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A New Method for the Preparation of 3,4-Dihydro- and 1,2,3,4-Tetrahydro-β-carbolines

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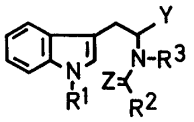
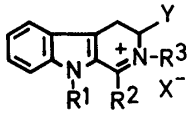
N-Alkylthiocarbonyltryptophan (**2a**—**i**) and tryptamine (**2j**—**m**) derivatives can be converted into the corresponding 3,4-dihydro-β-carbolines (**3**) under mild conditions by the use of alkylating or acylating agents. The $NaBH_4$ reduction of 1,3-disubstituted 3,4-dihydro-β-carbolines (**3a**—**i**) gave *cis*- (**5**) or *trans*-1,2,3,4-tetrahydro-β-carbolines (**6**) with satisfactory stereoselectivity. The synthesis of optically active **3a**, **b** and **5a**, **b** is also described.

Keywords——N^{α}-thioacyltryptophan; 3,4-dihydro-β-carboline-3-carboxylate 1-substituted; 1,2,3,4-tetrahydro-β-carboline-3-carboxylate 1-substituted; alkylthioiminium salt; Bischler–Napieralski reaction; Pictet–Spengler reaction; Lawesson's reagent

We recently reported a new synthetic route providing acid- and base-sensitive 3,4-dihydro- (**3**) and 1,2,3,4-tetrahydro-β-carboline nuclei, (**5** and **6**), from tryptophan and tryptamine derivatives under mild reaction conditions.[1,2] The route involves the preparation of an N^{α}-thioacyl derivative (**2**), cyclization of **2** to **3** *via* a thioiminium salt (**4**) by treatment with an alkylating or an acylating agent, and the stereoselective reduction of **3** to 1,2,3,4-tetrahydro-β-carbolines (**5** and/or **6**) with sodium borohydride. In this paper, we present full details of the above studies.



1 : Z=O
2 : Z=S



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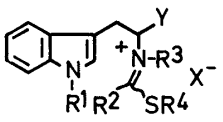

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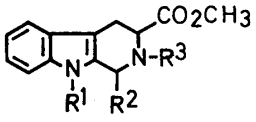


5 : 1,3-*cis*
6 : 1,3-*trans*

a: $R^1=R^3=H$, $R^2=CH_3$, $Y=CO_2CH_3$
b: $R^1=R^3=H$, $R^2=C_6H_5$, $Y=CO_2CH_3$
c: $R^1=R^3=H$, $R^2=C_6H_{11}$, $Y=CO_2CH_3$
d: $R^1=R^3=H$, $R^2=C(CH_3)_3$, $Y=CO_2CH_3$
e: $R^1=H$, $R^2+R^3=(CH_2)_3$, $Y=CO_2CH_3$
f: $R^1=H$, $R^2=CH_3$, $R^3=CH_2C_6H_5$, $Y=CO_2CH_3$
g: $R^1=CH_3$, $R^2=C_2H_5$, $R^3=H$, $Y=CO_2CH_3$
h: $R^1=CH_3$, $R^2=C_6H_5$, $R^3=H$, $Y=CO_2CH_3$
i: $R^1=CH_3$, $R^2=C_6H_{11}$, $R^3=H$, $Y=CO_2CH_3$
j: $R^1=R^3=Y=H$, $R^2=CH_3$
k: $R^1=R^3=Y=H$, $R^2=C_6H_5$
l: $R^1=R^3=Y=H$, $R^2=C_6H_{11}$
m: $R^1=Y=H$, $R^2=CH_3$, $R^3=CH_2C_6H_5$

Chart 1

Synthesis of 3,4-Dihydro-β-carbolines (3)

Although the Bischler–Napieralski (B.–N.) reaction is the most common method for the synthesis of **3**, the reaction is usually conducted by heating an amide with a dehydrating agent (phosphorus oxychloride or phosphorus pentoxide).[3] Under these rather drastic conditions, N^{α}-acetyltryptophan and its ester analogs yield 1-methyl-β-carboline (harman) instead of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid derivatives, owing to the accompanying aromatization and decarboxylation.[4] Several improved methods using polyphosphate ester,[5]

mercuric chloride,[6] and acetyl chloride–trifluoroacetic acid[7] under milder conditions have been reported by other groups. Recently we found that N^{α}-methylthiocarbonyltryptophan methyl ester (**2a**), prepared from the corresponding N^{α}-acetyl derivative (**1a**) by treatment with Lawesson's reagent,[8] was readily converted to methyl 1-methyl-3,4-dihydro-β-carboline-3-carboxylate (**3a**) by the reaction with methyl iodide in acetone at room temperature. Since the reaction conditions are very mild and almost non-acidic, this method should be applicable to the synthesis of a variety of sensitive 3,4-dihydro-β-carbolines as an improved B.–N. reaction.

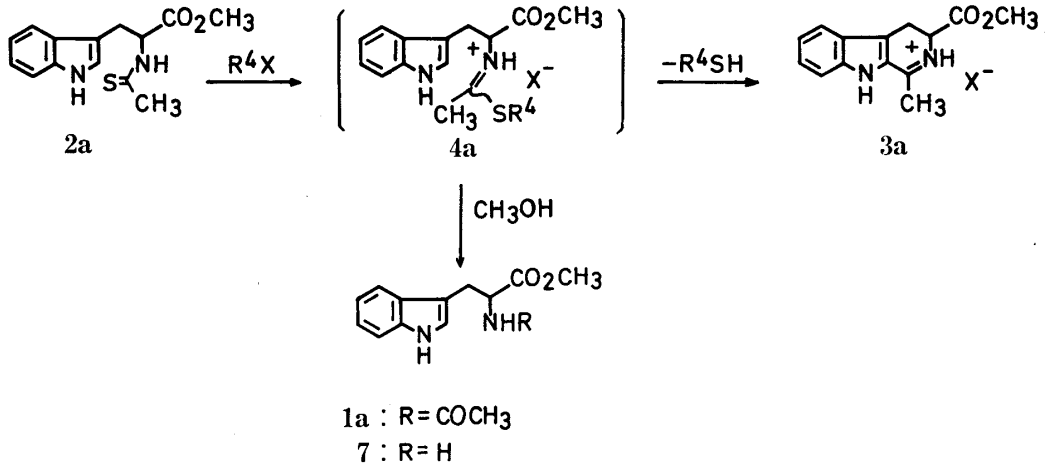
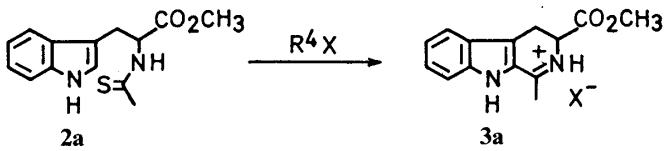


Chart 2

Initially we examined the reaction of **2a** with various alkylating and acylating agents (R^4X) in different solvents (Chart 2). Table I summarizes the results. Most reagents (R^4X) are effective for this cyclization reaction, giving **3a** in a fair to good yield. However, the Meerwein reagent ($Et_3O^+BF_4^-$), tosyl chloride, and trimethylchlorosilane were not favorable, because the reactions with these reagents were very slow and the reaction mixtures showed con-

TABLE I. The Cyclization of N^{α}-Methylthiocarbonyltryptophan Methyl Ester (**2a**)



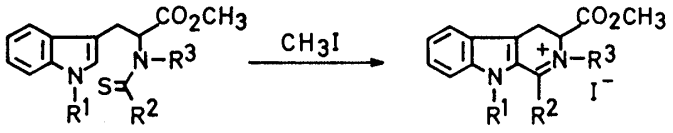
Entry	R^4X	Reaction conditions			Yield of **3a** (%)
		Solvent	Temp.	Time (h)	
1	CH_3I	CH_3OH	r.t.	24	—[a]
2	CH_3I	CH_3COCH_3	r.t.	24	90
3	CH_3I	CH_2Cl_2	Refl.	24	90
4	CH_3I	CH_3CN	50 °C	15	84
5	$C_6H_5CH_2Br$	CH_2Cl_2	Refl.	24	82
6	$CH_2=CHCH_2Br$	CH_2Cl_2	Refl.	48	84
7	$C_6H_5CH_2Cl$	CH_2Cl_2	Refl.	72	16
8	C_6H_5COCl	CH_2Cl_2	Refl.	24	83
9	CH_3COCl	CH_2Cl_2	Refl.	24	72
10	$ClCO_2C_2H_5$	CH_3COCH_3	r.t.	48	38

a) The reaction gave a mixture of **1a** and **7**.[9]

siderable coloration. As for solvents, aprotic ones are generally usable and no significant difference was observed among them. On the other hand, protic solvents such as methanol (entry 1) did not give a cyclized compound but a mixture of tryptophan methyl ester (**7**)[9] and its N^{α}-acetyl derivative (**1a**).

We next investigated the cyclization of a variety of N^{α}-thioacyltryptophans (**2b—i**) and N^{α}-thioacyltryptamines (**2j—m**) under similar conditions. Various tryptophan derivatives, upon treatment with methyl iodide, gave the corresponding 3,4-dihydro-β-carbolines in good yields (Table II). The compounds (**2c, d, f**) which have bulky substituents (cyclohexyl, *tert*-butyl, or N^{α}-benzyl) also cyclized under the conditions described to give **3c, d, f** in satisfactory yields (entries 12, 13, and 15). Only N^{α}-cyclohexylthiocarbonyl-1-methyltryptophan methyl ester (**2i**) did not undergo smooth cyclization. The reaction was very sluggish and gave a poor

TABLE II. The Cyclization of the Thioamides (**2b—i**) with Methyl Iodide

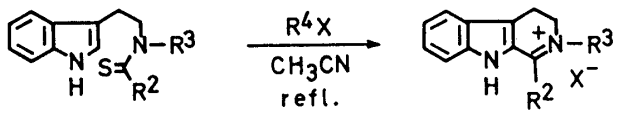


2b—i **3b—i**

Entry	2	Reaction conditions			Yield of 3 (%)	mp (dec.) °C
		Solvent	Temp.	Time (h)		
11	**b**	CH_2Cl_2	Refl.	24	83	191—193[c]
12	**c**	CH_3CN	50 °C	24	80	215—217[c]
13	**d**	CH_3CN	50 °C	60	52	180—181[d]
14	**e**	CH_3COCH_3	Refl.	48	86	169—170[e]
15	**f**	CH_2Cl_2	Refl.	24	62	203—205[d]
16	**g**	CH_3CN	50 °C	24	88	169—170[e]
17	**h**	CH_3CN	50 °C	96	79	180—181[c]
18	**i**	CH_3CN	50 °C	96	33[a,b]	159—161[c]

a) The starting material (**2i**) was recovered unchanged in around 35% yield. *b*) **3b** (X=Br) was obtained in 39% yield when 4-nitrobenzyl bromide was used instead of CH_3I. *c*) Recrystallized from CH_3OH–iso-Pr_2O. *d*) Recrystallized from CH_3OH. *e*) Recrystallized from iso-PrOH.

