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ELUCIDATION OF ABSOLUTE CONFIGURATION OF OPHIORRHISIDE A BY COMPARISON OF ECD SPECTRA WITH THAT OF MODEL CHIRAL COMPOUND HAVING A 1,2,3,4-TETRAHYDRO-β-CARBOLIN-3-ONE SKELETON

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Abstract – A chiral 1,2,3,4-tetrahydro-β-carbolin-3-one having a substituent at C-1 was synthesized from L-leucine and used to elucidate the absolute configuration at C-3 of ophiorrhiside A, a monoterpenoid glucoindole alkaloid.

INTRODUCTION

Ophiorrhiza plants belonging to Rubiaceae are known to produce diverse monoterpenoid indole alkaloids, such as camptothecins[1] that have potent antitumor activity, and β-carboline-type alkaloids.[2] Our studies on the chemical constituents of *Ophiorrhiza* plants distributed in Japan[3] and Thailand[4] have resulted in the isolation of new camptothecin-related and/or β-carboline-type alkaloids. Among them, ophiorrhiside A (**1**, Figure 1)[4a] isolated from *Ophiorrhiza trichocarpon* is a monoterpenoid glucoindole alkaloid

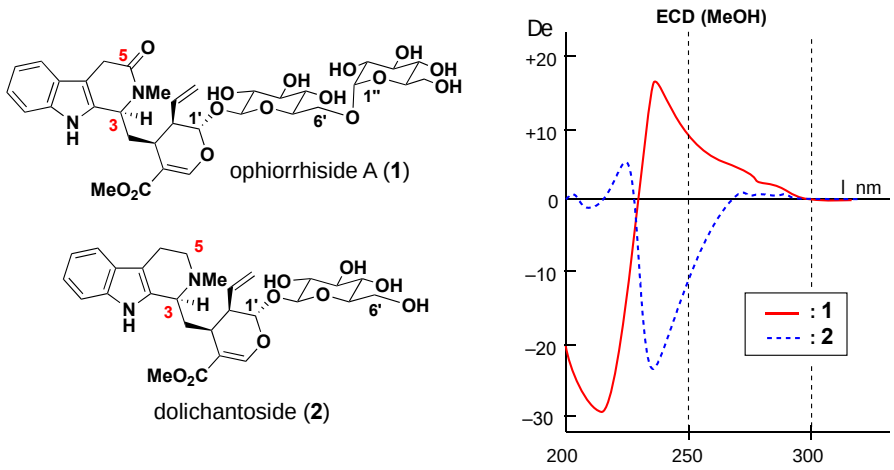
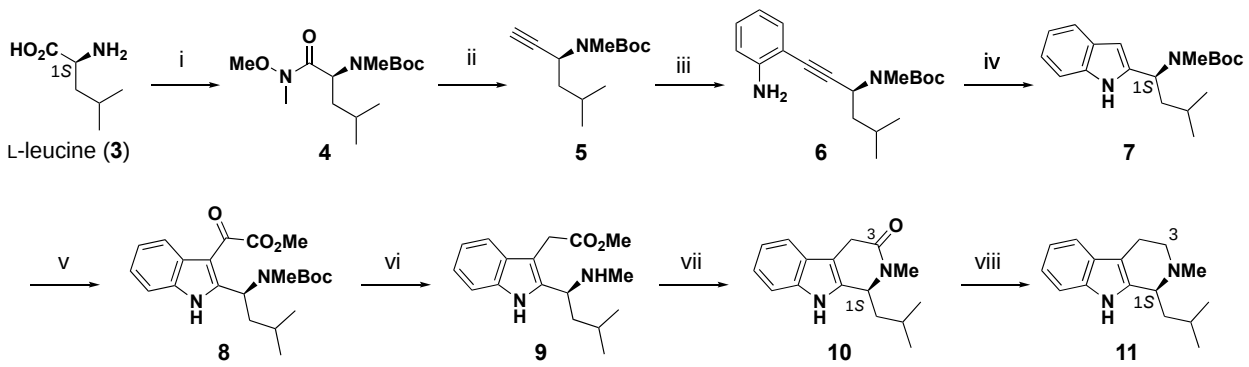


