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Divergent total synthesis of (−)-aspidophytine and its congeners via Fischer indole synthesis

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ABSTRACT

A total synthesis of (−)-aspidophytine and the first total syntheses of its congeners, (+)-cimicidine and (+)-cimicine, were accomplished in a divergent manner. Construction of the aspidosperma skeleton was executed by Fischer indole synthesis between substituted phenylhydrazines and tricyclic aminoketone. The regiochemistry of the Fischer indole synthesis was strongly dependent on the choice of acid, and a weak acid, such as acetic acid provided the desired indolenine isomer in high selectivity.

1. Introduction

Aspidosperma alkaloids have attracted long-standing interest as synthetic targets in the area of alkaloid synthesis due to its densely fused polycyclic structure and fascinating biological activities.[1-3] Furthermore, these compounds constitute medicinally important dimeric indole alkaloids, some of which are currently used in clinical practice. In 1952, Snyder et al. isolated the alkaloid (+)-haplophytine (**1**) from dried leaves of *Haplophyton cimicidum*.[4] Structural determination of this compound revealed a highly unique dimeric structure consisting of an aspidosperma skeleton possessing a γ-lactone ring.[5] In addition, a number of related dimeric and monomeric aspidosperma alkaloids, such as cimilophytine (**2**),[6] cimicidine (**4**),[7,8] and cimicine (**5**)[7,8] were found in *H. cimicidum* (Fig. 1).

In addition to the characteristic structure, these compounds possess intriguing biological activities, such as inhibitory activity against acetylcholine esterase[9] and insecticidal activity for cockroaches.[4]

Because of its unusual polycyclic structure, haplophytine (**1**),[5] a representative compound isolated from *H. cimicidum*, has attracted considerable attention from the synthetic community and tremendous efforts have been made to construct this molecule.[10] To date, five total syntheses of the left-half segment, aspidophytine (**3**), have been reported.[11] While the total synthesis of haplophytine (**1**) had not been reported for about a half century since its isolation, we recently achieved the first total synthesis,[12] which was followed by a total synthesis by Nicolaou and Chen.[13]

Our successful total synthesis of **1** depended on establishment of a facile assembly of tricyclic aminoketone **6** via stereoselective intramolecular Mannich reaction,[12b] and construction of the aspidosperma skeleton by Fischer indole synthesis[14] using **6** and phenylhydrazine derivative **7** at the later stage of the synthesis (Scheme 1). Taking advantage of the high convergence, we

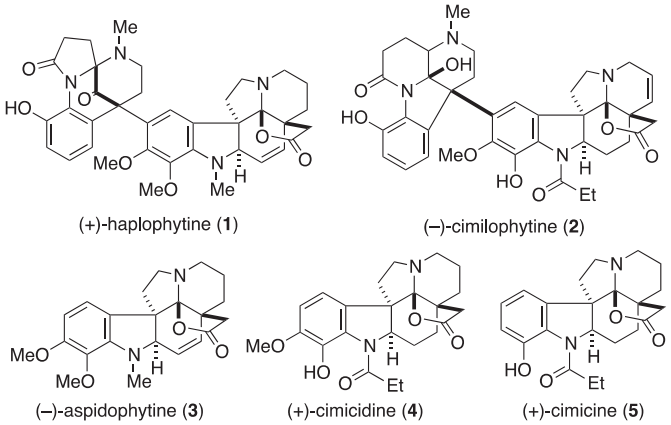

Fig. 1. Aspidosperma alkaloids isolated from *Haplophyton cimicidum*.

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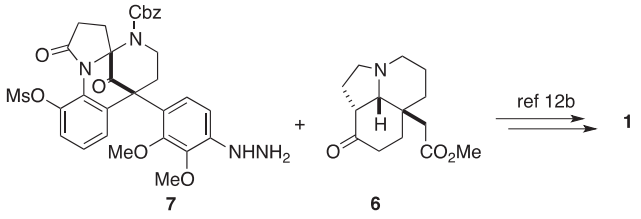
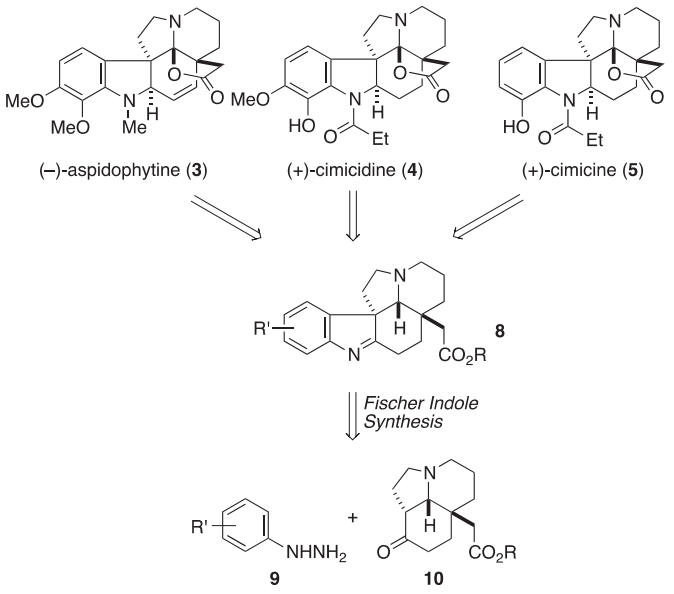
envisioned that our synthetic strategy would be a powerful tool for divergent synthesis of (−)-aspidophytine (**3**) and its congeners simply by switching of phenylhydrazine segment **9** (Scheme 2). Our strategy should be particularly suited for divergent synthesis because all of the previously established syntheses of aspidophytine (**3**) were based on construction of the aspidosperma skeleton on the initially-formed indole segment. Thus, it is inefficient to apply to the diversity-oriented synthesis regarding structural diversity on the indoline moiety. In this paper, we reported a total synthesis of aspidophytine (**3**) and the first total syntheses of its congeners, (+)-cimicidine (**4**) and (+)-cimicine (**5**) in a divergent manner, featuring construction of the aspidosperma skeleton by Fischer indole synthesis.



Scheme 1. The key Fischer indole synthesis in the first total synthesis of (+)-haplophytine (**1**).

