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A General Synthetic Route for 1-Substituted 4-Oxygenated β-Carbolines[1] (Synthetic Studies on Indoles and Related Compounds 41[2])

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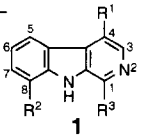
Abstract: A new synthetic route for two naturally occurring 1-substituted 4-methoxy-β-carbolines (**1b, c**) is described. This synthetic route involves elaboration of the ester groups in ethyl indole-2-carboxylate (**4b**) and its 1-benzyl derivative (**4a**), C_3-selective cyclization of the substituent at the C_2-position of the indole nucleus, and functionalization at the C_1-position of the β-carboline nucleus by a modified Reissert-Henze reaction. The synthetic β-carbolines (**1b, c**) should be key intermediates for the synthesis of their congeners, leading to a general synthetic route of 1-substituted 4-oxygenated β-carbolines.

Introduction

1-Substituted 4-oxygenated β–carboline alkaloids (**1, 2, 3**)[3, 4], representative examples of which are shown in **Table 1**, have recently become a large subfamily of β-carboline alkaloids.

Table 1. List of 4-Oxygenated β-Carboline Alkaloids

	R^1	R^2	R^3	Ref.
1a	OMe	H	CH_2CH_3	3c, 3k
1b	OMe	H	COMe	3b, 3m
1c	OMe	H	CO_2Me	3a, 3n
1d	OMe	H	$CH{=}CH_2$	3c, 3j
1e	OMe	H	$CH(OH)CH_2OH$	3b
1f	OMe	H	$CH(OCH_3)CH_2OH$	3d
1g	OMe	H	CH_2CH_2OH	3b
1h	OH	H	CHO	4a
1i	OH	H	CO_2Me	4a
1j	OMe	OMe	H	3f
1k	OMe	OMe	CH_2CH_3	3k
1l	OMe	OMe	$CH{=}CH_2$	3m
1m	OMe	OMe	CO_2Me	3q
1n	OMe	OH	CH_2CH_3	3e
1o	OMe	OH	$CH{=}CH_2$	3e
1p	OMe	OH	$CH_2CH_2N(Et)_2$	3e



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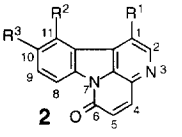
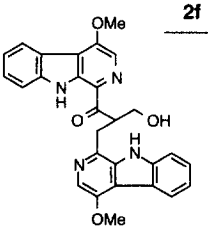
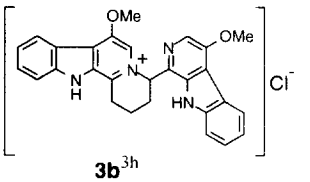


2

	R^1	R^2	R^3	Ref.
2a	OMe	H	H	3a
2b	OH	H	H	3o
2c	OMe	OMe	H	4b
2d	OMe	OH	H	3l, 3r
2e	OH	OMe	H	3p
2f	OMe	OMe	OMe	3i



3a[3g]

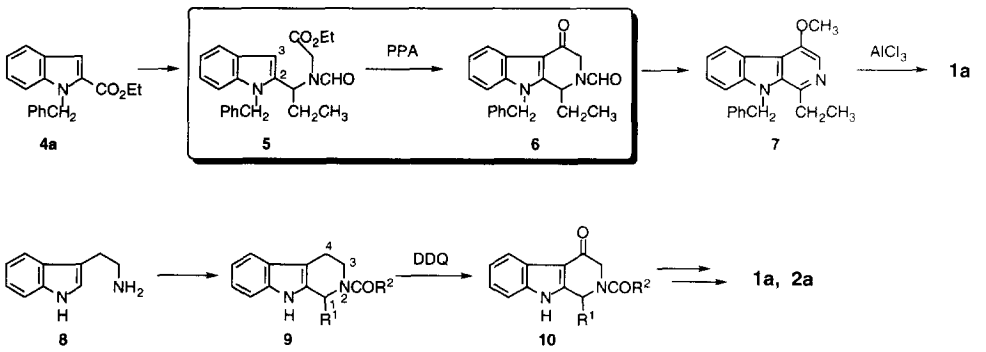


3b[3h]

Some of these compounds show interesting biological activities[4,5,6], but systematic biological evaluations have not yet been preformed because of their poor isolation yields from natural sources. Establishment of methods for their syntheses will thus be of pharmaceutical importance. Synthesis of the 4-oxygenated β-carboline structure was not easy, because the classical synthetic method for the β-carboline (cyclization of tryptamines by Bischler-Napieralski and Pictet-Spengler reactions) could not be applied[7].

We have already succeeded[7] in the synthesis of crenatine (**1a**) by the rarely used[8] intramolecular C_3-acylation of the 2-substituted indole (**5**) and $AlCl_3$-catalyzed *N*-debenzylation[9] of *N*-benzylcrenatine (**7**). The distinctive feature of this route is that the cyclization step simultaneously forms the C_4-oxygen functionality of the β-carboline nucleus . Cook reported[10] the synthesis of crenatine (**1a**) and 1-methoxycanthine-6-one (**2a**) utilizing selective C_4-oxidation of 1, 2, 3, 4-tetrahydro-β-carboline (**9**). However, the routes used previously both by ourselves and by Cook were not suitable for general synthesis of their various congeners, because they required the presence of an objective substituent on the C_1-position of β-carbolines during the early stages of synthesis (**Scheme 1**). In this paper, we report a general synthetic route for 1-substituted 4-oxygenated β-carbolines.

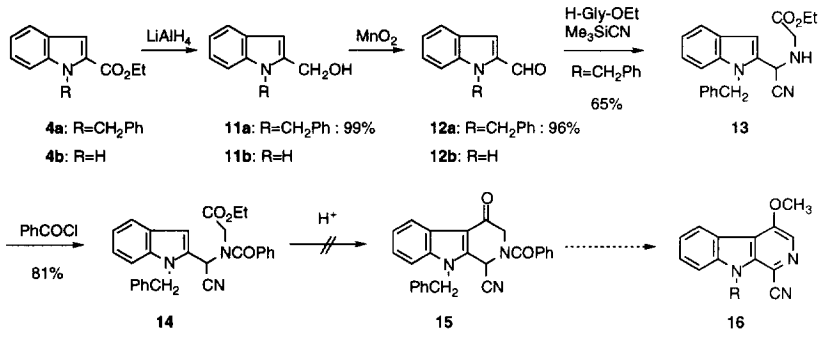
Scheme 1



Results and Discussion

We wished to develop a general synthetic method for 1-substituted 4-oxygenated β-carbolines *via* one key intermediate. We chose compound (**16**) as the key intermediate, as it has a cyano group at the C_1-position which can easily be converted to other various functional groups (**Scheme 2**). The synthetic strategy involves cyclization[7] from the C_2- to C_3-position of the *N*-benzylindole nucleus as the key step. We planned cyclization of the cyano derivative (**14**). Starting from ethyl *N*-benzylindole-2-carboxylate (**4a**), the aldehyde (**12a**) was synthesized according to Kruse's report[11]. The compound (**12a**) was converted to Schiff's base with ethyl glycinate, and then hydrocyanated with trimethylsilyl cyanide to give **13** as an unstable oil in moderate yield. Compound (**13**) was converted to stable benzoylamide (**14**) in good yield. Unfortunately, many attempts at acid-catalyzed cyclization of **14** were unsuccessful, giving only a complex mixture.

