Total Syntheses of Novel Cytocidal β-Carboline Alkaloids, Oxopropalines D and G

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A new type of β-carboline nucleus, *N*-methoxymethyl-4-methyl-β-carboline (4) was synthesized by thermal electrocyclic reaction of a 1-azahexatriene system, involving the indole 2,3-bond. The key compound *N*-methoxymethyl-1-methoxycarbonyl-4-methyl-β-carboline (2) was then prepared in a four-step sequence. The total synthesis of oxopropaline G (1e) was achieved from this key compound in four steps. Furthermore, the enantioselective total syntheses of (+)-oxopropaline D (1c) and its enantiomer were also achieved by application of the Sharpless oxidation-procedure in nine steps from 2.

Key words oxopropaline G; oxopropaline D; total synthesis; 4-methyl-β-carboline; electrocyclic reaction; 1-azahexatriene system

The novel cytocidal β-carboline alkaloids, oxopropalines (**1**) were isolated from *Streptomyces* sp. G324,[1)] which produces lavendamycin,[2)] by Abe and co-workers in 1993. These compounds are structurally composed of five distinct constituents, A (**1a**), B (**1b**), D (**1c**), E (**1d**) and G (**1e**), and were elucidated by NMR spectral analyses and other spectroscopic experiments.[1b)] These new β-carboline alkaloids, possessing an acyl group and a methyl group at the 1- and 4-positions, respectively, exhibit cytocidal activity.[1)]

We are currently interested in the synthetic development of biologically active condensed-heteroaromatic compounds, including natural products, by thermal electrocyclic reactions of conjugated hexatriene[3,4)] and monoazahexatriene[5)] systems incorporating one double bond from an aromatic or heteroaromatic portion. Recently, we reported a preliminary communication of the first total synthesis of oxopropaline G (**1e**).[6)] We describe herein the full details of the total synthesis of oxopropaline G (**1e**), and the first enantioselective total syntheses of oxopropaline D (**1c**) and its enantiomer. The present methodology is based on the thermal electrocyclic reaction of the 1-azahexatriene system (**5**), involving the indole 2,3-bond to prepare a new 4-methyl-β-carboline framework (**4**). 1-Methoxycarbonyl-4-methyl-β-carboline (**2**) derived from **4** was chosen as a common key compound for the total syntheses of oxopropalines G (**1e**) and D (**1c**), as depicted in Chart 1.

The required β-carboline (**4**) was prepared in a four-step sequence starting from 2-formyl-3-iodoindole (**6**)[4c)] as follows (Chart 2). The cross-coupling reaction between **6** and isopropenyl tributyltin[5b)] in the presence of $PdCl_2(PPh_3)_2$ in dimethyl formamide (DMF) gave the isopropenylindole (**7**) (93%), which on *N*-protection with chloromethyl methyl ether (MOMCl) provided *N*-MOM-indole (**8**) (99%). Subsequent treatment of **8** with hydroxyamine produced the oxime (**5**) as the 1-azahexatriene system, which was subjected to the thermal electrocyclic reaction in *o*-dichlorobenzene[5,6)] to yield the new type β-carboline nucleus, 4-methyl-β-carboline (**4**) (81% from **8**).

The key compound (**2**) was synthesized from β-carboline (**4**) in four steps. Treatment of **4** with *m*-chloroperbenzoic acid (*m*CPBA) followed by heating in acetic anhydride (Ac_2O) yielded the 1-hydroxy-β-carboline (**10**) (94% from **4**), which was treated with trifluoromethanesulfonic anhydride (Tf_2O) to obtain the triflate (**3**) (80%). The triflate (**3**) was converted to the desired 1-methoxycarbonyl-4-methyl-β-carboline (**2**) *via* a three component cross-coupling reaction[5a,7)] [triflate (**3**), carbon monoxide, methanol] in the presence of 1,1′-bis(diphenylphosphino)ferrocene (dppf) and $Pd(OAc)_2$ in 86% yield.

The synthesis of oxopropaline G (**1e**) was carried out in four steps from **2**. Nucleophilic addition reaction to **2** with the acetate carbanion produced the *N*-MOM-β-keto ester (**11**) in 99% yield, according to the procedure of Murakami and co-workers.[8)] Then we examined ketalization of **11** for selective reduction of the ester group to an alcohol. Although ketalization by the usual method and a recent procedure [trifluoromethanesulfonic acid in the presence of methanol and trimethyl orthoformate in nitromethane] by Rice and co-workers[9)] were carried out, the reaction did not proceed. However, it was found that the *N*-MOM-deprotected β-carboline (**12**) from **11** was obtained in 71% yield by the method of Rice and co-workers.[9)] Reduction of **12** with diborane in THF followed by selective oxidation of the 1,3-diol (**13**) with activated manganese dioxide provided oxopropaline G (**1e**) in 40% yield from **12**. All spectral data of synthetic oxopropaline G (**1e**) were in good agreement with that reported for the natural product.[1)]

Furthermore, we attempted the synthesis of oxopropaline D (**1c**) employing the *N*-MOM-1-methoxycarbonyl-4-methyl-β-carboline (**2**) as a common key compound. The *N*-MOM-β-carboline (**2**) was treated with trifluoromethanesulfonic acid in the presence of methanol and trimethyl orthoformate in nitromethane[9)] in a similar way to give the *N*-MOM-deprotected β-carboline (**14**) in 94% yield. Reduction of **14** with diisobutylaluminum hydride (DIBAL) afforded the aldehyde (**15**) (98%), which was treated with vinylmagnesium bromide (**16**; 91%) followed by silylation with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) to obtain the allyl silyl ether (**17**) (98%) (Chart 3).

