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SYNTHESIS OF 1-TRIFLUOROMETHYL-β-CARBOLINE DERIVATIVES

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SUMMARY

Benzene-ring substituted 1-trifluoromethyl-β-carbolines (IV) were synthesized in 23～27% overall yield by selenium dioxide dehydrogenation of the corresponding 1-trifluoromethyl-1,2,3,4-tetrahydro-β-carbolines(II); the latter compounds were obtained in high yield by Mannich-type condensation of the respective tryptamines with trifluoroacetaldehyde. Partial dehydrogenation of II with potassium permanganate provided 1-trifluoromethyl-3,4-dihydro-β-carbolines (III). L-tryptophan gave, following condensation, esterification and dehydrogenation, 3-carboethoxy-1-trifluoromethyl-β-carboline (IVf) in 84.8% overall yield. The halogenation and nitration of 1-trifluoromethyl-β-carboline (IVa) were also examined.

INTRODUCTION

We have recently described the facile synthesis of 1-trifluoromethyl-β-carboline (IVa, 1-trifluoromethyl-9H-pyrido[3,4-b]indole) [1]. As an extention of the study, we have now synthesized a number of substituted 1-trifluoromethyl-β-carbolines (IVb～f). The nonfluorinated parent compound, 1-methyl-β-carboline (named harman or aribin) has been found in plants[2] and shows a variety of biological activities: e.g., inhibition of enzymes, enhancement of mutagenicity, and antagonism of the benzodiazepine receptor. Other naturally occurring 1-methyl-β-carboline derivatives are known: particularly, harmala alkaloids (Figure 1), such as harmine, harmaline and harmalol; these alkaloids, isolated from the seeds

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of Peganum harmala L., have been of great interest in connection with their activities as central stimulants. Therefore, we considered 1-trifluoromethyl analogues of the alkaloids attractive targets for investigation.

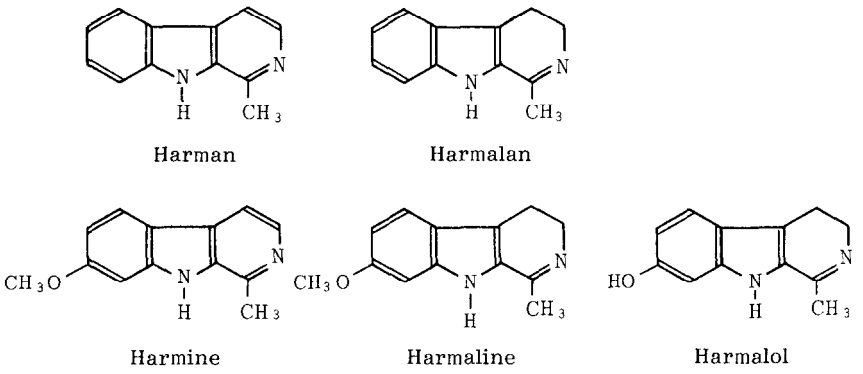
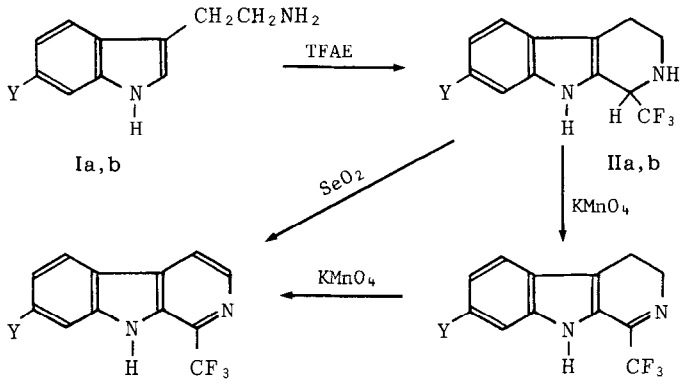


Fig. 1. Harmala Alkaloids.

RESULTS AND DISCUSSION

As in the case of tryptamine [1], 6-methoxytryptamine (Ib) condensed with trifluoromethylacetaldehyde ethyl hemiacetal (TFAE) to give 7-methoxy-1-trifluoromethyl-1,2,3,4-tetrahydro- β-carboline (IIb) in 98.4% yield. Dehydrogenation of IIb with selenium dioxide provided the fully aromatic 7-methoxy-1-trifluoromethyl- β-carboline (IVb) in 27.0% yield. Dehydrogenation with excess potassium permanganate afforded IVb in 22.5% yield, some material being lost by oxidative ring cleavage. Partial dehydrogenation of the nonfluorinated equivalent of IIa (1-methyl-1,2,3,4-tetrahydro-β-carboline) with potassium permanganate has been reported to give 1-methyl-3,4-dihydro-β-carboline [3]. A similar dehydrogenation of IIb with an equimolar amount of potassium permanganate gave 7-methoxy-1-trifluoromethyl-3,4-dihydro-β-carboline (IIIb) in 23.1% yield. Under the reaction conditions (acetone, 5 hours at 0°C), only 33% of IIb was consumed and a trace of IVb was detected by ^{19}F NMR; increase in reaction temperature or time resulted in even greater conversion to IVb. In view of the low yield of IIIb, and difficulties in the separation of IIIb from IVb, alternative methods for dehydrogenation were explored: studies with lead tetraacetate, hydrogen peroxide, sulfur or platinum on active carbon were unsuccessful.

The structure of IIIb was elucidated on the basis of its NMR spectrum: the methylene protons at C-3 (4.03 ppm) and at C-4 (2.89 ppm) show the triplets (J = 9 Hz) expected from simple coupling. In IIb, the fluorine atoms appear as a doublet (J = 8 Hz) due to coupling to the proton at C-1; such coupling is absent in IIIb, indicating the elimination of H-1 and demonstrating that dehydrogenation occurs selectively at the 1,2-bond.

