, m), 3.02—3.11 (5/6H, m), 3.32—3.40 (1/6H, m), 3.45—3.52 (5/6H, m), 4.19 (5/6H, m), 4.30—4.36 (1/6H, m), 4.71 (1/6H, br s, disappeared on addition of D_2O), 5.25 (5/6H,br s, disappeared on addition of D_2O), 5.92 (5/6H, s), 6.00 (1/6H, br s), 6.90 (5/6H, d, *J*=2.5 Hz), 6.93 (1/6H, d, *J*=2.5 Hz), 7.06—7.12 (1/6H, m), 7.09 (5/6H, ddd, *J*=8.1, 7.1, 1.0 Hz), 7.12—7.26 (8/6H, m), 7.16 (5/6H, td, *J*=7.6, 1.2 Hz), 7.22 (5/6H, d, *J*=7.6 Hz), 7.36 (5/6H, d, *J*=8.1 Hz), 7.38 (1/6H, d, *J*=8.1 Hz), 7.39 (1/6H, d, *J*=8.1 Hz), 7.54 (5/6H, d, *J*=8.1 Hz), 8.02 (5/6H, br s), 8.05 (1/6H, br s). High-resolution MS *m/z*: Calcd for $C_{20}H_{16}F_3N_3O$: 371.1245. Found: 371.1246. **6:** mp 114.5—115.5 °C (colorless needles, recrystallized from CH_2Cl_2–hexane). IR (KBr): 3430, 3340, 1700, 1563, 1349, 1206, 1172, 1119, 976, 952, 870 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.04 (2H, t, *J*=6.6 Hz), 3.15 (3H, s), 3.67 (2H, q, *J*=6.6 Hz), 6.37 (1H, br s), 7.05 (1H, d, *J*=8.8 Hz), 7.11 (1H, s), 7.37 (1H, s), 7.58 (1H, d, *J*=8.8 Hz), 8.26 (1H, br s). High resolution MS *m/z*: Calcd for $C_{13}H_{13}F_3N_2O_4S$: 350.0547. Found: 350.0539. **7**: very pale yellow oil. IR (film): 3402, 1709, 1213, 1180, 1167, 746 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.00 (2H, tm, *J*=8.1 Hz), 3.39—3.41 (2H, m), 7.02 (1H, ddd, *J*=8.0, 7.0, 1.1 Hz), 7.07 (1H, ddd, *J*=8.0, 7.0, 1.1 Hz), 7.11 (1H, ddd, *J*=8.0, 7.0, 1.1 Hz), 7.19 (1H, ddd, *J*=8.0, 7.0, 1.1 Hz), 7.38 (1H, d, *J*=8.0 Hz), 7.48 (1H, d, *J*=8.0 Hz), 7.55 (1H, d, *J*=8.0 Hz), 7.64 (1H, d, *J*=2.4 Hz), 7.72 (1H, d, *J*=8.0 Hz), 9.62 (1H, br t, *J*=5.6 Hz disappeared on addition of D_2O), 11.0 (1H, s), 11.5 (1H, br s, disappeared on addition of D_2O). High-resolution MS *m/z*: Calcd for $C_{20}H_{16}F_3N_3O$: 371.1245. Found: 371.1248. **8**: colorless oil. IR (film): 3370, 2940, 1694, 1612, 1486, 1471, 1255, 1206, 1145, 1101, 1066, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.69 (2H, m), 1.75—1.83 (2H, m), 2.34—2.41 (2/6H, m), 2.47—2.59 (10/6H, m), 3.15 (1H, dt, *J*=8.8, 6.4 Hz), 3.30 (1H, dt, *J*=8.8, 6.4 Hz), 3.36 (1H, dt, *J*=6,4, 11.2 Hz), 3.49 (2H, t, *J*=7.8 Hz), 3.95—3.98 (5/6H, m), 4.14—4.18 (1/6H, m), 5.52 (5/6H, s), 5.64 (1/6H, d, *J*=2.0 Hz), 6.65 (1H, d, *J*=7.8 Hz), 6.85 (1H, t, *J*=7.8 Hz), 7.22 (1H, t, *J*=7.8 Hz), 7.23 (1H, d, *J*=7.8 Hz). High resolution MS *m/z*: Calcd for $C_{16}H_{18}ClF_3N_2O_2$: 364.0978 and 362.1008. Found: 364.1003 and 362.1022.

[Entry 1] A solution of MsCl (67.0 mg, 0.59 mmol) in benzene (1.0 mL) was added to a solution of **2** (119.0 mg, 0.44 mmol) and indole (155.0 mg, 1.32 mmol) in benzene (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0°C for 1 h. After the same work-up and separation as described in Entry 4, **3** (19.9 mg, 18%), **5** (6.7 mg, 4%), and **7** (6.7 mg, 4%) were obtained in the order of elution.

[Entry 2] A solution of MsCl (73.4 mg, 0.64 mmol) in anhydrous $CHCl_3$ (1.0 mL) was added to a solution of **2** (113.5 mg, 0.42 mmol) and indole (146.1 mg, 1.25 mmol) in anhydrous $CHCl_3$ (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0°C for 1 h. After the same work-up and separation as described in Entry 4, **3** (15.2 mg, 14%), **4** (7.1 mg, 5%), **5** (33.1 mg, 21%), and **6** (5.7 mg,

4%) were obtained in the order of elution.