TABLE III. The Cyclization of the Thioamides (**2j—m**) with Alkyl Halide



2j—m **3j—m**

Entry	2	R^4X	Reaction time (h)	Yield of 3 (%)	mp (dec.) °C[b]
19	**j**	CH_3I	24	83	273—275
20	**k**	CH_3I	24	72	259—260
21	**l**	CH_3I	24	28[a]	—
22	**l**	$C_6H_5CH_2Br$	48	70	266—267
23	**l**	4-$NO_2C_6H_4CH_2Br$	15	90	266—267
24	**m**	CH_3I	5	43	263—264
25	**m**	$C_6H_5CH_2Br$	2	56	277—278
26	**m**	4-$NO_2C_6H_4CH_2Br$	4	76	277—278

a) Isolated as the free base, mp 198—200 °C. *b*) All products were recrystallized from CH_3OH.

yield of **3i**, along with the unchanged starting material. The use of other alkylating agents failed to improve the yield of **3i**.

Table III shows the results of the similar cyclization reaction of tryptamine derivatives. All the reactions were carried out in refluxing acetonitrile, because they were generally slower than those of tryptophan derivatives. Methyl iodide is not always effective in this series of compounds (entries 21 and 24). However, the use of benzyl bromides remarkably improved the yields of cyclization products (entries 22, 23, 25, and 26).

We presumed that this cyclization proceeds through the initial formation of an alkylthioiminium salt (**4**) followed by spontaneous cyclization and liberation of an alkanethiol at room temperature or in a refluxing solvent, giving a 3,4-dihydro-β-carboline (Chart 2). We have some experimental evidence (Chart 3) for this pathway.

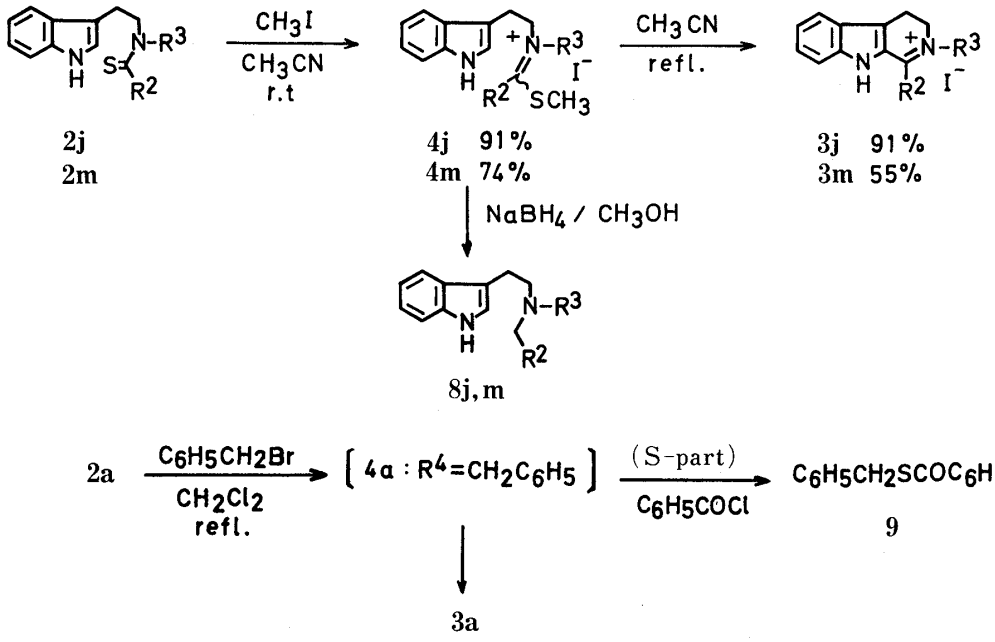


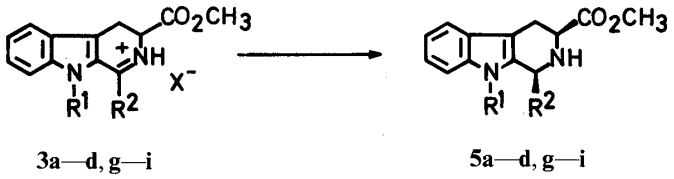
Chart 3

When **2j**, **m** in acetonitrile were allowed to react with methyl iodide at room temperature, the intermediary thioiminium salts (**4j**, **m**) were precipitated as crystals, whose structures were confirmed from their spectral data and also by converting them (with $NaBH_4$) to N^{α}-ethyltryptamine (**8j**) and N^{α}-benzyl-N^{α}-ethyltryptamine (**8m**), respectively. The isolated thioiminium salts (**4j**, **m**) were, in turn, heated at reflux in acetonitrile without addition of methyl iodide to give the cyclization products, **3j**, **m**, in good yields. In order to determine the liberated sulfur part, we examined the reaction using benzyl bromide as an alkylating agent. The reaction of **2a** with an equimolar amount of benzyl bromide gave 75% yield of **3a** and 95% yield of phenylmethanethiol, which was isolated as its benzoate (**9**) by treatment of the mother liquor with benzoyl chloride. A similar reaction with two molar amounts of benzyl bromide also gave **3a** in 75% yield and phenylmethanethiol in 72% yeild, together with dibenzylsulfide in 5% yield. These results indicate that alkyl halide is used only for the alkylation of **2** yielding **4**, and the sulfur part is eliminated as an alkanethiol rather than as a dialkylsulfide (a plausible alternative).

Reduction of 3,4-Dihydro-β-carboline with $NaBH_4$

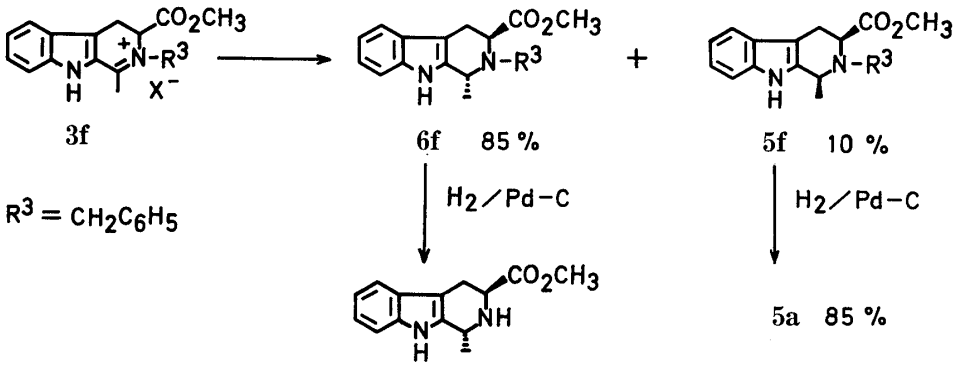
Many authors have described the synthesis of 1-substituted 1,2,3,4-tetrahydro-β-carboline-3-carboxylates (**5** and **6**) by the Pictet–Spengler (P.–S.) reaction of tryptophan

derivatives and various aldehydes or ketones, and have discussed the diastereoisomeric ratio of the products, **5** and **6**.[11] In general, the P.-S. reaction was reported to give a mixture of 1,3-*cis* (**5**) and 1,3-*trans* isomers (**6**), with some exceptions.[11a] On the other hand, Kanaoka *et al.*[5] synthesized **5a** by the hydride reduction of **3a** prepared by their improved B.–N. reaction. However, little work has been done on the latter synthetic route *via* the 3,4-dihydro-derivatives (**3**) because of difficulty in the preparation of **3** by the usual B.–N. reaction. Thus, we were interested in the conversion of a variety of **3**, prepared by our method described in the preceding section, into the 1,2,3,4-tetrahydro derivatives, **5** or **6**, by treatment with hydride reducing agents, and in the steric course of the reduction.



3a—d, g—i **5a—d, g—i**

Chart 4



3f **6f** 85 % **5f** 10 %

$R^3 = CH_2C_6H_5$

H_2/Pd-C H_2/Pd-C

6a 91 % **5a** 85 %

Chart 5

TABLE IV. The Reduction of **3** with $NaBH_4$

Entry	3	Yield (%) of reduction products				P.–S. reaction
		5	(mp, °C)	6	(mp, °C)	ratio (5 : 6)[a]
27	a	93	(133—134)	—[b]		91 : 6[c]
28	b	95	(209—210)	—[b]		40 : 60
29	c	85[d]	(154—155)	10	(147—148)	40 : 60
30	d	95	(116—117)	—		
31	f	11	(foam)	85	(144—145)	$5 \ll 6$[e]
32	g	94[d]	(73—74)	—		0 : 100
33	h	86	(138—139)	3	(197—198)	0 : 100
34	i	61	(128—129)	6	(149—150)	0 : 100

a) Ratios reported in ref. 11*g*, unless otherwise stated. *b*) A trace of **6** was detected in the reaction mixture by TLC. *c*) The P.–S. reaction of H–Trp–OH and acetaldehyde. (Ref. 11*a*). *d*) $NaBH_3CN$ was used. *e*) N^a-Benzyl H–Trp–OCH_3 and acetaldehyde gave 48% yield of **6f** and 9% yield of **5f** in our hands.

