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Synthesis of 1,2,3,4-Tetrahydro-β-carboline Derivatives as Hepatoprotective Agents. III. Introduction of Substituents onto Methyl 1,2,3,4-Tetrahydro-β-carboline-2-carbodithioate

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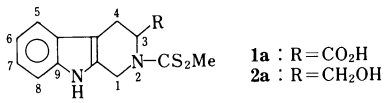
Dithiocarbamates of various substituted tetrahydro-β-carbolines were synthesized and tested for hepatoprotective activity against carbon tetrachloride (CCl_4)-induced liver damage in mice. Structure–activity relationships were investigated. Some neighboring group participation of the 3-substituent with the dithiocarbamate group appeared to be important for the manifestation of activity. The compounds (**1a**, **2a**, and **3i**) with hydrophilic substituents at the 3 poisition exhibited significant activity. Substitution at the 9 position of the 3-carboxylic acid (**1a**) lowered the activity.

Keywords——dithiocarbamate; substituted tetrahydro-β-carboline; hepatoprotective activity; carbon tetrachloride-induced liver damage; structure–activity relationship; neighboring group participation

In our previous paper,[1] 1,2,3,4-tetrahydro-2-methylthiothiocarbonyl-β-carboline-3-carboxylic acid (**1a**) was found to exhibit potent hepatoprotective activity against acutely carbon tetrachloride (CCl_4)-induced liver damage in mice. This observation was followed by the findings[2] that the corresponding 3-hydroxymethyl derivative (**2a**) is equipotent to **1a** and that the methyl dithiocarbamate exhibits the most potent activity in a series of alkyl congeners. Our continued interest in the structure–activity relationships (SAR) of **1a** and related compounds as new hepatoprotective agents led us to examine further the effects of substitution on C_3, the indole nitrogen, and the benzene ring of β-carboline. This paper describes the synthesis and hepatoprotective activity of various 3-substituted derivatives (**3a**—**i**) and several derivatives of **1a** and **2a** bearing substituents at the 6, 8, or 9 position.

Chemistry

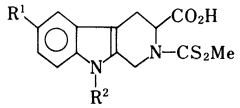
Since no difference between the activities of the optical isomers of **1a** and **2a** was observed,[2] the choice of the starting material (3*S*, 3*R*, or 3*RS*) was arbitrary in the present study. Conversion of the 2-benzyloxycarbonyl (Cbz)-3-carboxylic acid [(*RS*)-**5**][3] to (*RS*)-**6**, **7**, followed by reductive removal of the Cbz group gave the amides[4] [(*RS*)-**4a**, **b**]. Dehydration of (*RS*)-**6** with phosphorus oxychloride in pyridine gave the nitrile [(*RS*)-**8**]. Reaction of (*RS*)-



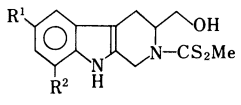
1a : R=CO_2H
2a : R=CH_2OH

Chart 1

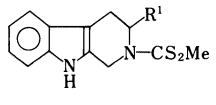
4 1–3



1a : R^1, R^2=H
1b : R^1=H, R^2=Me
1c : R^1=H, R^2=CH_2Ph
1d : R^1=Cl, R^2=H
1e : R^1=OH, R^2=H
1f : R^1=OMe, R^2=H
1g : R^1=Me, R^2=H

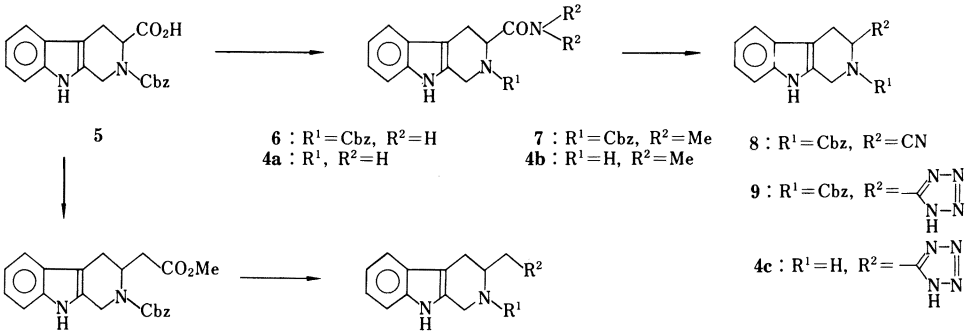


2a : R^1, R^2=H
2b : R^1=F, R^2=H
2c : R^1=Cl, R^2=H
2d : R^1=Me, R^2=H
2e : R^1=H, R^2=Me

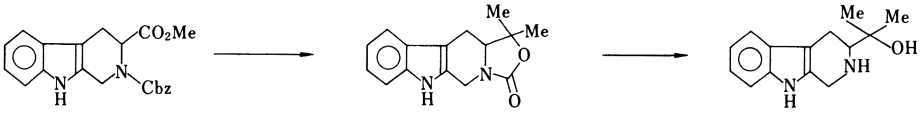


3a : R^1=H
3b : R^1=CO_2Me
3c : R^1=CH_2CO_2H
3d : R^1=$CONH_2$
3e : R^1=$CONMe_2$
3f : R^1= 
3g : R^1=CH_2OMe
3h : R^1= 
3i : R^1=CH_2CH_2OH

