Synthesis of Several 3-Substituted 2-Trifluoromethylindoles *via* Mannich Reaction of 2-Trifluoromethylindoles[1]

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Several 2-trifluoromethyl derivatives of biologically active indoles, tryptamine, indole-3-acetic acid, oxypertine and tryptophan, were synthesized starting from 2-trifluoromethylindoles by use of the Mannich reaction and subsequent nucleophilic substitution reaction as key steps. In this study, chemoselective hydrolysis and reductions of the nitrile group to the respective carboxylic acid, amine and aldehyde in the presence of the trifluoromethyl group were achieved.

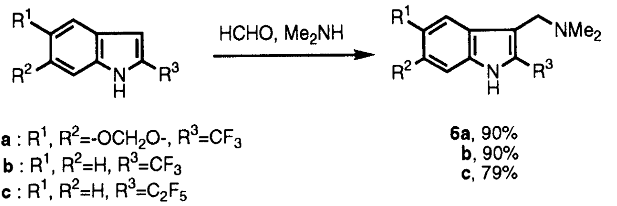
Key words 2-trifluoromethylindole; Mannich reaction; synthesis; nucleophilic substitution

In spite of the various biological activities of indoles, little work has been done on the modification of indoles with a fluorinated substituent with the aim of developing novel biologically active compounds.[2] In the previous paper, we reported the efficient synthesis of 2-trifluoromethylindoles by thermolysis of the 2-(*N*-acylamino)benzylphosphonium salts.[3] In this paper, we describe the introduction of a C_1-function at C-3 of the 2-trifluoromethylindoles by means of the Mannich reaction and subsequent derivatization to the 2-trifluoromethyl derivatives (**1**—**4**) of biologically active indoles, *N*-acetyltryptamine, indole-3-acetic acid, oxypertine and tryptophan (Fig. 1).

The electrophilic substitution at C-3 of the indole ring is a well-known reaction for the synthesis of 3-substituted indoles.[4] However, application of such a reaction to indoles having an electron-withdrawing group such as a trifluoromethyl group at C-2 has not been reported. The Mannich reaction of the indole **5a** under the usual conditions[4] afforded the dimethylaminomethyl derivative **6a** in good yield. Similarly, 2-trifluoromethyl and 2-pentafluoroethyl derivatives, **5b** and **5c**, neither of which possesses an oxygen function on the benzene ring, also reacted to afford the 3-dimethylaminomethyl derivatives **6b** and **6c** in 90 and 79% yields, respectively. These findings appear to suggest that this reaction is affected by the 2-substituent rather than the substituent on the benzene ring. The structures of these compounds **6a**—**c** were supported by their spectral properties.

Quaternization of these compounds **6a**—**c** with methyl iodide and subsequent nucleophilic substitution reaction with nucleophiles such as cyanide, phenylthio anion and diethyl malonate anion took place smoothly in good yields as outlined in Table 1 without affecting the fluoroalkyl function. These results indicate that this methodology (Mannich reaction and subsequent substitution reaction) should be useful for the synthesis of various 3-substituted 2-perfluoroalkylindole derivatives.

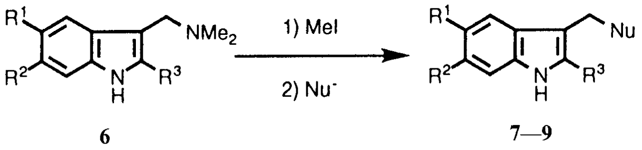
Next, we studied the chemoselective reduction and hydrolysis of the nitrile group of **7b** to 2-trifluoromethyltryptamine and 2-trifluoromethylindole-3-acetic acid, respectively. For the reduction of the nitrile group, we used Raney Ni as a reducing agent since a hydride reducing agent such as lithium aluminum hydride would reduce the trifluoromethyl group.[5] Treatment of the nitrile **7b** with Raney Ni in ethanol which had been presaturated with ammonia was found to afford the amine, which was acetylated to afford *N*-acetyl-2-trifluoromethyltryptamine (**1**). When hydrolysis of the nitrile **7b** was carried out under basic conditions, not only the nitrile group, but also