The osmium-catalyzed asymmetric dihydroxylation of the allyl ether (**17**) was carried out using the Sharpless procedure.[10)] Initially, the allyl ether (**17**) was treated with AD-

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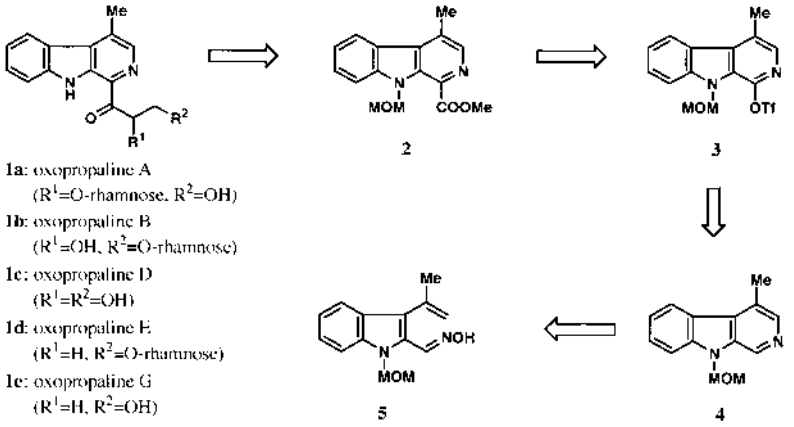


Chart 1

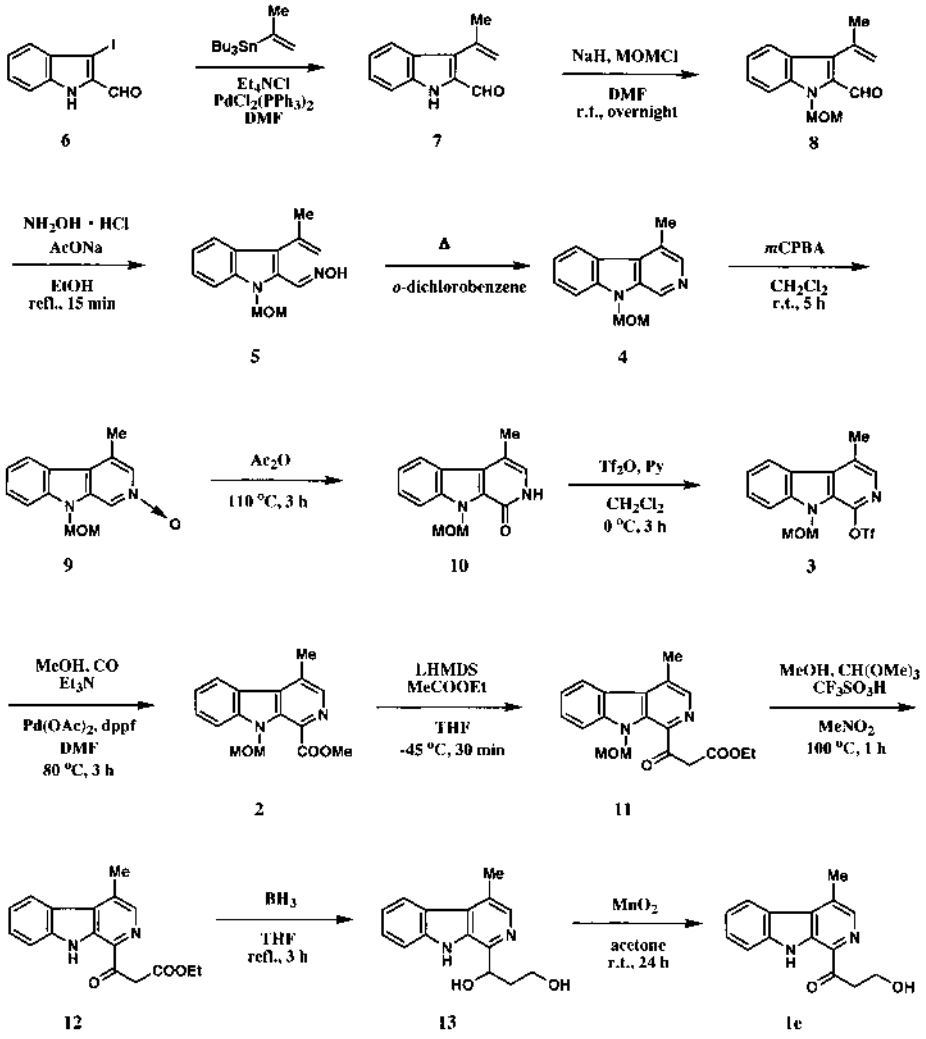
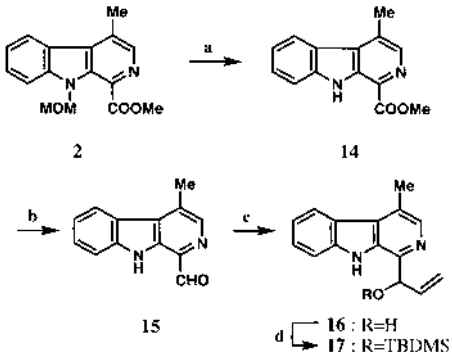


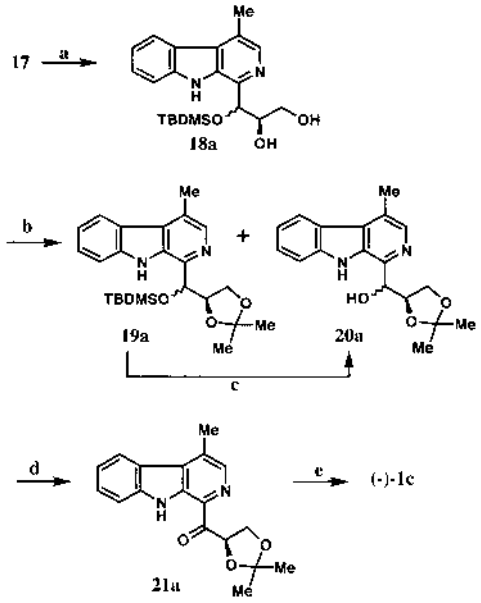
Chart 2

mix-α to produce the 1,2-diol (**18a**) (64%), which was then refluxed in acetone in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to yield the acetonide (**19a**) (45%) and its desilylated acetonide (**20a**) (45%). Removal of the TBDMS group of **19a** with tetrabutylammonium fluoride (TBAF) (**20a**: 96%) followed by oxidation of **20a** with activated manganese dioxide gave the ketone (**21a**) in 80% yield [90% ee by HPLC; $[\alpha]_D^{24}$ −15.3° (c=0.12, MeOH)] (Chart 4). On the other hand, the allyl ether (**17**) was oxidized with AD-mix-β to produce the other 1,2-diol (**18b**) (63%), which was subjected to acetonization to yield the acetonide (**19b**) (84%). Likewise, removal of the TBDMS group of **19b** followed by oxidation of the alcohol (**20b**) furnished the ketone (**21b**) in 49% yield from **19b** [95% ee by HPLC; $[\alpha]_D^{24}$ +20.8° (c=0.28, MeOH)]. Both keto-acetonides (**21a** and **21b**) were carefully treated with diluted sulfonic acid to give (−)-oxo-