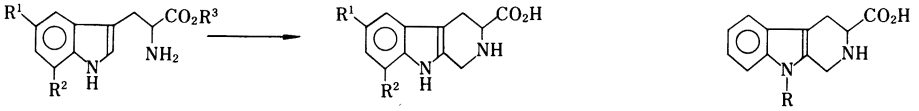
Chart 2



5
6 : R^1=Cbz, R^2=H
4a : R^1, R^2=H
7 : R^1=Cbz, R^2=Me
4b : R^1=H, R^2=Me
8 : R^1=Cbz, R^2=CN
9 : R^1=Cbz, R^2=
4c : R^1=H, R^2=
10
11 : R^1=Cbz, R^2=CO_2H
4d : R^1=H, R^2=CO_2H
12 : R^1=Cbz, R^2=CH_2OH
4e : R^1=H, R^2=CH_2OH



13 14 4f



15 : R^3=H
16 : R^3=Me
4g : R^1=Cl, R^2=H
4h : R^1=OH, R^2=H
4i : R^1=OMe, R^2=H
4j : R^1=Me, R^2=H
18a : R=Me
18b : R=CH_2Ph

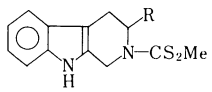
17
4k : R^1=F, R^2=H
4l : R^1=Cl, R^2=H
4m : R^1=Me, R^2=H
4n : R^1=H, R^2=Me

Chart 3

8 with sodium azide followed by removal of the Cbz group gave the 3-(5-tetrazolyl) derivative [(*RS*)-**4c**]. Homologenation of the 2-Cbz-3-carboxylic acid [(*R*)- and (*S*)-**5**] was effected by means of the Arndt–Eistert reaction in the usual manner, giving the homoester [(*R*)- and (*S*)-**10**]. Alkaline hydrolysis of (*S*)-**10** followed by reductive removal of the Cbz group gave the 3-acetic acid [(*S*)-**4d**]. The 3-ethanol derivative [(*R*)-**4e**] was also obtained from [(*R*)-**10**] by sodium borohydride ($NaBH_4$) reduction and subsequent hydrogenolysis. Grignard reaction of the 2-Cbz-3-methoxycarbonyl derivative [(*RS*)-**13**] with methylmagnesium iodide (MeMgI) gave the fused oxazolidinone [(*RS*)-**14**], which gave, on alkaline hydrolysis, the *gem*-dimethylcarbinol [(*RS*)-**4f**]. Various 3-substituted β-carbolines (**4**) thus obtained were allowed to react with carbon disulfide in the presence of potassium hydroxide or triethylamine and treated with methyl iodide, giving the corresponding methylthiothiocarbonyl derivatives (**3a**—**f**, **h**, **i**) listed in Table I. The 3-methoxymethyl derivative (**3g**) was prepared by the methylation of **2a** with diazomethane in the presence of silica gel.[5]

Pictet–Spengler cyclization[6] of the substituted tryptophans (**15**)[7] gave the β-carboline-3-carboxylic acids (**4g**—**j**), which were converted to the corresponding dithiocarbamates (**1d**—**g**, Table II) in the usual manner. The 9-substituted β-carboline-3-carboxylic acids[8] (**18a**, **b**) were similarly converted to the dithiocarbamates (**1b**, **c**, Table II). The 3-hydroxymethyl-β-carbolines (**4k**—**n**) bearing substituents at the 6 or 8 position were prepared from the substituted tryptophan methyl esters (**16**)[7] through the usual sequence of reactions (Chart 3) and converted to the dithiocarbamates (**2b**—**e**) listed in Table III.

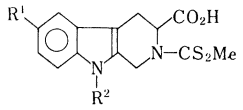
TABLE I. Dithiocarbamate Derivatives of 3-Substituted Tetrahydro-β-carbolines



Compd. No.	R	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Hepatoprotective activity[d] 100 mg/kg	10 mg/kg
1a[a]	CO_2H								AA	AA
2a[b]	CH_2OH								AA	AA
(*RS*)-**3a**	H	145—146 (EtOH)	30	$C_{13}H_{14}N_2S_2$	59.51 (59.45)	5.38 (5.40)	10.68 (10.69)	24.44 (24.26)	B	
(*RS*)-**3b**	CO_2Me	132—134 (Et_2O–hexane)	66	$C_{15}H_{16}N_2O_2S_2$	56.22 (56.46)	5.03 (5.05)	8.74 (8.67)	20.01 (20.01)	AA	D
(*S*)-**3c**[c]	CH_2CO_2H	219—220 (EtOH–H_2O)	12	$C_{15}H_{16}N_2O_2S_2 \cdot H_2O$	53.23 (53.36)	5.36 (5.29)	8.28 (8.05)	18.95 (18.78)	AA	D
(*RS*)-**3d**	$CONH_2$	224—225 (AcOEt)	41	$C_{14}H_{15}N_3OS_2$	55.19 (55.29)	4.95 (4.99)	13.76 (13.88)	21.00 (20.91)	A	
(*RS*)-**3e**	$CONMe_2$	211—213 (AcOEt)	29	$C_{16}H_{19}N_3OS_2$	57.63 (57.54)	5.74 (5.73)	12.60 (12.55)	19.23 (19.23)	AA	D
(*RS*)-**3f**	5-Tetrazolyl	203—205 (dec.) ($CHCl_3$)	27	$C_{14}H_{14}N_6S_2$	50.89 (50.78)	4.27 (4.24)	25.43 (25.27)	19.41 (19.13)	AA	C
(*RS*)-**3g**	CH_2OMe	162—164 (AcOEt–hexane)	21	$C_{15}H_{18}N_2OS_2$	58.79 (58.58)	5.92 (5.90)	9.14 (8.97)	20.93 (20.81)	AA	D
(*RS*)-**3h**	$C(Me)_2OH$	184—186 (EtOH–H_2O)	11	$C_{16}H_{20}N_2OS_2 \cdot 0.5H_2O$	58.33 (58.44)	6.42 (6.13)	8.50 (8.44)	19.46 (19.37)	B	
(*R*)-**3i**[c]	CH_2CH_2OH	166—167 (AcOEt–hexane)	38	$C_{15}H_{18}N_2OS_2$	58.79 (58.84)	5.92 (6.04)	9.14 (8.98)	20.93 (20.78)	AA	AA

