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

NUCLEOPHILIC SUBSTITUTION REACTIONS ON INDOLE NUCLE- US: 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-*Nb*-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 cation⁶ (C). It would be possible to trap it with suitable nucleophiles to give imine⁶ (D).

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

Subsequent cyclization of *Nb*-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-*Nb*-trifluoroacetyltryptamine (**2**) with indole

Nb-Trifluoroacetyltryptamine (**1**, Scheme 2) was converted to 1-hydroxy-*Nb*-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 (Et₃N) 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-trifluoroacetylpyrrolo[2,3-*b*]indole (**5**), and 6-mesyloxy-*Nb*-trifluoroacetyltryptamine^{8,9} (**6**), in 13, 5, 11, and 3%

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, CHCl₃, 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 CHCl₃ (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 Et₃N at 0 °C gave **3**, **4**, **5**, **6**, 3*H*-3-(indol-3-yl)-*Nb*-trifluoroacetyltryptamine (**7**), and (3a,8a-*cis*)-3a-(4-chlorobutoxy)-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetylpyrrolo[2,3-*b*]indole⁹ (**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

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p>(3 mol eq.)</p> <p>MsCl, Et₃N</p> </div> <div style="text-align: center;"> <p>3</p> </div> <div style="text-align: center;"> <p>4</p> </div> <div style="text-align: center;"> <p>5</p> </div> <div style="text-align: center;"> <p>6</p> </div> <div style="text-align: center;"> <p>7</p> </div> <div style="text-align: center;"> <p>8</p> </div> <div style="text-align: center;"> <p>9</p> </div> </div>								
Entry	Solvent (ε)	3	4	Yield (%)		of		
				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 ₂ CH ₂ Cl (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 ₃ N → Entries 8—10						* 1 was obtained in 6% yield.		
8	CHCl ₃ (4.8)	4	7	30	1	0	0	0
9	ClCH ₂ CH ₂ Cl (25)	8	5	18	2	0	0	0
10	EtOAc (30)	6	7	25	3	0	0	0

II. Reaction of 1-hydroxy-Nb-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 CHCl₃ in the presence of Et₃N (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-(Nb-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 NaHCO₃ 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. NaHCO₃. 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 CH₂N₂.

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 Ac₂O-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)

The structure of **6** was proved as reported in the previous paper⁹ by converting it to 1-acetyl-6-mesyloxy-Nb-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 Ac₂O-pyridine at rt. Treatment of **22** with Ac₂O-pyridine at 55 °C afforded **23** in 62% yield together with 26% yield of recovery. Hydrolysis of trifluoroacetyl group of **23** with aq. NaHCO₃ at rt provided (3a,8a-*cis*)-3a-acetoxy-8-acetyl-1,2,3,3a,8,8a-hexahydro- (**24**) and (3a,8a-*cis*)-8-acetyl-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 Ac₂O-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 Ac₂O-NaOAc. Aside from this, **26** was produced by the treatment with Ac₂O-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 K₂CO₃. 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-Nb-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 (¹H-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 (SiO₂, 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study. The solution of diazomethane (CH₂N₂) in diethylether (Et₂O) was prepared as follows: a solution of potassium hydroxide (KOH) (5.50 g, 98.0

mmol) in H₂O (8.0 mL) was placed in a 500 mL round bottom flask and cooled in an ice bath. The 95% EtOH (25 mL), Et₂O (60.0 mL), and *p*-tolylsulfonylmethylnitrosoamide (21.5 g, 100 mmol) were added and the whole was slowly distilled to give the Et₂O solution including about 3 g of CH₂N₂. Anhydrous *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), and CHCl₃ were prepared by distillation over calcium hydride, sodium, and calcium chloride, respectively.

