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THE PICTET-SPENGLER REACTION OF N_b-HYDROXYTRYPTAMINES AND CYSTEINALS. I. ISOLATION OF TETRACYCLIC INTERMEDIATES AND FORMATION OF OPTICALLY ACTIVE N_b-HYDROXY-TETRAHYDRO-β-CARBOLINES.†

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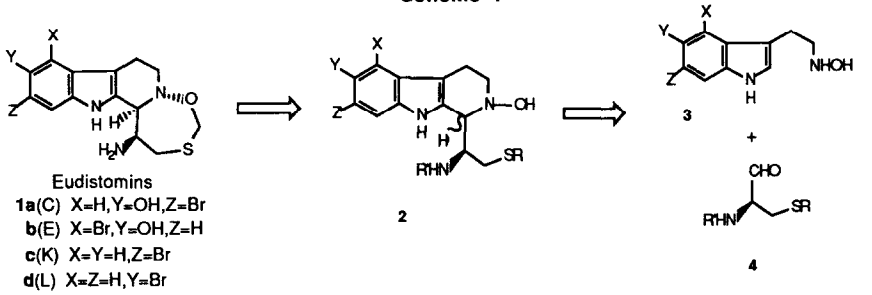
Abstract: The Pictet-Spengler(P-S) reaction of N_b-hydroxytryptamines **5** and cysteinals **6** in the presence of trifluoroacetic acid(TFA) at room temperature gave the tetracyclic compounds **7α** as well as the corresponding N_b-hydroxy-β-carbolines **8**. The optically active nitrones **9**, isolated from the similar reaction of **5** and optically active **6**, gave optically active **7α** and **8**.

In the continuation of our work directed toward the total synthesis of the potent antiviral marine alkaloid, eudistomins **1**,[1] the need arose for the synthesis of N_b-hydroxy-tetrahydro-β-carboline **2** which may be prepared by use of the Pictet-Spengler reaction (P-S reaction) of N_b-hydroxytryptamine **3** with cysteinal **4** (Scheme I). Recently, Ottenheijm and coworkers[2]

Scheme I



Eudistomins
1a(C) X=H,Y=OH,Z=Br
b(E) X=Br,Y=OH,Z=H
c(K) X=Y=H,Z=Br
d(L) X=Z=H,Y=Br

2

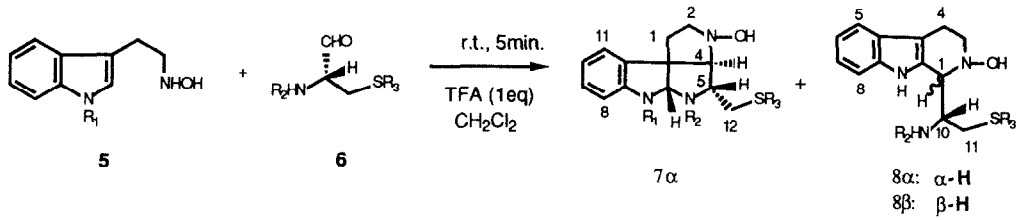
3 + **4**

reported the P-S reaction of N_b-hydroxytryptophan derivatives and cysteinal to yield a mixture of three diastereomers of racemic N_b-hydroxy-tetrahydro-β-carboline. Our approach was based on the idea that the stereochemistry of the C (1) of β-carboline would be controlled by the chirality of the cysteine moiety. The reaction of N_b-hydroxytryptamine with a chiral cysteinal derivative may provide two diastereomers of the corresponding N_b-hydroxy-tetrahydro-β-carboline and the ratio of the diastereomers should be influenced with the protective groups (R' and R) of the nitrogen and sulfur atoms adjacent to the chiral center. However there were only a few examples,[3] to our knowledge, that the stereochemistry of the β-carboline was

controlled by the chirality of an aldehyde used in the P-S reaction. We report here that our approach on this line is viable indeed. The P-S reaction of N_b-hydroxytryptamine **5** with the chiral aldehydes, L-cysteinals **6**, gave the optically active N_b-hydroxy-tetrahydro-β-carboline derivatives **8**, *via* the corresponding nitrones **9**, in high stereoselectivity.

The P-S reaction of N_b-hydroxytryptamine **5** and cysteinal **6** was carried out at room temperature using trifluoroacetic acid (TFA) as a catalyst.[4] Thus, treatment of **5a** with N,S-protected cysteinal **6a**,[5a] prepared from N-methoxycarbonyl-S-methyl-L-cysteine methyl ester,[5b] in the presence of TFA (1 mol equiv) at room temperature provided tetracyclic compound (±)-**7a**α unexpectedly in 75% yield together with the corresponding N_b-hydroxy-tetrahydro-β-carbolines (±)-**8a**α and (±)-**8a**β as a mixture of diastereoisomers (24%) which could be separated by column chromatography (Scheme II, R_1=H; R_2=COOMe; R_3=Me). A variety of N,S-protected cysteinals **6** and N_b-hydroxytryptamine derivatives have been employed in this condensation; the results are summarized in Table I (entry 1-6). The selectivity for the

Scheme II



5 **6** 7α 8α: α-H 8β: β-H

Table I The P-S reaction of N_b-hydroxytryptamines 5 and cysteinals 6

Entry	5		6			(±) 7α	(%)	(±) 8	(%)	8α:8β
1	a	R_1=H	a	R_2=COOMe,	R_3=Me	a	(75)	a	(24)	1:6[a]
2	a	R_1=H	b	R_2=CBZ,	R_3=COOMe	b	(39)	b	(51)	1:4[a]
3	a	R_1=H	c	R_2=CBZ,	R_3=Me	c	(76)	c	(18)	1:8[a]
4	a	R_1=H	d	R_2=TROC,	R_3=COOMe	d	(21)	d	(62)	1:8[b]
5	a	R_1=H	e	R_2=COOMe,	R_3=CBZ	e	(47)	e	(34)	1:5[b]
6	a	R_1=H	f	R_2=COOMe,	R_3=TROC	f	(33)	f	(56)	1:6[b]
7	b	R_1=Me	g	R_2=COOMe,	R_3=MEM	g	(88)			
8	b	R_1=Me	f	R_2=COOMe,	R_3=TROC	h	(90)			

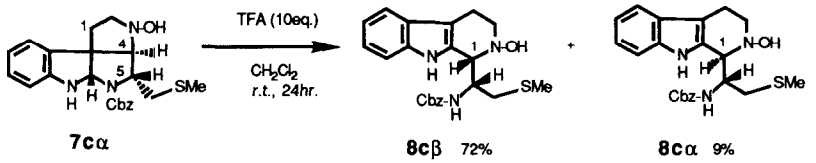
[a] Ratio by isolation; [b]Ratio by ^{1}H-NMR.

tetracyclic compounds (±)-7α seems to depend on the size of the protective group of cysteinals. Excellent yields of (±)-7α were obtained with the cysteinals which have smaller protective groups both on N and S (entry 1 and 3). While the influence of the protective groups to the ratio of the β-carbolines **8** were not so obvious, and fortunately, the major isomer of the β-carbolines, (±)-**8**β have a desirable stereochemistry for the synthesis of **1**. On the other hand, in the reaction of N_a-methyl-N_b-hydroxytryptamine like **5b** with **6** gave only the

corresponding tetracyclic compounds (±)-**7**α in high yield (entry 7, 8), and no corresponding N_b-hydroxy-tetrahydro-β-carbolines were detected perhaps due to the unfavorable interaction in the transition state between the bulky substituents (cysteine moiety) of position 1 and the indole N_a-Me function [$A^{(1,2)}$ strain].[6] The reaction proceeded rapidly at room temperature and in all cases was completed within 5 min, indicating the high reactivity of the N_b-hydroxytryptamine in the P-S reaction.[7]

