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FIRST TOTAL SYNTHESES OF 1,3-DISUBSTITUTED β-CARBOLINE ALKALOIDS, DICHOTOMIDE I AND MARINACARBOLINES A-D

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Abstract – The first total syntheses of dichotomide I (**1**), and marinacarbolines A-D (**3**-**6**) were achieved in four steps from methyl 1-chloro-β-carboline-3-carboxlyate (**9**), which was previously used as a synthetic intermediate of dichotomine C. The required compound **9** was prepared in a six-step sequence including a microwave-assisted thermal electrocyclic reaction of a 1-azahexatriene system.

INTRODUCTION

1,3-Disubstituted β-carboline alkaloids dichotomide I (**1**), II (**2**) and dichotomines A-D were isolated from *Stellaria dichotoma* by Yoshikawa and co-workers in 2004 (Figure 1).[1] Dichotomines A-D (**3**-**6**) have antiallergic effects by inhibiting the release of β-hexosaminidase in RBL-2H3 cells. Whether dichotomides I (**1**) and II (**2**) have similar biological activities, however, is unclear.[1] We previously reported the first total synthesis of dichotomine C by construction of a β-carboline framework based on a microwave-assisted thermal electrocyclic reaction of a 1-azahexatriene system involving the indole 2,3-bond, followed by enantioselective 1,2-dihydroxylation.[2] Nemet and co-workers reported the synthesis of racemic dichotomine A from L-tryptophan with methylglyoxal under acidic conditions.[3] Shi and co-workers recently reported the asymmetric syntheses of dichotomines A-D were achieved by using L-tryptophan methyl ester and 2,3-*O*-isopropylidene-D-glyceraldehyde.[4]

Closely related β-carboline alkaloids, marinacarbolines A-D (**3**-**6**) were recently isolated from the fermentation broth of the actinomycete *Marinactinospora thermotolerans* SCSIO 00652, belonging to the family *Nocardiopasaceae*, that was newly discovered by Ju and co-workers in 2011 (Figure 1).[5] The compounds were elucidated by NMR spectral analyses and other spectroscopic experiments. These

1,3-disubstituted β-carboline alkaloids, having an acetyl group at the C-1 position and a carbamoyl group at the C-3 position, exhibit antiplasmodial activities against *Plasmodium falciparum* lines 3D7 and Dd2. Synthetic studies of these compounds have not yet been reported.

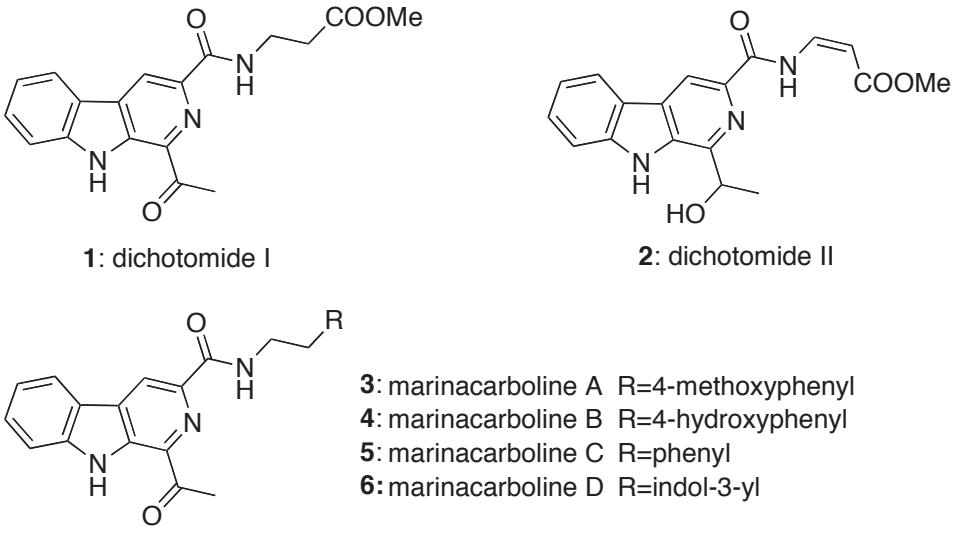
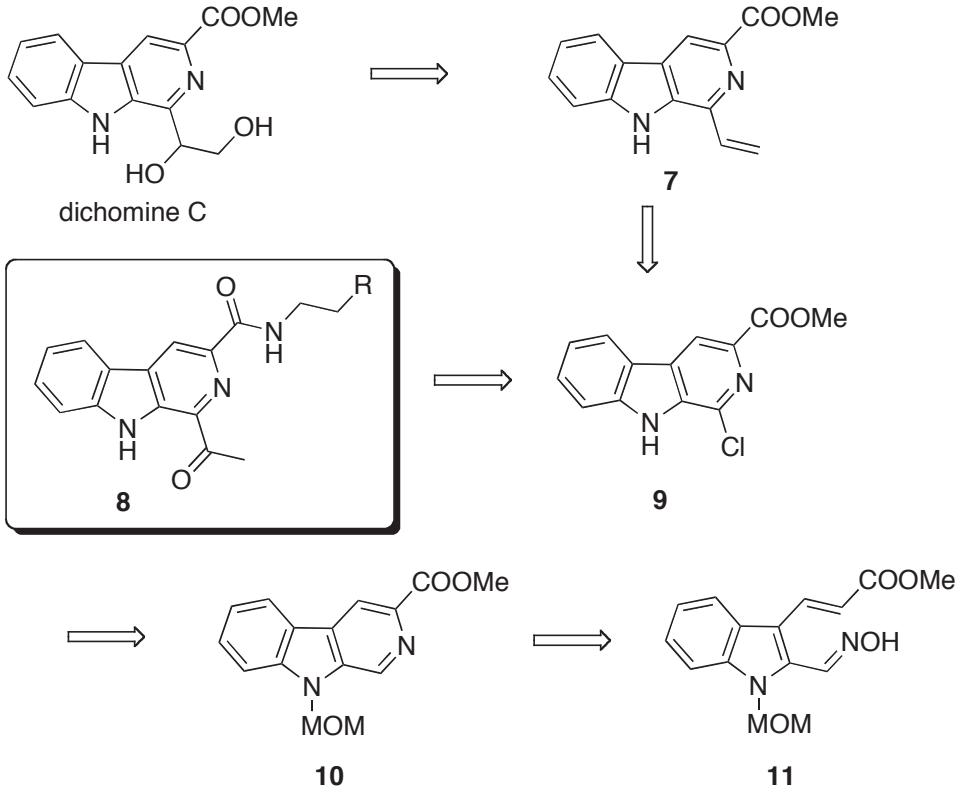


