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Total syntheses of (−)-vallesamidine and related *Aspidosperma* and *Hunteria* type indole alkaloids from the common intermediate

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Dedicated to Professor A. Ian Scott on the occasion of his 75th birthday

Abstract—A new synthetic method of (−)-vallesamidine, including a unique 2,2,3-trialkylindoline skeleton, was developed by reductive radical cyclization reaction from the 2,3-dialkylindole derivative, which has been known to be an intermediate for the synthesis of aspidospermidine.

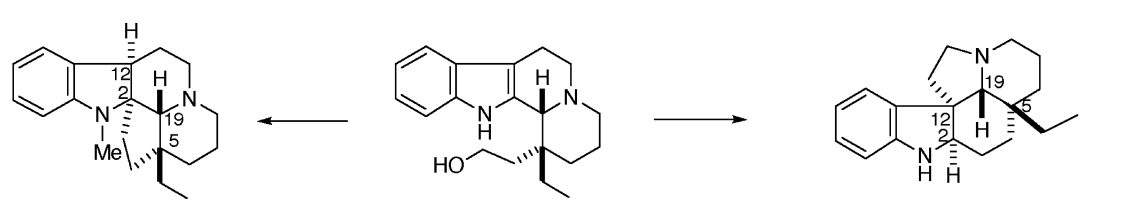
1. Introduction

Vallesamidine **1** is one of 28 alkaloids isolated from *Vallesia dichotoma* Ruiz and Pav in 1965 and its structure and absolute configuration were determined by Djerassi in 1968.[1] The defined structure shows a unique and abnormal indole alkaloid including a 2,2,3-trialkylindoline skeleton, which differs from (+)-aspidospermidine **2**, a typical indole alkaloid, having 2,3,3-trialkylindoline chromophore (Scheme 1). The stereochemistry of vallesamidine at C-5 and C-19 is identical to that of aspidospermidine, suggesting that these two alkaloids are possibly biosynthesized from the same intermediate. A great amount of research has been reported on the synthesis of 2,3,3-trialkylated indoline alkaloids such as *Aspidosperma* and *Strychnos* families,[2] but little research has been carried out on 2,2,3-trialkylated indoline alkaloids such as vallesamidine.[3]

In 1990, Heathcock reported the first total synthesis of (±)-vallesamidine via newly developed methodology, wherein the indolenine skeleton is formed in the late stage of its synthesis.[4] In his paper, it is noted that alkylation at C-2 of a 2,3-disubstituted indole **3** is not generally useful, because of the propensity of the resulting cation to rearrange to the more stable 2,3,3-trialkylindolenium ion. In fact, Harley-Mason,[5] Fuji[6] and Schultz[7] have succeeded in the synthesis of the aspidosperidine skeleton from **3**, being used as a key intermediate, in the cyclization which includes the interesting rearrangement as shown in Scheme 2.

On the other hand, Levy's elegant transformation of the pentacyclic vallesamidine skeleton from tabersonine was achieved by treatment with Zn powder in acetic acid.[8] It has been proposed that 2,2,3-trialkylindoline intermediate **6** is included in the equilibrium reaction mixture, in addition to 2,3,3-trialkylindoline **4** and quebrachamine chromophore **5** (Scheme 3). In this way, enantiomeric (+)-vallesamidine was obtained in 24% yield.

Because of the above discussion, we have been interested in investigating a new synthetic approach to vallesamidine wherein the reductive radical cyclization of the known 2,3-dialkylindole derivative **3a** provides the 2,2,3-trialkylindoline skeleton. Although many novel ring systems and



Scheme 1.

Keywords: Radical reaction; Cyclization; Indole; Asymmetric synthesis.
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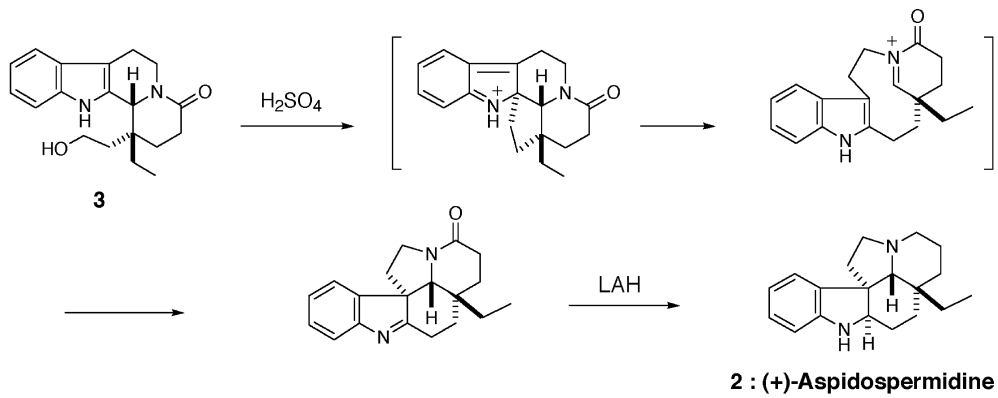
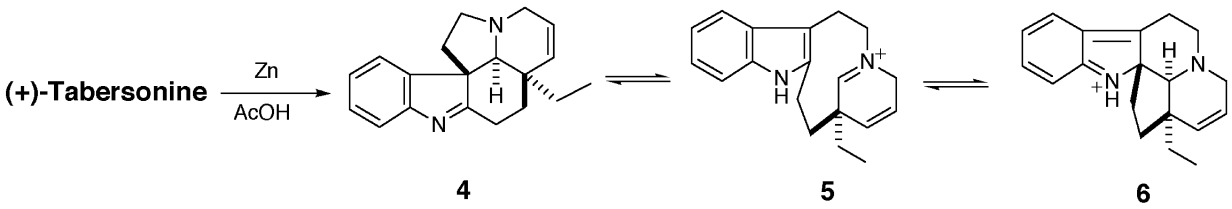


Scheme 2.



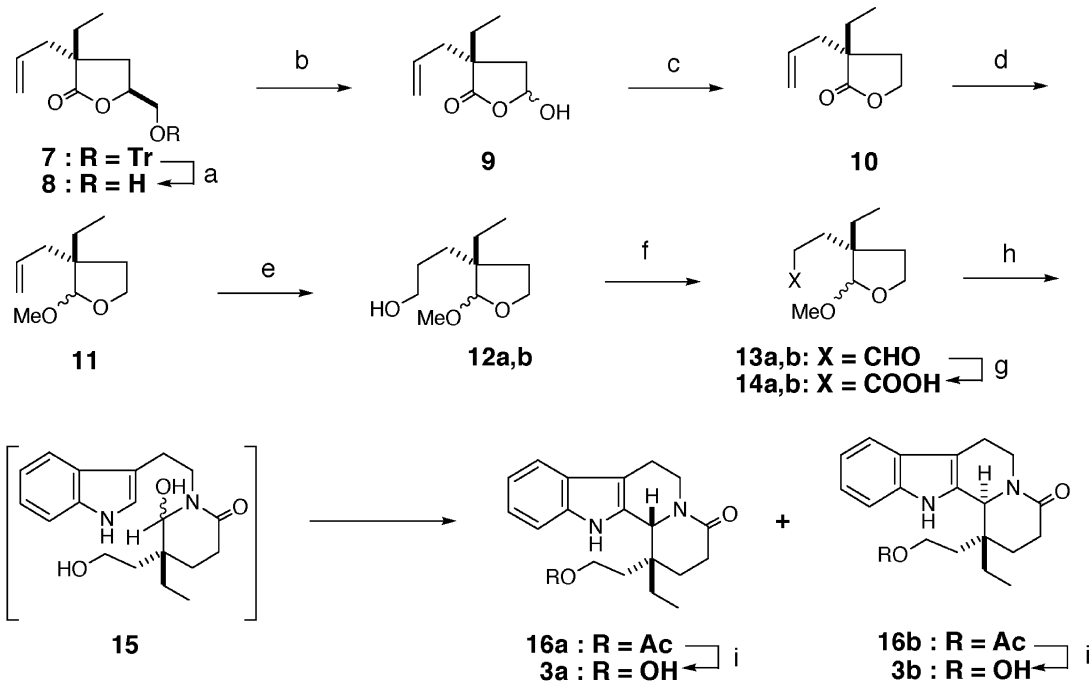
Scheme 3.

natural products have been synthesized by radical reactions, a small amount of research has been devoted to the synthesis of indoline alkaloids.[9] In this article, we first describe a successful total synthesis of (−)-vallesamidine **1** from **3a**, prepared by the following line (Scheme 4),[10] and second the additional transformation of **3a** into (+)-aspidospermidine **2** and (+)-dihydroeburnamenine **24a** from the common intermediate **3a**.