Figure 1. Structures of ophiorrhiside A (**1**) and dolichantoside (**2**), and their ECD spectra

possessing a characteristic 1,2,3,4-tetrahydro-β-carbolin-5-one ring system. It has been proposed that the stereochemistry at C-3 in those alkaloids is *S*, which is the same as that of co-existing dolichantoside (**2**) from a biogenetic point of view. However, as shown in Figure 1, the electronic circular dichroism (ECD) spectra of ophiorrhiside A (**1**) and dolichantoside (**2**) differ vastly. In general, the absolute stereochemistry at C-3 in 1,2,3,4-tetrahydro-β-carboline-type indole alkaloids could be deduced according to Klyne's empirical rule[5] by comparing the Cotton effect in the long-wavelength region of around 270−300 nm in the ECD spectra. The structural difference between **1** and **2** is the presence or absence of a carbonyl group at C-5. Then, to elucidate the absolute configuration at C-3 in **1**, we have synthesized chiral model compound **10** with a 1,2,3,4-tetrahydro-β-carbolin-3-one skeleton and compared ECD spectra, as described below.

RESULTS AND DISCUSSION

The asymmetric synthesis of target compound **10** was carried out as follows (Scheme 1) utilizing the chirality of L-leucine (**3**). Initially, **3** was converted into Weinreb amide **4** by a three-step operation, i.e., Boc protection of the amino group, *N*-methylation with NaH and iodomethane, and condensation with *N*,*O*-dimethyl hydroxylamine. DIBAL-H reduction of **4** in THF at –78 °C afforded the corresponding aldehyde, which was directly treated with the Ohira-Bestmann reagent at room temperature to give alkyne **5** in 85% yield. Sonogashira coupling of **5** with 2-iodoaniline using catalytic amounts of CuI and $Pd(PPh_3)_2Cl_2$ in the presence of Et_3N in degassed DMF gave aniline derivative **6** in 80% yield. Then, indole **7** was prepared in 82% yield by gold-catalyzed cyclization[6,7] using 10 mol% of $NaAuCl_4{\cdot}2H_2O$ in THF at room temperature. With indole **7** in hand, we next attempted to construct a 6-membered lactam.



(i) (a) Boc_2O, 1 *N* NaOH aq., THF, rt, 19.5 h, (b) MeI, NaH, THF/DMF (20:1), rt, 14.5 h, (c) CDI, NH(OMe)Me·HCl, DCM, rt, 2 h, 72% (3 steps); (ii) DIBAL-H, DCM, –78 °C, 45 min, then MeOH, K_2CO_3, Ohira-Bestmann reagent, rt, 20 h, 85%; (iii) 2-iodoaniline, CuI, $Pd(PPh_3)_2Cl_2$, Et_3N, DMF, rt, 2 h, 80%; (iv) $NaAuCl_4{\cdot}2H_2O$ (10 mol%), THF, rt, 2 h, 82%; (v) $(COCl)_2$, THF, 0 °C, 3.5 h then MeOH, Et_3N, 0 °C, 15 min, quant; (vi) Et_3SiH, TFA, rt, 21.5 h, quant; (vii) $LiOH{\cdot}H_2O$, wet-MeOH, rt, 17.5 h, 91%; (viii) $LiAlH_4$, THF, 50 °C, 2 h, 97%.

Scheme 1. Synthesis of model compounds **10** and **11** from L-leucine (**3**)

Installation of the side chain at the β-position of the indole nucleus was achieved by treatment with freshly distilled $(COCl)_2$ in THF and methanolysis of the resulting carboxylic chloride in the presence of Et_3N to afford α-ketoester **8** in a quantitative yield. Chemoselective reduction of the ketone and simultaneous Boc deprotection in **8** were achieved in a quantitative yield by using Et_3SiH in the presence of TFA. Finally, treatment of **9** with LiOH in wet methanol afforded target compound **10** in 91% yield. Furthermore, to examine the enantiomeric excess (*ee*) of the chiral center at C-1 in **10**, 1,2,3,4-tetrahydro-β-carboline **11** was prepared by reduction of the lactam function and subjected to chiral HPLC analysis[8]. It was revealed that the *ee* of **11** was 99%, meaning that the chirality of L-leucine was retained in high purity.