Scheme 2



Next, we planned to synthesize 4-methoxy-β-carboline (**23a**), and then to introduce the cyano group into its C_1-position. The synthetic route is shown in **Scheme 3**. Initially, we attempted acid-catalyzed cyclization of Schiff's base (**17**) prepared from *N*-benzylindole-2-carboxaldehyde (**12a**), but the reaction gave only a complex mixture. Hence, **12a** was converted to the glycine derivative (**18a**) *via* reductive coupling, and formylated to **19a** in good yield. Cyclization of **19a** with polyphosphoric acid (PPA) occurred smoothly at the C_3-position to give the cyclic formamide (**20a**) in good yield (89%). Cyclization of **19a** with methanesulfonic acid gave an excellent yield (94%) (**Table 2**). The cyclic formamide (**20a**) was hydrolyzed to the amine (**21**), followed by aromatization with Pd-C to give the 4-hydroxy-β-carboline (**22**) in good yield. However, methylation of 4-hydroxy-β-carboline (**22**) with various reagents [CH_2N_2, $(CH_3)_2SO_4$, CH_3I] gave 4-methoxy compound (**23a**) in yields of less than 20%. During the course of this reaction, we observed that a water-soluble fluorescent spot had appeared at the bottom of the TLC plate. This would be a quaternary *N*-methylpyridinium salt (**24**) formed by undesirable methylation of the pyridine nitrogen.

Scheme 3. Synthesis of the 4-Methoxy-β-carbolines (**23a, b**)

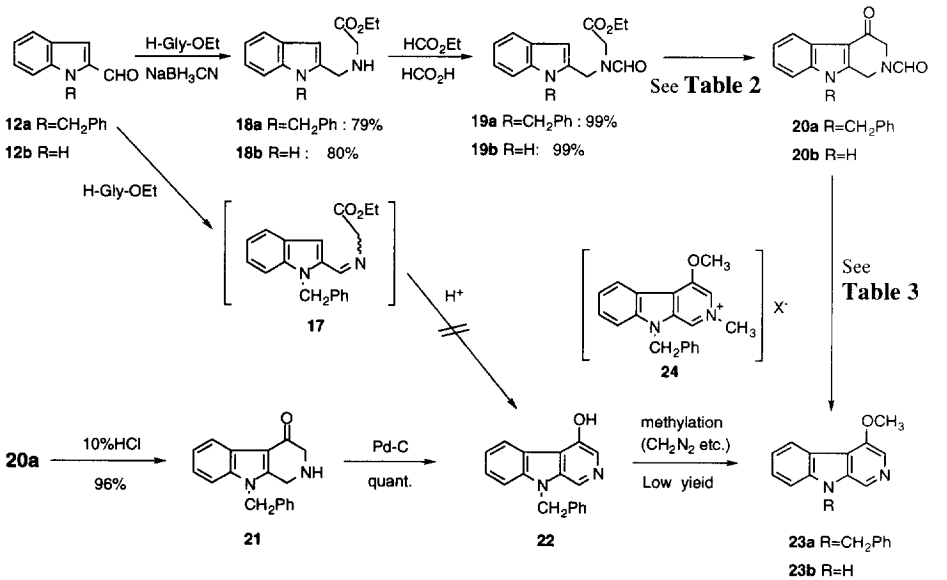
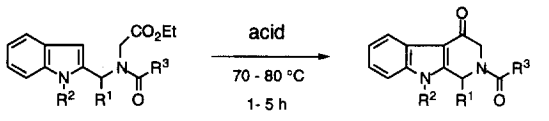
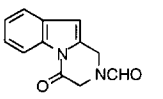


Table 2. Acid Catalyzed Cyclization





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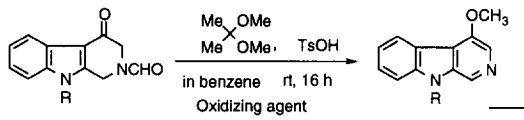
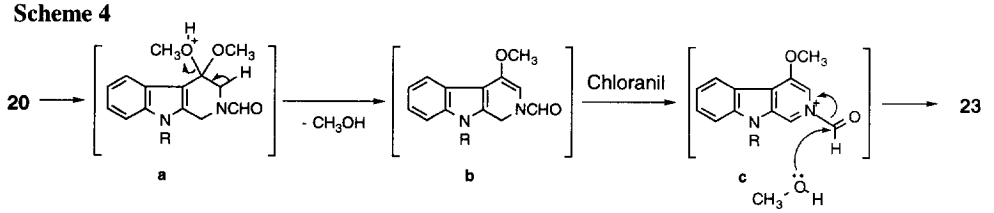
Substrate	R^1	R^2	R^3	Product	Yield PPA	Yield $MeSO_3H$
5	Et	CH_2Ph	H	**6**	80% [7a,b]	—
14	CN	CH_2Ph	Ph	**15**	decomposition	—
19a	H	CH_2Ph	H	**20a**	89%	94%
19b	H	H	H	**20b**	30 - 67%	75%

Table 3. Oxidative Ketalization to 4-Methoxy-β-carbolines



20	**23**	Yield MnO_2	Yield Benzoquinone (2.0 eq.)	Yield Chloranil (2.0 eq.)
20a ($R=CH_2Ph$)	**23a**	0%	60%	75%
20b (R=H)	**23b**	—	—	72%

Scheme 4



We then attempted one-step conversion of **20a** to **23a**. Cook[10c] reported the synthesis of 4-methoxy-β-carboline (**23b**) from 4-keto-2-benzoyl compound (**10,** R^1=H, R^2=Ph) by ketalization with trimethyl orthoformate under acidic conditions, followed by spontaneous air-oxidation. However, this required a long reflux time (3 days), and gave only a moderate yield (64%). We attempted the same reaction with **20a** in the presence of various oxidizing agents and found that addition of chloranil shortened the reaction time and increased the yield of **23a** (room temperature, 16 h, 75%) (**Table 3**). This reaction should be achieved by dehydrogenation with chloranil for the intermediate (**b**), followed by ready methanolysis of *N*-formyl pyridinium intermediate (**c**). (**Scheme 4**). Functionalization of the C_1-position of β-carboline nucleus was achieved by cyanation. There have been few reports of C_1-cyanation[12a,b] of β-carboline derivatives. We attempted to introduce the cyano group to *N*-benzyl-4-methoxy-β-carboline (**23a**) by modified Reissert-Henze reaction[13] using diethyl phosphorocyanidate (DEPC) in an aprotic solvent. *N*-Benzyl-4-methoxy-β-carboline (**23a**) was converted to the corresponding *N*-oxide (**25a**) with *m*-chloroperbenzoic acid (*m*-CPBA) (**Scheme 5**). Reaction of **25a** with DEPC gave the cyanated compound (**16a**) as a single product in 62% yield. The

cyanated position of **16a** (C_1-position or C_3-position) was confirmed from the H-H NOE spectrum as shown in **Fig. 1**. NOE observation showed that the neighboring position (C_3-position) of the C_4-methoxy group was unsubstituted.

