Synthetic studies on indoles and related compounds. Part 46.[1] First total syntheses of 4,8-dioxygenated β-carboline alkaloids

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Total syntheses of naturally occurring 4,8-dioxygenated β-carboline alkaloids **2a**, **2d**, **2g**, and **2h** are described. The synthetic route involves two methodologies that we developed; (i) an improved Fischer indolization for the synthesis of a 7-oxygenated indole using a tosyl group for protection of the phenolic group, (ii) construction of a 4-methoxy-β-carboline skeleton by the C-3-selective cyclization of the C-2-substituent of the indole nucleus. The phenolic O-tosyl group of the β-carboline skeleton was successfully cleaved to the phenol by Na-anthracenide, and this phenol was methylated with $TMSCH_2N_2$.

Introduction

4-Oxygenated β-carboline alkaloids[2] **1** have recently been identified as a large subfamily of β-carboline alkaloids isolated from *Simarubaceae* plants. In this family, there are many derivatives possessing oxygen substituents (a hydroxy or methoxy group) at the C-8 position of the β-carboline skeleton **2**, as shown in Chart 1.[3] Some of these compounds show interesting biological activities,[4] but systematic biological evaluations have not yet been performed because of their poor isolation yields from natural sources. Thus, establishment of methods for their synthesis will be of pharmaceutical importance.

There are only a few reports of attempts at synthesizing 4,8-dioxygenated β-carboline derivatives. Cook *et al.*[5a,b] reported the syntheses of 4-methoxy-β-carbolines utilizing C-4-selective DDQ oxidation of 1,2,3,4-tetrahydro-β-carbolines, but the DDQ oxidation of 6,8-dimethoxy-1,2,3,4-tetrahydro-β-carboline could not give C-4-oxygenated compound, but gave only an indoloquinone compound derived from oxidation of the 8-methoxy group on the β-carboline skeleton.[5c] Recently, we have developed two new methodologies; (1) the improved Fischer indolization[6] for the efficient synthesis of 7-oxygenated indoles **4** using 2-(sulfonyloxy)phenylhydrazones **3** as starting material, and its application for the total synthesis of eudistomidin-A,[6] murrayaquinone-A,[7] and murrayafoline-A,[7] and (2) a general synthetic method[8,9] for 1-substituted 4-methoxy-β-carbolines **8** using acid-catalyzed cyclization to the C-3 position of the C-2 substituent of *N*-unprotected indole **6** (Scheme 1).

The combination of the above two methodologies will make it possible to synthesize 4,8-dioxygenated β-carboline alkaloids **2**. We report here the first total synthesis of compounds **2a**, **2d**, **2g**, and **2h** by applying such methodologies and by successfully using the tosyl group as a protective group.

Results and discussion

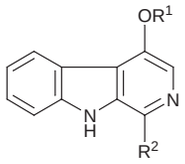
Starting from **4a**, methyl 4-methoxy-8-tosyloxy-β-carboline-1-carboxylate **19** was synthesized (Scheme 2) by a route similar to that we reported[9a] previously. Differences in reactivities caused by the existence of an oxygen function at the 7-position are as follows; (1) the reduction of ester **4a** with $LiAlH_4$, a reaction which reduces parent ester **5** in quantitative yield, gave alcohol **9** in only 60% yield (not reproducible), but the use of DIBAL-H gave **9** in quantitative yield, and (2) in contrast to the C-1-cyanation of the 8-H compound which was simultaneously phosphorylated at the indole nitrogen, the reaction of 8-tosyloxy compound **16** gave only 1-cyanide **17** in 65% yield. The presence of the 8-tosyloxy group prevented N-phosphorylation, probably by a steric effect.

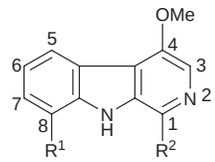
Polyphosphonic acid (PPA) cyclization of **12** gave **13** in poor yield (15%), while the use of methanesulfonic acid[9a,10] (MsOH) gave **13** in good yield (80%). Ketone **13** was converted to 4-methoxy-β-carboline **14** by ketalization followed by oxidation with chloranil, without affecting the oxygenated benzene ring. Then, 4-methoxy-β-carboline **14** was converted into 1-cyanide **17** with diethylphosphoryl cyanide (DEPC) *via* *N*-oxide **16** by a modified Reissert–Henze reaction. The 1-cyanide **17** was treated with HCl–MeOH at room temperature to give only 1-carboxamide **18**, whereas the same reaction under reflux for 5 h gave the desired 1-methoxycarbonyl compound **19** in high yield (80%).

1-Methoxycarbonyl compound **19** was reduced to aldehyde **20** in good yield (80%). It is noted that the reduction of the ester group of **19** with DIBAL-H stopped at the stage of aldehyde **20**, in contrast to reduction of the ester group of **4a**. Wittig reaction of aldehyde **20** gave the 1-vinyl compound **21**, which was then reduced to the 1-ethyl compound **22** by H_2/Pd-C (Scheme 3).

For the synthesis of natural products, effective cleavage of the tosyl group of 8-tolylsulfonyloxy-β-carbolines was required. At first, 1-unsubstituted compound **14** was treated with KOH (in EtOH at room temperature) to give the desired 8-hydroxy compound **15** under 40% yield, accompanied by decomposition products. However, treatment of compound **14** with Na-naphthalenide gave only the desired phenolic compound **15** in excellent yield (90%), as a result of desired and chemoselective cleavage of the S–O bond (Table 1).

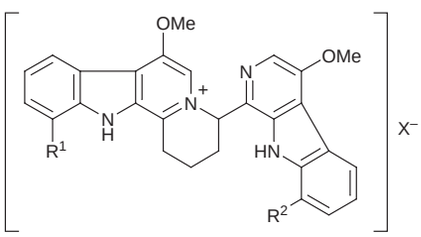
In our previous report,[7] treatment of 8-[methylsulfonyl (mesyl)oxy]carbazole derivative **26** with Na-naphthalenide[11a] gave 8-hydroxy compound **27** only in low yield (46%) with an undesired C–O bond-cleaved compound **28** (54%) as the main product (Scheme 4). The different reactivity of the two sulfonyloxy groups can be explained as follows: The more electron-attractive sulfonyl group (TsO) was reduced more easily than the less electron-attractive group (MsO). Therefore, in the case of the TsO group, the S–O bond was cleaved more easily than the C–O bond. Treatment of 1-ethyl compound **22** with Na-naphthalenide also gave the corresponding 8-hydroxy compound **2g** in excellent yield (97%). However, treatment of 1-vinyl compound **21** with Na-naphthalenide gave only the