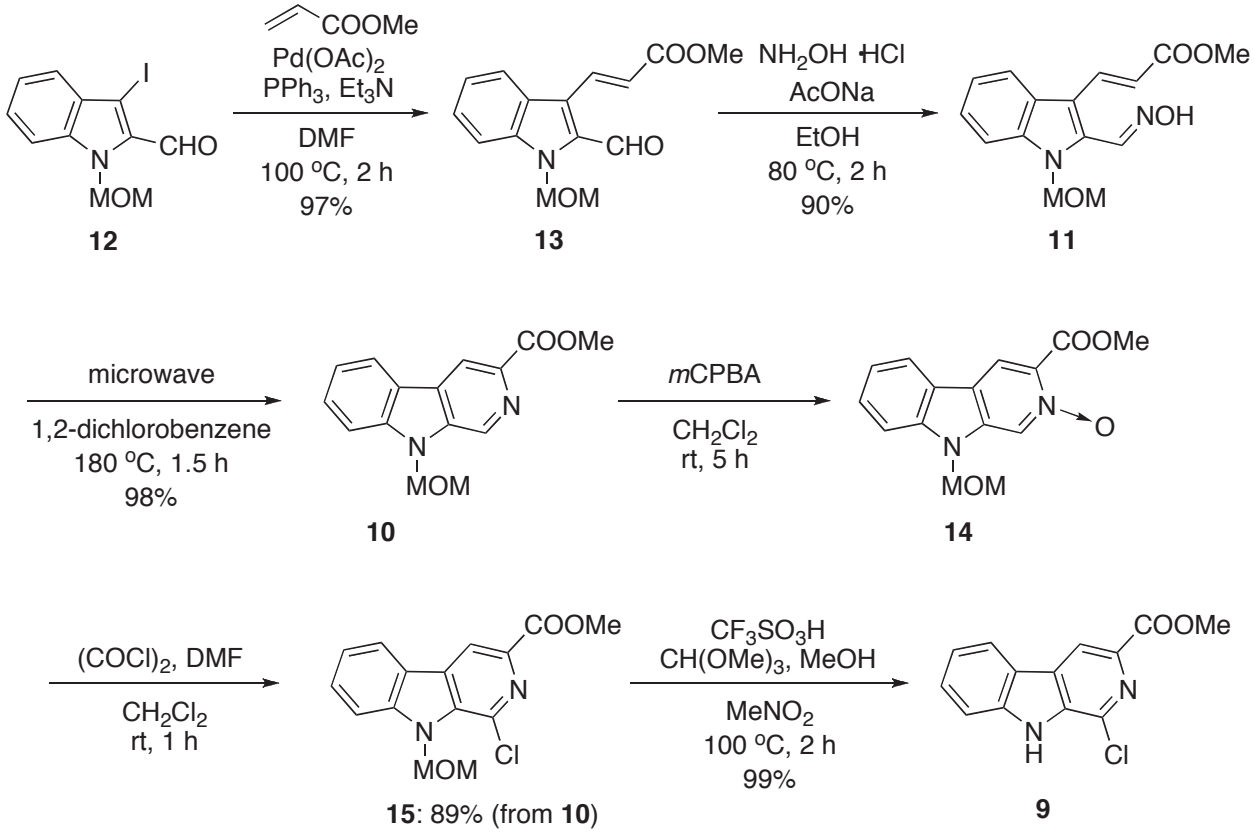
Figure 1



Scheme 1

We have focused our efforts on developing the synthesis of bioactive nitrogen containing fused-heteroaromatic compounds including natural products based on a thermal electrocyclic reaction of

either a 6π- or an aza 6π-electron system involving an aromatic or heteroaromatic double bond in principle.[6] Recently, we reported the total synthesis of furoisoquinoline,[7] phenanthridine,[8] azaanthraquinone,[9] benzo[*c*]phenanthridine,[10] and indoloquinoline alkaloids[11] based on a microwave (MW)-assisted electrocyclic reaction of the aza 6π-electron system. Herein, we describe the details of the first total syntheses of dichotomide I (**1**) and marinacarbolines A-D (**3**-**6**). In the retrosynthetic analysis shown in Scheme 1, we planned to derive β-carboline alkaloids **8** from methyl 1-chloro-β-carboline-3-carboxylate (**9**) for use in the asymmetric synthesis of dichotomine C.[2]