5a : R^1, R^2=-OCH$_2$O-, R^3=CF$_3$
b : R^1, R^2=H, R^3=CF$_3$
c : R^1, R^2=H, R^3=C$_2$F$_5$

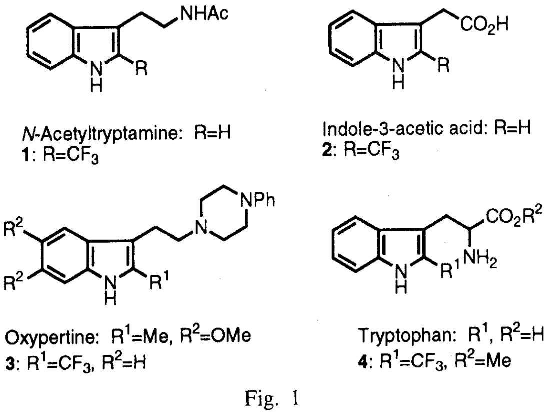
Chart 1

Table 1. Nucleophilic Substitution Reaction of **6**



6 **7**—**9**

Compd.	R^1 R^2	R^3	Nu$^-$	Product	Yield %
6a	–OCH$_2$O–	CF$_3$	CN$^-$	**7a**	85
6a	–OCH$_2$O–	CF$_3$	PhS$^-$	**8**	81
6a	–OCH$_2$O–	CF$_3$	$^-$CH(CO$_2$Et)$_2$	**9**	62
6b	H H	CF$_3$	CN$^-$	**7b**	74
6c	H H	C$_2$F$_5$	CN$^-$	**7c**	44



N-Acetyltryptamine: R=H
1: R=CF$_3$

Indole-3-acetic acid: R=H
2: R=CF$_3$

Oxypertine: R^1=Me, R^2=OMe
3: R^1=CF$_3$, R^2=H

Tryptophan: R^1, R^2=H
4: R^1=CF$_3$, R^2=Me

Fig. 1

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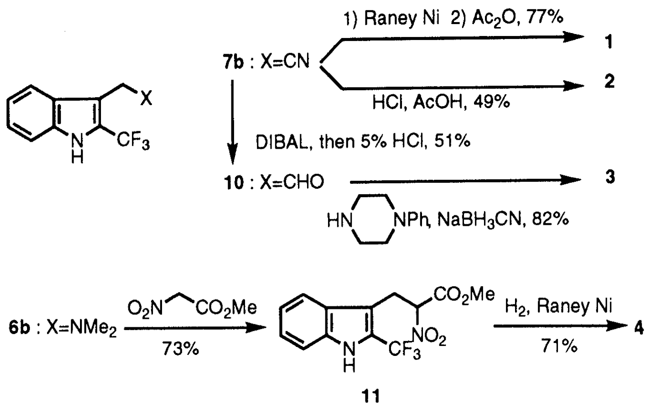

Chart 2

the trifluoromethyl group was hydrolyzed. In contrast, chemoselective hydrolysis of the nitrile group occurred under acidic conditions, affording 2-trifluoromethylindole-3-acetic acid (**2**) in 49% yield. This is probably because the nitrile group is particularly activated by protonation under acidic conditions.

A partial reduction of the nitrile group, to afford indole-3-acetaldehyde (**10**), would be useful for the synthesis of various types of *N*-substituted tryptamine derivatives, such as oxypertine, *via* reductive amination. Reduction of the nitrile **7b** with diisobutylaluminum hydride at $-78\,^{\circ}C$ and subsequent aqueous work-up with diluted HCl afforded the aldehyde **10** in 51% yield. Reductive amination of the aldehyde **10** with *N*-phenylpiperazine and sodium cyanoborohydride ($NaBH_3CN$) took place smoothly to afford the 2-trifluoromethyl analogue of oxypertine **3** in good yield.