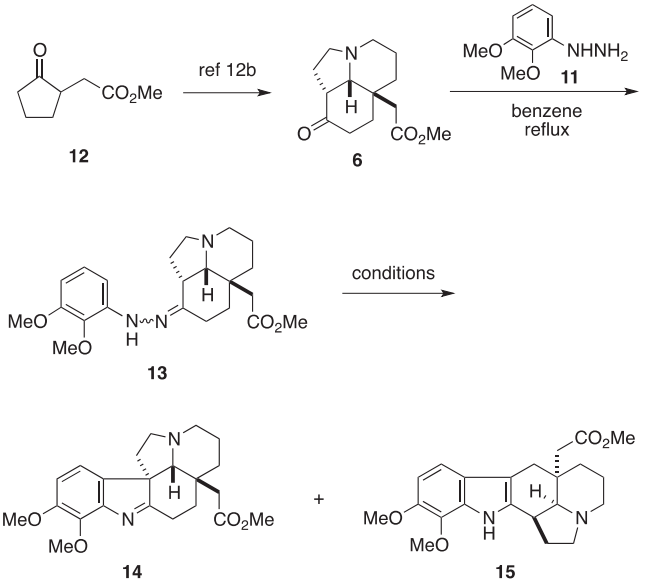


Scheme 2. Synthetic strategy for divergent synthesis of (−)-aspidophytine (**3**) and its congerners.

2. Results/discussion

First, we chose 2,3-dimethoxyphenylhydrazine (**11**),[15] which is required for synthesis of aspidophytine (**3**), and investigated Fischer indole synthesis. The optically active tricyclic aminoketone **6** was prepared from commercially available ketoester **12** according to our protocol[12b] and condensed with **12** in refluxing benzene. The resultant hydrazone **13** was subjected to various acidic conditions (Table 1). Disappointingly, the conditions established in our total synthesis of haplophytine (**1**)[12b] using TsOH in *t*-BuOH at room temperature resulted in formation of the desired indolenine **14** and indole by-product **15** with poor regioselectivity and low chemical yields (entry 1). Elevating the reaction temperature up to 80 °C improved yield of indolenine **14**, though the regioselectivity was still low (entry 2). Interestingly, exploration of other acids led us to find the regiochemical outcome was strongly dependent on the acidity. Thus, the ratio of the desired indolenine **14** increased as acidity decreased. Eventually, we succeeded in obtaining the desired indolenine **14** in 48% associated with 5% of indole **15** when reaction was executed in acetic acid at 100 °C (entry 4).[14]

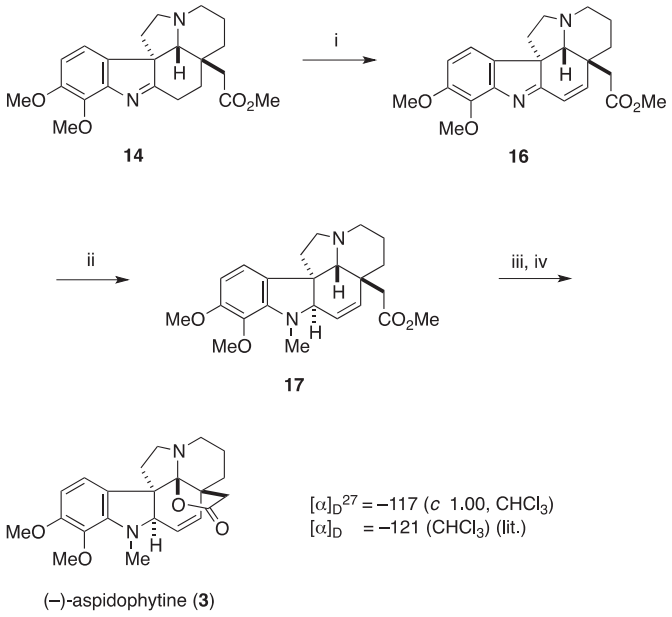
Table 1
Fischer indole synthesis with various acids



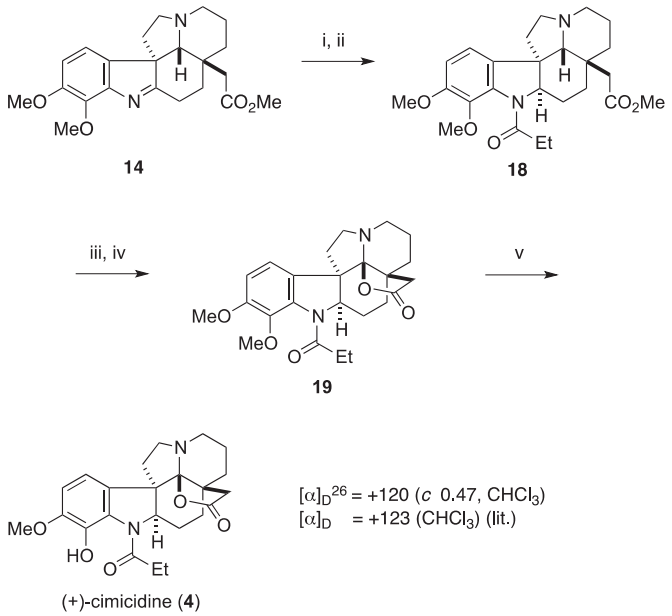
Entry	Acid	Solvent	Temp	Yield (2 steps)	
				14	**15**
1	TsOH (3 equiv)	*t*-BuOH	rt	15%	12%
2	TsOH (3 equiv)	*t*-BuOH	80 °C	32%	22%
3	TFA (30 equiv)	*t*-BuOH	80 °C	39%	10%
4	AcOH	None	100 °C	48%	5%

With pentacyclic indolenine **14** in hand, we proceeded to advance **14** toward (−)-aspidophytine (**3**) (Scheme 3). The literature protocol[11b,c] including oxidation of imine **14** to conjugated imine **16** and one-pot transformation including 1,2-reduction of the conjugated imine and reductive methylation to **17** resulted in low yield. Thus, it was necessary to reinvestigate these steps. After extensive optimization, we found that the appropriate choice of solvent was crucial to conduct the oxidation of imine smoothly at a lower temperature. Thus, treatment of **14** with benzeneseleninic anhydride in dichloromethane at 0 °C gave the desired conjugated imine **16** in good yield. Since one-pot 1,2-reduction and reductive methylation of imine **16** based on the previously established conditions unexpectedly promoted the retro-Mannich type reaction to give a ring-opening side product.[16] This side reaction was successfully suppressed by execution of this one-pot reaction under a weakly acidic condition. As a result, we succeeded in improving the yield of the desired amine **17** in 89% yield. Finally, saponification of the ester and subsequent formation of the lactone ring with potassium ferricyanide[11a] furnished (−)-aspidophytine (**3**).[11]