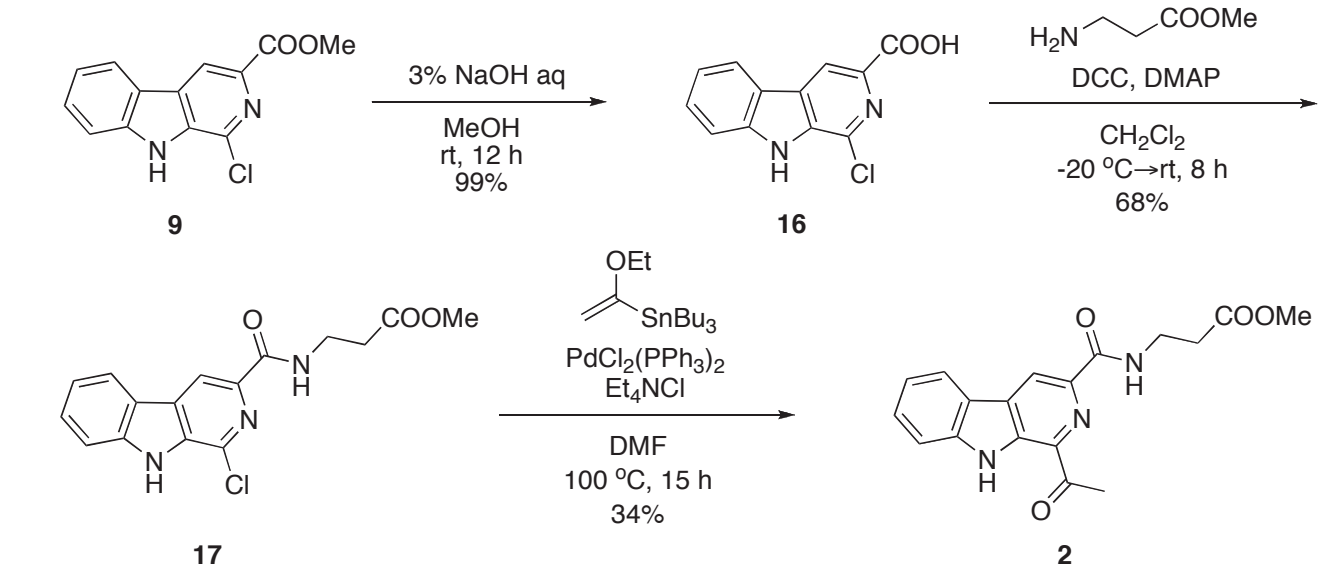
Scheme 2

RESULTS AND DISCUSSION

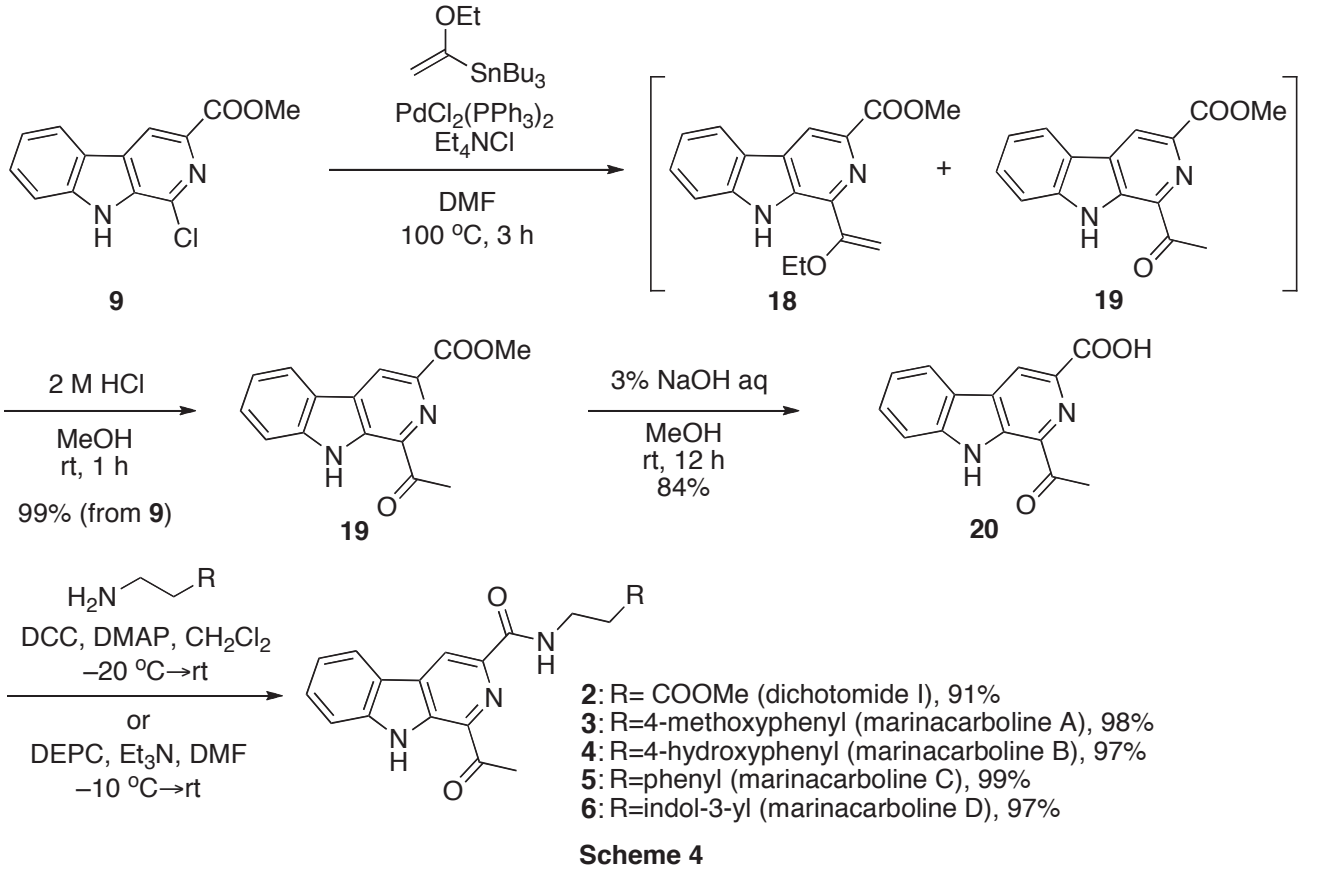
The required β-carboline **9** was prepared in a six-step sequence starting from *N*-MOM-3-iodoindole-2-carbaldehyde **12**[12] (Scheme 2). The Heck reaction between **12** and methyl acrylate in the presence of $Pd(OAc)_2$ gave the 3-alkenylindole **13** (97%). Subsequent treatment of **13** with hydroxylamine produced the oxime **11** (90%), which was subjected to the microwave-assisted thermal electrocylic reaction in 1,2-dichlorobenzene to yield the β-carboline **10** (98%). Oxidation of **10** with *m*-chloroperbenzoic acid (*m*CPBA) followed by treatment with oxalyl chloride[13] and DMF in CH_2Cl_2 yielded the 1-chloro-β-carboline **15** (89% from **10**), which was heated with trifluoromethanesulfonic acid, trimethyl orthoformate, and MeOH in nitromethane to produce the desired methyl 1-chloro-β-carboline-3-carboxylate (**9**) (99%).[14] The yield of **9** from **12** significantly increased to 75%

from the previously reported 45%.[2]

As shown in Scheme 3, we initially attempted the synthesis of dichotomide I (**1**). Hydrolysis of the β-carboline **9** with aqueous 3% NaOH in MeOH afforded the β-carboline-3-carboxylic acid **16** in excellent yield (99%). The carboxylic acid **16** was treated with β-alanine methyl ester in the presence of DCC and DMAP to give the amide **17** (68%). Subsequently, the Stille reaction of the amide **17** and 1-ethoxyvinyltin in the presence of $PdCl_2(PPh_3)_2$ provided dichotomide I (**1**) in low yield (34%) without the isolation of 1-(1-ethoxyvinyl)-β-carboline.



Scheme 3



Scheme 4