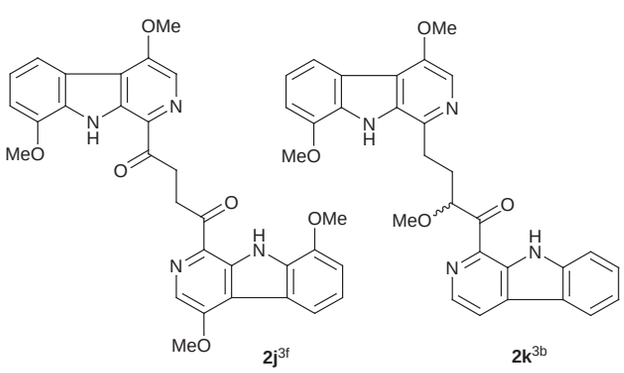


1 R^1 = Me,H
R^2 = Et, Ac, CO_2Me etc.

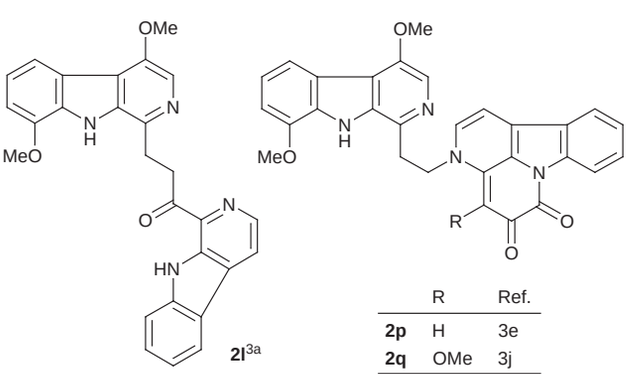
	R^1	R^2	Ref.
2a	OMe	H	3e
2b	OMe	Et	3k, l, m, n
2c	OMe	$CH{=}CH_2$	3d, n
2d	OMe	CO_2Me	3o
2e	OMe	CH_2CH_2OMe	3a
2f	OMe	$COCH{=}CHCO_2Me$	3c
2g	OH	Et	3d
2h	OH	$CH{=}CH_2$	3d
2i	OH	$CH_2CH_2N(Et)_2$	3d



	R^1	R^2	Ref.
2m	H	OMe	3g
2n	OMe	OMe	3h
2o	OH	OH	3i



2j[3f] **2k**[3b]



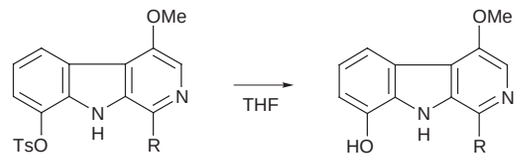
2l[3a]

	R	Ref.
2p	H	3e
2q	OMe	3j

Chart 1

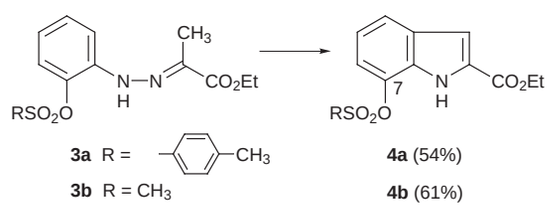
1-ethyl-8-hydroxy compound **2g** due to the simultaneous reduction of the 1-vinyl group by Na-naphthalenide in 85% yield. However, use of a milder reagent, Na-anthracenide,[11b] was successful in the selective cleavage of the O-tosyl group to give the desired 8-hydroxy-1-vinyl compound **2h** in 79% yield.

Table 1



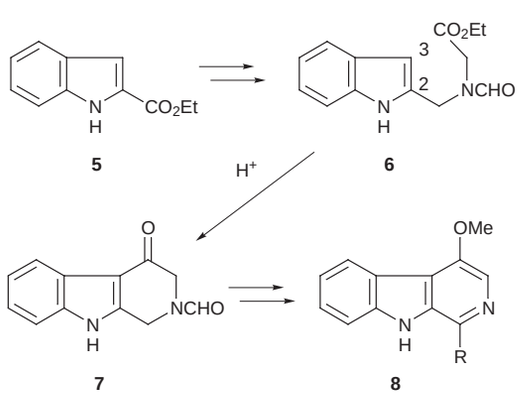
Substrate	R	Reagent[a]	Product	Yield (%)
14	H	KOH (in EtOH, rt)	**15**	40
		A (rt)	**15**	90
22	Et	A (0 °C)	**2g**	97
21	$CH{=}CH_2$	A (0 °C)	**2g** (R = Et)	85
		B (0 °C)	**2h** (R = $CH{=}CH_2$)	79
19	CO_2Me	B (0 °C)		complex mixture
		B (−45 °C)	**23**	53
17	CN	B (0 °C)	**24**	71
18	$CONH_2$	B (0 °C)	**25**	85

[a] A: Na-naphthalenide. B: Na-anthracenide.



3a R = **4a** (54%)

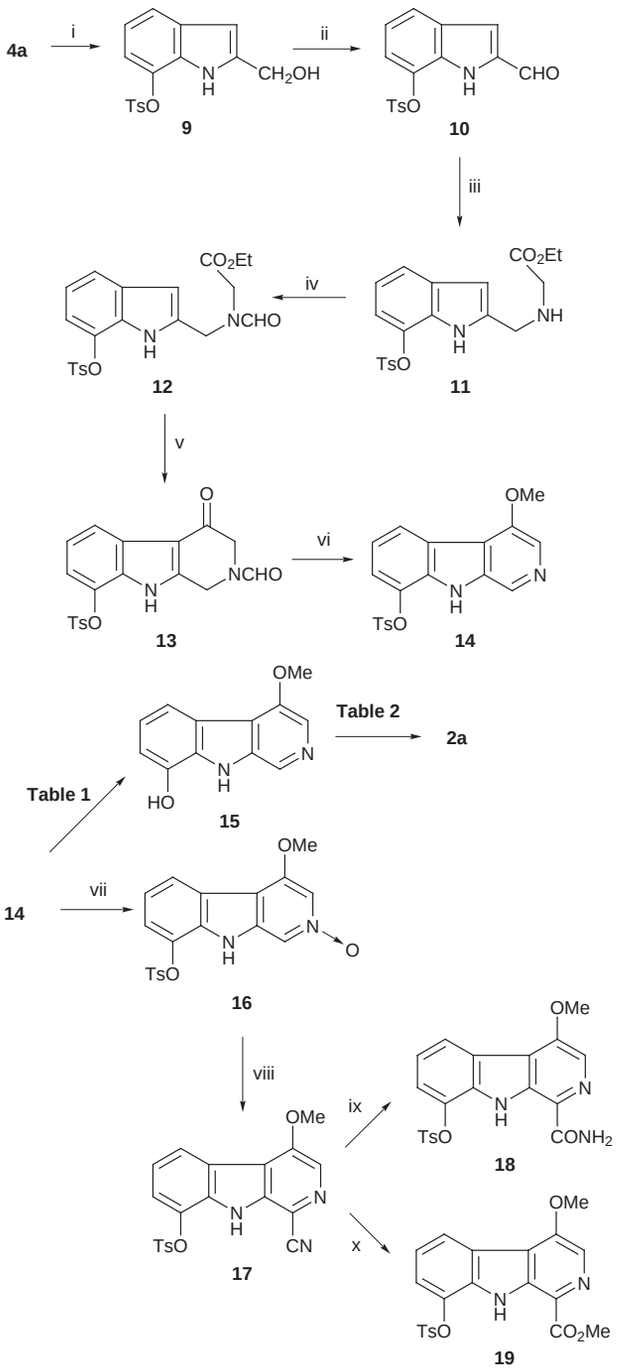
3b R = CH_3 **4b** (61%)