Scheme 5. C_1-Functionalization of the 4-Methoxy-β-carbolines

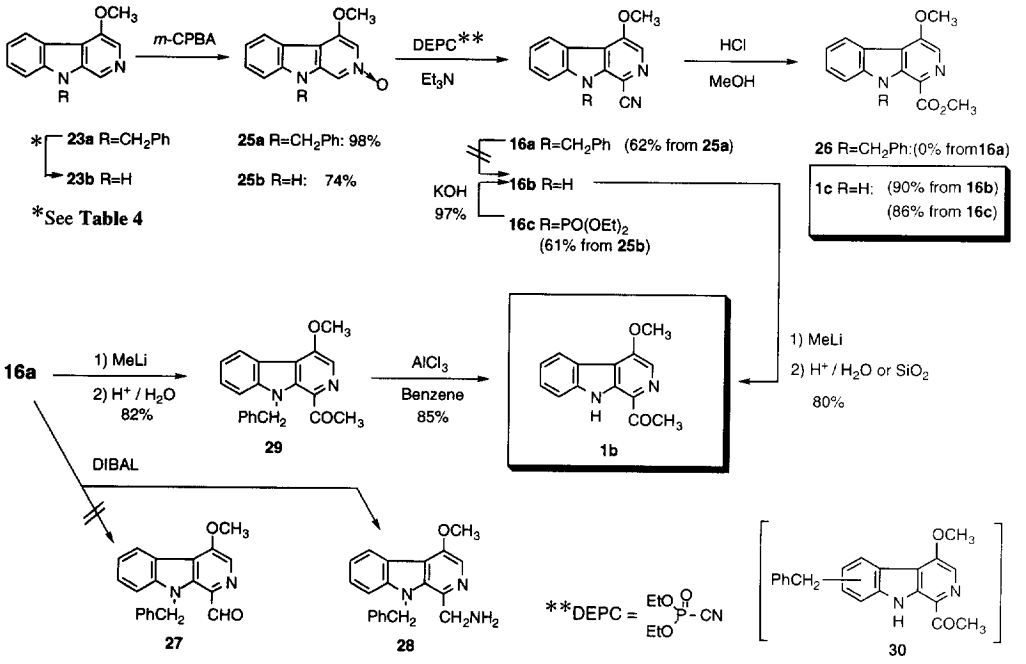
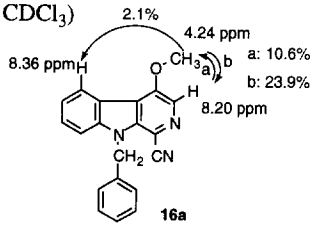


Fig. 1. NOE Observation (in $CDCl_3$)



Modification of the cyano group in the *N*-benzyl compound (**16a**) caused some difficulties. Acid-catalyzed methanolysis aiming at yielding **26** did not occur and resulted in recovery of the starting material. Reduction with diisobutylaluminum hydride (DIBAL) aiming at yielding the aldehyde (**27**) gave only an over-hydrogenated product [the amine (**28**)].

Finally, reaction of the cyano compound (**16a**) with MeLi, followed by treatment with SiO_2 or dil. HCl gave the 1-acetyl compound (**29**) in good yield. Debenzylation of **29** with $AlCl_3$ in benzene[9] gave one (**1b**) of the target compounds in good yield, while the reaction in anisole as solvent gave an inseparable mixture of benzyl compound (**30**) and **1b**. The synthetic sample of **1b** was identical with the natural product[3b, m] in all respects.

As the cyano group of the 9-benzyl compound (**16a**) could not be converted to an ester group as mentioned above, debenzylation of **16a** was attempted. However, no debenzylation occurred by the $AlCl_3$ method, with recovery of the starting material (**16a**). We then tried debenzylation at the stage of the cyclic ketone (**20a**) and the 1-H β-carboline (**23a**) with $AlCl_3$ in benzene or anisole, but obtained only a complex mixture (**Table 4**).

On the other hand, we found[14] that treatment of *N*-benzylindole derivative with lithium base at room temperature gave the corresponding debenzylated product in moderate yield. Application of this reaction to the benzyl compound (**23a**) with lithium diisopropylamide (LDA) gave the desired debenzylated 4-methoxy-β-carboline (**23b**) in 65% yield (**Table 4**).

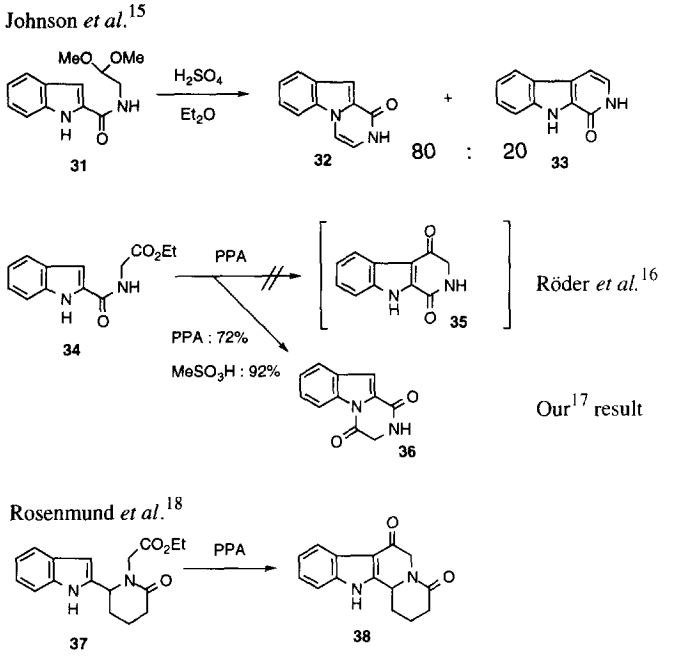
Table 4. Debenzylation of the 4-Methoxy-β-carbolines

Substrate	Product	Yield: $AlCl_3$ method[9]	Yield: LDA method[14]
7 (R = Et)[7a,b]	**1a**	71% (in anisole)	—
16a (R = CN)	**16b**	no reaction	—
29 (R = $COCH_3$)	**1b**	85% (in benzene)	—
23a (R = H)	**23b**	complex mixture	65%
20a	**20b**	complex mixture	—

The *N*-H compound (**23b**) was converted to the *N*-oxide (**25b**) by *m*-CPBA as described for the *N*-benzyl compound (**23a**) (**Scheme 5**). Reissert-Henze reaction of the *N*-oxide (**25b**) with DEPC gave the 1-cyano-*N*-phosphorylated compound (**16c**) in 61% yield. The Reissert-Henze reaction with DEPC accompanied undesirable *N*-phosphorylation in the *N*-H series. Dephosphorylation was successful with KOH to give the key intermediate (**16b**) in good yield. Treatment of both **16b** and **16c** with HCl / MeOH easily gave the *N*-H ester (**1c**) in good yield in contrast to the *N*-benzyl compound (**16a**). The synthetic sample of **1c** was identical to the natural product[3a, n] in all respects. Furthermore, reaction of the key intermediate (**16b**) with MeLi gave *N*-H 1-acetyl compound (**1b**) in good yield.

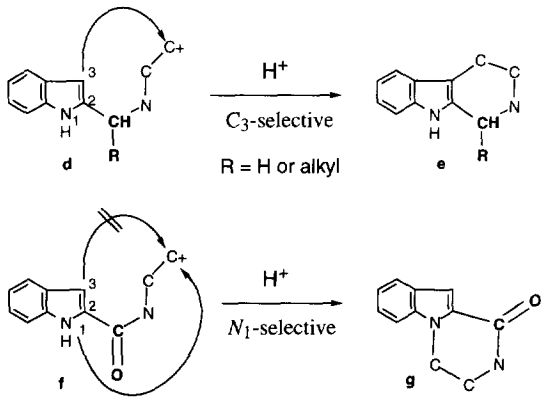
In this synthetic route, the benzyl group on the indole nitrogen resisted deprotection and decreased the reactivity of the C_1-cyano group, while protection of indole nitrogen was not necessary during reactions from **23b** to the natural products (**1b**, **1c**). Then, we planned to develop a shorter route for synthesis of *N*-H compound (**23b**) from ethyl indole-2-carboxylate (**4b**) without *N*-protection (**Scheme 3**). The starting aldehyde (**12b**) was obtained from **4b** according to Kruse's method[11]. Reductive coupling of **12b** with ethyl glycinate to **18b**, followed by formylation gave **19b** in good yield. The next cyclization of the *N*-H-glycine derivative (**19b**) is the most important step in the *N*-H-series, because cyclization could occur in two directions. Johnson[15] reported that acid-catalyzed cyclization of the *N*-H acetal of 2-ketoindole derivative (**31**) gave an 80 : 20 mixture of the *N*-cyclic compound (**32**) and the C_3-cyclic compound (**33**) (**Scheme 6**). On the other hand, Röeder[16] reported that cyclization of the *N*-H ester of 2-acylindole derivative (**34**) gave only the C_3-cyclic compound (**35**). However, we had already re-examined cyclization of the 2-acylindole (**34**) and found[17] that the structure of the product formed from **34** was the *N*-cyclic compound (**36**) as the sole product, but not the C_3-cyclic compound (**35**). In contrast, Rosenmund[18] reported that cyclization of the *N*-H ester of 2-alkylindole derivative (**37**) gave only the C_3-cyclic compound (**38**).