Therefore, we next introduced the acetyl group at the C-1 position of β-carboline at first (Scheme 4). The Stille reaction of the β-carboline **9** and 1-ethoxyvinyltin in the presence of a Pd-catalyst, followed by treatment with 2 M HCl in MeOH afforded the 1-acetyl-β-carboline **19** (99% from **9**). Hydrolysis of 1-acetyl-β-carboline **19** with aqueous 3% NaOH in MeOH afforded the carboxylic acid **20** in 84% yield. Subsequent treatment of **20** with β-alanine methyl ester in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave dichotomide I (**1**) in excellent yield (91%). In the case of marinacarbolines, the carboxylic acid **20** was treated with amines (three type of phenylethylamines and tryptamine) in the presence of diethylphosphorylcyanide (DEPC) and triethylamine to provide marinacarbolines A (**3**) (98%), B (**4**) (97%), C (**5**) (99%), and D (**6**) (97%). Physical and spectroscopic data of our synthetic dichotomide I (**1**) and marinacarbolines A-D (**3**-**6**) were identical with those of previously reported data.[1,5]

CONCLUSION

In conclusion, the first total syntheses of dichotomide I (**1**) and marinacarbolines A-D (**3**-**6**), having an acetyl group at the C-1 position and a carbamoyl group at the C-3 position of the β-carboline nucleus, were achieved from methyl 1-chloro-β-carboline-3-carboxylate (**9**) in four steps. Dichotomide I (**1**) and marinacarbolines A-D (**3**-**6**) were obtained in an overall yield of 57%, 61%, 61%, 62%, and 61%, respectively. Further studies in this series are now in progress.

EXPERIMENTAL

All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel $60PF_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60N (63-210 μm, KANTO CHEMICAL Co. Ltd.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). NMR spectra was measured with $CDCl_3$ unless otherwise noted. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.7). Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and technologies DuraScop. Low and high resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system.