a) CF_3SO_3H, MeOH, $CH(OMe)_3$, $MeNO_2$, 100°C, 1 h; b) DIBAL, CH_2Cl_2, -78°C, 1 h; c) vinylmagnesium bromide, THF, 0°C, 30 min; d) TBDMSCl, imidazole, DMF, 60°C, 1 h

Chart 3

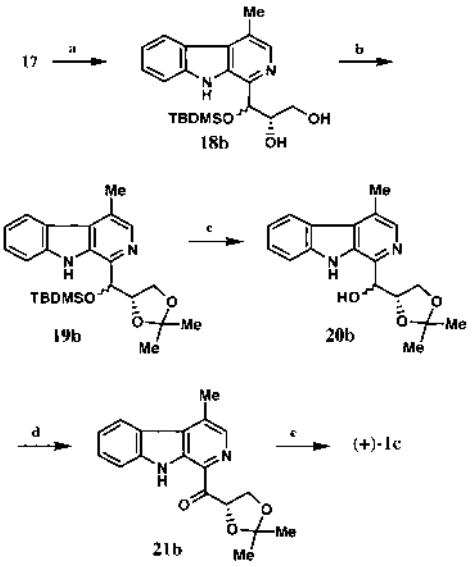


a) AD-mix-α, *t*-BuOH, H_2O, 0°C, 24 h; b) *p*-TsOH, Me_2CO, reflux, 24 h; c) TBAF, THF, r.t., 15 min; d) act. MnO_2, CH_2Cl_2, r.t., 8 h; e) dil. H_2SO_4, MeOH, r.t., 1 h

Chart 4

propaline D (**1c**) [86% yield, 72% ee by HPLC; $[\alpha]_D^{24}$ −10° (c=0.22, MeOH)] and (+)-oxopropaline D (**1c**) [63% yield, 93% ee by HPLC; $[\alpha]_D^{24}$ +27° (c=0.39, MeOH)] (Chart 5), whose spectroscopic data were identical with those of the natural product.[1b] The specific rotation of the latter (+)-oxopropaline D (**1c**) showed the same direction of rotation and the approximate value in comparison with the reported data ($[\alpha]_D^{20}$ +30° (c=0.1, MeOH)) of natural oxopropaline D.[1b] The absolute configurations of both enantiomers [(−)-**1c** and (+)-**1c**] seem to correspond to *R* and *S*-configurations, respectively, in accordance with the Sharpless rule.[10]

In conclusion, the first total synthesis of the new type cytocidal β-carboline alkaloid, oxopropaline G (**1e**) was established in a twelve-step sequence (11.7% overall yield from **6**). Moreover, enantioselective first total syntheses of (+)-oxopropaline D (**1c**) and its enantiomer were also completed in a nine-step sequence [(+)-**1c**: 13.4% overall yield from **2**] using the common key compound, *N*-MOM-1-methoxycarbonyl-4-methyl-β-carboline (**2**), prepared by thermal electrocyclic reaction of a 1-azahexatriene system involving the indole 2,3-bond. In addition, we found that the ketalization-procedure of Rice and co-workers[9] could be utilized as a novel deprotection-procedure for the *N*-MOM group at β-carbolines in this work.



a) AD-mix-β, *t*-BuOH, H_2O, 0°C, 24 h; b) *p*-TsOH, Me_2CO, reflux, 24 h; c) TBAF, THF, r.t., 15 min; d) act. MnO_2, CH_2Cl_2, r.t., 8 h; e) dil. H_2SO_4, MeOH, r.t., 1 h

Chart 5

Experimental

Melting points were determined with a Yanagimoto micro-melting point apparatus MP-500D without correction. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8500 spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) and carbon nuclear magnetic resonance spectra (^{13}C-NMR) were taken on JEOL-AL300 and JNM A500 spectrometers with Me_4Si as an internal standard unless otherwise stated. Electron impact ionization (EI), chemical ionization (CI), and high-resolution mass spectra (HRMS) were measured with a Shimadzu 9020DF or Shimadzu QP5500. All air-sensitive reactions were run under an argon atmosphere. Solvents were distilled by normal methods (tetrahydrofran (THF) dried over sodium benzophenone ketyl, dichloromethane dried over CaH_2, DMF dried over CaH_2). Silica gel (60—100 mesh, Merck Art 7734) was used for column chromatography. Silica gel $60PF_{254}$ (Merck Art 7744) was used for preparative TLC. Enantiomeric excesses were determined by HPLC (CHIRALPAK AD) using iso-PrOH–hexane (7 : 3) as an eluent.

3-Isopropenylindole-2-carbaldehyde (7) A mixture of 3-iodoindole **6** (4.2 g, 15.6 mmol), isopropenyltributyltin (6.2 g, 18.7 mmol), Et_4NCl (2.6 g, 15.6 mmol), and $PdCl_2(PPh_3)_2$ (328 mg, 0.47 mmol) in DMF (15 ml) was heated at 80 °C for 4 h. After being cooled to room temperature, the reaction mixture was treated with 30% aqueous KF solution (5 ml) at room temperature. The mixture was stirred for 30 min and filtered through Celite. The filtrate was extracted with EtOAc. The EtOAc layer was washed with water and brine, and then dried over Na_2SO_4. The organic layer was evaporated *in vacuo* and the residue purified by column chromatography using EtOAc–hexane (1 : 9) as eluent to give 3-isopropenylindole **7** (2.7 g, 93%), mp 82—83 °C (hexane). IR (KBr) cm^{-1}: 1658. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, d, J=1 Hz), 5.16 (1H, d, J=2 Hz), 5.41 (1H, dd, J=1, 2 Hz), 7.00—7.46 (3H, m), 7.73 (1H, d, J=8 Hz), 9.86 (1H, s). MS *m/z*: 185 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.61; H, 6.02; N, 7.73.