Next, we moved to synthesis of (+)-cimicidine (**4**) from the common intermediate **14** (Scheme 4). After reduction of imine **14**, the resultant secondary amine was acylated with propionic anhydride to afford amide **18**. Oxidative lactonization[11a] proceeded smoothly to provide lactonic compound **19** in high yield. Finally, regioselective demethylation was effected with a combination of BCl_3 and TBAI[17] to complete the first total synthesis of (+)-cimicidine (**4**).[8]



Scheme 3. Reagents and conditions; (i) benzeneseleninic anhydride, CH_2Cl_2, 0 °C to rt, 83%; (ii) HCHO (37%), $NaBH_3CN$, AcOH, MeOH, −78 °C to rt, 89%; (iii) 1 M NaOH, MeOH, 60 °C; (iv) $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH/H_2O, rt, 46% (2 steps).

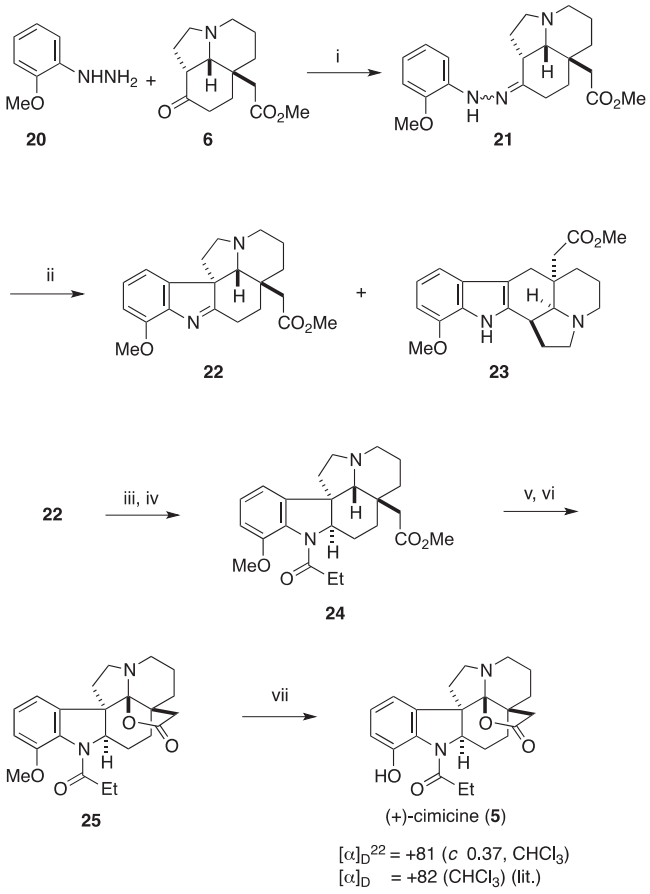


Scheme 4. Reagents and conditions; (i) $NaBH_4$, MeOH, −78 to 0 °C; (ii) propionic anhydride, pyridine, rt, 92% (2 steps); (iii) 1 M NaOH, MeOH, 60 °C; (iv) $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH/H_2O, rt, 94% (2 steps); (v) BCl_3, TBAI, CH_2Cl_2, −78 to 0 °C, 79%.

The utility of the convergent synthetic strategy was also demonstrated by accomplishment of the first total synthesis of (+)-cimicine (**5**) (Scheme 5). Thus, Fischer indole synthesis with 2-methoxyphenylhydrazine (**20**)[18] afforded the desired indolenine compound **22** in high regioselectivity. Then, 1,2-reduction of imine **22** with $NaBH_4$ and acylation of the resultant secondary amine gave amide **24**. Finally, basic hydrolysis of ester, oxidative lactonization,[11a] and demethylation of the methyl group[17] on the phenolic hydroxyl group furnished (+)-cimicine (**5**).[8]

3. Conclusion

In conclusion, we have achieved a total synthesis of (−)-aspidophytine (**3**), and the first total syntheses of (+)-cimicidine (**4**) and



Scheme 5. Reagents and conditions; (i) benzene, reflux; (ii) AcOH, 95 °C, **22** 41% (2 steps), **23** 6% (2 steps); (iii) $NaBH_4$, MeOH, −78 to 0 °C; (iv) propionic anhydride, pyridine, rt, 81% (2 steps); (v) 1 M NaOH, MeOH, 50 °C; (vi) $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH/H_2O, rt, quant. (2 steps); (vii) BCl_3, TBAI, CH_2Cl_2, −78 to rt, 75%.

(+)-cimicine (**5**). The utility of our synthetic strategy for synthesizing highly functionalized aspidosperma alkaloids was fully demonstrated by the divergent synthesis of these three aspidosperma alkaloids from the common tricyclic aminoketone intermediate. In addition, we have found that the regiochemistry of Fischer indole synthesis using unsymmetrical ketone was strongly influenced by acidity of acids. The synthetic methodology established in this work would be applicable to synthesis of not only monomeric and dimeric indole alkaloids found in *H. cimicidum*, such as cimilophytine (**2**), but also to a range of natural and unnatural aspidosperma-type compounds.

4. Experimental section

4.1. General remarks

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. All reactions were carried out in oven-dried glasswares under a slight positive pressure of argon unless otherwise noted. CH_2Cl_2 was purchased from Kanto Chemical Co. Inc. Anhydrous benzene, *t*-BuOH, AcOH, and pyridine were dried and distilled according to the standard protocols. Column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm) and NH Silica Gel (Fuji Silysia) using the indicated eluent. Preparative TLC was performed on Merck 60 F_{254} glass plates pre-coated with a 0.50 or a 0.25 mm thickness of silica gel and preparative NH TLC was performed on Fuji Silysia glass plates pre-coated with the NH Silica

Gel. Analytical TLC was performed on Merck 60 F_{254} glass plates pre-coated with a 0.25 mm thickness of silica gel. All melting points (mp) were determined on a Yanaco micro melting point apparatus and uncorrected. IR spectra were measured on a SHIMADZU FTIR–8300 spectrometer. NMR spectra were recorded on a JNM-AL400 spectrometer, a GX500 spectrometer, and a JEOL ECA600 spectrometer with tetramethylsilane (0 ppm) or chloroform (7.24 ppm) or MeCN (1.93 ppm) as an internal standard. Mass spectra were recorded on a JEOL JMS-DX-303 or a JMS-700 or a JMS-T100GC or a MS-50070BU spectrometers. Optical rotations were measured on a Horiba SEPA-300 and a JASCO P-2200.