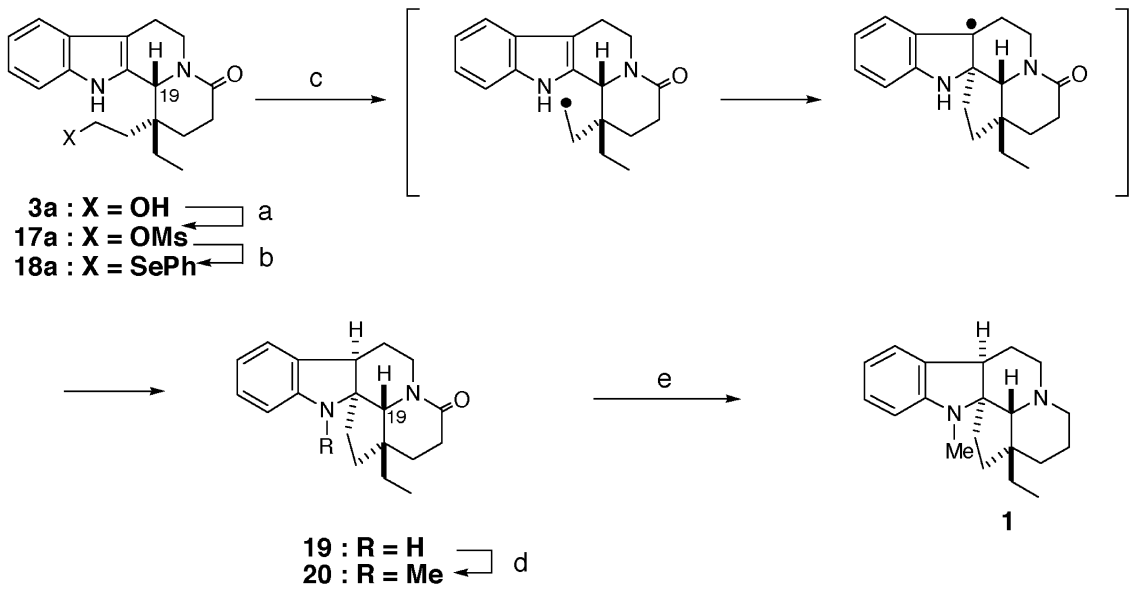
2. Results and discussion

2.1. Synthesis of (−)-vallesamidine

The synthesis of the chiral key intermediate **3a** was started from **7**, which was obtained from the double alkylation of (*S*)-γ-trityloxymethyl-γ-butyrolactone by using the method reported by Koga.[11] Detritylation of **7** afforded an alcohol **8**



Scheme 4. Reagents and conditions: (a) 80% AcOH, 80 °C, 1 h; (i) 4 M aq. NaOH, dioxane, 100 °C, 1 h; (ii) CO_2; (iii) aq. $NaIO_4$, rt, 3 h; (iv) 1 M HCl; (c) (i) $NaBH_4$, MeOH, rt, 1 h; (ii) 4 M HCl–MeOH, 70 °C, 1 h; (d) (i) DiBAL–H, Et_2O, −78 °C, 1 h; (ii) $CH(OMe)_3$, *p*-TsOH, MeOH, 80 °C, 40 min; (e) (i) 9-BBN, THF, rt, overnight; (ii) 30% H_2O_2, 3 M aq. NaOH, THF, rt, 1 h; (f) SO_3-Py, DMSO, TEA, CH_2Cl_2, rt, 0.5 h; (g) $NaClO_2$, *t*-BuOH, aq. NaH_2PO_4, $Me_2C{=}CHMe$, rt, 1 h; (h) tryptamine, AcOH, 125 °C, 6 days; (i) 20% aq. NaOH, MeOH, rt, 1 h.



Scheme 5. Reagents and conditions: (a) MsCl, pyridine, 0 °C, 2 h; (b) $(PhSe)_2$, $NaBH_4$, EtOH, 0 °C→rt, 3 h; (c) *n*-Bu_3SnH, AIBN, toluene, 100 °C, 0.5 h; (d) 35% HCHO, $NaBH_3CN$, CH_3CN, then AcOH, rt, 1 h; (e) LAH, THF, 70 °C, 0.5 h.

in 98% yield, which was hydrolyzed with 4 M aqueous NaOH in dioxane followed by neutralization with CO_2. The resulting mixture was oxidized with sodium periodate to give hemiacetal **9** in 95% yield. Reduction of **9** with sodium borohydride in methanol gave γ-lactones **10** (92%). The lactone was then converted to methylacetal **11** by reduction with diisobutylaluminum hydride at −78 °C, followed by treatment with trimethyl orthoformate and *p*-toluenesulfonic acid in methanol, in 84% yield in two steps. Transformation of the double bond in **11** into primary alcohols **12a**,**b** was performed by following successive reactions of hydroboration with 9-BBN in THF and oxidation with hydrogenperoxide in alkali in 87% yield. The alcohols **12a**,**b** were further oxidized to carboxylic acids **14a**,**b** (95% yield)[12] via **13a**,**b** in the usual way.

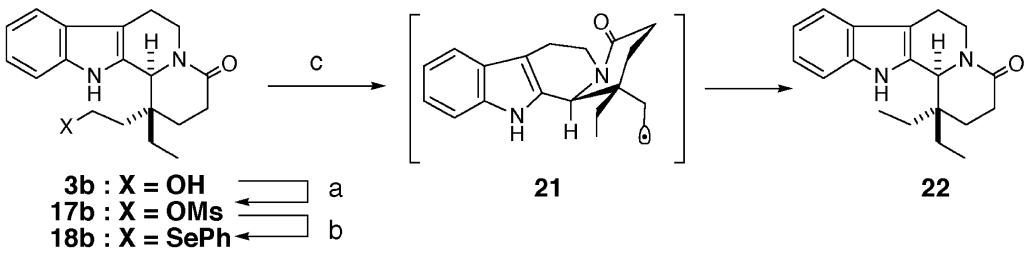
The next condensation reaction was performed by heating the mixture of carboxylic acids **14a**,**b** with tryptamine in AcOH at refluxing temperature. In this reaction mixture, the intermediate **15** was always detected on a silica gel TLC. The structure of **15** was proposed by spectral data and further confirmed by its chemical transformation into the same products **16a**,**b**. After 6 days, the intermediate **15** completely disappeared and then, the reaction mixture was separated by using a silica gel column chromatography to give a tetracyclic indole lactam derivatives **16a** (43%) and **16b** (44%)[6] as acetates. Exposure of **16a** to 20% aqueous NaOH in MeOH solution afforded the desired alcohol **3a**, corresponding to the natural form, and **16b** gave another stereoisomer **3b** under the same conditions. The stereochemistry of each product was characterized by comparison with ^{1}H NMR spectra of the authentic samples.[6] The structure of **3a** was further confirmed by the conversion into the known compound (+)-aspidospermidine **2** under the usual acidic conditions followed by LAH reduction.[6] The next approach from **3a** to **1** is outlined in Scheme 5.

The primary hydroxy group in the side chain of **3a** was converted into mesylate by using MsCl–DMAP in pyridine at 0 °C in 92% yield. The resulting mesylate **17a** was treated with diphenydiselenide and $NaBH_4$ in EtOH at room temperature, giving the desired selenide **18a** in 68% yield together with N-alkylated product (4% yield, *Hunteria* type chromophore). Treatment of the selenide **18a** with a mixture of tributyltin hydride (*n*-Bu_3SnH) and 2,2′-azobisisobutyronitrile (AIBN) in toluene at 100 °C under argon for 30 min gave a single product in 91% yield, the structure of which was assumed to be pentacyclic compound **19** based on the following physical data; in ^{1}H NMR (δ): the signal at 4.77 ppm (lH, s; C19-proton) of **18a** moved to 3.28 ppm (lH, s); in ^{13}C NMR (δ): two sp^2 carbon signals at 126–136 ppm, corresponding to α and β-carbon in the indole ring of **18a**, disappeared and in place of these signals, two new signals were observed at 44.6 ppm (–CH–) and 76.3 ppm (quaternary carbon). N-Methylation of **19** with the mixture of HCHO–$NaBH_3CN$–AcOH in acetonitrile gave **20** in 87% yield.

Finally, reduction of the lactam **20** by using LAH in THF under refluxing temperature for 30 min was achieved to provide (−)-vallesamidine **1** in 82% yield. The structure of the synthetic material was confirmed by comparison with the physical data reported by Heathcock.[4b]

2.2. Radical reduction of the epimer 18b

Another stereoisomer **3b** was also converted into phenylselenide **18b** through mesylate **17b** as shown in Scheme 6. Exposure of the isomer **18b** with *n*-Bu_3SnH and AIBN in toluene at 100 °C for 1 h under an argon atmosphere gave a single product **22** in 70% yield. None of the cyclized product was detected on silica gel TLC. The ^{1}H NMR spectrum of **22** indicated the presence of two methyl groups. This observation may reflect a reduction of the radical intermediate generated from the 2′-phenylselenylethyl side chain in **18b**, because the location of the radical is separated from indole ring as depicted in **21**.



Scheme 6. Reagents and conditions: (a) MsCl, DMAP, pyridine, 0 °C, 2 h; (b) $(PhSe)_2$, $NaBH_4$, EtOH, 0 °C, 0.5 h→rt, 3 h; (c) *n*-Bu_3SnH, AlBN, toluene, 100 °C, 1 h.

2.3. Syntheses of (+)-dihydroeburnamenine 24a and (−)-epidihydroeburnamenine 24b

It is interesting to note that the mesylate **17b** was readily converted into N-alkylated pentacyclic product **23b** by treatment with NaOH in THF at room temperature in 88% yield, although ring closure of **18b** was not observed under radical reaction conditions as described above. The other stereoisomer of the masylate **17a** was also converted into a cyclization product **23a** in 94% yield with alkali. (+)-Dihydroeburnamenine **24a** was obtained from **23a** on reduction with $LiAlH_4$ in THF under refluxing temperature in 91% yield. Reduction of another isomer **23b** was not succeeded under the same conditions because of decomposition. However, when **23b** was treated with an excess amount of $NaBH_4$–TFA in dioxane, the desired (−)-epidihydroeburnamenine **24b** was obtained in 87% yield (Scheme 7). The structures of **24a**[6] and **24b**[3,6,13] were characterized by comparison with the physical data reported in the literature, respectively.