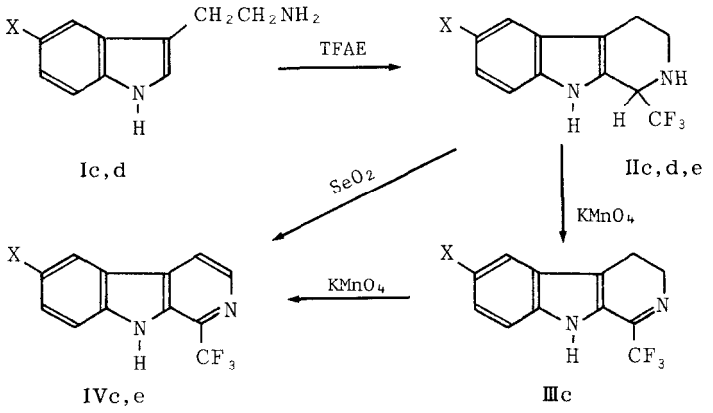


a) Y = H b) Y = CH_3O

The parent compound of IVb, harmine, has attracted much investigation because of its isolation as a major alkaloid from the hallucinogenic plants, 'Ayahuasca' (Banisteria caapi) and 'Yage' (Prestonia amazonicum)[4]; early workers named the compound banisterine, yageine (yajeine) and telepathine. The 3,4-dihydro derivative of harmine, harmaline, is also isolated from plants and shows activity as a central stimulant. The trifluorinated derivatives of harmine (IVb) and harmaline (IIIb) should be more lipophilic and less basic than the methyl compounds, may enter the brain more readily, should be more stable to metabolic destruction and, thus, may show stronger activity; pharmacological studies are in progress.

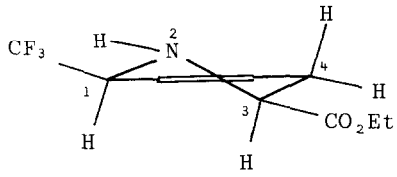
The partial dehydrogenation of IIa with an equimolar amount of potassium permanganate gave 3,4-dihydro-1-trifluoromethyl-β-carboline (IIIa) in 26.9% yield. Similarly, 5-methoxytryptamine (Ic) was used to prepare the 6-methoxy series (IIc, IIIc, IVc). 5-Hydroxytryptamine (serotonin, Id) condensed with TFAE to give 6-hydroxy-1-trifluoromethyl-1,2,3,4-tetrahydro-β-carboline (IId) in 98.8 % yield. However, attempts to dehydrogenate IId with selenium dioxide, potassium permanganate or hydrogen

peroxide gave only tarry material. The O-acetyl derivative (IIe) was prepared from IId with acetic anhydride; dehydrogenation of IIe with selenium dioxide gave 6-acetoxy-1-trifluoromethyl-β-carboline (IVe) in low yield (14.5%).



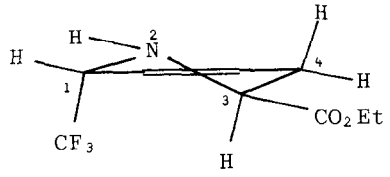
c) X = CH_3O d) X = OH e) X = AcO

The condensation of L-tryptophan ethyl ester with TFAE provides a mixture of two diastereoisomers (A and B) of 3-carboethoxy-1-trifluoromethyl-1,2,3,4-tetrahydro-β-carboline (IIf). The ratio estimated from integration of ^{19}F NMR peak areas is A/B = 59/41. Separation of the isomers was achieved by silica gel chromatography. The configurations of the isomers (A = cis, B = trans) were initially assigned on the basis of their ^{1}H and ^{19}F NMR spectra (Figure 2). The high J values (A, 11 Hz; B, 8 Hz) between 3-H and 4-H correspond to axial-axial coupling; thus, the carboethoxy group at C-3 is probably equatorial in both isomers. Since an equatorial trifluoromethyl group is generally found at higher ^{19}F field than axial [5], isomer A (3.63 ppm) is considered to have the cis configuration, and B (4.33 ppm) is the trans. However, this assignment is not in accord with the order of chemical shift values expected for the C-1 hydrogens; thus, axial hydrogen is usually found at higher field than equatorial [6], but 1-H is found at 4.78 ppm in A and at 4.66 ppm in B. This reversal may be due to the magnetic anisotropic effect of the adjacent 9-NH group or of the pyrrole ring. Additional support for our assignments was based on ^{13}C NMR data. It has been shown that ^{13}C NMR signals for C-1 and C-3 of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines



IIf-A, Cis-Form

J 3Hax-4Hax	11 Hz
J 3Hax-4Heq	4 Hz
δ 1F	3.63 ppm
δ C-1	55.49 ppm
δ C-3	55.36 ppm



IIf-B, Trans-Form

J 3Hax-4Hax	8 Hz
J 3Hax-4Heq	5 Hz
δ 1F	4.33 ppm
δ C-1	54.05 ppm
δ C-3	52.67 ppm

Fig. 2. Stereo Isomers of IIf.

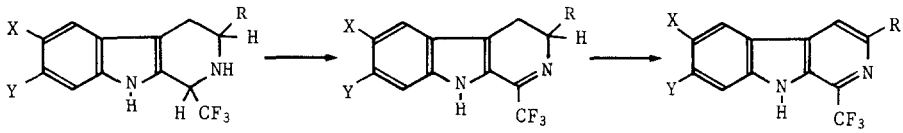
are slightly higher for the cis than for the trans isomers [7]. Since the ^{13}C NMR signals (in $CDCl_3$) for IIf-A (C-1, 55.49; C-3, 55.36) are upfield from those for IIf-B (C-1, 54.05; C-3, 52.67), this criterion supports our original assignments. Although the condensation of D,L-tryptophan methyl ester with free trifluoroacetaldehyde has already been reported [8], the patent describes neither the separation of the diastereoisomers nor spectral data, and TFAE is a more convenient reagent than gaseous free trifluoroacetaldehyde.

When free L-tryptophan is used, ethyl esterification is partly incident to the condensation with TFAE, and a mixture of IIf and 3-carboxy-1-trifluoromethyl-1,2,3,4-tetrahydro-β-carboline (IIg) is obtained. After complete esterification of the mixture, IIf (A + B) was obtained in 98.9% yield. Dehydrogenation of IIf (A + B) with selenium dioxide provides 3-carboethoxy-1-trifluoromethyl-β-carboline (IVf) in 85.7% yield. Although IIf-A was found to undergo dehydrogenation with potassium permanganate somewhat faster than IIf-B, IIIf could not be detected in either case, nor in dehydrogenation with other reagents and reaction conditions. Thus, the consecutive dehydrogenation steps for IIf may not be separable. The results of dehydrogenation studies with various substrates and reagents are summarized in Table 1.