A comparison of the experimental ECD spectra between ophiorrhiside A (**1**) and model compound **10** is shown in Figure 2. The Cotton effects of **1** and **10** were quite similar, demonstrating that the absolute configuration at C-3 in **1** was *S*, as proposed.[4a]

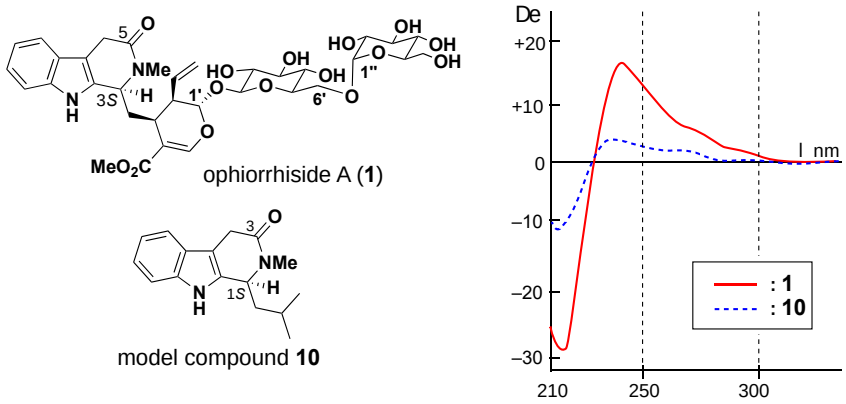


Figure 2. Comparison of experimental ECD spectra of compounds **1** and **10**

In conclusion, we have elucidated the absolute configuration at C-3 in monoterpenoid glucoindole alkaloid ophiorrhiside A by comparing the experimental ECD spectrum of ophiorrhiside A (**1**) with that of chiral model compound **10**, which was synthesized from L-leucine and has the 1,2,3,4-tetrahydro-β-carbolin-3-one skeleton.

EXPERIMENTAL

UV spectra were recorded in MeOH on a JASCO V-560 instrument. IR spectra were recorded on a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on JNM ECZ-600 and JNM ECA-600 at 600 MHz (^1H) or 150 MHz (^{13}C), respectively. ESIMS spectra were recorded on a JEOL JMS T100GCV. HRESIMS spectra were recorded on a JEOL JMS-T100LP (AccuTOF LC-plus). Optical rotation was measured with JASCO P-2200 polarimeter. ECD was measured with JASCO J-720WI. Melting point (m.p.) was measured with Yanagimoto Micro Melting Point Apparatus 1631A.

TLC was performed on precoated silica gel 60 F_{254} plates (Merck, 0.25 mm thick) and precoated amino-silica gel plates (Fuji Silysia Chemical). Column chromatography was carried out on silica gel 60N [Kanto Chemical, 40–50 μm (for flash chromatography)], Chromatorex NH-DM2035 [Fuji Silysia Chemical (for amino-silica gel flash chromatography)], and Chromatorex NH [Fuji Silysia Chemical, 100–200 mesh (for amino-silica gel chromatography)].