3. Conclusions

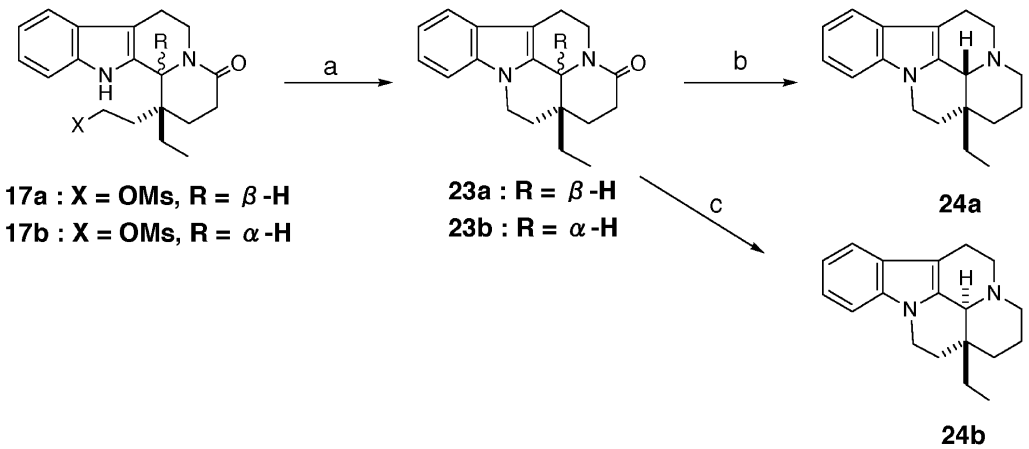
We have developed a new strategy for preparation of the 2,2,3-trialkylindoline skeletons via reductive radical cyclization reaction, and demonstrated five steps for the synthesis of vallesamidine **1** from the intermediate **3a**, which has been known to be a common substrate for the synthesis of *Aspidosperma* and *Hunteria* type indole alkaloids. It is noteworthy that vallesamidine **1** and the co-occurring aspidosperma-type indole alkaloids have been shown to have the same absolute configuration at carbon 2, 5, 12, 19, which may suggest one route for biosynthesis of these alkaloids is carried out from the common intermediate **3a**.

4. Experimental

4.1. General information

All melting points were uncorrected. ^1H NMR spectra (600 MHz) and ^{13}C NMR spectra (150 MHz) were recorded on a JEOL JNM-A 600 spectrometer. ^{13}C NMR assignments were carried out using DEPT experiments. IR spectra were recorded on a JASCO IR-810 spectrometer. UV spectrum was recorded on a JASCO UVIDEC-6100 spectrometer. MS spectra were recorded on a JEOL-MS700. Optical rotations were measured on a JASCO DIP-370 polarimeter. Separation of the products by flash column chromatography was carried out on silica gel (Fuji Silysia Chem. Co., BW-300). Separation of the products by TLC was carried out on silica gel (MERCK 1.05744).

4.1.1. (2*R*)-2,3-Dideoxy-2-ethyl-2-(2-propenyl)-D-glyceropentanoic acid γ-lactone (8). A solution of **7** (1.96 g, 4.60 mmol) in 80% AcOH (15.5 mL) was stirred at 80 °C for 1 h. After the mixture was concentrated under reduced pressure, the residue was diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The residual oil was purified by flash column chromatography on silica gel with hexane–AcOEt (1:1) as eluant to give **8** (827 mg, 98%) as a colorless oil; $[\alpha]_D^{20}$ +22.3° (*c* 1.7, $CHCl_3$); IR (neat) 3450, 1760, 1645, 1195, 930 cm^{-1}; ^1H



Scheme 7. Reagents and conditions: (a) NaOH, THF, rt, 20 min; (b) LAH, TAF, 70 °C, 0.5 h; (c) $NaBH_4$, TFA, dioxane, 100 °C, 45 min.

NMR ($CDCl_3$): δ 0.93 (3H, t, J=7.3 Hz), 1.58–1.73 (2H, m), 2.03 (1H, dd, J=13.2, 7.8 Hz), 2.09 (1H, dd, J=13.2, 9.3 Hz), 2.30 (1H, dd, J=13.7, 7.8 Hz), 2.37 (1H, dd, J=13.7, 7.3 Hz), 3.59 (1H, dd, J=12.7, 4.9 Hz), 3.88 (1H, dd, J=12.7, 2.9 Hz), 4.44–4.54 (1H, m), 5.13–5.22 (2H, m), 5.71–5.86 (1H, m); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.6 (CH_3), 29.2 (CH_2), 31.6 (CH_2), 41.5 (CH_2), 48.6 (C), 63.9 (CH_2), 77.7 (CH), 119.5 (CH_2), 132.6 (CH), 180.8 (C); MS (EI): 184 (M^+); HRMS (EI), calcd for $C_{10}H_{16}O_3$: 184.1099; found: 184.1122.

4.1.2. (3*R*)-3-Ethyldihydro-5-hydroxy-3-(2-propenyl)-2(3*H*)-furanone (9). To a solution of **8** (827 mg, 4.49 mmol) in dioxane (113 mL) was added 4 M aqueous NaOH (45 mL) and the mixture was heated at 100 °C for 1 h. After cooling, the reaction mixture was neutralized with dry ice. To the milky suspension was added a solution of $NaIO_4$ (2.42 g, 11.3 mmol) in H_2O (20 mL) and the suspension was stirred at room temperature for 3 h. After quenched with 1 M HCl–H_2O (180 mL), the reaction mixture was extracted with CH_2Cl_2 (3×100 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4 and concentrated. The residual oil was purified by flash column chromatography on silica gel with hexane–AcOEt (2:1) as eluant to afford diastereoisomers **9** (727 mg, 95%) as colorless oil. The ratio of the diastereoisomeric mixture could not be determined because of broad signals observed in the ^{1}H NMR spectrum; IR (neat) 3400, 1750, 1645, 1195, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.94 (3H, br s), 68 (2H, br s), 2.07 (1H, br s), 2.35 (2H, br s), 4.98 (1H, br s), 5.10–5.20 (2H, br m), 5.73 (1H, br s), 5.83 (1H, br s); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.7 (CH_3), 29.8 (CH_2), 38.4 (CH_2), 41.0 (CH_2), 48.4 (C), 96.9 (CH), 119.7 (CH_2), 132.8 (CH), 180.6 (C); MS (EI): 170 (M^+); HRMS (EI), calcd for $C_9H_{14}O_3$: 170.0943; found: 170.0932.

4.1.3. (3*R*)-3-Ethyldihydro-3-(2-propenyl)-2(3*H*)-furanone (10). Sodium borohydride (156 mg, 4.12 mmol) was added to a solution of **9** (350 mg, 2.06 mmol) in MeOH (7.7 mL). After stirring at room temperature for 1 h, the reaction mixture was acidified with 4 M HCl–MeOH (0.94 mL) and heated at 70 °C for 1 h. After the reaction mixture was allowed to cool to room temperature, the resulting mixture was diluted with CH_2Cl_2 and the solution was washed with saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4 and concentrated. The residual oil was purified by flash column chromatography on silica gel with hexane–AcOEt (4:1) as eluant to afford **10** (293 mg, 92%) as a colorless oil; $[\alpha]_D^{20}$ −23.3° (c 1.6, $CHCl_3$); IR (neat) 2980, 1770, 1375, 1190, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96 (3H, t, J=7.3 Hz), 1.65 (2H, qd, J=7.3, 1.5 Hz), 2.10 (1H, dq, J=14.6, 7.3 Hz), 2.19 (1H, dq, J=14.6, 7.3 Hz), 2.30 (1H, ddt, J=13.7, 8.3, 1.0 Hz), 2.17 (1H, ddt, J=13.7, 6.8, 1.5 Hz), 4.22 (2H, t, J=7.3 Hz), 5.12–5.19 (2H, m), 5.68–5.82 (1H, m); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.7 (CH_3), 29.2 (CH_2), 30.8 (CH_2), 40.4 (CH_2), 46.5 (C), 65.3 (CH_2), 119.3 (CH_2), 132.9 (CH), 180.8 (C); MS (EI): 154 (M^+); HRMS (EI), calcd for $C_9H_{14}O_2$: 154.0994; found: 154.0985.

4.1.4. (3*R*)-3-Ethyltetrahydro-2-methoxy-3-(2-propenyl)furan (11). A solution of 0.95 M diisobutylalminum hydride in hexane (0.95 mol/L, 6.0 mL, 5.70 mmol) was added dropwise to a stirred solution of **10** (385 mg, 2.50 mmol) in anhydrous ether (19.0 mL) at −78 °C under nitrogen. The mixture was stirred at the same temperature for 1 h. After the reaction mixture was allowed to warm to room temperature, MeOH (12 mL), methyl orthoformate (1.0 mL, 9.14 mmol) and *p*-toluenesulfonic acid (1.59 g, 8.36 mmol) were added to the mixture, and the resulting solution was heated at refluxing temperature for 40 min. After cooling, the mixture was diluted with AcOEt and the organic solution was washed with saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4 and then concentrated. The residual oil was purified by flash column chromatography on silica gel with hexane–AcOEt (10:1) as eluant to afford **11** (355 mg, 84%) as an inseparable mixture of diastereoisomers (17:14). IR (neat) 1645, 1455, 1105, 1030, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.87 and 0.88 (3H, t, J=7.3 Hz), 1.25–1.59 (2H, m), 1.66–1.81 (2H, m), 2.03–2.34 (2H, m), 3.33 and 3.34 (3H, s), 3.84–3.92 (1H, m), 3.93–3.98 (1H, m), 4.47 and 4.48 (1H, s), 5.00–5.10 (2H, m), 5.72–5.83 (1H, m); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.2 and 9.2 (CH_3), 24.5 and 26.8 (CH_2), 33.7 and 33.8 (CH_2), 36.0 and 37.9 (CH_2), 49.5 and 50.0 (C), 54.6 and 54.7 (CH_3), 65.9 and 65.9 (CH_2), 108.6 and 108.8 (CH), 116.7 and 117.7 (CH_2), 134.4 and 135.8 (CH); MS (EI): 170 (M^+); HRMS (EI), calcd for $C_{10}H_{18}O_2$: 170.1307; found: 170.1332.

