The Pictet–Spengler Reaction of N_b-Hydroxytryptamines and Cysteinals. II. Temperature Effects, Stereochemistry and Mechanism

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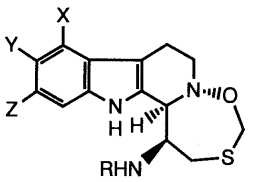
The effect of temperature on the Pictet–Spengler reaction of N_b-hydroxytryptamines (1) and cysteinals (2) has been examined. The optically active nitrones (3), obtained from 1 and 2, gave the corresponding N_b-hydroxy-β-carbolines (4α and 4β) exclusively at −78 °C in the presence of an excess of trifluoroacetic acid. The mechanism is discussed in relation to the stereochemistry.

Keywords Pictet–Spengler reaction; N_b-hydroxytryptamine; cysteinal; N_b-hydroxy-β-carboline; nitrone; spiroindolenine; mechanism; temperature effect

Recently potent antiviral compounds, eudistomins, have been isolated from Caribbean and New Zealand colonial tunicates. They contain the previously unreported oxathiazepine ring system condensed with tetrahydro-β-carboline[1] (Chart 1).

In connection with our studies on the synthesis of eudistomins, we reported the Pictet–Spengler (P–S) reaction of hydroxytryptamine and aldehydes.[2] In the preceding paper,[2] we described the P–S reaction of N_b-hydroxytryptamines (**1**) and cysteinals (**2**) in the presence of trifluoroacetic acid (TFA) (1 mol eq) at room temperature, which provided a mixture of the corresponding N_b-hydroxytetrahydro-β-carbolines (**4**α and **4**β) together with unexpected tetracyclic compounds (**5**) (Table I, entries 8—14). Although both of the products (**5** and **4**) can be considered as precursors for the synthesis of the natural eudistomins, the tetracyclic compounds (**5**), which can easily be transformed into the corresponding β-carbolines (**4**) by treatment with excess TFA, seem to be more useful intermediates considering the ease of introduction of a substituent into the benzene ring by electrophilic substitution.[2b,3] In order to improve the selectivity for the tetracyclic compounds (**5**), we have investigated the effect of temperature on this P–S reaction.



	X	Y	Z	R
eudistomin	H	H	H	H
eudistomin L	H	Br	H	H
eudistomin K	H	H	Br	H
eudistomin C	H	OH	Br	H
eudistomin E	Br	OH	H	H
eudistomin F	H	OH	Br	CO_2Me

Chart 1

Generally, the P–S reaction of tryptamine and an aldehyde has been carried out at room temperature[4] or at an elevated temperature[5] with an acid catalyst. On the other hand, unlike these Schiff's bases, the nitrones formed from N_b-hydroxytryptamine with an aldehyde were shown to have higher reactivity in the P–S reaction, and the reaction proceeded rapidly within 5 min,[6] so it was expected that the P–S reaction of nitrones could be achieved at lower temperature. Actually, the reaction occurred smoothly at −78 °C, although prolonged treatment (1—2 h) with an excess (2 or 5 eq) of TFA was necessary. When the optically active nitrone (**3a**) having no substituent at the indole nitrogen, obtained from N_b-hydroxytryptamine (**1a**) and *N*-methoxycarbonyl-*S*-methyl-L-cysteinal (**2a**), was treated with TFA (2 eq) at −78 °C, the reaction was completed within 1 h, and we unexpectedly obtained only two isomers of the N_b-hydroxytetrahydro-β-carboline (**4a**). None of the tetracyclic compound was detected (Table I, R_1=H, R_2=COOMe, R_3=Me). Furthermore, the ratio of **4a**α/**4a**β increased to 1/41, whereas the ratio of **4a**α/**4a**β obtained at room temperature was 1/7[2a] (Table I, entry 8).

The result at −78 °C was surprising, since the tetracyclic compound (**5a**) was most likely formed by an intramolecular cyclization of the spiroindolenine intermediate, and could be considered as a kinetically controlled product. This fact suggests that the formation of β-carboline (**4a**) at −78 °C may not have occurred *via* a spiroindolenine intermediate.