Finally, 2-trifluoromethyltryptophan methyl ester (**4**) was synthesized according to the procedure reported by Lyttle and Weisblat.[6)] The *N*,*N*-dimethylaminomethyl derivative **6b** was heated at 120 °C with methyl nitroacetate in xylene to furnish the nitro derivative **11** in 73% yield. Chemoselective reduction of the nitro group to the amino group in the presence of the trifluoromethyl group was carried out by hydrogenation with Raney Ni in methanol to give the desired compound **4** in 71% yield.

In summary, we have described some chemoselective transformations of the nitrile group, which leave the trifluoromethyl group intact, and have demonstrated the usefulness of 2-trifluoromethylindoles as synthetic intermediates for various 2-trifluoromethyl derivatives of biologically active indoles.

Experimental

All melting points (mps) were taken on a Yanagimoto micro-melting point apparatus without correction. Infrared spectra were measured on a JASCO FT/IR-200 Fourier-transform infrared spectrometer. Hydrogen nuclear magnetic resonance spectra (^{1}H-NMR) were measured on a JEOL GX-500 (500 MHz), Hitachi R-250HT (250 MHz), or Varian VXR-200 (200 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Fluorine nuclear magnetic resonance spectra (^{19}F-NMR) were taken on a Varian VXR-200 (188 MHz) with hexafluorobenzene (0.0 ppm) as an internal standard. Low- and high-resolution mass spectra (EI-MS and HR-MS) were obtained by use of a JEOL D-300 mass spectrometer. For silica gel column chromatography, E. Merck Kieselgel 60 (0.063—0.200 mm) was used.

3-(*N*,*N*-Dimethylaminomethyl)-5,6-(methylenedioxy)-2-trifluoromethylindole (6a) Acetic acid (2.10 g, 34.9 mmol) and 37% aqueous formaldehyde (1.40 g, 17.4 mmol) were added to a 40% aqueous solution of dimethylamine (2.00 g, 17.7 mmol) under stirring at 0 °C and then the indole **5a** (0.50 g, 2.18 mmol) was added to the mixture at room temperature. After having been stirred at 60 °C for 6 h, the reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (hexane : dichloromethane = 1 : 3) to afford the title compound **6a** (0.56 g, 90%) as colorless crystals, mp 124—125 °C (hexane–dichloromethane). IR (KBr) ν: 3380, 2958, 2867, 1640, 1615, 1567, 1467, 1253, 1187, 1110, 1034 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (6H, s, NMe_2), 3.61 (2H, s, CH_2N), 5.95 (2H, s, $-OCH_2O-$), 6.79, 7.22 (each 1H, s, aromatic H), 8.18 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 104.5. EI-MS *m*/*z*: 286 (M^+, 37), 242 (M^+-NMe_2, 100), 241 (M^+-HNMe_2, 41). *Anal.* Calcd for $C_{13}H_{13}N_2O_2F_3$: C, 54.55; H, 4.58; N, 9.79. Found: C, 54.25; H, 4.58; N, 9.79.

The Mannich reactions of the other indoles, **5b** and **5c**, were carried out similarly.

3-(*N*,*N*-Dimethylaminomethyl)-2-trifluoromethylindole (6b) Yield 90%, colorless crystals, mp 83—84 °C (hexane–dichloromethane). IR (KBr) ν: 3398, 1567, 1464, 1170, 1113 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (6H, s, NMe_2), 3.71 (2H, s, CH_2N), 7.15—7.4 (3H, m, aromatic H), 7.87 (1H, d, $J=8.2$ Hz, aromatic H), 8.39 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 104.1. EI-MS *m*/*z*: 242 (M^+, 52), 198 (M^+-NMe_2, 100). *Anal.* Calcd for $C_{12}H_{13}N_2F_3$: C, 59.50; H, 5.41; N, 11.56. Found: C, 59.44; H, 5.42; N, 11.46.