TABLE 1

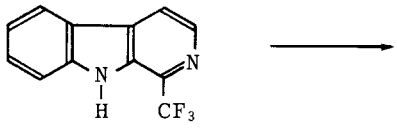
Dehydrogenation of 1,2,3,4-Tetrahydro-β-carbolines (II)

	II			Reaction Conditions			Yields (%)	
	X	Y	R	Reagents	Solvents	Temp.(°C)	III	IV
a	H	H	H	$KMnO_4$	acetone	0 ~ 5	27	5
a	H	H	H	SeO_2	AcOH	reflux	0	83
a	H	H	H	S	xylene	reflux	no reaction	
a	H	H	H	H_2O_2	acetone	20 ~ 25	no reaction	
a	H	H	H	$Pb(OAc)_4$	AcOH	reflux	no reaction	
a	H	H	H	Pt/C	EtOH	reflux	trace	trace
b	H	CH_3O	H	$KMnO_4$	acetone	0 ~ 5	23	1
b	H	CH_3O	H	SeO_2	AcOH	reflux	0	27
c	CH_3O	H	H	$KMnO_4$	acetone	0 ~ 5	28	trace
c	CH_3O	H	H	SeO_2	AcOH	reflux	0	23
d	OH	H	H	H_2O_2	acetone	0 ~ 5	decomp.	
d	OH	H	H	$KMnO_4$	acetone	0 ~ 5	decomp.	
e	AcO	H	H	H_2O_2	acetone	0 ~ 5	no reaction	
e	AcO	H	H	$KMnO_4$	acetone	0 ~ 5	no reaction	
e	AcO	H	H	SeO_2	AcOH	reflux	0	15
f	H	H	CO_2Et	S	xylene	reflux	0	trace
f	H	H	CO_2Et	H_2O_2	acetone	20 ~ 25	0	22
f	H	H	CO_2Et	$KMnO_4$	acetone	0 ~ 5	0	55
f	H	H	CO_2Et	SeO_2	AcOH	reflux	0	86

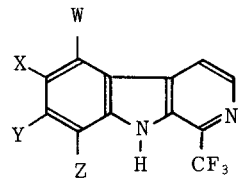


II III IV

Bromination of IVa with 1.1 molar equivalent of N-bromosuccinimide in acetic acid provided 6-bromo-1-trifluoromethyl-β-carboline (Va) and 6,8-dibromo-1-trifluoromethyl-β-carboline (Vc) in yields of 78.1% and 14.2%, respectively. A small amount of another isomer of monobromide (Vb) was separated; the position of bromine is not certain but may be C-8. When IVa was brominated with hydrobromic acid and hydrogen peroxide, Vc was obtained in 93.1% yield. Bromination with excess bromine in acetic acid also gave Vc as the main product. Addition of periodic acid to bromine leads to 5,6,7,8-tetrabromo-1-trifluoromethyl-β-carboline (Vd) in 71.6% yield.



IVa



Va,b,c,d
VIa,b,c
VIIc

a) W = Y = Z = H, X = Br or Cl
b) W = X = Y = H, Z = Br or Cl
c) W = Y = H, X = Z = Br or Cl or NO_2
d) W = X = Y = Z = Br

Chlorination of IVa with 1.1 molar equivalent of N-chlorosuccinimide in acetic acid afforded a 62.1% yield of 6-chloro-1-trifluoromethyl-β-carboline (VIa) together with a mixture of 8-chloro-1-trifluoromethyl-β-carboline (VIb) and 6,8-dichloro-1-trifluoromethyl-β-carboline (VIc) the latter compounds were difficult to separate by silica gel chromatography. Excess (2.5 molar equivalent) N-chlorosuccinimide gave VIc (64.5% yield) as the main product together with VIa (25.9% yield). Chlorination with hydrochloric acid and hydrogen peroxide gave VIa and VIb in yields of 50.5% and 7.4%, respectively.

Nitration of IVa with concentrated nitric acid in sulfuric acid afforded 6,8-dinitro-1-trifluoromethyl-β-carboline (VIIc) in 81.0% yield. Attempts to prepare a mononitro derivative were unsuccessful.

The structures of the products obtained by electrophilic substitution of IVa were elucidated on the basis of chemical shifts and coupling constants of their aromatic protons, as shown in Table 2. The four aromatic protons of IVa give complex multiplets [1] with 18 peaks, which were analyzed by computer using a modification of the LAOCN 3 program [9]. All NMR prameters are obtained with errors estimated at less than 0.2 Hz, and so the proton chemical shifts of the substituted 1-trifluoromethyl-β-carbolines are calculated by combining the IVa values and the substitution effects predicted for aromatic compounds [10]. Satisfactory agreement was found between the calculated and observed chemical shift values.

As reported for harman [11], electrophilic substitution occurs predominantly at C-6 and then at C-8.

The substituted 1-trifluoromethyl-β-carbolines have been evaluated as agricultural chemicals. The halogeno or nitro derivatives (V, VI, VII) were found to show activity as fungicides, especially effective against Phytophthora infestans and Venturia inaequalis which injure tomatoes and apple trees, respectively [12].

EXPERIMENTAL

Materials

TFAE was obtained from Central Glass Co. Ltd., and was distilled (bp. 103 ~ 105°C) prior to use. 5-Methoxytryptamine, 6-methoxytryptamine, and 6-hydroxytryptamine were obtained from Sigma Chemical Co., and were used without further purification. L-Tryptophan ethyl ester was prepared by Fischer esterification, and 1-trifluoromethyl-1,2,3,4-tetrahydro-β-carboline (IIa) and 1-trifluoromethyl-β-carboline (IVa) were prepared by the method reported in the previous paper [1].