The reduction was carried out at −20——78 °C in methanol with $NaBH_4$ or sodium cyanoborohydride ($NaBH_3CN$), and the results are summarized in Table IV. As can be seen in the table, the reduction proceeded almost stereoselectively to give the 1,3-*cis* isomers (**5**) as

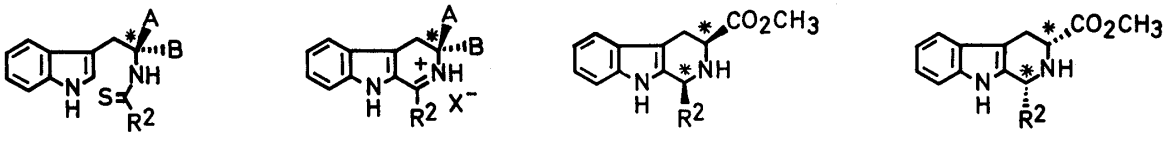
major products in most cases; these products could be isolated in pure form by simple recrystallization in good yields. The amounts of the *trans* isomers (**6**) formed were very small or detectable only by thin-layer chromatography (TLC). Only the N^{α}-benzyl derivative (**3f**) afforded the 1,3-*trans* isomer (**6f**) predominantly, together with a small amount of the *cis*-isomer (**5f**) (entry 31); the hydrogenolysis of **5f** and **6f** gave **5a** and **6a**, respectively (Chart 5).

The stereochemistry of the reduction products was deduced from the spectral (proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C-NMR)) and physical (mp and *Rf* values) properties, as compared with those reported in the literature,[11] and also from chemical correlation with known compounds. Particularly informative was a characteristic ABX pattern for the C-3 methine and C-4 methylene protons in the ^{1}H-NMR spectra (J_{AB} = 14—16 Hz, J_{AX} = 10—12 Hz, J_{BX} = 3—5 Hz); this was observed with all the 1,3-*cis* isomers (**5a—i**), in agreement with the results reported by several authors.[11b,d,12] In the ^{13}C-NMR spectra, the signals for C-1 and C-3 in the 1,3-*trans* isomers (**6**) appeared at higher field than those of the corresponding *cis* isomers (**5**), as Cook *et al.*[11g] described for typical 1,3-disubstituted 1,2,3,4-tetrahydro-β-carboline derivatives. The 1-*tert*-butyl derivative (**5d**) (entry 30) is a new compound. Therefore, the 1,3-*cis* relationship follows only from the analogy with other 1,3-*cis* homologs (an ABX pattern for the C-3 and C-4 protons in the ^{1}H-NMR; signals due to C-1 at 62.2 ppm and C-3 at 56.2 ppm in the ^{13}C-NMR).

It is of interest to compare the diastereoisomeric ratio with that of the P.–S. reaction products (also shown in Table IV). A great difference is observed with N^9-methyl derivatives (entries 32, 33, and 34); in contrast to the 1,3-*trans* predominance[11g] in the P.–S. reaction, mainly the 1,3-*cis* isomers (**5g—i**) were obtained by our method. On the other hand, the result with the N^2-benzyl derivative (entry 31) is parallel with the well-known results of the P.-S. reaction of various N^{α}-benzyltryptophan derivatives.[11c,h,i]

Optically Active 3,4-Dihydro- and 1,2,3,4-Tetrahydro-β-carbolines

Previero *et al.*[7a] and Kametani *et al.*[7b] have synthesized optically active 1-methyl-3,4-dihydro-β-carboline-3-carboxylates by the reaction of (*R*)- and (*S*)-N^{α}-acetyltryptophan derivatives and acetyl chloride in trifluoroacetic acid. More recently, Szántay *et al.*[13a] intensively studied the B.–N. reaction of (*S*)-N^{α}-acyltryptophans and succeeded in the asymmetric synthesis[13b] of Vinca alkaloids *via* chiral 1-substituted 3,4-dihydro-β-carboline-3-carboxylates.



2a, b **3a, b** (1*S*,3*S*)**5a, b** (1*R*,3*R*)**5a, b**

(*S*) A = CO_2CH_3 B = H
(*R*) A = H B = CO_2CH_3

Chart 6

We are also interested in the formation of a chiral β-carboline nucleus by using our cyclization-reduction method, and we attempted to synthesize methyl (*R*)- and (*S*)-1-methyl-3,4-dihydro- and 1,2,3,4-tetrahydro-β-carboline-3-carboxylates, (*R*)- and (*S*)-**3a**, **5a**, and also the 1-phenyl homologs, (*R*)- and (*S*)-**3b**, **5b**, from D- and L-tryptophans. Optically active thioamides, (*R*)- and (*S*)-**2a**, **b**, were prepared by the reaction of the corresponding amides, (*R*)- and (*S*)-**1a**, **b**, with Lawesson's reagent, which was reported to be a non-racemizing thionation reagent for peptides.[14] The optical purity of (*S*)-**2a** was also confirmed experimentally by reconverting it into the original amide, (*S*)-**1a**; treatment of the thioamide, (*S*)-**2a**, with methyl iodide in methanol,[9] followed by acetylation with acetic anhydride gave a 92%

TABLE V. The Cyclization and Reduction of the Optically Active Isomers

Entry	2	R^4X	Cyclization (2→3)					Reduction	
			Conditions[a]			3 (%)[b]	$[\alpha]_D^{20}$[c]	5 (%)[d]	$[\alpha]_D^{20}$[d]
35	(*S*)-**a**	CH_3I	CH_3COCH_3	r.t.	24 h	90	+221°	90	−83.2°
36	(*R*)-**a**	CH_3I	CH_3COCH_3	r.t.	24 h	90	−222°	90	+82.4°
37	(*S*)-**a**	$C_6H_5CH_2Br$	CH_2Cl_2	Refl.	24 h	76	+263°	93	−81.6°
38	(*R*)-**a**	$C_6H_5CH_2Br$	CH_2Cl_2	Refl.	24 h	77	−264°	91	+81.0°
39	(*S*)-**a**	$CH_2=CHCH_2Br$	CH_2Cl_2	Refl.	48 h	84	+260°		
40	(*S*)-**a**	CH_3COCl	CH_2Cl_2	Refl.	24 h	72	+299°		
41	(*S*)-**a**	C_6H_5COCl	CH_2Cl_2	Refl.	24 h	83	+305°	90	−80.6°
42	(*R*)-**a**	C_6H_5COCl	CH_2Cl_2	Refl.	24 h	82	−308°	90	+80.2°
43	(*S*)-**b**	CH_3I	CH_2Cl_2	Refl.	24 h	Not purified		78[e]	−91.8°[f]
44	(*R*)-**b**	CH_3I	CH_2Cl_2	Refl.	24 h	Not purified		73[e]	+89.8°[f]

a) Solvent, temp, time. *b*) Yields of isolated products as HX salts corresponding to R^4X used. *c*) $[\alpha]_D^{20}$ ($c=1.0$, CH_3OH). *d*) Yields and $[\alpha]_D^{20}$ ($c=1.0$, CH_3OH) of isolated products as HCl salts. The authentic (1*S*,3*S*)-isomer[15a]; $[\alpha]_D^{20}$ −82.4° ($c=1.0$, CH_3OH). *e*) Yield from **2b**. Isolated as the free base. *f*) Measured in 1 N aqueous HCl solution.

yield of the amide, (*S*)-**1a**, whose optical rotation coincided with that of authentic (*S*)-**1a**. The cyclization of (*R*)- and (*S*)-**2a** (entries 35—42) was examined with several different reagents as shown in Table V. All of the reagents employed gave the corresponding salts (X=I, Br, and Cl) of optically active (*R*)- and (*S*)-**3a** in good yields. Each salt was stereoselectively converted into the 1,3-*cis* isomer ((1*R*, 3*R*)-**5a** or (1*S*, 3*S*)-**5a**) with $NaBH_4$. Specific rotation values of the products (entries 35, 36, 37, 38, 41, and 42) coincided with one another and also with that of an authentic sample.[15] This indicates that the reduction, and thus the cyclization, proceeded without racemization. As with the (*R*)- and (*S*)-phenythiocarbonyl derivatives ((*R*)- and (*S*)-**2b**) (entries 43 and 44), the cyclization products ((*R*)- and (*S*)-**3b**) could not be obtained in crystalline form, so we converted the crude products into the tetrahydro-β-carbolines, (1*R*, 3*R*)- and (1*S*, 3*S*)-**5b**, without purification. Although not determined precisely, the optical purity[16] of the products ((*R*)- and (*S*)-**5b**) thus obtained is presumed to be high, since the reaction conditions were as mild as those used for the preparation of optically active 1-methyl derivatives (**3a** and **5a**).

Experimental

Melting points were determined on a Yanaco MP-J2 hot stage microscope and with a Yamato MP-21 melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were obtained with a Hitachi 260-10 or an FX-6200 FT-IR spectrophotometer. ^1H and ^{13}C-NMR spectra were measured with a JEOL JNM-PMX 60 or a JEOL FX-100 S spectrometer. Mass spectra (MS) were recorded on a Hitachi RMU-6M mass spectrometer. Optical rotations were recorded with an automatic digital polarimeter (PM-201, Union Giken).

Preparation of the Thioamides (2)——The thioamides (**2**) were prepared by treatment of the appropriate amide (**1**) with Lawesson's reagent (0.6 eq) in dimethoxyethane (DME) at 20—50 °C. The general procedure is exemplified by the preparation of **2a**.

N^{α}-Methylthiocarbonyltryptophan Methyl Ester (2a)——A mixture of **1a** (5.2 g, 20 mmol) and Lawesson's reagent (4.84 g, 12 mmol) in DME (100 ml) was stirred at room temperature for 3 h. The DME was removed under reduced pressure. The residue was taken up in AcOEt, and the solution was washed with saturated aqueous $NaHCO_3$ solution and H_2O, then dried. Removal of the AcOEt gave a crude product which was purified by column chromatography on silica gel (×10). Elution with hexane–AcOEt (1 : 1) gave 5.39 g (98%) of **2a**, mp 99—101 °C (Lit.[6] mp 102—104 °C). IR (Nujol) cm^{-1}: 3300—3400, 1730. MS *m/e*: 276 (M^+), 201. ^1H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.45 (2H, t), 3.68 (3H, s), 5.45 (1H, m), 6.87 (1H, d), 6.95—7.80 (5H, m), 8.30 (1H, br).

N^{α}-Phenylthiocarbonyltryptophan Methyl Ester (2b)——This compound (**2b**) was obtained from **1b** in 95% yield as a foam. IR ($CHCl_3$) cm^{-1}: 3450, 3350, 1730. MS *m/e*: 338 (M^+), 201. ^1H-NMR ($CDCl_3$) δ: 3.60 (2H, quasi-q), 3.70 (3H, s), 5.70 (1H, m), 6.90 (1H, d), 6.95—7.75 (9H, m), 7.95 (1H, br), 8.10 (1H, br).