Scheme 6. Reported Cyclization of the C_2-Substituents of Indoles



Fortunately, the acid-catalyzed cyclization of **19b** occurred exclusively at the C_3-position to give the desired 4-oxo-1,2,3,4-tetrahydro-β-carboline (**20b**) without formation of the *N*-cyclic compound (**39**) (**Table 2**). Cyclization of the *N*-H compound (**19b**) with PPA gave variable yields (30% - 67%) in comparison with the *N*-benzyl compound (**19a**), whereas the use of methanesulfonic acid reproducibly gave good yield (75%). Methanesulfonic acid was thus a better acid catalyst for this type of cyclization. The above results showed that the direction of cyclization clearly depended on the C_2-substituent. Cyclization of 2-alkylindole derivatives (**19b, 37 = d**) gave the C_3-cyclic compounds (**20b, 38 = e**), whereas that of 2-acylindole derivatives (**31, 34 = f**) gave *N*-cyclic compounds (**32, 36 = g**) (**Scheme 7**).

Scheme 7. Cyclizing Directions of the C_2-Substituent of *N*-Unprotected Indoles



The *N*-H-cyclic ketone **(20b)** was converted to 4-methoxy-β-carboline **(23b)** in 72% yield utilizing acid-catalyzed ketalization, followed by oxidative aromatization **(Table 3)**. Thus, **23b** was synthesized from ethyl indole-2-carboxylate **(4b)** in 6 steps **(Scheme 2, 3)**. Although the total yield of **23b** from **4a** (7 steps in benzyl series) and that from **4b** (in *N*-H series) were the same (ca. 35%), *N*-H series was superior to the *N*-benzyl series because of its simplicity.

Conclusions

We developed a general synthetic route for 1-substituted 4-methoxy-β-carbolines **(1b, c)** starting from ethyl 1-benzyl or 1-H-indole-2-carboxylates **(4a** and **4b)**. The key steps were C_3-cyclization of **19a, b** and C_1-selective cyanation of **23a, b**. It is noteworthy that the cyclization of **19b** in the *N*-H series occurred exclusively at the C_3-position. 1-Cyano-, 1-acetyl-, and 1-methoxycarbonyl-4-methoxy-β-carbolines **(16b, 1b, 1c)** thus synthesized should be key intermediates leading to the general synthesis of this family of compounds **(Table 1)**, and this synthetic route should be applied to the synthesis of congeners which have a substituent on the benzene part of the β-carboline nucleus.

Experimental

All melting points were determined on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-300 or on a Shimadzu IR-400 spectrophotometer (in Nujol mulls, unless otherwise stated). ^{1}H-NMR spectra were recorded on a Hitachi R-24B (60 MHz) (unless otherwise stated), JEOL GX-400 (400 MHz), EX-400 (400 MHz), and α-500 (500 MHz) spectrometers in deuteriochloroform unless otherwise stated, with tetramethylsilane as an internal reference. The data at 60 MHz were recorded, unless otherwise stated. Mass spectra (MS) were measured on JEOL JMS D-300, DX-303 and HX110A spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70 - 230 mesh ASTM, Merck), and for thin layer chromatography (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., diffused; Ar, aromatic; BP, base peak.

(1-Benzylindol-2-yl)methanol (11a)

A solution of ethyl 1-benzylindole-2-carboxylate **(4a)** (5.587 g, 20.0 mmol) in tetrahydrofuran (THF) (35 ml) was added to a suspension of $LiAlH_4$ (2.28 g, 60 mmol) in THF (10 ml) at 0 °C under argon atmosphere. The mixture was stirred at room temperature for 30 min, and then quenched by the sequential addition of water (2 ml), 10% aqueous NaOH (3.5 ml), and water (6 ml) under ice-cooling. Then the mixture was stirred at room temperature for an additional 0.5 h. White precipitates were removed by vacuum filtration through a celite pad and washed with CH_2Cl_2-MeOH (10 : 1). Combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give the *title compound* **(11a)** (4.720 g, 99%) as crystals. Recrystallization from AcOEt-hexane gave colorless needles, mp 101.5-103 °C. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.13; H, 6.36; N, 5.81. IR $\upsilon_{max}cm^{-1}$: 3210 (OH). ^{1}H-NMR δ: 1.55 (1H, m, OH), 4.66 (2H, d, *J*=6 Hz, -$\underline{CH_2}$OH), 5.41 (2H, s, -CH_2Ph), 6.47 (1H, s, C_3-H), 6.80-7.75 (9H, m, Ar-H). MS *m/z*; 237 (M^+, 70%), 91 (BP).

1-Benzylindole-2-carboxaldehyde (12a)

A mixture of (1-benzylindol-2-yl)methanol **(11a)** (4.509 g, 19.0 mmol) and activated MnO_2 (22.5 g) in CH_2Cl_2 (100ml) was stirred at room temperature for 6 h. Precipitates were removed by vacuum filtration through a short column of silica gel, and washed with CH_2Cl_2-MeOH (10:1). Combined organic layer was evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using hexane-AcOEt (5 : 1) to give the *title compound* **(12a)** (4.273 g, 96%) as crystals. Recrystallization from EtOH gave colorless needles, mp 76.0-77.0 °C. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.97; H, 5.58; N, 6.01. IR $\upsilon_{max}cm^{-1}$: 1662 (C=O). ^{1}H-NMR δ: 5.77 (2H, s, -CH_2Ph), 6.85-7.85 (10H, m, Ar-H), 9.81 (1H, s, -CHO). MS *m/z*; 235 (M^+, 66%), 91 (BP).

Ethyl *N*-[(1-benzylindol-2-yl)cyanomethyl]aminoacetate (13)

A solution of 1-benzylindole-2-carboxaldehyde **(12a)** (988 mg, 4.2 mmol) and Me_3SiCN (0.67 ml, 5.0

mmol) in absolute 2-propanol (15 ml) was added to a solution of ZnI_2 (34 mg, 0.11 mmol) in absolute 2-propanol (1 ml) under argon atmosphere at 0 °C. The mixture was stirred at 0 °C for 0.5 h. A solution of ethyl aminoacetate (freshly prepared from commercially available hydrochloride salt, 1.87 g, 18 mmol) in absolute 2-propanol (9 ml) was then added to the above solution at room temperature. The mixture was stirred at room temperature for 3.5 h, poured into 300 ml of water, and extracted with Et_2O. The organic layer was washed with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using hexane-AcOEt (10 : 1) to give the *title compound* **(13)** (945 mg, 65%) as a yellow oil, accompanied with the starting material **(12a)** (273 mg, 28%) recovered. IR (neat) $\upsilon_{max}cm^{-1}$: 3325 (NH), 2230(CN), 1735 (C=O). ^{1}H-NMR δ: 1.25 (3H, t, *J*=7 Hz, -$CH_2\underline{CH_3}$), 1.80-2.40 (1H, br, -NH-CH_2), 3.46 (2H, br d, *J*=6 Hz, -NH-$\underline{CH_2}$-CO), 4.14 (2H, q, *J*=7 Hz, -COO-$\underline{CH_2}$-CH_3), 4.97 [1H, br d, *J*=8 Hz, -$\underline{CH}$(CN)-NH-] 5.51 (2H, br s, -$\underline{CH_2}$Ph) 6.83-7.75 (10H, m, Ar-H). This compound was immediately benzoylated without further purification owing to its instability.