Scheme 1

Although treatment of 1-methoxycarbonyl compound **19** with Na-anthracenide at room temperature gave a complex mixture, the reaction at −45 °C proceeded smoothly to give 8-hydroxy-1-methoxycarbonyl compound **23** in 53%. Thus, the selective cleavage of the 8-*O*-tosyl group with Na-anthracenide at low temperature was most effective in the presence of other reactive functional groups at the C-1-position; the reaction of 1-cyanide **17** and 1-carboxamide **18** gave **24** (71%) and **25** (85%), respectively (Table 1). The above results clearly show that the tosyl group was superior to the mesyl group as a protective group for the phenol.

The treatment of the 8-hydroxy compound **15** with CH_2N_2 gave 4,8-dimethoxy-β-carboline **2a** only in poor yield (15%) without recovery of starting material (Table 2). We considered that this low yield was caused by the formation of a water-soluble quaternary pyridinium salt by methylation of the pyridine nitrogen of **15**. We found that trimethylsilyldiazomethane[12] ($TMSCHN_2$) was an excellent reagent for this selective methylation. Treatment of **15** with $TMSCHN_2$ gave only the desired 8-methoxy compound **2a** in quantitative yield. Although the methylation of 1-methoxycarbonyl-8-hydroxy compound **23**



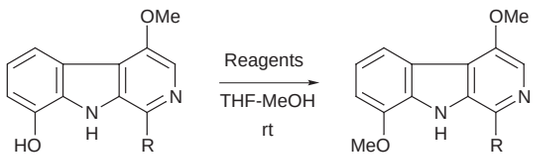
Scheme 2 *Reagents and conditions (and yields)*: (i) DIBAL-H, CH_2Cl_2, −78 °C (quant.) (ii) act. MnO_2, CH_2Cl_2, rt (89%) (iii) H-Gly-OEt, $NaBH_3CN$, MeOH, rt (79%) (iv) HCO_2Et, HCO_2H, rt (100%) (v) MsOH, 55 °C (80%) (vi) $(MeO)_2CMe_2$, TsOH, chloranil, benzene, rt (70%) (vii) MCPBA, CH_2Cl_2, rt (98%) (viii) DEPC, Et_3N, $Cl(CH_2)_2Cl$, 80 °C (65%) (ix) HCl/MeOH, rt (88%) (x) HCl/MeOH, reflux (80%).

with diazomethane also gave a complex mixture, treatment of **23** with $TMSCHN_2$ in the presence of diisopropylethylamine (DIPEA) gave the target methoxy compound **2d** in 95% yield. Shioiri reported[12] that the methylation of phenol with $TMSCHN_2$ was accelerated by the addition of DIPEA. Based on the results that methylation of **15** proceeded smoothly without addition of the base, the pyridine ring of **15** might act as an internal base, whereas in the case of **23** the basicity of the pyridine ring might be lowered by the electron-attractive 1-methoxycarbonyl group.

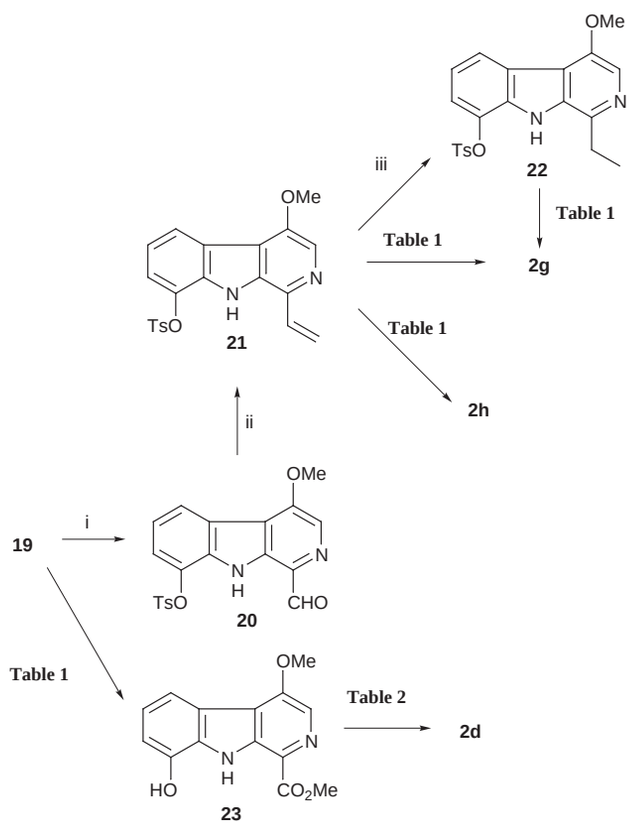
Conclusions

We succeeded in the first total synthesis of naturally occurring 4,8-dioxygenated β-carboline alkaloids **2a**, **2d**, **2g** and **2h**, which were identical with the natural products[3d,3e,3o] in all respects. 8-Hydroxy-4-methoxy compounds **2g**, **2h**, **15**, and **23** were synthesized using a tosyl group as protection for the 8-hydroxy group, and then **15** and **23** were converted to 4,8-dimethoxy compounds **2a, 2d** by *O*-selective methylation with $TMSCHN_2$. As there are only limited reports[13] concerning the use of the tosyl group to protect phenolic groups, the present study showed that the tosyloxy group can be useful for this purpose. Because of its stability under acidic, oxidative, and high-temperature conditions, and selective deprotection was easily

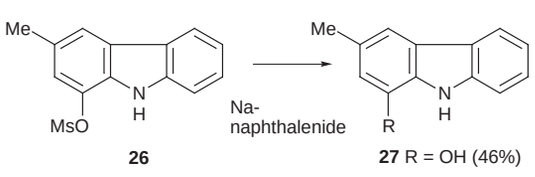
Table 2



Substrate	R	Reagents	Product	Yield (%)
15	H	CH_2N_2	**2a**	15
		$TMSCHN_2$	**2a**	100
23	CO_2Me	CH_2N_2		complex mixture
		$TMSCHN_2$/DIPEA	**2d**	95



Scheme 3 *Reagents and conditions (and yields)*: (i) DIBAL-H, CH_2Cl_2, −50 °C (80%) (ii) CH_2=PPh_3, THF, 70 °C (49%) (iii) H_2/Pd-C, MeOH, rt (74%).