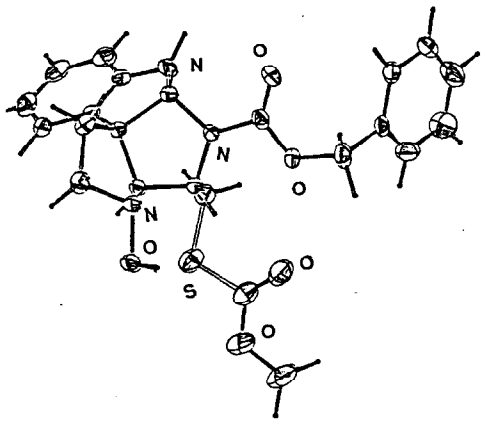
The isolation of (±)-**7**α suggests the presence of the spiroindolenine intermediate in the P-S reaction. In fact, the tetracyclic compounds rearranged to the corresponding β-carbolines when treated with excess TFA. Treatment of (±)-**7c**α with TFA (10 mol equiv) in CH_2Cl_2 at room temperature for 24 h afforded the corresponding β-carbolines (±)-**8c**α (19%) and (±)-**8c**β (72%)

Scheme III



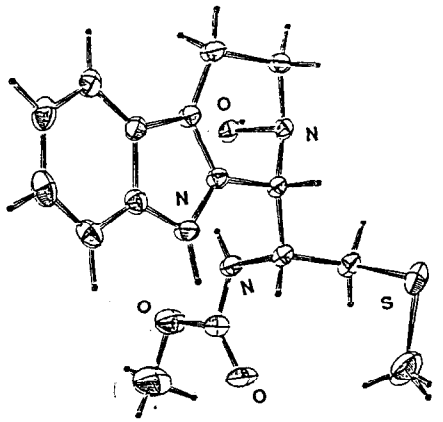
(Scheme III). The major isomer of the β-carbolines (**8c**β), however, has the opposite configuration at C (1) position compared with the same carbon, C (4), of **7c**α. On the other hand, N_a-protected tetracyclic compounds did not convert to the corresponding β-carbolines under identical reaction conditions: 95% of the starting material was recovered when **7h**α was treated with TFA (10 mol equiv) in CH_2Cl_2 at room temperature for 18 h.

The structures of the products were determined from their spectral data. The stereochemistry



ORTEP drawing of (±)-**7b**α

Figure 1

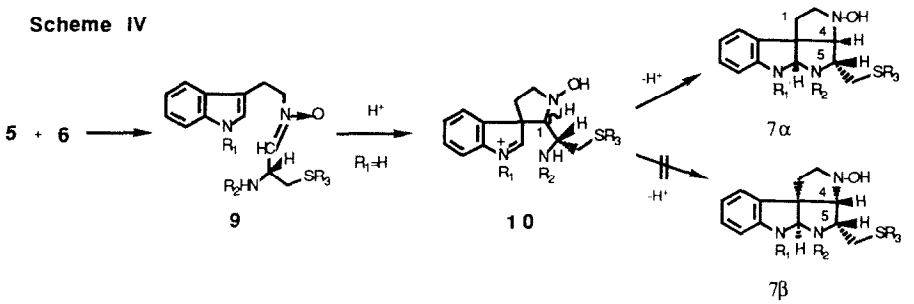


ORTEP drawing of (±)-**8a**β

of 7α and 8β were established by X-ray analysis[4c] of (±)-**7b**α and (±)-**8a**β, respectively (Figure I). Thus, the major isomer of the N_b-hydroxy-tetrahydro-β-carboline, **8a**β, has a β-H at C (1) of the β-carboline ring, and the relative configuration is the same as that of the natural eudistomins. Subsequently, structures **8b**β–**8g**β were assigned by comparison of their ^{1}H-NMR spectra with those of **8a**β in which the peak of the C(1) proton (δ 4.47) shifted markedly downfield comparing with that (δ 4.23) of the minor isomer, **8a**α. On the other hand, the tetracyclic compound **7b**α has a *trans* relationship between C(4) and C(5).

To our knowledge this is the first example that such tetracyclic compounds were obtained from the P-S reaction. It is likely that the tetracyclic compounds are formed by an intramolecular cyclization of the corresponding spiroindolenine intermediate **10** (Scheme IV).

Scheme IV



Only the *trans* isomer 7α was isolated in our case probably due to the instability of the all-*cis* isomer 7β. Clearly, the isolation of the tetracyclic compounds affords a new evidence for the existence of the spiroindolenine intermediate in P-S reaction.[8]

It had to be noted that both of the β-carbolines and the tetracyclic compounds obtained in Table I gave no specific rotation, the racemization might have occurred during the chromatographic purification of the cysteinals as reported.[5] In order to obtain the optically active **7** and **8**, crude cysteinals were used in the following P-S reaction without chromatographical purification. During our preliminary examination,[7] we found that N_b-hydroxytryptamine easily reacts with various aldehydes without any catalyst to give the corresponding nitrones. Furthermore, the nitrones are, unlike the Schiff base obtained from tryptamine and aldehyde, very stable and could be purified and isolated by means of chromatography. We purified the crude cysteinals **6** as its nitrones **9** and this method was found to be useful to overcome the racemization. Thus, the mixture of the crude cysteinals **6** and N_b-hydroxytryptamine **5** in dry CH_2Cl_2 was stirred at room temperature for about 2 h to give the corresponding nitrones (+)-**9** (Scheme V) in excellent yield after chromatographic purification (Table II). Only a single isomer (Z isomer) of the nitrones was detected from their ^{1}H-NMR spectra.[9] In addition, all of the products gave satisfactory $[\alpha]_D$ value, suggesting no racemization occurred during the nitrone formation.[10]

From the nitrones (+)-**9**, the desired optically active N_b-hydroxy-tetrahydro-β-carboline (-)-**8** as well as the tetracyclic compounds (-)-**7α** were easily obtained by using the same conditions as described in scheme II (TFA, 1 mol equiv, rt, 5 min). (Scheme VI) (Table III)

Scheme V

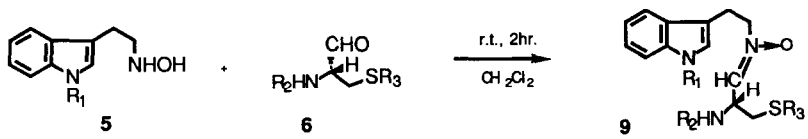


Table II Isolation of the optically active nitrones 9

Entry	9	R_1	R_2	R_3	yield(%)	$[\alpha]_D$(°)	mp(°C)
1	a	H	COOMe	Me	97.0	+56.9	
2	f	H	COOMe	TROC	91.2	+13.5	
3	h	Me	COOMe	TROC	95.4	+30.0	96-97
4	i	H	BOC	TROC	96.7	+35.5	
5	j	H	TROC	Me	92.0	+41.0	
6	k	H	BOC	Me	92.8	+67.3	135.5-136.5

Scheme VI

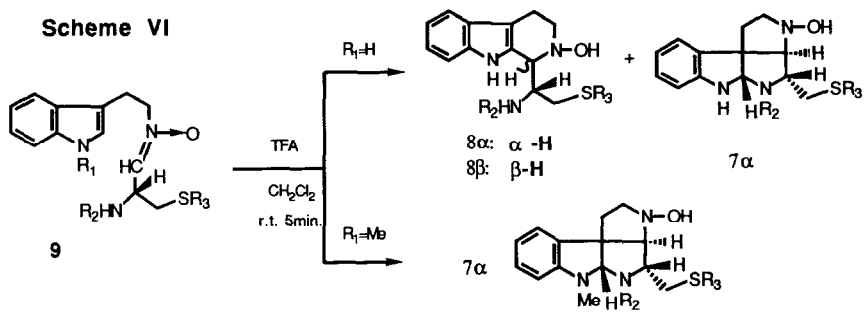


Table III Cyclization of the nitrones 9

Entry	9	R_1	R_2	R_3	7(%)	$[\alpha]_D$(°)	8(%)	8α:8β
1	a	H	COOMe	Me	a(77)	-113.8	a(22)	1:6*
2	f	H	COOMe	TROC	f(35)	-86.9	f(59)	1:6#
3	h	Me	COOMe	TROC	h(90)	-93.0		
4	i	H	BOC	TROC	j(49)	-98.1	j(48)	1:5#
5	j	H	TROC	Me	k(68)	-110.0	k(25)	1:6*
6	k	H	BOC	Me	l(70)	-139.2	l(21)	1:5*

*Ratio by isolation; #Ratio by ^{1}H-NMR

The optical purity of the products were determined from their ^{1}H-NMR in the presence of a shift reagent. Thus, ^{1}H-NMR spectrum of the β-carbolines, (-)-**8a**β, in the presence of tris [3-heptafluoropropylhydroxy-methylene-d-camphorato] derivative of europium (III) showed a singlet peak downfield at δ 7.50-8.00, while a pair of peaks were observed in that of (±)-**8a**β in Table I.