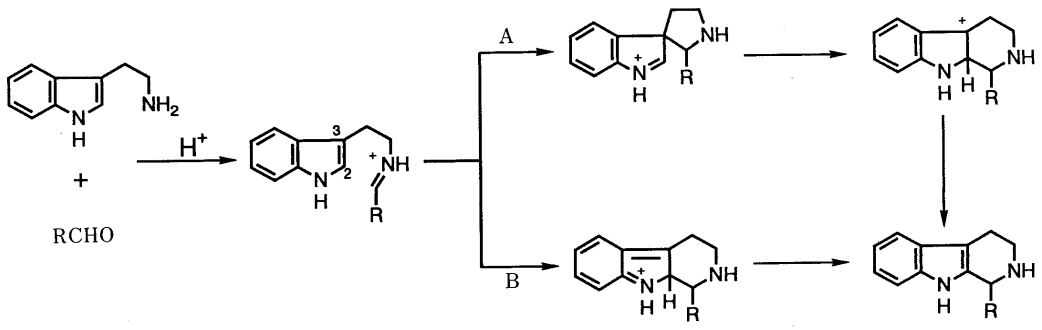
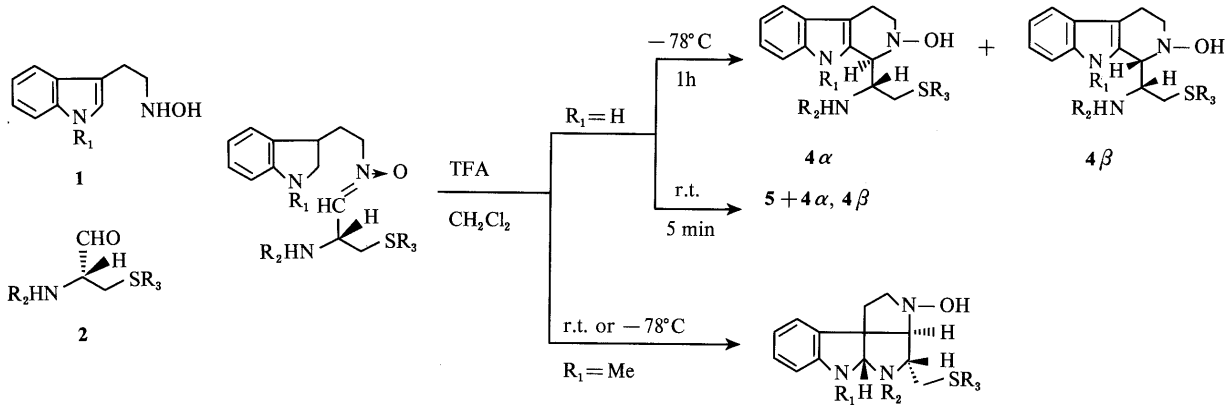