4.1.5. (3*R*)-3-Ethyltetrahydro-2-methoxy-3-furanpropanol (12a,b). To a solution of **11** (976 mg, 5.73 mmol) in absolute THF (23 mL) was added a solution of 0.5 M 9-borabicyclo[3,3,1]nonane (9-BBN; 36.7 mL, 18.4 mmol) in hexane dropwise for a period of 15 min under nitrogen atmosphere and the mixture was stirred at room temperature overnight. The mixture was allowed to cool to 0 °C. To the cold solution was added H_2O (20 mL), 3 M aqueous NaOH (31.2 mL, 93.6 mmol), and 30% H_2O_2 (8.33 mL, 81.5 mmol) and the mixture was warmed again to room temperature. After stirring for 1 h, the mixture was extracted with ether (twice). The combined organic extracts were washed with H_2O and brine, and dried over anhydrous Na_2SO_4 and concentrated to give an oil that was purified by flash column chromatography on silica gel with hexane–AcOEt (1:1) as eluant to afford **12a**,**b** (567 mg, 87% as collected yield) as a mixture of diastereomers (17:14) and recovered **11** (377 mg, 39%). The sample for physical analysis was separated by repeated TLC on silica gel with hexane–AcOEt (2:3). **12a**: $[\alpha]_D^{20}$ +79.9° (c 1.6, $CHCl_3$); IR (neat) 3400, 1460, 1100, 1055, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.86 (3H, t, J=7.3 Hz), 1.34 (1H, dq, J=14.7, 7.3 Hz), 1.43 (1H, dq, J=14.7, 7.3 Hz), 1.48–1.53 (4H, m), 1.67–1.77 (2H, m), 3.33 (3H, s), 3.58–3.70 (2H, m), 3.87 (1H, q, J=8.4 Hz), 3.93 (1H, td, J=8.4, 4.3 Hz), 4.47 (1H, s); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.2 (CH_3), 26.2 (CH_2), 26.9 (CH_2), 28.1 (CH_2), 34.1 (CH_2), 49.4 (C), 54.5 (CH_3), 63.4 (CH_2), 65.8 (CH_2), 108.9 (CH); MS (EI): 187 (M^+-1); HRMS (EI), calcd for $C_{10}H_{19}O_3$ (M^+-1): 187.1334; found: 187.1342. **12b**: $[\alpha]_D^{20}$ −83.7° (c 0.99, $CHCl_3$); IR (neat) 3400, 1460, 1100, 1055, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, J=7.3 Hz), 1.31–1.39 (1H, m), 1.40–1.46 (1H, m), 1.46–1.60 (4H, m), 1.67–1.78 (2H, m), 3.33 (3H, s), 3.64 (2H, t, J=6.6 Hz), 3.88 (1H, q, J=8.4 Hz), 3.94 (1H, td, J=8.4, 4.0 Hz), 4.47 (1H, s); ^{13}C NMR ($CDCl_3$; DEPT): δ

9.2 (CH_3), 24.2 (CH_2), 27.3 (CH_2), 29.6 (CH_2), 34.4 (CH_2), 49.5 (C), 54.7 (CH_3), 63.5 (CH_2), 65.8 (CH_2), 109.0 (CH); MS (EI): 187 (M^+-1); HRMS (EI), calcd for $C_{10}H_{19}O_3$ (M^+-1): 187.1334; found: 187.1353.

4.1.6. (3*R*)-3-Ethyltetrahydro-2-methoxy-3-furanpropanal (13a,b). Surfur trioxide pyridine complex (1.90 g, 11.9 mmol) was added to a solution of **12a**,**b** (274 mg, 1.46 mmol), methyl sulfoxide (14.0 mL, 197 mmol) and triethylamine (5.5 mL, 39.5 mmol) in CH_2Cl_2 (5.5 mL) and the mixture was stirred at room temperature for 0.5 h under nitrogen atmosphere. The resulting mixture was diluted with AcOEt and washed with H_2O, saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Concentration of the solvent under reduced pressure provided crude aldehyde **13a**,**b** which was used for next reaction without any purification; **13a** (prepared from **12a**): $[\alpha]_D^{20}$ +89.6° (*c* 1.4, $CHCl_3$); IR (neat) 1730, 1460, 1100, 1055, 920 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (3H, t, *J*=7.3 Hz), 1.34 (1H, dq, *J*=14.7, 7.3 Hz), 1.42 (1H, dq, *J*=14.7, 7.3 Hz), 1.68–1.78 (2H, m), 1.79–1.89 (2H, m), 2.30–2.44 (2H, m), 3.30 (3H, s), 3.88 (1H, q, *J*=8.1 Hz), 3.94 (1H, td, *J*=8.1, 5.1 Hz), 9.74 (1H, t, *J*=2.2 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.2 (CH_3), 23.7 (CH_2), 26.4 (CH_2), 33.8 (CH_2), 39.8 (CH_2), 49.1 (C), 54.5 (CH_3), 65.8 (CH_2), 108.7 (CH), 202.7 (CH); MS (EI): 186 (M^+); HRMS (EI), calcd for $C_{10}H_{18}O_3$: 186.1256; found: 186.1237. **13b** (prepared from **12b**): $[\alpha]_D^{20}$ −91.4° (*c* 1.5, $CHCl_3$); IR (neat) 1730, 1460, 1380, 1100, 1060, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (3H, t, *J*=7.3 Hz), 1.48 (1H, dq, *J*=14.7, 7.3 Hz), 1.56 (1H, dq, *J*=14.7, 7.3 Hz), 1.62–1.72 (3H, m), 1.73–1.82 (1H, m), 2.35–2.45 (2H, m), 3.31 (3H, s), 3.89 (1H, q, *J*=8.1 Hz), 3.95 (1H, td, *J*=8.1, 4.0 Hz), 9.80 (1H, t, *J*=1.5 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 9.1 (CH_3), 24.3 (CH_2), 25.5 (CH_2), 34.2 (CH_2), 39.1 (CH_2), 49.2 (C), 54.7 (CH_3), 65.7 (CH_2), 108.6 (CH), 202.0 (CH); MS (EI): 186 (M^+); HRMS (EI), calcd for $C_{10}H_{18}O_3$: 186.1256; found: 186.1243.

4.1.7. (3*R*)-3-Ethyltetrahydro-2-methoxy-3-furanpropanoic acid (14a,b). To a solution of aldehydes **13a**,**b** in *tert*-butylalcohol (11.8 mL) was added 2-methyl-2-butene (0.68 mL, 6.42 mmol), sodium dihydrogenphosphate dihydrate (228 mg, 1.46 mmol) and H_2O (3.0 mL) and sodium chlorite (544 mg, 6.02 mmol) portionwise over 1 h under vigorous stirring. After cooling to 0 °C, the mixture was acidified with 1 M HCl, and then extracted with CH_2Cl_2 (three times). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to give an oil which was purified by flash column chromatography on silica gel with hexane–AcOEt (1:1) as eluant to afford **14a**,**b** (280 mg, 95%) as a mixture of diastereomers (17:14). **14a** (prepared from **13a**): $[\alpha]_D^{20}$ +77.8° (*c* 1.3, $CHCl_3$); IR (neat) 1710, 1460, 1100, 1050, 975 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (3H, t, *J*=7.3 Hz), 1.33 (1H, dq, *J*=14.7, 7.3 Hz), 1.42 (1H, dq, *J*=14.7, 7.3 Hz), 1.69–1.80 (2H, m), 1.80–1.90 (2H, m), 2.26–2.37 (2H, m), 3.32 (3H, s), 3.88 (1H, q, *J*=8.1 Hz), 3.95 (1H, td, *J*=8.1, 5.1 Hz), 4.46 (1H, s); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.2 (CH_3), 26.3 (CH_2), 26.4 (CH_2), 29.9 (CH_2), 33.8 (CH_2), 49.1 (C), 54.6 (CH_3), 65.8 (CH_2), 108.7 (CH), 180.0 (C); MS (EI): 201 (M^+-1); HRMS (EI), calcd for $C_{10}H_{17}O_4$ (M^+-1): 201.1127; found: 201.1119. **14b** (prepared from **13b**): mp 41–42 °C; $[\alpha]_D^{20}$ −83.2° (*c* 1.2, $CHCl_3$); IR (KBr) 1710, 1450, 1190, 1100, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (3H, t, *J*=7.3 Hz), 1.47 (1H, dq, *J*=14.7, 7.3 Hz), 1.56 (1H, dq, *J*=14.7, 7.3 Hz), 1.65–1.81 (4H, m), 2.27–2.37 (2H, m), 3.33 (3H, s), 3.90 (1H, q, *J*=8.1 Hz), 3.95 (1H, td, *J*=8.1, 4.4 Hz), 4.48 (1H, s); ^{13}C NMR ($CDCl_3$; DEPT) δ 9.1 (CH_3), 24.2 (CH_2), 28.3 (CH_2), 29.2 (CH_2), 34.1 (CH_2), 49.3 (C), 54.8 (CH_3), 65.7 (CH_2), 108.5 (CH), 179.7 (C); MS (EI): 201 (M^+-1). Anal. calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 58.99; H, 8.99.