In summary, the Pictet-Spengler reaction of N_b-hydroxytryptamines **5** and cysteinals **6** has been shown to form the corresponding N_b-hydroxy-β-carbolines (±)-**8** as well as the tetracyclic compounds (±)-**7**α which gave a new evidence for the intermediary of a spiroindolenine in the Pictet-Spengler reaction. On the other hand, by isolating nitrones,(+)-**9**, optically active N_b-hydroxy-tetrahydro-β-carbolines (-)-**8** and tetracyclic compounds (-)-**7** were synthesized.

Experimental Section

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus, and are uncorrected. UV spectra were recorded on a Hitachi 323 a spectrophotometer. IR spectra were obtained with a Hitachi 260-10 spectrophotometer. Mass spectra were recorded on a Hitachi M-60 or a JMS-HX 100 mass spectrometer. ^{1}H-NMR spectra were recorded on 270 MHz with a JEOL JNM-FX 270 or a JEOL JNM-GX 270, or on 500 MHz with.a JEOL JNM-GSX500. All chemical shifts are reported downfield from an internal Me_4Si standard and given as δ values (ppm). Optical rotations were recorded with a JASCO DIP-140 polarimeter. Microanalyses were performed on a Perkin-Elmer 240 C, H, and N analyzer. Unless otherwise noted, UV spectra (λ in nm) refer to a solution in 95% EtOH, IR spectra (ν in cm^{-1}) to KBr disks, and ^{1}H-NMR spectra to solutions in $CDCl_3$.

General procedure for the preparation of N_b-hydroxytryptamines. N_b-hydroxytryptamines **5a** and **5b** were prepared by a Al(Hg) reduction[11] of the corresponding nitroethylindoles which were in turn prepared by a $NaBH_4$ reduction[12] of the nitroethyleneindoles obtained from the condensation[13] of nitromethane with 3-formylindole derivatives. As an example, the preparation of N_a-methyl-N_b-hydroxytryptamine **5b** is described.

$NaBH_4$ (1.92 g, 50.5 mmol) was added in portions at room temperature to a suspension of N_a-methyl-nitroethyleneindole (3.4 g, 16.8 mmol) in MeOH-THF (250 ml-50 ml) with vigorous stirring. After the mixture was stirred for 1 h, 10 ml of AcOH was added and the mixture was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 and washed successively with water and brine. Drying over Na_2SO_4 and removal of the solvent gave a residue which was chromatographed over SiO_2 to give N_a-methyl-nitroethylindole (3.09 g, 90.2 %): mp. 46-47°C; λmax (EtOH) 224, 275, 288, 294 nm; νmax (KBr) 1620, 1495, 1300, 1250, 750 cm^{-1}; m/z (%) 204(M^+), 157(100); δ 7.56-7.14 (4H, m, ArH), 6.91 (1H, s, C_2-H), 4.64 (2H, t, J = 7.2 Hz, N-CH_2), 3.74 (3H, s, Me), 3.47 (2H, t, J = 7.2 Hz, CH_2); Anal. Calcd. for $C_{11}H_{12}N_2O_2$(M^+): 204.0897. Found: 204.0897(HRMS). To a solution of N_a-methyl-nitroethylindole obtained as above (1.02 g, 5.0 mmol) in THF-H_2O (50 ml-5 ml) was added freshly prepared Al(Hg) (from 2 g of Al) at 0°C with vigorous stirring.

After stirring for 15 min, the reaction mixture was filtered through a Büchner funnel and then a celite filter. The filtrates were evaporated and the residue was diluted with CH_2Cl_2 and washed successively with water and brine. Drying over Na_2SO_4 and removal of the solvent gave a residue which was chromatographed over SiO_2 to give N_a-methyl-N_b-hydroxytryptamine **5b** (0.73 g, 76.8 %): mp. 66-67°C; λmax (EtOH) 227, 279, 298, 300 nm; νmax (KBr) 3270, 1620, 1480, 1380, 1120, 740, 730 cm^{-1}; m/z (%) 190(M^+), 144(100); δ 7.62-7.08 (4H, m, ArH), 6.91 (1H, s, C_2-H), 6.30-5.20 (1H, br, OH, exchangeable), 3.75 (3H, s, Me), 3.24 (2H, t, J = 7.2 Hz, N-CH_2), 3.03 (2H, t, J = 7.2 Hz, CH_2).

General procedure for the Pictet-Spengler reaction in Table I To a mixture of N_b-hydroxytryptamine **5** and cysteinal **6** (1.5 mol equiv) prepared from L-cysteine and purified through a SiO_2 column in dry CH_2Cl_2 was added trifluoroacetic acid (1 mol equiv) by injection at room temperature in an atmosphere of Ar. After stirring for 5 min, the reaction mixture was diluted with CH_2Cl_2 and quenched with sat. $NaHCO_3$, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give the products (*vide infra* for the optically active compounds).

Tetracyclic compound (±)-**7a**: chromatographycally homogeneous amorphous; λmax (EtOH) 245, 303 nm; νmax (KBr) 3350, 1715, 1680, 1605, 1450, 740 cm^{-1}; m/z (%) 335(M^+), 143(100); δ (27°C) 7.19-7.05 (2H, m, ArH), 6.80(1H, ArH), 6.76(1H, m, C_8-H), 5.93, 5.84(1H, br, OH, exchangeable), 5.44, 5.35 (1H, s, C_{6a}-H), 4.97 ,4.68 (1H, br, NH, exchangeable), 4.29, 4.17 (1H, dd, J = 4.2, 11.3 Hz, C_5-H), 3.77, 3.75 (3H, s, OMe), 3.64 (1H, s, C_4-H), 3.45 (1H, m, C_2-H), 3.21 (1H, m, C_2-H), 2.64 (1H, m, C_{12}-H), 2.22 (2H, m, C_1-H), 2.09, 2.03 (3H, s, SMe), 1.85 (1H, m, C_{12}-H); δ (55°C) 5.93, 5.84 (1H, br, OH, exchangeable), 5.38 (1H, s, C_{6a}-H), 4.97 ,4.68 (1H, br, NH, exchangeable), 4.22 (1H, br, C_5-H), 3.75 (3H, s, OMe), 2.04 (3H, s, SMe); Anal. Calcd. for $C_{16}H_{21}N_3O_3S$(M^+): 335.1302. Found: 335.1302(HRMS).

1-[1-(N-(Methoxycarbonyl)amino)-2-(methylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline (±)-**8aα**, **8aβ**. (±)-**8aα**: chromatographycally homogeneous amorphous; λmax (EtOH) 227, 275, 284, 291 nm; νmax (KBr) 3370, 3290, 1685, 1500 cm^{-1}; m/z (%) 335 (M^+), 171 (100); δ 8.45 (1H, br, N_9-H, exchangeable), 7.47-7.08(4H, m, ArH), 5.85 (1H, br, NH, exchangeable), 5.11 (1H, br, OH, exchangeable), 4.54 (1H, br, C_{10}-H), 4.23 (1H, br, C_1-H), 3.69 (3H, s, OMe), 3.50 (1H, br, C_3-H), 3.18 (1H, m, SCH), 3.05 (2H, m, C_3-H, SCH), 2.80 (2H, m, C_4-H), 2.13 (3H, s, SMe); Anal. Calcd. for $C_{16}H_{21}N_3O_3S$(M^+): 335.1302. Found: 335.1301(HRMS). (±)-**8aβ**: mp 180.5-181°C(dec.;AcOEt/n-Hex); λmax (EtOH) 226.5, 275, 283, 291 nm; νmax (KBr) 3370, 3290, 1690, 1500 cm^{-1}; m/z (%) 335(M^+),171 (100); δ 8.50 (1H, br, N_9-H, exchangeable), 7.48-7.07(4H, m, ArH), 5.59 (1H, br, NH, exchangeable), 5.00 (1H, br, OH, exchangeable), 4.54 (1H, br, C_{10}-H), 4.47 (1H, br, C_1-H), 3.61 (3H, s, OMe), 3.61 (1H, br, C_3-H), 3.23 (1H, m, SCH), 3.09 (2H, m, C_3-H, SCH), 2.80 (2H, m, C_4-H), 2.20 (3H, s, SMe); Anal. Calcd. for $C_{16}H_{21}N_3O_3S$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.13; H, 6.23; N, 12.38.