Chart 2

TABLE I. Cyclization of the Nitrones **3**



Entry	3	R_1	R_2	R_3	TFA (eq)	Conditions	5	Yield (%)	4	Yield (%)	(α:β)
1	**3a**	H	COOMe	Me	2	−78 °C/1 h			**4a**	97	(1:41)[a]
2	**3b**	H	Boc	Me	2	−78 °C/1 h			**4b**	96	(1:10)[b]
3	**3c**	H	COOMe	Troc	2	−78 °C/1 h			**4c**	100	(1:12)[b]
4	**3d**	H	Boc	Troc	5	−78 °C/2 h			**4d**	94	(1:10)[b]
5	**3e**	H	Cbz	Troc	2	−78 °C/1 h			**4e**	97	(1:12)[b]
6	**3f**	H	Troc	Me	5	−78 °C/2 h			**4f**	96	(1:21)[a]
7	**3g**	H	Troc	Cbz	5	−78 °C/1 h			**4g**	82	(1:8)[b]
8	**3a**	H	COOMe	Me	1	r.t./5 min	**5a**	75	**4a**	24	(1:7)[a]
9	**3b**	H	Boc	Me	1	r.t./5 min	**5b**	70	**4b**	21	(1:5)[b]
10	**3c**	H	COOMe	Troc	1	r.t./5 min	**5c**	35	**4c**	59	(1:6)[b]
11	**3d**	H	Boc	Troc	1	r.t./5 min	**5d**	49	**4d**	48	(1:5)[b]
12	**3e**	H	Cbz	Troc	2	r.t./1 hr	**5e**	28	**4e**	67	(1:4)[b]
13	**3f**	H	Troc	Me	1	r.t./5 min	**5f**	68	**4f**	25	(1:6)[a]
14	**3g**	H	Troc	Cbz	1[c]	r.t./1 h	**5g**	23	**4g**	58	(3:5)[b]
15	**3h**	Me	COOMe	Troc	1	r.t./5 min	**5h**	90			
16	**3i**	Me	COOMe	Me	1	r.t./5 min	**5i**	90			
17	**3h**	Me	COOMe	Troc	5	−78 °C/1 h	**5h**	93			
18	**3i**	Me	COOMe	Me	5	−78 °C/1 h	**5i**	90			

a) Ratio by isolation. *b*) Ratio by ^{1}H-NMR. *c*) TsOH was used instead of TFA. r.t. = room temperature.

Therefore, it was decided to make a detailed study of this observation.

A variety of nitrones (**3**) were employed in this cyclization at −78 °C; the results are shown in Table I together with the results obtained at room temperature.[2a] Excellent yields and high diastereoselectivity of tetrahydro-β-carbolines **4** (entries 1—7) were obtained with various nitrones **3** (R_1 = H) at −78 °C. On the other hand, *N*-methylated nitrones (**3h** and **3i**) gave the corresponding tetracyclic compounds (**5h** and **5i**) regardless of the reaction temperature (entries 15—18) as single isomers in high yields.

Two possible mechanistic pathways (Chart 2) for the P–S reaction of tryptamine and tryptophan derivatives have been proposed,[7] which involve either direct attack at the indole 2-position (path B) or attack at the 3-position of the indole ring to give a spiroindolenine intermediate followed by rearrangement (path A).

There is an increasing volume of data on the mechanisms and, in general, the cyclization is strongly suggested to proceed *via* the spiroindolenine intermediate (path A), whereas the direct attack at the indole 2-position could proceed through the geometrically more favoured 6-*endo*-Trig cyclization (path B).[8] Jackson and coworkers[9] have reported a substantial amount of evidence in support of the spiroindolenine mechanism stemming from an investigation of the electrophilic reactivity at the 3-position of the indole,

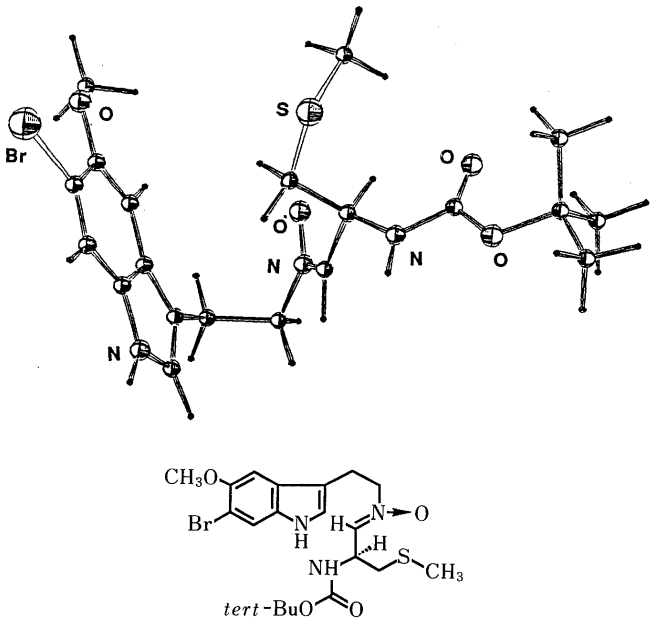


Fig. 1. ORTEP Drawing of (−)-**3k**

while Casnati and coworkers[10] have shown that direct attack at the 2-position (path B) competed with attack at the 3-position under some circumstances.