Scheme 4

achieved by Na-anthracenide in the presence of various reactive functional groups, the tosyl group has some synthetic advantages over other phenol-protective groups.

Experimental

Mps were determined on a micro-melting-point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300 or on a Shimadzu IR-400 spectrophotometer (for Nujol mulls, unless otherwise stated). ^{1}H-NMR spectra were recorded on a Hitachi R-24B (60 MHz) (unless otherwise stated), JEOL EX-400 (400 MHz) or α-500 (500 MHz) spectrometer for samples in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal reference. Mass spectra (MS) were measured on a JEOL JMS D-300, DX-303 or a JMS-HX110 spectrometer with a direct-inlet system. For column chromatography, silica gel 60 (70–230 mesh ASTM, Merck), and for TLC, silica gel 60F_{254} (Merck) were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; dif., diffuse; BP, base peak.

7-Tosyloxyindole-2-methanol 9

To a stirred solution of ethyl 7-tosyloxyindole-2-carboxylate[6] **4a** (7.50 g, 20.9 mmol) in CH_2Cl_2 (300 ml) was added DIBAL-H solution (1.0 M in CH_2Cl_2; 83.0 ml, 83 mmol) at −78 °C under an argon atmosphere. The mixture was stirred at −78 °C for 5 min, and then quenched by the sequential addition of MeOH (15 ml) and 10% NaOH (40 ml) at −78 °C. Then the mixture was stirred at room temperature for an additional 0.5 h. Precipitates were removed with suction through a Celite pad and washed with $CHCl_3$–MeOH (10 : 1). The combined organic filtrate was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give the *title compound* **9** (6.60 g, 100%) as crystals. Recrystallization from CH_2Cl_2–hexane gave colorless prisms, mp 194–196 °C. (Calc. for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41. Found: C, 60.35; H, 4.71; N, 4.50%). ν_{max}/cm^{-1} 3525 and 3250 (NH and OH). δ (DMSO-d_6) 2.38 (3H, s, Ar-CH_3), 4.55 (2H, d, *J* 6 Hz, CH_2OH), 5.10 (1H, t, *J* 6 Hz, -CH_2O*H*), 6.20–7.35 (4H, m, ArH), 7.35 (2H, d, *J* 8 Hz, ArH), 7.76 (2H, d, *J* 8 Hz, ArH), 11.21 (1H, br s, NH); *m*/*z* 317 (M$^+$, 55%), 162 (BP).

7-Tosyloxyindole-2-carbaldehyde 10

A mixture of alcohol **9** (3.41 g, 0.011 mol) and activated MnO_2 (28.1 g) in CH_2Cl_2 (500 ml) was stirred at rt for 3 h. Precipitates were removed with suction through a Celite pad and washed with $CHCl_3$–MeOH (10 : 1). The combined organic filtrate was evaporated to dryness *in vacuo* to give the *title compound* **10** (3.00 g, 89%) as crystals. Recrystallization from benzene–hexane gave colorless needles, mp 159–160.5 °C. (Calc. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 60.92; H, 4.12; N, 4.49%). ν_{max}/cm^{-1} 3290 (NH), 1680, 1667 (C=O). δ 2.40 (3H, s, Ar-CH_3), 6.65–7.85 (8H, m, ArH), 9.10 (1H, br s, NH), 9.70 (1H, s, -CHO); *m*/*z* 315 (M$^+$, 73%), 160 (BP).

Ethyl [(7-tosyloxyindol-2-ylmethyl)amino]acetate 11

To a stirred solution of aldehyde **10** (570 mg, 1.81 mmol) and ethyl aminoacetate hydrochloride (758 mg, 5.43 mmol) in MeOH (30 ml) were sequentially added Et_3N (0.183 ml, 1.31 mmol) and $NaBH_3CN$ (114 mg, 1.81 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h, poured into ice–water, and extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using benzene–AcOEt (4 : 1) to give the *title compound* **11** (573 mg, 79%) as pale brown crystals. Recrystallization from AcOEt–hexane gave colorless prisms, mp 97–99 °C. (Calc. for $C_{20}H_{22}N_2O_5S$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.49; H, 5.49; N, 6.94%). ν_{max}/cm^{-1} 3330 (NH), 1735 (C=O). δ 1.27 (3H, t, *J* 7 Hz, -CH_2CH_3), 2.04 (1H, br s, CH_2NHCH_2), 2.38 (3H, s, Ar-CH_3), 3.36 (2H, s, NHCH_2CO), 3.92 (2H, s, ArCH_2NH), 4.17 (2H, q, *J* 7 Hz, OCH_2CH$_3$), 6.21–7.80 (8H, m, ArH), 8.93 (1H, br s, indole NH); *m*/*z* 402 (M$^+$, 48%), 315 (BP).

Ethyl [*N*-(7-tosyloxyindol-2-ylmethyl)-*N*-formylamino]acetate 12

Ethyl [(7-tosyloxyindol-2-ylmethyl)amino]acetate **11** (476 mg, 1.18 mmol) was dissolved in a mixture of ethyl formate (2.4 ml) and formic acid (0.1 ml), and stirred at rt for 24 h. The reaction mixture was diluted with AcOEt, washed successively with saturated aq. $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The organic layer was evaporated to dryness *in vacuo* to give the *title compound* **12** (510 mg, 100%) as a pale brown oil. ν_{max}($CHCl_3$)/cm^{-1} 3460–3350 (NH), 1740, 1679 (C=O). δ 1.05–1.40 (3H, m, -CH_2CH_3), 2.41 (3H, s, Ar-CH_3), 3.85–4.40 (4H, m, -CH_2CH$_3$ and Ar-CH_2N), 4.65 (2H, s, NCH_2CO), 6.25–7.90 (8H, m, ArH), 8.15 and 8.30 (1H, each s, CHO), 9.01 (1H, br s, NH); HRMS (EI) *m*/*z* 430.1208 (Calc. for $C_{21}H_{22}N_2O_6S$: *M*, 430.1199).