Tetracyclic compound (±)-**7b**: mp 142.5-143°C(AcOEt/n-Hex); λmax (EtOH) 245, 302 nm; νmax (KBr) 3350, 1715, 1685, 1605, 1420, 1140 cm^{-1}; m/z (%) 453 (M^+-2), 91 (100); δ 7.40 (5H,bs, PhH), 7.06-7.18 (2H, m, ArH), 6.80 (1H, ArH), 6.56 (1H, d, J = 8.1 Hz, C_8-H), 5.53, 5.49 (1H, br, OH, exchangeable), 5.47, 5.38 (1H, s, C_{6a}-H), 5.20 (2H, s, CH_2Ph), 4.95, 4.63 (1H, br, NH,

exchangeable), 4.37 (1H, m, C_5-H), 3.75 (1H, s, OMe), 3.61 (2H, s, OMe), 3.49 (1H, s, C_4-H), 3.40 (1H, m, C_2-H), 3.16 (1H, dd, J = 5.1, 14.3 Hz, C_2-H), 3.03 (1H, dd, J = 5.0, 14.4 Hz, SCH), 2.32 (1H, m, SCH), 2.20 (2H, m, C_1-H); Anal. Calcd. for $C_{23}H_{25}N_3O_5S$: C, 60.65; H, 5.53; N, 9.23. Found: C, 60.53; H, 5.55; N, 9.11.

1-[1-(N-(Benzyloxycarbonyl)amino)-2-(methoxycarbonylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline (±)-**8bα, 8bβ**. (±)-**8bα**: chromatographycally homogeneous amorphous; λmax (EtOH) 226., 275, 283, 291 nm; νmax (KBr) 3440, 3350, 1685, 1520 cm^{-1}; m/z (%) 421 (M^+-34), 229 (100); δ 8.81 (1H, br, N_9-H, exchangeable), 7.47 (1H, d, J = 8.1 Hz, ArH), 7.36 (1H, d, J = 8.3 Hz, ArH), 7.33 (5H, s, PhH), 7.22-7.08 (2H, m, ArH), 5.80-5.60 (2H, br, OH, NH, exchangeable), 5.14 (1H, d, J = 12.2 Hz, CHPh), 5.08 (1H, d, J = 12.2 Hz, CHPh), 4.57 (1H, br, C_{10}-H), 4.25 (1H, br, C_1-H), 3.78 (3H, s, OMe), 3.49 (1H, m, C_3-H), 3.05-3.20 (3H, m, C_3-H, SCH), 2.90 (1H, m, C_4-H), 2.80 (1H, m, C_4-H). (±)-**8bβ**: chromatographycally homogeneous amorphous; λmax (EtOH) 226., 275, 283, 291 nm; νmax (KBr) 3440, 3350, 1685, 1520 cm^{-1}; m/z (%) 455 (M^+), 91 (100); δ 8.56 (1H, br, N_9-H, exchangeable), 7.48 (1H, d, J = 7.2 Hz, ArH), 7.08-7.32 (8H, m, ArH, PhH), 5.71 (1H, br, NH, exchangeable), 5.20 (1H, br, OH, exchangeable), 5.05 (2H, s, CH_2Ph), 4.56 (1H, br, C_{10}-H), 4.45 (1H, br, C_1-H), 3.81 (3H, s, OMe), 3.60 (1H, m, C_3-H), 3.42 (1H, dd, J = 5.3, 14.1 Hz, SCH), 3.20 (2H, m, C_3-H, SCH), 3.02 (1H, m, C_4-H), 2.80 (1H, m, C_4-H); Anal. Calcd. for $C_{23}H_{25}N_3O_5S(M^+)$: 455.1514. Found: 455.1520(HRMS).

Tetracyclic compound (±)-**7c**: chromatographycally homogeneous amorphous; λmax (EtOH) 245, 302 nm; νmax (KBr) 3370, 1690, 1605, 1410, 750 cm^{-1}; m/z (%) 411(M^+), 91 (100); δ(55°C) 7.40(5H, bs, PhH), 7.16(1H, d, J = 6.7 Hz, C_{11}-H), 7.06 (1H, t-like, C_9-H), 6.73(1H, m, C_{10}-H), 6.55(1H, d, J = 7.9 Hz, C_8-H), 5.43(1H, s, C_{6a}-H), 5.19(2H, s, CH_2Ph), 4.95 (1H, br, OH, exchangeable), 4.60 (1H, br, NH, exchangeable), 4.17 (1H, br, C_5-H), 3.64 (1H, s, C_4-H), 3.44 (1H, m, C_2-H), 3.20 (1H, t-like, C_2-H), 2.80-2.50 (1H, br, SCH), 2.20 (2H, m, C_1-H), 1.95 (4H, br, SCH, SMe); Anal. Calcd. for $C_{22}H_{25}N_3O_3S(M^+)$: 411.1614. Found: 411.1599(HRMS).

1-[1-(N-(Benzyloxycarbonyl)amino)-2-(methylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline (±)-**8cα, 8cβ**: (±)-**8cα**: chromatographycally homogeneous amorphous; λmax (EtOH) 226, 275, 284, 291 nm; νmax (KBr) 3350, 1685, 1510 cm^{-1}; m/z (%) 411 (M^+), 171(100); δ 8.34 (1H, br, N_9-H, exchangeable), 7.47 (1H, d, J = 7.7 Hz, ArH), 7.34 (5H, s, PhH), 7.31 (1H, m, ArH), 7.24-7.09 (2H, m, ArH), 5.80 (1H, br, OH, exchangeable), 5.58 (1H, d, J = 9.6 Hz, NH, exchangeable), 5.15 (1H, d, J = 12.4 Hz, CHPh), 5.10 (1H, d, J = 12.1 Hz, CHPh), 4.54 (1H, bs, C_{10}-H), 4.23 (1H, bs, C_1-H), 3.48 (1H, m, C_3-H), 3.16 (1H, m, C_3-H), 2.91 (1H, m, C_4-H), 2.88 (1H, dd, J = 13.8, 7.2 Hz, SCH), 2.80 (1H, m, C_4-H), 2.73 (1H, dd, J = 13.8, 5.5 Hz, SCH), 2.12 (1H, s, SMe). (±)-**8cβ**: chromatographycally homogeneous amorphous; λmax (EtOH) 226, 275, 283, 291 nm; νmax (KBr) 3350, 1695, 1510, 1260, 745 cm^{-1}; m/z (%) 411 (M^+), 171 (100); δ 8.42 (1H, br, N_9-H, exchangeable), 7.48 (1H, d, J = 7.3 Hz, ArH), 7.36-7.07 (8H, m, ArH), 5.65 (1H, d, J = 7.9 Hz, NH, exchangeable), 5.04 (2H, s, CH_2Ph), 4.94 (1H, br, OH, exchangeable), 4.54 (1H, br, C_{10}-H), 4.50 (1H, br, C_1-H), 3.62 (1H, m, C_3-H), 3.22 (1H, m, C_3-H), 3.14-3.07 (2H, m, C_4-H, SCH), 2.81 (2H, m, C_4-H, SCH), 2.19 (3H, s, SMe); Anal. Calcd. for $C_{22}H_{25}N_3O_3S(M^+)$: 411.1614. Found: 411.1619(HRMS).