Reaction of 1-hydroxy-Nb-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-chlorobutoxy)-1,2,3,3a,8,8a-hexahydro-1-trifluoroacetylpyrrolo[2,3-*b*]indole (8), 6-mesyloxy-Nb-trifluoroacetyltryptamin (6), 3*H*-3-(indol-3-yl)-Nb-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 Et₃N (1.6 mL, 11.5 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After addition of H₂O under ice cooling, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ successively with CHCl₃–hexane (1:1, v/v), CHCl₃, CHCl₃–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 CH₂Cl₂–hexane). IR (KBr): 3370, 1670, 1446, 1351, 1278, 1233, 1203, 1139, 1069, 746 cm⁻¹. ¹H-NMR (CDCl₃) 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 C₁₂H₉F₃N₂O: 254.0666. Found: 254.0662. **4**: mp 223.0—225.0 °C (decomp., colorless prisms, recrystallized from CHCl₃). IR (KBr): 3365, 1676, 1605, 1482, 1465, 1453, 1205, 1183, 1179, 745 cm⁻¹. ¹H-NMR (CDCl₃) 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 D₂O), 5.30 (10/11H, s, disappeared on addition of D₂O), 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 C₂₀H₁₆F₃N₃O: 371.1246. Found: 371.1244.

5: colorless oil. IR (film): 3405, 1681, 1467, 1460, 1204, 1185, 1145, 744 cm^{-1} . $^1\text{H-NMR}$ (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 $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$: 371.1245. Found: 371.1246. **6:** mp 114.5—115.5 $^\circ\text{C}$ (colorless needles, recrystallized from CH_2Cl_2 –hexane). IR (KBr): 3430, 3340, 1700, 1563, 1349, 1206, 1172, 1119, 976, 952, 870 cm^{-1} . $^1\text{H-NMR}$ (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 $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_4\text{S}$: 350.0547. Found: 350.0539. **7:** very pale yellow oil. IR (film): 3402, 1709, 1213, 1180, 1167, 746 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) 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 $\text{C}_{20}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$: 371.1245. Found: 371.1248. **8:** colorless oil. IR (film): 3370, 2940, 1694, 1612, 1486, 1471, 1255, 1206, 1145, 1101, 1066, 750 cm^{-1} . $^1\text{H-NMR}$ (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 $\text{C}_{16}\text{H}_{18}\text{ClF}_3\text{N}_2\text{O}_2$: 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 $^\circ\text{C}$ and the mixture was stirred at 0 $^\circ\text{C}$ 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 $^\circ\text{C}$ and the mixture was stirred at 0 $^\circ\text{C}$ 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 ClCH₂CH₂Cl (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 ClCH₂CH₂Cl (3.0 mL) and Et₃N (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 Et₃N (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 Et₃N (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 Et₃N (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 CHCl₃–hexane). IR (KBr): 3336, 3282, 1697, 1685, 1469, 1250, 1201, 1147, 750 cm⁻¹. ¹H-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 C₁₂H₁₁F₃N₂O₂: 272.0773. Found: 272.0772.

[Entry 8] A solution of MsCl (63.3 mg, 0.55 mmol) in anhydrous CHCl₃ (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 CHCl₃ (3.0 mL) and Et₃N (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 ClCH₂CH₂Cl (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 ClCH₂CH₂Cl (3.0

mL) and Et₃N (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 Et₃N (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 H₂O and EtOAc, the organic layer was washed with H₂O and brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ 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-(Nb-trifluoroacetyl)-aminoethylindol-1-yl]pyrrolo[2,3-b]indole (11a) from 2 — A solution of MsCl (55.1 mg, 0.48 mmol) in anhydrous CHCl₃ (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 CHCl₃ (3.0 mL) and Et₃N (0.4 mL, 2.87 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. After addition of H₂O under ice cooling, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ successively with CHCl₃–hexane (1:1, v/v), CHCl₃–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. ¹H-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 C₂₁H₂₁F₃N₂O₄: 422.1453. Found: 422.1448. **11a**: colorless oil. IR (film): 1689, 1209, 1186, 1153, 752 cm⁻¹. ¹H-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 C₂₄H₂₀F₆N₄O₂: 510.1490. Found: 510.1486.