2-Formyl-4-oxo-8-tosyloxy-1,2,3,4-tetrahydro-β-carboline 13

A mixture of ethyl [*N*-(7-tosyloxyindol-2-ylmethyl)-*N*-formylamino]acetate **12** (662 mg, 1.54 mmol) and methanesulfonic acid (4.5 ml) was stirred at 55 °C for 5 h under an argon atmosphere. The reaction mixture was poured into ice–water, neutralized with 10% aq. $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using $CHCl_3$–MeOH (50 : 1) to give the *title compound* **13** (472 mg, 80%) as crystals. Recrystallization from AcOEt–hexane gave colorless prisms, mp 200–201 °C. (Calc. for $C_{19}H_{16}N_2O_5S$: C, 59.37; H, 4.20; N, 7.29. Found: C, 59.47; H, 4.13; N, 7.33%). ν_{max}($CHCl_3$)/cm^{-1} 3410 (NH), 1675 (C=O). δ (400 MHz) 2.46 (3H, s, Ar-CH_3), 4.25 and 4.43 (total 2H, each s, 5 : 1, 1- or 3-H), 4.92 and 5.10 (total 2H, each s, 1 : 5, 3- or 1-H_2), 6.47 and 6.55 (total 1H, each d, 1 : 5, *J* 7.9 Hz, 7-H), 7.07 (1H, t, *J* 7.9 Hz, 6-H), 7.32 (2H, d, *J* 8.1 Hz, ArH), 7.71 (2H, d, *J* 8.1 Hz, ArH), 8.04 and 8.06 (total 1H, each d, 5 : 1, *J* 7.9 Hz, 5-H), 8.27 and 8.32 (total 1H, each s, 5 : 1, CHO), 9.97 and 10.16 (total 1H, each br s, 1 : 5, NH); *m*/*z* 384 (M$^+$, BP). The product **13** existed as a mixture of two rotamers.

4-Methoxy-8-tosyloxy-β-carboline 14

A solution of toluene-*p*-sulfonic acid monohydrate (128 mg, 0.67 mmol) in benzene (20 ml) was heated under azeotropic conditions for 1 h. After cooling of this mixture, 2-formyl-4-oxo-8-tosyloxy-1,2,3,4-tetrahydro-β-carboline **13** (234 mg, 0.61 mmol) and 2,2-dimethoxypropane (0.226 ml, 1.84 mmol) was added to the benzene solution, and the mixture was stirred at rt for 30 min. After chloranil (301 mg, 1.22 mmol) had been added, the reaction mixture was stirred at rt for 12 h. The reaction mixture was poured into 5% NaOH, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using $CHCl_3$–MeOH (20 : 1) to give the *title compound* **14** (157 mg, 70%) as crystals. Recrystallization from AcOEt–hexane gave colorless prisms, mp 204–205 °C. (Calc. for $C_{19}H_{16}N_2O_4S$: C, 61.94; H, 4.38; N, 7.60. Found: C, 61.84; H, 4.37; N, 7.60%). ν_{max} ($CHCl_3$)/cm^{-1} 3440 (NH). δ (400 MHz) 2.42 (3H, s, Ar-CH_3), 4.16 (3H, s, OCH_3), 6.93 (1H, br d, *J* 8.0 Hz, 7-H), 7.10 (1H, t, *J* 8.0 Hz, 6-H), 7.29 (2H, d, *J* 8.0 Hz, ArH), 7.74 (2H, d, *J* 8.0 Hz, ArH), 8.16 (1H, br s, 3-H), 8.19 (1H, br d, *J* 8.0 Hz, 5-H),

8.63 (1H, br s, 1-H), 9.18 (1H, br s, NH); *m/z* 368 (M^+, 12%), 213 (BP).

4-Methoxy-8-tosyloxy-β-carboline *N*-oxide 16

A solution of 4-methoxy-8-tosyloxy-β-carboline **14** (2.62 g, 7.11 mmol) and MCPBA (3.681 g, 21.33 mmol) in CH_2Cl_2 (150 ml) was stirred at room temperature for 24 h. Hexane was added to the mixture. The precipitates were collected by filtration, washed successively with 10% K_2CO_3 and water, and dried under reduced pressure to give the *title compound* **16** (2.68 g, 98%) as crystals. Recrystallization from AcOEt–hexane gave colorless prisms, mp 240–244 °C. ν_{max}/cm^{-1} 3200–2400 (NH). δ (DMSO-d_6; 400 MHz) 2.38 (3H, s, Ar-CH_3), 4.04 (3H, s, OCH_3), 6.95 (1H, d, *J* 7.8 Hz, 7-H), 7.13 (1H, t, *J* 7.8 Hz, 6-H), 7.44 (2H, d, *J* 8.3 Hz, ArH), 7.82 (2H, d, *J* 8.3 Hz, ArH), 7.91 (1H, d, *J* 1.0 Hz, 1- or 3-H), 7.93 (1H, d, *J* 7.8 Hz, 5-H), 8.17 (1H, d, *J* 1.0 Hz, 3- or 1-H), 11.93 (1H, br s, NH); *m/z* 384 (M^+, 45%), 213 (BP); HRMS (EI) *m/z* 384.0823 (Calc. for $C_{19}H_{16}N_2O_5S$: *M* 384.0780).

4-Methoxy-8-tosyloxy-β-carboline-1-carbonitrile 17

A solution of 4-methoxy-8-tosyloxy-β-carboline *N*-oxide **16** (2.676 g, 6.96 mmol), DEPC (8.45 ml, 55.7 mmol), and Et_3N (1.94 ml, 13.9 mmol) in 1,2-dichloroethane (300 ml) was heated at 60 °C for 1.5 h and at 80 °C for 2 h. The mixture was poured into ice–water, extracted with $CHCl_3$, and the extract washed successively with saturated aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using benzene–AcOEt (3 : 1) to give the *title compound* **17** (1.787 g, 65%) as crystals. Recrystallization from benzene–AcOEt gave colorless prisms, mp 244–248 °C. (Calc. for $C_{20}H_{15}N_3O_4S$: C, 61.06; H, 3.84; N, 10.68. Found: C, 61.14; H, 3.81; N, 10.58%). ν_{max}/cm^{-1} 3380–3130 (NH), 2230 (CN). (400 MHz) δ 2.46 (3H, s, Ar-CH_3), 4.26 (3H, s, OCH_3), 7.19 (1H, dd, *J* 7.8 and 1.0 Hz, 7-H), 7.25 (1H, t, *J* 7.8 Hz, 6-H), 7.36 (2H, d, *J* 8.3 Hz, ArH), 7.78 (2H, d, *J* 8.3 Hz, ArH), 8.18 (1H, dif d, *J* 7.8 Hz, 5-H), 8.22 (1H, s, 3-H), 8.79 (1H, br s, NH); *m/z* 393 (M^+, 42%), 238 (BP).