4.1.8. (1*R*,12b*R*)-1-Ethyl-2,3,6,7,12,12b-hexahydro-1-(2-acetoxyethyl)-indolo[2,3-*a*]quinolizin-4 (1*H*)-one (16a) and (1*R*,12b*S*)-1-ethyl-2,3,6,7,12,12b-hexahydro-1-(2-acetoxyethyl)-indolo[2,3-*a*]quinolizin-4(1*H*)-one (16b). A mixture of **14a**,**b** (205 mg, 1.01 mmol) and tryptamine (211 mg, 1.32 mmol) in AcOH (3.0 mL) was heated at 125 °C for 6 days. After the solvent was removed under reduced pressure, the resulting residue was purified by flash column chromatography on silica gel with CH_2Cl_2–MeOH (20:1) as eluant to afford **16a** (154 mg, 43%) and **16b** (158 mg, 44%) as a crystalline solid. Additional product **15** was isolated as an intermediate in this reaction; **16a** (recrystallization from AcOEt–hexane): mp 79–81 °C; $[\alpha]_D^{20}$ +77.8° (*c* 1.3, $CHCl_3$); IR (KBr) 1740, 1620, 1240, 1135, 745 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.08 (3H, t, *J*=7.3 Hz), 1.16 (1H, ddd, *J*=14.7, 9.9, 5.9 Hz), 1.51 (1H, ddd, *J*=14.7, 9.9, 5.9 Hz), 1.52–1.59 (1H, m), 1.78 (1H, dq, *J*=14.7, 7.3 Hz), 1.87 (3H, s), 1.89–1.96 (1H, m), 1.99 (1H, dq, *J*=14.7, 7.3 Hz), 2.31–2.44 (2H, m), 2.54–2.61 (1H, m), 2.65 (1H, td, *J*=11.7, 2.2 Hz), 2.72 (1H, br d, *J*=14.3 Hz), 3.79 (1H, td, *J*=10.6, 5.9 Hz), 3.95 (1H, td, *J*=10.6, 5.9 Hz), 4.88 (1H, s), 4.88–4.91 (1H, m), 6.99 (1H, td, *J*=7.7, 1.0 Hz), 7.07 (1H, td, *J*=7.7, 1.0 Hz), 7.42 (1H, dd, *J*=7.7, 1.0 Hz), 7.45 (1H, dd, *J*=7.7, 1.0 Hz), 10.31 (1H, br s); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.2 (CH_3), 20.9 (CH_3), 21.1 (CH_2), 27.5 (CH_2), 28.9 (CH_2), 30.3 (CH_2), 30.5 (CH_2), 38.8 (C), 41.2 (CH_2), 60.3 (CH_2), 60.7 (CH), 111.1 (CH), 113.5 (C), 118.3 (CH), 119.9 (CH), 122.4 (CH), 126.4 (C), 130.4 (C), 136.3 (C), 169.8 (C), 171.1 (C); MS (EI): 354 (M^+). Anal. calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.74; H, 7.51; N, 7.86. **16b** (recrystallization from AcOEt–hexane): mp 75–77 °C; $[\alpha]_D^{20}$ −84.0° (*c* 1.3, $CHCl_3$); IR (KBr) 1720, 1630, 1235, 1035, 740 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.64 (3H, t, *J*=7.3 Hz), 0.89 (1H, dq, *J*=14.7, 7.3 Hz), 1.28 (1H, dq, *J*=14.7, 7.3 Hz), 1.60 (1H, ddd, *J*=13.6, 6.2, 4.4 Hz), 1.90–2.02 (2H, m), 2.06 (3H, s), 2.18 (1H, ddd, *J*=15.0, 8.8, 6.6 Hz), 2.26 (1H, ddd, *J*=17.6, 11.0, 6.2 Hz), 2.38 (1H, ddd, *J*=17.6, 6.2, 4.4 Hz), 2.53–2.60 (1H, m), 2.65 (1H, td, *J*=11.7, 3.0 Hz), 2.68–2.74 (1H, m), 4.29 (1H, ddd, *J*=11.0, 8.8, 6.6 Hz), 4.39 (1H, ddd, *J*=11.0, 8.8, 5.9 Hz), 4.88 (1H, dd, *J*=11.7, 3.0 Hz), 4.94 (1H, s), 6.99 (1H, td, *J*=7.3, 1.0 Hz), 7.07 (1H, td, *J*=7.3, 1.0 Hz), 7.41 (1H, dd, *J*=7.3, 1.0 Hz), 7.42 (1H, dd, *J*=7.3, 1.0 Hz), 10.32 (1H, br s); ^{13}C NMR ($CDCl_3$; DEPT) δ 6.9 (CH_3), 21.2 (2 carbons: CH_3 and CH_2), 23.8 (CH_2), 27.2 (CH_2), 28.9 (CH_2), 34.9 (CH_2), 38.9 (C), 40.8 (CH_2), 60.5 (CH), 61.4 (CH_2), 111.4 (CH), 112.9 (C), 117.9 (CH), 119.4 (CH), 122.0 (CH), 126.2 (C), 129.8 (C), 136.7 (C), 169.7 (C), 172.8 (C); MS (EI): 354 (M^+). Anal. calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.09; H, 7.48; N, 7.89.

Compound **15**. $[\alpha]_D^{20}$ +27.4° (*c* 1.2, $CHCl_3$); IR (neat) 3300,

1635, 1460, 1040, 740 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.75 (3H, t, J=7.3 Hz), 1.23 (1H, dq J=14.7, 7.3 Hz), 1.30 (1H, dq, J=14.7, 7.3 Hz), 1.50 (1H, ddd, J=13.6, 9.9, 5.5 Hz), 1.67 (1H, dt, J=13.6, 5.5 Hz), 1.73 (1H, ddd, J=12.8, 8.4, 6.6 Hz), 1.83 (1H, ddd, J=12.8, 8.1, 5.9 Hz), 2.21 (1H, dt, J=17.2, 5.5 Hz), 2.33 (1H, ddd, J=17.2, 9.9, 5.5 Hz), 2.85 (1H, ddd, J=13.9, 9.2, 4.8 Hz), 2.95 (1H, ddd, J=13.9, 9.5, 7.0 Hz), 3.40 (1H, ddd, J=13.2, 9.2, 7.0 Hz), 3.65 (1H, ddd, J=13.2, 9.5, 4.8 Hz), 3.69 (1H, td, J=8.4, 5.9 Hz), 3.79 (1H, q, J=8.4 Hz), 4.50 (1H, s), 6.98 (1H, t, J=7.3 Hz), 7.06 (1H, t, J=7.3 Hz), 7.13 (1H, d, J=2.2 Hz), 7.33 (1H, d, J=7.3 Hz), 7.57 (1H, d, J=7.3 Hz), 10.80 (1H, br s); ^{13}C NMR (DMSO-d_6; DEPT) δ 8.4 (CH_3), 23.5 (CH_2), 26.4 (CH_2), 28.2 (CH_2), 29.7 (CH_2), 34.1 (CH_2), 42.9 (C), 46.1 (CH_2), 64.1 (CH_2), 94.7 (CH), 111.3 (CH), 111.5 (C), 118.1 (CH), 118.2 (CH), 120.8 (CH), 122.6 (CH), 127.2 (C), 136.2 (C), 169.7 (C); MS (EI): 312 (M^+-H_20); HRMS (EI), calcd for $C_{19}H_{24}N_2O_2$ (M^+-H_20): 312.1838; found: 312.1837.

4.1.9. (1*R*,12b*R*)-1-Ethyl-2,3,6,7,12,12b-hexahydro-1-(2-hydroxyethyl)-indolo[2,3-*a*]quinolizin-4 (1*H*)-one (3a) and (1*R*,12b*S*)-1-ethyl-2,3,6,7,12,12b-hexahydro-1-(2-hydroxyethyl)-indolo[2,3-*a*]quinolizin-4(1*H*)-one (3b). To a solution of **16a** (72.2 mg, 0.204 mmol) in MeOH (2.0 mL) was added 20% aqueous NaOH solution (80 μL, 0.40 mmol). After stirring at room temperature for 1 h, the reaction mixture was neutralized with AcOH. The resulting mixture was diluted with AcOEt and washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The resulted crystalline solid was washed with AcOEt and collected by filtration to give **3a** (45.9 mg, 72%); **3a** (recrystallization from CH_2Cl_2–MeOH): mp 264–268 °C decomp.; $[\alpha]_D^{20}$ +188.1° (*c* 0.15, CH_3OH); IR (KBr) 3300, 1610, 1415, 1155, 745 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.01–1.07 (1H, m), 1.06 (3H, t, J=7.3 Hz), 1.39 (1H, ddd, J=13.9, 10.3, 5.9 Hz), 1.54 (1H, dt, J=13.2, 5.1 Hz), 1.76 (1H, dq, J=14.7, 7.3 Hz), 1.87 (1H, ddd, J=13.2, 10.3, 7.3 Hz), 1.96 (1H, dq, J=14.7, 7.3 Hz), 2.32–2.40 (2H, m), 2.52–2.60 (1H, m), 2.60–2.68 (1H, m), 2.68–2.74 (1H, m), 3.22 (1H, td, J=10.3, 5.9 Hz), 3.30 (1H, td, J=10.3, 5.5 Hz), 4.83 (1H, s), 4.87–4.93 (1H, m), 6.98 (1H, t, J=7.3 Hz), 7.06 (1H, t, J=7.3 Hz), 7.41 (1H, d, J=7.3 Hz), 7.45 (1H, d, J=7.3 Hz), 10.30 (1H, br s); ^{13}C NMR (DMSO-d_6; DEPT) δ 8.3 (CH_3), 20.8 (CH_2), 27.2 (CH_2), 28.8 (CH_2), 29.4 (CH_2), 35.0 (CH_2), 38.2 (C), 40.0 (CH_2), 56.3 (CH_2), 60.0 (CH), 110.9 (C), 111.6 (CH), 117.3 (CH), 118.5 (CH), 120.9 (CH), 125.8 (C), 131.6 (C), 136.5 (C), 169.0 (C); MS (EI): 312 (M^+). Anal. calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.73; H, 7.84; N, 8.93.