[Entry 3] A solution of MsCl (60.3 mg, 0.53 mmol) in anhydrous $ClCH_2CH_2Cl$ (1.0 mL) was added to a solution of **2** (111.6 mg, 0.41 mmol) and indole (143.7 mg, 1.23 mmol) in anhydrous $ClCH_2CH_2Cl$ (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After the same work-up and separation as described in Entry 4, **3** (13.8 mg, 13%), **4** (7.6 mg, 5%), **5** (16.4 mg, 11%), and **6** (3.8 mg, 3%) were obtained in the order of elution.

[Entry 5] A solution of MsCl (59.4 mg, 0.52 mmol) in anhydrous DMF (1.0 mL) was added to a solution of **2** (101.0 mg, 0.37 mmol) and indole (131.9 mg, 1.13 mmol) in anhydrous DMF (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After the same work-up and separation as described in Entry 4, **3** (28.2 mg, 30%), **4** (1.6 mg, 1%), **5** (9.8 mg, 7%), and **6** (1.9 mg, 2%) were obtained in the order of elution.

[Entry 6] A solution of MsCl (59.2 mg, 0.52 mmol) in MeCN (1.0 mL) was added to a solution of **2** (107.8 mg, 0.39 mmol) and indole (137.8 mg, 1.18 mmol) in MeCN (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After the same work-up and separation as described in Entry 4, **3** (10.0 mg, 10%), **4** (1.5 mg, 1%), **5** (12.2 mg, 8%), and **1** (5.8 mg, 6%) were obtained in the order of elution.

[Entry 7] A solution of MsCl (57.5 mg, 0.50 mmol) in anhydrous MeNHCHO (1.0 mL) was added to a solution of **2** (108.2 mg, 0.39 mmol) and indole (140.5 mg, 1.20 mmol) in anhydrous MeNHCHO (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After the same work-up and separation as described in Entry 4, **3** (1.7 mg, 2%), **4** (1.1 mg, 1%), **5** (4.4 mg, 4%), (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-3a-hydroxy-1-trifluoroacetylpyrrolo[2,3-*b*]indole (**9**) (21.2 mg, 20%), and unreacted **2** (22.0 mg, 20%) were obtained in the order of elution. **9**: mp 115.0—115.5 °C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3336, 3282, 1697, 1685, 1469, 1250, 1201, 1147, 750 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 120°C) δ: 2.14—2.53 (2H, m), 3.22—3.43 (1H, m), 3.84—4.03 (1H, m), 5.36 (1H, br s), 5.56 (1H, br s), 6.26 (1H, br s), 6.60 (1H, d, *J*=7.6 Hz), 6.69 (1H, br t, *J*=7.6 Hz), 7.06 (1H, t, *J*=7.6 Hz), 7.21 (1H, d, *J*=7.6 Hz). High-resolution MS *m/z*: Calcd for $C_{12}H_{11}F_3N_2O_2$: 272.0773. Found: 272.0772.

[Entry 8] A solution of MsCl (63.3 mg, 0.55 mmol) in anhydrous $CHCl_3$ (1.0 mL) was added to a solution of **2** (111.7 mg, 0.41 mmol) and indole (481.0 mg, 4.11 mmol) in anhydrous $CHCl_3$ (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After the same work-up and separation as described in Entry 4, **3** (4.4 mg, 4%), **4** (10.3 mg, 7%), **5** (46.1 mg, 30%), and **6** (1.9 mg, 1%) were obtained in the order of elution.

[Entry 9] A solution of MsCl (57.4 mg, 0.50 mmol) in anhydrous $ClCH_2CH_2Cl$ (1.0 mL) was added to a solution of **2** (103.8 mg, 0.38 mmol) and indole (444.7 mg, 3.80 mmol) in anhydrous $ClCH_2CH_2Cl$ (3.0

mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After the same work-up and separation as described in Entry 4, **3** (7.4 mg, 8%), **4** (7.3 mg, 5%), **5** (25.5 mg, 18%), and **6** (2.3 mg, 2%) were obtained in the order of elution.

[Entry 10] A solution of MsCl (59.3 mg, 0.52 mmol) in anhydrous EtOAc (1.0 mL) was added to a solution of **2** (111.7 mg, 0.41 mmol) and indole (479.8 mg, 4.10 mmol) in anhydrous EtOAc (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After the same work-up and separation as described in Entry 4, **3** (6.4 mg, 6%), **4** (11.1 mg, 7%), **5** (38.6 mg, 25%), and **6** (4.9 mg, 3%) were obtained in the order of elution.

7 from 5 — A solution of **5** (10.0 mg, 0.03 mmol) in DMSO (2.0 mL) was stirred at 130 °C for 3 h. After addition of H_2O and EtOAc, the organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1:5, v/v) to give **7** (8.9 mg, 89%).