4-Methoxy-8-tosyloxy-β-carboline-1-carboxamide 18

A solution of 1-cyano-4-methoxy-8-tosyloxy-β-carboline **17** (80 mg, 0.20 mmol) in MeOH (8 ml, saturated with dry HCl gas) was stirred at rt for 2.5 h. Solvent was evaporated *in vacuo*. Saturated aq. $NaHCO_3$ was added to the residue, and the mixture was extracted with $CHCl_3$. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using benzene–AcOEt (3 : 1) to give the *title compound* **18** (73.6 mg, 88%) as crystals. Recrystallization from benzene gave colorless prisms (mp 211–216 °C). (Calc. for $C_{20}H_{17}N_3O_5S$: C, 58.38; H, 4.16; N, 10.21. Found: C, 58.56; H, 4.12; N, 10.00%). ν_{max}/cm^{-1} 3420, 3400(NH), 1680 (CO). δ (400 MHz) 2.37 (3H, s, Ar-CH_3), 4.21 (3H, s, OCH_3), 5.52 (1H, br s, CONH), 7.20 (1H, t, *J* 7.8 Hz, 6-H), 7.24–7.28 (3H, m, 7-H and ArH), 7.66 (1H, br s, CONH), 7.77 (2H, d, *J* 8.3 Hz, ArH), 8.03 (1H, s, 3-H), 8.18 (1H, br d, *J* 7.8 Hz, 5-H), 10.03 (1H, br s, NH); *m/z* 411 (M^+, 28%), 256 (BP).

Methyl 4-methoxy-8-tosyloxy-β-carboline-1-carboxylate 19

A solution of 1-cyano-4-methoxy-8-tosyloxy-β-carboline **17** (100 mg, 0.25 mmol) in MeOH (10 ml, saturated with dry HCl gas) was stirred under reflux for 5 h. After the reaction was over, the solvent was evaporated *in vacuo*. Saturated aq. $NaHCO_3$ was added to the residue, and the mixture was extracted with $CHCl_3$. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using benzene–AcOEt (1 : 1) to give the *title compound* **19** (86.7 mg, 80%) as crystals. Recrystallization from benzene gave colorless prisms, mp 183–185 °C. (Calc. for $C_{21}H_{18}N_2O_6S$: C, 59.15; H, 4.25; N, 6.57. Found: C, 59.08; H, 4.17; N, 6.58%). ν_{max}/cm^{-1} 3390 (NH), 1680 (CO). δ (400 MHz) 2.39 (3H, s, Ar-CH_3), 4.11 and 4.24 (each 3H, s, OCH_3 and CO_2CH_3), 7.17 (1H, dd, *J* 7.3 and 1.5 Hz, 7-H), 7.20 (1H, t, *J* 7.3 Hz, 6-H), 7.28 (2H, d, *J* 8.3 Hz, ArH), 7.77 (2H, d, *J* 8.3 Hz, ArH), 8.19 (1H, br d, *J* 7.8 Hz, 5-H), 8.22 (1H, s, 3-H), 9.89 (1H, br s, NH); *m/z* 426 (M^+, 32%), 271 (BP).

4-Methoxy-8-tosyloxy-β-carboline-1-carbaldehyde 20

To a stirred solution of methyl 4-methoxy-8-tosyloxy-β-carboline-1-carboxylate **19** (1.585 g, 3.72 mmol) in CH_2Cl_2 (300 ml) was added DIBAL-H solution (1.0 M in CH_2Cl_2; 22.3 ml, 22.3 mmol) at −50 °C under an argon atmosphere. The mixture was stirred at −50 °C for 5 min and quenched by sequential addition of MeOH (3 ml) and 10% NaOH (20 ml) at −50 °C. Then the mixture was stirred at room temperature for an additional 0.5 h. The precipitates were removed with suction through a Celite pad and washed with $CHCl_3$–MeOH (10 : 1). The combined filtrate was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was subjected to column chromatography using benzene–AcOEt (1 : 1) to give the *title compound* **20** (1.18 g, 80%) as crystals. Recrystallization from AcOEt gave colorless prisms, mp 222–224 °C. (Calc. for $C_{20}H_{16}N_2O_5S$: C, 60.60; H, 4.07; N, 7.07. Found: C, 60.48; H, 4.08; N, 7.15%). ν_{max}/cm^{-1} 3405 (NH), 1675 (CO). (400 MHz) δ 2.37 (3H, s, Ar-CH_3), 4.27 (3H, s, OCH_3), 7.22–7.28 (2H, m, 6-H, and 7-H), 7.28 (2H, d, *J* 8.3 Hz, ArH), 7.77 (2H, d, *J* 8.3 Hz, ArH), 8.16–8.20 (1H, m, 5-H), 8.27 (1H, s, 3-H), 9.84 (1H, br s, NH), 10.17 (1H, s, CHO); *m/z* 396 (M^+, 15%), 241 (BP).

4-Methoxy-8-tosyloxy-1-vinyl-β-carboline 21

To a stirred solution of methyltriphenylphosphonium iodide (2.52 g, 6.2 mmol) in THF (40 ml), was added *n*-BuLi (1.6 M in hexane; 3.25 ml, 5.2 mmol) at 0 °C. The mixture was then stirred at rt for 2 h. 4-Methoxy-8-tosyloxy-β-carboline-1-carbaldehyde **20** (250 mg, 0.63 mmol) in THF (40 ml) was added to the above mixture at 0 °C, and then the whole was heated at 70 °C for 2 h. The reaction mixture was poured into ice–water containing NH_4Cl and extracted with $CHCl_3$. The organic layer was washed successively with saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using $CHCl_3$ to give the *title compound* **21** (121 mg, 49%) as crystals. Recrystallization from benzene gave colorless prisms, mp 128–130 °C. (Calc. for $C_{21}H_{18}N_2O_4S$: C, 63.94; H, 4.60; N, 7.10. Found: C, 63.98; H, 4.55; N, 7.23%). ν_{max}/cm^{-1} 3100–3380 (NH). δ (DMSO-d_6; 400 MHz) 2.27 (3H, s, Ar-CH_3), 4.10 (3H, s, OCH_3), 5.44 (1H, dd, *J* 10.7 and 2.4 Hz, CH=CH*H*), 6.28 (1H, dd, *J* 17.0 and 2.4 Hz, CH=C*H*H), 7.14–7.19 (2H, m, 6-H and 7-H), 7.33 (2H, d, *J* 8.3 Hz, ArH), 7.52 (1H, dd, *J* 17.0, and 10.7 Hz, C*H*=CH_2), 8.02–8.07 (1H, m, 5-H), 8.11 (1H, s, 3-H), 9.78 (2H, d, *J* 8.3 Hz, ArH), 11.76 (1H, br s, NH); *m/z* 394 (M^+, 21%), 239 (BP).