Weinreb amide 4. To a solution of L-leucine (**3**, 1.31 g, 10.0 mmol) in THF (20 mL, 0.5 M) and 1 *N* NaOH aq. (10 mL, 1.0 eq.) was added Boc_2O (2.41 mL, 1.05 eq.) at room temperature under an Ar atmosphere. After stirring for 19.5 h at the same temperature, the reaction was quenched by adding 10% citric acid aq. to pH 4-5. The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was used in the next reaction without further purification. To a solution of the above residue in THF (20 mL, 0.5 M) was added portionwise NaH (2.4 g, 6 eq.) at 0 °C under an Ar atmosphere. After the reaction mixture was stirred for 30 min at the same temperature, MeI (1.9 mL, 3.0 eq.) and DMF (1 mL, 5% v/v) were added to the reaction mixture. After stirring for 14.5 h at room temperature under an Ar atmosphere, the reaction mixture was diluted with AcOEt and water at 0 °C. The aqueous layer was washed with AcOEt, acidified with 1 *N* HCl aq. to pH 4-5, and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was used in the next reaction without further purification. To a solution of the above residue in DCM (45 mL, 0.2 M) was added CDI (1.84 g, 1.2 eq.) at 0 °C. After stirring for 40 min at the same temperature under an Ar atmosphere, NH(OMe)Me·HCl (1.08 g, 1.2 eq.) was added to the reaction mixture. The reaction mixture was stirred for 2 h at room temperature, diluted with Et_2O, washed two times with 1 *N* HCl aq. and then with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (AcOEt/*n*-hexane = 1:4) to afford **4** (2.08 g, 72% over 3 steps) as a colorless oil; $[\alpha]_D^{23}$ –61.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) (mixture of rotational isomers) δ ppm 5.29 (0.5H, br s), 5.07 (0.5H, br s), 3.75 (1.5H, s), 3.70 (1.5H, s), 3.18 (3H, s), 2.85 (3H, s), 1.66 (1H, m), 1.56–1.48 (2H, overlapped), 1.46 (4.5H, s), 1.45 (4.5H, s), 0.95–0.94 (6H, overlapped); ^{13}C NMR (150 MHz, $CDCl_3$) (mixture of rotational isomers) δ ppm 173.3, 172.5, 156.0, 155.4, 80.0, 79.9, 79.5, 61.5, 61.3, 52.9, 51.7, 37.6, 37.4, 32.2, 31.9, 29.9, 29.4, 28.4, 28.3, 24.8, 24.4, 23.1, 21.74, 21.67; HRMS (ESI) *m*/*z* found 311.1950 $[M+Na]^+$, calcd for $C_{14}H_{28}N_2NaO_4$ 311.1947; IR (ATR) ν_{max} cm^{-1} 2958, 1695, 1674, 1456, 1392, 1367, 1325, 1157, 1127, 996.

Alkyne 5. To a solution of **4** (609 mg, 2.1 mmol) in DCM (5.3 mL, 0.4 M) was added DIBAL-H (1.0 M in hexane, 3.1 mL, 1.5 eq.) at –78 °C under Ar atmosphere. After stirring for 45 min at the same temperature, the reaction was quenched by adding dry MeOH (5.3 mL, 100% v/v) at the same temperature and then stirred for 10 min. To the reaction mixture were added Ohira-Bestmann reagent (475 μL, 1.5 eq.) and K_2CO_3 (1.02 g, 3.5 eq.) at 0 °C. After stirring for 20 h at room temperature, the reaction was quenched by adding saturated potassium sodium tartrate aq. at the same temperature and then stirred for 3 h at room temperature. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (AcOEt/*n*-hexane = 0:1 to 1:19 gradient) to afford **5** (406 mg, 85% over 2 steps) as a colorless oil; $[\alpha]_D^{24}$ –46.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C) δ ppm 5.00 (1H, br s), 2.82 (3H, s), 2.25 (1H, d, *J* = 1.4 Hz), 1.65 (1H, m), 1.56–1.49 (2H, overlapped), 1.46 (9H, s), 0.95 (3H, d, *J* = 6.2 Hz), 0.93 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, 55 °C) δ ppm 155.1, 82.6, 79.9, 71.8, 46.3, 42.6, 28.8, 28.4, 24.9, 22.4, 22.2; HRMS (ESI) *m*/*z* found 248.1622 $[M+Na]^+$, calcd for $C_{13}H_{23}NNaO_2$ 248.1627; IR (ATR) ν_{max} cm^{-1} 3314, 3249, 2960, 2933, 2871, 1688, 1470, 1455, 1389, 1366, 1319, 1255, 1146, 1109.