Analytical methods and instrumentation

Melting points are uncorrected. ^{1}H NMR spectra (90 MHz) were recorded on a Hitachi R22 spectrometer with TMS as internal reference. ^{19}F NMR spectra (56.45 MHz) were recorded on a Hitachi R20b spectrometer; positive δ values are downfield from the external reference, trifluoroacetic acid. NMR spectra were measured in $CDCl_3$ unless otherwise noted. UV spectral data were obtained in methanol from a Hitachi 320 spectrophotometer, and mass spectral data from a Hitachi M-80 instrument (electron impact ionization at 20eV). Elemental analyses were performed on a Perkin-Elmer 240B analyzer. The homogeneity and identity of each product were verified by NMR, UV, MS, GLC, and TLC.

TABLE 2

^{1}H NMR data for Aromatic Protons in 1-Trifluoromethyl-β-carbolines

Compounds	Chemical shifts[a] (ppm)				Coupling constants (Hz)					
	5-H	6-H	7-H	8-H	5-6	5-7	5-8	6-7	6-8	7-8
IVa	7.96	7.21	7.47	7.40	8.0	1.2	0.0	6.9	1.1	8.9
Va	8.33 (8.18)	Br	7.73 (7.69)	7.46 (7.27)	—	2	0	—	—	9
Vc	8.22 (8.15)	Br	7.92 (7.91)	Br	—	2	—	—	—	—
VIa	8.12 (7.98)	Cl	7.59 (7.49)	7.52 (7.34)	—	2	1	—	—	9
VIb	7.86 (7.92)	7.15 (7.15)	7.47 (7.49)	Cl	8	1	—	8	—	—
VIc	7.93 (7.94)	Cl	7.52 (7.51)	Cl	—	2	—	—	—	—
VIIc	8.95 (9.24)	NO_2	9.11 (9.37)	NO_2	—	2	—	—	—	—

[a] Calculated values (in parentheses) are obtained from the values of IVa and substitution effects [10]: *o*-Br 0.22, *m*-Br - 0.13, *p*-Br - 0.18, *o*-Cl 0.02, *m*-Cl - 0.06, *p*-Cl - 0.04, *o*-NO_2 0.95, *m*-NO_2 0.33, *p*-NO_2 0.17

Thermal condensation of tryptamines with TFAE

A suspension of 6-methoxytryptamine (Ib, 1.90g, 10 mmol) in TFAE (1.73g, 12 mmol) was heated at reflux in an oil bath (110 ~ 120°C) under argon for 5 hours. With a rise of temperature, the mixture became homogeneous. Excess TFAE, ethanol, and water were removed by evaporation and the residual material was recrystallized from ethanol to give 2.50g of 7-methoxy-1-trifluoromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole(IIb) as colorless plates: mp. 158 ~ 159°C; UV λ max 293, 268 nm; MS m/e (relative intensity) 270 (42) M^+, 202 (14), 201 (100) $M^+ - CF_3$, ^1H NMR (in acetone-d_6) δ 2.64 (t, 2, J = 5 Hz, 4-H), 3.14 (t, 2, J = 5 Hz, 3-H), 3.74 (s, 3, 7-OCH_3), 4.61 (q, 1, J = 8 Hz, 1-H), 5.54 (d-d, 1, J = 9 Hz and 2 Hz, 6-H), 5.79 (d, 1, J = 2 Hz, 8-H), 7.31 (d, 1, J = 9 Hz, 5-H); ^{19}F NMR δ 3.68 (d, J = 8 Hz, 1-CF_3); Elemental analysis, Found C 58.03%, N 10.42%, H 4.73%, Calcd. as $C_{13}H_{13}F_3N_2O$, C 57.78%, N 10.37%, H 4.85%. From the mother liquor, an additional 0.16g (98.4% total yield) of IIb was obtained.

This procedure is representative of the thermal condensations of the other tryptamines, 5-methoxytryptamine and 5-hydroxytryptamine, and the following products were obtained respectively.

6-Methoxy-1-trifluoromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (IIc): 99.7% yield; mp. 123 ~ 124°C; colorless needles recrystallized from ethanol; UV λ max 274 nm; MS m/e (relative intensity) 270 (98) M^+, 241 (25) $M^+ - CH_2NH$, 202 (24), 201 (100) $M^+ - CF_3$; ^1H NMR (in acetone-d_6) δ 2.64 (t, 2, J = 6 Hz, 4-H), 3.14 (t, 2, J = 6 Hz, 3-H), 3.77 (s, 3, 6-OCH_3), 4.62 (q, 1, J = 8 Hz, 1-H), 6.73 (d-d, 1, J = 8 Hz and 2 Hz, 7-H), 6.93 (d, 1, J = 2 Hz, 5-H), 7.20 (d, 1, J = 8 Hz, 8-H0; ^{19}F NMR δ 3.87 (d, J = 8 Hz, 1-CF_3); Elemental analysis, Found C 57.70%, N 10.41%, H 4.94%, Calcd. as $C_{13}H_{13}F_3N_2O$, C 57.78%, N 10.37%, H 4.85%.

6-Hydroxy-1-trifluoromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (IId): 98.8% yield; mp. 199 ~ 200°C (decomp.); colorless needles recrystallized from ethanol; UV λ max 276 nm; MS m/e (relative intensity) 256 (50) M^+, 227 (12) $M^+ - CH_2NH$, 207 (16) $M^+ - CH_2NH - HF$, 187 (100) $M^+ - CF_3$; ^1H NMR (in acetone-d_6) δ 3.0 ~ 3.4 (m, 4, 3 and 4-H), 4.56 (q, 1, J = 8 Hz, 1-H), 6.69 (d-d, 1, J = 9 Hz and 2 Hz, 7-H), 6.86 (d, 1, J = 2 Hz, 5-H), 7.17 (d, 1, J = 9 Hz, 8-H); ^{19}F NMR δ 4.0 (d, J = 9 Hz, 1-CF_3); Elemental analysis, Found C 56.09%, N 10.82%, H 4.27%, Calcd. as $C_{12}H_{11}F_3N_2O$, C 56.25%, N 10.93%, H 4.33%.