N^{α}-Cyclohexylthiocarbonyltryptophan Methyl Ester (2c)——This compound (**2c**) was obtained from **1c** in 90% yield as a foam. IR (film) cm^{-1}: 3200—3500, 1730. MS *m/e*: 344 (M^+), 201. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.0 (11H, m), 2.40 (1H, br), 3.50 (2H, quasi-t), 3.70 (3H, s), 5.50 (1H, m), 6.95 (1H, d), 7.0—7.8 (4H, m), 8.20 (1H, br).

N^{α}-(*tert*-Butylthiocarbonyl)tryptophan Methyl Ester (2d)——This compound (**2d**) was obtained from **1d** in 76% yield, mp 122—123 °C. IR (Nujol) cm^{-1}: 3270, 1730. MS *m/e*: 318 (M^+), 201. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s), 3.1—3.7 (2H, quasi-t), 3.71 (3H, s), 5.40—5.65 (1H, m), 6.90 (1H, d), 6.95—7.6 (4H, m), 7.75 (1H, br), 8.15 (1H, br). *Anal.* Calcd for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80; S, 10.07. Found: C, 64.13; H, 7.03; N, 8.80; S, 10.00.

Methyl 3-(3-Indolyl)-2-(2-thioxopyrrolidin-1-yl)propionate (2e)——This compound (**2e**) was obtained from **1e** in 84% yield, mp 117—118 °C. IR (Nujol) cm^{-1}: 3200, 1740. ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.2 (2H, m), 2.70—3.15 (2H, quasi-t), 3.2—3.6 (4H, m), 3.70 (3H, s), 6.05 (1H, quasi-q), 7.0—7.7 (5H, m), 8.20 (1H, br). *Anal.* Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.25; S, 10.60. Found: C, 63.35; H, 6.11; N, 9.05; S, 10.36.

N^{α}-Benzyl-N^{α}-methylthiocarbonyltryptophan Methyl Ester (2f)——This compound (**2f**) was obtained from **1f** in 74% yield as a foam. IR ($CHCl_3$) δ: 3400, 1730. MS *m/e*: 366 (M^+), 201. ^{1}H-NMR ($CDCl_3$) δ: 2.55, 2.60 (3H, a pair of singlets) 3.30, 3.45 (3H, a pair of singlets), 3.90, 4.50 (2H, a pair of doublets), 3.3—3.7 (2H, m), 5.4—6.0 (1H, m), 6.8—7.7 (9H, m), 8.20 (1H, br). *Anal.* Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.83; H, 6.05; N, 7.65; S, 8.74. Found: C, 68.99; H, 6.13; N, 7.78; S, 9.01.

N^{α}-Ethylthiocarbonyl-1-methyltryptophan Methyl Ester (2g)——This compound (**2g**) was obtained from **1g** in 98% yield, mp 73—74 °C. IR (Nujol) cm^{-1}: 3420, 1740. MS *m/e*: 304 (M^+), 215. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t), 2.60 (2H, q), 3.50 (2H, quasi-t), 3.70 (6H, s), 5.50 (1H, m), 6.80 (1H, s), 6.9—7.8 (5H, m). *Anal.* Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 63.06; H, 6.74; N, 9.22; S, 10.49.

N^{α}-Phenylthiocarbonyl-1-methyltryptophan Methyl Ester (2h)——This compound (**2h**) was obtained from **1h** in 87% yield, mp 125—126 °C. IR (Nujol) cm^{-1}: 3360, 3060, 1740. MS *m/e*: 352 (M^+), 215. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (2H, q), 3.68, 3.72 (6H, 2s), 5.65 (1H, m), 6.80 (1H, s), 7.0—7.8 (9H, m), 8.05 (1H, br). *Anal.* Calcd for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.10. Found: C, 68.34; H, 5.66; N, 7.81; S, 9.02.

N^{α}-Cyclohexylthiocarbonyl-1-methyltryptophan Methyl Ester (2i)——This compound (**2i**) was obtained from **1i** in 95% yield as a foam. IR ($CHCl_3$) cm^{-1}: 3200—3400, 1740. MS *m/e*: 358 (M^+), 215. ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.05 (10H, m), 2.45 (1H, br), 3.50 (2H, t), 3.73 (6H, s), 5.50 (1H, m), 6.80 (1H, s), 7.0—7.7 (5H, m).

***N*-[2-(3-Indolyl)ethyl]thioacetamide (2j)**——This compound (**2j**) was obtained from **1j** in 95% yield, mp 128—129 °C (lit.[6] mp 126—127 °C). IR (Nujol) cm^{-1}: 3400, 3200, 3050. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.05 (2H, t), 3.95 (2H, q), 6.9—7.7 (6H, m), 8.13 (1H, br).

***N*-[2-(3-Inodolyl)ethyl]thiobenzamide (2k)**——This compound (**2k**) was obtained from **1k** in 95% yield, mp 117—118 °C (Lit.[6] mp 117—119 °C). IR (Nujol) cm^{-1}; 3420, 3220, 3060. ^{1}H-NMR ($CDCl_3$) δ: 3.15 (2H, t), 4.10 (2H, d), 6.85—7.80 (11H, m), 8.05 (1H, br).

***N*-[2-(3-Indolyl)ethyl]cyclohexanecarbothioamide (2l)**——This compound (**2l**) was obtained from **11** in 88% yield, mp 115—116 °C. IR (Nujol) cm^{-1}: 3340, 3300. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.0 (10H, m), 2.40 (1H, br), 3.10 (2H, t), 4.00 (2H, q), 7.0—7.8 (6H, m), 8.15 (1H, br). *Anal.* Calcd for $C_{17}H_{22}N_2S$: C, 71.29; H, 7.74; N, 9.78; S, 11.19. Found: C, 71.22; H, 7.78; N, 9.93; S, 11.09.

***N*-Benzyl-*N*-[2-(3-indolyl)ethyl]thioacetamide (2m)**——This compound (**2m**) was obtained from **1m** in 95% yield, mp 92—93 °C. IR (Nujol) cm^{-1}: 3460, 3400, 3000. ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s), 3.15 (2H, q), 3.70 (1H, m), 4.15 (1H, m), 4.55, 5.30 (2H, 2s), 6.8—7.8 (10H, m), 8.17 (1H, br). *Anal.* Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.08; S, 10.39. Found: C, 74.13; H, 6.55; N, 9.18; S, 10.33.

Preparation of 3 (X=I): Cyclization of 2 with Methyl Iodide——Cyclization was carried out under an argon atmosphere in the dark. The general procedure is exemplified by the preparation of **3a**.

3-Methoxycarbonyl-1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3a, X=I)——A solution of **2a** (5.52 g, 20 mmol) and CH_3I (5.5 ml) in acetone (55 ml) was stirred for 24 h at room temperature. The acetone solution was concentrated under reduced pressure. The resulting precipitates were collected by filtration and recrystallized from CH_3OH to give 6.66 g (90%) of **3a** (X=I), mp 214—216 °C (dec.). IR (Nujol) cm^{-1}: 3250, 1730, 1620, 1550. MS *m/e*: 242 (M^+), 183. ^{1}H-NMR (DMSO-d_6) δ: 2.85 (3H, s), 3.65 (2H, quasi-d), 3.75 (3H, s), 5.25 (1H, quasi-t), 7.0—8.0 (4H, m), 12.40 (1H, br s). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HI$: C, 45.42; H, 4.08; N, 7.57; I, 34.28. Found: C, 45.28; H, 4.12; N, 7.55; I, 34.03.

3-Methoxycarbonyl-1-phenyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3b, X=I)——IR (Nujol) cm^{-1}: 3200, 3140, 1760, 1600. MS *m/e*: 304 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.70 (3H, s), 3.80 (2H, quasi-q), 5.30 (1H, quasi-q), 6.9—8.15 (9H, m), 12.0 (1H, br s). *Anal.* Calcd for $C_{19}H_{16}N_2O_2 \cdot HI$: C, 52.79; H, 3.96; N, 6.48; I, 29.36. Found: C, 52.23; H, 3.97; N, 6.37; I, 29.46.

1-Cyclohexyl-3-methoxycarbonyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3c, X=I)——IR (Nujol) cm^{-1}: 3160, 3120, 3070, 1750 1620. MS *m/e*: 310 (M^+), 251. ^{1}H-NMR (DMSO-d_6) δ: 1.1—2.2 (11H, m), 3.1—3.6 (2H, m), 3.75 (3H, s), 5.20 (1H, quasi-q), 7.0—8.0 (4H, m), 12.45 (1H, br s). *Anal.* Calcd for $C_{19}H_{22}N_2O_2 \cdot HI$: C, 52.07; H, 5.29; N, 6.39; I, 28.95. Found: C, 52.03; H, 5.29; N, 6.38; I, 29.24.

1-*tert*-Butyl-3-methoxycarbonyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3d, X=I)——IR (Nujol) cm^{-1}: 3170, 1740, 1590. MS *m/e*: 284 (M^+), 225. ^{1}H-NMR (DMSO-d_6) δ: 1.60 (9H, s), 3.4—3.8 (2H, m), 3.70 (3H, s), 5.15

(1H, quasi-q). 7.0—8.0 (4H, m), 12.00 (1H, br s). *Anal.* Calcd for $C_{17}H_{20}N_2O_2 \cdot HI$: C, 49.53; H, 5.13; N, 6.80; I, 30.78. Found: C, 49.69; H, 5.38; N, 6.56; I, 30.93.

1,2,3,5,6,11-Hexahydro-5-methoxycarbonylindolizino[8,7-*b*]indol-4-ium Iodide (3e, X=I)——A solution of **2e** (3.02 g, 10 mmol) and CH_3I (3 ml) in acetone (30 ml) was stirred for 15 h at room temperature. Removal of the solvent and excess CH_3I gave 4.4 g of a methylthioiminium salt (**4e**, X=I) as an oil. IR (Nujol) cm^{-1}: 3480—3240, 1750, 1570. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.6 (2H, m), 2.75 (3H, s), 3.3—3.8 (4H, m), 3.80 (3H, s), 4.20 (2H, quasi-t), 5.00 (1H, t), 7.0—7.8 (5H, m), 9.70 (1H, br s). This oil was dissolved again in acetone (30 ml) and refluxed for 60 h. After cooling, the precipitated crystals were collected and recrystallized from iso-PrOH to give 3.40 g (86%) of **3e** (X=I), IR (Nujol) cm^{-1}: 3080, 1750, 1620, 1580. MS *m/e*: 268 (M^+), 209. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.9—2.7 (2H, m), 3.5—4.0 (4H, m), 3.75 (3H, s), 4.0—4.7 (2H, m), 5.30 (1H, br), 6.9—7.8 (4H, m), 11.95 (1H, br s). *Anal.* Calcd for $C_{16}H_{17}IN_2O_2$: C, 48.50; H, 4.32; I, 32.03; N, 7.07. Found: C, 48.34; H, 4.27; I, 31.84; N, 7.03.