Aniline derivative 6. To a solution of CuI (19.0 mg, 10 mol%) and $Pd(PPh_3)_2Cl_2$ (35.8 mg, 5 mol%) in degassed DMF (5 mL) and Et_3N (1.1 mL, 8 eq.) was added a solution of **5** (226.0 mg, 1.0 mmol) and 2-iodoaniline (268.2 mg, 1.2 eq.) in degassed DMF (5 mL) via cannula over 25 min at room temperature under an Ar atmosphere. After stirring for 2 h at the same temperature, the reaction was quenched by adding saturated NH_4Cl aq. at 0 °C. The aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (Et_2O/*n*-hexane = 1:4) to afford **6** (253.5 mg, 80%) as a yellowish oil; $[\alpha]_D^{25}$ –82.7 (*c* 0.81, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C) δ ppm 7.23 (1H, d, *J* = 7.6 Hz), 7.08 (1H, dd, *J* = 7.6, 7.6 Hz), 6.66–6.64 (2H, overlapped), 5.24 (1H, br s), 4.12 (2H, br s), 2.88 (3H, s), 1.71 (1H, m), 1.65 (1H, dd, *J* = 13.1, 7.6 Hz), 1.61 (1H, dd, *J* = 13.1, 7.6 Hz), 1.48 (9H, s), 0.99 (3H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, 55 °C) δ ppm 155.2, 147.9, 132.3, 129.5, 117.9, 114.3, 107.9, 93.3, 80.9, 80.0, 47.3, 43.1, 29.2, 28.5, 25.2, 22.6, 22.3; HRMS (ESI) *m*/*z* found 339.2056 $[M+Na]^+$, calcd for $C_{19}H_{28}N_2NaO_2$ 339.2049; IR (ATR) ν_{max} cm^{-1} 3475, 3365, 2957, 2933, 2871, 1684, 1615, 1492, 1456, 1389, 1366, 1319, 1147.

Indole 7. To a solution of **6** (166.8 mg, 0.53 mmol) in THF (5.3 mL, 0.1 M) was added $NaAuCl_4 \cdot 2H_2O$ (21 mg, 10 mol%) at room temperature under an Ar atmosphere. After stirring for 2 h at the same temperature, the reaction mixture was evaporated under reduced pressure and then passed through a pad

of amino-silica gel (AcOEt/*n*-hexane = 1:1). The filtrate was concentrated under reduced pressure and then purified by silica gel flash chromatography (acetone/*n*-hexane = 1:15) to afford **7** (136.6 mg, 82%) as a white amorphous powder; $[\alpha]_D^{22}$ –130.4 (*c* 1.0, $CHCl_3$); UV (MeOH) λ_{max} nm 289, 280, 270, 223; ^{1}H NMR (600 MHz, $CDCl_3$, 55 °C) δ ppm 8.56 (1H, br s), 7.54 (1H, d, *J* = 7.6 Hz), 7.29 (1H, d, *J* = 7.6 Hz), 7.13 (1H, dd, *J* = 7.6, 7.6 Hz), 7.06 (1H, dd, *J* = 7.6, 7.6 Hz), 6.35 (1H, d, *J* = 0.9 Hz), 5.41 (1H, dd, *J* = 8.9, 6.2 Hz), 2.61 (3H, s), 1.89 (1H, m), 1.81 (1H, m), 1.65 (1H, m), 1.51 (9H, s), 1.00 (6H, d, *J* = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, 55 °C) δ ppm 157.0, 138.9, 136.2, 128.1, 122.0, 120.4, 119.7, 110.8, 100.4, 80.2, 51.2, 39.1, 28.8, 28.6, 25.0, 23.2, 22.2; HRMS (ESI) *m*/*z* found 339.2043 $[M+Na]^+$, calcd for $C_{19}H_{28}N_2NaO_2$ 339.2049; IR (ATR) ν_{max} cm^{-1} 3312, 2957, 2931, 1671, 1478, 1457, 1393, 1367, 1339, 1326, 1288, 1217, 1155, 1110, 790, 758.