a) See reference 1. *b*) See reference 2. *c*) (*S*)-**3c**, $[\alpha]_D^{20}$ +184.0° (*c*=1.0, MeOH); (*R*)-**3i**, $[\alpha]_D^{20}$ −178.0° (*c*=1.0, MeOH). *d*) AA=significantly effective; A, B, and C=effective; D=ineffective. For criteria, see reference 1.

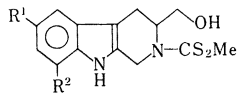
TABLE II. Dithiocarbamate Derivatives of 6-, and 9-Substituted Tetrahydro-β-carboline-3-carboxylic Acid



Compd. No.	R^1	R^2	mp (°C) (Recryst. solvent)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Hepatoprotective activity[b] 100 mg/kg	10 mg/kg
(*RS*)-**1b**	H	Me	212—213 (EtOH)	87	$C_{15}H_{16}N_2O_2S_2$	56.21 (56.23)	5.03 (5.01)	8.80 (8.67)	20.01 (19.91)	A	
(*RS*)-**1c**	H	CH_2Ph	Powder	52	$C_{21}H_{20}N_2O_2S_2$	63.61 (63.53)	5.08 (5.01)	7.06 (6.98)	16.17 (15.88)	A	
(*R*)-**1d**[a]	Cl	H	Powder	25	$C_{14}H_{13}ClN_2O_2S_2$	49.33 (49.23)	3.84 (3.63)	8.22 (8.11)	18.81 (18.83)	AA	AA
(*RS*)-**1e**	OH	H	Powder	26	$C_{14}H_{14}N_2O_3S_2 \cdot H_2O$	47.39 (47.58)	5.00 (4.85)	7.89 (7.79)	18.07 (18.13)	B	
(*S*)-**1f**[a]	OMe	H	Powder	52	$C_{15}H_{16}N_2O_3S_2$	53.55 (53.58)	4.79 (4.92)	8.33 (8.03)	19.06 (18.97)	AA	B
(*S*)-**1g**[a]	Me	H	200—201 ($EtOH-H_2O$)	66	$C_{15}H_{16}N_2O_2S_2$	56.23 (56.34)	5.03 (5.03)	8.74 (8.70)	20.01 (20.13)	AA	AA

a) **1d**, $[\alpha]_D^{20}$ −210.8° (*c*=0.5, MeOH); **1f**, $[\alpha]_D^{20}$ +228.6° (*c*=1.0, MeOH); **1g**, $[\alpha]_D^{20}$ +240.8° (*c*=0.8, MeOH). *b*) See footnote *d*) in Table I.

TABLE III. Dithiocarbamate Derivatives of 6-, and 8-Substituted Tetrahydro-3-hydroxymethyl-β-carbolines



Compd. No.	R^1	R^2	mp (°C) (Recryst. solvent)	Yield (%)	$[\alpha]_D^{20}$ (°) in MeOH (*c*)	Formula	Analysis (%) Calcd (Found) C	H	N	S	Hepatoprotective activity[a] 100 mg/kg	10 mg/kg
(*S*)-**2b**	F	H	Powder	95	+132.0 (0.5)	$C_{14}H_{15}FN_2OS_2$	54.17 (53.88)	4.87 (4.79)	9.02 (8.93)	20.66 (20.41)	AA	AA
(*S*)-**2c**	Cl	H	180—184 ($EtOH-H_2O$)	86	+98.0 (1.0)	$C_{14}H_{15}ClN_2OS_2$	51.44 (51.46)	4.63 (4.65)	8.57 (8.77)	19.62 (19.67)	AA	C
(*S*)-**2d**	Me	H	170—172 (EtOH)	78	+108.0 (1.0)	$C_{15}H_{12}N_2OS_2$	58.79 (58.50)	5.92 (5.68)	9.14 (8.97)	20.93 (20.63)	AA	A
(*S*)-**2e**	H	Me	Powder	83	+199.2 (1.0)	$C_{15}H_{18}N_2OS_2$	58.79 (58.61)	5.92 (5.93)	9.14 (9.06)	20.92 (20.72)	AA	A

a) See footnote *d*) in Table I.

Pharmacology and SAR

The dithiocarbamates (**1**, **2**, and **3**) were tested for hepatoprotective activity against CCl_4-induced liver damage in mice after oral administration by the method reported previously.[1] The results were evaluated according to the criteria defined previously[1] and are included in Tables I—III.