Methyl 3-(*N*-methoxymethyl-2-formylindol-3-yl)acrylate (13)

A mixture of the 3-iodoindole **12**[12] (6.6 g, 20.9 mmol), methyl acrylate (3.78 mL, 41.9 mmol), Et_3N (5.78 mL, 41.9 mmol), PPh_3 (164 mg, 0.63 mmol), and $Pd(OAc)_2$ (13.5 mg, 0.42 mmol) in DMF (100 mL) was heated at 100 ºC for 2 h under an argon atmosphere. After being cooled to rt, the reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 40 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the acrylate **13** (5.6 g, 97%), mp 104-106 ºC (EtOAc). IR (ATR) ν: 1710, 1644 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 3.32 (3H, s), 3.86 (3H, s), 6.01 (2H, s), 6.69 (1H, d, *J*=16.0 Hz), 7.35 (1H, t, *J*=8.1 Hz), 7.52 (1H, t, *J*=8.1 Hz), 7.62 (1H, d, *J*=8.1 Hz), 8.01 (1H, d, *J*=8.1 Hz), 8.32 (1H, d, *J*=16.0 Hz), 10.38 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 51.9, 56.1, 74.9, 111.9, 121.3, 122.5, 123.3, 124.3, 124.8, 128.1, 132.5, 134.0, 139.9, 167.2, 181.4. MS (EI) *m/z*: 273 (M^+); HRMS (EI) Calcd for $C_{15}H_{15}NO_4$: 273.1001. Found: 273.1016.

Methyl 3-(*N*-methoxymethyl-2-hydroxyiminoindol-3-yl)acrylate (11)

A mixture of the acrylate **13** (3.7 g, 13.5 mmol), $NH_2OH \cdot HCl$ (1.88 g, 27.1 mmol), and AcONa (2.27 g, 27.1 mmol) in EtOH (100 mL) was heated at 80 ºC for 2 h. After removal of solvent followed by addition of water, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 40 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the oxime **11** (3.5 g, 90%), mp 182-184 ºC (EtOAc). IR (ATR) ν: 3349, 1681 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 3.30 (3H, s), 3.84 (3H, s), 5.82 (2H, s), 6.60 (1H, d, *J*=15.8 Hz), 7.30 (1H, d, *J*=8.1 Hz), 7.39 (1H, t, *J*=8.1 Hz), 7.54 (1H, d, *J*=8.1 Hz), 7.95 (1H, d, *J*=8.1 Hz), 8.13 (1H, d, *J*=15.8 Hz), 8.16 (1H, br s), 8.61 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 51.7, 56.1, 75.2, 110.9, 116.1, 117.0, 121.2, 122.5, 125.3, 125.6, 132.0, 136.2, 139.3, 141.8, 168.2. MS (EI) *m/z*: 288 (M^+); HRMS (EI) Calcd for $C_{15}H_{16}N_2O_4$: 288.1110. Found: 288.1117.

Methyl *N*-(methoxymethyl)pyrido[3,4-*b*]indole-3-carboxylate (10)

A solution of the oxime **11** (100 mg, 0.35 mmol) in 1,2-dichlorobenzene (8 mL) was stirred at 180 ºC for 1.5 h under N_2 atmosphere under microwave irradiation. After removal of solvent, the residue was purified by column chromatography (silica gel) using EtOAc-hexane (3:7 v/v) as an eluent to give the β-carboline **10** (92 mg, 98%), mp 148-149 ºC (EtOAc). IR (ATR) ν: 1704 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 3.33 (3H, s), 4.08 (3H, s), 5.81 (2H, s), 7.38-7.46 (1H, m), 7.66-7.69 (2H, m), 8.22 (1H, d, *J*=7.7 Hz), 8.91 (1H, s), 9.08 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 52.8, 56.6, 74.6, 110.5, 117.8, 121.7, 121.8, 122.1, 129.3, 129.4, 132.2, 138.2, 138.6, 141.7, 166.6. MS (EI) *m/z*: 270 (M^+); HRMS (EI) Calcd for $C_{15}H_{14}N_2O_3$: 270.1004. Found: 270.0994.

Methyl 1-chloro-*N*-(methoxymethyl)pyrido[3,4-*b*]indole-3-carboxylate (15)

*m*CPBA (1.92 g, 11.1 mmol) was added to a solution of the β-carboline **10** (1.0 g, 3.70 mmol) in CH_2Cl_2 (100 mL) under cooling with ice under N_2 atmosphere. After being stirred at rt for 5 h, the reaction mixture was quenched with water, and then the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with aqueous $NaHCO_3$ (saturated) solution, water and brine, dried over Na_2SO_4, and concentrated in vacuo to give the *N*-oxide **14**. The *N*-oxide **14** was used without further purification. Oxalyl chloride (0.97 mL, 11.1 mmol) was added dropwise to a solution of the *N*-oxide **14** in CH_2Cl_2 (100 mL) under cooling with ice, followed by slow addition of DMF (2 mL, 25.9 mmol). After being stirred at rt for 1 h, the reaction mixture was quenched with water, and then the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 40 g) using EtOAc (1:4 v/v) as an eluent to give the *N*-MOM-1-chloro-β-carboline **15** (1.0 g, 89%), mp 154-155 ºC (EtOAc). IR (ATR) ν: 1714 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 3.38 (3H, s), 4.06 (3H, s), 6.19 (2H, s), 7.40-7.48 (1H, m), 7.66-7.74 (2H, m), 8.18 (1H, d, *J*=7.0 Hz), 8.84 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 52.9, 55.9, 74.3, 111.3, 117.0, 121.5, 121.7, 122.3, 129.8, 129.8, 132.7, 134.0, 137.7, 142.5, 165.3. MS (EI) *m/z*: 304 (M^+), 306 (M^++2); HRMS (EI) Calcd for $C_{15}H_{13}ClN_2O_3$: 304.0615. Found: 304.0625.