Tetracyclic compound (±)-**7d**; chromatographycally homogeneous amorphous; λmax (EtOH) 245, 302 nm; νmax (KBr) 3365, 1690, 1605, 1410, 750 cm^{-1}; m/z (%) 495 (M^+-2), 130 (100); δ 7.08-7.20 (2H, m, ArH), 6.81(1H, m, ArH), 6.60(1H, d, J = 8.2 Hz, C_8-H), 5.49 (1H, br, OH, exchangeable), 5.48, 5.49 (1H, s, C_{6a}-H), 4.86-4.96 (1H, br, NH, exchangeable), 4.70-4.96 (2H, m, CH_2CCl_3), 4.40 (1H, m, C_5-H), 3.74, 3.77 (3H, s, OMe), 3.53, 3.60 (1H, s, C_4-H), 3.45 (1H, m, C_2-H), 3.20 (1H,m, C_2-H), 2.40 (1H, m, SCH), 3.10 (1H, m, SCH), 2.20 (2H, m, C_1-H).

1-[1-(N-(2,2,2-Trichloroethoxycarbonyl)amino)-2-(methoxycarbonylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline (±)-**8dα, 8dβ**; chromatographycally homogeneous amorphous; λmax (EtOH) 226, 274, 283, 291 nm; νmax (KBr) 3350, 1685, 1515 cm^{-1}; δ 8.60 (8/9H, br, N_9-H, exchangeable), 8.39 (1/9H, br, N_9-H, exchangeable), 7.09-7.49 (4H, m, ArH), 5.93 (1H, br, NH, exchangeable), 5.14 (1H, br, OH, exchangeable), 4.71 (1H, d, J = 12.0 Hz, $CHCCl_3$), 4.62 (1H, d, J = 12.0 Hz, $CHCCl_3$), 4.58 (1H, br, C_{10}-H), 4.46 (8/9H, br, C_1-βH), 4.30 (1/9H, br, C_1-αH), 3.86, 3.83 (3H, s, OMe), 3.60 (1H, m, C_3-H), 3.43 (1H, dd, J =5.1, 14.4 Hz, SCH), 3.20 (2H, m, C_3-H, SCH), 3.13 (1H, m, C_4-H), 2.80 (1H, m, C_4-H).

Tetracyclic compound (±)-**7e**; chromatographycally homogeneous amorphous; λmax (EtOH) 245, 302 nm; νmax (KBr) 3370, 1710, 1690, 1605, 1130, 750 cm^{-1}; m/z (%) 455 (M^+), 130 (100); δ 7.36(5H, br, PhH), 7.09-7.14 (2H, m, ArH), 6.77(1H, ArH), 6.55(1H, d, J = 8.2 Hz, C_8-H), 5.47(1H, s, C_{6a}-H), 5.34, 5.46 (1H, br, NH, exchangeable), 5.22 (1H, d, J = 12.0 Hz, CHPh), 5.16 (1H, d, J = 12.0 Hz, CHPh), 4.93, 4.66 (1H, br, OH, exchangeable), 4.36, 4.30 (1H, m, C_5-H), 3.77, 3.71 (3H, s, OMe), 3.47 (1H, s, C_4-H), 3.40 (1H, m, C_2-H), 3.16 (1H, m, C_2-H), 2.99 (1H, dd, J = 5.1, 14.4 Hz, SCH), 2.34 (1H, m, SCH), 2.19 (2H, m, C_1-H); Anal. Calcd. for $C_{23}H_{25}N_3O_5S$(M^+): 455.1513. Found: 455.1523(HRMS).

1-[1-(N-(Methoxycarbonyl)amino)-2-(benzyloxycarbonylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline (±)-**8eα, 8eβ**; chromatographycally homogeneous amorphous; λmax (EtOH) 226, 274, 283, 291 nm; νmax (KBr) 3440, 3350, 1690, 1520 cm^{-1}; m/z (%) 269 (9), 168 (27), 79 (100); δ 8.82-8.59 (1H, br, N_9-H, exchangeable), 7.48 (1H, d, J = 7 Hz, ArH), 7.38-7.27 (6H, m, ArH), 7.18-7.06 (2H, m, ArH), 5.66 (1H, br, NH, exchangeable), 5.31-5.21 (1H, br, OH, exchangeable), 5.29 (1H, d, J = 12.0 Hz, CHPh), 5.24 (1H, d, J = 12.0 Hz, CHPh), 4.52 (1H, m, C_{10}-H), 4.43 (5/6H, br, C_1-βH), 4.24 (1/6H, br, C_1-αH), 3.60 (4H, br, s, C_3-H, OMe), 3.41 (1H, dd, J = 5.1, 14.4 Hz, SCH), 3.20 (2H, m, C_3-H, SCH), 3.02 (1H, m, C_4-H), 2.75-2.81 (1H, m, C_4-H); Anal. Calcd. for $C_{23}H_{25}N_3O_5S$(M^+): 455.1513. Found: 455.1518(HRMS).

Tetracyclic compound (±)-**7f**; chromatographycally homogeneous amorphous; λmax (EtOH) 245, 302 nm; νmax (KBr) 3370, 1720, 1690, 1120 cm^{-1}; m/z (%) 495 (M^+-2), 130 (100); δ 7.17-7.11 (2H, m, ArH), 6.79(1H, m, ArH), 6.58 (1H, d, J = 8.2 Hz, C_8-H), 5.47 (1H, br, OH, exchangeable), 5.46, 5.36 (1H, s, C_{6a}-H), 4.96, 4.69 (1H, br, NH, exchangeable), 4.82 (1H, d, J = 11.9 Hz, $CHCCl_3$), 4.76 (1H, d, J = 11.9 Hz, $CHCCl_3$), 4.39, 4.31 (1H, m, C_5-H), 3.78 (3H, s, OMe), 3.49 (1H, s, C_4-H), 3.43 (1H, m, C_2-H), 3.18 (1H, m, C_2-H), 3.07 (1H, m, SCH), 2.41 (1H, dd, J = 1,3 Hz, SCH), 2.21 (2H, m, C_1-H); Anal. Calcd. for $C_{18}H_{20}N_3O_5SCl_3$(M^+): 497.0157/495.0188. Found: 497.0173/495.0164(HRMS).

1-[1-(N-(Methoxycarbonyl)amino)-2-(2,2,2-trichloroethoxycarbonylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline (±)-**8fα, 8fβ**; chromatographycally homogeneous amorphous; λmax (EtOH) 226, 275, 284, 291.5 nm; m/z (%) 269 (12), 168 (51), 31 (100); δ 8.60, 8.53 (1H, br, N_9-H,

exchangeable), 7.48-7.07 (4H, m, ArH), 5.75, 5.61 (1H, br, NH, exchangeable), 5.10 (1H, br, OH, exchangeable), 4.92 (1H, d, J = 12.0 Hz, $CHCCl_3$), 4.82 (1H, d, J = 12.0 Hz, $CHCCl_3$), 4.47 (6/7H, br, C_1-βH), 4.59 (1H, br, C_{10}-H), 4.25 (1/7H, br, C_1-αH), 3.68, 3.60 (3H, s, OMe), 3.60 (1H, m, C_3-H), 3.47 (1H, dd, J = 5.2, 14.4 Hz, SCH), 3.30 (1H, br, SCH), 3.22 (1H, m, C_3-H), 3.05 (1H, m, C_4-H), 2.80 (1H, m, C_4-H); Anal. Calcd. for $C_{18}H_{20}N_3O_5SCl_3(M^+)$: 497.0157/495.0188. Found: 497.0141/495.0195(HRMS).

Tetracyclic compound (±)-**7g**: chromatographycally homogeneous amorphous; λmax (EtOH) 253.5, 310 nm; m/z (%) 423 (5, M^+), 157 (100); δ 7.09 (2H, m, ArH), 6.68(1H, m, ArH), 6.32 (1H, m, C_8-H), 6.04 (1H, br, OH, exchangeable), 5.42(1H, s, C_{6a}-H), 4.57, 4.73 (1H, d, J = 12 Hz, SCHO), 4.47 (1H, br, C_5-H), 3.82-3.70 (1H, m, OCH_2CH_2O), 3.77 (3H, s, COOMe), 3.64-3.58 (3H, m, OCH_2CH_2O), 3.37 (3H, s, OMe), 3.55-3.30 (2H, m, C_2-H, C_4-H), 3.21-3.06 (1H, m, C_2-H), 2.94 (3H, s, NMe), 2.72 (1H, m, SCH), 2.32-2.20 (2H, m, C_1-H), 2.18-2.04 (1H, m, SCH); Anal. Calcd. for $C_{20}H_{29}N_3O_5S(M^+)$: 423.1825. Found: 423.1814(HRMS).