3-(*N*,*N*-Dimethylaminomethyl)-2-pentafluoromethylindole (6c) Yield 79%, colorless crystals, mp 67—68 °C (hexane). IR (KBr) ν: 3397, 1561, 1460, 1207, 1172, 1113, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (6H, s, NMe_2), 3.68 (2H, s, CH_2N), 7.15—7.4 (3H, m, aromatic H), 7.97 (1H, d, $J=8.3$ Hz, aromatic H), 8.23 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 50.5 (3F, s), 77.21 (2F, s). EI-MS *m*/*z*: 292 (M^+, 42), 248 (M^+-NMe_2, 100). *Anal.* Calcd for $C_{13}H_{13}N_2F_5$: C, 53.43; H, 4.48; N, 9.59. Found: C, 53.40; H, 4.51; N, 9.48.

5,6-(Methylenedioxy)-2-trifluoromethylindole-3-acetonitrile (7a) Methyl iodide (4.4 μl, 0.070 mmol) was added to a solution of the dimethylamino derivative **6a** (10 mg, 0.035 mmol) in dichloromethane (0.5 ml) at 0 °C and the mixture was stirred overnight at room temperature. The resultant precipitate was collected and washed with hexane to afford the crude ammonium salt, which was immediately used for the next substitution reaction without purification. Potassium cyanide (4.6 mg, 0.070 mmol) was added to a stirred solution of the above ammonium salt in DMF (1 ml) and stirring was continued for 18 h at room temperature. After evaporation of DMF under reduced pressure, the residue was dissolved in ethyl acetate and the ethyl acetate solution was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The crude nitrile was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to afford the title compound **7a** (8.0 mg, 85%) as colorless crystals, mp 149—150 °C (hexane–benzene). IR (KBr) ν: 3342, 2899, 2260, 1640, 1614, 1574, 1472, 1262, 1166, 1110, 1033 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (2H, s, CH_2CN), 6.01 (2H, s, $-OCH_2O-$), 6.84, 7.09 (each 1H, s, aromatic H), 8.42 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.6. EI-MS *m*/*z*: 268 (M^+, 100), 242 (M^+-CN, 7), 199 (M^+-CF_3, 14). *Anal.* Calcd for $C_{12}H_7N_2O_2F_3$: C, 53.74; H, 2.63; N, 10.45. Found: C, 53.67; H, 2.91; N, 10.40.

The other nitriles, **7b** and **7c**, were synthesized similarly.

2-Trifluoromethylindole-3-acetonitrile (7b) Yield 74%, colorless crystals, mp 106—107 °C (hexane–dichloromethane). IR (KBr) ν: 3294, 2917, 2261, 1571, 1463, 1269, 1165, 1119 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.97 (2H, s, CH_2CN), 7.2—7.5 (3H, m, aromatic H), 7.78 (1H, d, $J=8.2$ Hz, aromatic H), 8.58 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.2. EI-MS *m*/*z*: 224 (M^+, 100), 198 (M^+-CN, 18), 155 (M^+-CF_3, 72). *Anal.* Calcd for $C_{11}H_7N_2F_3$: C, 58.93; H, 3.15; N, 12.50. Found: C, 58.89; H, 3.33; N, 12.42.

2-Pentafluoroethylindole-3-acetonitrile (7c) Yield 44%, colorless crystals, mp 118—120 °C (hexane–dichloromethane). IR (KBr) ν: 3303, 2258, 1568, 1456, 1200, 1170, 1142, 1024 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (2H, s, CH_2CN), 7.2—7.5 (3H, m, aromatic H), 7.81 (1H, d, $J=8.3$ Hz, aromatic H), 8.49 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 148.9 (2F, s), 77.0 (3F, s). EI-MS *m*/*z*: 274 (M^+, 100), 248 (M^+-CN, 8), 205 (M^+-CF_3, 85), 155 ($M^+-C_2F_5$, 41). *Anal.* Calcd for $C_{12}H_7N_2F_5$: C, 52.57; H, 2.57; N, 10.22. Found: C, 52.34; H, 2.77; N, 10.30.