1-Ethyl-4-methoxy-8-tosyloxy-β-carboline 22

A solution of the vinyl compound **21** (50 mg, 0.13 mmol) in MeOH (15.0 ml) was hydrogenated in the presence of 10% Pd-C (5 mg) under an atmospheric pressure at rt for 10 min. Pd-C was removed by filtration, and the solvent was evaporated *in vacuo*. The residue was subjected to column chromatography using $CHCl_3$–MeOH to give the *title compound* **22** (37 mg, 74%) as crystals. Recrystallization from benzene gave colorless prisms, mp 171–173 °C. (Calc. for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.07. Found: C, 63.54; H, 5.07; N, 7.05%). ν_{max}/cm^{-1}

2780–3300 (NH). δ (400 MHz) 1.43 (3H, t, *J* 7.8 Hz, CH_2CH_3), 2.43 (3H, s, Ar-CH_3), 3.04 (2H, q, *J* 7.8 Hz, CH_2CH_3), 4.12 (3H, s, OCH_3), 6.91 (1H, dd, *J* 7.8 and 1.0 Hz, 7-H), 7.09 (1H, t, *J* 7.3 Hz, 6-H), 7.30 (2H, d, *J* 7.8 Hz, ArH), 7.74 (2H, d, *J* 7.8 Hz, ArH), 8.02 (1H, s, 3-H), 8.18 (1H, br d, *J* 7.8 Hz, 5-H), 8.46 (1H, br s, NH); *m*/*z* 396 (M^+, 44%), 241 (BP).

General procedure for detosylation of 8-tosyloxy-β-carboline derivatives using sodium anthracenide (or naphthalenide)

To a stirred solution of anthracene or naphthalene (10 mmol) in THF (20 ml) was added a slight excess of sodium (0.28 g, 12 mg-atom) under argon at room temperature, and the whole was stirred at room temperature for 1 h. The reaction mixture changed to dark blue to dark green. A large excess of the arenoid ion solution (3 equiv.) prepared above was added to a solution of a 8-tosyloxy-β-carboline derivative in THF, and the whole was stirred for 5 min. The reaction mixture was poured into ice–water containing NH_4Cl and extracted with AcOEt. The organic layer was washed successively with saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over $MgSO_4$, and evaporated *in vacuo* to give crude product.

8-Hydroxy-4-methoxy-β-carboline 15

8-Tosyloxy compound **14** (570 mg, 1.55 mmol) in THF (20 ml) was treated with Na-naphthalenide at rt according to the general procedure for detosylation. The crude product was subjected to column chromatography using $CHCl_3$–MeOH to give the *title compound* **15** [297 mg, 90%, mp 250–265 °C (decomp.)]. ν_{max}/cm^{-1} 3375 (NH and OH). δ (DMSO-d_6; 400 MHz) 4.09 (3H, s, OCH_3), 6.92 (1H, br d, *J* 7.8 Hz, 7-H), 7.03 (1H, t, *J* 7.8 Hz, 6-H), 7.63 (1H, br d, *J* 7.8 Hz, 5-H), 8.02 (1H, br s, 3-H), 8.52 (1H, br s, 1-H), 10.00 (1H, br s, OH), 11.47 (1H, br s, NH); HRMS (EI) *m*/*z* 214.0723 (Calc. for $C_{12}H_{10}N_2O_2$: *M* 214.0742).

1-Ethyl-8-hydroxy-4-methoxy-β-carboline 2g (picrasidine J)

(i) With Na-naphthalenide (from entry R = Et in Table 1). 8-Tosyloxy-1-ethyl compound **22** (10 mg, 0.025 mmol) in THF (1 ml) was treated with Na-naphthalenide at 0 °C according to the general procedure for detosylation. The crude product was subjected to column chromatography using $CHCl_3$–MeOH to give the title compound **2g** (5.9 mg, 97%). Recrystallization from $CHCl_3$–hexane gave pale yellow prisms, mp 190–194 °C. ν_{max}/cm^{-1} 3650–2280 (NH and OH). δ (400 MHz) 1.29 (3H, t, *J* 7.3 Hz, CH_2CH_3), 3.10 (2H, q, *J* 7.3 Hz, CH_2CH_3), 4.05 (3H, s, OCH_3), 6.91 (1H, dd, *J* 7.8 and 1.0 Hz, 7-H), 7.02 (1H, t, *J* 7.8 Hz, 6-H), 7.63 (1H, br d, *J* 7.8 Hz, 5-H), 7.90 (1H, s, 3-H), 9.92 (1H, br s, OH), 11.31 (1H, br s, NH); HRMS (EI) *m*/*z* 242.1058 (Calc. for $C_{14}H_{14}N_2O_2$: *M* 242.1055). This sample was identical with the reported compound (lit.,[3d] mp 212–213 °C).

(ii) With Na-naphthalenide (from entry R = CH=CH_2 in Table 1). 8-Tosyloxy-1-vinyl compound **21** (10 mg, 0.025 mmol) in THF (1 ml) was treated with Na-naphthalenide at 0 °C according to the general procedure for detosylation. The crude product was subjected to column chromatography using $CHCl_3$–MeOH to give the title compound **2g** (5.2 mg, 85%).

8-Hydroxy-4-methoxy-1-vinyl-β-carboline 2h (picrasidine I)

8-Tosyloxy-1-vinyl compound **21** (60 mg, 0.15 mmol) in THF (5 ml) was treated with Na-anthracenide at 0 °C according to the general procedure for detosylation. The crude product was subjected to column chromatography using $CHCl_3$–MeOH to give the title compound **2h** (29 mg, 79%). Recrystallization from AcOEt gave colorless prisms, mp 234–236 °C (decomp.). ν_{max}/cm^{-1} 3400 and 3320 (NH and OH). δ (DMSO-d_6; 400 MHz) 4.11 (3H, s, OCH_3), 5.40 (1H, dd, *J* 10.7 and 2.4 Hz, CH=CH*H*), 6.29 (1H, dd, *J* 17.1 and 2.4 Hz, CH=C*H*H), 6.94 (1H, dd, *J* 7.8 and 1.0 Hz, 7-H), 7.05 (1H, t, *J* 7.8 Hz, 6-H), 7.60 (1H, dd, *J* 17.1 and 10.7 Hz, C*H*=CH_2), 7.64 (1H, br d, *J* 7.8 Hz, 5-H), 8.06 (1H, s, 3-H), 10.02 (1H, br s, OH), 11.52 (1H, br s, NH); HRMS (EI) *m*/*z* 240.0918 (Calc. for $C_{14}H_{12}N_2O_2$: *M* 240.0899). This sample was identical with the natural product [lit.,[3d] mp 240–241 °C (decomp.)].