Tetracyclic compound (±)-**7h**: chromatographycally homogeneous amorphous; λmax (EtOH) 253, 310 nm; νmax(KBr) 3400, 1730, 1710, 1120 cm^{-1}; m/z (%) 495 (M^+-16), 493 (1), 144 (100); δ 7.12 (2H, m, ArH), 6.70 (1H, m, ArH), 6.35 (1H, d, J=7.3 Hz, C_8-H), 5.68 (1H, br, OH, exchangeable), 5.45 (1H, s, C_{6a}-H), 4.78 (2H, s, CH_2CCl_3), 4.51 (1H, m, C_5-H), 3.78 (3H, s, OMe), 3.37 (1H, s, C_4-H), 3.32 (1H, m, C_2-H), 3.17 (1H, m, C_2-H), 2.93 (3H, s, NMe), 2.85 (1H, dd, J = 14.4, 8.3 Hz, SCH), 2.74 (1H, dd, J = 14,8 Hz, SCH), 2.32 (1H, m, C_1-H), 2.10 (1H, m, C_1-H).

Transformation of the tetracyclic compound 7cα to tetrahydro-β-carboline 8ca, 8cβ: To a solution of tetracyclic compound **7cα** (250 mg, 0.60 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (684 mg, 6.00 mmol) by injection at room temperature in atmosphere of Ar. After stirring for 24 h, the reaction mixture was diluted with CH_2Cl_2 and quenched with sat. $NaHCO_3$, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give tetrahydro-β-carboline **8cα** (23 mg, 9.2 %), **8cβ** (181 mg, 72.4 %), and tetracyclic compound **7cα** (15 mg, 6 %).

General procedure for the preparation of the optically active nitrones 9 from N,S-disubstituted-L-cysteine methyl ester and N_b-hydroxytryptamine: To a solution of N,S-disubstituted-L-cysteine methyl esters in dry toluene was added DIBAH (2.5 mol equiv; 1M solution in toluene) by injection for 20 min. at -78°C under an argon atmosphere. After stirring for 2 h at the same temperature, the excess of reagent was quenched by careful addition of 10% HCl into the reaction mixture and then the organic layer was separated. The aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. to give a crude cysteinals which were used in the next step without chromatographic purification.

The crude cysteinals **6** were dissolved in dry CH_2Cl_2 and stirred at room temperature under an argon atmosphere. To this solution was added N_b-hydroxytryptamine **5** in one portion. After 2 h, the reaction mixture was evaporated *in vacuo*. and the residue was chromatographed over SiO_2 to gave the nitrones **9** which were chromatographycally homogeneous.

(+)-**9a**(Nc-COOMe,S-Me): chromatographycally homogeneous amorphous; $[\alpha]_D^{24}$ +56.9° (c.0.68, MeOH); λmax (EtOH) 222, 275, 283, 291 nm; vmax (KBr) 3310, 1690, 1540, 1270, 1150 cm^{-1}; m/z 317(M^+-H_2O); δ 8.12 (1H, bs, exchangeable, N_1-H), 7.59 (1H, d, J = 8.0 Hz, C_7-H), 7.37 (1H, d, J = 8.3 Hz, C_4-H), 7.21 (1H, t-like, C_6-H or C_5-H), 7.13 (1H, t-like, C_6-H or C_5-H), 7.05 (1H, d, J = 2.5 Hz, C_2-H), 6.57 (1H, bs, N=CH), 6.19 (1H, bs, exchangeable, N_{10}-H), 4.57 (1H, m, C_{12}-H), 4.01 (2H, t, J = 6.6 Hz, C_9-H), 3.66 (3H, s, OMe), 3.36 (2H, m, C_8-H), 2.89 (1H, m, C_{13}-H), 2.71 (1H, m, C_{13}-H), 2.07 (3H, s, SMe).

(+)-**9f**(Nc-COOMe,S-TROC): chromatographycally homogeneous amorphous; $[\alpha]_D^{24}$ +13.5° (c.0.60, MeOH); λmax (EtOH) 222, 275, 283, 291 nm; vmax (KBr) 3350, 1735, 1540, 1250 cm^{-1}; δ 8.17 (1H, bs, exchangeable, N_1-H), 7.10-7.59 (4H, m, ArH), 7.04 (1H, d, J = 2.5 Hz, C_2-H), 6.50 (1H, d, J = 4.0 Hz, N=CH), 6.24 (1H, bs, exchangeable, N_{10}-H), 4.85 (1H, d, J = 11.9 Hz, CH_aCCl_3), 4.77 (1H, d, J = 11.9 Hz, CH_bCCl_3), 4.62 (1H, m, C_{12}-H), 4.01 (2H, m, C_9-H), 3.65 (3H, s, OMe), 3.36 (2H, m, C_8-H), 3.25 (2H, m, C_{13}-H); Anal. Calcd. for $C_{18}H_{20}N_3O_5SCl_3(M^+)$: 497.0157/495.0188. Found: 497.0160/495.0168(HRMS).

(+)-**9h**(Na-Me, Nc-COOMe, S-TROC): mp 96-97°C(AcOEt-nHex); $[\alpha]_D^{21}$ +30.0° (c.1.0, MeOH); λmax (EtOH) 226, 276, 288, 300 nm; vmax (KBr) 3300, 1735, 1540, 1250, 1100 cm^{-1}; δ 7.58-7.12 (4H, m, ArH), 6.90 (1H, s, C_2-H), 6.50 (1H, d, J = 5.5 Hz, N=CH), 6.22 (1H, br, exchangeable, N_{10}-H), 4.84 (1H, d, J = 11.9 Hz, CH_aCCl_3), 4.77 (1H, d, J = 11.9 Hz, CH_bCCl_3), 4.63 (1H, m, C_{12}-H), 4.00 (2H, t-like, C_9-H), 3.75 (3H, s, OMe), 3.64 (3H, s, NMe), 3.34 (2H, t-like, C_8-H), 3.27 (2H, m, C_{13}-H).

(+)-**9i**(Nc-BOC,S-TROC): chromatographycally homogeneous amorphous; $[\alpha]_D^{24}$ +35.5° (c.1.0, MeOH); λmax (EtOH) 222, 275, 284, 291 nm; vmax (KBr) 3320, 1720, 1505, 1130 cm^{-1}; δ 8.12 (1H, br, exchangeable, N_1-H), 7.59 (1H, d, J=7.9 Hz, C_7-H), 7.37 (1H, dd, J = 7.9, 1.2 Hz, C_4-H), 7.24-7.11 (2H, m, $C_{5,6}$-H), 7.05 (1H, d, J = 2.2 Hz, C_2-H), 6.50 (1H, d, J = 5.5 Hz, N=CH), 5.99 (1H, d, J = 5.5 Hz, exchangeable, N_{10}-H), 4.85 (1H, d, J = 11.9 Hz, CH_aCCl_3), 4.77 (1H, d, J = 11.9 Hz, CH_bCCl_3), 4.59 (1H, m, C_{12}-H), 4.01 (2H, t-like, C_9-H), 3.36 (2H, t-like, C_8-H), 3.24 (2H, d, J = 6.7 Hz, C_{13}-H), 1.42 (9H, s, t-Bu).