In our cases, the P–S reaction of N_b-hydroxytryptamine (**1**) and cysteinal (**2**) generates the corresponding nitrones (**3**) as the first intermediates which, unlike the imines from tryptamine derivatives, were isolable in a stable form as a single isomer. The configuration of the nitrones (**3**) has been confirmed as *Z*-form by X-ray analysis of the nitrone (**3k**) (Fig. 1, see also the experimental section).

Our result obtained at room temperature is qualitatively similar to the known mechanism which proceeds through the spiroindolenine intermediate. On the assumption that there is an allylic strain ($A^{1,3}$ strain)[11] in the stage of nitronium ions, the most stable conformation of the nitronium ions would be like **6**. The 3-position of the indole ring attacks on either the top or bottom face of the C=N bond to give the two corresponding spiroindolenine intermediates (**7**); the ratio of these spiroindolenines (**7**α and **7**β) may be governed by the chiral center adjacent to the C=N bond. The spiroindolenine (**7**α) would either rearrange to the minor isomer of β-carboline (**4**α) or be trapped by intramolecular cyclization to give the tetracyclic compound (**5**), competitively, whereas the spiroindolenine (**7**β) would preferentially rearrange to the major isomer of β-carboline (**4**β), or revert to **6** due to the instability of the corresponding tetracyclic compound (**5'**) (three five-membered rings are all *cis*-fused) (Chart 3).

Clearly, the isolation of the tetracyclic compound (**5**) provided strong evidence for the participation of the spiroindolenines in the P–S reaction. The results, however, can not exclude the other possibility that the spiroindolenines only take part in an equilibrium between spiroindolenines (**7**) and imininium ion (**6**) without leading to the corresponding β-carboline (**4**).[12] In fact, the presence of this equilibration was demonstrated by the formation of two β-carbolines, **4**β (major product) and **4**α (minor product) when the tetracyclic compound (**5**) was treated for a long time (24 h) with excess (10 mol eq) of TFA[2a] compared