Thermal condensation of L-tryptophan and its ethyl ester

A suspension of L-tryptophan ethyl ester (4.65g, 20 mmol) and TFAE (3.17g, 22 mmol) was heated at reflux under argon for 5 hours. The reaction mixture was analyzed by ^{19}F NMR: two doublets were found at 2.8 ppm (A, J = 6 Hz) and 3.6 ppm (B, J = 8 Hz) in a ratio of 59 : 41. After evaporation of ethanol, excess TFAE, and water, the residual material was separated by silica gel chromatography (100 ml, dichloromethane-2% ether in dichloromethane-5% ether in dichloromethane as eluting solvents) to give (a) Cis-3-carboethoxy-1-trifluoromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (IIf-A): 2.68g (42.9% yield); mp. 121∼123°C, colorless needles recrystallized from ethanol; UV λ max 272, 278, 289 nm; MS m/e (relative intensity) 312 (90) M^+, 243 (55) $M^+ - CF_3$, 239 (100) M^+ - COOEt, 211 (34), 191 (16), 168 (53); ^1H NMR δ 1.32 (t, 3, J = 7 Hz, CH_3), 2.47 (s, 1, 2-NH), 3.02 (AB-d-d, 1, J = 16 Hz, 11 Hz and 2 Hz, 4-axH), 3.13 (AB-d-d, 1, J = 16 Hz, 4 Hz and 2 Hz, 4-eqH), 3.74 (d-d, 1, J = 11 Hz and 4 Hz, 3-axH), 4.27 (q, 2, J = 7 Hz, CH_2), 4.78 (q, 1, J = 6 Hz, 1-H), 7.0∼7.6 (m, 4, 5∼8-H), 8.01 (broad s, 1, 9-NH); ^{19}F NMR δ 3.63 (d, J = 6 Hz, 1-CF_3); $[\alpha]_D^{20}$ - 79.2° (c 0.4, 95% ethanol); Elemental analysis, Found C 57.69%, N 8.97%, H 4.84%, Calcd as $C_{15}H_{15}F_3N_2O_2$, C 57.48%, H 8.92%, H 4.87% and (b) Trans-3-carboethoxy-1-trifluoromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (IIf-B): 1.54g (24.7% yield); colorless amorphous solid; UV λmax 271, 288 nm; MS m/e (relative intensity) 312 (95) M^+, 243 $M^+ - CF_3$, 239 (100) M^+ - COOEt, 237 (19), 211 (25), 191 (14), 169 (51); ^1H NMR δ 1.23 (t, 3, J = 7 Hz, CH_3), 2.52 (s, 1, 2-NH), 2.86 (AB-d-d, 1, J = 15 Hz, 8 Hz and 2 Hz, 4-axH), 3.13 (AB-d, 1, J = 15 Hz and 5 Hz, 4-eqH), 4.04 (d-d, 1, J = 8 Hz and 5 Hz, 3-H), 4.17 (q, 2, J = 7 Hz, CH_2), 4.66 (q, 1, J = 7 Hz, 1-H), 7.0∼7.6 (m, 4, 5∼8-H), 8.08 (s, 1, 9-NH); ^{19}F NMR δ 4.33 (d, 3, J = 7 Hz, 1-CF_3); $[\alpha]_D^{20}$ - 17.4° (c 0.5, 95% ethanol); Elemental analysis, Found C 57.70%, N 9.19%, H 4.98%, Calcd. as $C_{15}H_{15}F_3N_2O_2$, C 57.48%, N 8.92%, H 4.87%.

A suspension of L-tryptophan (10.21g, 50 mmol) in TFAE (7.92g, 55 mmol) was heated at reflux under argon for 7 hours. L-Tryptophan dissolved slowly and the reaction mixture became homogeneous after 30 minutes. Direct analysis by ^{19}F NMR showed four doublets at 2.33 ppm (A, J = 6 Hz), 3.54 ppm (B, J = 8 Hz), 2.29 ppm (C, J = 6 Hz), and 3.43 ppm (D, J = 8 Hz). MS showed A and B were ethyl esters (IIf-A and IIf-B) whereas C and D were free acids (IIg-A and IIg-B). The ratio of A + C and B + D was 64 : 36, obtained from integration of ^{19}F

NMR peak areas. The reaction mixture was evaporated to dryness and the residual material was recrystallized from ethanol. Colorless needles (5.26g, a mixture of A and B) were collected by filtration and were washed twice with ethanol. The filtrate and washings were combined and were diluted with ethanol (150 ml). Into the solution, dry hydrogen chloride was bubbled until saturation and the mixture was heated at reflux for 3 hours. The reaction mixture was evaporated to dryness and the residual material was dissolved in ethanol (100 ml). The solution was cooled by dryice and was neutralized with triethylamine. After evaporation of the solvent, the products were purified by passage through a silica gel column (180 ml, 5% ether in dichloromethane as eluting solvent). There was obtained an additional 10.18g (total yield 98.9%) of IIf as colorless needles, which was a mixture of the stereoisomers.

Dehydrogenation of II with selenium dioxide

To a solution of IIb (1.35g, 5 mmol) in acetic acid (60 ml), selenium dioxide (1.11g, 10 mmol) was added and the mixture was heated at reflux for 3 hours. A black precipitate (elemental Se) was filtered off and the filtrate was evaporated to dryness. The residual material was fractionated on a silica gel column (100 ml, eluted with dichloromethane) and there was obtained 0.36g (27.1% yield) of 7-methoxy-1-trifluoromethyl-9H-pyrido-[3,4-b]indole (IVb): mp. 139～140°C; colorless needles from chloroform; UV λ max 242, 304 nm; MS m/e (relative intensity) 266 (100) M^+, 251 (12) $M^+ - CH_3$, 246 (12) M^+ - HF, 231 (31) $M^+ - CH_3$ - HF, 203 (15), 153 (5); ^1H NMR δ 3.81 (s, 3, 7-CH_3O), 6.88 (d-d, 1, J = 7 Hz and 1 Hz, 6-H), 6.93 (d, 1, J = 1 Hz, 8-H), 7.93 (d, 1, J = 6 Hz, 4-H), 7.94 (d, 1, J = 7 Hz, 5-H), 8.42 (d, 1, J = 6 Hz, 3-H); ^{19}F NMR δ 14.4 (s, 1-CF_3); Elemental analysis, Found C 58.60%, N 10.57%, H 3.47%, Calcd. as $C_{13}H_9F_3N_2O$, C 58.65%, N 10.52%, H 3.41%.