(3a,8a-*cis*)-1,2,3,3a,8,8a-Hexahydro-1-trifluoroacetyl-3a-(2,3,4-trimethoxyphenyl)pyrrolo[2,3-*b*]indole (10), and (3a,8a-*cis*)-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetyl-3a-[3-(*N*b-trifluoroacetyl)-aminoethylindol-1-yl]pyrrolo[2,3-*b*]indole (11a) from 2 — A solution of MsCl (55.1 mg, 0.48 mmol) in anhydrous $CHCl_3$ (1.0 mL) was added to a solution of **2** (100.1 mg, 0.37 mmol) and 1,2,3-trimethoxybenzene (619.0 mg, 3.69 mmol) in anhydrous $CHCl_3$ (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 successively with $CHCl_3$–hexane (1:1, v/v), $CHCl_3$–MeOH (98:2, v/v), and EtOAc–hexane (1:5,v/v) to give **3** (14.2 mg, 15%), **10** (2.4 mg, 2%), **11a** (11.8 mg, 13%), **1** (4.0 mg, 4%), and **6** (5.4 mg, 4%) in the order of elution. **10**: colorless oil. IR (film): 1684, 1466, 1203, 1144, 1103, 752 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 120°C) δ: 2.36—2.58 (1H, m), 2.71—2.92 (1H, m), 3.19—3.34 (1H, m), 3.65 (3H, br s), 3.74 (3H, s), 3.77 (3H, s), 3.90—4.10 (1H, m), 5.86 (1H, br s), 6.37 (1H, br s), 6.61—6.70 (2H, m), 6.66 (1H, d, *J*=8.8 Hz), 6.87 (1H, d, *J*=8.8 Hz), 7.01 (1H, t, *J*=7.3 Hz), 6.99—7.10 (1H, m). High-resolution MS *m/z*: Calcd for $C_{21}H_{21}F_3N_2O_4$: 422.1453. Found: 422.1448. **11a**: colorless oil. IR (film): 1689, 1209, 1186, 1153, 752 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 120 °C) δ: 2.58—3.03 (4H, m), 3.27—3.47 (1H, m), 3.42 (2H, q, *J*=6.6 Hz), 4.02—4.12 (1H, m), 5.87 (1H, br s), 6.64—6.75 (3H, m), 7.00—7.07 (2H, m), 7.11 (1H, t, *J*=8.2 Hz), 7.16 (1H, t, *J*=8.2 Hz), 7.21 (1H, d, *J*=8.2 Hz), 7.26 (1H, d, *J*=8.2 Hz), 7.49 (1H, d, *J*=8.2 Hz), 8.96 (1H, br s). High-resolution MS *m/z*: Calcd for $C_{24}H_{20}F_6N_4O_2$: 510.1490. Found: 510.1486.

(3a,8a-*cis*)-1,2,3,3a,8,8a-Hexahydro-3a-[3-(*N*b-trifluoroacetyl)aminoethylindol-1-yl]pyrrolo[2,3-*b*]-indole (11b) from (11a) — Sat. aq. $NaHCO_3$ (2.0 mL, 2.1 mmol) was added to a solution of **11a** (25.3 mg, 0.05 mmol) in MeOH (4.0 mL) and the mixture was stirred at rt for 3 h. After addition of H_2O, the

whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil. Then H_2O layer was evaporated under reduced pressure to leave an oil. These oils were combined and column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **11b** (13.8 mg, 67%). **11b**: colorless oil. IR (film): 1709, 1213, 1182, 1161, 746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36—2.42 (1H, m), 2.61—2.70 (1H, m), 2.85 (2H, t, *J*=6.6 Hz), 2.94—3.02 (1H, m), 3.22—3.30 (1H, m), 3.48—3.60 (2H, m), 4.20 (1H, br s, disappeared on addition of D_2O), 5.31 (1H, s), 6.26 (1H, br s), 6.59 (1H, d, *J*=7.7 Hz), 6.64 (1H, s), 6.83 (1H, t, *J*=7.7 Hz), 7.11 (1H, t, *J*=7.7 Hz), 7.19 (1H, t, *J*=7.7 Hz), 7.24 (1H, t, *J*=7.7 Hz), 7.33 (1H, d, *J*=7.7 Hz), 7.38 (1H, d, *J*=7.7 Hz), 7.46 (1H, d, *J*=7.7 Hz). High-resolution MS *m/z*: Calcd for $C_{22}H_{21}F_3N_4O$: 414.1668. Found: 414.1647.

(3a,8a-*cis*)-1,2,3,3a,8,8a-Hexahydro-3a-(4-methoxyphenyl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (12) from 2 — A solution of MsCl (56.8 mg, 0.49 mmol) in anhydrous $CHCl_3$ (1.0 mL) was added to a solution of **2** (99.4 mg, 0.37 mmol) and anisole (2 mL, 18.4 mmol) in anhydrous $CHCl_3$ (1.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1:7, v/v) to give **3** (16.5 mg, 18%), **12** (6.0 mg, 5%), **11a** (9.6 mg, 10%), and **1** (6.0 mg, 6%) in the order of elution. **12**: colorless oil. IR (film): 1684, 1252, 1186, 1144 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52—2.58 (1/11H, m), 2.61—2.67 (1/11H, m), 2.67—2.80 (20/11H, m), 3.22—3.31 (1/11H, m), 3.38 (10/11H, td, *J*=11.3, 6.2 Hz), 3.79 (30/11H, s), 3.88 (3/11H, s), 4.01—4.09 (10/11H, m), 4.24—4.30 (1/11H, m), 4.65 (1/11H, br s, disappeared on addition of D_2O), 5.22 (10/11H, br s, disappeared on addition of D_2O), 5.65 (10/11H, s), 5.71 (1/11H, br s), 6.68 (1H, d, *J*=7.5 Hz), 6.79 (10/11H, td, *J*=7.5, 0.8 Hz), 6.77—6.87 (1/11H, m), 6.83 (20/11H, dm, *J*=8.9 Hz), 6.85 (2/11H, dm, *J*=8.9 Hz), 7.01 (1/11H, d, *J*=7.5 Hz), 7.06 (10/11H, d, *J*=7.5 Hz), 7.12 (10/11H, td, *J*=7.5, 1.3 Hz), 7.10—7.15 (1/11H, m), 7.20 (2/11H, dm, *J*=8.9 Hz), 7.26 (20/11H, dm, *J*=8.9 Hz). High-resolution MS *m/z*: Calcd for $C_{19}H_{17}F_3N_2O_2$: 362.1242. Found: 362.1244.