2-Benzyl-3-methoxycarbonyl-1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indolium Iodide (3f, X=I)——IR (Nujol) cm^{-1}: 3090, 1750, 1580. MS *m/e*: 332 (M^+), 273. ^{1}H-NMR (DMSO-d_6) δ: 3.10 (3H, br s), 3.2—4.2 (2H, m), 3.65 (3H, s), 4.9—5.9 (3H, m), 6.9—8.0 (9H, m), 12.55 (1H, br s). *Anal.* Calcd for $C_{21}H_{21}IN_2O_2$: C, 54.80; H, 4.60; N, 6.09; I, 27.57. Found: C, 54.78; H, 4.54; N, 6.04; I, 27.55.

1-Ethyl-3-methoxycarbonyl-9-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3g, X=I)——IR (Nujol) cm^{-1}: 3120, 1730, 1610. MS *m/e*: 270 (M^+), 211. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 1.45 (3H, t), 3.25 (2H, quasi-q), 3.65 (2H, quasi-d), 3.75 (3H, s), 4.05 (3H, s), 5.15 (1H, quasi-q), 7.0—7.8 (4H, m). *Anal.* Calcd for $C_{16}H_{18}N_2O_2 \cdot HI$: C, 48.26; H, 4.81; N, 7.03; I, 31.86. Found: C, 48.12; H, 4.74; N, 7.00; I, 31.85.

3-Methoxycarbonyl-9-methyl-1-phenyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3h, X=I)——IR (Nujol) cm^{-1}: 1740, 1600. MS *m/e*: 318 (M^+), 259. ^{1}H-NMR (DMSO-d_6) δ: 3.30 (3H, s), 3.75 (3H, s), 3.80 (2H, m), 5.30 (1H, m), 7.1—8.1 (9H, m). *Anal.* Calcd for $C_{20}H_{18}N_2O_2 \cdot HI$: C, 53.83; H, 4.29; N, 6.28; I, 28.44. Found: C, 53.56; H, 4.19; N, 6.15; I, 28.27.

1-Cyclohexyl-3-methoxycarbonyl-9-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3i, X=I)——IR (Nujol) cm^{-1}: 1740, 1590. MS *m/e*: 324 (M^+), 265. ^{1}H-NMR (DMSO-d_6) δ: 1.1—2.3 (11H, m), 3.1—3.8 (2H, m), 3.70 (3H, s), 4.05 (3H, s), 5.10 (1H, m), 7.0—8.0 (4H, m). *Anal.* Calcd for $C_{20}H_{24}N_2O_2 \cdot HI$: C, 53.11; H, 5.57; N, 6.19; I, 28.06. Found: C, 53.05; H, 5.58; N, 6.16; I, 28.14.

1-Methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3j, X=I)——A solution of **2j** (1.09 g, 5 mmol) and CH_3I (1 ml) in CH_3CN (10 ml) was stirred for 4 h at room temperature and then concentrated *in vacuo*. The resulting crystals were collected, rinsed with CH_3CN, and dried to give 1.64 g (91%) of **4j**, mp 144—146 °C. IR (Nujol) cm^{-1}: 3300, 3120, 1610. MS *m/e*: 232 (M^+), 185. ^{1}H-NMR (DMSO-d_6) δ: 2.70 (3H, s), 2.80 (3H, s), 3.15 (2H, t), 3.80 (2H, t), 6.95 (1H, d), 7.0—7.7 (4H, m), 10.90 (1H, br). *Anal.* Calcd for $C_{13}H_{16}N_2S \cdot HI$: C, 43.34; H, 4.76; N, 7.78; S, 8.90; I, 35.23. Found: C, 43.23; H, 4.73; N, 7.58; S, 9.08; I, 34.98. A solution of **4j** (1.44 g, 4 mmol) in CH_3CN (20 ml) was refluxed for 24 h. Removal of the solvent, followed by recrystallization from CH_3OH, gave 1.14 g (91%) of **3j** (X=I). IR (Nujol) cm^{-1}: 3000—3600, 1650, 1580. MS *m/e*: 184 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.70 (3H, s), 3.20 (2H, t), 3.90 (2H, t), 7.0—8.0 (4H, m), 12.25 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}N_2 \cdot HI$: C, 46.17; H, 4.20; N, 8.97; I, 40.65. Found: C, 46.33; H, 4.26; N, 8.83; I, 40.35. In a separate experiment (entry 19), **3j** (X=I) was directly obtained from **2j** in 83% yield by heating **2j** with CH_3I in CH_3CN.

1-Phenyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole Hydriodide (3k, X=I)——IR (Nujol) cm^{-1}: 3180, 3120, 3050, 1600. ^{1}H-NMR (DMSO-d_6) δ: 3.35 (2H, t), 4.10 (2H, t), 7.0—8.1 (9H, m), 11.95 (1H, br s). *Anal.* Calcd for $C_{17}H_{14}N_2 \cdot HI$: C, 54.56; H, 4.04; N, 7.49; I, 33.91. Found: C, 54.70; H, 3.96; N, 7.38; I, 34.21.

1-Cyclohexyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole (3l)——A solution of **2l** (1.43 g, 5 mmol) and CH_3I (1 ml) in CH_3CN (10 ml) was refluxed for 24 h. The CH_3CN was removed under reduced pressure. Aqueous NH_4OH solution was added to the residue and the mixture was extracted with $CHCl_3$. After evaporation, the residual oil was chromatographed on silica gel ($CHCl_3$–CH_3OH (9 : 1) as an eluent) to give 0.35 g (28%) of **3l** (free base), mp 198—200 °C. Treatment with HBr–CH_3OH gave **3l** (X=Br), mp 265—267 °C (dec.).

2-Benzyl-1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indolium Iodide (3m, X=I)——A solution of **2m** (1.23 g, 4 mmol) and CH_3I (1 ml) in CH_3CN (10 ml) was stirred for 3 h at room temperature and then concentrated *in vacuo*. The resulting crystals were collected, rinsed with acetone and dried to give 1.33 g (74%) of **4m**, mp 151—153 °C. IR (Nujol) cm^{-1}: 3200, 1570. ^{1}H-NMR (DMSO-d_6) δ: 2.70, 2.80 (3H, a pair of singlets), 2.90, 2.95 (3H, a pair of singlets), 2.7—3.4 (2H, m), 3.7—4.4 (2H, m), 5.25 (2H, m), 6.9—7.7 (10H, m), 10.90 (1H, br s). *Anal.* Calcd for $C_{20}H_{23}IN_2S$: C, 53.34; H, 5.15; I, 28.18; N, 6.22; S, 7.12. Found: C, 53.51; H, 5.20; I, 27.88; N, 6.15; S, 7.18. A solution of **4m** (408 mg, 0.9 mmol) in CH_3CN (10 ml) was refluxed for 5 h. Removal of the solvent, followed by recrystallization from CH_3OH, gave 200 mg (55%) of **3m** (X=I). IR (Nujol) cm^{-1}: 3100, 1610, 1550. MS *m/e*: 274 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.00 (3H, s), 3.22 (2H, quasi-t), 4.14 (2H, quasi-t), 5.35 (2H, s), 7.1—8.0 (9H, m), 12.45 (1H, br s). *Anal.* Calcd for $C_{19}H_{19}IN_2$: C, 56.73; H, 4.76; I, 31.55; N, 6.96. Found: C, 56.55; H, 4.66; I, 31.28; N, 6.78. In a separate experiment (entry 24), **3m** (X=I) was directly obtained from **2m** in 43% yield by heating **2m** with CH_3I in CH_3CN.

Preparation of 3 (X=Br): Cyclization of 2 with Benzyl Bromides or Allyl Bromide——Cyclization was carried out under an argon atmosphere with protection from light. The general procedure is exemplified by the preparation of **3a**

(X=Br).

3a (X=Br)——i) From **2a** and Benzyl Bromide (Entry 5): A solution of **2a** (1.10 g, 4 mmol) and benzyl bromide (1.37 g, 8 mmol) in CH_2Cl_2 (10 ml) was refluxed for 24 h, then concentrated *in vacuo*. The resulting crystals were collected and recrystallized from CH_3OH–ether to give 1.06 g (82%) of **3a** (X=Br), mp 205—207 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HBr$: C, 52.03; H, 4.68; N, 8.68; Br, 24.72. Found: C, 52.31; H, 4.70; N, 8.88; Br, 24.94.

ii) From **2a** and Allyl Bromide (Entry 6): A solution of **2a** (2.00 g, 7.2 mmol) and allyl bromide (1.32 g, 11 mmol) in CH_2Cl_2 (40 ml) was refluxed for 48 h. Work-up gave 1.95 g (84%) of **3a** (X=Br), mp 205—207 °C (dec.).

3i (X=Br)——Treatment of **2i** with 4-nitrobenzyl bromide (1.5 eq) in CH_3CN gave **3i** (X=Br), mp 190—192 °C (dec.) (recrystallized from iso-PrOH–iso-Pr_2O). *Anal.* Calcd for $C_{20}H_{24}N_2O_2 \cdot HBr$: C, 59.26; H, 6.21; N, 6.91; Br, 19.71. Found: C, 59.38; H, 6.22; N, 6.74; Br, 19.51.