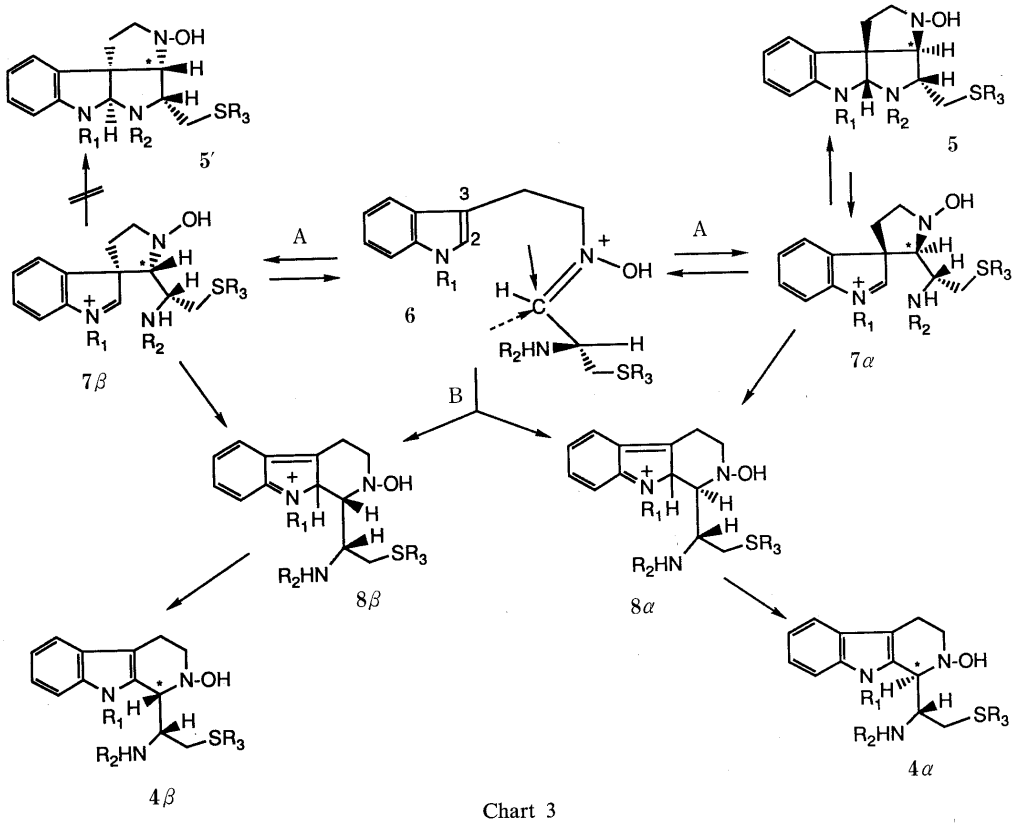


Chart 3

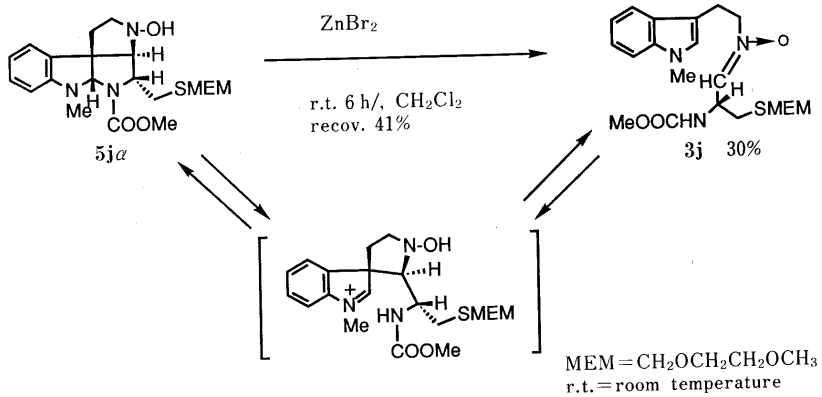


Chart 4

with that used in the direct reactions[1] (Table I, entries 8—14). Recent isotopic labelling experiments reported by Bailey[13] also suggested the presence of this equilibration in the P–S reaction.

Furthermore, more direct evidence for the presence of an equilibrium between **5** and **6** was obtained in our case. Thus, when the N_a-methyltetracyclic compound (**5j**)[2] was treated with $ZnBr_2$ in CH_2Cl_2 at room temperature for 6 h, the corresponding nitrone (**3j**) was obtained in 30% yield with recovery of the starting tetracyclic compound (**5j**) in 41% yield (Chart 4). The nitrone could only have been formed through the corresponding spiroindolenine; consequently, the result again supported the presence of an equilibrium between spiroindolenines (**7**) and nitrones (**3**).

Indeed, if the equilibration had to be considered, the isolation of the tetracyclic compounds (**5**) described herein and some other reported evidence[14,9d] are not necessarily significant support for a spiroindolenine intermediate for tetrahydro-β-carboline formation, and if the spiroindolenines only participate in the equilibration, β-carbolines must be formed *via* path B. Our results obtained from the low temperature experiments (Table I, entries 1—6) favor this possibility. Thus, the iminium ion (**6**) might cyclize to the intermediate (**8**) (Chart 3), *via* direct attack at the 2-position, and **8** in turn might deprotonate to give the corresponding β-carboline (**4**). On the other hand, when N_a-methyl nitrones (**3**) were used, the indolenium cation of the spiroindolenines (**7**) may be stabilized by the methyl group, so that the spiroindolenines (**7**) could be formed even at low temperature and then cyclized to give the tetracyclic compound (**5f**) while the corresponding β-carbolines (**4**) can not be formed, due to unfavorable $A^{1,2}$ strain,[11,15] by direct attack either at the 2-position or at the 3-position (*via* **7**).