With regard to the effect of modifying the 3-substituent (Table I), most of the derivatives (**3b**, **c**, **3e—g**, **3i**) displayed significant activity (AA) at 100 mg/kg orally. Two exceptions of

significant interest are the unsubstituted derivative (**3a**) and the sterically hindered *gem*-dimethylcarbinol (**3h**), which showed much reduced activity. These results appear to suggest that some neighboring group participation of the 3-substituent with the dithiocarbamate group is important for the appearance of activity. Looking at the results at 10 mg/kg, one observes that the presence of a hydrophilic substituent at the 3-position has a favorable effect. The 3-carboxylic acid (**1a**), 3-hydroxymethyl derivative (**2a**) and its homologue (**3i**) thus exhibit significant activity (AA). Neither the corresponding ester (**3b**) nor the methyl ether (**3g**) was effective at this dose.

Substitution at the 9 position of **1a** lowered the activity, as exemplified by the methyl (**1b**) and benzyl (**1c**) derivatives (Table II). The effects of substitution on the benzene ring of **1a** and **2a** were examined in a series of derivatives listed in Tables II and III. Although no clear SAR can be deduced, 6-Cl(**1d**), 6-Me(**1g**), and 6-F(**2b**) derivatives retain the activity of the parent compounds (**1a** and **2a**). Other substitutions on the benzene ring resulted in a decrease of the activity.

Further studies on the synthesis and hepatoprotective activity of new β-carbolines are in progress.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a JEOL model 60 instrument. Chemical shifts are given as δ values from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, and br = broad. Mass spectra (MS) were measured with a Hitachi RMU-6M instrument. Optical rotations were determined on a Union PM-201 automatic digital polarimeter.

(3*RS*)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide [(*RS*)-6]——Ethyl chloroformate (6.6 g, 60 mmol) was added dropwise to a solution of (*RS*)-**5** (21.0 g, 60 mmol) and Et_3N (8.4 ml, 60 mmol) in tetrahydrofuran (THF) (320 ml), and the whole was stirred at -10 °C for 40 min. After addition of 28% NH_4OH (5.9 ml), the mixture was stirred at 0 °C for 3 h. Insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. The residue was extracted with AcOEt, and the extract was washed with sat. aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated. The residue was triturated with hexane to give (*RS*)-**6** (17.9 g, 85%) as a powder. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3280, 1680. NMR ($CDCl_3$–dimethylsulfoxide-d_6 (DMSO-d_6)) δ: 5.17 (2H, s). MS *m/z*: 349 (M^+). *Anal.* Calcd for $C_{20}H_{19}N_3O_3 \cdot 0.25CH_3CO_2C_2H_5$: C, 67.91; H, 5.70; N, 11.31. Found: C, 68.16; H, 5.63; N, 11.30.

(3*RS*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxamide [(*RS*)-4a]——The amide [(*RS*)-**6**] (2.47 g, 7 mmol) was hydrogenated over 10% Pd–C in EtOH (350 ml) containing AcOH (2 drops) under ordinary pressure and temperature. After removal of Pd–C and the solvent, the resulting foam was crystallized from ether to give (*RS*)-**4a** (1.21 g, 79%), mp 212—216 °C (dec.). (lit.[4] mp 216—219 °C).

(3*RS*)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline-3-*N*,*N*-dimethylcarboxamide [(*RS*)-7]——A mixture of (*RS*)-**5** (21 g, 60 mmol), 1-hydroxybenzotriazole (8.1 g, 60 mmol), $HNMe_2 \cdot HCl$ (4.9 g, 60 mmol), Et_3N (8.4 ml, 60 mmol), dicyclohexylcarbodiimide (DCC, 12.4 g, 60 mmol) and THF (200 ml) was stirred at 5 °C for 1 h and then at room temperature for 16 h. The solvent was evaporated off under reduced pressure, and AcOEt (500 ml) was added to the residue. Insoluble material was filtered off, and the filtrate was washed with 10% HCl, water, sat. aqueous $NaHCO_3$, and water. After removal of the solvent, the residue was crystallized from AcOEt to give (*RS*)-**7** (15.0 g, 67%), mp 179—180 °C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1700, 1640. NMR ($CDCl_3$) δ: 2.90 (3H, br s), 3.10 (3H, br s), 5.20 (2H, s). MS *m/z*: 377 (M^+), 305. *Anal.* Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.47; H, 6.15; N, 11.01.

(3*RS*)-1,2,3,4-Tetrahydro-β-carboline-3-*N*,*N*-dimethylcarboxamide [(*RS*)-4b]——This compound was prepared from (*RS*)-**7** in a manner similar to that described for (*RS*)-**4a**. mp 199—200 °C (dec.), 91%. IR ν_{max}^{Nujol} cm^{-1}: 3400, 1655. NMR ($CDCl_3$) δ: 2.91 (3H, s), 2.99 (3H, s). MS *m/z*: 243 (M^+). *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 68.88; H, 7.01; N, 17.30.