3l (X=Br)——i) From **2l** and Benzyl Bromide (Entry 22): Treatment of **2l** with benzyl bromide (1.4 eq) in refluxing CH_3CN gave **3l** (X=Br), IR (Nujol) cm^{-1}: 3000—3300, 1630. ^{1}H-NMR (DMSO-d_6) δ: 1.0—2.3 (10H, m), 2.95—3.65 (3H, m), 3.7—4.2 (2H, m), 7.0—7.9 (4H, m), 12.40 (1H, br s). *Anal.* Calcd for $C_{17}H_{20}N_2 \cdot HBr$: C, 61.27; H, 6.35; N, 8.41; Br, 23.98. Found: C, 61.25; H, 6.35; N, 8.36; Br, 23.86.

ii) From **2l** and 4-Nitrobenzyl Bromide (Entry 23): Treatment of **2l** (1.43 g, 5 mmol) with 4-nitrobenzyl bromide (1.40 g, 6.5 mmol) in CH_3CN (20 ml) gave 1.50 g (90%) of **3l** (X=Br).

3m (X=Br)——i) From **2m** with Benzyl Bromide (Entry 25): Treatment of **2m** with benzyl bromide (1.5 eq) in CH_3CN gave **3m** (X=Br). *Anal.* Calcd for $C_{19}H_{19}BrN_2$: C, 64.23; H, 5.39; Br, 22.49; N, 7.89. Found: C, 64.08; H, 5.37; Br, 22.21; N, 7.76.

ii) From **2m** with 4-Nitrobenzyl Bromide (Entry 26): Treatment of **2m** with 4-nitrobenzyl bromide (1.5 eq) gave **3m** (X=Br) in 76% yield.

Preparation of 3a (X=Cl)——Cyclization was carried out under an argon atmosphere with protection from light.

i) From **2a** and Benzoyl Chloride (Entry 8): A solution of **2a** (1.10 g, 4 mmol) and benzoyl chloride (1.02 g, 8 mmol) in CH_2Cl_2 (10 ml) was refluxed for 24 h. The solution was concentrated *in vacuo*. The resulting crystals were collected and recrystallized from CH_3OH–ether to give 920 mg (83%) of **3a** (X=Cl), mp 210—212 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HCl$: C, 60.33; H, 5.45; N, 10.05; Cl, 12.72. Found: C, 60.05; H, 5.38; N, 9.89; Cl, 12.93.

ii) From **2a** and Acetyl Chloride (Entry 9): Treatment of **2a** with acetyl chloride (2 eq) in CH_2Cl_2 gave **3a** (X=Cl), mp 210—212 °C (dec.).

iii) From **2a** and Ethyl Chloroformate (Entry 10): Treatment of **2a** with ethyl chloroformate (3 eq) in acetone gave **3a** (X=Cl), mp 210—212 °C (dec.).

iv) From **2a** and Benzyl Chloride (Entry 7): Treatment of **2a** with benzyl chloride (2 eq) in CH_2Cl_2 gave **3a** (X=Cl), mp 210—212 °C (dec.).

Isolation of Sulfur-Containing Product——A solution of **2a** (1.02 g, 3.7 mmol) and benzyl bromide (632 mg, 3.7 mmol) in CH_2Cl_2 (20 ml) was refluxed for 20 h under an argon atmosphere with protection from light. The resulting precipitates (893 mg (75%) of **3a** (X=Br)) were collected by filtration. Benzoyl chloride (624 mg, 4.4 mmol) and triethylamine (562 mg, 5.6 mmol) were added to the filtrate at 0 °C. After 24 h at 0 °C, the solvent was removed and the residue was chromatographed on silica gel. Elution with hexane–AcOEt (10:1) gave 804 mg (95%) of **9**. Spectral data of **9** were identical with those of an authentic sample.

Reduction of Thioiminium Salts 4j and 4m[10]——$NaBH_4$ (114 mg, 3 mmol) was added to a stirred solution of **4j** (1.00 g, 2.8 mmol) in CH_3OH (30 ml) at −78 °C. Stirring was continued for 1 h at −78 °C, then the reaction was quenched by addition of acetone (1 ml) and the CH_3OH was evaporated off. The residual oil was taken up into $CHCl_3$, washed with brine, and dried. Removal of the solvent, followed by recrystallization from ether–hexane gave 450 mg (86%) of **8j**, mp 81—82 °C. Similarly, $NaBH_4$ reduction of **4m** (477 mg, 1.1 mmol) gave 279 mg (95%) of **8m** as an oil. Treatment with HCl–CH_3OH gave **8m**·HCl, mp 230—232 °C.

Conversion of 3 into 5 and/or 6 with Hydride Reducing Agents——1,3-Disubstituted 3,4-dihydro-β-carbolines (**3**) were reduced to 1,2,3,4-tetrahydro-β-carbolines (**5** and/or **6**) with $NaBH_4$ (1.2 eq) or $NaBH_3CN$ (1.5 eq) at −20—−78 °C. The general procedure is exemplified by the preparation of **5a**.

***cis*-3-Methoxycarbonyl-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5a)**——$NaBH_4$ (456 mg, 12 mmol) was added to a stirred solution of **3a** (3.70 g, 10 mmol) in CH_3OH (350 ml) at −78 °C. The mixture was stirred for 1 h at −78 °C, and the reaction was quenched by addition of acetone (1 ml). After concentration, the resulting oil was dissolved in CH_2Cl_2, washed with brine, and dried. Removal of the solvent and treatment of the residue with HCl–ether gave colorless crystals, which were recrystallized from CH_3OH to give 2.61 g (93%) of **5a** (HCl salt), mp 242—244 °C (dec.). Treatment of the HCl salt with dil. aqueous NH_4OH solution gave **5a**, mp 133—134 °C (Lit.[5] mp 130—131 °C). IR (Nujol) cm^{-1}: 3300, 3150, 3050, 1730. MS *m/e*: 244 (M^+), 229. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, d, J=6.8 Hz, C_1-CH_3), 1.90 (1H, br, NH), 2.83 (1H, ddd, J=15.1, 11.2 and 2.7 Hz, C_4-H), 3.13 (1H, ddd, J=15.1, 4.4 and 2.0 Hz, C_4-H), 3.83 (3H, s, OCH_3), 3.87 (1H, dd, J=11.2 and 4.4 Hz, C_3-H), 4.27 (1H, br q, C_1-H, on irradiation at 1.51, br t), 7.07—7.17 (2H, m), 7.33 (1H, br d), 7.48 (1H, br d), 7.85 (1H, br s, NH). The ^{13}C-NMR spectrum of **5a** was consistent with that reported in the literature.[11g]

***cis*-3-Methoxycarbonyl-1-phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5b)**——$NaBH_4$ reduction of **3b**

(1.73 g, 4 mmol) in CH_3OH gave 1.16 g (95%) of **5b**, mp 209—210 °C (Lit.[11f] mp 201—203 °C, Lit.[11d] mp 220—222 °C). IR (Nujol) cm^{-1}: 3400, 3330, 1740. MS *m/e*: 306 (M^+), 245, 218. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (1H, br, NH), 2.97 (1H, ddd, J=15.1, 10.5 and 2.5 Hz, C_4-H), 3.23 (1H, ddd, J=15.1, 5.0 and 1.9 Hz, C_4-H), 3.79 (3H, s, OCH_3), 3.96 (1H, dd, J=10.5 and 5.0 Hz, C_3-H), 5.22 (1H, br s, C_1-H), 6.8—7.7 (5H, m), 7.36 (5H, s). The ^{13}C-NMR spectrum of **5b** was consistent with that reported in the literature.[11g]

***cis*-1-Cyclohexyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole (5c)**——$NaBH_3CN$ reduction of **3c** (1.75 g, 4 mmol) in CH_3OH gave a mixture of *cis*- and *trans*-tetrahydro-β-carboline (**5c** and **6c**). The mixture was separated by column chromatography on silica gel (× 100). Elution with CH_2Cl_2–AcOEt (50 : 1) gave 1.06 g (85%) of **5c**, mp 154—155 °C (Lit.[11f] mp 153—154 °C). IR (Nujol) cm^{-1}: 3360, 1730. MS *m/e*: 312 (M^+), 255, 229. ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.0 (11H, m), 1.96 (1H, br s, NH), 2.75 (1H, ddd, J=15.4, 11.2 and 2.5 Hz, C_4-H), 3.11 (1H, ddd, J=15.4, 4.3 and 2.0 Hz, C_4-H), 3.71 (1H, dd, J=11.2 and 4.3 Hz, C_3-H), 3.80 (3H, s, OCH_3), 4.12 (1H, br, C_1-H), 7.0—7.4 (3H, m), 7.46 (1H, m), 7.83 (1H, br s, NH). The ^{13}C-NMR spectrum of **5c** was consistent with that reported in the literature.[11g] Further elution with CH_2Cl_2–AcOEt (50 : 1) gave 125 mg (10%) of **6c**, mp 147—148 °C (Lit.[11f] mp 147—149 °C). The spectral data were consistent with those reported in the literature.[11f,g]

***cis*-1-*tert*-Butyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5d)**——$NaBH_4$ reduction of **3d** (1.24 g, 3 mmol) in CH_3OH gave 815 mg (95%) of **5d**, mp 116—117 °C (recrystallized from iso-Pr_2O). IR (Nujol) cm^{-1}: 3430, 1730. MS *m/e*: 286 (M^+), 229. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (9H, s, *tert*-Bu), 2.17 (1H, br, NH), 2.75 (1H, ddd, J=14.5, 11.0 and 2.4 Hz, C_4-H), 3.13 (1H, ddd, J=14.5, 3.7 and 1.7 Hz, C_4-H), 3.65 (1H, ddd, J=11.0 and 3.7 Hz, C_3-H), 3.82 (3H, s, OCH_3), 3.97 (1H, br s, C_1-H), 7.10—7.20 (2H, m), 7.33 (1H, br d), 7.50 (1H, br d), 7.87 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 26.2 (t), 3 × 26.8 (q), 35.4 (s), 51.8 (q), 56.2 (d), 62.2 (d), 110.4 (s), 110.4 (d), 117.5 (d), 119.1 (d), 121.3 (d), 126.5 (s), 134.0 (s), 135.6 (s), 173.3 (s). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.38; H, 7.77; N, 9.79.