This procedure is representative of all the dehydrogenations with selenium dioxide and the following products were obtained.

6-Methoxy-1-trifluoromethyl-9H-pyrido[3,4-b]indole(IVc): 23.3% yield; mp. 177～178°C; colorless needles from chloroform; UV λmax 233, 250, 299, 368 nm; MS m/e (relative intensity) 266 (100) M^+, 251 (27) $M^+ - CH_3$, 246 (15) M^+ - HF, 231 (70) $M^+ - CH_3$ - HF, 203 (10), 181 (4), 153 (4); ^1H NMR δ 3.86 (s, 3, 6-CH_3O), 7.26 (d-d, 1, J = 9 Hz and 2 Hz, 7-H), 7.45 (d, 1, J = 9 Hz, 8-H), 7.56 (d, 1, J = 2 Hz, 5-H), 8.05 (d, 1, J = 6 Hz, 4-H), 8.49 (d, 1, J = 6 Hz, 3-H); ^{19}F NMR δ 14.4 (s, 1-CF_3);

Elemental analysis, Found C 58.45%, N 10.37%, H 3.48%, Calcd. as $C_{13}H_9F_3N_2O$, C 58.65%, N 10.52%, H 3.41%.

6-Acetoxy-1-trifluoromethyl-9H-pyrido[3,4-b]indole (IVe): 14.5% yield; mp. 198~199°C; colorless needles from chloroform; UV λmax 236, 292, 348 nm; MS m/e (relative intensity) 294 (22) M^+, 253 (18), 252 (100) M^+ - CH_2CO, 232 (82) M^+ - CH_2CO - HF; ^1H NMR δ 2.37 (s, 3, 6-CH_3COO), 7.21 (AB-d, 1, J = 9 Hz and 2 Hz, 7-H), 7.31 (AB, 1, J = 9 Hz, 8-H), 7.70 (d, 1, J = 2 Hz, 5-H), 7.76 (d, 1, J = 5 Hz, 4-H), 8.40 (d, 1, J = 5 Hz, 3-H); ^{19}F NMR δ 14.2 (s, 1-CF_3); Elemental analysis, Found C 57.53%, N 9.13%, H 3.31%, Calcd as $C_{14}H_9F_3N_2O_2$, C 57.15%, N 9.52%, H 3.08%.

3-Carboethoxy-1-trifluoromethyl-9H-pyrido[3,4-b]indole(IVf): 85.7% yield; mp. 217~218°C; colorless columns from benzene; UV λ max 270, 340nm; MS m/e (relative intensity) 308 (20) M^+, 263 (4) M^+ - OEt, 236 (100) M^+ - CO_2 - CH_2CH_2, 216 (16); ^1H NMR δ 1.44 (t, 3, J = 7 Hz, CH_3), 4.52 (q, 2, J = 7 Hz, CH_2), 7.39 (d-d, 1, J = 8 Hz and 4 Hz, 6-H), 7.57 (AB-d, 1, J = 8 Hz and 1 Hz, 8-H), 7.63 (AB-d, 1, J = 4 Hz and 2 Hz, 7-H), 8.18 (d, 1, J = 8 Hz, 5-H), 8.98 (s, 1, 4-H), 9.19 (broad s, 1, 9-NH); ^{19}F NMR δ 14.5 (s, 1-CF_3); Elemental analysis, Found C 58.23%, N 9.15%, H 3.67%, Calcd. as $C_{15}H_{11}F_3N_2O_2$ C 58.45%, N 9.09%, H 3.60%.

Dehydrogenation of IIb with potassium permanganate

To an ice-cooled solution of IIb (1.35g, 5 mmol) in acetone (20 ml), powdered potassium permanganate (0.79g, 5 mmol) was added in small portions, and stirring was continued for 5 hours at 0°C. A brown precipitate (MnO_2) was filtered off, the filtrate was concentrated by evaporation, and was analyzed by ^{19}F NMR (acetone solution). Three peaks were found at 4.1 ppm (IIb, as doublet), at 7.8 ppm (as singlet), and at 13.4 ppm (IVb as singlet) in the ratio of 4.8 : 1.7 : 0.1. The solvent was removed by evaporation and the residual material was separated on a silica gel column (100 ml, eluted with (a) dichloromethane (b) ether-dichloromethane 1 : 4). There was obtained 0.31g (23.1% yield) of 7-methoxy-1-trifluoromethyl-3,4-dihydro-9H-pyrido[3,4-b]indole (IIIb): mp. 127~130°C; slightly yellow grains from chloroform-cyclohexane; UV λmax 337 nm; MS m/e (relative intensity) 268 (100) M^+, 267 (93) M^+ - H, 247 (15) M^+ - H - HF; ^1H NMR δ 2.89 (t, 2, J = 9 Hz, 4-H), 3.82 (s, 7-CH_3O), 4.03 (t-q, 2, J = 9 Hz and 2 Hz, 3-H), 6.82 (d, 1, J = 2 Hz, 8-H), 6.83 (AB-d, 1, J = 10 Hz and 2 Hz, 6-H), 7.45 (AB, 1, J = 10 Hz, 5-H); ^{19}F NMR δ 8.9 (t, J

= 2 Hz, 1-CF_3); Elemental analysis, Found C 57.97%, N 10.44%, H 4.18%, Calcd. as $C_{13}H_{11}F_3N_2O$ C 58.21%, N 10.44%, H 4.13%. Compound IIIb was eluted mainly with solvent (a), and 0.90g (66.7% recovered) of IIb was eluted with solvent (b).

By a similar procedure, the following 1-trifluoromethyl-3,4-dihydro-β-carbolines (III) were obtained.