(+)-**9j**(Nc-TROC,S-Me): chromatographycally homogeneous amorphous; $[\alpha]_D^{27}$ +41.0° (c.0.30, MeOH); λmax (EtOH) 222, 275, 284, 291 nm; vmax (KBr) 3350, 1725, 1600, 1240, 1140 cm^{-1}; m/z 436(M^+-16); δ 8.16 (1H, bs, exchangeable, N_1-H), 7.59 (1H, d, J = 7.6 Hz, C_7-H), 7.37 (1H, d, J = 7.9 Hz, C_4-H), 7.24-7.11 (2H, m, $C_{5,6}$-H), 7.05 (1H, d, J = 2.4 Hz, C_2-H), 6.63 (1H, d, J = 8.2 Hz, exchangeable, N_{10}-H), 6.55 (1H, d, J = 5.8 Hz, N=CH), 4.75 (1H, d, J = 11.9 Hz, CH_aCCl_3), 4.67 (1H, d, J = 11.9 Hz, CH_bCCl_3), 4.57 (1H, m, C_{12}-H), 4.03 (2H, t-like, C_9-H), 3.37 (2H, t-like, C_8-H), 2.90 (1H, dd, J = 7.0, 13.7 Hz, C_{13}-H), 2.72 (1H, dd, J = 6.7, 13.7 Hz, C_{13}-H), 2.07 (3H, s, SMe); Anal. Calcd. for $C_{17}H_{20}N_3O_3SCl_3(M^+)$: 453.0260/451.0288. Found: 453.0268/453.0262(HRMS).

(+)-**9k**(Nc-BOC,S-Me): mp 135.5-136.5°C(AcOEt-nHex); $[\alpha]_D^{24}$ +67.3° (c.0.78, MeOH); λmax (EtOH) 222, 275, 284, 291 nm; vmax (KBr) 3310, 1670, 1555, 1150 cm^{-1}; m/z 378 (M^++1); δ 8.12 (1H, bs, exchangeable, N_1-H), 7.59 (1H, d, J = 8.0 Hz, C_7-H), 7.37 (1H, d, J = 8.3 Hz, C_4-H), 7.21 (1H, t-like, C_6-H or C_5-H), 7.13 (1H, t-like, C_6-H or C_5-H), 7.06 (1H, d, J = 2.2 Hz, C_2-H), 6.57 (1H, bs, N=CH), 5.96 (1H, bs, exchangeable, N_{10}-H), 4.55 (1H, m, C_{12}-H), 4.01 (2H, t-like, C_9-H), 3.36 (2H, t-like, C_8-H),

2.90 (1H, m, C_{13}-H), 2.71 (1H, m, C_{13}-H), 2.07 (3H, s, SMe), 1.43 (9H, s, t-Bu); Anal. Calcd. for $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21; N, 11.13; S, 8.49. Found: C, 60.34; H, 7.12; N, 11.01; S, 8.66.

General procedure for the cyclization of nitrones (+)-9 in Table III: Trifluoroacetic acid (1 mol equiv) was added by injection at room temperature in atmosphere of Ar to a solution of nitrones (+)-**9** (1 mol equiv) in dry CH_2Cl_2. After stirring for 5 min., the reaction mixture was diluted with CH_2Cl_2 and quenched with sat. $NaHCO_3$, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give the products.

Tetracyclic compound (-)-**7a**α: chromatographycally homogeneous amorphous; $[\alpha]_D^{18}$ -113.8° (c.0.34, MeOH); (-)-**8a**β: chromatographycally homogeneous amorphous; $[\alpha]_D^{19}$ -22.2° (c.0.55, MeOH).

Tetracyclic compound (-)-**7f**α: chromatographycally homogeneous amorphous; $[\alpha]_D^{19}$ -86.9° (c.0.99, MeOH).

Tetracyclic compound (-)-**7h**α: chromatographycally homogeneous amorphous; $[\alpha]_D^{25}$ -93.0° (c.0.99, MeOH).

Tetracyclic compound (-)-**7i**α: chromatographycally homogeneous amorphous; $[\alpha]_D^{25}$ -98.1° (c.0.55, MeOH); λmax (EtOH) 245, 303 nm; νmax (KBr) 3350, 1720, 1680, 1360 cm^{-1}; m/z 539/537 (M+), 523/521 (M^+-16), 143 (100); δ 7.10 (2H, m, ArH), 6.80 (1H, m, ArH), 6.59 (1H, m, ArH), 5.85,5.69 (1H, br, OH, exchangeable), 5.41,5.27 (1H, s, C_{6a}-H), 4.98,4.60 (1H, br, NH, exchangeable), 4.78 (2H, s, CH_2CCl_3), 4.35,4.24 (1H, dd, J = 9.8, 4.9 Hz, C_5-H), 3.49 (1H, s, C_4-H), 3.43 (1H, m, C_2-H), 3.20 (2H, m, C_2-H, SCH), 2.85 (3H, m SCH, C_1-H); Anal. Calcd. for $C_{21}H_{26}N_3O_5SCl_3(M^+)$: 539.0627/537.0656. Found: 539.0619/537.0642(HRMS).

1-[1-(N-(t-Butyloxycarbonyl)amino)-2-(2,2,2-trichloroethoxycarbonylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline **8i**α, **8i**β: inseparable mixture; λmax (EtOH) 226, 275, 284, 291 nm; νmax (KBr) 3400, 1710,1695, 1505, 1130 cm^{-1}; δ 8.61 (1H, bs, N9-H, exchangeable), 7.50-7.06 (4H, m, ArH), 5.35 (1H, br, NH, exchangeable), 5.10 (1H, br, OH, exchangeable), 4.92(1H, d, J = 12.0 Hz, $CHCCl_3$), 4.81 (1H, d, J = 12.0 Hz, $CHCCl_3$),4.60 (1H, bs, C_{10}-H), 4.48 (5/6H, br, C_1-βH), 4.23 (1/6H, br, C_1-αH), 3.62 (1H, br, C_3-H), 3.45 (1H, dd, J = 14.0, 5.0 Hz, C_{11}-H), 3.20 (2H, m, C_3-H, C_{11}-H), 3.10 (1H, m, C_4-H), 2.78 (1H, m, C_4-H).

Tetracyclic compound (-)-**7j**: chromatographycally homogeneous amorphous; $[\alpha]_D^{27}$ -110.0° (c.0.30, MeOH); λmax (EtOH) 245, 302 nm ; νmax (KBr) 3330, 1680, 1400 cm^{-1}; m/z 453/451(M^+); δ 7.17 (1H, dd, J = 7.3, 0.6 Hz, C_{11}-H), 7.10 (1H, m, C_9-H), 6.80 (1H, m, C_{10}-H), 6.59 (1H, d, J = 7.6 Hz, C_8-H), 5.70 (1H, br, exchangeable, OH), 5.47 (1H, bs, C_{6a}-H), 4.98, 4.81 (1H, bs, exchangeable, N_7-H), 4.92,4.90 (1H, d, J = 12.2 Hz, $CHCCl_3$), 4.69,4.63 (1H, d, J = 11.9 Hz, $CHCCl_3$), 4.32 (1H, m, C_5-H), 3.76,3.69 (1H, s, C_4-H), 3.47 (1H, m, C_2-H), 3.23 (1H, m, C_2-H), 2.83-2.67 (1H, m, C_{12}-H), 2.35-2.14 (2H, m, C_1-H), 2.08 (3H, s, SMe), 1.86 (1H, t-like, C_{12}-H); Anal. Calcd. for $C_{17}H_{20}N_3O_3SCl_3(M^+)$: 453.0259/451.0289. Found: 453.0257/451.0280(HRMS).

1-[1-(N-(2,2,2-trichloroethoxycarbonyl)amino)-2-(methylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline **8j**α,**8j**β: (+) **8j**α: chromatographycally homogeneous amorphous; $[\alpha]_D^{26}$

+6.4° (c.0.33, MeOH); λmax (EtOH) 227, 274, 284, 292 nm; νmax (KBr) 3360, 1700, 1500, 740 cm^{-1}; m/z 437/435 (M^+-16); δ 8.20 (1H, bs, N9-H, exchangeable), 7.49 (1H, d, J = 7.0 Hz, C8-H), 7.34 (1H, d, J = 6.4 Hz, C5-H), 7.22-7.07 (2H, m, C7-H,C6-H), 5.98 (1H, br, OH, exchangeable), 5.02 (1H, d-like, NH, exchangeable), 4.78 (2H, s, CH_2CCl_3), 4.55 (1H, bs, C10-H), 4.27 (1H, br, C1-H), 3.50 (1H, br, C3-H), 3.40 (1H, m, C11-H), 3.19 (1H, m, C3-H), 3.95-3.70 (3H, m, H11, C4-H). 2.16 (3H, s, SMe).