Ethyl *N*-[(1-benzylindol-2-yl)cyanomethyl]-*N*-benzoylaminoacetate (14)

Benzoyl chloride (0.628 ml, 5.5 mmol) was added to a solution of ethyl *N*-[(1-benzylindol-2-yl)cyanomethyl]aminoacetate **(13)** (945 mg, 2.7 mmol) in pyridine (10 ml) under argon atmosphere. The mixture was stirred at room temperature for 4.5 h, poured into ice-water, neutralized with conc. HCl, and extracted with benzene. The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using hexane-AcOEt (10 : 1) to give the *title compound* **(14)** (989 mg, 81%) as crystals. Recrystallization from EtOH gave colorless needles, mp 138.5-140.5 °C. Anal. Calcd for $C_{28}H_{25}N_3O_3$: C, 74.48; H, 5.58; N, 9.31. Found: C, 74.79; H, 5.59; N, 9.27. IR $\upsilon_{max}cm^{-1}$ (KBr): 2251(CN), 1741, 1647 (C=O). ^{1}H-NMR δ: 0.92 (3H, t, *J*=7 Hz, -$CH_2\underline{CH_3}$), 3.71 (2H, q, *J*=7 Hz, -COO-$\underline{CH_2}$-CH_3), 3.99 (2H, s, -N-CH_2-CO), 5.33 (2H, s, -CH_2Ph) 6.76-7.75 [16H, m, Ar-H and -CH(CN)-]. MS *m/z*; 451 (M^+, 95%), 346 (BP).

Ethyl *N*-[(1-benzylindol-2-yl)methyl]aminoacetate (18a)

Et_3N (1.46 ml, 10.5 mmol) and $NaBH_3CN$ (660 mg, 10.5 mmol) was sequentially added to a solution of 1-benzylindole-2-carboxaldehyde **(12a)** (2.353 g, 10.0 mmol) and ethyl aminoacetate hydrochloride (4.187 g, 30.0 mmol) in EtOH (55 ml) at 0 °C. The reaction mixture was stirred at room temperature for 14 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 hexane-AcOEt (3 : 1) to give the *title compound* **(18a)** (2.539 g, 79%) as a colorless oil. IR $\upsilon_{max}cm^{-1}$: 3330 (NH), 1730 (C=O). ^{1}H-NMR δ: 1.19 (3H, t, *J*=7 Hz, -$CH_2\underline{CH_3}$), 1.87 (1H, br s, CH_2-$\underline{NH}$-CH_2, D_2O exchangeable), 3.31 and 3.83 (each 2H, s, Ar-$\underline{CH_2}$-NH- and -NH-$\underline{CH_2}$-CO) 4.10 (2H, q, *J*=7 Hz, -COO-$\underline{CH_2}$-CH_3), 5.44 (2H, s, -CH_2Ph) 6.43 (1H, s, C_3-H) 6.78-7.35 (8H, m, Ar-H) 7.37-7.73 (1H, m, C_4-H). HRMS (FAB) *m/z*; 323.1759 (Calcd, M+H), 323.1766 (Found, M+H).

Ethyl *N*-(indol-2-ylmethyl)aminoacetate (18b)

Indole-2-carboxaldehyde[11] **(12b)** (4.352 g, 30.0 mmol) was treated with Et_3N (4.20 ml, 30.1 mmol), $NaBH_3CN$ (1.875 g, 29.8 mmol), and ethyl aminoacetate hydrochloride (12.567 g, 90.0 mmol) in EtOH (100 ml) at 0 °C for 14 h by the same method used for preparing **18a**. The product **(18b)** (5.540 g, 80%) was recrystallized from AcOEt-hexane to give pale brown prisms, mp 72-74 °C. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.20; H, 7.00; N, 11.92. IR $\upsilon_{max}cm^{-1}$: 3320, 3310 (NH), 1720 (C=O). ^{1}H-NMR δ: 1.21 (3H, t, *J*=7 Hz, -$CH_2\underline{CH_3}$), 2.04 (1H, br s, CH_2-$\underline{NH}$-CH_2), 3.35 and 3.92 (each 2H, s, Ar-$\underline{CH_2}$-NH- and -NH-$\underline{CH_2}$-CO), 4.14 (2H, q, *J*=7 Hz, -COO-$\underline{CH_2}$-CH_3), 6.30 (1H, br s, C_3-H), 6.92-7.69 (4H, m, Ar-H), 8.68 (1H, br s, NH). MS *m/z*; 232 (M^+, 61%), 130 (BP).

Ethyl *N*-[(1-benzylindol-2-yl)methyl]-*N*-formylaminoacetate[19] (19a)

Ethyl *N*-[(1-benzylindol-2-yl)methyl]aminoacetate **(18a)** (2.366 g) was dissolved in a mixture of ethyl formate (30 ml) and formic acid (0.3 ml), and stirred at room temperature for 20 h. The organic layer was diluted with AcOEt, washed with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo* to give the *title compound* **(19a)** (2.556 g, 99%) as crystals. Recrystallization from benzene-hexane gave colorless prisms, mp 115.5-117 °C. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.05; H, 6.38; N, 7.99. IR $\upsilon_{max}cm^{-1}$: 1740, 1690 (C=O). ^{1}H-NMR δ: 1.17 (3H, t, J=8 Hz, -$CH_2\underline{CH_3}$), 3.53, 3.91, 4.51, and 4.77 (4H, each s, Ar-CH_2-N and -NH-CH_2-CO), 4.06 (2H, q, J=7 Hz,

-COO-CH_2-CH_3), 5.30 (2H, s, -CH_2Ph), 6.49 (1H, s, C_3-H), 6.70-7.49 (8H, m, Ar-H), 7.40-7.80 (1H, m, C_4-H), 7.70 and 8.12 (1H, each s, -CHO). MS *m/z*; 350 (M^+, 70%), 231 (BP).

Ethyl *N*-[(indol-2-yl)methyl]-*N*-formylaminoacetate[19] (19b)

Ethyl *N*-[(indol-2-yl)methyl]aminoacetate (**18b**) (2.10 g) was treated with ethyl formate (27 ml) and formic acid (0.3 ml) at room temperature for 12 h by the same method used for preparing **19a**. The product (**19b**) (2.35 g, 99%) was obtained as a pale brown oil. IR $\upsilon_{max}cm^{-1}$: 3420, 3280 (NH), 1738, 1664 (C=O). ^{1}H-NMR δ: 1.20 and 1.29 (3H, each t, *J*=8 Hz, -CH_2CH_3), 3.90, 4.02, 4.65 and 4.71 (4H, each s, Ar-CH_2-N and N-CH_2-CO), 4.13 (2H, q, *J*=8 Hz, -COO-CH_2-CH_3), 6.40 and 6.45 (1H, each br s, C_3-H), 7.01-7.72 (4H, m, Ar-H), 8.10 and 8.32 (1H, each s, -CHO), 9.20 and 9.69 (1H, each br s, NH). MS *m/z*; 260 (M^+, 80%), 130 (BP). HRMS *m/z*; 260.1161 (Calcd.), 260.1147 (Found).