α-Ketoester 8. To a solution of **7** (170.0 mg, 0.54 mmol) in THF (5.4 mL, 0.1 M) was added fleshly distilled $(COCl)_2$ (141 μL, 3 eq.) at 0 °C under an Ar atmosphere. After the reaction mixture was stirred for 3.5 h at the same temperature, a solution of Et_3N (0.75 mL, 10 eq.) in MeOH (2.7 mL, 50% v/v) was added to the reaction mixture. After stirring for 30 min at 0 °C, the reaction mixture was diluted with water and extracted three times with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (AcOEt/*n*-hexane = 1:4) to afford **8** (218.7 mg, quant) as a yellowish amorphous powder; $[\alpha]_D^{23}$ +148.1 (c 1.0, $CHCl_3$); UV (MeOH) λ_{max} nm 317, 268 (sh), 249, 219; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 11.27 (1H, br s), 7.66 (1H, d, *J* = 7.6 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.26–7.24 (2H, overlapped), 5.42 (1H, br s), 4.02 (3H, s), 3.02 (3H, s), 2.43 (1H, br s), 1.82 (1H, m), 1.56 (1H, m), 1.49 (9H, s), 0.99–0.97 (6H, overlapped); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 182.0, 166.1, 157.9, 157.4, 150.8, 135.1, 125.3, 123.6, 122.7, 119.6, 112.2, 108.4, 80.8, 55.9, 53.6, 52.7, 41.1, 39.0, 28.4, 25.5, 23.0, 22.0; HRMS (ESI) *m*/*z* found 425.2066 $[M+Na]^+$, calcd for $C_{22}H_{30}N_2NaO_5$ 425.2052; IR (ATR) ν_{max} cm^{-1} 3283 (br), 2959, 1742, 1668, 1643, 1489, 1450, 1390, 1367, 1331, 1275, 1246, 1152, 1115, 998, 757.

Compound 9. Compound **8** (282.2 mg, 0.70 mmol) was dissolved in TFA (7.0 mL, 0.1 M) with stirring at 0 °C under an Ar atmosphere. To the solution was added Et_3SiH (0.46 mL, 4 eq.) at the same temperature, and the reaction mixture was stirred for 7.5 h at room temperature. After adding an additional amount of Et_3SiH (0.23 mL, 2.0 eq.) at room temperature, the reaction mixture was stirred for additional 14 h at the same temperature. The reaction was quenched by adding saturated $NaHCO_3$ aq. at 0 °C and extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by amino-silica gel flash chromatography (acetone/*n*-hexane = 1:9 to 1:4 gradient) to afford **9** (202.6 mg, quant) as a

yellowish oil; $[\alpha]_D^{23}$ –13.0 (c 0.82, MeOH); UV (MeOH) λ_{max} nm 290, 282, 274, 223; ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.52 (1H, br s), 7.58 (1H, d, *J* = 7.6 Hz), 7.30 (1H, d, *J* = 7.6 Hz), 7.15 (1H, br dd, *J* = 7.6, 7.6 Hz), 7.10 (1H, br ddd, *J* = 7.6, 7.6, 1.4 Hz), 3.95 (1H, dd, *J* = 6.9, 6.9 Hz), 3.76 (2H, s), 3.64 (3H, s), 2.29 (3H, s), 1.61 (2H, t, *J* = 6.9 Hz), 1.55 (1H, m), 0.94 (3H, d, *J* = 6.2 Hz), 0.89 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 172.2, 138.2, 135.1, 128.4, 121.6, 119.4, 118.4, 110.7, 105.3, 54.9, 51.8, 46.1, 34.8, 30.2, 25.0, 23.0, 22.7; HRMS (ESI) *m*/*z* found 289.1903 $[M+H]^+$, calcd for $C_{17}H_{25}N_2O_2$ 289.1916; IR (ATR) ν_{max} cm^{-1} 2954, 2871, 1732, 1462, 1435, 1307, 1272, 1163, 1013, 743.