1-Trifluoromethyl-3,4-dihydro-9H-pyrido[3,4-b]indole (IIIa): 26.9% yield; slightly yellow amorphous solid; UV λ max 324nm; MS m/e (relative intensity) 238 (82) M^+, 237 (100) M^+ - H, 217 (40) M^+ - H - HF; ^1H NMR 2.87(t, 2, J = 9 Hz, 4-H), 3.99 (t-q, 2, J = 9 Hz and 2 Hz, 3-H), 7.0 7.4 (m, 3, 6 8-H), 7.55 (d-m, 1, J = 8 Hz, 5-H); ^{19}F NMR δ 8.6 (t, J = 2 Hz, 1-CF_3).

6-Methoxy-1-trifluoromethyl-3,4-dihydro-9H-pyrido[3,4-b]indole(IIIc): 28.3% yield; mp. 148～150°C; colorless needles from chloroform; UV λ max 337nm; MS m/e (relative intensity) 268 (100) M^+, 267 (98) M^+ - H, 247 (15) M^+ - H - HF; ^1H NMR δ 2.92 (t, 2, J = 9 Hz, 4-H), 3.85 (s, 3, 6-CH_3O), 4.07 (t-q, 2, J = 9 Hz and 2 Hz, 3-H), 6.96 (d, 1, J = 2 Hz, 5-H), 7.02 (AB-d, 1, J = 10 Hz and 2 Hz, 7-H), 7.29 (AB, 1, J = 10 Hz, 8-H); ^{19}F NMR δ 8.9 (t, J = 2 Hz, 1-CF_3); Elemental analysis, Found C 58.13%, N 10.29%, H 4.02%, Calcd. as $C_{13}H_{11}F_3N_2O$ C 58.21%, N 10.44%, H 4.13%.

Bromination of IVa with N-bromosuccinimide

To a suspension of IVa (1.18g, 5 mmol) in acetic acid (25 ml), N-bromosuccinimide (0.98g, 5.5 mmol) was added and the mixture was heated at reflux for 1 hour. The reaction mixture was cooled and poured into an ice-cold 5% sodium hydrogen sulfite solution. A white precipitate was collected by filtration and was washed with water. The white solid was fractionated by silica gel chromatography (180 ml, dichloromethane-hexane, 1 : 1) and there were obtained (a) 6,8-Dibromo-1-trifluoromethyl-9H-pyrido[3,4-b]indole (Vc): 0.28g (14.2% yield); mp. 200～201°C; colorless plates from chloroform; UV λ max 241, 291, 358nm; MS m/e (relative intensity) 396 (47), 394 (100), 392 (49) M^+, 376 (31), 374 (63), 372 (31) M^+ - HF, 324 (11), 234 (7), 214 (26); ^1H NMR δ 7.92 (d, 1, J = 2 Hz, 7-H), 8.09 (d, 1, J = 6 Hz, 4-H), 8.22 (d, 1, J = 2 Hz, 5-H), 8.63 (d, 1, J = 6 Hz, 3-H); ^{19}F NMR δ 14.3 (s, 1-CF_3); Elemental analysis, Found C 36.53%, N 6.76%, H 1.33%, Calcd. as $C_{12}H_5Br_2F_3N_2$ C 36.58%, N 7.11%, H 1.28%; and (b) 6-Bromo-1-trifluoromethyl-9H-pyrido[3,4-b]indole (Va):

1.23g (78.1% yield); mp. 172~174°C; colorless grains from chloroform; UV λ max 239, 293, 355nm; MS m/e (relative intensity) 316 (100), 314 (99) M^+, 296 (73), 294 (75) M^+ - HF, 246 (13), 244 (12), 215 (12), 165 (20); ^1H NMR δ 7.46 (AB, 1, J = 9 Hz, 8-H), 7.73 (AB-d, 1, J = 9 Hz and 2 Hz, 7-H), 8.12 (d, 1, J = 5 Hz, 4-H), 8.33 (d, 1, J = 2 Hz, 5-H), 8.65 (d, 1, J = 5 Hz, 3-H); ^{19}F NMR δ 14.3 (s, 1-CF_3); Elemental analysis, Found C 45.89%, N 8.66%, H 2.11%, Calcd. as $C_{12}H_6BrF_3N_2$ C 45.74%, N 8.89%, H 1.92%. In column chromatography, Vc moved faster than Va. A small amount of another isomer of monobromide (Vb) was separated but the position of the bromine is not certain because of low yield.

Bromination of IVa with hydrobromic acid and hydrogen peroxide

To a suspension of IVa (0.71g, 3 mmol) in 5% hydrobromic acid (50 ml), 30% hydrogen peroxide (2.5 ml) was added dropwise with stirring at 60°C, and the reaction mixture was stirred for 3 hours. After cooling, solid material was collected by filtration and was washed with water. Recrystallization from ethanol gave 1.10g (93.1% yield) of Vc.

Bromination of IVa with bromine and periodic acid

To a solution of IVa (0.47g, 2 mmol) in acetic acid (20 ml), bromine (3.2g, 20 mmol) and periodic acid dihydrate (0.91g, 4 mmol) were added. The mixture was heated at reflux with stirring for 3 hours. After cooling, additional periodic acid (0.91g) was added and the mixture was heated again for 4 hours. The reaction mixture was poured into an ice-cold 5% sodium hydrogen sulfite solution and was extracted twice with ether (100 ml x 2). The ether solution was dried over magnesium sulfate and was evaporated to dryness. The residual solid was purified by passage through a silica gel column eluted with dichloromethane. There was obtained 0.79g (71.6% yield) of 5,6,7,8-tetrabromo-1-trifluoromethyl-9H-pyrido-[3,4-b]-indole (Vd): mp. 219 ~ 221°C; colorless needles from ethanol; UV λ max 249, 261, 298, 375nm; MS m/e (relative intensity) 556 (16), 554 (67), 552 (100), 550 (67), 548 (18) M^+, 534 (23), 532 (36), 530 (25) M^+ - HF; ^1H NMR δ 8.01 (d, 1, J = 5 Hz, 4-H), 8.92 (d, 1, J = 5 Hz, 3-H); ^{19}F NMR δ 14.5 (s, 1-CF_3); Elemental analysis, Found C 25.91%, N 5.13%, H 0.22%, Calcd. as $C_{12}H_3Br_4F_3N_2$ C 26.17%, N 5.09%, H 0.37%.