4.2. Pentacyclic indolenine 14

A stirred solution of aminoketone **6** (438 mg, 1.74 mmol), 2,3-dimethoxyphenylhydrazine (**11**) (310 mg, 1.84 mmol), and MS3Å (610 mg) in benzene (6.0 mL) was heated at reflux for 6 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was diluted with benzene (12 mL), and the resulting solution was stirred at reflux with a Dean–Stark trap for 2.5 h. The organic solvents were removed under reduced pressure to afford a crude phenylhydrazone **13** (779 mg), which was subjected to the next reaction without further purification. A solution of the crude phenylhydrazone **13** (779 mg) in acetic acid (20 mL) was heated at 100 °C for 80 min. After cooling to room temperature, the reaction mixture was basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 five times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes–ethyl acetate=1:4) to afford a mixture of indole and indolenine products. These products were separated by silica gel column chromatography (methanol–chloroform=3:97) to afford the desired indolenine **14** (323 mg, 1.90 mmol, 48% over 2 steps) as red crystals and the undesired indole **15** (35.1 mg, 0.0914 mmol, 5% over 2 steps).

Indolenine **14**: $[\alpha]_D^{27}$ +209 (*c* 3.00, $CHCl_3$); mp 115–118 °C; IR (neat, cm^{-1}) 2937, 2779, 1732, 1493, 1258, 1080; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J*=8.0 Hz, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 4.16 (s, 3H), 3.88 (s, 3H), 3.43 (s, 3H), 3.27–3.06 (m, 3H), 2.86 (ddd, *J*=14.2, 10.6, 3.6 Hz, 1H), 2.63–2.50 (m, 2H), 2.43 (s, 1H), 2.29–2.11 (m, 2H), 1.96–1.80 (m, 2H), 1.78 (d, *J*=14.8 Hz, 1H), 1.72–1.50 (m, 3H), 1.60 (d, *J*=14.8 Hz, 1H), 1.29 (ddd, *J*=13.6, 13.2, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 171.6, 151.9, 145.9, 141.3, 140.9, 114.7, 109.2, 78.7, 61.8, 60.7, 56.4, 54.3, 51.8, 50.9, 41.4, 36.3, 35.4, 33.8, 27.7, 23.5, 21.8; HRMS (EI) calcd for $C_{22}H_{28}N_2O_4$ [M^+] 384.2049, found 384.2028.

Indole **15**: $[\alpha]_D^{27}$ +258 (*c* 0.48, $CHCl_3$); IR (neat, cm^{-1}) 3371, 2934, 2785, 1732, 1510, 1463, 1234, 1090, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.06 (d, *J*=8.5 Hz, 1H), 6.76 (d, *J*=8.5 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.54 (s, 3H), 3.48–3.42 (m, 1H), 3.17–3.10 (m, 2H), 2.97 (dd, *J*=15.5, 1.5 Hz, 1H), 2.58 (d, *J*=15.5 Hz, 1H), 2.36 (d, *J*=14.0 Hz, 1H), 2.27 (d, *J*=14.0 Hz, 1H), 2.24–2.12 (m, 2H), 2.02–1.79 (m, 5H), 1.67–1.62 (m, 1H), 1.54 (ddd, *J*=13.0, 12.5, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 146.7, 134.9, 134.2, 131.0, 124.9, 113.0, 107.3, 106.4, 71.1, 60.8, 57.3, 54.9, 53.5, 51.1, 42.8, 36.8, 34.0, 33.7, 27.9, 25.2, 22.0; HRMS (EI) calcd for $C_{22}H_{28}N_2O_4$ [M^+] 384.2049, found 384.2043.

4.3. Conjugated imine 16

To a stirred solution of indolenine **14** (67.5 mg, 0.176 mmol) in CH_2Cl_2 (880 μL) was added benzeneseleninic anhydride (70% content, 94.9 mg, 0.184 mmol) at 0 °C. The resulting solution was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2, basified with saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2 five times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol–dichloromethane=1:99 to 3:97, gradient) to afford pure conjugated imine **16** (55.9 mg, 0.146 mmol, 83%) as an orange foam; $[\alpha]_D^{27}$ +258 (*c* 0.48, $CHCl_3$); IR (neat, cm^{-1}) 2937, 1734, 1493, 1255, 1138, 1080; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J*=8.0 Hz, 1H), 6.84 (d, *J*=8.0 Hz, 1H), 6.72 (d, *J*=10.0 Hz, 1H), 6.52 (d, *J*=10.0 Hz, 1H), 4.19 (s, 3H), 3.89 (s, 3H), 3.50 (s, 3H), 3.15 (br d, *J*=11.2 Hz, 1H), 3.08 (dd, *J*=7.2, 7.6 Hz, 1H), 2.65 (s, 1H) 2.72–2.61 (m, 1H), 2.43 (ddd, *J*=11.2, 10.8, 3.6 Hz, 1H), 2.33–2.29 (m, 1H), 2.20 (ddd, *J*=11.2, 10.8, 6.4 Hz, 1H), 1.82 (d, *J*=15.6 Hz, 1H), 1.73 (d, *J*=15.6 Hz, 1H), 1.74–1.65 (m, 3H), 1.35 (ddd, *J*=13.6, 13.2, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 170.8, 151.9, 149.1, 145.5, 141.9, 139.4, 124.2, 113.9, 109.5, 69.0, 62.4, 61.8, 56.5, 52.6, 51.3, 50.6, 45.1, 39.7, 38.1, 34.1, 22.9; HRMS (EI) calcd for $C_{22}H_{26}N_2O_4$ [M^+] 382.1893, found 382.1881.