Methyl 1-chloropyrido[3,4-*b*]indole-3-carboxylate (9)

CF_3SO_3H (5.4 mL, 0.06 mmol) was added to a solution of the *N*-MOM-1-chloro-β-carboline **15** (3.7 g, 12.1 mmol), MeOH (19 mL, 150 mmol) and $CH(OMe)_3$ (15.9 mL, 150 mmol) in $MeNO_2$ (100 mL) under cooling with ice, and then the mixture was heated at 100 ºC for 2 h. After cooling to rt, the reaction mixture was quenched with aqueous Na_2CO_3 (saturated) solution, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 40 g) using EtOAc-hexane (3:7 v/v) as an eluent to give the 1-chloro-β-carboline **9** (3.2 g, 99%), mp 238-240 ºC (EtOAc). IR (ATR) ν: 1724 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 4.06 (3H, s), 7.37-7.45 (1H, m), 7.60-7.72 (2H, m), 8.19 (1H, d, *J*=8.1 Hz), 8.69 (1H, br s), 8.85 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 52.90, 112.2, 117.5, 121.8, 121.8, 122.3, 129.7, 130.5, 133.4, 134.5, 137.6, 140.2, 165.6. MS (EI) *m/z*: 260 (M^+), 262 (M^++2); HRMS (EI) Calcd for $C_{13}H_9ClN_2O_2$: 260.0353. Found: 260.0339.

1-Chloropyrido[3,4-*b*]indole-3-carboxylic acid (16)

A mixture of methyl ester **9** (89 mg, 0.34 mmol) and 3% NaOH (10 mL) in MeOH (10 mL) was stirred at rt for 12 h. The mixture was adjusted with AcOH to pH 5, and then the resulting mixture was extracted with $CHCl_3$-MeOH (9:1). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the carboxylic acid **16** (84 mg, 99%), mp 226-228 ºC (EtOAc). IR (ATR) ν: 3120, 1689 cm^{-1}. ^1H NMR (300 MHz DMSO-d_6) δ: 7.37 (1H, t, *J*=7.9 Hz), 7.66 (1H, t, *J*=7.9 Hz), 7.70 (1H, d, *J*=7.9 Hz), 8.42 (1H, d, *J*=7.9 Hz), 8.94 (1H, s), 12.41 (1H, s). ^{13}C NMR (75 MHz DMSO-d_6) δ: 112.8, 117.5,

120.9, 121.4, 122.5, 129.3, 129.9, 132.4, 134.2, 137.0, 141.1, 165.8. MS (EI) *m/z*: 246 (M^+), 248 (M^++2); HRMS (EI) Calcd for $C_{12}H_7ClN_2O_2$: 246.0196. Found: 246.0213.

Methyl 3-[(1-chloropyrido[3,4-*b*]indole-3-carbonyl)animo]propanoate (17)

A solution of DCC (94 mg, 0.46 mmol), and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (20 mL) was added to a solution of carboxylic acid **20** (100 mg, 0.41 mmol) and methyl β-alanine (71 mg, 0.51 mmol) in CH_2Cl_2 (20 mL) at -20 ºC, and then the mixture was stirred at the same temperature for 30 min. After being gradually raised up to rt, the reaction mixture was stirred at rt for 8 h. The mixture was filtered off through Celite pad and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (1:4 v/v) as an eluent to give the amide **17** (92 mg, 68%), mp 154-155 ºC (EtOAc). IR (ATR) ν: 1724 cm^{-1}. ^1H NMR (300 MHz DMSO-d_6) δ: 2.65 (2H, t, *J*=6.6 Hz), 3.59 (2H, q, *J*=6.2 Hz), 3.61 (3H, s), 7.33 (1H, t, *J*=7.8 Hz), 7.68 (1H, d, *J*=7.8 Hz), 8.40 (1H, d, *J*=7.8 Hz), 8.63 (1H, t, *J*=6.0 Hz), 8.84 (1H, s), 12.33 (1H, br s). ^{13}C NMR (75 MHz DMSO-d_6) δ: 33.7, 35.1, 51.4, 112.7, 114.2, 120.8, 121.4, 122.6, 129.3, 130.4, 131.4, 133.9, 139.4, 141.2, 163.6, 172.0. MS (EI) *m/z*: 331 (M^+), 333 (M^++2); HRMS (EI) Calcd for $C_{16}H_{14}ClN_3O_3$: 331.0724. Found: 331.0724.