Methyl 8-hydroxy-4-methoxy-β-carboline-1-carboxylate 23

8-Tosyloxy compound **19** (13 mg, 0.03 mmol) in THF (3 ml) was treated with Na-anthracenide at −45 °C according to the general procedure for detosylation. The crude product was subjected to column chromatography using $CHCl_3$–MeOH to give the *title compound* **23** (4.4 mg, 53%). Recrystallization from AcOEt gave colorless prisms, mp 254–259 °C. ν_{max}/cm^{-1} 3450 (NH and OH), 1690 (C=O). δ (DMSO-d_6; 400 MHz) 4.00 and 4.22 (each 3H, s, OCH_3 and CO_2CH_3), 6.98 (1H, dd, *J* 7.8 and 1.0 Hz, 7-H), 7.15 (1H, t, *J* 7.8 Hz, 6-H), 7.71 (1H, br d, *J* 7.8 Hz, 5-H), 8.24 (1H, s, 3-H), 9.98 (1H, br s, OH), 11.7 (1H, br s, NH); HRMS (FAB) *m*/*z* 273.0876 (Calc. for $C_{14}H_{13}N_2O_4$: *m*/*z* 273.0875).

8-Hydroxy-4-methoxy-β-carboline-1-carbonitrile 24

8-Tosyloxy compound **17** (100 mg, 0.25 mmol) in THF (10 ml) was treated with Na-anthracenide at 0 °C according to the general procedure for detosylation. The crude product was subjected to column chromatography using $CHCl_3$–MeOH to give the *title compound* **24** (43 mg, 71%). Recrystallization from AcOEt gave orange prisms, mp >300 °C. ν_{max}/cm^{-1} 3300–2450 (NH and OH), 2240 (CN). δ (DMSO-d_6; 400 MHz) 4.20 (3H, s, OCH_3), 7.01 (1H, dd, *J* 7.8 and 1.0 Hz, 7-H), 7.13 (1H, t, *J* 7.8 Hz, 6-H), 7.66 (1H, dd, *J* 7.8 and 1.0 Hz, 5-H), 8.26 (1H, s, 3-H), 10.03 (1H, br s, OH), 12.25 (1H, br s, NH); HRMS (EI) *m*/*z* 239.0683 (Calc. for $C_{13}H_9N_3O_2$: *M* 239.0695).

8-Hydroxy-4-methoxy-β-carboline-1-carboxamide 25

8-Tosyloxy compound **18** (30 mg, 0.07 mmol) in THF (3 ml) was treated with Na-anthracenide at 0 °C according to the general procedure for detosylation. The crude product was subjected to column chromatography using $CHCl_3$–MeOH to give the *title compound* **25** (16 mg, 85%), mp >300 °C. ν_{max}/cm^{-1} 3430, 3305 (NH and OH), 1650 (C=O). δ (DMSO-d_6; 500 MHz) 4.20 (3H, s, OCH_3), 6.95 (1H, br d, *J* 7.6 Hz, 7-H), 7.12 (1H, t, *J* 7.6 Hz, 6-H), 7.64 (1H, br s, CONH), 7.70 (1H, br d, *J* 7.6 Hz, 5-H), 8.10 (1H, br s, CONH), 8.12 (1H, s, 3-H), 10.02 (1H, br s, OH), 11.20 (1H, br s, NH); HRMS (EI) *m*/*z* 257.0726 (Calc. for $C_{13}H_{11}N_3O_3$: *M* 257.0800).

4,8-Dimethoxy-β-carboline 2a (picrasidine P)

To a stirred solution of 8-hydroxy compound **15** (30 mg, 0.14 mmol) in THF (5.0 ml) and MeOH (2.0 ml) was added $TMSCHN_2$ (2.0 M solution in hexane; 0.21 ml, 0.42 mmol) at rt, and the whole was stirred at room temperature for 20 h. A few drops of AcOH were added to the reaction mixture, and the mixture was evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using $CHCl_3$–MeOH (10:1) to give the title compound **2a** (32 mg, 100%) as crystals. Recrystallization from AcOEt–hexane gave colorless prisms (mp 190–192 °C). ν_{max}(KBr)/cm^{-1} 3210–2350 (NH). δ (400 MHz) 4.02 and 4.15 (each 3H, s, 4- and 8-OCH_3), 6.98 (1H, br d, *J* 7.8 Hz, 7-H), 7.21 (1H, t, *J* 7.8 Hz, 6-H), 7.91 (1H, br d, *J* 7.8 Hz, 5-H), 8.09 (1H, br s, 3-H), 8.64 (1H, br s, 1-H), 9.08 (1H, br s, NH); HRMS (EI) *m*/*z* 228.0889 (Calc. for $C_{13}H_{12}N_2O_2$: *M* 228.0899). This sample was identical with the natural product (lit.,[3e] mp 198 °C).

Methyl 4,8-dimethoxy-β-carboline-1-carboxylate 2d

To a stirred solution of 8-hydroxy compound **23** (1.3 mg, 4.8 μmol) in THF (0.5 ml) and MeOH (0.05 ml) were added

$TMSCHN_2$ (2.0 M solution in hexane; 9.6 μl, 19.2 μmol) and DIPEA (1.2 μl, 6.9 μmol) at rt, and the whole was stirred at room temperature for 24 h. A few drops of AcOH was added to the reaction mixture, and the mixture was evaporated to dryness *in vacuo*. The residue was subjected to column chromatography using $CHCl_3$–MeOH (20:1) to give the title compound **2d** (1.3 mg, 95%) as crystals. Recrystallization from AcOEt–hexane gave colorless prisms, mp 218–219.5 °C. δ (400 MHz) 4.04, 4.10 and 4.24 (each 3H, s, 4-OCH_3, 8-OCH_3 and CO_2CH_3), 7.02 (1H, br d, *J* 7.8 Hz, 7-H), 7.25 (1H, t, *J* 7.8 Hz, 6-H), 7.90 (1H, br d, *J* 7.8 Hz, 5-H), 8.20 (1H, s, 3-H), 9.95 (1H, br s, NH); HRMS (FAB) *m*/*z* 287.1034 (Calc. for $C_{15}H_{15}N_2O_4$: *M* 287.1032). The synthetic sample of **2d** was identical with the natural product (lit.,[3o] mp 184–185 °C) in all respects except mp. The natural product could not be purified completely.

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