5,6-(Methylenedioxy)-3-(phenylthiomethyl)-2-trifluoromethylindole (8)

The phenylthiomethyl derivative **8** was obtained in 81% yield by treatment of the ammonium salt with thiophenol instead of potassium cyanide in the synthesis of the nitrile **7a**. Colorless crystals, mp 106—107.5 °C (hexane–dichloromethane). IR (KBr) ν: 3389, 2901, 2870, 1640, 1615, 1570, 1500, 1266, 1160, 1108, 1031 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.32 (2H, s, CH_2S), 5.97 (2H, s, $-OCH_2O-$), 6.79, 7.06 (each 1H, s, aromatic H), 7.1—7.3 (3H, m, aromatic H), 7.35 (2H, d, $J=7.3$ Hz, aromatic H), 8.15 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.6. EI-MS *m/z*: 351 (M^+, 62), 242 (M^+-SPh, 100). *Anal.* Calcd for $C_{17}H_{12}NO_2F_3S \cdot 1/8H_2O$: C, 57.75; H, 3.49; N, 3.96. Found: C, 57.73; H, 3.74; N, 3.96.

Ethyl α-Ethoxycarbonyl-5,6-(methylenedioxy)-2-trifluoromethylindole-3-propanoate (9) Diethyl malonate (7.4 μl, 0.049 mmol) was added to a stirred solution of NaH (1.7 mg, 0.042 mmol) in DMF (1 ml) at 0 °C and stirring was continued for 30 min at room temperature. The above solution was added to a chilled solution of the crude ammonium salt in DMF (1 ml), prepared by the same method as described for **7a**. The reaction mixture was stirred for 14 h at room temperature, then extracted with water and ethyl acetate. The ethyl acetate layer was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to afford the desired product **9** (8.7 mg, 62%) as colorless crystals, mp 107—109 °C (hexane–ethyl acetate). IR (KBr) ν: 3355, 2983, 1722, 1638, 1567, 1472, 1258, 1160, 1110, 1034 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (6H, t, $J=7.0$ Hz, $OCH_2C\underline{H}_3$), 3.43 (2H, d, $J=7.3$ Hz, 3-H), 3.66 (1H, t, $J=7.3$ Hz, 2-H), 4.13 (4H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 5.96 (2H, s, $-OCH_2O-$), 6.76, 7.01 (each 1H, s, aromatic H), 8.21 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.6. EI-MS *m/z*: 401 (M^+, 55), 356 (M^+-OEt, 6), 328 (M^+-CO_2Et, 28). *Anal.* Calcd for $C_{18}H_{18}NO_6F_3$: C, 53.87; H, 4.52; N, 3.49. Found: C, 53.64; H, 4.54; N, 3.48.