(3a,8a-*cis*)-1,2,3,3a,8,8a-Hexahydro-3a-(4-methoxyphenyl)pyrrolo[2,3-*b*]indole (13) from 12 — Sat. aq. $NaHCO_3$ (0.5 mL, 0.53 mmol) was added to a solution of **12** (6.2 mg, 0.02 mmol) in MeOH (1.0 mL) and the mixture was refluxed for 40 min with stirring. The solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (95:5, v/v) to give **13** (4.3 mg, 94%). **13**: pale yellow oil. IR (film): 2929, 1606, 1512, 1250, 746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.56—2.05 (2H, m, disappeared on addition of D_2O), 2.41 (1H, dd, *J*=11.5, 5.1 Hz), 2.49 (1H, td, *J*=11.5, 6.6 Hz), 2.81 (1H, td, *J*=11.5, 5.1 Hz), 3.21 (1H, dd, *J*=11.5, 6.6 Hz), 3.77 (3H, s), 5.12 (1H, s), 6.63 (1H, d, *J*=7.6 Hz), 6.70 (1H, t, *J*=7.6 Hz), 6.82 (2H, dm, *J*=8.7 Hz), 6.93 (1H, dd, *J*=7.6, 0.9 Hz), 7.04 (1H, td,

J=7.6, 0.9 Hz), 7.25 (2H, dm, *J*=8.7 Hz). High-resolution MS *m/z*: Calcd for $C_{17}H_{18}N_2O$: 266.1419. Found: 266.1412.

(3a,8a-*cis*)-1,2,3,3a,8,8a-Hexahydro-3a-(4-hydoroxyphenyl)- (14) and -3a-(2-hydoroxyphenyl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (15) from 2 — A solution of MsCl (226.7 mg, 1.99 mmol) in anhydrous $CHCl_3$ (1.0 mL) was added to a solution of **2** (107.2 mg, 0.39 mmol) and phenol (370.5 mg, 3.94 mmol) in anhydrous $CHCl_3$ (3.0 mL) and Et_3N (0.27 mL, 1.94 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 successively with $CHCl_3$–hexane (2:1, v/v) and EtOAc–hexane (1:5, v/v) to give **11a** (8.0 mg, 8%), **1** (7.6 mg, 8%), **15** (7.4 mg, 5%), **14** (4.0mg, 3%), and **6** (5.1 mg, 4%) in the order of elution. **14**: colorless oil. IR (film): 1678, 1203, 1188, 1151, 754 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66—2.79 (2H, m), 3.32—3.41 (1H, m), 4.00—4.09 (1H, m), 4.91 (1H, br s, disappeared on addition of D_2O), 5.21 (1H, br s, disappeared on addition of D_2O), 5.64 (1H, s), 6.68 (1H, d, *J*=7.6 Hz), 6.76 (2H, m), 6.79 (1H, td, *J*=7.6, 0.6 Hz), 7.05 (1H, d, *J*=7.6 Hz), 7.12 (1H, td, *J*=7.6, 1.1 Hz), 7.26 (2H, m). High-resolution MS *m/z*: Calcd for $C_{18}H_{15}F_3N_2O_2$: 348.1086. Found: 348.1086. **15**: colorless oil. IR (film): 1709, 1211, 1184, 1165, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.34—2.43 (1H, m), 2.43—2.52 (1H, m), 3.22—3.32 (1H, m), 3.35—3.45 (1H, m), 5.04 (1H, br s), 6.21 (1H, d, *J*=1.7 Hz, collapsed to s on addition of D_2O), 6.31 (1H, br s), 6.70 (1H, d, *J*=7.6 Hz), 6.78 (1H, d, *J*=7.6 Hz), 6.81 (1H, td, *J*=7.6, 0.9 Hz), 6.91 (1H, td, *J*=7.6, 0.9 Hz), 7.09 (1H, td, *J*=7.6, 1.3 Hz), 7.12 (1H, td, *J*=7.6, 1.3 Hz), 7.19 (1H, d, *J*=7.6 Hz), 7.32 (1H, dd, *J*=7.6, 1.3 Hz). High-resolution MS *m/z*: Calcd for $C_{18}H_{15}F_3N_2O_2$: 348.1085. Found: 348.1084.

12 from 14 — Excess CH_2N_2 in Et_2O was added to a solution of **14** (3.7 mg, 0.01 mmol) in MeOH (0.5 mL) and the mixture was stirred at rt for 30 min. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–hexane (2:1, v/v) to give **12** (2.8 mg, 73%).

(3a,8a-*cis*)-1,2,3,3a,8,8a-Hexahydro-3a-(pyrrol-2-yl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (16) from 2 — A solution of MsCl (60.1 mg, 0.53 mmol) in anhydrous $CHCl_3$ (1.0 mL) was added to a solution of **2** (106.2 mg, 0.39 mmol) and pyrrole (263.6 mg, 3.93 mmol) in anhydrous $CHCl_3$ (3.0 mL) and Et_3N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1:5, v/v) and $CHCl_3$–MeOH (99:1, v/v) to give **3** (5.6mg, 6%), **16** (36.5mg, 29%), **11a** (8.3 mg, 8%), and **1** (6.9mg, 7%) in the order of elution. **16**:

colorless oil. IR (film): 1684, 1483, 1468, 1205, 1188, 1747, 754 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.34—2.70 (2H, m), 3.04—3.13 (1/5H, m), 3.16—3.27 (4/5H, m), 3.90—3.98 (4/5H, m), 3.99—4.06 (1/5H, m), 5.61 (4/5H, s), 5.62—5.67 (1H, m), 5.67—5.71 (1/5H, m), 5.83—5.89 (1H, m), 6.62 (4/5H, d, *J*=7.6 Hz), 6.65 (1/5H, d, *J*=7.6 Hz), 6.67—6.76 (3H, m), 7.04 (4/5H, td, *J*=7.6, 1.2 Hz), 7.07 (1/5H, td, *J*=7.6, 1.2 Hz), 7.41 (1/5H, d, *J*=7.6 Hz), 7.22 (4/5H, d, *J*=7.6 Hz), 10.81 (1H, br s). High-resolution MS *m/z*: Calcd for $C_{16}H_{14}F_3N_3O$: 321.1089. Found: 321.1083.