9-Benzyl-2-formyl-4-oxo-1,2,3,4-tetrahydro-β-carboline[19] (20a)

i) With PPA

A mixture of ethyl *N*-[(1-benzylindol-2-yl)methyl]-*N*-formylaminoacetate (**19a**) (12.81 g, 36.6 mmol) and polyphosphoric acid (PPA) (92 g) was mechanically stirred at 80 °C for 3 h. The reaction mixture was poured into ice-water, and neutralized with 10% aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was recystallized from AcOEt to give the *title compound* (**20a**) (6.79 g) as crystals. The mother liquor was subjected to column-chromatography using AcOEt-hexane (1 : 1) to give the second crop of the *title compound* (**20a**) (3.10 g) as crystals (totally 9.89 g, 89%). Recrystallization from EtOH gave pale brown prisms, mp 140-143.5 °C and 157.5-160 °C. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.04; H, 5.28; N, 9.18. IR $\upsilon_{max}cm^{-1}$: 1660, 1640 (C=O). ^{1}H-NMR δ: 4.09, 4.27, 4.56, and 4.78 (4H, each s, C_1- and C_3-H), 5.28 (2H, s, -CH_2Ph), 6.85-7.50 (8H, m, Ar-H), 8.00-8.30 (1H, m, C_5-H), 8.08 (1H, s, -CHO). MS *m/z*; 304 (M^+, BP).

ii) With methanesulfonic acid

A mixture of *N*-[(1-benzylindol-2-yl)methyl]-*N*-formylaminoacetate (**19a**) (351 mg, 1.0 mmol) and methanesulfonic acid (3.5 ml) was stirred at 70 °C for 1 h. The reaction mixture was poured into ice-water, and neutralized with 10% aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using AcOEt-hexane (2 : 1) to give the *title compound* (**20a**) (286 mg, 94%).

2-Formyl-4-oxo-1,2,3,4-tetrahydro-β-carboline[19] (20b)

i) With PPA

Ethyl *N*-[(indol-2-yl)methyl]-*N*-formylaminoacetate (**19b**) (3.690 g, 14.2 mmol) was treated with PPA (37 g) at 80 °C for 1.2 h by the same method used for preparing **20a**. Column chromatography for purification was carried out with CH_2Cl_2-MeOH. The product (**20b**) (1.797 g, 67%) was recrystallized from EtOH to give pale brown prisms, mp 224-225 °C. IR $\upsilon_{max}cm^{-1}$: 3200, (NH), 1660, 1640 (C=O). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 4.21, 4.25, 4.93, and 4.97(4H, each s, C_1- and C_3-H), 7.22 (1H, dif. t, *J*=7.5 Hz, C_6- or C_7-H), 7.25 (1H, dif. t, *J*=7.5 Hz, C_6- or C_7-H), 7.51 (1H, dif. d, *J*=7.5 Hz, C_5- or C_8-H), 7.95 (1H, dif. d, *J*=7.5 Hz, C_5- or C_8-H), 8.22 and 8.30 (1H, each s, -CHO), 12.20 (1H, br s, NH). HRMS *m/z*; 214.0740 (Calcd), 214.0852 (Found).

ii) With methanesulfonic acid

Ethyl *N*-[(indol-2-yl)methyl]-*N*-formylaminoacetate (**19b**) (501 mg, 1.93 mmol) was treated with methanesulfonic acid (5 ml) at 70 °C for 3.5 h by the same method used for preparing **20a** to give the product (**20b**) (310 mg, 75%).

9-Benzyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (21)

A solution of 9-benzyl-2-formyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**20a**) (915 mg, 3.0 mmol) in 10% HCl (30 ml) and dioxane (20ml) was heated under reflux for 0.5 h. The reaction mixture was poured into water, neutralized by K_2CO_3, and extracted with AcOEt. The organic layer was dried over anhydrous $MgSO_4$, evaporated to dryness *in vacuo* to give the *title compound* (**21**) (799 mg, 96%) as crystals. Recrystallization from EtOH gave colorless needles, mp 179-181 °C. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.06; H, 5.88; N, 10.00. IR $\upsilon_{max}cm^{-1}$: 3170 (NH), 1640 (C=O). ^{1}H-NMR δ: 2.06 (1H, s, NH), 3.48 and 3.99 (each 2H, s, C_1- and C_3-H), 5.16 (2H, s, -CH_2Ph), 6.84-7.50 (8H, m, Ar-H),

8.05-8.35 (1H, m, C_5-H). MS *m/z*; 276 (M^+, 62%), 247 (BP).

9-Benzyl-4-hydroxy-β-carboline (22)

A mixture of 9-benzyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**21**) (402 mg, 1.5 mmol), 10% Palladium on charcoal (100 mg) in decaline (10 ml) was heated at 200 °C for 7.5 h. Palladium charcoal was removed by filtration and washed with AcOEt and EtOH. Combined organic layer was evaporated *in vacuo* to remove the AcOEt and EtOH. Hexane (50 ml) was added, the precipitates were collected by filtration to give the *title compound* (**22**) (398 mg, 100%) as pale brown prisms, mp 225-243 °C (dec.). IR $\upsilon_{max}cm^{-1}$ (KBr): 3421 (OH). ^{1}H-NMR (DMSO-d_6) δ: 5.69 (2H, s, CH_2Ph), 7.00-7.85 (9H, m, Ar-H and -OH), 7.98 (1H, br s, C_1- or C_3-H), 8.25 (1H, dif. d, *J*= 7 Hz, C_5-H), 8.49 (1H, br s, C_1- or C_3-H). HRMS (FAB) *m/z*; 275.1184 (Calcd, M+H), 275.1177 (Found, M+H).

9-Benzyl-4-methoxy-β-carboline (23a)

i) From 9-benzyl-4-hydroxy-β-carboline (22)

A solution of **22** (100 mg, 0.36 mmol) in DMF (3 ml) was added to 50% NaH (21 mg, 0.43 mmol) at 0 °C under argon atmosphere. Dimethyl sulfate (40 μl, 0.43 mmol) was added, and the whole was stirred at 0 °C for 2 min. The mixture was poured into 5% aqueous ammonia, and stirred for 5 min. The mixture was extracted with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using hexane-AcOEt (1:1) to give the *title compound* (**23a**) (19.6 mg, 19%) as crystals. Recrystallization from EtOH-AcOEt gave colorless prisms (mp 126-129 °C). Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.26; H, 5.56; N, 9.60. IR $\upsilon_{max}cm^{-1}$: no characteristic absorption. ^{1}H-NMR δ: 4.13 (3H, s, $-OCH_3$), 5.49 (2H, s, $-CH_2Ph$), 6.90-7.55 (8H, m, Ar-H), 8.06 (1H, s, C_1- or C_3-H), 8.32 (1H, dif. d, *J*= 8 Hz, C_5-H), 8.48 (1H, s, C_1- or C_3-H). MS *m/z*; 288 (M^+, 61%), 91(BP).

ii) From 9-benzyl-2-formyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (20a)

A solution of *p*-toluenesulfonic acid monohydrate (1.67 g, 8.8 mmol) in benzene (55 ml) was heated under azeotropic conditions for 1 h. After cooling, **20a** (2.608 g, 8.8 mmol) and dimethoxypropane (3.25 ml, 26.4 mmol) was added to the benzene solution, and the mixture was stirred at room temperature for 1 h. Chloranil (4.325 g, 17.6 mmol) was then added, and the whole was stirred at room temperature for 15 h. The reaction mixture was poured into 5% aqueous NaOH, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to Al_2O_3 column-chromatography using benzene-AcOEt (10:1) to give the *title compound* (**23a**) (1.85 g, 75%).