***N*-Acetyl-2-trifluoromethyltryptamine (1)** A suspension of Raney Ni in ethanol (1.5 ml) was added to a stirred solution of the nitrile **7b** (30 mg, 0.134 mmol) in ethanol (1 ml), which had been presaturated with ammonia, at room temperature. The mixture was stirred for 10 min at room temperature, then the catalyst was filtered off and washed with ethanol. The filtrate and washing were combined and concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude amine as a yellow oil, which was immediately acetylated without further purification. Acetic anhydride (16 μl, 0.17 mmol) was added to a pyridine (1 ml) solution of the amine obtained above under stirring at 0 °C. The rection mixture was stirred at room temperature overnight, poured into saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with 5% HCl, water, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 2) to afford the title compound **1** (28 mg, 77%) as colorless crystals, mp 154—156 °C (hexane–ethyl acetate). IR (KBr) ν: 3250, 2952, 1624, 1569, 1314, 1153, 1102, 1063 cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 1.87 (3H, s, MeCO), 3.08 (2H, t, $J=7.4$ Hz, 3-CH_2), 3.42 (2H, t, $J=7.4$ Hz, CH_2N), 7.1—7.4 (3H, m, aromatic H), 7.68 (1H, d, $J=8.3$ Hz, aromatic H). ^{19}F-NMR (CD_3OD) δ_F: 105.7. EI-MS *m/z*: 270 (M^+, 11), 211 (M^+-AcNH_2, 100). *Anal.* Calcd for $C_{13}H_{13}ON_2F_3$: C, 57.78; H, 4.85; N, 10.37. Found: C, 57.95; H, 4.98; N, 10.39.

2-Trifluoromethylindole-3-acetic Acid (2) A stirred solution of the nitrile **7b** (30 mg, 0.13 mmol) in 80% acetic acid was treated with 3 N HCl (0.5 ml) at room temperature. The reaction mixture was heated at 100 °C for 72 h, cooled, adjusted to pH 4 with saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to afford the title compound **2** (16 mg, 49%) as a yellow solid. IR (KBr) ν: 3370, 3400—2500, 1713, 1596, 1267, 1162, 1118 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (2H, s, $C\underline{H}_2CO_2H$), 7.2—7.4 (3H, m, aromatic H), 7.65 (1H, d, $J=8.3$ Hz, aromatic H), 8.37 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.2. EI-MS *m/z*: 243 (M^+, 45), 198 (M^+-CO_2H, 100). HR-MS Calcd for $C_{11}H_8NO_2F_3$ 243.0508. Found 243.0514.

2-Trifluoromethylindole-3-acetaldehyde (10) Diisobutylaluminum hydride (1.0 M solution in toluene, 0.54 ml, 0.54 mmol) was added dropwise to a stirred solution of the nitrile **7b** (100 mg, 0.45 mmol) in toluene (10 ml) at −78 °C and under a nitrogen atmosphere. The reaction mixture was stirred for 10 min at the same temperature, poured into 5% HCl and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : ether = 4 : 1) to afford the aldehyde **10** (52 mg, 51%) as a white solid. IR (KBr) ν: 3349, 2838, 2736, 1721, 1570, 1165, 1116, 746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (2H, s, 3-CH_2), 7.2—7.45 (3H, m, aromatic H), 7.57 (1H, d, $J=8.3$ Hz), 8.53 (1H, br s, NH), 9.72 (1H, s, CHO). ^{19}F-NMR ($CDCl_3$) δ_F: 103.5. EI-MS *m/z*: 227 (M^+, 35), 198 (M^+-CHO, 100). HR-MS Calcd for $C_{11}H_8NOF_3$ 227.0558. Found 227.0558.