The preparation of **3b** was carried out under the same procedure described above in 85% yield; **3b** (recrystallization from CH_2Cl_2–MeOH): mp 123–127 °C; $[\alpha]_D^{20}$ −141.2° (*c* 0.24, CH_3OH); IR (KBr) 3380, 1615, 1440, 1305, 745 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.74 (3H, t, J=7.3 Hz), 1.21 (1H, dq, J=14.7, 7.3 Hz), 1.29 (1H, dq, J=14.7, 7.3 Hz), 1.52 (1H, ddd, J=13.2, 6.6, 3.7 Hz), 1.79 (1H, dt, J=15.4, 5.9 Hz), 1.94–2.02 (1H, m), 2.05 (1H, ddd, J=15.4, 8.1, 5.9 Hz), 2.24 (1H, ddd, J=17.6, 11.0, 6.6 Hz), 2.38 (1H, ddd, J=17.6, 6.6, 3.7 Hz), 2.51–2.59 (1H, m), 2.62 (1H, td, J=11.7, 2.2 Hz), 2.70 (1H, dt, J=13.9, 2.2 Hz), 3.71–3.80 (1H, br m), 3.82–3.90 (1H, br m), 4.87–4.93 (1H, m), 5.03 (1H, br s, OH), 5.06 (1H, s), 6.98 (1H, t, J=7.3 Hz), 7.06 (1H, t, J=7.3 Hz), 7.41 (1H, d, J=7.3 Hz), 7.43 (1H, d, J=7.3 Hz), 10.29 (1H, br s); ^{13}C NMR (DMSO-d_6; DEPT) δ 7.0 (CH_3), 20.8 (CH_2), 24.4 (CH_2), 26.8 (CH_2), 28.8 (CH_2), 38.2 (CH_2), 38.4 (C), 40.1 (CH_2), 56.6 (CH_2), 60.2 (CH), 110.9 (C), 111.5 (CH), 117.3 (CH), 118.5 (CH), 120.9 (CH), 125.9 (C), 132.0 (C), 136.0 (C), 169.0 (C); MS (EI): 312 (M^+). Anal. calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.81; H, 7.90; N, 8.80.

4.1.10. (1*R*,12b*R*)-1-Ethyl-2,3,6,7,12,12b-hexahydro-1-[2-[(methanesulfonyl)oxy]ethyl]indolo[2,3-*a*]quinolizin-4(1*H*)-one (17a) and (1*R*,12b*S*)-1-ethyl-2,3,6,7,12,12b-hexahydro-1-[2-[(methanesulfonyl)oxy]ethyl]-indolo[2,3-*a*]quinolizin-4(1*H*)-one (17b). Methanesulfonyl chloride (40.7 mg, 0.355 mmol) was added dropwise to a solution of **3a** (11.1 mg, 0.0355 mmol) and 4-(dimethylamino)pyridine (14.7 mg, 0.120 mmol) in pyridine (1.3 mL) at 0 °C under N_2 atmosphere. After stirring at 0 °C for 2 h, the reaction mixture was diluted with AcOEt. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (25:1) to afford **17a** (12.7 mg, 92%) as a colorless oil; $[\alpha]_D^{20}$ +110.0° (*c* 0.69, $CHCl_3$); IR (neat) 1630, 1355, 1175, 955, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (3H, t, J=7.3 Hz), 1.53 (1H, dq, J=14.7, 7.3 Hz), 1.69 (1H, ddd, J=13.9, 6.6, 2.9 Hz), 1.82–1.98 (2H, m), 1.99–2.07 (1H, m), 2.52 (1H, ddd, J=14.9, 11.7, 6.6 Hz), 2.60 (1H, ddd, J=18.3, 6.6, 2.9 Hz), 2.71–2.82 (3H, m), 2.81 (3H, s), 3.94–4.02 (1H, m), 4.06–4.15 (1H, m), 4.82 (1H, s), 5.13–5.19 (1H, m), 7.14 (1H, t, J=7.3 Hz), 7.22 (1H, t, J=7.3 Hz), 7.38 (1H, d, J=7.3 Hz), 7.52 (1H, d, J=7.3 Hz), 7.98 (1H, br s); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.3 (CH_3), 21.1 (CH_2), 28.0 (CH_2), 29.0 (CH_2), 30.4 (CH_2), 31.1 (CH_2), 37.2 (CH_3), 39.3 (C), 40.8 (CH_2), 60.3 (CH), 65.7 (CH_2), 111.1 (CH), 113.7 (C), 118.3 (CH), 120.1 (CH), 122.7 (CH), 126.3 (C), 130.1 (C), 136.2 (C), 169.7 (C); MS (EI): 294 (M^+−MsOH); HRMS (EI), calcd for $C_{19}H_{22}N_2O$ (M^+−MsOH): 294.1732; found: 294.1744.

The preparation of **17b** was carried out under the same procedure described above in 90% yield; **17b** (colorless oil): $[\alpha]_D^{20}$ −77.8° (*c* 1.0, $CHCl_3$); IR (neat) 3400, 1625, 1355, 1180, 955 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.75 (3H, t, J=7.3 Hz), 0.99 (1H, dq J=14.7, 7.3 Hz), 1.52 (1H, dq, J=14.7, 7.3 Hz), 1.73 (1H, ddd, J=13.9, 6.6, 3.7 Hz), 1.90 (1H, td, J=13.9, 6.6 Hz), 2.20 (1H, ddd, J=14.7, 8.8, 5.8 Hz), 2.42 (1H, dt, J=15.4, 8.1 Hz), 2.49 (1H, ddd, J=17.6, 11.7, 6.6 Hz), 2.55 (1H, ddd, J=17.6, 6.6, 3.7 Hz), 2.69–2.83 (2H, m), 3.11 (3H, s), 4.50–4.59 (1H, m), 4.70 (1H, dt, J=15.4, 8.1 Hz), 4.91 (1H, s), 5.12–5.17 (1H, m), 7.12 (1H, t, J=7.3 Hz), 7.19 (1H, t, J=7.3 Hz), 7.39 (1H, d, J=7.3 Hz), 7.51 (1H, d, J=7.3 Hz), 8.72 (1H, br s); ^{13}C NMR ($CDCl_3$; DEPT) δ 7.0 (CH_3), 21.1 (CH_2), 24.0 (CH_2), 27.2 (CH_2), 28.8 (CH_2), 36.4 (CH_2), 38.2 (CH_3), 39.3 (C), 40.9 (CH_2), 60.7 (CH), 66.3 (CH_2), 111.3 (CH), 113.7 (C), 118.1 (CH), 119.8 (CH), 122.3 (CH), 126.3 (C), 129.8 (C), 136.6 (C), 169.6 (C); MS (EI): 294 (M^+−MsOH); HRMS (EI), calcd for $C_{19}H_{22}N_2O$ (M^+−MsOH): 294.1732; found: 294.1776.

4.1.11. (1*R*,12b*R*)-1-Ethyl-2,3,6,7,12,12b-hexahydro-1-[2-[(phenylseleno)ethyl]-indolo[2,3-*a*]quinolizin-4(1*H*)-one (18a) and (1*R*,12b*S*)-1-ethyl-2,3,6,7,12,12b-hexahydro-1-[2-[(phenylseleno)ethyl]-indolo[2,3-*a*]quinolizin-4(1*H*)-one (18b). Sodium borohydride (11 mg, 0.29 mmol) was added to a solution of **17a** (29.3 mg, 0.065 mmol) and diphenyl diselenide (47.9 mg, 0.153 mmol) in EtOH (2.5 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature. Sodium borohydride (20 mg, 0.53 mmol) was frequently added to the reaction mixture during 3 h. The mixture was allowed to cool to 0 °C, neutralized with AcOH, and then diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC on silica gel with AcOEt–hexane (3:1) to afford **18a** (23.0 mg, 68%) and **23a** (0.8 mg, 4%) as a colorless oil; **18a** (recrystallized from MeOH): mp 180–181 °C; $[\alpha]_D^{20}$ +151.9° (*c* 0.40, $CHCl_3$); IR ($CDCl_3$) 1630, 1440, 1420, 1305 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (3H, t, *J*=7.3 Hz), 1.50 (1H, dt, *J*=13.9, 4.4 Hz), 1.62 (1H, ddd, *J*=13.9, 6.6, 3.7 Hz), 1.74 (1H, dt, *J*=13.9, 4.4 Hz), 1.81 (1H, dq, *J*=14.7, 7.3 Hz), 1.85–1.94 (2H, m), 2.37 (1H, ddd, *J*=18.3, 11.6, 6.6 Hz), 2.46–2.55 (2H, m), 2.61–2.76 (4H, m), 4.77 (1H, s), 5.05–5.13 (1H, m), 7.08–7.19 (4H, m), 7.22 (1H, t, *J*=7.3 Hz), 7.24–7.30 (2H, m), 7.33 (1H, d, *J*=7.3 Hz), 7.52 (1H, d, *J*=7.3 Hz), 7.78 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$; DEPT) δ 8.2 (CH_3), 21.0 (CH_2), 21.9 (CH_2), 27.8 (CH_2), 28.9 (CH_2), 30.0 (CH_2), 33.1 (CH_2), 40.5 (C), 40.9 (CH_2), 60.4 (CH), 111.0 (CH), 113.5 (C), 118.3 (CH), 120.0 (CH), 122.4 (CH), 126.4 (C), 127.2 (CH), 129.0 (CH), 129.5 (C), 130.5 (C), 133.3 (C), 136.1 (C), 169.8 (C); MS (EI): 452 (M^+). Anal. calcd for $C_{25}H_{28}N_2OSe$: C, 66.51; H, 6.25; N, 6.21. Found: C, 66.28; H, 6.31; N, 6.21.