(3a,8a-*cis*)-8-Acetyl-1,2,3,3a,8,8a-hexahydro-3a-(pyrrol-2-yl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (18) from 16 — Ac_2O (2.0 mL) was added to a solution of **16** (36.2mg, 0.11 mmol) in pyridine (2.0 mL) and the mixture was stirred at 65 °C for 10 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1:4, v/v) to give **18** (33.9 mg, 83%). **18**: mp 218.0—220.0 °C (colorless powder, recrystallized from EtOAc–hexane). IR (KBr): 3263, 1705, 1662, 1151, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 2.62 (1H, dd, *J*=12.7, 5.3 Hz), 2.78 (1H, td, *J*=12.7, 7.5 Hz), 3.22 (1H, td, *J*=12.7, 5.3 Hz), 4.02 (1H, m), 6.02 (1H, s), 6.16—6.22 (2H, m), 6.74—6.78 (1H, m), 7.19—7.28 (2H, m), 7.39 (1H, ddd, *J*=8.1, 7.1, 1.8 Hz), 7.79 (1H, br s, disappeared on addition of D_2O), 8.06 (1H, d, *J*=8.1 Hz). *Anal*. Calcd for $C_{18}H_{16}F_3N_3O_2$: C, 59.50; H, 4.44; N, 11.57. Found: C, 59.61; H, 4.43; N, 11.56.

(3a,8a-*cis*)-8-Acetyl-1,2,3,3a,8,8a-hexahydro-3a-(indol-3-yl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (19) from 5 — Ac_2O (3.0 mL) was added to a solution of **5** (22.0 mg, 0.06 mmol) in pyridine (3.0 mL) and the mixture was stirred at 62 °C for 9.5 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1:2, v/v) to give **19** (12.5 mg, 51%). **19**: mp 219.0—220.5°C (colorless prisms, recrystallized from $CHCl_3$). IR (KBr): 3360, 1679, 1479, 1462, 1388, 1206, 1142, 740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.58 (1H, dd, *J*=12.5, 5.1 Hz), 3.04 (1H, td, *J*=12.5, 7.3 Hz), 3.30 (1H, td, *J*=12.5, 5.1 Hz), 4.09 (1H, m), 6.43 (1H, br s), 6.71 (1H, d, *J*=2.7 Hz), 7.13 (1H, t, *J*=8.1 Hz), 7.22 (1H, t, *J*=8.1 Hz), 7.23 (1H, t, *J*=8.1 Hz), 7.30—7.34 (2H, m), 7.38 (1H, t, *J*=8.1 Hz), 7.39 (1H, d, *J*=8.1 Hz), 8.10 (1H, br s), 8.16 (1H, br s). High-resolution MS *m/z*: Calcd for $C_{22}H_{18}F_3N_3O_2$: 413.1351. Found: 413.1353. *Anal*. Calcd for $C_{22}H_{18}F_3N_3O_2 \cdot 1/4H_2O$: C, 63.23; H, 4.34; N, 10.05. Found: C, 63.00; H, 4.37; N, 9.81.

(3a,8a-*cis*)-8-Acetyl-1,2,3,3a,8,8a-hexahydro-3a-(indol-2-yl)-1-trifluoroacetylpyrrolo[2,3-*b*]indole (20) from 4 — Ac_2O (2.0 mL) was added to a solution of **4** (20.5 mg, 0.03 mmol) in pyridine (2.0 mL) and the mixture was stirred at 63 °C for 10 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc–hexane (1:5, v/v) to give **20** (22.1 mg, 97 %). **20**: mp 147.0—150.0 °C (colorless fine needles, recrystallized from $CHCl_3$–hexane). IR (KBr): 1709, 1662, 1479, 1394, 1147, 1142, 1124, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 2.71 (1H, dd,

J=12.5, 5.1 Hz), 2.91 (1H, td, *J*=12.5, 7.2 Hz), 3.27 (1H, td, *J*=12.5, 5.1 Hz), 4.09 (1H, m), 6.19 (1H, s), 6.51 (1H, dd, *J*=2.2, 0.7 Hz), 7.11 (1H, ddd, *J*=8.1, 7.0, 1.1 Hz), 7.17 (1H, ddd, *J*=8.1, 7.0, 1.1 Hz), 7.21—7.29 (3H, m), 7.38—7.45 (1H, m), 7.58 (1H, dd, *J*=8.1, 1.1 Hz), 7.94 (1H, br s), 8.11 (1H, d, *J*=8.1Hz). High-resolution MS *m/z*: Calcd for $C_{22}H_{18}F_3N_3O_2$: 413.1351. Found: 413.1351.