3-[2-(4-Phenylpiperazin-1-yl)ethyl]-2-trifluoromethylindole (3) To a stirred solution of *N*-phenylpiperazine (0.28 ml, 1.8 mmol) in methanol (3 ml), methanol (0.12 ml) presaturated with HCl gas, the aldehyde **10** (69 mg, 0.30 mmol), and $NaBH_3CN$ (40 mg, 0.65 mmol) were successively added at room temperature. The mixture was stirred for 1 h at room temperature, then saturated $NaHCO_3$ solution was added and almost all of the methanol was evaporated off under reduced pressure. After extraction with ethyl acetate, the organic layer was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ether = 10 : 1) to afford the title compound **3** (93 mg, 82%) as a white powder, IR (KBr) ν: 3397, 2826, 1599, 1495, 1453, 1390, 1320, 1238, 1160, 1119, 925, 745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.70 (2H, t, $J=7.9$ Hz, CH_2N), 2.76 (4H, t, $J=4.9$ Hz, $N(C\underline{H}_2CH_2)_2NPh$), 3.15 (2H, t, $J=7.9$ Hz, 3-H), 3.27 (4H, d, $J=4.9$ Hz, $N(CH_2C\underline{H}_2)_2NPh$), 6.87 (1H, t, $J=7.2$ Hz, aromatic H), 6.95 (2H, d, $J=7.9$ Hz, aromatic H), 7.1—7.5 (5H, m, aromatic H), 7.74 (1H, d, $J=7.9$ Hz, aromatic H), 8.38 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.4. EI-MS *m/z*: 373 (M^+, 4), 198 ($M^+-CH_2N(CH_2CH_2)_2NPh$, 3), 195 ($[CH_2N(CH_2CH_2)_2NPh]^+$, 100). HR-MS Calcd for $C_{21}H_{22}N_3F_3$ 373.1763. Found 373.1763.

Methyl α-Nitro-2-trifluoromethylindole-3-propanoate (11) A solution of **6b** (100 mg, 0.41 mmol) and methyl nitroacetate (75 μl, 0.82 mmol) in xylene (3 ml) was heated at 120 °C for 5 h under stirring. After evaporation of the solvent, the residue was dissolved in chloroform. Then the chloroform solution was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : dichloromethane = 1 : 1) to afford the title compound **11** (95 mg, 73%) as colorless crystals, mp 97—99 °C (hexane–dichloromethane). IR (KBr) ν: 3384, 2959, 1754, 1595, 1565, 1455, 1438, 1376, 1321, 1256, 1167, 1121, 748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s, CO_2Me), 3.81 (1H, dd, $J=6.4$, 16.0 Hz, 3-CH_2), 3.94 (1H, dd, $J=8.2$, 16.0 Hz, 3-CH_2), 5.42 (1H, dd, $J=6.4$, 8.2 Hz, $CHNO_2$), 7.2—7.45 (3H, m, aromatic H), 7.64 (1H, d, $J=7.4$ Hz, aromatic H), 8.43 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.2. EI-MS *m/z*: 316 (M^+, 78), 270 (M^+-NO_2, 28). *Anal.* Calcd for $C_{13}H_{11}N_2O_4F_3$: C, 49.37; H, 3.51; N, 8.86. Found: C, 49.22; H, 3.79; N, 8.81.

Methyl α-Amino-2-trifluoromethylindole-3-propanoate (4) An ethanolic suspension of Raney Ni (1 ml) was added to a solution of the nitro compound **11** (48 mg, 0.152 mmol) in methanol (1 ml) and the whole was stirred under a hydrogen atmosphere for 5 h. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and extracted with 5% HCl. The aqueous phase was washed with ethyl acetate, basified with saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure to afford the title compound **4** (31 mg, 71%) as colorless crystals, mp 97—99 °C (ethyl acetate–methanol). IR (KBr) ν: 3364, 3293, 2882, 1733, 1583, 1560, 1446, 1291, 1224, 1158, 1108, 950 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (2H, br s, NH_2), 3.12 (1H, dd, $J=8.5$, 14.4 Hz, 3-H), 3.38 (1H, m, 3-H), 3.66 (3H, s, CO_2Me), 3.84 (1H, m, 2-H), 7.0—7.5 (3H, m, aromatic H), 7.71 (1H, d, $J=7.8$ Hz, aromatic H), 8.45 (1H, br s, NH). ^{19}F-NMR ($CDCl_3$) δ_F: 103.9. EI-MS *m/z*: 286 (M^+, 8), 227 (M^+-CO_2Me, 6). *Anal.* Calcd for $C_{13}H_{13}N_2O_2F_3 \cdot 1/5H_2O$: C, 53.87; H, 4.67; N, 9.67. Found: C, 53.92; H, 4.76; N, 9.43.

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