(3*RS*)-2-Benzyloxycarbonyl-3-cyano-1,2,3,4-tetrahydro-β-carboline [(*RS*)-8]——$POCl_3$ (0.37 ml, 4 mmol) was added to a solution of (*RS*)-**6** (1.05 g, 3 mmol) in pyridine (6 ml) at -5 °C, and the mixture was stirred at room temperature for 2 h. The mixture was poured onto ice-water and extracted with AcOEt. The extract was washed with 10% HCl and water, and then dried over $MgSO_4$. The solvent was evaporated off to give (*RS*)-**8** (810 mg, 82%) as a powder. IR ν_{max}^{Nujol} cm^{-1}: 2210, 1690. MS *m/z*: 331 (M^+), 240, 196. *Anal.* Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.42; H, 5.12; N, 12.46.

(3*RS*)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-3-(1*H*-tetrazol-5-yl)-β-carboline [(*RS*)-9]——A mixture of (*RS*)-**8** (663 mg, 2 mmol), NaN_3 (143 mg, 2.2 mmol), NH_4Cl (118 mg, 2.2 mmol), and dimethylformamide (DMF) (2 ml) was heated at 95—100 °C for 6 h and poured onto ice-water. The mixture was acidified with 10% HCl and extracted with AcOEt. The extract was washed with water, dried, and concentrated. The residue was crystallized from AcOEt to yield (*RS*)-**9** (358 mg, 48%), mp 218—219 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3380, 1700. MS *m/z*: 374 (M^+), 329, 240. *Anal.* Calcd for $C_{20}H_{18}N_6O_2$: C, 64.16; H, 4.85; N, 22.45. Found: C, 63.95; H, 4.75; N, 22.28.

(3*RS*)-1,2,3,4-Tetrahydro-3-(1*H*-tetrazol-5-yl)-β-carboline [(*RS*)-4c]·Hydrobromide——A 25% HBr–AcOH solution (2 ml) was added to a solution of (*RS*)-**9** (300 mg, 0.8 mmol) in AcOH (1 ml), and the whole was stirred at room temperature for 20 min. Ether was added to the mixture, and a precipitated solid was filtered off, washed with ether, and then dried. The tetrazole [(*RS*)-**4c**]·hydrobromide (257 mg, quantitative yield) was obtained as a pale yellow powder. IR ν_{max}^{Nujol} cm^{-1}: 3240, 1630. MS *m/z*: 240 (M^+), 171. *Anal.* Calcd for $C_{12}H_{12}N_6 \cdot HBr$: C, 44.88; H, 4.08; Br, 24.88; N, 26.17. Found: C, 45.12; H, 4.19; Br, 24.99; N, 26.01.

Methyl (3*R*)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline-3-acetate [(*R*)-10]——*N*-Methylmorpholine (0.30 g, 3 mmol) and isobutyl chloroformate (0.39 ml, 3 mmol) were added to a solution of (*R*)-**5** (1.05 g, 3 mmol) in THF (50 ml) at −5 °C, and the whole was stirred at −5 °C for 40 min. An ethereal solution of diazomethane [prepared from *N*-methylnitrosourea (1.55 g, 15 mmol) and 40% KOH (4.5 ml) in ether (15 ml)] was added dropwise to the mixture, and the whole was stirred at the same temperature for 4.5 h. After removal of the solvent, the residue was dissolved in MeOH (40 ml), and a solution of silver benzoate (90 mg) in Et_3N (0.9 ml) was added. The whole was stirred for 1 h, and insoluble material was filtered off. The filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt, washed with 10% HCl, water, sat. aqueous $NaHCO_3$, and water, and dried over $MgSO_4$. The solvent was evaporated off to give a pale yellow oil, which was purified by thin layer chromatography (AcOEt : hexane = 4 : 6) to provide (*R*)-**10** (345 mg, 30%), mp 173—174 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 1735, 1680. NMR ($CDCl_3$) δ: 3.53 (3H, s), 5.15 (2H, s). MS *m/z*: 378 (M^+), 347, 305, 287, 243. $[\alpha]_D^{23}$ −54.6° (*c* = 1.0, THF). *Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.54; H, 5.83; N, 7.26.

Methyl (3*S*)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline-3-acetate [(*S*)-10]——The ester [(*S*)-**10**] was similarly prepared from (*S*)-**5** in 42% yield. mp 174—176 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 1735, 1680. NMR ($CDCl_3$) δ: 3.55 (3H, s), 5.17 (2H, s). MS *m/z*: 378 (M^+), 305, 287, 243. $[\alpha]_D^{22}$ +54.4° (*c* = 1.0, THF). *Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.77; N, 7.40.

(3*S*)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-β-carboline-3-acetic Acid [(*S*)-11]——A mixture of (*S*)-**10** (870 mg, 2.3 mmol), 1 N NaOH (5 ml), and THF (12 ml) was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in water and extracted with AcOEt. The aqueous phase was acidified with 10% HCl, and extracted with AcOEt. The extract was washed with water, dried, and then evaporated to give an oil. Trituration of this oil with hexane yielded (*S*)-**11** (630 mg, 75%) as a pale yellow powder. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1700, 1670. NMR ($CDCl_3$) δ: 5.17 (2H, s). MS *m/z*: 364 (M^+), 273, 229. $[\alpha]_D^{20}$ +68.0° (*c* = 1.0, MeOH). *Anal.* Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.09; H, 5.42; N, 7.48.