The preparation of **18b** was carried out under the same procedure described above in 88% yield and **23b** at 5.6% yield as a by-product; **18b** (a colorless oil): $[\alpha]_D^{20}$ −20.8° (*c* 0.64, $CHCl_3$); IR (neat) 3320, 1620, 1440, 1310, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.69 (3H, t, *J*=7.3 Hz), 0.89 (1H, dq *J*=14.7, 7.3 Hz), 1.40 (1H, dq, *J*=14.7, 7.3 Hz), 1.67 (1H, ddd, *J*=13.9, 6.6, 3.7 Hz), 1.92 (1H, td *J*=13.9, 6.6 Hz), 2.04 (1H, ddd, *J*=14.7, 12.5, 5.1 Hz), 2.23 (1H, ddd, *J*=14.7, 12.5, 5.1 Hz), 2.44 (1H, ddd, *J*=18.3, 11.7, 6.6 Hz), 2.52 (1H, ddd, *J*=18.3, 6.6, 3.7 Hz), 2.65–2.77 (3H, m), 3.05 (1H, dt, *J*=12.5, 5.1 Hz), 3.12 (1H, td, *J*=12.5, 5.1 Hz), 4.85 (1H, s), 5.12 (1H, dt, *J*=11.7, 2.9 Hz), 7.07–7.12 (2H, m), 7.16 (1H, t, *J*=7.3 Hz), 7.33 (1H, br s), 7.40 (2H, t, *J*=7.3 Hz), 7.43 (1H, d, *J*=7.3 Hz), 7.47 (1H, d, *J*=7.3 Hz), 7.67 (2H, d, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 7.0 (CH_3), 21.1 (CH_2), 22.1 (CH_2), 24.1 (CH_2), 26.9 (CH_2), 28.9 (CH_2), 38.4 (CH_2), 40.5 (C), 40.9 (CH_2), 60.1 (CH), 111.0 (CH), 113.5 (C), 118.1 (CH), 119.8 (CH), 122.2 (CH), 126.2 (C), 128.2 (CH), 129.0 (C), 129.7 (CH), 130.4 (C), 134.1 (CH), 136.0 (C), 169.8 (C); MS (EI): 452 (M^+); HRMS (EI), calcd for $C_{25}H_{28}N_2OSe$: 452.1386; found: 452.1378.

4.1.12. (6a*R*,11a*S*,13a*S*,13b*R*)-13a-Ethyl-1,2,5,6,6a,11,12,13,13a,13b-decahydro-3*H*-cyclopenta[*ij*]-indolo[2,3-*a*]quinolizin-3-one (19). To a solution of **18a** (7.5 mg, 0.017 mmol) and 2,2′-azobisisobutyronitrile (0.67 mg, 0.0041 mmol) in toluene (0.75 mL) was added tributyltin hydride (19.4 mg, 0.067 mmol), and the mixture was stirred at 100 °C for 0.5 h under argon atmosphere. After the solvent was removed under reduced pressure, the residual crude material was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (25:1) to afford **19** (4.5 mg, 91%) as a colorless needles (re-crystallization from benzene); mp 194–195 °C; $[\alpha]_D^{20}$ +26.6° (*c* 0.23, $CHCl_3$); IR (neat) 3340, 1635, 1465, 1270, 750 cm^{-1}; UV (MeOH, log ε) 245.8 (3.57), 296.4 (3.18) nm; ^1H NMR ($CDCl_3$): δ 0.96 (3H, t, *J*=7.3 Hz), 1.63–1.96 (9H, m), 1.96–2.03 (1H, m), 2.27 (1H, ddd, *J*=17.2, 10.6, 5.1 Hz), 2.38 (1H, dt, *J*=17.2, 4.8 Hz), 2.75 (1H, ddd, *J*=12.8, 8,1, 4.8 Hz), 3.15 (1H, t, *J*=5.9 Hz), 3.28 (1H, s), 4.34 (1H, dt, *J*=12.8, 6.6 Hz), 6.63 (1H, d, *J*=7.3 Hz), 6.78 (1H, t, *J*=7.3 Hz), 7.06 (1H, t, *J*=7.3 Hz), 7.17 (1H, d, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 9.1 (CH_3), 24.6 (CH_2), 28.8 (CH_2), 29.1 (CH_2), 35.2 (CH_2), 36.2 (CH_2), 36.5 (CH_2), 40.1 (CH_2), 43.6 (C), 44.6 (CH), 69.7 (CH), 76.3 (C), 109.7 (CH), 119.4 (CH), 123.5 (CH), 127.9 (CH), 130.8 (C), 149.1 (C), 171.0 (C); MS (EI): 296 (M^+); HRMS (EI), calcd for $C_{19}H_{24}N_2O$: 296.1889; found: 296.1867.

4.1.13. (6a*R*,11a*S*,13a*S*,13b*R*)-13a-Ethyl-1,2,5,6,6a,11,12,13,13a,13b-decahydro-11-methyl-3*H*-cyclopenta[*ij*]-indolo[2,3-*a*]quinolizin-3-one (20). To a solution of **19** (4.4 mg, 0.015 mmol) and 35% formaldehyde (24 μL, 0.30 mmol) in acetonitrile (0.66 mL) was added sodium cyanoborohydride (2.8 mg, 0.045 mmol) and the mixture was stirred at room temperature. After 10 min, acetic acid (30 μL, 0.50 mmol) was added to the reaction mixture, which was further stirred at room temperature for 1 h. The mixture was diluted with AcOEt and washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (20:1) to afford **20** (4.0 mg, 87%) as a colorless oil; $[\alpha]_D^{20}$ −37.5° (*c* 0.40, $CHCl_3$); IR (neat) 2880, 1645, 1480, 1210, 755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (3H, t, *J*=7.3 Hz), 1.58–1.68 (2H, m), 1.69–1.86 (6H, m), 1.96–2.06 (2H, m), 2.28–2.40 (2H, m), 2.56 (1H, ddd, *J*=13.2, 11.0, 5.1 Hz), 2.80 (3H, s), 3.06 (1H, t, *J*=6.6 Hz), 3.40 (1H, s), 4.46 (1H, ddd, *J*=13.2, 6.6, 3.7 Hz), 6.55 (1H, d, *J*=7.3 Hz), 6.77 (1H, t, *J*=7.3 Hz), 7.03 (1H, d, *J*=7.3 Hz), 7.12 (1H, t, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 8.9 (CH_3), 26.2 (CH_2), 27.6 (CH_2), 28.4 (CH_2), 31.4 (CH_2), 32.5 (CH_2), 32.8 (CH_3), 34.5 (CH_2), 39.7 (CH_2), 44.3 (C), 44.4 (CH), 70.3 (CH), 78.5 (C), 110.2 (CH), 119.4 (CH), 122.8 (CH), 127.7 (CH), 134.8 (C), 152.0 (C), 170.4 (C); MS (EI): 310 (M^+); HRMS (EI), calcd for $C_{20}H_{26}N_2O$: 310.2045; found: 310.2046.

4.1.14. (−)-Vallesamidine (1). To a solution of **20** (6.9 mg, 0.022 mmol) in anhydrous THF (1.5 mL) was added lithium aluminum hydride (6.0 mg, 0.16 mmol), and the mixture was heated with stirring at 70 °C for 0.5 h under an argon atmosphere. After cooling to 0 °C, two drops of water were added to the reaction mixture, which was then diluted with AcOEt, and filtered through a hyflo super-cel. Evaporation of the solvent afforded an oil. The crude material was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (10:1) to afford (−)-vallesamidine (**1**) (5.4 mg, 82%) as a colorless oil; $[\alpha]_D^{20}$ −76.6° (*c* 0.25, $CHCl_3$); IR (neat) 2750, 1610, 1485, 1115, 735 cm^{-1}; UV (MeOH, log ε)

258.6 (3.69), 302.4 (3.18) nm; ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, t, J=7.3 Hz), 1.35–2.15 (12H, m), 2.25–2.50 (3H, m), 2.78 (3H, s), 2.70–3.00 (3H, br m), 6.44 (1H, br d, J=7.3 Hz), 6.67 (1H, br t, J=7.3 Hz), 7.03 (1H, d, J=7.3 Hz), 7.07 (1H, t, J=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 9.1 (CH_3), 18.1 (CH_2), 26.4 (CH_2), 27.3 (CH_2), 30.1 (CH_2), 31.0 (CH_3), 31.2 (CH_2), 35.4 (CH_2), 44.0 (CH), 44.4 (C), 49.6 (CH_2), 50.1 (CH_2), 72.6 (CH), 78.6 (C), 107.6 (CH), 117.7 (C), 122.9 (CH), 127.3 (CH), 134.6 (C), 151.3 (C); MS (EI): 296 (M^+); HRMS (EI), calcd for $C_{20}H_{28}N_2$: 296.2252; found: 296.2216.

4.1.15. (12b*S*)-1,1-Diethyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (22). Tributyltin hydride (20.4 mg, 0.070 mmol) was added to a solution of **18b** (8.9 mg, 0.020 mmol) and 2,2′-azobisisobutyronitrile (1.8 mg, 0.011 mmol) in toluene (0.9 mL), and the mixture was stirred at 100 °C for 1 h under an argon atmosphere. After the solvent was removed under reduced pressure, obtained the residue was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (25:1) to afford **22** (4.1 mg, 70%) as a colorless needles (recrystallization from CH_2Cl_2–MeOH); mp 293–294 °C; $[\alpha]_D^{20}$ −91.8° (*c* 0.41, $CHCl_3$); IR (neat) 3270, 1620, 14440, 1310, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.74 (3H, t, J=7.3 Hz), 0.99 (1H, dq J=14.7, 7.3 Hz), 1.20 (1H, t, J=7.3 Hz), 1.48 (1H, dq, J=14.7, 7.3 Hz), 1.62 (1H, ddd J=11.7, 6.6, 2.9 Hz), 1.81 (1H, dq, J=14.7, 7.3 Hz), 1.86–1.96 (2H, m), 2.46 (1H, ddd, J=17.6, 11.7, 6.6 Hz), 2.53 (1H, ddd, J=17.6, 6.6, 2.9 Hz), 2.53 (1H, ddd, J=17.6, 6.6, 2.9 Hz), 2.70–2.80 (3H, m), 4.85 (1H, s), 5.17 (1H, ddd, J=10.3, 3.7, 1.5 Hz), 7.13 (1H, t, J=8.1 Hz), 7.19 (1H, t, J=8.1 Hz), 7.35 (1H, d, J=8.1 Hz), 7.51 (1H, d, J=8.1 Hz), 7.80 (1H, br s); ^{13}C NMR ($CDCl_3$; DEPT) δ 7.1 (CH_3), 8.2 (CH_3), 21.1 (CH_2), 24.3 (CH_2), 26.5 (CH_2), 28.9 (CH_2), 29.9 (CH_2), 39.1 (C), 40.9 (CH_2), 60.4 (CH), 110.8 (CH), 113.2 (C), 118.2 (CH), 119.8 (CH), 122.2 (CH), 126.4 (C), 131.2 (C), 136.0 (C), 170.0 (C); MS (EI): 296 (M^+); HRMS (EI), calcd for $C_{19}H_{24}N_2O$: 296.1889; found: 296.1903.