1-Acetyl-6-mesyloxy-*N*b-trifluoroacetyltryptamine (21) from 6 — Reported in our previous paper.[9]

(3a,8a-*cis*)-3a-Acetoxy- (22) and (3a,8a-*cis*)-3a-acetoxy-8-acetyl-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetylpyrrolo[2,3-*b*]indole (23) from 9 — Ac_2O (5.0 mL) was added to a solution of **9** (40.9 mg, 0.15 mmol) in pyridine (5.0 mL) and the mixture was stirred at rt for 18 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 successively with $CHCl_3$–hexane (1:2, v/v/) and $CHCl_3$ to give **22** (33.5 mg, 71%) and **23** (9.0 mg, 17%) in the order of elution. **22**: colorless oil. IR (film): 1741, 1693, 1240, 1205, 1146 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (12/5H, s), 2.05 (3/5H, s), 2.51—2.60 (1/5H, m), 2.68 (4/5H, ddd, *J*=12.9, 11.6, 8.3 Hz), 2.77 (1/5H, dd, *J*=12.4, 6.0 Hz), 3.04 (4/5H, ddd, *J*=12.9, 6.2, 1.5 Hz), 3.17 (1/5H, td, *J*=12.4, 6.0 Hz), 3.41 (4/5H, td, *J*=11.6, 6.2 Hz), 4.02 (4/5H, m), 4.22 (1/5H, dd, *J*=12.4, 8.3 Hz), 4.81 (1/5H, br d, *J*=4.0 Hz disappeared on addition of D_2O), 5.18 (4/5H, br s, disappeared on addition of D_2O), 5.81 (4/5H, d, *J*=2.0 Hz, collapsed to s on addition of D_2O), 5.95—5.98 (1/5H, m), 6.67 (4/5H, d, *J*=7.6 Hz), 6.69 (1/5H, d, *J*=7.6 Hz), 6.82 (4/5H, td, *J*=7.6, 1.1 Hz), 6.86 (1/5H, td, *J*=7.6, 1.1 Hz), 7.22 (4/5H, td, *J*=7.6, 1.3 Hz), 7.23 (1/5H, td, *J*=7.6, 1.3 Hz), 7.41 (1/5H, d, *J*=7.6 Hz), 7.51(4/5H, d, *J*=7.6 Hz). High-resolution MS *m/z*: Calcd for $C_{14}H_{13}F_3N_2O_3$: 314.0878. Found: 314.0881. **23**: mp 117.5—118.0 °C (colorless prisms, recrystallized from EtOAc–hexane). IR (KBr): 1745, 1701, 1685, 1373, 1242, 1133, 758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s), 2.59 (3H, s), 2.59 (1H, td, *J*=12.7, 7.8 Hz), 2.90 (1H, dd, *J*=12.7, 5.1 Hz), 3.13 (1H, ddd, *J*=12.7, 11.7, 5.1 Hz), 4.00 (1H, m), 6.40 (1H, br s), 7.19 (1H, td, *J*=7.4, 1.0 Hz), 7.42 (1H, ddd, *J*=8.1, 7.4, 1.2 Hz), 7.53 (1H, dd, *J*=8.1, 1.0 Hz), 8.04 (1H, br d, *J*=7.4 Hz). High-resolution MS *m/z*: Calcd for $C_{16}H_{15}F_3N_2O_4$: 356.0984. Found: 356.0994. *Anal*. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.94; H, 4.24; N, 7.86. Found: C, 53.98; H, 4.18; N, 7.62.

23 from 22 — Ac_2O (5.0 mL) was added to a solution of **22** (33.5 mg, 0.10 mmol) in pyridine (5.0 mL) and the mixture was stirred at 55 °C for 32 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–hexane (1:1, v/v/) to give unreacted **22** (8.7 mg, 26%) and **23** (23.7 mg, 62%) in the order of elution.

(3a,8a-*cis*)-3a-Acetoxy-8-acety-1,2,3,3a,8,8a-hexahydro- (24) and (3a,8a-*cis*)-8-acety-1,2,3,3a,8,8a-hexahydro-3a-hydroxypyrrolo[2,3-*b*]indole (25) from 23 — Sat. aq. $NaHCO_3$ (4.0 mL, 4.2 mmol) was added to a solution of **23** (39.7 mg, 0.11 mmol) in MeOH (5.0 mL) and the mixture was stirred at rt for 20 min. The solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 successively with $CHCl_3$–MeOH–AcOH (46:1:0.1, v/v) and

$CHCl_3$–MeOH–AcOH (46:10:1, v/v) to give **24** (23.3 mg, 80%) and **25** (4.5 mg, 19%) in the order of elution. **24**: mp 125.0—126.0 °C (very pale yellow prisms, recrystallized from EtOAc–hexane). IR (KBr): 3315, 1739, 1649, 1483, 1408, 1238, 1047 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.99 (3H, s), 2.24 (3H, s), 2.29—2.54 (3H, m), 2.97—3.09 (1H, m), 3.37 (1H, br s, disappeared on addition of D_2O), 5.63 (1H, br d, *J*=2.2 Hz, collapsed to s on addition of D_2O), 7.06 (1H, td, *J*=7.6, 1.1 Hz), 7.28 (1H, ddd, *J*=8.3, 7.6, 1.1 Hz), 7.45 (1H, dd, *J*=7.6, 1.1 Hz), 8.01 (1H, d, *J*=8.3 Hz). *Anal*. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.50; H, 6.26; N, 10.63. **25**: mp 196.0—197.0 °C (colorless prisms, recrystallized from MeOH–EtOAc). IR (KBr): 3342, 3294, 1641, 1483, 1406, 762 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.28—2.34 (2H, m), 2.31 (3H, s), 2.53—2.63 (1H, m), 3.06—3.14 (1H, m), 5.25 (1H, s), 7.16 (1H, td, *J*=7.4, 1.0 Hz), 7.30 (1H, ddd, *J*=8.3, 7.4, 1.0 Hz), 7.44 (1H, d, *J*=7.4 Hz), 8.12 (1H, d, *J*=8.3 Hz). *Anal*. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03 H, 6.47; N, 12.84. Found: C, 66.01; H, 6.48; N, 12.82.