(-) **8jβ**: chromatographycally homogeneous amorphous; $[\alpha]_D^{27}$ -15.7° (c.0.35, MeOH); λmax (EtOH) 227, 274, 284, 292 nm; νmax (KBr) 3360, 1710, 1500, 740 cm^{-1}; m/z 437/435 (M^+-16); δ 8.28 (1H, bs, C9-H, exchangeable), 7.48 (1H, d, J = 7.3 Hz, C8-H), 7.30 (1H, m, C5-H), 7.15 (1H, m, C7-H), 7.09 (1H, m, C6-H), 5.89 (1H, d,J = 8.2 Hz, NH, exchangeable), 5.02 (1H, br, OH, exchangeable), 4.67 (2H, s, CH_2CCl_3), 4.55 (1H, bs, C1-H), 4.49 (1H, br, C10-H), 3.63 (1H, br, C3-H), 3.24 (1H, m, C11-H), 3.14 (1H, m, C3-H), 3.07 (1H, br, C4-H), 2.88-2.76 (2H, m, C11-H, C4-H), 2.23 (3H, s, SMe); Anal. Calcd. for $C_{17}H_{20}N_3O_3SCl_3$(M^+): 453.0260/451.0288. Found: 453.0261/453.0270(HRMS).

Tetracyclic compound(-) **-7k**: mp 169.5-171°C(AcOEt-nHex); $[\alpha]_D^{24}$ -139.2° (c.0.47, MeOH); λmax (EtOH) 245, 302 nm ; νmax (KBr) 3330, 1675, 1400 cm^{-1}; m/z 378 (M^++1); δ 7.16 (1H, d, J = 7.4 Hz, C11-H), 7.07 (1H, m, C9-H), 6.77 (1H, m, C10-H), 6.58 (1H, m, C4-H), 5.45 (1H, br, exchangeable, OH), 5.40, 5.26 (1H, bs, C6a-H), 5.07, 4.71 (1H, bs, exchangeable, NH), 4.25, 4.10 (1H, m, C5-H), 3.63 (1H, s, C4-H), 3.45 (1H, m, C2-H), 3.21 (1H, m, C2-H), 2.64 (1H, m, C12-H), 2.23 (2H, m, C1-H), 2.14 (3H, s, SMe), 1.85 (1H, m, C12-H),1.45 (9H, s, t-Bu); Anal. Calcd. for $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21; N, 11.13; Found: C, 60.47; H, 7.23; N, 11.11.

1-[1-(N-(t-Butyloxycarbonyl)amino)-2-(methylthio)-ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carboline **8kα,8kβ**: (-) **8kα**: chromatographycally homogeneous amorphous; $[\alpha]_D^{18}$ -22.0° (c.0.12, MeOH); λmax (EtOH) 227, 274, 284, 292 nm; νmax (KBr) 3410, 3350, 1650, 1525, 1170, 745 cm^{-1}; m/z 377 (M^+), 171 (100); δ 8.66 (1H, bs, N9-H, exchangeable), 7.49(1H, d, J = 7.7 Hz, C8-H), 7.30 (1H, d, J = 8.0 Hz, C5-H), 7.15 (1H, m, C7-H), 7.09 (1H, m, C6-H), 5.36 (1H, br, NH, exchangeable), 4.95 (1H, br, OH, exchangeable), 4.56 (1H, bs, C1-H), 4.45 (1H, br, C10-H), 3.64 (1H, br, C3-H), 3.24 (1H, m, C11-H), 3.09 (2H, m, C4-H, C3-H), 2.77 (2H, m, C11-H, C4-H), 2.20 (3H, s, SMe), 1.36 (9H, s, t-Bu).

(-) **8kβ**: chromatographycally homogeneous amorphous; $[\alpha]_D^{22}$ -19.8° (c.0.41, MeOH); λmax (EtOH) 227, 274, 284, 292 nm; νmax (KBr) 3350, 1690, 1495, 745 cm^{-1}; m/z 377 (M^+), 171 (100); δ 8.39 (1H, bs, N9-H, exchangeable), 7.48 (1H, d, J = 7.7 Hz, C8-H), 7.31 (1H, d, J = 7.7 Hz, C5-H), 7.17 (1H, t-like, C7-H), 7.11 (1H, t-like, C6-H), 5.90 (1H, br, OH, exchangeable), 5.30 (1H, d, J = 9.6 Hz, NH, exchangeable), 4.45 (1H, br, C10-H), 4.21 (1H, bs, C1-H), 3.50 (1H, m, C3-H), 3.19 (1H, m, C11-H), 2.93 (1H, m, C3-H), 2.89 (1H, m, C4-H), 2.82 (1H, m, C4-H), 2.74 (1H, m, C11-H), 2.15 (3H, s, SMe), 1.45 (9H, s, t-Bu).

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References

† Preliminary result has been published: M. Nakagawa, Jinjun Liu, K. Ogata, and T. Hino, *J. Chem. Soc., Chem. Commun.*, **1988**, 464; M. Nakagawa, Jinjun Liu, and T. Hino, *J. Am. Chem. Soc.*, **1989**, *111*, 2721.

(1) (a) K. L. Reinhart, Jr., J. Kobayashi, G. C. Harbour, R. G. Hughes, Jr.,S. A. Mizsak, and T. A. Scahill, *J. Am. Chem. Soc.*, **1984**, *106*, 1524; (b) K. L. Reinhart, Jr., J. Kobayashi, G. C. Harbour, J. Gilmore, M. Mascal, T. G. Holt, L. S. Shield, and F. Lafargne, *J. Am. Chem. Soc.*, **1987**, *109*, 3378; (c) J. W. Blunt, R. J. Lake, and M. H. G. Munro, *Tetrahedron Lett.*, **1987**, *28*, 1825; (d) R. J. Lake, M. M. Brennan, J. W. Blunt, and M. H. G. Munro, *Tetrahedron Lett.*, **1988**, *29*, 2255.

(2) R. Plate, R. H. M. Van Hout, H. Behm, and H. C. J. Ottenheijm, *J. Org. Chem.*, **1987**, *52*, 555.

(3) (a) P. Flecker, E. Winterfeldt, *Tetrahedron* , **1984**, *40*, 4853; (b) D. B. Maclean, W. A. Szarek, and I. Kvarnstrom, *J. Chem. Soc., Chem. Commun.*, **1983**, 602.

(4) (a) M. Nakagawa, H. Fukushima, T. Kawate, M. Hongu, T. Une, S. Kodato, M. Taniguchi, and T. Hino, *Chem. Pharm. Bull.* **1989**, *31*, 23; (b) S. Kodato, M. Nakagawa, M. Hongu, T. Kawate, and T. Hino, *Tetrahedron* , **1988**, *44*, 359.

(5) (a) The cysteinal used here was purified by column chromatography, and was found to be racemized; (b) A. Ito, R. Takahashi, Y. Baba, *Chem. Pharm. Bull.* **1975**, *23*, 3081.

(6) (a) F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, and J. M. Cook, *J. Am. Chem. Soc.*, **1980**, *102*, 6976; (b) J. Sandrin, D. Soerens, and J. M. Cook, *Heterocycles*, **1976**, *4*, 1249.

(7) Unpublished data, T. Hino, A. Hasegawa, J. J. Liu, and M. Nakagawa.

(8) Details of the mechanism will be reported elsewhere.

(9) Result on X-ray analysis of a nitrone will be reported elsewhere.

(10) The optical purity of the nitrones were based on their ^{1}H-NMR data in the presence of shift reagent (tris [3-heptafluoropropylhydroxy-methylene-d-camphorato] derivative of europium (III)).

(11) S. Y. Han, M. V. Lakshmikantham, and M. P. Cava, *Heterocycles*, **1985**, *23*, 1671.

(12) H. Shechter and D. E. Roberson, Jr, *J. Am. Chem. Soc.*, **1956**, *78*, 4984.

(13) E. H. P. Young, *J. Chem. Soc.*, **1958**, 3494.