***trans*-2-Benzyl-3-methoxycarbonyl-1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (6f)**——$NaBH_4$ reduction of **3f** (2.30 g, 5 mmol) in CH_3OH gave a mixture of *cis*- and *trans*-tetrahydro-β-carboline (**5f** and **6f**). The mixture was separated by column chromatography on silica gel (× 50). Elution with $CHCl_3$ gave 1.42 g (85%) of **6f**, mp 144—145 °C (recrystallized from CH_3OH). IR (Nujol) cm^{-1}: 3380, 1720. MS *m/e*: 334 (M^+), 319, 275, 243. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, d, J=6.3 Hz, CH_3), 2.98 (1H, ddd, J=16.0, 5.8 and 1.4 Hz, C_4-H), 3.20 (1H, ddd, J=16.0, 6.4 and 1.1 Hz, C_4-H), 3.68 (3H, s, OCH_3), 3.80, 3.93 (2H, ABq, J=13.0 Hz, $NCH_2C_6H_5$), 4.00 (1H, dd, J=5.8 and 6.4 Hz, C_3-H), 4.17 (1H, br q, C_1-H), 7.0—7.6 (9H, m), 7.62 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 21.9 (q), 22.4 (t), 51.0 (d), 51.6 (q), 53.9 (t), 57.0 (d), 106.1 (s), 110.7 (d), 118.0 (d), 119. 3 (d), 121.5 (d), 127.0 (d), 4 × 128.4 (d), 3 × 136.1 (s), 139.9 (s), 173.6 (s). *Anal.* Calcd for $C_{21}H_{22}N_2O_2$: C, 75.45; H, 6.63; N, 8.38. Found: C, 75.40; H, 6.63; N, 8.38. Further elution with $CHCl_3$ gave 184 mg (11%) of the 1,3-*cis* isomer (**5f**) as a foam. IR (Nujol) cm^{-1}: 3380, 1720. MS *m/e*: 334 (M^+), 319, 275, 243. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=7.0 Hz, C_1-CH_3), 2.95 (1H, ddd, J=16.0, 5.5 and 2.2 Hz, C_4-H), 3.26 (1H, ddd, J=16.0, 6.0 and 1.7 Hz, C_4-H), 3.60 (3H, s), 3.88 (1H, dd, J=5.5 and 6.0 Hz, C_3-H), 4.01 (2H, quasi-s, $NCH_2C_6H_5$), 4.21 (1H, br q, C_1-H), 6.9—7.6 (9H, m), 7.64 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 18.2 (q), 22.2 (t), 51.6 (q), 52.7 (d), 55.2 (t), 59.7 (d), 106.2 (s), 110.8 (d), 118.1 (d), 119.4 (d), 121.5 (d), 126.9 (s), 127.1 (d), 128.2 (d), 128.4 (d), 128.8 (d), 129.0 (d), 135.5 (s), 136.0 (s), 139.9 (s), 174.2 (s).

***cis*-1-Ethyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5g)**——$NaBH_3CN$ reduction of **3g** (432 mg, 1.1 mmol) in CH_3OH gave 278 mg (94%) of **5g**, mp 73—74 °C (recrystallized from ether–petroleum ether). IR (Nujol) cm^{-1}: 3330, 1730. MS *m/e*: 272 (M^+), 243. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t), 1.96 (3H, m, CH_2, NH), 2.76 (1H, ddd, J=15.0, 10.5 and 2.5 Hz, C_4-H), 3.14 (1H, ddd, J=15.0, 3.7 and 1.7 Hz, C_4-H), 3.65 (1H, dd, J=10.5 and 3.7 Hz, C_3-H), 3.67 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 4.30 (1H, m, C_1-H, on irradiation at 1.96, br s), 7.0—7.30 (3H, m), 7.48 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 8.9 (q), 26.7 (t), 28.0 (5), 30.8 (q), 51.9 (q), 52.8 (d), 56.0 (d), 108.5 (s), 108.5 (d), 117.5 (d), 118.8 (d), 121.0 (d), 126.3 (s), 135.9 (s), 137.3 (s), 173.3 (s). *Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.69; H, 7.44; N, 10.27.

***cis*-1-Phenyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5h)**——$NaBH_4$ reduction of **3h** (1.00 g, 2.2 mmol) in CH_3OH gave a mixture of *cis*- and *trans*-tetrahydro-β-carboline (**5h** and **6h**). The mixture was separated by column chromatography on silica gel. Elution with $CHCl_3$–AcOEt (20 : 1) gave 617 mg (86%) of **5h**, mp 138—139 °C (recrystallized from benzene–hexane). IR (Nujol) cm^{-1}: 3340, 1740. MS *m/e*: 320 (M^+), 243. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (1H, s, NH), 2.98 (1H, ddd, J=15.5, 10.6 and 2.5 Hz, C_4-H), 3.14 (3H, s, N–CH_3), 3.24 (1H, ddd, J=15.5, 4.2 and 1.7 Hz, C_4-H), 3.76 (3H, s, OCH_3), 3.84 (1H, dd, J=10.6 and 4.2 Hz, C_3-H), 5.28 (1H, br t, C_1-H), 7.0—7.24 (3H, m), 7.29 (5H, s), 7.54 (1H, m), ^{13}C-NMR ($CDCl_3$) δ: 26.4 (t), 30.4 (q), 51.9 (q), 56.4 (d), 57.8 (d), 108.5 (s), 108.6 (d), 117.8 (d), 118.8 (d), 121. 2 (d), 126.0 (s), 127.9 (d), 2 × 128.0 (d), 2 × 128.6 (d), 134.8 (s), 137.0 (s), 141.3 (s), 172.7 (s). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 75.01; H, 6.25; N, 8.77. Further elution with $CHCl_3$–AcOEt (20 : 1) gave 22 mg (3%) of **6h**, mp 197—199 °C (Lit.[11g] mp 196—198 °C). The spectral data of **6h** were consistent with those reported in the literature.[11g]

***cis*-1-Cyclohexyl-3-methoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (5i)**——$NaBH_4$ reduction of **3i** (250 mg, 0.6 mmol) in CH_3OH gave a mixture of *cis*- and *trans*-tetrahydro-β-carboline (**5i** and **6i**). The mixture was separated by column chromatography on silica gel. Elution with $CHCl_3$–CH_3OH (20 : 1) gave 117 mg (61%) of **5i**, mp 128—129 °C (recrystallized from CH_3OH). ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.3 (12H, m), 2.73 (1H, ddd,

J=15.2, 10.5 and 2.4 Hz, C_4-H), 3.15 (1H, ddd, J=15.2, 3.5 and 1.8 Hz, C_4-H), 3.65 (1H, dd, J=10.5 and 3.5 Hz, C_3-H), 3.68 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 4.32 (1H, br, C_1-H), 6.96—7.36 (3H, m), 7.48 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 25.1 (t), 26.2 (t), 26.4 (t), 26.6 (t), 27.0 (t), 29.9 (t), 31.1 (q), 42.2 (d), 51.8 (q), 55.9 (d), 56.5 (d), 108.5 (d), 109.2 (s), 117.4 (d), 118.8 (d), 120.8 (d), 126.2 (s), 135.5 (s), 137.5 (s), 173.3 (d). *Anal.* Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.62; H, 8.05; N, 8.55. Further elution with $CHCl_3$–CH_3OH (20 : 1) gave 11 mg (6%) of **6i**, mp 149—150 °C (Lit.[11g] mp 151—152 °C). The spectral data of **6i** were consistent with those reported in the literature.[11g]

Hydrogenation of 5f——A solution of **5f** (200 mg, 0.6 mmol) in CH_3OH (10 ml) was hydrogenated in the presence of 10% Pd–C catalyst (50 mg) at room temperature for 3 h under atmospheric pressure of hydrogen. After removal of the catalyst, the filtrate was evaporated to dryness, and the residue was recrystallized from iso-Pr_2O to give 125 mg (85%) of **5a**, mp 133—134 °C.

Hydrogenation of 6f——A solution of **6f** (1.34 g, 4 mmol) in CH_3OH (60 ml) was hydrogenated in the presence of 10% Pd–C (450 mg) under conditions similar to those described for **5f**. Work-up gave 887 mg (91%) of **6a**, mp 155—156 °C (recrystallized from iso-Pr_2O). IR (Nujol) cm^{-1}: 3320, 1730. MS m/e: 244 (M^+), 229, 185. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, d, J=6.8 Hz, CH_3), 2.16 (1H, br NH), 2.99 (1H, ddd, J=15.4, 7.3 and 1.5 Hz, C_4-H), 3.12 (1H, ddd, J=15.4, 5.2 and 1.1 Hz, C_4-H), 3.75 (3H, s, OCH_3), 4.00 (1H, dd, J=7.3 and 5.2 Hz, C_3-H), 4.40 (1H, br q, C_1-H, on irradiation at 1.45, br s), 7.05—7.16 (2H, m), 7.30 (1H, br d), 7.50 (1H, br d), 7.80 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 21.6 (q), 25.1 (t), 45.7 (d), 52.0 (d), 52.5 (q), 106.5 (s), 110.7 (d), 118.0 (d), 119.4 (d), 121.7 (d), 127.1 (s), 136.0 (s), 136.3 (s), 174.2 (s). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.33; H, 6.60; N, 11.47. Found: C, 68.59; H, 6.54; N, 11.56.

Preparation of (*S*)- and (*R*)-Thioamide (2a, b)——These compounds were prepared from the corresponding optically active amides with Lawesson's reagent in the same manner as described for *dl*-**2**. (*S*)-**2a**; 98% yield, foam. $[\alpha]_D^{20}$ +75.2° (c=1.0, CH_3OH). (*R*)-**2a**; 98% yield, foam. $[\alpha]_D^{20}$ −74.5° (c=1.0, CH_3OH). (*S*)-**2b**; 97% yield, foam. $[\alpha]_D^{20}$ +79.6° (c=1.3, CH_3OH). (*R*)-**2b**; 95% yield, foam. $[\alpha]_D^{20}$ −78.3° (c=1.0, CH_3OH).

Reconversion of (*S*)-2a into (*S*)-1a——(*S*)-**2a** (1.00 g, 3.6 mmol), prepared from (*S*)-**1a** ($[\alpha]_D^{20}$ +14.2° (c=1.0, CH_3OH), mp 155—156 °C), was dissolved in CH_3OH (100 ml). Then CH_3I (1 ml) was added, and the mixture was stirred for 24 h at room temperature under an argon atmosphere with protection from light. Removal of the solvent gave a crystalline mixture of (*S*)-**1a** and (*S*)-tryptophan methyl ester (*S*)-**7**.[9] Without separation, this mixture was dissolved in CH_2Cl_2 (10 ml). Ac_2O (220 mg) and *N*-methylmorpholine (436 mg) were added to the above solution at 0 °C, and the mixture was stirred for 1.5 h at room temperature, then poured into ice-water. The CH_2Cl_2 layer was separated, washed with H_2O, and then dried. Removal of the CH_2Cl_2, followed by recrystallization from iso-PrOH, gave 857 mg (92%) of (*S*)-**1a**, mp 154—156 °C. $[\alpha]_D^{20}$ +13.0° (c=1.0, CH_3OH).