Dichotomide I (1)

A solution of tributyl(1-ethoxyvinyl)tin (0.19 mL, 0.55 mmol) was added to a mixture of the amide **17** (92 mg, 0.28 mmol), $PdCl_2(PPh_3)_2$ (3 mg, 4.7 mmol), and Et_4NCl (50 mg, 0.31 mmol) in DMF (10 mL) at rt under an argon atmosphere. The stirred mixture was heated at 100 ºC for 2 h, which was cooled to rt. After being quenched with an aqueous solution of 30% KF (10 mL), and then the mixture was stirred at rt for 30 min. The mixture was filtered off through Celite pad and the filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc-hexane (3:7 v/v) as an eluent to give dichotomide I (**1**) (32 mg, 34%), mp 199-201 ºC (EtOAc). IR (ATR) ν: 3376, 1727 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.74 (2H, t, *J*=7.0 Hz), 2.94 (3H, s), 3.75 (3H, s), 3.86 (2H, q, *J*=7.0 Hz), 7.38-7.42 (1H, m), 7.61-7.64 (2H, m), 8.23 (1H, d, *J*=8.0 Hz), 8.63 (1H, br s), 9.10 (1H, s), 10.41 (1H, br s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.6, 34.2, 34.9, 51.9, 112.2, 118.4, 121.1, 121.6, 122.3, 129.8, 132.7, 133.7, 136.4, 139.2, 141.6, 164.7, 173.0, 202.4. MS (EI) *m/z*: 339 (M^+); HRMS (EI) Calcd for $C_{18}H_{17}N_3O_4$: 339.1219. Found: 339.1216.

Methyl 1-acetylpyrido[3,4-*b*]indole-3-carboxylate (19)

A solution of tributyl(1-ethoxyvinyl)tin (0.16 mL, 0.48 mmol) was added to a mixture of the 1-chloro-β-carboline **9** (100 mg, 0.38 mmol), $PdCl_2(PPh_3)_2$ (4 mg, 6.3 mmol), and Et_4NCl (70 mg, 0.42 mmol) in DMF (5 mL) at rt under an argon atmosphere. The stirred mixture was heated at 100 ºC for 3 h, which was cooled to rt. After being quenched with aqueous solution of 30% KF (10 mL), and then the mixture was stirred at rt for 2 h. The mixture was filtered off through Celite pad and the filtrate was

extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. 2 M HCl (2 mL) and MeOH (4 mL) was added to the residue without purification, and then the resulting mixture was stirred at rt for 1 h. The mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, g) using EtOAc-hexane (1:9 v/v) as an eluent to give the 1-acetyl-β-carboline **19** (102 mg, 99%), mp 226-227 ºC (EtOAc) (lit.,[15] mp 234-236 ºC). IR (ATR) ν: 1708, 1670 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.97 (3H, s), 4.09 (3H, s), 7.37-7.43 (1H, m), 7.64-7.66 (2H, m), 8.22 (1H, *J*=8.0 Hz), 9.04 (1H, s), 10.49 (1H, br s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.7, 52.8, 112.4, 121.0, 121.3, 121.7, 122.1, 129.8, 131.9, 135.3, 136.5, 136.9, 141.4, 166.1, 203.2. MS (EI) *m/z*: 268 (M^+); HRMS (EI) Calcd for $C_{15}H_{12}N_2O_3$: 268.0848. Found: 268.0877.

1-Acetylpyrido[3,4-*b*]indole-3-carboxylic acid (20)

A mixture of 1-acetyl-β-carboline **19** (100 mg, 0.37 mmol) and 3% NaOH (12 mL) in MeOH (12 mL) was heated at rt for 12 h. The mixture was adjusted with AcOH to pH 5, and then the resulting mixture was extracted with $CHCl_3$-MeOH (9:1). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the carboxylic acid **20** (84 mg, 84%), mp 265-266 ºC (EtOAc). IR (ATR) ν: 3325, 1701, 1670 cm^{-1}. ^1H NMR (300 MHz DMSO-d_6) δ: 2.91 (3H, s), 7.40 (1H, t, *J*=8.0 Hz), 7.68 (1H, t, *J*=8.0 Hz), 7.90 (1H, d, *J*=8.0 Hz), 8.49 (1H, d, *J*=8.0 Hz), 9.20 (1H, s), 12.3 (1H, s). ^{13}C NMR (75 MHz DMSO-d_6) δ: 25.8, 113.4, 120.2, 121.0, 121.0, 122.2, 129.3, 131.5, 135.0, 135.1, 136.3, 142.3, 166.3, 201.1. MS (EI) *m/z*: 254 (M^+); HRMS (EI) Calcd for $C_{14}H_{10}N_2O_3$: 254.0691. Found: 254.0720.

Dichotomide I (1)

A solution of DCC (47 mg, 0.22 mmol), and DMAP (2 mg, 0.015 mmol) in CH_2Cl_2 (10 mL) was added to a solution of carboxylic acid **20** (50 mg, 0.20 mmol) and methyl β-alanine (36 mg, 0.25 mmol) at -20 ºC, and then the mixture was stirred at same temperature for 30 min. After being gradually raised up to rt, the reaction mixture was stirred at rt for 8 h. The mixture was filtered off through Celite pad and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (1:3 v/v) as an eluent to give dichotomide I (**1**) (61 mg, 91%).