4.4. *N*-Methyl indoline 17

To a stirred solution of conjugated imine **16** (127 mg, 0.332 mmol) and HCHO (37% solution, 490 μL, 6.58 mmol) in MeOH (7.2 mL) were added $NaBH_3CN$ (104 mg, 1.65 mmol) and AcOH (13.3 μL, 0.232 mmol) at −78 °C. The resulting solution was allowed warm up to room temperature, and stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2, poured into saturated aqueous $NaHCO_3$ and brine, and the resulting mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 four times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol–dichloromethane=3:97) to afford indoline **17** (118 mg, 0.296 mmol, 89%); $[\alpha]_D^{28}$ +64.6 (*c* 0.54, $CHCl_3$); IR (neat, cm^{-1}) 2934, 2835, 2783, 1732, 1611, 1475, 1265, 1163, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J*=8.0 Hz, 1H), 6.24 (d, *J*=8.0 Hz, 1H), 6.10 (dd, *J*=10.0, 5.2 Hz, 1H), 5.96 (d, *J*=10.0 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.62 (d, *J*=5.2 Hz, 1H), 3.50 (s, 3H), 3.09 (s, 3H), 3.13–3.05 (m, 2H), 2.39 (d, *J*=15.2 Hz, 1H), 2.32 (dd, *J*=9.4, 8.4 Hz, 1H), 2.21 (s, 1H), 2.14–1.97 (m, 3H), 2.01 (d, *J*=15.2 Hz, 1H), 1.91 (d, *J*=13.2 Hz, 1H), 1.63–1.56 (m, 2H), 1.37 (ddd, *J*=13.2, 12.8, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 153.5, 143.4, 137.6, 133.7, 130.8, 125.4, 118.2, 101.9, 75.8, 72.9, 60.5, 55.9, 53.1, 52.4, 51.7, 50.9, 45.1, 44.9, 37.7, 36.2, 34.8, 22.8; HRMS (EI) calcd for $C_{23}H_{30}N_2O_4$ [M^+] 398.2206, found 398.2203.

4.5. (−)-Aspidophytine (3)

To a stirred solution of indoline **17** (35.5 mg, 89.1 μmol) in MeOH (1.8 mL) was added 1 M NaOH (1.8 mL) at room temperature. The resulting solution was heated at 60 °C for 1 h. After cooling to 0 °C, the resulting mixture was acidified with 1 M HCl until the pH 6–7 and concentrated under reduced pressure to afford a crude carboxylic acid. To a stirred solution of the crude carboxylic acid in a mixture of *t*-BuOH (1.0 mL) and H_2O (2.0 mL) were added $K_3Fe(CN)_6$ (440 mg, 1.34 mmol) and $NaHCO_3$ (225 mg, 2.67 mmol) at 0 °C. After stirring for 15 min, the resulting solution was allowed warm up to room temperature and stirred for 20 min. Then, the reaction mixture was poured into H_2O. The resulting mixture was extracted with CH_2Cl_2 four times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (methanol–chloroform=3:97) to afford pure (−)-aspidophytine (**3**) (15.8 mg, 41.3 μmol, 46% over 2 steps) as a white solid; $[\alpha]_D^{23}$ −117 (*c* 0.37, $CHCl_3$) (lit.[11a] $[\alpha]_D$ −121 (*c* 0.37, $CHCl_3$)); mp 199–202 °C (lit.[5] 201–203); IR (neat, cm^{-1}) 2943,

2839, 1751, 1609, 1495, 1466, 1418, 1265, 1169; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J=8.4 Hz, 1H), 6.19 (d, J=8.4 Hz, 1H), 5.83 (dd, J=10.4, 2.4 Hz, 1H), 5.51 (dd, J=10.4, 1.2 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.17 (q, J=8.4 Hz, 1H), 3.15 (s, 3H), 3.10–3.06 (m, 1H), 2.93–2.87 (m, 1H), 2.76–2.71 (m, 1H), 2.36 (d, J=16.4 Hz, 1H), 2.29 (ddd, J=12.4, 8.8, 3.2 Hz, 1H), 2.23 (d, J=16.4 Hz, 1H), 2.08 (ddd, J=13.2, 10.8, 7.2 Hz, 1H), 1.72–1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 153.8, 143.6, 133.7, 130.4, 125.5, 125.4, 120.1, 107.1, 102.1, 71.8, 61.1, 57.0, 55.7, 47.7, 47.2, 43.3, 41.4, 35.3, 35.2, 34.5, 21.6; HRMS (EI) calcd for $C_{22}H_{26}N_2O_4$ [M^+] 382.1893, found 382.1887.

4.6. Anilide 18

To a stirred solution of indolenine **14** (27.3 mg, 0.0708 mmol) in MeOH (0.70 mL) was added $NaBH_4$ (13.4 mg, 0.354 mmol) at −78 °C. After 5 min, the resulting mixture was allowed to warm up to 0 °C. After stirring for 100 min, $NaBH_4$ (2.7 mg, 0.071 mmol) was added to the reaction mixture. After stirring for an hour, the reaction was quenched with saturated aqueous $NaHCO_3$ and the reaction mixture was concentrated under reduced pressure. The residue was poured into saturated aqueous Na_2CO_3 and the resulting mixture was extracted with CH_2Cl_2 five times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol–dichloromethane=1:49) to afford secondary amine compound (27.1 mg). To a stirred solution of the secondary amine (27.1 mg) in pyridine (0.17 mL) was added propionic anhydride (0.17 mL) at room temperature. The resulting mixture was stirred for 6.5 h. After cooling to 0 °C, the reaction was quenched with 28% aqueous ammonia solution and the mixture was extracted with CH_2Cl_2 four times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol–dichloromethane=1:49) to afford anilide **18** (28.8 mg, 0.0651 mmol, 92% over 2 steps) as a yellow foam; $[\alpha]_D^{27}$ −95.9 (c 0.345, $CHCl_3$); IR (neat, cm^{-1}) 2937, 1732, 1651, 1495, 1454, 1385, 1335, 1275, 1225, 1177, 1088, 754; ^{1}H NMR (600 MHz, CD_3CN, 65 °C) δ 6.93 (d, J=8.4 Hz, 1H), 6.75 (d, J=8.4 Hz, 1H), 4.33 (dd, J=11.1, 6.3 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.54 (s, 3H), 3.09 (ddd, J=9.0, 9.0, 3.8 Hz, 1H), 3.02–2.97 (m, 1H), 2.65 (dq, J=15.3, 7.7 Hz, 1H), 2.46 (s, 1H), 2.37 (dq, J=15.3, 7.7 Hz, 1H), 2.31–2.25 (m, 1H), 2.23–2.15 (m, 1H), 2.18 (d, J=14.4 Hz, 1H), 2.07–1.89 (m, 5H), 1.75 (dddd, J=26.1, 13.1, 4.1, 4.1 Hz, 1H), 1.66–1.60 (m, 1H), 1.56–1.45 (m, 2H), 1.37 (ddd, J=13.7, 13.7, 4.6 Hz, 1H), 1.28–1.22 (m, 1H), 1.12 (t, J=7.7 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN, 65 °C) δ 174.9, 173.0, 154.2, 142.0, 135.8, 135.3, 118.8, 111.2, 70.4, 70.1, 60.4, 57.5, 54.5, 54.3, 53.0, 51.8, 43.2, 39.0, 37.1, 36.0, 28.9, 26.7, 25.6, 22.7, 10.5; HRMS (EI) calcd for $C_{25}H_{34}N_2O_5$ [M^+] 442.2468, found 442.2455.