3-Isopropenyl-*N*-(methoxymethyl)indole-2-carbaldehyde (8) A solution of 3-isopropenylindole **7** (500 mg, 2.70 mmol) in DMF (10 ml) was slowly added to a suspension of 60% NaH (130 mg, 3.24 mmol) in DMF (5 ml) under ice water cooling. After stirring at the same temperature for 30 min, MOMCl (246 μl, 3.24 mmol) was added. The mixture was stirred at

room temperature overnight and then poured into ice-water and extracted with EtOAc. The EtOAc layer was washed with water and brine, and dried over Na_2SO_4. The organic layer was concentrated to dryness and the residue purified by column chromatography using EtOAc–hexane (1 : 9) as eluent to yield oily *N*-MOM indole **8** (615 mg, 99%). IR (neat) cm^{-1}: 1668. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, d, J=1 Hz), 3.32 (3H, s), 5.14 (1H, d, J=2 Hz), 5.51 (1H, dd, J=1, 2 Hz), 5.98 (2H, s), 7.21 (1H, t, J=8 Hz), 7.44 (1H, t, J=8 Hz), 7.54 (1H, d, J=8 Hz), 7.75 (1H, d, J=8 Hz), 10.01 (1H, s). MS *m/z*: 229 (M^+). HRMS Calcd for $C_{14}H_{15}NO_2$: 229.2802. Found: 229.2813.

***N*-Methoxymethyl-4-methyl-9*H*-pyrido[3,4-*b*]indole (4)** A suspension of the aldehyde **8** (630 mg, 2.75 mmol), NH_2OH–EHCl (382 mg, 5.50 mmol), and AcONa (451 mg, 5.50 mmol) in EtOH (15 ml) was heated at 80 °C for 15 min, and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc. The EtOAc layer was washed with brine and dried over Na_2SO_4. Removal of solvent gave oxime **5**. Oxime **5** was used for the next step without further purification.

A solution of **5** in *o*-dichlorobenzene (15 ml) was heated at 180 °C for 3 h. After cooling to room temperature, the mixture was concentrated to dryness under reduced pressure. The residue was purified by column chromatography using EtOAc–hexane (6 : 4) as eluent to give β-carboline **4** (502 mg, 81%), mp 108—109 °C (Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 2.79 (3H, s), 3.26 (3H, s), 5.66 (2H, s), 7.17—7.59 (4H, m), 8.07 (1H, s), 8.20 (1H, s). MS *m/z*: 226 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 69.99; H, 5.03; N, 11.66. Found: C, 71.05; H, 4.99; N, 11.60.

***N*-Methoxymethyl-4-methyl-9*H*-pyrido[3,4-*b*]indole-1(2*H*)-one (10)** A solution of β-carboline **4** (850 mg, 3.76 mmol) and *m*CPBA (778 mg, 4.51 mmol) in CH_2Cl_2 (25 ml) was stirred at room temperature for 5 h. The reaction mixture was then diluted with MeOH–$CHCl_3$ (1 : 9) and the organic layer washed with aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The organic layer was evaporated *in vacuo* and the resulting *N*-oxide **9** used in the next step without further purification.

A solution of *N*-oxide **9** in acetic anhydride (30 ml) was heated at 110 °C for 3 h. After cooling to room temperature, acetic anhydride was removed under reduced pressure. A mixture of the residue, 3 M NaOH (15 ml), MeOH (50 ml) and THF (10 ml) was stirred at room temperature for 30 min. The reaction mixture was then extracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from EtOH to give pyridone **10** (860 mg, 94% from 4), mp 210—212 °C (EtOH). IR (KBr) cm^{-1}: 1653. ^{1}H-NMR (DMSO-d_6) δ: 3.17 (3H, s), 3.30 (3H, s), 6.22 (2H, s), 6.92 (1H, s), 7.28 (1H, t, J=8.1 Hz), 7.51 (1H, t, J=8.1 Hz), 7.73 (1H, d, J=8.1 Hz), 8.13 (1H, d, J=8.1 Hz). MS *m/z*: 242 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.33; H, 6.08; N, 11.32.

***N*-Methoxymethyl-4-methyl-1-(trifluoromethanesulfonyloxy)-9*H*-pyrido[3,4-*b*]indole (3)** Trifluoromethanesulfonic anhydride (0.42 ml, 2.47 mmol) was added dropwise to a solution of pyridone **10** (500 mg, 2.06 mmol) and pyridine (501 μl, 6.19 mmol) in CH_2Cl_2 (25 ml) under cooling with ice-water. After stirring at the same temperature for 3 h, the reaction mixture was extracted with EtOAc. The EtOAc layer was washed with aqueous $NaHCO_3$ solution, water and brine, and dried over Na_2SO_4 and the solvent evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (1 : 9) as an eluent to give the triflate **3** (617 mg, 80%), mp 118—120 °C (Et_2O–hexane). IR (KBr) cm^{-1}: 1416, 1242. ^{1}H-NMR ($CDCl_3$) δ: 2.79 (3H, s), 3.30 (3H, s), 5.79 (2H, s), 7.26—7.73 (3H, m), 7.92 (1H, s), 8.20 (1H, d, J=8 Hz). MS *m/z*: 374 (M+). *Anal.* Calcd for $C_{15}H_{13}F_3N_2O_4S$: C, 48.13; H, 3.50; N, 7.48. Found: C, 48.24; H, 3.67; N, 7.60.