Preparation of (*S*)- and (*R*)-3a——These compounds were prepared from (*S*)- and (*R*)-**2a** using several kinds of alkylating and acylating agents under conditions similar to those described for *dl*-**3a**. (*S*)-**3a** (X=I): mp 204—206 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HI$: C, 45.42; H, 4.08; N, 7.57; I, 34.28. Found: C, 45.45; H, 4.04; N, 7.61; I, 34.53. (*R*)-**3a** (X=I): mp 204—206 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HI$: C, 45.42; H, 4.08; N, 7.57; I, 34.28. Found: C, 45.51; H, 4.09; N, 7.72; I, 34.54. (*S*)-**3a** (X=Br): mp 196—198 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HBr$: C, 52.03; H, 4.68; N, 8.67; Br, 24.72. Found: C, 51.99; H, 4.64; N, 8.61; Br, 24.79. (*R*)-**3a** (X=Br): mp 196—198 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HBr$: C, 52.03; H, 4.68; N, 8.67; Br, 24.72. Found: C, 52.09; H, 4.76; N, 8.81; Br, 25.01. (*S*)-**3a** (X=Cl): mp 202—204 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HCl$: C, 60.33; H, 5.42; N, 10.05; Cl, 12.72. Found: C, 60.17; H, 5.38; N, 9.95; Cl, 12.52. (*R*)-**3a** (X=Cl): mp 204—206 °C (dec.). *Anal.* Calcd for $C_{14}H_{14}N_2O_2 \cdot HCl$: C, 60.33; H, 5.42; N, 10.05; Cl, 12.72. Found: C, 60.31; H, 5.36; N, 9.99; Cl, 12.60.

Preparation of (1*S*,3*S*)-5a and (1*R*,3*R*)-5a——$NaBH_4$ reduction of (*S*)-**3a** (X=I, Br, Cl) was carried out under conditions similar to those described for the preparation of *dl*-**5a**. After usual work-up and treatment with HCl–ether, the resulting precipitate was recrystallized from CH_3OH to give (1*S*, 3*S*)-**5a** (HCl salt) in 90—93% yield, mp 252—254 °C (dec.). *Anal.* Calcd for $C_{14}H_{16}N_2O_2 \cdot HCl$: C, 59.89; H, 6.10; N, 9.98; Cl, 12.63. Found: C, 59.80; H, 6.08; N, 9.92; Cl, 12.35. The spectral data of (1*S*, 3*S*)-**5a** were consistent with those of an authentic sample.[15a] Similarly, (1*R*, 3*R*)-**5a** (HCl salt) was obtained by reduction of (*R*)-**3a** (X=I, Br, Cl) with $NaBH_4$ in 90—91% yield, mp 252—254 °C (dec.) (recrystallized from CH_3OH). *Anal.* Calcd for $C_{14}H_{16}N_2O_2 \cdot HCl$: C, 59.89; H, 6.10; N, 9.98; Cl, 12.63. Found: C, 59.85; H, 6.12; N, 9.91; Cl, 12.48. The spectral data of (1*R*, 3*R*)-**5a** were identical with those of (1*S*, 3*S*)-**5a**.

Preparation of (1*S*, 3*S*)-5b and (1*R*, 3*R*)-5b from (*S*)- and (*R*)-2b——A solution of (*S*)-**2b** (1.20 g, 3.6 mmol) and CH_3I (1 ml) in CH_2Cl_2 (20 ml) was stirred for 24 h under conditions similar to those described for the preparation of *dl*-**3b**. Work-up gave 1.67 g (100%) of crude (*S*)-**3b** as an oil. Without purification, this oil was dissolved in CH_3OH (40 ml) and treated with $NaBH_4$ (129 mg, 3.4 mmol) at −78 °C. After 1 h, the reaction mixture was worked up as described above. The crude product was chromatographed on silica gel (hexane–CH_2Cl_2–AcOEt (1 : 4 : 1) as an eluent) to give 843 mg (78%) of (1*S*, 3*S*)-**5b**, mp 233—235 °C (recrystallized from CH_3OH). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.95; N, 9.15. Found: C, 74.44: H, 5.84; N, 9.10. The spectral data of (1*S*, 3*S*)-**5b** were identical with those of *dl*-**5b**. Similarly, (1*R*, 3*R*)-**5b** was obtained by cyclization of (*R*)-**2b**, followed by reduction with $NaBH_4$: 73% yield, mp 234—235 °C (recrystallized from CH_3OH). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.95; N, 9.15. Found: C, 74.40; H, 6.03; N, 9.10. The spectral data of (1*R*, 3*R*)-**5b** were identical with those of *dl*-**5b**.

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References and Notes

1) A. Ishida, T. Nakamura, K. Irie, and T. Oh-ishi, *Chem. Pharm. Bull.*, **30**, 4226 (1982).
2) T. Nakamura, A. Ishida, K. Irie, and T. Oh-ishi, *Chem. Pharm. Bull.*, **32**, 2859 (1984).
3) *a*) W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. 6, John Wiley and Sons, Inc., New York, 1951, p. 74; *b*) R. A. Abramovitch and I. D. Spenser, "Advances in Heterocyclic Chemistry," Vol. 3, Academic Press, New York, 1964, p. 74.
4) *a*) H. R. Snyder and F. X. Werber, *J. Am. Chem. Soc.*, **72**, 2962 (1950); *b*) I. Murakoshi, *Yakugaku Zasshi*, **77**, 550 (1957); *c*) D. G. Harvey, E. J. Miller, and W. Robson, *J. Chem. Soc.*, **1941**, 153.
5) Y. Kanaoka, E. Sato, and Y. Ban, *Chem. Pharm. Bull.*, **15**, 101 (1967).
6) A-M. M. E. Omar and S. Yamada, *Chem. Pharm. Bull.*, **14**, 856 (1966).
7) *a*) A. Previero, G. Prota, and M.-A. Goletti-previero, *Biochim. Biophys. Acta*, **285**, 269 (1972); *b*) T. Kametani, N. Takagi, N. Kanaya, and T. Honda, *Heterocycles*, **19**, 535 (1982).
8) (p-CH_3O-C_6H_4)$_2P_2S_4$, [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane- 2,4-disulfide]. S. Scheibye, B. S. Pedersen, and S. O. Lawesson, *Bull. Soc. Chim. Belg.*, **87**, 229 (1978).
9) From the reaction mixture, the HI salt of **7** was readily isolated as pure crystals in high yield. This provided a facile deblocking method for the N^{α}-acetyl group of (*R*)- and (*S*)-**1a**. Compound (*R*)-**1a** gave (*R*)-**2a** in 98% yield, as described in Experimental. Conversion of (*R*)-**2a** into (*R*)-**7**·HI was performed as follows. A solution of (*R*)-**2a** (1.5 g, 5.4 mmol) and CH_3I (5 ml) in CH_3OH (150 ml) was stirred for 2 d at room temperature under an argon atmosphere in the dark. Concentration of the solution *in vacuo* and recrystallization of the crystalline residue from iso-PrOH–ether gave 1.43 g (76%) of (*R*)-**7**·HI, mp 198—199 °C (dec.), $[\alpha]_D^{20}$ −10.9° (c=1.0, CH_3OH). The spectral data and physical properties were consistent with those of the authentic (*S*)-isomer, mp 200—201 °C (dec.), $[\alpha]_D^{20}$ +10.7° (c=1.0, CH_3OH), prepared from (*S*)-**7**.
10) *a*) S. Raucher and P. Klein, *Tetrahedron Lett.*, **21**, 4061 (1980); *b*) R. J. Sundberg, C. P. Walters, and J. D. Bloom, *J. Org. Chem.*, **46**, 3730 (1981).
11) *a*) A. Brossi, A. Focella, and S. Teitel, *J. Med. Chem.*, **16**, 418 (1973); *b*) K. T. D. Desilva, D. King, and G. N. Smith, *J. Chem. Soc., Chem. Commun.*, **1971**, 908; *c*) R. T. Brown and C. Chapple, *J. Chem. Soc.*, **1973**, 886; *d*) F. Hamaguchi, T. Nagasaka, and S. Oki, *Yakugaku Zasshi*, **94**, 351 (1974); *e*) A. K. Saxena, P. C. Jain, and N. Anand, *Indian J. Chem.*, **12**, 892 (1974); *f*) D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. Dipierro, and J. M. Cook, *J. Org. Chem.*, **44**, 535 (1979); *g*) F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silverton, *J. Am. Chem. Soc.*, **102**, 6976 (1980); *h*) F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, *J. Org. Chem.*, **46**, 164 (1981); *i*) G. Massiot and T. Mulamba, *J. Chem. Soc., Chem. Commun.*, **1983**, 1147.
12) H. Irikawa and Y. Okumura, *Chem. Lett.*, **1983**, 1055.
13) *a*) L. Szabó, G. Kalaus, K. Nógrádi, and Cs. Szántay, *Acta Chim. Acad. Sci. Hung.*, **99**, 73 (1979); *b*) L. Szabó, J. Sápi, K. Nógrádi, G. Kalaus, and Cs. Szántay, *Tetrahedron*, **39**, 3749 (1983).
14) *a*) K. Clausen, M. Thorsen, and S. O. Lawesson, *Tetrahedron*, **37**, 3635 (1981); *b*) U. Pedersen, M. Thorsen, E. E. A. M. EL-Khrisy, K. Clausen, and S. O. Lawesson, *ibid.*, **38**, 3267 (1982); *c*) M. Thorsen, B. Yde, U. Pedersen, K. Clausen, and S. O. Lawesson, *ibid.*, **39**, 3429 (1983).
15) *a*) Esterification of (*S*)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid with $SOCl_2$–CH_3OH gave authentic (1*S*,3*S*)-**5a**. Yamada *et al.* similarly prepared the optically active ethyl ester.[15b] *b*) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **22**, 2614 (1974).
16) The optically active 1-phenyl derivatives, (1*R*,3*R*)-**5b** and (1*S*,3*S*)-**5b**, are unknown in the literature.