4.7. Hemiaminal 19

To a stirred solution of anilide **18** (28.8 mg, 0.0651 mmol) in MeOH (0.3 mL) was added 1 M NaOH (0.3 mL) at room temperature. The resulting solution was heated at 60 °C for 3.5 h. After cooling to room temperature, the resulting mixture was acidified with 1 M HCl until pH 6–7 and concentrated under reduced pressure to afford a crude carboxylic acid. To a stirred solution of the crude carboxylic acid in a mixture of t-BuOH (0.22 mL) and H_2O (0.43 mL) were added $K_3Fe(CN)_6$ (214 mg, 0.651 mmol) and $NaHCO_3$ (109 mg, 1.30 mmol) at room temperature. After stirring for 1.5 h, the reaction mixture was poured into H_2O and the resulting mixture was extracted with CH_2Cl_2 seven times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes–ethyl acetate=1:1 to methanol–dichloromethane=1:9, gradient) to afford pure hemiaminal **19** (26.1 mg, 0.0612 mmol, 94% over 2 steps) as a white solid; $[\alpha]_D^{24}$ −66.3 (c 0.395, $CHCl_3$); mp 148–154 °C; IR (neat, cm^{-1}) 2936, 2855, 1771, 1749, 1651, 1495, 1456, 1254, 752; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J=8.3 Hz, 1H), 6.65 (d, J=8.3 Hz, 1H), 4.53–4.45 (m, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.14 (ddd, J=8.9, 8.9, 5.7 Hz, 1H), 3.04 (ddd, J=10.4, 8.4, 4.9 Hz, 1H), 2.92 (ddd, J=11.9, 11.9, 2.3 Hz, 1H), 2.82–2.70 (m, 2H), 2.38 (d, J=16.0 Hz, 1H), 2.35 (dq, J=15.4, 7.7 Hz, 1H), 2.09–1.74 (m, 5H), 1.93 (d, J=16.0 Hz, 1H), 1.63–1.50 (m, 4H), 1.36 (ddd, J=15.0, 15.0, 4.0 Hz, 1H), 1.14 (t, J=15.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 175.0, 152.8, 139.4, 134.2, 132.1, 119.7, 109.3, 107.9, 67.9, 60.0, 59.1, 56.0, 48.5, 43.5, 42.6, 40.4, 34.1, 34.0, 27.7, 25.2, 24.4, 20.3, 9.8; HRMS (EI) calcd for $C_{24}H_{30}N_2O_5$ [M^+] 426.2155, found 426.2159.

4.8. (+)-Cimicidine (4)

To a stirred solution of hemiaminal **19** (12.4 mg, 0.0291 mmol) and tetrabutylammonium iodide (35.2 mg, 0.0952 mmol) in CH_2Cl_2 (0.29 mL) was added BCl_3 (1 M in CH_2Cl_2, 58 μL, 0.058 mmol) at −78 °C. After 10 min, the resulting solution was allowed to warm up to 0 °C. After stirring for 2.5 h, BCl_3 (1 M solution in CH_2Cl_2, 58 μL, 0.058 mmol) was added to the reaction mixture. After stirring for additional 45 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 five times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol–dichloromethane=1:4), column chromatography on NH Silica Gel (acetone–hexanes=2:3) and preparative TLC (methanol–dichloromethane=1:9) to afford (+)-cimicidine (**4**) (9.5 mg, 0.023 mmol, 79%) as a white solid, associated with a recovery of the starting compound **19** (0.4 mg, 0.9 μmol, 3%); $[\alpha]_D^{26}$ +120 (c 0.47, $CHCl_3$) (lit.[4a] $[\alpha]_D^{25}$ +123.0 ($CHCl_3$)); mp 262–265 °C (lit.[8] 266–268); IR (neat, cm^{-1}) 2937, 2855, 2800 (br), 1771, 1747, 1634, 1599, 1456, 1254, 752; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.6 (s, 1H), 6.98 (d, J=8.3 Hz, 1H), 6.69 (d, J=8.3 Hz, 1H), 3.94 (dd, J=11.3, 4.8 Hz, 1H), 3.85 (s, 3H), 3.13 (ddd, J=8.8, 8.8, 5.5 Hz, 1H), 3.06 (ddd, J=10.5, 8.5, 5.0 Hz, 1H), 2.92 (ddd, J=11.9, 11.9, 2.7 Hz, 1H), 2.81–2.75 (m, 1H), 2.61 (dq, J=15.2, 7.6 Hz, 1H), 2.53 (dq, J=15.2, 7.6 Hz, 1H), 2.49 (d, J=16.3 Hz, 1H), 2.12 (ddd, J=13.9, 8.9, 5.1 Hz, 1H), 1.98–1.90 (m, 3H), 1.97 (d, J=16.3 Hz, 1H), 1.86–1.70 (m, 2H), 1.65–1.52 (m, 3H), 1.44 (ddd, J=14.5, 3.8, 3.8 Hz, 1H), 1.29 (t, J=7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 172.3, 150.1, 137.4, 129.6, 128.1, 114.7, 110.4, 106.3, 67.9, 58.2, 56.3, 48.4, 43.6, 42.5, 40.5, 35.0, 33.9, 28.4, 25.07, 25.06, 20.3, 9.7; HRMS (EI) calcd for $C_{23}H_{28}N_2O_5$ [M^+] 412.19982, found 412.19923.