Chlorination of IVa with N-chlorosuccinimide

To a suspension of IVa (1.18g, 5 mmol) in acetic acid (25 ml), N-chlorosuccinimide (0.73g, 5.5 mmol) was added and the mixture was heated at reflux for 1 hour. The reaction mixture was cooled and poured into an ice-cold 5% sodium hydrogen sulfite solution. A white precipitate generated was collected by filtration and was washed twice with water. The white solid was recrystallized from ethanol to give colorless needles (0.34g). The mother liquor was evaporated to dryness and the residual material was separated by silica gel chromatography (100 ml, eluted with dichloromethane). There were obtained an additional 0.50g (62.1% total yield) of 6-chloro-1-trifluoromethyl-9H-pyrido[3,4-b]indole (VIa): mp. 163 ~165°C; colorless grains from chloroform; UV λ max 238, 292, 355nm; MS m/e (relative intensity) 272 (33), 270 (84) M^+, 252 (26), 250 (100) M^+ - HF, 200 (16), 165 (16); ^{1}H NMR δ 7.52 (AB-d, 1, J = 9 Hz and 1 Hz, 8-H), 7.59 (AB-d, 1, J = 9 Hz and 2 Hz, 7-H), 8.10 (d, 1, J = 5 Hz, 4-H), 8.12 (m, 1, 5-H), 8.59 (d, 1, J = 5 Hz, 3-H); ^{19}F NMR δ 14.2 (s, 1-CF_3); Elemental analysis, Found C 53.31%, N 10.14%, H 1.71%, Calcd. as $C_{12}H_6ClF_3N_2$ C 53.26%, N 10.35%, H 2.23%; and 0.32g of a mixture of 8-chloro-1-trifluoromethyl-9H-pyrido[3,4-b]indole (VIb) and 6,8-dichloro-1-trifluoro-methyl-9H-pyrido[3,4-b]indole (VIc).

A similar chlorination of IVa (0.71g, 3 mmol) with N-chlorosuccinimide (1.00g, 7.5 mmol) in acetic acid (30 ml) gave 0.21g (25.9% yield) of VIa and 0.59g (yield 64.5%) of VIc: mp. 180 ~181°C; colorless grains from chloroform; UV λmax 240, 290, 359 nm; MS m/e (relative intensity) 308 (14), 306 (68), 304 (96) M^+, 286 (81), 284 (100) M^+ - HF, 236 (17), 234 (24); ^{1}H NMR δ 7.52 (d, 1, J = 2 Hz, 7-H), 7.93 (d, 1, J = 2 Hz, 5-H), 7.99 (d, 1, J = 5 Hz, 4-H), 8.56 (d, 1, J = 5 Hz); ^{19}F NMR δ 14.2 (s, 1-CF_3); Elemental analysis, Found C 47.30%, N 9.23%, H 1.71%, Calcd. as $C_{12}H_5Cl_2F_3N_2$ C 47.24%, N 9.18%, H 1.65%.

Chlorination of IVa with hydrochloric acid and hydrogen peroxide

To a suspension of IVa (0.71g, 3 mmol) in 5% hydrochloric acid (50 ml), 30% hydrogen peroxide (2.5 ml) was added dropwise with stirring at 60°C, and stirring was continued at 80°C for 2 hours. After cooling, a yellow solid was collected by filtration and was washed with water. The solid material was recrystallized from ethanol to give slightly yellow needles (0.20g) of VIa. The mother liquor was evaporated to dryness and the residual material was separated by silica gel chromatography. There were obtained 0.06g (7.4% yield) of VIb: mp. 111~113°C; colorless needles from

chloroform; UV λ max 238, 287, 349 nm; MS m/e (relative intensity) 272 (32), 270 (100) M^+, 252 (32), 251 (22), 250 (95) M^+ - HF, 200 (17), 165 (18); ^{1}H NMR δ 7.15 (t, 1, J = 8 Hz, 6-H), 7.47 (d-d, 1, J = 8 Hz and 1 Hz, 7-H), 7.86 (d-d, 1, J = 8 Hz and 1 Hz, 5-H), 7.93 (d, 1, J = 5 Hz, 4-H), 8.46 (d, 1, J = 5 Hz, 3-H); ^{19}F NMR δ 14.3 (s, 1-CF_3); Elemental analysis, Found C 53.34%, N 10.58%, H 2.53%, Calcd. as $C_{12}H_6ClF_3N_2$ C 53.26%, N 10.35%, H 2.23%: and an additional 0.21g (50.5% total yield) of VIa.

Nitration of IVa with nitric acid

To a solution of IVa (1.18g, 5 mmol) in concentrated sulfuric acid (5 ml), concentrated nitric acid (5 ml) was added slowly at 10∼15°C; the mixture was allowed to stand overnight at ambient temperature and was then poured into ice-water. A yellow solid was collected by filtration and was washed with water. Recrystallization from ethanol gave 1.32g (81.0% yield) of 6,8-dinitro-1-trifluoromethyl-9H-pyrido[3,4-b]indole (VIIc) : mp. over 300°C; colorless grains from acetone; UV λ max 231, 299, 379 nm; MS m/e (relative intensity) 326 (100) M^+, 280 (6) M^+ - NO_2, 276 (9), 234 (23), 214 (15); ^{1}H NMR (in acetone-d_6) δ 8.61 (AB, 1, J = 5 Hz, 4-H), 8.69 (AB, 1, J = 5 Hz, 3-H), 8.95 (d, 1, J = 2 Hz, 7-H), 9.11 (d, 1, J = 2 Hz, 5-H); ^{19}F NMR δ 12.5 (s, 1-CF_3); Elemental analysis, Found C 44.41, N 17.19%, H 1.60%, Calcd. as $C_{12}H_5F_3N_4O_4$ C 44.19%, N 17.18%, H 1.55%.

All the products synthesized in this work are new compounds.

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