(3a,8a-cis)-1,2,3,3a,8,8a-Hexahydro-3a-[3-(Nb-trifluoroacetyl)aminoethylindol-1-yl]pyrrolo[2,3-b]indole (11b) from (11a) — Sat. aq. NaHCO₃ (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 H₂O, 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} . ^1H -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 $\text{C}_{22}\text{H}_{21}\text{F}_3\text{N}_4\text{O}$: 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} . ^1H -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 $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2$: 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} . ^1H -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-hydroxyphenyl)- (14) and -3a-(2-hydroxyphenyl)-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** (4.0 mg, 3%), and **6** (5.1 mg, 4%) in the order of elution. **14**: colorless oil. IR (film): 1678, 1203, 1188, 1151, 754 cm^{-1} . 1H -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} . 1H -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** (5.6 mg, 6%), **16** (36.5 mg, 29%), **11a** (8.3 mg, 8%), and **1** (6.9 mg, 7%) in the order of elution. **16**:

colorless oil. IR (film): 1684, 1483, 1468, 1205, 1188, 1747, 754 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) 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 $\text{C}_{16}\text{H}_{14}\text{F}_3\text{N}_3\text{O}$: 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** (36.2 mg, 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} . $^1\text{H-NMR}$ (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 $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2$: 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} . $^1\text{H-NMR}$ (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 $\text{C}_{22}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_2$: 413.1351. Found: 413.1353. *Anal.* Calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_2 \cdot 1/4\text{H}_2\text{O}$: 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} . $^1\text{H-NMR}$ (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, $J=8.1$ Hz). High-resolution MS m/z : Calcd for $C_{22}H_{18}F_3N_3O_2$: 413.1351. Found: 413.1351.

1-Acetyl-6-mesyloxy-Nb-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} . 1H -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} . 1H -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-acetyl-1,2,3,3a,8,8a-hexahydro- (24) and (3a,8a-cis)-8-acetyl-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

CHCl₃–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. ¹H-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 D₂O), 5.63 (1H, br d, *J*=2.2 Hz, collapsed to s on addition of D₂O), 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 C₁₄H₁₆N₂O₃: 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. ¹H-NMR (CD₃OD) 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 C₁₂H₁₄N₂O₂: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.01; H, 6.48; N, 12.82.

25 from 23 — Sat. aq. NaHCO₃ (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 SiO₂ with CHCl₃–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 — Ac₂O (2.0 mL) was added to a solution of **24** (18.6 mg, 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 SiO₂ with CHCl₃–MeOH (98:2, v/v) to give **26** (20.8 mg, 96%).

26 from 25 — Ac₂O (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 SiO₂ with CHCl₃–MeOH (98:2, v/v) to give **26** (40.9 mg, 99%).

26 from Nb-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 Ac₂O (2.0 mL) and the mixture was stirred at 118–122 °C for 4.5 h. After addition of H₂O under ice cooling, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–MeOH (98:2, v/v) to give **26** (20.5 mg, 47%). **26**: mp 190.0–191.0 °C (colorless prisms, recrystallized from CHCl₃–hexane). IR (KBr): 3535, 2875, 1742, 1623, 1603, 1477, 1404, 1239, 1043, 904, 789, 769 cm⁻¹. ¹H-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 C₁₆H₁₈N₂O₄: 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) — K₂CO₃ (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 H₂O, the whole was extracted with CHCl₃–MeOH (95:5, v/v). The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO₂ with CHCl₃–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. ¹H-NMR (CDCl₃) δ: 2.03 (3H, s), 2.45 (1H, s, disappeared on addition of D₂O), 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 D₂O), 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 C₁₂H₁₄N₂O₂: 218.1056. Found: 218.1056.

26 from 29 — Ac₂O (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 SiO₂ 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 CHCl₃. All measurements was made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-*Kα* radiation (λ =1.54178 Å). Crystal data: C₂₀H₁₆F₃N₃O, *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) Å³, *Z*=4, *D*_{calc}=1.451 g/cm³, *F*(000)=768, and μ (Cu*Kα*)=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*>3.00σ(*I*), 2θ<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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