4.9. Indolenine 22

A mixture of ketone **6** (47.1 mg, 0.187 mmol) and 2-methoxyphenylhydrazine **20** (27.2 mg, 0.197 mmol) in benzene (0.94 mL) was heated at reflux for a day. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to afford a crude phenylhydrazone derivative **21**, which was subjected to the next reaction without further purification. A stirred solution of the crude phenylhydrazone **21** in acetic acid (2.3 mL) was heated at 95 °C for 90 min. After cooling to room temperature, the reaction mixture was basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified sequentially by column chromatography on NH silica gel (hexanes–ethyl acetate=1:9), column chromatography on silica gel (hexanes–ethyl acetate=7:3 and then methanol–chloroform=1:99), and preparative

TLC coated by NH Silica Gel (hexanes–ethyl acetate=1:1) to afford the desired indolenine product **22** (28.8 mg, 0.813 mmol, 41% over 2 steps) as a yellow foam and the undesired indole product **23** (3.9 mg, 0.011 mmol, 6% over 2 steps) as red crystals.

Indolenine **22**: $[\alpha]_D^{25}$ +241 (*c* 0.82, $CHCl_3$); IR (neat, cm^{-1}) 2937, 2779, 1732, 1487, 1281, 1254, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J*=7.8, 7.8 Hz, 1H), 6.93 (dd, *J*=7.8, 0.6 Hz, 1H), 6.84 (d, *J*=7.8 Hz, 1H), 3.96 (s, 3H), 3.42 (s, 3H), 3.20–3.14 (m, 2H), 3.08 (ddd, *J*=14.3, 11.9, 4.7 Hz, 1H), 2.91 (ddd, *J*=14.3, 10.3, 3.9 Hz, 1H), 2.65–2.56 (m, 2H), 2.47 (s, 1H), 2.27–2.13 (m, 2H), 1.95–1.83 (m, 2H), 1.80 (d, *J*=14.4 Hz, 1H), 1.68–1.51 (m, 4H), 1.27 (ddd, *J*=13.5, 13.5, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 171.4, 151.0, 148.5, 142.0, 126.4, 113.5, 110.3, 78.2, 61.7, 55.7, 54.3, 51.7, 50.9, 41.5, 36.4, 35.0, 33.7, 27.6, 23.4, 21.9; HRMS (EI) calcd for $C_{21}H_{26}N_2O_3$ [M^+] 354.1943, found 354.1941.

Indole **23**: $[\alpha]_D^{25}$ −105 (*c* 0.32, $CHCl_3$); mp 146–152 °C; IR (neat, cm^{-1}) 3377, 2932, 2851, 2785, 1732, 1574, 1470, 1339, 1256, 756; ^1H NMR (600 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.96 (dd, *J*=8.0, 8.0 Hz, 1H), 6.58 (d, *J*=8.0 Hz, 1H), 3.93 (s, 3H), 3.54 (s, 3H), 3.58–3.46 (m, 1H), 3.20–3.12 (m, 2H), 3.07–2.98 (m, 1H), 2.60 (d, *J*=15.6 Hz, 1H), 2.34 (d, *J*=13.8 Hz, 1H), 2.30–2.22 (m, 2H), 2.20–2.12 (m, 1H), 2.10–1.80 (m, 4H), 1.69–1.51 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.4, 145.6, 129.4, 126.9, 119.4, 111.3, 106.7, 101.6, 71.1, 55.3, 55.0, 53.5, 51.2, 42.8, 36.9, 33.9, 33.6, 29.7, 28.2, 25.5, 22.0; HRMS (EI) calcd for $C_{21}H_{26}N_2O_3$ [M^+] 354.1943, found 354.1950.

4.10. Anilide 24

To a stirred solution of indolenine **22** (16.4 mg, 0.0463 mmol) in MeOH (0.46 mL) was added $NaBH_4$ (5.3 mg, 0.14 mmol) at −78 °C. After 10 min, the resulting mixture was allowed to warm up to 0 °C. After stirring for an hour, $NaBH_4$ (1.6 mg, 0.042 mmol) was added to the reaction mixture. After stirring for 50 min, another portion of $NaBH_4$ (1.3 mg, 0.034 mmol) was added to the reaction mixture and the mixture was stirred for 10 min. After quenching with saturated aqueous $NaHCO_3$ and saturated aqueous Na_2CO_3, the reaction mixture was concentrated under reduced pressure. The residue was poured into water and the resulting mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (methanol–chloroform=1:19) to afford secondary amine product (18.2 mg). To a stirred solution of the secondary amine (18.2 mg) in pyridine (0.12 mL) was added propionic anhydride (0.12 mL) at room temperature. The resulting mixture was stirred for 7 h. After cooling to 0 °C, the reaction was quenched with 28% aqueous ammonia solution and the resulting mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane–ethyl acetate=1:1 to methanol–dichloromethane=3:97, gradient) to afford anilide **24** (15.4 mg, 0.0373 mmol, 81% over 2 steps) as a yellow foam; $[\alpha]_D^{24}$ −91.2 (*c* 0.77, $CHCl_3$); IR (neat, cm^{-1}) 2939, 2787, 1732, 1651, 1487, 1454, 1393, 1385, 1227, 746; ^1H NMR (600 MHz, CD_3CN, 65 °C) δ 7.13 (dd, *J*=8.0, 8.0 Hz, 1H), 6.95 (d, *J*=8.0 Hz, 2H), 4.42 (dd, *J*=11.1, 6.3 Hz, 1H), 3.89 (s, 3H), 3.55 (s, 3H), 3.13 (ddd, *J*=9.2, 9.2, 3.4 Hz, 1H), 3.05–3.01 (m, 1H), 2.65 (dq, *J*=15.0, 7.5 Hz, 1H), 2.51 (s, 1H), 2.35–2.29 (m, 1H), 2.33 (dq, *J*=15.0, 7.5 Hz, 1H), 2.22 (ddd, *J*=13.8, 13.8, 2.8 Hz, 1H), 2.15 (d, *J*=14.1 Hz, 1H), 2.08–1.90 (m, 4H), 1.92 (d, *J*=14.1 Hz, 1H), 1.78 (dddd, *J*=26.2, 13.2, 4.1, 4.1 Hz, 1H), 1.71–1.66 (m, 1H), 1.60–1.44 (m, 2H), 1.40 (ddd, *J*=13.5, 13.5, 4.6 Hz, 1H), 1.28–1.23 (m, 1H), 1.13 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ; 175.3, 172.8, 151.6, 143.8, 131.2, 127.4, 116.8, 113.3, 70.4, 70.0, 56.6, 54.9, 54.2, 53.0, 51.7, 43.1, 38.6, 37.1, 36.0, 28.9, 26.5, 25.4, 22.6, 10.5; HRMS (EI) calcd for $C_{24}H_{32}N_2O_4$ [M^+] 412.2362, found 412.2355.