25 from 23 — Sat. aq. $NaHCO_3$ (4.0 mL, 4.2 mmol) was added to a solution of **23** (40.2 mg, 0.11 mmol) in MeOH (5.0 mL) and the mixture was refluxed for 30 min with stirring. The solvent was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH–AcOH (46:5:0.5, v/v) to give **25** (24.2 mg, 98%).

(3a,8a-*cis*)-3a-Acetoxy-1,8-diacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (26) from 24 — Ac_2O (2.0 mL) was added to a solution of **24** (18.6mg, 0.07 mmol) in pyridine (4.0 mL) and the mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (98:2, v/v/) to give **26** (20.8 mg, 96%).

26 from 25 — Ac_2O (3.0 mL) was added to a solution of **25** (29.7 mg, 0.14 mmol) in pyridine (6.0 mL) and the mixture was stirred at rt for 16 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (98:2, v/v/) to give **26** (40.9 mg, 99%).

26 from *N*b-acetyl-1-hydroxytryptamine (27) — NaOAc (23.9 mg, 0.29 mmol) was added to a solution of **27** (31.3 mg, 0.14 mmol) in Ac_2O (2.0 mL) and the mixture was stirred at 118–122 °C for 4.5 h. After addition of H_2O under ice cooling, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (98:2, v/v) to give **26** (20.5 mg, 47%). **26**: mp190.0—191.0 °C (colorless prisms, recrystallized from $CHCl_3$–hexane). IR (KBr): 3535, 2875, 1742, 1623, 1603, 1477, 1404, 1239, 1043, 904, 789, 769 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 60 °C) δ: 1.99, (3H, s), 2.04 (3H, br s), 2,43 (3H, s), 2.45—2.58 (1H, m), 2.64 (1H, br dd, *J*=11.5, 4.4 Hz), 2.82 (1H, m), 3.84 (1H, m), 6.34 (1H, br s), 7.16 (1H, t, *J*=7.6 Hz), 7.35 (1H, t, *J*=7.6 Hz), 7.52 (1H, d, *J*=7.6 Hz), 7.86 (1H, br s). MS *m/z*: 302 (M^+). *Anal*. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.42; H,

6.00; N, 9.17.

(3a,8a-cis)-1-Acetyl-1,2,3,3a,8,8a-hexahydro-3a-hydroxypyrrolo[2,3-*b*]indole (29) from 8b-(2-acetylaminoethyl)-2,2-dimethyl-4*H*-1,3-dioxolo[4,5-*b*]indole (28) — K_2CO_3 (16.6 mg, 0.12 mmol) was added to a solution of **28** (6.5 mg, 0.02 mmol) in MeOH (1.0 mL) and the mixture was stirred at rt for 45 min. After addition of H_2O, the whole was extracted with $CHCl_3$–MeOH (95:5, v/v). The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (97:3, v/v) to give **29** (4.1 mg, 80%). **29**: colorless oil. IR (film): 3320, 1613, 1470, 1449, 1423, 1060, 752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s), 2.45 (1H, s, disappeared on addition of D_2O), 2.41—2.57 (2H, m), 3.25—3.33 (1H, m), 3.67—3.75 (1H, m), 5.27 (1H, br s, disappeared on addition of D_2O), 5.33 (1H, s), 6.63 (1H, d, *J*=7.6, 1.0 Hz), 6.81 (1H, td, *J*=7.6, 1.0 Hz), 7.19 (1H, td, *J*=7.6, 1.2 Hz), 7.31 (1H, d, *J*=7.6, 1.2 Hz). High-resolution MS *m/z*: Calcd for $C_{12}H_{14}N_2O_2$: 218.1056. Found: 218.1056.

26 from 29 — Ac_2O (0.5 mL) was added to a solution of **29** (6.5 mg, 0.03 mmol) in pyridine (1.0 mL) at 0 °C and the mixture was stirred at rt for 8 h. The solvent was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO_2 with EtOAc to give **26** (7.2 mg, 80%).

X-Ray Crystallographic Analysis of 4 — A single crystal (0.20x0.20x0.20 mm) of **4** was obtained by recrystallization from $CHCl_3$. All measurements was made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-$K\alpha$ radiation (λ=1.54178 Å). Crystal data: $C_{20}H_{16}F_3N_3O$, *M*=454.52, monoclinic, space group *P*21/n (#14), *a*=8.8339 (5) Å, *b*=12.1938 (8) Å, *c*=15.7993 (9) Å, β=93.072 (5)°, *V*=1699.4 (2) $Å^3$, *Z*=4, *D*calc=1.451 g/cm^3, *F*(000)=768, and μ(Cu$K\alpha$)=9.40 cm^{-1}. The structure was solved by direct methods using MITHRIL.[14] The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1866 observed reflections ($I>3.00\sigma(I)$, $2\theta<120.2°$) and 308 variable parameters. The final refinement converged with *R*=0.046 and *R*w=0.056.