(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-acetic Acid [(*S*)-4d]·Hydrochloride——A solution of (*S*)-**11** (550 mg, 1.5 mmol) in 80% EtOH (12 ml)–10% HCl (3 ml) was hydrogenated in the presence of 10% Pd–C (500 mg) under ordinary pressure and temperature. After removal of Pd–C and the solvent, the resulting solid was recrystallized from AcOEt to give (*S*)-**4d**·hydrochloride (290 mg, 72%), mp 233—235 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3100—3420, 1680. MS *m/z*: 230 (M^+), 169, 143. $[\alpha]_D^{20}$ −16.0° (*c* = 1.0, H_2O). *Anal.* Calcd for $C_{13}H_{14}N_2O_2 \cdot HCl$: C, 58.54; H, 5.67; Cl, 13.29; N, 10.50. Found: C, 58.38; H, 5.53; Cl, 13.35; N, 10.47.

(3*R*)-2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-3-(2-hydroxyethyl)-β-carboline [(*R*)-12]——A solution of $NaBH_4$ (347 mg, 9.2 mmol) in 80% EtOH (5 ml) was added dropwise to a solution of (*R*)-**10** (580 mg, 1.53 mmol) in 80% EtOH (10 ml) under cooling in an ice-bath, and the mixture was stirred at room temperature for 16 h. After removal of the solvent, the residue was diluted with water, and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from AcOEt–hexane to give (*R*)-**12** (481 mg, 90%), mp 125—127 °C. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3360, 1670. NMR ($CDCl_3$) δ: 5.20 (2H, s). MS *m/z*: 350 (M^+), 259, 215. $[\alpha]_D^{20}$ −39.2° (*c* = 1.0, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.82; H, 6.30; N, 7.88.

(3*R*)-1,2,3,4-Tetrahydro-3-(2-hydroxyethyl)-β-carboline [(*R*)-4e]——A mixture of (*R*)-**12** (440 mg, 1.25 mmol) in EtOH (10 ml) was shaken with H_2 in the presence of 10% Pd–C (200 mg) under ordinary pressure and temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was treated with hexane to afford (*R*)-**4e** (205 mg, 75%) as a powder. IR ν_{max}^{Nujol} cm^{-1}: 3150—3280 (br). MS *m/z*: 216 (M^+), 169, 143. *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.03; H, 7.45; N, 12.88.

(11a *RS*)-5,5a,11,11a-Tetrahydro-1,1-dimethyl-1*H*,3*H*-oxazolo[4′,3′ : 6,1]pyrido[3,4-*b*]indol-3-one[(*RS*)-14]——A solution of (*RS*)-**13**[4] (1.82 g, 5 mmol) in THF (10 ml) was added dropwise to a solution of MeMgI [prepared from Mg (0.49 g, 20 matm) and MeI (1.25 ml, 20 mmol) in ether (10 ml)–THF (20 ml)], and the mixture was stirred at room temperature for 1 h and then refluxed for 3 h. After removal of the solvent, 5% NH_4Cl was added to the residue. The mixture was extracted with AcOEt, and the extract was washed with water, dried over $MgSO_4$, and then concentrated. The residue was dissolved in AcOEt and allowed to stand at room temperature to give (*RS*)-**14**

(410 mg, 32%) as colorless needles, mp 204—206 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1685 (sh). NMR ($CDCl_3$) δ: 1.50 (3H, s), 1.55 (3H, s). MS *m/z*: 256 (M^+), 241, 223. *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.17; H, 6.11; N, 10.85.

(3*RS*)-1,2,3,4-Tetrahydro-3-(2-hydroxypropan-2-yl)-β-carboline [(*RS*)-4f]——A mixture of (*RS*)-**14** (128 mg, 0.5 mmol), 10 N NaOH (2 ml, 20 mmol), and MeOH (4 ml) was refluxed for 22 h. After cooling, the mixture was made acidic with 10% HCl. Insoluble material was filtered off, and the filtrate was basified with 10% NaOH. The precipitate was filtered off, washed with water, and dried to give (*RS*)-**4f** (61 mg, 54%) as a powder. IR ν_{max}^{Nujol} cm^{-1}: 3350 (br). NMR (DMSO-d_6) δ: 1.22 (6H, s). MS *m/z*: 230 (M^+), 171. *Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.92; H, 7.65; N, 12.03.

(3*R*)-6-Chloro-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid [(*R*)-4g]——A solution of D-5-chlorotryptophan[7] (**15**, R^1=Cl, R^2=R^3=H) (0.61 g, 2.56 mmol), 35% formalin (0.27 g, 3 mmol), and 0.1 N H_2SO_4 (4 ml) in H_2O (1.4 ml)–EtOH (2 ml) was stirred at room temperature for 18 h. The resulting solid was filtered off, washed with water, and dried to give (*R*)-**4g** (0.64 g, 99%), mp 272—274 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3280, 1640. MS *m/z*: 252, 250 (M^+). $[\alpha]_D^{20}$ +89.6° (*c*=0.5, 0.1 N, NaOH). *Anal.* Calcd for $C_{12}H_{11}ClN_2O_2 \cdot 1.5H_2O$: C, 51.90; H, 5.08; Cl, 12.77; N, 10.09. Found: C, 52.19; H, 4.92; Cl, 13.05; N, 9.87. The following compounds were similarly synthesized from DL-5-hydroxy-, L-5-methoxy- and L-5-methyltryptophan,[7] respectively.