1-Methoxycarbonyl-*N*-methoxymethyl-4-methyl-9*H*-pyrido[3,4-*b*]indole (2) Carbon monoxide was bubbled for 5 min to a mixture of the triflate **3** (555 mg, 1.48 mmol), MeOH (1.2 ml, 29.7 mmol), triethylamine (0.41 ml, 2.97 mmol), dppf (65 mg, 0.12 mmol) and $Pd(OAc)_2$ (13 mg, 0.059 mmol) in DMF (15 ml). The resulting mixture was stirred at 80 °C for 3 h under a CO atmosphere. After cooling to room temperature, the mixture was extracted with EtOAc and the organic layer washed with water, brine, and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure and the residue purified by column chromatography using EtOAc–hexane (1 : 1) as eluent to give methyl ester **2** (364 mg, 86%), mp 82—83 °C (Et_2O). IR (neat) cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 2.90 (3H, s), 3.02 (3H, s), 4.09 (3H, s), 5.94 (2H, s), 7.35—7.40 (1H, m), 7.60—7.68 (1H, m), 8.23 (1H, d, J=8 Hz), 8.35 (1H, s). MS *m/z*: 284 (M^+). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.51; H, 5.89; N, 9.58.

Ethyl 3-Oxo-3-(*N*-methoxymethyl-4-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)- propionate (11) EtOAc (0.28 ml, 2.90 mmol) was added to a solution of lithium bis(trimethylsilyl)amide (486 mg, 2.90 mmol) in THF (7 ml) at −45 °C. After stirring at the same temperature for 30 min, a solution of the methyl ester **2** (165 mg, 0.58 mmol) in THF (8 ml) was added dropwise to the reaction mixture. The mixture was stirred for 30 min at the same temperature and quenched with an aqueous NH_4Cl solution (saturated). The mixture was extracted with EtOAc and the organic layer washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (3 : 7) as eluent to give β-ketoester **11** (195 mg, 99%). IR (neat) cm^{-1}: 1740, 1693. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.4 Hz), 2.93 (3H, s), 3.05 (3H, s), 4.25 (2H, q, J=7.4 Hz), 4.40 (2H, s), 7.35—7.40 (1H, m), 7.58—7.62 (2H, m), 8.21 (1H, d, J=7.8 Hz), 8.32 (1H, s), 10.30 (1H, br s). MS *m/z*: 340 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.87; H, 5.82; N, 7.99.

Ethyl 3-Oxo-3-(4-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)propionate (12) Trifluoromethansulfonic acid (1 μl, 0.012 mmol) was added to an ice-cooled mixture of β-ketoester **11** (21 mg, 0.062 mmol), MeOH (25 μl, 0.62 mmol), and trimethyl orthoformate (68 μl, 0.62 mmol) in nitromethane (1 ml). The resulting mixture was heated at 100 °C for 1 h. After cooling to room temperature, the mixture was extracted with EtOAc and the organic layer washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (2 : 8) as eluent to give *N*-deprotected β-ketoester **12** (13 mg, 71%), mp 144—145 °C (Et_2O). IR (KBr) cm^{-1}: 1719, 1680. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.9 Hz), 2.93 (3H, s), 4.18 (2H, q, J=7.9 Hz), 4.42 (2H, s), 5.95 (2H, s), 7.36—7.43 (1H, m), 7.63—7.70 (2H, m), 8.25 (1H, d, J=7.7 Hz), 8.33 (1H, s). MS *m/z*: 296 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.16; H, 5.43; N, 9.56.

1-(1,3-Dihydroxypropyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (13) Diborane (1 M in THF, 2.2 ml, 2.26 mmol) was added to a solution of β-ketoester **12** (67 mg, 0.22 mmol) in dry THF (10 ml). The mixture was refluxed for 3 h. After cooling to room temperature, the mixture was quenched with water and extracted with MeOH–$CHCl_3$ (1 : 9). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by preparative TLC using EtOAc as eluent to give 1,3-diol **13** (49 mg, 85%), mp 208—210 °C ($CHCl_3$). IR (KBr) cm^{-1}: 3250. ^{1}H-NMR (MeOH-d_4) δ: 2.11—2.18 (2H, m), 2.80 (3H, s), 3.92 (2H, t, J=6.9 Hz), 6.14—6.21 (1H, m), 7.30 (3H, t, J=8.0 Hz), 7.60 (1H, t, J=8.0 Hz), 7.71 (1H, d, J=8.0 Hz), 8.21 (1H, s), 8.23 (1H, d, J=8.0 Hz). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.43; H, 6.17; N, 11.02.

Oxopropaline G (1e) A mixture of 1,3-diol **13** (13 mg, 0.051 mmol) and activated MnO_2 (260 mg) in dry acetone (4 ml) was stirred at room temperature for 24 h. The reaction mixture was filtered though Celite and the Celite washed with acetone. The combined filtrates were concentrated under reduced pressure and the residue purified by preparative TLC using MeOH–$CHCl_3$ (1 : 99) as eluent to give oxopropaline G (**1e**) (6 mg, 47%), mp 155—157 °C ($CHCl_3$). IR (KBr) cm^{-1}: 3518, 3320, 1663. ^{1}H-NMR (500 MHz, MeOH-d_4) δ: 2.90 (3H, s), 3.54 (2H, t, J=6.4 Hz), 4.07 (2H, t, J=6.4 Hz), 7.33 (1H, dd, J=7.9, 7.1 Hz), 7.58 (1H, dd, J=8.2, 7.1 Hz), 7.71 (1H, d, J=8.2 Hz), 8.23 (1H, d, J=7.9 Hz), 8.24 (1H, s). ^{13}C-NMR (125 MHz, MeOH-d_4) δ: 17.9, 41.8, 58.8, 113.3, 121.7, 122.1, 124.5, 129.6, 131.1, 134.0, 135.2, 135.9, 139.7, 143.2, 203.1. MS (CI) *m/z*: 255 (M^++1). *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.11; H, 5.45; N, 11.00.