4-Methoxy-β-carboline (23b)

i) From 9-benzyl-4-methoxy-β-carboline (23a) *via* debenzylation using LDA

n-BuLi (1.6M in hexane) (1.6 ml, 2.7 mmol) was added to a solution of diisopropylamine (0.50 ml, 3.3 mmol) in THF (2.5 ml) at -50 °C under argon atmosphere. After the solution was stirred at room temperature for 10 min, and then cooled at -50 °C, the solution of **23a** (144 mg, 0.50 mmol) in THF (5 ml) was added to the solution. The whole was stirred at -50 °C for 2 h, and room temperature for 3 h. The reaction mixture was poured into ice water, and extracted with ethyl acetate. 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 AcOEt to give the *title compound* (**23b**) (64.6 mg, 65%) as crystals. Recrystallization from CH_2CH_2-MeOH-AcOEt gave pale brown prisms (mp 250-252 °C). Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.51; H, 5.03; N, 13.91. IR $\upsilon_{max}cm^{-1}$: 3110 (NH). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 4.12 (3H, s, $-OCH_3$), 7.24 (1H, dif. t, *J*=7.3 Hz, C_6- or C_7-H), 7.51 (1H, dif. t, *J*=7.3 Hz, C_6- or C_7-H), 7.59 (1H, dif. d, *J*=7.3 Hz, C_5- or C_8-H), 8.09 (1H, s, C_1- or C_3-H), 8.19 (1H, dif. d, *J*=7.3 Hz, C_5- or C_8-H), 8.58 (1H, s, C_1- or C_3-H), 11.64 (1H, br s, NH). MS *m/z*; 198 (M^+, BP).

ii) From 2-formyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (20b)

The substrate (**20b**) (2.143 g, 10.0 mmol) was treated at room temperature for 12 h with *p*-toluenesulfonic acid monohydrate (1.902 g, 10.0 mmol), dimethoxypropane (3.67 ml, 30.0 mmol), and chloranil (4.92 g, 20.0 mmol) in benzene (150 ml) by the same method used for preparing **23a** to give the product (**23a**) (1.421 g, 72%).

9-Benzyl-4-methoxy-β-carboline-*N*-oxide monohydrate (25a)

A solution of 9-benzyl-4-methoxy-β-carboline (**23a**) (577 mg, 2.0 mmol) and *m*-CPBA (518 mg, 3.0 mmol)

in CH_2CH_2 (12ml) was stirred at room temperature for 4 h. After CH_2Cl_2 (12 ml) was added to the mixture, the organic layer was washed with aqueous 10% K_2CO_3 and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo* to give the *title compound* **(25a)** (0.63 g, 98%) as crystals. Recrystallization from CH_2Cl_2-AcOEt gave colorless needles, mp 229-234 °C. Anal. Calcd for $C_{19}H_{16}N_2O_2 \cdot H_2O$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.78; H, 5.59; N, 8.68. IR $\upsilon_{max}cm^{-1}$: 3500 - 3100 (H_2O). ^{1}H-NMR δ: 4.03 (3H, s, $-OCH_3$), 5.35 (2H, s, $-CH_2Ph$), 6.90-7.55 (8H, m, Ar-H), 7.82 (1H, br s, C_1- or C_3-H), 8.15 (1H, br s, C_1- or C_3-H), 8.0-8.32 (1H, m, C_5-H). MS *m/z*; 304 (M^+, 44%), 288 (BP), 91 (57%).

4-Methoxy-β-carboline-*N*-oxide monohydrate (25b)

m-CPBA (3.529 g, 20.45 mmol) was added to a suspension of 4-methoxy-β-carboline **(23b)** (2.702 g, 13.63 mmol) in CH_2CH_2 (300 ml) at room temperature, and then stirred at room temperature for 24 h. Hexane was added to the mixture. The precipitates were collected by filtration, washed with 10% aqueous K_2CO_3 and water, and dried under reduced pressure to give the *title compound* **(25b)** (2.336 g, 74%) as crystals . Recrystallization from CH_2Cl_2-MeOH-AcOEt gave colorless needles, mp 273-276 °C. Anal. Calcd for $C_{12}H_{10}N_2O_2 \cdot H_2O$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.84; H, 5.17; N, 11.99. IR $\upsilon_{max}cm^{-1}$: 3500 - 2600 (NH and H_2O). ^{1}H-NMR (DMSO-d_6) δ: 4.01 (3H, s, $-OCH_3$), 6.99-7.60 (3H, m, Ar-H), 7.84 (1H, d, *J*=1.5 Hz, C_1- or C_3-H), 8.00 (1H, dif. d, *J*=7 Hz, C_5-H), 8.25 (1H, d, *J*=1.5 Hz, C_1- or C_3-H), 11.11 (1H, br s, NH). MS *m/z*; 214 (M^+, BP).

9-Benzyl-1-cyano-4-methoxy-β-carboline (16a)

A solution of 9-benzyl-4-methoxy-β-carboline-*N*-oxide monohydrate **(25a)** (322 mg, 1.00 mmol), DEPC (0.639 ml, 4.00 mmol), and Et_3N (0.140 ml, 1.00 mmol) in CH_3CN (15 ml) was heated under reflux for 3 h. The mixture was poured into ice-water, and extracted with CH_2CH_2. 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 hexane-AcOEt (2:1) to give the *title compound* **(16a)** (195 mg, 62%) as crystals. Recrystallization from $CHCl_3$-AcOEt-MeOH gave colorless prisms, mp 216-219 °C. Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.72; H, 4.86; N, 13.48. IR $\upsilon_{max}cm^{-1}$: 2225 (CN). ^{1}H-NMR (500 MHz) δ: 4.24 (3H, s, $-OCH_3$), 5.88 (2H, s, $-CH_2Ph$), 7.00-7.10 (2H, m, Ar-H), 7.20-7.27 (3H, m, Ar-H), 7.37 (1H, dif. t, *J*=8.0 Hz, C_6- or C_7-H), 7.43 (1H, dif. d, *J*=8.0 Hz, C_8-H), 7.58 (1H, dif. t, *J*=8.0 Hz, C_6- or C_7-H), 8.20 (1H, s, C_3-H), 8.36 (1H, dif. d, *J*=8.0 Hz, C_5-H),. MS *m/z*; 313 (M^+, 33%), 91 (BP).

9-Diethoxyphosphoryl-1-cyano-4-methoxy-β-carboline (16c)

4-Methoxy-β-carboline-*N*-oxide monohydrate **(25b)** (1.071 g, 4.61 mmol) was treated with DEPC (3.79 ml, 25.0 mmol) and Et_3N (1.39 ml, 10.0 mmol) in CH_3CN (75 ml) at 70 °C for 5 h by the same method used for preparing **16a**. Column chromatography for purification was carried out with CH_2Cl_2-MeOH (30:1). The product **(16c)** (1.005 g, 61%) was recrystallized from AcOEt-hexane to give colorless prisms, mp 139-142 °C. Anal. Calcd for $C_{17}H_{18}N_3O_4P$: C, 56.83; H, 5.05; N, 11.69. Found: C, 56.71; H, 5.00; N, 11.60. IR $\upsilon_{max}cm^{-1}$: 2240 (CN). ^{1}H-NMR δ: 1.34 (6H, t, J=7 Hz, $-OCH_2\underline{CH_3}$), 4.02-4.55 (4H, m, $-O\underline{CH_2}CH_3$), 4.20 (3H, s, $-OCH_3$), 7.15-7.71 (2H, m, Ar-H), 8.10-8.59 (2H, m, Ar-H), 8.24 (1H, s, C_3-H). MS *m/z*; 359 (M^+, 87%), 223 (BP).