4.1.16. (3*R*,16*R*)-14,15-Dihydroeburnamenin-19-one (23a). A powder of NaOH (2 mg, 0.05 mmol) was added to a solution of **17a** (12.4 mg, 0.0318 mmol) in THF (1.0 mL) and the mixture was stirred at room temperature for 20 min. The reaction mixture was diluted with AcOEt and then washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (25:1) to afford **23a** (8.8 mg, 94%) as a colorless oil; $[\alpha]_D^{20}$ +81.9° (*c* 0.45, $CHCl_3$); IR (neat) 2930, 1650, 1460, 1010, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.01 (3H, t, J=7.3 Hz), 1.45–1.60 (3H, m), 2.03–2.11 (2H, m), 2.11–2.18 (1H, m), 2.26 (1H, ddd, J=17.6, 5.1, 1.5 Hz), 2.45 (1H, ddd, J=17.6, 13.2, 5.9 Hz), 2.70 (1H, dd, J=15.4, 5.1 Hz), 3.03 (1H, td, J=12.5, 5.1 Hz), 3.07–3.15 (1H, m), 3.69 (1H, td, J=11.7, 5.2 Hz), 4.23 (1H, ddd, J=11.7, 5.9, 1.5 Hz), 4.36 (1H, s), 4.96 (1H, dd, J=12.5, 5.9 Hz), 7.13 (1H, t, J=7.3 Hz), 7.20 (1H, t, J=7.3 Hz), 7.29 (1H, d, J=7.3 Hz), 7.47 (1H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 7.3 (CH_3), 20.8 (CH_2), 22.3 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 31.0 (CH_2), 33.4 (C), 38.6 (CH_2), 43.3 (CH_2), 60.7 (CH), 107.7 (C), 109.6 (CH), 118.4 (CH), 120.0 (CH), 121.4 (CH), 128.2 (C), 133.8 (C), 136.8 (C), 169.5 (C); MS (EI): 294 (M^+); HRMS (EI), calcd for $C_{19}H_{22}N_2O$: 194.1732; found: 194.1746.

4.1.17. 14,15-Dihydroeburnamenine (24a). Lithium aluminum hydride (11.1 mg, 0.298 mmol) was added to a solution of **23a** (9.3 mg, 0.032 mmol) in anhydrous THF (4.5 mL) and the mixture was stirred at 70 °C for 0.5 h under argon atmosphere. After cooling, two drops of water were added to the reaction mixture, which was then diluted with AcOEt. The mixture was filtered through hyflo super-cel and the filtrate was dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (10:1) to afford **24a** (8.1 mg, 91%) as a colorless oil; $[\alpha]_D^{20}$ +17.3° (*c* 0.23, CH_3OH); IR (neat) 2940, 1460, 1355, 1100, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, J=7.3 Hz), 1.09 (1H, dt, J=13.9, 4.4 Hz), 1.31 (1H, dt, J=13.9, 1.5 Hz), 1.38 (1H, dt, J=13.9, 1.5 Hz), 1.56 (1H, dq, J=14.7, 7.3 Hz), 1.73–1.83 (1H, m), 1.90–2.02 (2H, m), 2.15 (1H, dq, J=14.7, 7.3 Hz), 2.47 (1H, td, J=11.7, 2.9 Hz), 2.55–2.65 (2H, m), 2.95–3.05 (1H, m), 3.24–3.37 (2H, m), 3.78 (1H, td, J=11.7, 5.9 Hz), 3.93 (1H, s), 4.16 (1H, ddd, J=11.7, 5.9, 1.5 Hz), 7.11 (1H, t, J=7.3 Hz), 7.17 (1H, t, J=7.3 Hz), 7.29 (1H, d, J=7.3 Hz), 7.49 (1H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 7.5 (CH_3), 17.0 (CH_2), 20.6 (CH_2), 23.8 (CH_2), 28.9 (CH_2), 31.9 (CH_2), 34.1 (C), 38.4 (CH_2), 44.5 (CH_2), 51.2 (CH_2), 59.2 (CH), 104.3 (C), 109.2 (CH), 118.1 (CH), 119.3 (CH), 120.6 (CH), 127.9 (C), 136.3 (C); MS (EI): 280 (M^+); HRMS (EI), calcd for $C_{19}H_{24}N_2$: 280.1939; found: 280.1919.

4.1.18. (3*R*,16*S*)-14,15-Dihydroeburnamenin-19-one (23b). The synthesis of **23b** was carried out under the same procedure described above in 88% yield; **23b** (colorless oil): $[\alpha]_D^{20}$ −132.6° (*c* 0.49, $CHCl_3$); IR (neat) 2930, 1650, 1460, 1310, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.62 (1H, dq, J=14.7, 7.3 Hz), 0.79 (3H, t, J=7.3 Hz), 1.35 (1H, dq, J=14.7, 7.3 Hz), 1.63 (1H, td, J=13.2, 7.3 Hz), 1.87 (1H, td, J=13.9, 7.3 Hz), 2.01 (1H, ddd. J=13.2, 7.3, 0.7 Hz), 2.21 (1H, dd, J=13.9, 5.9 Hz), 2.47–2.61 (2H, m), 2.70–2.88 (2H, m), 3.07 (1H, ddd, J=13.2, 10.3, 5.1 Hz), 3.79 (1H, td, J=11.7, 5.9 Hz), 4.22 (1H, dd, J=11.7, 6.6 Hz), 4.44 (1H, s), 4.90 (1H, ddd, J=13.2, 5.1, 2.2 Hz), 7.14 (1H, t, J=7.3 Hz), 7.21 (1H, t, J=7.3 Hz), 7.29 (1H, d, J=7.3 Hz), 7.50 (1H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 7.1 (CH_3), 16.9 (CH_2), 20.2 (CH_2), 28.7 (CH_2), 29.3 (CH_2), 30.4 (CH_2), 35.7 (C), 38.9 (CH_2), 39.8 (CH_2), 60.0 (CH), 106.5 (C), 109.7 (CH), 118.5 (CH), 119.9 (CH), 121.4 (CH), 127.7 (C), 132.1 (C), 138.3 (C), 169.7 (C); MS (EI): 294 (M^+); HRMS (EI), calcd for $C_{19}H_{22}N_2O$: 294.1732; found: 294.1703.

4.1.19. (3*S*)-14,15-Dihydroeburnamenine (24b). Sodium borohydride (9.0 mg, 0.24 mmol) was added to a solution of **23b** (7.0 mg, 0.024 mmol) and TFA (19.0 μL, 0.25 mmol) in absolute dioxane (1.2 mL), and the mixture was stirred at 100 °C for 45 min under nitrogen atmosphere. Concentration of the solvent under reduced pressure to give a residual oil which was purified by preparative TLC on silica gel with CH_2Cl_2–MeOH (20:1) to afford **24b** (5.8 mg, 87%) as a colorless oil; $[\alpha]_D^{20}$ −54.4° (*c* 0.55, CH_3OH); IR (neat) 2940, 1635, 1470, 1135, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.76 (3H, t, J=7.3 Hz), 0.74–0.84 (1H, m), 1.12 (1H, td,

J=13.2, 4.4 Hz), 1.60 (1H, br d, J=13.6 Hz), 1.68–1.82 (2H, m), 1.88 (1H, br dt, J=12.8, 2.2 Hz), 1.91–2.02 (1H, m), 2.06 (1H, dd. J=13.9, 5.1 Hz), 2.24 (1H, td, J=12.8, 2.2 Hz), 2.47 (1H, td, J=12.1, 4.4 Hz), 2.71 (1H, dt, J=15.4, 2.6 Hz), 2.90–2.99 (1H, m), 2.95 (1H, s), 3.02–3.12 (2H, m), 3.77 (1H, td, J=12.1, 5.5 Hz), 4.11 (1H, dd, J=11.7, 6.6 Hz), 7.09 (1H, t, J=7.3 Hz), 7.14 (1H, t, J=7.3 Hz), 7.25 (1H, d, J=7.3 Hz), 7.46 (1H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$; DEPT) δ 7.3 (CH_3), 18.5 (CH_2), 21.4 (CH_2), 21.6 (CH_2), 31.4 (CH_2), 32.0 (CH_2), 35.2 (C), 39.3 (CH_2), 53.5 (CH_2), 56.1 (CH_2), 68.0 (CH), 105.2 (C), 109.1 (CH), 118.1 (CH), 119.2 (CH), 120.3 (CH), 127.9 (C), 134.0 (C), 137.3 (C); MS (EI): 280 (M^+); HRMS (EI), calcd for $C_{19}H_{24}N_2$: 280.1939; found: 280.1910.

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