The mechanisms outlined in Chart 3 provide a rational explanation for the results obtained at room temperature or at low temperature, as well as the stereochemical features of the P–S reaction of N_b-hydroxytryptamine (**1**) and cysteinals (**2**). The results described herein have been applied to the synthesis of the natural eudistomins.[16]

Experimental

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus, and are uncorrected. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrophotometer. Infrared (IR) spectra were obtained with a Hitachi 260-10 spectrophotometer. Mass spectra (MS) were recorded on a Hitachi M-60 or a JMS-HX 100 mass spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on JEOL JNM-FX 270, JNM-GX 270, and JNM-GSX 500 apparatus. 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 Cyclization of the Nitrones (3) in Table I A solution of a nitrone (**3**) in dry CH_2Cl_2 was cooled to −78 °C and TFA (2—5 mol eq) was added by injection over 5 min in an argon atmosphere. After being stirred for 2 h at the same temperature, the reaction mixture was quenched carefully with saturated $NaHCO_3$ at −78 °C, diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over SiO_2 to give the product. For the structures of compounds **4a—d, f** and **5a—d, f**, see the preceding paper.[2a]

Compounds (**3e, g, 4e, g, 5e, g**) were prepared according to the procedure described in the preceding paper[2a] **4e**α and **4e**β (1 : 4 at room temperature, 1 : 12 at −78 °C): amorphous (diastereoisomeric mixture). UV λ_{max}^{EtOH} nm: 226, 275, 284, 291. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.46 (1H, br, NH, exchangeable), 7.08—7.50 (9H, m, ArH), 5.80 (1/5H, d, J=5 Hz, NH, exchangeable), 5.64 (4/5H, d, J=9Hz, NH), 5.12 (1H, d, J=12 Hz, OCHPh), 5.04 (1H, d, J=12 Hz, OCHPh), 5.04 (1H, br, OH, exchangeable), 4.87 (1H, d, J=12 Hz, $CHCCl_3$), 4.80 (1H, d, J=12 Hz, $CHCCl_3$), 4.65 (1H, br, $C\underline{H}NHCO_2$), 4.47 (4/5H, br, C_1-βH), 4.25 (1/5H, br, C_1-αH), 3.65 (1H, m, CHN), 3.43 (1H, dd, J=5, 15 Hz, CHS), 3.30 (2H, m, CHS, $C\underline{H}NOH$), 3.10 (1H, m, CH-Ind), 2.80 (1H, m, CH-Ind). **5e**: amorphous. UV λ_{max}^{EtOH} nm: 245, 303. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.39 (5H, s, PhH), 7.07—7.18 (2H, m, ArH), 6.80 (1H, m, ArH), 6.58 (1H, d, J=8 Hz, ArH), 5.60 (1H, br, OH, exchangeable), 5.39, 5.48 (1H, s, NCHN), 5.20 (2H, s, CH_2Ph), 5.00 (1H, br, NH, exchangeable), 4.60—4.80 (2H, m, CH_2CCl_3), 4.40 (1H, m, CHN), 3.50 (1H, s, $C\underline{H}NOH$), 3.42 (1H, m, CH_2N), 3.17 (1H, m, CH_2N), 3.10 (1H, m, CHS), 2.40 (1H, m, CHS), 2.20 (2H, m, CH_2). MS *m/z*: 554, 552, 130, 91. **3g**: amorphous (64.5%), $[\alpha]_D^{17}$ +21.1° (c=0.65, MeOH). UV λ_{max}^{EtOH} nm: 220, 275, 284, 291. IR ν_{max}^{KBr} cm^{-1}: 3350, 1740, 1720, 1510, 1140. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.07 (1H, br s, NH, exchangeable), 7.57 (1H, m, ArH), 7.35 (5H, s, PhH), 7.10—7.33 (3H, m, ArH), 7.02 (1H, d, J=2 Hz, C_2-H), 6.67 (1H, br s, NH, exchangeable), 6.47 (1H, d, J=6 Hz, =CH), 5.21 (2H, s, CH_2Ph), 4.72 (1H, d, J=11 Hz, $CHCCl_3$), 4.68 (1H, d, J=11 Hz, $CHCCl_3$), 4.64 (1H, m, CH), 3.99 (2H, m, CH_2), 3.35 (2H, m, CH_2), 3.19 (2H, m, SCH_2). MS *m/z*: 368, 239, 186, 130. **4g**α and **4g**β (1 : 8): amorphous (diastereoisomeric mixture). IR ν_{max}^{KBr} cm^{-1}: 3340, 1710, 1510, 1140. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.58, 8.35 (1H, br s, NH, exchangeable), 7.06—7.48 (9H, m, ArH), 5.94 (1H, d, J=9 Hz, NH), 5.27 (2H, t-like q, J=7 Hz, OCH_2Ph), 5.18 (1H, br s, OH, exchangeable), 4.65 (2H, s, CH_2CCl_3), 4.60 (1H, m, NCH), 4.46 (8/9H, br, C_1-βH), 4.28 (1/9H, br, C_1-αH), 3.60 (1H, m, C_3-H), 3.42 (1H, m, SCH), 3.40 (1H, m, C_3-H), 3.30 (1H, m, SCH), 3.10 (1H, m, C_4-H), 2.80 (1H, m, C_4-H). MS *m/z*: 330, 239, 168, 91. **5g**: amorphous. UV λ_{max}^{EtOH} nm: 244, 300. IR ν_{max}^{KBr} cm^{-1}: 3400, 1710, 1140. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.28—7.40 (5H, s, PhH), 7.07—7.18 (2H, m, ArH), 6.80 (1H, m, ArH), 6.55—6.59 (1H, m, C_8-H), 5.40—5.50 (1H, br s, OH, exchangeable), 5.48 (1H, s, NCHN), 5.16—5.25 (2H, m, CH_2Ph), 4.86, 4.93 (1H, br s, NH, exchangeable), 4.69—4.95 (2H, m, CH_2CCl_3), 4.38—4.46 (1H, m, TrocNCH), 3.52, 3.59 (1H, s, $C\underline{H}NOH$), 3.43 (1H, m, C_2-H), 3.18 (1H, m, C_2-H), 3.10 (1H, m, CHS), 2.37, 2.46 (1H, dd, J=10, 14 Hz, CHS), 2.17—2.26 (2H, m, CH_2). MS *m/z*: 555, 553, 480, 478, 130, 91.

Preparation of the Nitrone (3k) Freshly prepared Al(Hg) (from 4 g of Al) was added to a solution of 5-methoxy-6-bromo-3-nitroethylindole[6a] (1.00 g, 3.34 mmol) in tetrahydrofuran (THF)–H_2O (150 ml–15 ml) at 0 °C with vigorous stirring. After being stirred for 15 min, the reaction mixture was filtered through a Buchner funnel and then a Celite pad. The filtrates were evaporated and the residue was diluted with CH_2Cl_2 and washed successively with water and brine. Drying over $MgSO_4$ and removal of the solvent gave crude 5-methoxy-6-bromo-N_b-hydroxytryptamine (1.06 g), which was used in the next step without purification. A solution of the crude 5-methoxy-6-bromo-N_b-hydroxytryptamine in dry CH_2Cl_2 (50 ml) was treated with (−)-*N*-Boc-*S*-methylcysteinal (1.18 g, 5.39 mmol) at room temperature. After 2 h, the reaction mixture was evaporated *in vacuo* and the residue was chromatographed over SiO_2 to give **3k** (1.51 g, 92.9% from 5-methoxy-6-bromo-3-nitroethylindole) as a white solid, which was recrystallized from a mixture of MeOH–AcOEt to give colorless prisms, mp 163.5—165.5 °C, $[\alpha]_D^{22}$ −54.0° (c=0.20, MeOH). UV λ_{max}^{EtOH} nm: 226.5, 290s, 303, 315s. IR ν_{max}^{KBr} cm^{-1}: 3270, 1680, 1542. MS *m/z*: 423, 421 (M^+ − OH − SMe; 2, 2%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.03 (1H, br s, NH, exchangeable), 7.56 (1H, s, C_7-H), 7.06 (1H, s, C_4-H), 7.03 (1H, d, J=2.5 Hz, C_2-H), 6.61 (1H, br s, N=CH), 5.90 (1H, br s, NHBoc, exchangeable), 4.56 (1H, m, $C\underline{H}NHBoc$), 3.99 (2H, t, J=6.6 Hz, CH_2N), 3.94 (3H, s, OMe), 3.32 (2H, t-like, CH_2), 2.89 (1H, m, SCH), 2.70 (1H, m, SCH), 2.07 (3H, s, SMe), 1.43 (9H, s, *tert*-Bu). *Anal.* Calcd for $C_{20}H_{28}BrN_3O_4S$: C, 49.38; H, 5.80; N, 8.64. Found: C, 49.49; H, 5.77; N, 8.64.