1-Methoxycarbonyl-4-methyl-9*H*-pyrido[3,4-*b*]indole (14) Trifluoromethanesulfonic acid (13 μl, 0.15 mmol) was added to an ice-cooled mixture of *N*-MOM-β-carboline **2** (84 mg, 0.30 mmol), MeOH (127 μl, 2.95 mmol), and trimethyl orthoformate (323 μl, 2.95 mmol) in nitromethane (5 ml). The resulting mixture was heated at 100 °C for 1 h. After cooling to room temperature, the mixture was extracted with EtOAc and the organic layer washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (7 : 3) as eluent to give *N*-deprotected β-carboline **14** (67 mg, 94%). mp 184—185 °C (EtOAc–hexane). IR (KBr) cm^{-1}: 1676. ^{1}H-NMR ($CDCl_3$) δ: 2.94 (3H, s), 4.12 (3H, s), 7.34—7.40 (1H, m), 7.60—7.63 (2H, m), 8.23 (1H, d, J=8 Hz), 8.39 (1H, s), 9.98 (1H, br s). MS *m/z*: 240 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.01; H, 5.19; N, 11.38.

4-Methyl-9*H*-pyrido[3,4-*b*]indole-1-carbaldehyde (15) DIBAL (0.96 M in hexane, 2.18 ml, 2.10 mmol) was added to a stirred solution of β-carboline **14** (187 mg, 0.78 mmol) in CH_2Cl_2 (20 ml) at −78 °C. The mixture was stirred for 1 h at the same temperature and then was quenched with an aqueous NH_4Cl solution (saturated). The mixture was filtered through Celite and the Celite washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 and

the organic layer washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (7 : 3) as eluent to give aldehyde **15** (160 mg, 98%), mp 209—211 °C (Et_2O). IR (KBr) cm^{-1}: 1656. ^{1}H-NMR ($CDCl_3$) δ: 2.95 (3H, s), 7.26—7.40 (1H, m), 7.60—7.63 (2H, m), 8.23 (1H, d, J=8.8 Hz), 8.43 (1H, s), 10.31 (1H, s). MS *m/z*: 210 (M^+). *Anal.* Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.38; H, 4.56; N, 13.21.

1-(1-Hydroxyprop-2-en-1-yl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (16) Vinylmagnesium bromide (1.04 M in THF, 1.64 ml, 1.71 mmol) was added to a solution of aldehyde **15** (72 mg, 0.34 mmol) in THF (10 ml) under cooling with ice-water. After stirring at the same temperature for 30 min , the reaction mixture was quenched with aqueous NH_4Cl solution (saturated). The mixture was extracted with EtOAc and the organic layer washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (1 : 1) as eluent to give allyl alcohol **16** (74 mg, 91%), mp 148—151 °C (EtOAc–hexane). IR (KBr) cm^{-1}: 3100. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (3H, s), 5.38 (1H, d, J=10 Hz), 5.61 (1H, d, J=7 Hz), 5.64 (1H, d, J=16 Hz), 6.18 (1H, ddd, J=7, 10, 16 Hz), 7.27—7.34 (1H, m), 7.54—7.56 (2H, m), 8.16 (1H, s), 8.21 (1H, d, J=8.4 Hz), 8.74 (1H, br s). MS *m/z*: 238 (M^+), 221 (M^+-17). *Anal.* Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.45; H, 6.11; N, 11.58.

1-(1-*tert*-Butyldimethylsilyloxyprop-2-en-1-yl)-4-methyl-9*H*-pyrido-[3,4-*b*]indole (17) A solution of allyl alcohol **16** (84 mg, 0.35 mmol) in DMF (1 ml) was added to a solution of *tert*-butyldimethylsilyl chloride (159 mg, 1.06 mmol) and imidazole (179 mg, 2.63 mmol) in DMF (2 ml) at room temperature. The mixture was heated at 60 °C for 1 h. After cooling to room temperature, the mixture was extracted with EtOAc and the organic layer washed with water, brine, and dried over Na_2SO_4. The organic layer was evaporated *in vacuo* and the residue purified by column chromatography using EtOAc–hexane (1 : 9) as eluent to give silyl ether **17** (122 mg, 98%). ^{1}H-NMR ($CDCl_3$) δ: 0.00 (3H×2, s), 0.92 (9H, s), 2.83 (3H, s), 5.15 (1H, ddd, J= 1.8, 1.8, 10 Hz), 5.49 (1H, ddd, J= 1.8, 1.8, 16 Hz), 5.67 (1H, ddd, J=1.8, 1.8, 4.7 Hz) 6.15 (1H, ddd, J=4.7, 10, 16 Hz), 7.26—7.32 (1H, m), 7.49—7.58 (2H, m), 8.12 (1H, s), 8.21 (1H, d, J= 8.0 Hz), 9.05 (1H, br s). MS (CI) *m/z*: 353 (M^++1). HRMS (CI, isobutane) Calcd for $C_{21}H_{29}N_2OSi$: 353.2048. Found: 353.2053.

1-(1-*tert*-Butyldimethylsilyloxy-2,3-dihydroxypropyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (18a) A solution of silyl ether **17** (74 mg, 0.21 mmol) in *tert*-butanol (2.5 ml) was added to a suspension of AD-mix-α (1.4 g) in *tert*-butanol–H_2O (2.5 ml+5 ml) at 0 °C. The mixture was stirred at the same temperature for 24 h. After addition of Na_2SO_3 (1.5 g), the mixture was allowed to warm to room temperature and stirred for 30 min. EtOAc (10 ml) was added to the reaction mixture. After separation of the EtOAc layer, the aqueous phase was further extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4, and then evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc as eluent to give the diol **18a** (52 mg, 64%) as a mixture of diastereomers (58 : 42). IR (KBr) cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: −0.11 (3H, s), 0.16 (3H, s), 0.96 (9H, s), 2.83 (3H, s), 3.39—3.46 (1H, m), 3.54—3.71 (2H, m), 3.64—3.70 (1H, m), 3.78—3.86 (1H, m), 3.97—4.04 (1H, m), 4.09—4.12 (1H, m), 5.25 (1H, d, J=5.0 Hz), 5.26 (1H, d, J=5.0 Hz), 7.26—7.33 (1H, m), 7.48—7.57 (2H, m), 8.13 (1H, s), 8.21 (1H, d, J=8.1 Hz), 9.19 (1H, br s), 9.22 (1H, br s). MS (CI) *m/z*: 387 (M^++1). HRMS (CI, isobutane) Calcd for $C_{21}H_{31}N_2O_3Si$: 387.2103. Found: 387.2109.