1-Cyano-4-methoxy-β-carboline (16b)

A solution of 9-diethoxyphosphoryl-1-cyano-4-methoxy-β-carboline **(16c)** (1.252 g, 3.48 mmol) and KOH (1.17 g, 17.7 mmol) in CH_3CN (60 ml) and H_2O (3 ml) was stirred at room temperature for 14 h. Solvent was evaporated to dryness *in vacuo*, and water was added to the residue. The precipitates were collected by filtration to give the *title compound* **(16b)** (757 mg, 97%) as crystals. Recrystallization from AcOEt gave colorless prisms, mp 279-281 °C. Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 70.03; H, 4.10; N, 18.54. IR $\upsilon_{max}cm^{-1}$: 3140 (NH), 2230 (CN). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 4.24 (3H, s, $-OCH_3$), 7.34 (1H, dif. t, *J*=7.8 Hz, C_6- or C_7-H), 7.62 (1H, dif. t, *J*=7.8 Hz, C_6- or C_7-H), 7.65 (1H, dif. d, *J*=7.8 Hz, C_5- or C_8-H), 8.21 (1H, dif. d, *J*=7.8 Hz, C_5- or C_8-H), 8.32 (1H, s, C_3-H), 12.48 (1H, br s, NH). MS *m/z*; 223 (M^+, BP).

1-Acetyl-9-benzyl-4-methoxy-β-carboline (29)

MeLi (1.5 M solution in hexane) (6.6 ml, 10 mmol) was added to a solution of 9-benzyl-1-cyano-4-methoxy-β-carboline **(16a)** (617 mg, 1.97 mmol) in THF (30 ml) at -50 °C under argon atmosphere. The mixture was stirred at -50 °C for 25 min, poured into saturated aqueous NH_4Cl, and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and

evaporated to dryness *in vacuo*. The residue (imine intermediate) was dissolved in a mixture of conc. HCl (10 ml) and MeOH (15 ml), and heated under reflux for 5 min. The cold mixture was poured into saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using hexane-AcOEt (4:1) to give the *title compound* (**29**) (534 mg, 82%) as crystals. Recrystallization from AcOEt-hexane gave colorless needles, mp 161.5-162.5 °C. Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.44; H, 5.48; N, 8.41. IR (KBr) $\upsilon_{max}cm^{-1}$: 1678 (CO). ^{1}H-NMR δ: 2.49 (3H, s, -$COCH_3$), 4.16 (3H, s, -OCH_3), 5.79 (2H, s, -CH_2-Ph), 6.60-7.70 (8H, Ar-H), 8.00 (1H, s, C_3-H), 8.33 (1H, dif. d, *J*=7 Hz, C_5-H). MS *m/z*; 330 (M^+, 19%), 149 (BP).

1-Acetyl-4-methoxy-β-carboline (1b)

i) From 1-acetyl-9-benzyl-4-methoxy-β-carboline (29)

A solution of **29** (661 mg, 2.0 mmol) in benzene (80 ml) was added to a suspension of $AlCl_3$ (1.60 g, 12 mmol) in benzene (120 ml) at 0 °C under argon atmosphere, and then stirred at room temperature for 2 h. The mixture was poured into ice-water, neutralized with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using hexane-AcOEt (2:1) to give the *title compound* (**1b**) (407 mg, 85%) as crystals. Recrystallization from AcOEt-hexane gave colorless prisms, mp 212.5-214 °C [lit.,[3b] 204-205 °C (benzene)]. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.04; H, 5.03; N, 11.64. IR (KBr) $\upsilon_{max}cm^{-1}$: 3330 (NH), 1658 (CO). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 2.74 (3H, s, -$COCH_3$), 4.25 (3H, s, -OCH_3), 7.29 (1H, dif. t, *J*=7.8 Hz, C_6- or C_7-H), 7.55 (1H, dif. t, *J*=7.8 Hz, C_6- or C_7-H), 7.81 (1H, dif. d, *J*=7.8 Hz, C_5- or C_8-H), 8.20 (1H, dif. d, *J*=7.8 Hz, C_5- or C_8-H), 8.28 (1H, s, C_3-H), 11.86 (1H, br s, NH). MS *m/z*; 240 (M^+, BP). The synthetic **1b** was identical with the natural product[3b] in all respects.

ii) From 1-cyano-4-methoxy-β-carboline (16b)

The substrate (**16b**) (22.3 mg, 0.10 mmol) was treated with MeLi (1.5 M solution in hexane) (0.40 ml, 0.60 mmol) in THF (2 ml) at -50 °C for 30 min by the same method used for preparing **29**. The imine intermediate (0.03 g) was adsorbed on SiO_2 (3 g) and allowed to stand for a week to hydrolyze. The SiO_2 was extracted with AcOEt-MeOH, and the organic layer was evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using hexane-AcOEt (2:1) to give the *title compound* (**1b**) (19.1 mg, 80%).

4-Methoxy-1-methoxycarbonyl-β-carboline (1c)

i) From 1-cyano-4-methoxy-β-carboline (16b)

A solution of **16b** (30 mg, 0.13 mmol) in MeOH (10 ml, saturated with dry. HCl gas) and CH_2Cl_2 (6 ml) was stirred at room temperature for 24 h, and then heated under reflux for 10 h. Solvent was evaporated *in vacuo*. Saturated aqueous $NaHCO_3$ was added to the residue, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to column-chromatography using CH_2Cl_2-MeOH (50:1) to give the *title compound* (**1c**) (31mg, 90%) as crystals. Recrystallization from AcOEt gave colorless prisms, mp 196-197 °C [lit.,[3a] 191-192 °C (benzene)]. Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.60; H, 4.78; N, 10.98. IR (KBr) $\upsilon_{max}cm^{-1}$: 3340 (NH), 1670 (CO). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 3.99 (3H, s, -$COOCH_3$), 4.24 (3H, s, -OCH_3), 7.30 (1H, dif. t, *J*=7.8 Hz, C_6- or C_7-H), 7.57 (1H, dif. t, *J*=7.8 Hz, C_6- or C_7-H), 7.79 (1H, dif. d, *J*=7.8 Hz, C_5- or C_8-H), 8.21 (1H, dif. d, *J*=7.8 Hz, C_5- or C_8-H), 8.27 (1H, s, C_3-H), 11.62 (1H, br s, NH). MS *m/z*; 256 (M^+, BP). The synthetic **1c** was identical with the natural product[3a, n] in all respects.

ii) From 9-diethoxyphosphoryl-1-cyano-4-methoxy-β-carboline (16c)

The substrate (**16c**) (35 mg, 0.1 mmol) was treated in MeOH (2 ml) saturated with dry. HCl gas at room temperature for 24 h, and then heated under reflux for 22 h by the same method used for preparing **16b** to give the product (**1c**) (21.5 mg, 86%).

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References and Notes

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19. These compounds showed a mixture of two kinds of the amide conformers in the NMR, IR spectrum and TLC analysis, and sample (**20a**) showed two kinds of melting points due to dimorphism : see experimental section.

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