(3*RS*)-1,2,3,4-Tetrahydro-6-hydroxy-β-carboline-3-carboxylic Acid [(*RS*)-4h]——mp 269 °C (dec.), 91%. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1650 (sh), 1620. MS *m/z*: 232 (M^+) 215, 184, 159. *Anal.* Calcd for $C_{12}H_{12}N_2O_3 \cdot 1.5H_2O$: C, 55.59; H, 5.83; N, 10.80. Found: C, 55.81; H, 5.50; N, 10.74.

(3*S*)-1,2,3,4-Tetrahydro-6-methoxy-β-carboline-3-carboxylic Acid [(*S*)-4i]——mp 285—286 °C (dec.), 68%. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1640. MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.37. Found: C, 63.13; H, 5.57; N, 11.36.

(3*S*)-1,2,3,4-Tetrahydro-6-methyl-β-carboline-3-carboxylic Acid [(*S*)-4j]——mp 298—300 °C (dec.), 86%. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1635. MS *m/z*: 230 (M^+). $[\alpha]_D^{20}$ −119.8° (*c*=1.0, 0.1 N NaOH). *Anal.* Calcd for $C_{13}H_{14}N_2O_2 \cdot 0.25H_2O$: C, 66.51; H, 6.23; N, 11.93. Found: C, 66.51; H, 6.02; N, 11.83.

Methyl (3*S*)-6-Fluoro-1,2,3,4-tetrahydro-β-carboline-3-carboxylate [(*S*)-17, R^1=F, R^2=H]·Hydrochloride——A mixture of L-5-fluorotryptophan methyl ester hydrochloride [(*S*)-**15**·HCl, R^1=F, R^2=H] (0.927 g, 3.4 mmol), 35% formalin (0.52 g, 6 mmol), and MeOH (14 ml) was stirred for 20 h at room temperature and concentrated. The residual solid was crystallized from MeOH–ether to give (*S*)-**17** (R^1=F, R^2=H)·HCl (0.66 g, 68%), mp 246—248 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3230, 1745. $[\alpha]_D^{20}$ −66.0° (*c*=0.2, MeOH). *Anal.* Calcd for $C_{13}H_{13}FN_2O_2 \cdot HCl$: C, 52.64; H, 5.21; Cl, 11.95; F, 6.40; N, 9.44. Found: C, 52.79; H, 5.11; Cl, 11.87; F, 6.68; N, 9.37. The esters [(*S*)-**17** (R^1=Cl, R^2=H), (*S*)-**17** (R^1=Me, R^2=H), and (*S*)-**17** (R^1=H, R^2=Me)] were prepared in a similar manner.

Methyl (3*S*)-6-Chloro-1,2,3,4-tetrahydro-β-carboline-3-carboxylate [(*S*)-17, (R^1=Cl, R^2=H)]·Hydrochloride——mp 248—250 °C (dec.) (MeOH–ether), 56%. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1755. $[\alpha]_D^{20}$ −47.8° (*c*=1.0, MeOH). *Anal.* Calcd for $C_{13}H_{13}ClN_2O_2 \cdot HCl$: C, 51.85; H, 4.69; Cl, 23.54; N, 9.30. Found: C, 52.09; H, 4.64; Cl, 23.32; N, 9.42.

Methyl (3*S*)-1,2,3,4-Tetrahydro-6-methyl-β-carboline-3-carboxylate [(*S*)-17, (R^1=Me, R^2=H)]·Hydrochloride——mp 284—285 °C (dec.) (MeOH), 80%. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1760. $[\alpha]_D^{20}$ −57.2° (*c*=0.5, MeOH). *Anal.* Calcd for $C_{14}H_{16}N_2O_2 \cdot HCl$: C, 59.89; H, 6.10; Cl, 12.63; N, 9.98. Found: C, 59.91; H, 6.04; Cl, 12.87; N, 9.93.

Methyl (3*S*)-1,2,3,4-Tetrahydro-8-methyl-β-carboline-3-carboxylate [(*S*)-17, (R^1=H, R^2=Me)]——mp 146—148 °C ($CHCl_3$), 63%. IR ν_{max}^{Nujol} cm^{-1}: 1710. $[\alpha]_D^{20}$ −52.0° (*c*=1.0, MeOH). *Anal.* Calcd for $C_{14}H_{16}N_2O_2 \cdot 0.5CHCl_3$: C, 57.29; H, 5.47; Cl, 17.49; N, 9.22. Found: C, 57.03; H, 5.45; Cl, 17.59; N, 9.18.

(3*S*)-6-Fluoro-1,2,3,4-tetrahydro-3-hydroxymethyl-β-carboline [(*S*)-4k]——$NaBH_4$ (0.32 g, 8.4 mmol) was added to a solution of [(*S*)-**17**, (R^1=F, R^2=H)]·HCl (0.577 g, 2 mmol) in EtOH (20 ml)–H_2O (10 ml) at 5 °C, and the whole was stirred at room temperature for 21 h. After removal of the solvent, water was added, and the precipitate was filtered off, washed with water, and dried to afford (*S*)-**4k** (0.286 g, 65%), mp 210—211 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3230. $[\alpha]_D^{20}$ −76.0° (*c*=0.5, MeOH). *Anal.* Calcd for $C_{12}H_{13}FN_2O \cdot 0.5H_2O$: C, 62.87; H, 6.16; F, 8.29; N, 12.22. Found: C, 62.65; H, 5.93; F, 8.26; N, 12.18. The following compounds were prepared in a similar manner.