Compound 10. To a solution of **9** (106.8 mg, 0.37 mmol) in wet-MeOH (7.4 mL, 0.025 M) was added $LiOH\cdot H_2O$ (31.1 mg, 2.0 eq.) at room temperature under an Ar atmosphere. After stirring for 17.5 h at the same temperature, the reaction mixture was diluted with water and extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by amino-silica gel flash chromatography (AcOEt/*n*-hexane = 3:1) to afford **10** (85.9 mg, 91%) as a white solid. Recrystallization of **10** with vapor diffusion method between AcOEt and *n*-hexane afforded colorless crystal; mp 201–202 °C; $[\alpha]_D^{24}$ +6.9 (*c* 0.58, MeOH, 99% *ee*); UV (MeOH) λ_{max} nm 289, 281, 273, 223; ECD (*c* 0.38 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ nm) 0 (290), +1.6 (266), +3.7 (237), 0 (228), –10.9 (215); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.25 (1H, br s), 7.48 (1H, d, *J* = 8.3 Hz), 7.37 (1H, d, *J* = 8.3 Hz), 7.21 (1H, ddd, *J* = 8.3, 8.3, 1.4 Hz), 7.14 (1H, dd, *J* = 8.3, 8.3 Hz), 4.68 (1H, m), 3.78 (1H, dd, *J* = 20.7, 2.1 Hz), 3.67 (1H, dd, *J* = 20.7, 2.8 Hz), 3.13 (3H, s), 1.88 (1H, ddd, *J* = 14.5, 6.9, 5.5 Hz), 1.80 (1H, ddd, *J* = 14.5, 7.6, 3.5 Hz), 1.64 (1H, m), 0.90 (3H, d, *J* = 6.2 Hz), 0.82 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 169.4, 136.7, 130.8, 125.9, 122.4, 119.9, 118.3, 111.0, 106.1, 57.8, 43.3, 33.9, 29.5, 24.0, 23.7, 22.8; HRMS (ESI) *m*/*z* found 279.1478 $[M+Na]^+$, calcd for $C_{16}H_{20}N_2NaO$ 279.1473; IR (ATR) ν_{max} cm^{-1} 3254 (br), 2954, 2930, 2873, 1620, 1491, 1461, 1420, 1403, 1324, 1277, 1230, 742.

1,2,3,4-Tetrahydro-β-carboline 11. To a solution of **10** (8.3 mg, 0.03 mmol) in THF (0.65 mL, 0.05 M) was added $LiAlH_4$ (6.7 mg, 5.0 eq.) at 0 °C. After stirring for 2 h at 50 °C under an Ar atmosphere, the reaction mixture was quenched by adding saturated potassium sodium tartrate aq. at 0 °C and then stirred for 1 h at room temperature. The aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by amino-silica gel flash chromatography (AcOEt/*n*-hexane = 3:17) to afford **11** (7.6 mg, 97%) as a white solid. Recrystallization of **11** from hot *n*-hexane afforded colorless crystal; mp 109–110 °C; $[\alpha]_D^{24}$ –4.5 (*c* 0.44, MeOH, 99% *ee*); UV (MeOH) λ_{max} nm 289, 281, 274, 225; ECD (*c* 0.50 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ nm) 0 (306), +0.5 (295), +0.35 (290), +0.5 (286), +0.47 (282),

+0.75 (271), 0 (255), –0.8 (243), 0 (239), +1.2 (234), 0 (229), –6.1 (216); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.65 (1H, br s), 7.49 (1H, d, *J* = 7.6 Hz), 7.31 (1H, d, *J* = 8.3 Hz), 7.14 (1H, br ddd, *J* = 8.3, 7.6, 1.4 Hz), 7.09 (1H, br dd, *J* = 7.6, 7.6 Hz), 3.61 (1H, dd, *J* = 6.5, 6.5 Hz, H-3), 3.19 (1H, ddd, *J* = 13.1, 8.3, 5.5 Hz, H-6), 2.88 (1H, ddd, *J* = 13.1, 4.8, 4.8 Hz, H-6), 2.88 (1H, m), 2.65 (1H, ddd, *J* = 15.2, 5.5, 4.1 Hz), 2.47 (3H, s), 1.93 (1H, m), 1.73 (1H, ddd, *J* = 14.2, 7.8, 6.0 Hz), 1.56 (1H, ddd, *J* = 14.2, 7.8, 5.5 Hz), 1.01 (3H, d, *J* = 6.9 Hz), 0.96 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 135.7, 135.5, 127.3, 121.3, 119.3, 118.0, 110.6, 107.4, 57.6, 47.6, 43.2, 41.4, 25.3, 23.2, 22.7, 17.7; HRMS (ESI) *m*/*z* found 243.1858 $[M+H]^+$, calcd for $C_{16}H_{23}N_2$ 243.1861; IR (ATR) ν_{max} cm^{-1} 2954, 2928, 1465, 1445, 1365, 1341, 1302, 1158, 1030, 1007, 742, 616.

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8. Chiral HPLC analysis: Daicel CHIRALPAK® (25 cm × 0.46 cm) AD-H; eluent: *i*-PrOH/*n*-hexane = 1:4; flow rate: 0.50 mL/min; temperature: 40 °C; retention time: t_r (minor) = 7.67 min, t_r (major) = 8.74.