4.11. Hemiaminal 25

To a stirred solution of anilide **24** (4.7 mg, 0.011 mmol) in MeOH (0.12 mL) was added 1 M NaOH (0.12 mL) at room temperature. After stirring for 6.5 h, the reaction mixture was heated at 50 °C for an hour. After cooling to 0 °C, the resulting mixture was acidified with 1 M HCl until pH 6–7 and concentrated under reduced pressure to afford a crude carboxylic acid. To a stirred solution of the crude carboxylic acid in a mixture of *t*-BuOH (0.12 mL) and H_2O (0.25 mL) were added $K_3Fe(CN)_6$ (38 mg, 0.11 mmol) and $NaHCO_3$ (19 mg, 0.23 mmol) at room temperature. After stirring for 40 min, the reaction mixture was poured into H_2O and the resulting mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Pure hemiaminal **25** (4.3 mg, 0.011 mmol, quant. over 2 steps) was obtained as a white solid without further purification; $[\alpha]_D^{25}$ −88.5 (*c* 0.93, $CHCl_3$); IR (neat, cm^{-1}) 2932, 2849, 1773, 1643, 1493, 1447, 1387, 1252, 1188, 881, 754; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J*=8.1 Hz, 1H), 7.08 (dd, *J*=8.1, 8.1 Hz, 1H), 6.84 (d, *J*=8.1 Hz, 1H), 4.53–4.44 (m, 1H), 3.86 (s, 3H), 3.14 (ddd, *J*=8.8, 8.8, 5.5 Hz, 1H), 3.04 (ddd, *J*=10.4, 8.1, 4.9 Hz, 1H), 2.92 (ddd, *J*=11.9, 11.9, 2.8 Hz, 1H), 2.81–2.75 (m, 1H), 2.64 (dq, *J*=15.1, 7.5 Hz, 1H), 2.33 (d, *J*=16.5 Hz, 1H), 2.27 (dq, *J*=15.1, 7.5 Hz, 1H), 2.08 (ddd, *J*=13.5, 9.0, 4.8 Hz, 1H), 2.04–1.74 (m, 4H), 1.91 (d, *J*=16.5 Hz, 1H), 1.63–1.49 (m, 4H), 1.34 (ddd, *J*=14.5, 4.0, 4.0 Hz, 1H), 1.15 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 174.9, 149.5, 140.4, 129.7, 127.1, 117.2, 111.7, 107.8, 67.9, 59.7, 55.5, 48.6, 43.5, 42.6, 40.6, 34.1, 33.7, 28.0, 25.2, 24.3, 20.4, 10.0; HRMS (EI) calcd for $C_{23}H_{28}N_2O_4$ [M^+] 396.2049, found 396.2030.

4.12. (+)-Cimicine (5)

To a stirred solution of hemiaminal **25** (11.8 mg, 0.0298 mmol) and tetrabutylammonium iodide (14.3 mg, 0.0387 mmol) in CH_2Cl_2 (0.3 mL) was added BCl_3 (1 M solution in CH_2Cl_2, 74 μL, 0.074 mmol) at −78 °C. After 15 min, the resulting solution was allowed warm up to 0 °C, and stirred for 135 min. Then, the resulting solution was allowed to warm up to room temperature, and the mixture was stirred for 130 min. After cooling to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified sequentially by column chromatography on silica gel (methanol–dichloromethane=1:9 to 2:8, gradient), preparative TLC (methanol–dichloromethane=1:9), reverse-phase preparative TLC (MeOH), and preparative TLC coated with NH Silica Gel (acetone–hexanes=3:7) to afford (+)-cimicine (**5**) (8.6 mg, 0.022 mmol, 75%) as a white solid, associated with a recovery of the starting compound **25** (0.4 mg, 1 μmol, 3%); $[\alpha]_D^{22}$ +81.3 (*c* 0.37, $CHCl_3$) (lit.[8] $[\alpha]_D$ +82 ($CHCl_3$)); mp 220–223 °C (lit.[8] 229–231); IR (neat, cm^{-1}) 2937, 2856, 2800 (br), 1771, 1747, 1632, 1599, 1470, 1454, 1435, 1261, 1198, 748; ^1H NMR (500 MHz, $CDCl_3$) δ 10.5 (s, 1H), 7.09–7.03 (m, 2H), 6.85 (dd, *J*=7.0, 2.0 Hz, 1H), 3.95 (dd, *J*=11.3, 4.8 Hz, 1H), 3.14 (ddd, *J*=8.9, 8.9, 5.2 Hz, 1H), 3.06 (ddd, *J*=9.6, 9.6, 5.2 Hz, 1H), 2.93 (ddd, *J*=11.8, 2.5, 2.5 Hz, 1H), 2.82–2.76 (m, 1H), 2.60 (dq, *J*=15.3, 7.7 Hz, 1H), 2.53 (dq, *J*=15.3, 7.7 Hz, 1H), 2.46 (d, *J*=16.5 Hz, 1H), 2.13 (ddd, *J*=13.6, 8.9, 4.9 Hz, 1H), 2.01–1.90 (m, 4H), 1.87–1.70 (m, 2H), 1.66–1.53 (m, 3H), 1.45 (ddd, *J*=14.5, 3.8, 3.8 Hz, 1H), 1.29 (t, *J*=7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 172.2, 147.2, 137.8, 128.7, 127.4, 118.7, 115.3, 106.1, 67.3, 58.8, 48.4,

43.6, 42.4, 40.5, 34.6, 33.8, 28.4, 25.1, 24.9, 20.3, 9.6; HRMS (EI) calcd for $C_{22}H_{26}N_2O_4$ [M^+] 382.1893, found 382.1891.

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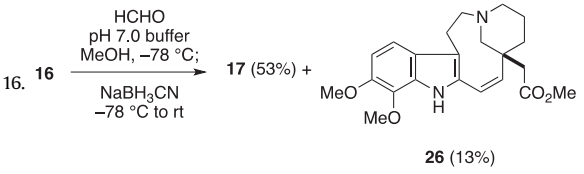
16. 

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