(3*S*)-6-Chloro-1,2,3,4-tetrahydro-3-hydroxymethyl-β-carboline [(*S*)-4l]——mp 225—227 °C (dec.) (aq. EtOH), 52%. IR ν_{max}^{Nujol} cm^{-1}: 3300. $[\alpha]_D^{20}$ −67.6° (*c*=1.0, MeOH). *Anal.* Calcd for $C_{12}H_{13}ClN_2O_2 \cdot 0.25H_2O$: C, 59.76; H, 5.64; N, 11.61. Found: C, 59.68; H, 5.42; N, 11.53.

(3*S*)-1,2,3,4-Tetrahydro-3-hydroxymethyl-6-methyl-β-carboline [(*S*)-4m]——mp 206—207 °C (iso-PrOH), 73%. IR ν_{max}^{Nujol} cm^{-1}: 3290. $[\alpha]_D^{20}$ −72.8° (*c*=1.0, MeOH). *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.39; H, 7.35; N, 13.08.

(3*S*)-1,2,3,4-Tetrahydro-3-hydroxymethyl-8-methyl-β-carboline [(*S*)-4n]——mp 246—248 °C (EtOH), 63%. IR ν_{max}^{Nujol} cm^{-1}: 3240. $[\alpha]_D^{20}$ −87.4° (*c*=1.0, MeOH). *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.11; H, 7.44; N, 12.97.

(3*R*)-9-Benzyl-1,2,3,4-tetrahydro-2-(methylthiothiocarbonyl)-β-carboline-3-carboxylic Acid [(*R*)-1c]——A solution of (*R*)-**18b** (1.225 g, 4 mmol), 10 N NaOH (0.8 ml, 8 mmol), and CS_2 (0.24 ml, 4 mmol) in DMSO (20 ml) was stirred at room temperature for 10 min, and then methyl iodide (MeI) (0.29 ml, 4.4 mmol) was added. After being stirred for 20 min, the mixture was diluted with H_2O (100 ml), acidified with 10% HCl and extracted with AcOEt. The

extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel using $CHCl_3$–MeOH (90 : 5) as the eluent to yield (*R*)-**1c** (0.89 g, 52%) as a pale yellow powder. IR ν_{max}^{Nujol} cm^{-1}: 1700. NMR ($CDCl_3$) δ: 2.65 (3H, s), 5.17 (2H, s). MS *m/z*: 396 (M^+), 348 ($M^+ - CH_3SH$). Compounds **1b**, **1d**—**g**, and **3c** were prepared in a similar manner and are listed in Tables I and II.

Methyl (3*S*)-6-Chloro-1,2,3,4-tetrahydro-3-hydroxymethyl-β-carboline-2-carbodithioate [(*S*)-2c]——CS_2 (0.13 ml, 2.2 mmol) was added to a solution of (*S*)-**4l** (0.473 g, 2 mmol) and Et_3N (0.31 ml, 2.2 mmol) in DMSO (5 ml), and the whole was stirred for 30 min. After addition of MeI (0.14 ml, 2.2 mmol), the mixture was stirred at room temperature for 5 h, diluted with water, and extracted with AcOEt. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from aq. EtOH to give (*S*)-**2c** (560 mg, 86%), mp 180—184 °C. IR ν_{max}^{Nujol} cm^{-1}: 3300—3370, 1590. NMR ($CDCl_3$–DMSO-d_6) δ: 2.70 (3H, s), 3.65 (2H, d, J=7.2 Hz). MS *m/z*: 328, 326 (M^+), 280, 278 ($M^+ - CH_3SH$). Compounds **2b**, **2d**—**e**, **3a**—**b**, and **3d**—**i** were similarly prepared and are listed in Tables I and III.

Methyl (3*S*)-1,2,3,4-Tetrahydro-3-methoxymethyl-β-carboline-2-carbodithioate [(*S*)-3g]——An ethereal CH_2N_2 solution [prepared from *N*-methylnitrosourea (20.6 g, 200 mmol) and 40% KOH (63 ml) in ether (200 ml)] was added dropwise to a suspension of (*S*)-**2a** (1.46 g, 5 mmol) and silica gel (10 g) in ether (50 ml) at 5 °C, and the whole was stirred at the same temperature for 2 h. The same amount of a solution of CH_2N_2 was added to the mixture, and the suspension was stirred for 1 h. The silica gel was filtered off, and washed with AcOEt, and the filtrate and washing were combined. After removal of the solvent, the residue was dissolved in AcOEt and allowed to stand at room temperature to give (11a*S*)-5,5a,11,11a-tetrahydro-1*H*,3*H*-oxazolo[4′,3′ : 6,1]pyrido[3,4-*b*]indol-3-one (270 mg, 24%), mp 227—229 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1750, 1730. MS *m/z*: 228 (M^+), 213, 167, 143. $[\alpha]_D^{20}$ −125.2° (c=1.0, dioxane). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.18; H, 5.25; N, 12.09. The mother liquor (AcOEt) was evaporated, and the residue was purified by chromatography on silica gel with hexane–AcOEt (8 : 2) to give (*S*)-**3g** (315 mg, 21%), mp 162—164 °C. NMR ($CDCl_3$) δ: 2.72 (3H, s), 3.30 (3H, s). MS *m/z*: 306 (M^+), 291, 274, 259, 227. $[\alpha]_D^{20}$ +114.4° (c=1.0, $CHCl_3$).

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