Numbering of Atoms

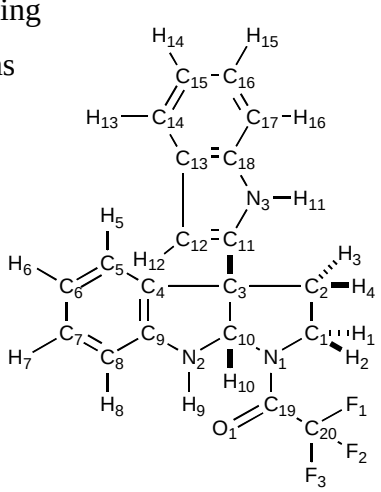
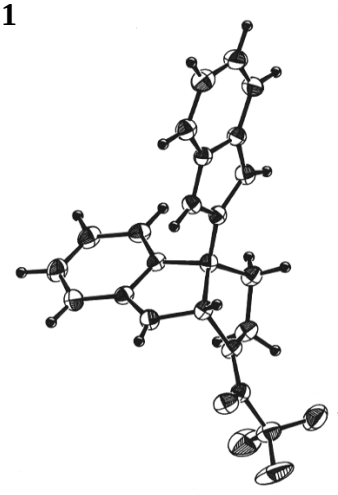


Figure 1



ORTEP Drawing of **4** (*R* = 0.046)

Table 2. Positional Parameters and *B* (eq) for 4

atom	x	y	z	**B (eq)**	atom	x	y	z	**B (eq)**
F (1)	0.8894 (4)	0.3539 (2)	-0.0913 (1)	9.5 (2)	C (16)	1.2211 (5)	-0.2951 (4)	0.3706 (3)	5.2 (2)
F (2)	0.9224 (3)	0.4006 (2)	0.0360 (1)	6.9 (1)	C (17)	1.1484 (4)	-0.2638 (3)	0.2948 (2)	4.2 (2)
F (3)	0.7035 (3)	0.3547 (2)	-0.0115 (2)	8.4 (2)	C (18)	1.0776 (3)	-0.1627 (3)	0.2925 (2)	3.2 (1)
O (1)	0.9367 (3)	0.1526 (2)	-0.0456 (1)	4.5 (1)	C (19)	0.8815 (3)	0.2115 (3)	0.0073 (2)	3.5 (1)
N (1)	0.8435 (3)	0.1775 (2)	0.0829 (1)	3.2 (1)	C (20)	0.8490 (5)	0.3308 (3)	-0.0157 (2)	4.9 (2)
N (2)	0.7651 (3)	-0.0136 (2)	0.0658 (2)	3.7 (1)	H (1)	0.659 (4)	0.235 (3)	0.141 (2)	4.85 (2)
N (3)	0.9933 (3)	-0.1117 (2)	0.2279 (2)	3.3 (1)	H (2)	0.802 (4)	0.313 (3)	0.143 (2)	4.82 (2)
C (1)	0.7749 (5)	0.2386 (3)	0.1515 (2)	4.0 (2)	H (3)	0.775 (4)	0.191 (3)	0.278 (2)	4.65 (2)
C (2)	0.8370 (4)	0.1792 (3)	0.2289 (2)	3.8 (2)	H (4)	0.943 (4)	0.202 (3)	0.246 (2)	4.46 (2)
C (3)	0.8378 (3)	0.0585 (2)	0.2022 (2)	3.0 (1)	H (5)	0.611 (3)	0.023 (3)	0.318 (2)	4.11 (2)
C (4)	0.6797 (3)	0.0077 (2)	0.1983 (2)	3.0 (1)	H (6)	0.377 (4)	-0.067 (3)	0.288 (2)	5.31 (2)
C (5)	0.5790 (4)	-0.0033 (3)	0.2614 (2)	3.8 (2)	H (7)	0.319 (4)	-0.138 (3)	0.150 (2)	6.04 (2)
C (6)	0.4432 (4)	-0.0568 (3)	0.2429 (3)	4.6 (2)	H (8)	0.489 (4)	-0.117 (3)	0.044 (2)	4.73 (2)
C (7)	0.4104 (4)	-0.0976 (3)	0.1633 (3)	5.1 (2)	H (9)	0.755 (4)	-0.019 (3)	0.021 (2)	4.46 (2)
C (8)	0.5101 (4)	-0.0868 (3)	0.0987 (3)	4.5 (2)	H (10)	0.972 (3)	0.038 (2)	0.097 (2)	3.09 (2)
C (9)	0.6449 (3)	-0.0331 (2)	0.1181 (2)	3.3 (1)	H (11)	0.985 (3)	-0.136 (2)	0.175 (2)	3.58 (2)
C (10)	0.8709 (3)	0.0615 (2)	0.1066 (2)	3.0 (1)	H (12)	0.976 (3)	0.066 (3)	0.373 (2)	4.43 (2)
C (11)	0.9450 (3)	-0.0108 (3)	0.2557 (2)	3.2 (1)	H (13)	1.156 (4)	-0.078 (3)	0.489 (2)	5.69 (2)
C (12)	0.9957 (4)	0.0028 (3)	0.3377 (2)	3.8 (2)	H (14)	1.271 (4)	-0.249 (3)	0.494 (2)	6.35 (3)
C (13)	1.0796 (3)	-0.0923 (3)	0.3630 (2)	3.6 (1)	H (15)	1.266 (4)	-0.362 (3)	0.373 (2)	5.70 (3)
C (14)	1.1544 (4)	-0.1271 (3)	0.4388 (2)	4.7 (2)	H (16)	1.143 (3)	-0.310 (3)	0.246 (2)	4.57 (2)
C (15)	1.2235 (5)	-0.2281 (4)	0.4415 (3)	5.4 (2)					

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