Marinacarboline A (3)

DEPC (14 mL, 0.088 mmol) and Et_3N (23 mL, 0.16 mmol) were added to a solution of carboxylic acid **20** (20 mg, 0.08 mmol) and 2-(4-methoxyphenyl)ethylamine (15 mg, 0.10 mmol) in DMF (5 mL) at -10 ºC, and then the mixture was stirred at the same temperature for 30 min. After being gradually raised up to rt, the mixture was stirred at rt for 12 h. The reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc-hexane (1:3 v/v) as an eluent to give the marinacarboline A (**3**) (30 mg, 98%), mp 177-178 ºC (EtOAc). IR (ATR) ν:

3232, 1695, 1654 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.78 (3H, s), 2.96 (2H, t, *J*=7.0 Hz), 3.81 (3H, s), 3.82 (2H, q, *J*=7.0 Hz), 6.90 (2H, d, *J*=8.5 Hz), 7.23-7.26 (2H, m), 7.37-7.42 (1H, m), 7.58-7.64 (2H, m), 8.06 (1H, br s), 8.23 (1H, d, *J*=8.0 Hz), 9.10 (1H, s), 10.37 (1H, br s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.7, 35.0, 40.7, 55.3, 112.2, 114.2(x2), 118.4, 121.1, 121.6, 122.3, 129.7, 129.9(x2), 131.0, 132.7, 133.5, 136.3, 139.3, 141.5, 158.4, 164.5, 202.3. MS (EI) *m/z*: 387 (M^+); HRMS (EI) Calcd for $C_{23}H_{21}N_3O_3$: 387.1583. Found: 387.1594.

Marinacarboline B (4)

The same procedure as above was carried out using the carboxylic acid **20** (30 mg, 0.12 mmol) and 2-(4hydroxyphenyl)ethylamine (20 mg, 0.15 mmol) to give the marinacarboline B (**4**) (43 mg, 97%), mp 271-273 ºC (EtOAc). IR (ATR) ν: 3332, 1693, 1643 cm^{-1}. ^1H NMR (300 MHz DMSO-d_6) δ: 2.82 (2H, t, *J*=7.0 Hz), 2.87 (3H, s), 3.59 (2H, q, *J*=7.0 Hz), 6.72 (2H, d, *J*=8.0 Hz), 7.12 (2H, d, *J*=8.0 Hz), 7.34 (1H, t, *J*=8.0 Hz), 7.63 (1H, t, *J*=8.0 Hz), 7.84 (1H, d, *J*=8.0 Hz), 8.45 (1H, d, *J*=8.0 Hz), 8.68 (1H, t, *J*=6.0 Hz), 9.06 (1H, s), 9.23 (1H, br s), 12.16 (1H, br s). ^{13}C NMR (75 MHz DMSO-d_6) δ: 26.0, 34.5, 40.8, 113.3, 115.3(x2), 117.8, 120.3, 120.8, 122.3, 129.3, 129.5, 129.6, 132.0, 1339.9, 134.8, 138.7, 142.4, 155.7, 164.0, 201.0. MS (EI) *m/z*: 373 (M^+); HRMS (EI) Calcd for $C_{22}H_{19}N_3O_3$: 373.1426. Found: 373.1433.

Marinacarboline C (5)

The same procedure as above was carried out using the carboxylic acid **20** (20 mg, 0.08 mmol) and phenylethylamine (13 mL, 0.088 mmol) to give the marinacarboline C (**5**) (28 mg, 99%), mp 195-196 ºC (EtOAc). IR (ATR) ν: 3239, 1695, 1658 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.76 (3H, s), 3.02 (2H, t, *J*=7.0 Hz), 3.86 (2H, q, *J*=7.0 Hz), 7.34-7.42 (6H, m), 7.59-7.67 (2H, m), 8.08 (1H, br s), 8.23 (1H, d, *J*=8.0 Hz), 9.10 (1H, s), 10.38 (1H, br s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.7, 35.9, 40.5, 112.2, 118.4, 121.1, 121.6, 122.3, 126.6, 128.8(x2), 129.0(x2), 129.7, 132.6, 133.5, 136.3, 139.1, 139.3, 141.5, 164.5, 202.3. MS (EI) *m/z*: 357 (M^+); HRMS (EI) Calcd for $C_{22}H_{19}N_3O_2$: 357.1477. Found: 357.1455.

Marinacarboline D (6)

The same procedure as above was carried out using the carboxylic acid **20** (20 mg, 0.08 mmol) and the tryptamine (14 mg, 0.088 mmol) to give the marinacarboline D (**6**) (30 mg, 97%), mp 244-245 ºC (EtOAc). IR (ATR) ν: 3421, 3343, 1670, 1650 cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ: 2.63 (3H, s), 3.19 (2H, t, *J*=7.0 Hz), 3.94 (2H, q, *J*=7.0 Hz), 7.12 (1H, t, *J*=8.0 Hz), 7.18 (1H, d, *J*=2.5 Hz), 7.22 (1H, t, *J*=8.0 Hz), 7.36-7.42 (2H, m), 7.58-7.63 (2H, m), 7.68 (1H, d, *J*=8.0 Hz), 8.08 (1h, br s), 8.15 (1H, t, *J*=6.0 Hz), 8.23 (1H, d, *J*=8.0 Hz), 9.11 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ: 25.5(x2), 39.8, 111.2, 112.2(x2), 113.4, 118.4, 118.9, 119.6, 121.1, 121.5, 122.1, 122.3(x2), 127.5, 129.7, 132.6, 136.3, 136.5, 139.4, 141.5, 164.6, 202.3. MS (EI) *m/z*: 396 (M^+); HRMS (EI) Calcd for $C_{24}H_{20}N_4O_2$: 396.1586. Found: 396.1565.

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