Crystal Data for **3k**: $C_{20}H_{28}BrN_3O_4S$, monoclinic, space group $P2_1$, a=10.522 (7), b=11.547 (17), c=9.710 (8) Å, β=94.305°, U=1176.52 Å^3, Z=2, D_c=1.372 g cm^{-3}. Lattice constants and intensity data were measured using graphite-monochromated CuK_α (λ=1.542) radiation on a Rigaku AFC-5 diffractometer. A total of 1935 unique reflections with $F(\theta) > 3\sigma(F_o)$ were obtained using the $\omega < 30° < \omega - 2\theta$ scanning method with a 2θ scan speed of 4° min^{-1} to 2θ=120°. The structure was solved by the UNICS-III system MULTAN 80 (Library of Computer Center of Tokyo University, T. Sakurai and K. Kobayashi, *Rep. Inst. Phys. and Chem. Res.*, **55**, 69 (1979) based on direct methods and refined to a final

R value of 0.0546.

Transformation of the Tetracyclic Compound (5j) to the Nitrone (3j) Dry zinc bromide (200 mg, 0.89 mmol) was added to a solution of **5j** (100 mg, 0.24 mmol)[2a] in dry CH_2Cl_2 (20 ml) at room temperature in an atmosphere of Ar. After being stirred for 6 h, the reaction mixture was diluted with CH_2Cl_2 and filtered through a Celite pad. The filtrate was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (110 mg) was chromatographed over SiO_2 to give the starting **5j** (41 mg, 41%) and **3j** (30 mg, 30%). **3j**: UV λ_{max}^{EtOH} nm: 226, 276, 288, 300. IR ν_{max}^{KBr} cm^{-1}: 3400—3200, 1705, 1545, 1270. MS *m/z*: 424 ($M^+ + 1$), 157, 144. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.58—7.10 (4H, m, ArH), 6.92 (1H, s, C_2-H), 6.63 (2H, d, J=6.0 Hz, N=CH and NH, exchangeable), 4.77 (1H, m, CHNBoc), 4.68 (1H, d, J=12 Hz, SCHO), 4.56 (1H, d, J=12 Hz, SCHO), 3.99 (2H, t, J=7.0 Hz, CH_2), 3.74 (3H, s, NMe), 3.64 (3H, s, COOMe), 3.46—3.60 (4H, m, OCH_2CH_2O), 3.35 (2H, m, CH_2), 3.29 (3H, s, OMe), 3.19 (1H, d, J=14, 5 Hz, SCH), 2.92 (1H, d, J=14, 5 Hz, SCH). Exact MS *m/z*: M^+ Calcd for $C_{20}H_{29}N_3O_5S$: 423.1825. Found: 423.1824 (HRMS).

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References and Notes

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