1-(1-*tert*-Butyldimethylsilyloxy-2,3-dihydroxypropyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (18b) The diol **18b** (63%) was prepared by AD-mix-β from **17** as a mixture of diastereomers (57 : 43), using the same procedure as above. IR (KBr) cm^{-1}: 3390. ^{1}H-NMR ($CDCl_3$) δ: −0.11 (3H, s), 0.17 (3H, s), 0.96 (9H, s), 2.84 (3H, s), 3.34—3.50 (1H, m), 3.56—3.63 (1H, m), 3.64—3.70 (1H, m), 3.78—3.86 (1H, m), 3.97—4.04 (1H, m), 4.09—4.12 (1H, m), 5.25 (1H, d, J=5.0 Hz), 5.26 (1H, d, J=5.0 Hz), 7.32 (1H, t, J=8.1 Hz), 7.50—7.61 (2H, m), 8.12 (1H, s), 8.23 (1H, d, J=7.9 Hz), 9.19 (1H, br s), 9.23 (1H, br s). MS (CI) *m/z*: 387 (M^++1). HRMS (CI, isobutane) Calcd for $C_{21}H_{31}N_2O_3Si$: 387.2103. Found: 387.2098.

1-(1-*tert*-Butyldimethylsilyloxy-2,3-*O*-isopropylidenepropyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (19a) A solution of the diol **18a** (40 mg, 0.10 mmol) and *p*-toluenesulfonic acid (catalytic amounts) in dry acetone (10 ml) was heated at 65 °C for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was extracted with EtOAc and washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC using EtOAc as eluent to give oily acetonide **19a** (20 mg, 45%) and oily desilylated acetonide **20a** (14 mg, 45%) as a mixture of diastereomers (63 : 37), respectively. ^{1}H-NMR ($CDCl_3$) δ: −0.19 (3H, s), −0.15 (3H, s), 0.12 (3H, s), 0.13 (3H, s), 0.90 (9H, s), 0.96 (3H, s), 1.28 (3H, s), 1.31 (3H, s), 1.54 (3H, s), 2.83 (3H, s), 3.83—3.88 (1H, m), 4.00—4.10 (2H, m), 4.40—4.51 (1H, m), 4.56—4.64 (1H, m), 5.06 (1H, d, J=4.8 Hz), 5.19 (1H, d, J=4.0 Hz), 7.26—7.32 (1H, m), 7.48—7.58 (2H, m), 8.12 (1H, dd, J=1.0, 10 Hz), 8.19 (1H, s), 8.22 (1H, s), 9.14 (1H, s), 9.21 (1H, s). MS (CI) *m/z*: 427 (M^++1). HRMS (CI, isobutane) Calcd for $C_{24}H_{35}N_2O_3Si$: 427.2415. Found: 427.2418.

1-(1-*tert*-Butyldimethylsilyloxy-2,3-*O*-isopropylidenepropyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (19b) The acetonide **19b** was obtained from **18b** in 84% yield as a mixture of diastereomers (57 : 43), using the same procedure as above. ^{1}H-NMR ($CDCl_3$) δ: −0.19 (3H, s), 0.12, 0.13 (3H, s), 0.90 (9H, s), 0.96, 1.28, 1.31, 1.54 (3H×2, s), 2.84 (3H, s), 3.82—3.87 (1H, m), 3.94—4.10 (2H, m), 4.43—4.50 (1H, m), 4.57—4.63 (1H, m), 5.06 (1H, d, J=4.8 Hz), 5.19 (1H, d, J=4.0 Hz), 7.26—7.32 (1H, m), 7.48—7.58 (2H, m), 8.12 (1H, dd, J=1.0, 10 Hz), 8.20 (1H, s), 8.23 (1H, s), 9.14 (1H, br s), 9.22 (1H, br s). MS (CI) *m/z*: 427 (M^++1). HRMS (CI, isobutane) Calcd for $C_{24}H_{35}N_2O_3Si$: 427.2415. Found: 427.2411.

1-(1-Hydroxy-2,3-*O*-isopropylidenepropyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (20a) TBAF (1 M in THF, 0.1 ml, 0.11 mmol) was added to a solution of acetonide **19a** (20 mg, 0.047 mmol) in THF (1 ml). The mixture was stirred at room temperature for 15 min and then exracted with EtOAc. The EtOAc layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC using EtOAc–hexane (1 : 1) as eluent to give alcohol **20a** (14 mg, 96%) as a mixture of diastereomers (62 : 38). IR (KBr) cm^{-1}: 3200. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, s), 1.38 (3H, s), 1.39 (3H, s), 1.63 (3H, s), 2.82 (3H, s), 2.84 (3H, s), 3.91—4.04 (1H, m), 4.08—4.25 (1H, m), 4.35—4.45 (1H, m), 4.63—4.70 (1H, m), 5.13 (1H, d, J=6.9 Hz), 5.26 (1H, d, J=6.2 Hz), 7.24—7.33 (1H, m), 7.54—7.56 (2H, m), 8.14 (1H, br s), 8.20 (1H, d, J=7.3 Hz), 8.21 (1H, d, J=7.3 Hz), 9.29 (1H, br s), 9.56 (1H, br s). MS *m/z*: 312 (M^+), 297, 211. HRMS Calcd for $C_{18}H_{20}N_2O_3$: 312.3705. Found: 312.3709.

1-(1-Hydroxy-2,3-*O*-isopropylidenepropyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (20b) The acetonide **20b** was obtained from **19b** in 95% yield as a mixture of diastereomers (58 : 42), using the same procedure as above. IR (KBr) cm^{-1}: 3180. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, s), 1.38 (3H, s), 1.40 (3H, s), 1.65 (3H, s), 2.83 (3H, s), 2.85 (3H, s), 3.91—4.05 (1H, m), 4.11—4.27 (1H, m), 4.36—4.46 (1H, m), 4.63—4.72 (1H, m), 5.13 (1H, d, J=6.9 Hz), 5.27 (1H, d, J=6.0 Hz), 7.24—7.35 (1H, m), 7.51—7.57 (2H, m), 8.14 (1H, br s), 8.21 (1H, d, J=7.9 Hz), 8.22 (1H, d, J=7.9 Hz), 9.28 (1H, br s), 9.56 (1H, br s). MS *m/z*: 312 (M^+), 297, 211. HRMS Calcd for $C_{18}H_{20}N_2O_3$: 312.3705. Found: 312.3698.

1-(2,3-*O*-Isopropylidenepropionyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (21a) A suspension of alcohol **20a** (24 mg, 0.077 mmol) and activated MnO_2 (240 mg) in CH_2Cl_2 (10 ml) was stirred at room temperature for 8 h. The reaction mixture was then filtered through Celite and the filtrate evaporated *in vacuo*. The residue was purified by preparative TLC using EtOAc–hexane (2 : 3) as eluent to give ketone **21a** (19 mg, 80%), 90% ee by HPLC, $[\alpha]_D^{24}$ −15.3° (c=0.12, MeOH), mp 161—163 °C (Et_2O). IR (KBr) cm^{-1}: 1672. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s), 1.61 (3H, s), 2.92 (3H, s), 4.11 (1H, dd, J=6.2, 8.5 Hz), 4.74 (1H, t, J=8.5 Hz), 5.98 (1H, dd, J=6.2, 8.5 Hz), 7.30—7.39 (1H, m), 7.57—7.61 (2H, m), 8.21 (1H, d, J=8.1 Hz), 8.27 (1H, s), 10.27 (1H, br s). MS (CI) *m/z*: 311 (M^++1). *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.75; H, 5.93; N, 9.17.

1-(2,3-*O*-Isopropylidenepropionyl)-4-methyl-9*H*-pyrido[3,4-*b*]indole (21b) Ketone **21b** was obtained from **20b** in 52% yield using the same procedure as above, 95% ee by HPLC, $[\alpha]_D^{24}$ +20.8° (c=0.28, MeOH), mp 154—156 °C (Et_2O). IR (KBr) cm^{-1}: 1674. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, s), 1.62 (3H, s), 2.93 (3H, s), 4.11 (1H, dd, J=6.2, 8.5 Hz), 4.75 (1H, t, J=8.5 Hz), 5.98 (1H, dd, J=6.2, 8.5 Hz), 7.34—7.40 (1H, m), 7.61—7.62 (2H, m), 8.22 (1H, d, J=8.1 Hz), 8.28 (1H, s), 10.29 (1H, br s). MS (CI) *m/z*: 311 (M^++1). *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.74; H, 5.93; N, 9.00.

(−)-Oxopropaline D (1c) A solution of acetonide **21a** (4 mg, 0.013 mmol) in 0.8% H_2SO_4 MeOH solution (1 ml) was stirred at room temperature for 1 h. The mixture was neutralized with aqueous 10% Na_2CO_3 solution, and then extracted with MeOH–$CHCl_3$ (1 : 9). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from $CHCl_3$–hexane to give (−)-oxopropaline **1c** (3 mg, 86%), 72% ee by HPLC, $[\alpha]_D^{24}$ −10° (c=0.22, MeOH), mp 188—190 °C ($CHCl_3$–hexane). IR (KBr) cm^{-1}: 3302, 1668. ^{1}H-NMR (300 MHz, MeOH-d_4) δ: 2.93 (3H, s), 4.09 (2H, d, J=4 Hz), 5.58 (1H, t, J=4 Hz), 7.34 (1H, dd, J=7.2, 8.0 Hz), 7.60 (1H, dd, J=7.2, 8.1 Hz), 7.73 (1H, d, J=8.1 Hz), 8.26 (1H, d, J=8.0 Hz), 8.28 (1H, s). ^{13}C-NMR (75 MHz, MeOH-d_4) δ: 18.0, 66.3, 76.5, 113.5, 121.9, 122.2, 124.6, 129.8, 131.3, 133.7, 134.7, 136.4, 139.9, 143.3, 202.0. MS (CI) *m/z*: 271 (M^++1). *Anal.* Calcd for

$C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.52; H, 5.13; N, 10.44.

(+)-Oxopropaline D (1c) (+)-Oxopropaline **1c** was obtained from **21b** in 63% yield using the same procedure as above, 93% ee by HPLC, $[\alpha]_D^{24}$ +27° (*c*=0.39, MeOH), mp 182—183 °C ($CHCl_3$–hexane). IR (KBr) cm^{-1}: 3314, 1668. ^{1}H-NMR (300 MHz, MeOH-d_4) δ: 2.93 (3H, s), 4.09 (2H, d, *J*=4 Hz), 5.58 (1H, t, *J*=4 Hz), 7.34 (1H, dd, *J*=7.2, 8.0 Hz), 7.60 (1H, dd, *J*=7.2, 8.1 Hz), 7.73 (1H, d, *J*=8.1 Hz), 8.26 (1H, d, *J*=8.0 Hz), 8.28 (1H, s). ^{13}C-NMR (75 MHz, MeOH-d_4) δ: 18.0, 66.3, 76.5, 113.5, 121.9, 122.2, 124.6, 129.8, 131.3, 133.7, 134.7, 136.4, 139.9, 143.3, 202.0. MS (CI) *m/z*: 271 (M^++1). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.58; H, 5.26; N, 10.57.

Acknowledgement We thank Dr. Abe (School of Food Nutritional Sciences, University of Shizuoka) for useful information concerning natural oxopropaline D. This work was partly supported by a Sasakawa Scientific Research Grant (to Matsuya Y.) from The Japan Science Society.

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