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Full Paper

Alkaloid Synthesis

Concise Total Syntheses of Pyrido[4,3-*b*]carbazole Alkaloids Using Copper-Mediated 6π-Electrocyclization

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Abstract: Concise syntheses of 9-methoxyellipticine, 3,4-dihydroellipticine (μ-alkaloid D), 1,2,3,4-tetrahydroellipticine, 2-methyl-1,2,3,4-tetrahydroellipticine, olivacine, 3,4-dihydroolivacine, (±)-guatambuine, and (±)-janetine were developed starting from hexatriene intermediates readily obtained by Pd-catalyzed tandem cyclization/cross-coupling reaction of indolylborates. The route enables the facile construction of pyrido[4,3-*b*]carbazoles by Cu-catalyzed 6π-electrocyclization and subsequent transformation of the pyridocarbazole intermediates into pyrido[4,3-*b*]carbazole alkaloids.

Introduction

Alkaloids with a pyrido[4,3-*b*]carbazole framework, represented by ellipticine (**1**)[1] and olivacine (**6**),[2] have been isolated from various plants[3] and display a broad range of biological activities such as antitumor activity based on DNA intercalation and/or topoisomerase II inhibition as well as antimalarial activity (Figure 1).[4] Many structural analogues of **1** and **6** have recently been synthesized and several have been found to display broad spectrum anticancer activity.[5] The diverse biological activities and structural intricacy of these alkaloids have elicited intense synthetic interest.[6] In the course of our ongoing studies on the synthetic use of indolylborate **11** generated in situ from indole **10**,[7] we previously reported a total synthesis of ellipticine (**1**)[8] and a formal synthesis of olivacine (**6**).[9] Both syntheses featured facile formation of pyridocarbazole **14** from triene **13** obtained by the Pd-catalyzed tandem cyclization/cross-coupling of **11** with bromide **12** in a one-pot reaction. Here, we report the total syntheses of the pyrido[4,3-*b*]carbazole alkaloids 9-methoxyellipticine (**2**), 3,4-dihydroellipticine (μ-alkaloid D) (**3**), 1,2,3,4-tetrahydroellipticine (**4**), 2-methyl-1,2,3,4-tetrahydroellipticine (**5**), olivacine (**6**), 3,4-dihydroolivacine (**7**), (±)-janetine (**8**),

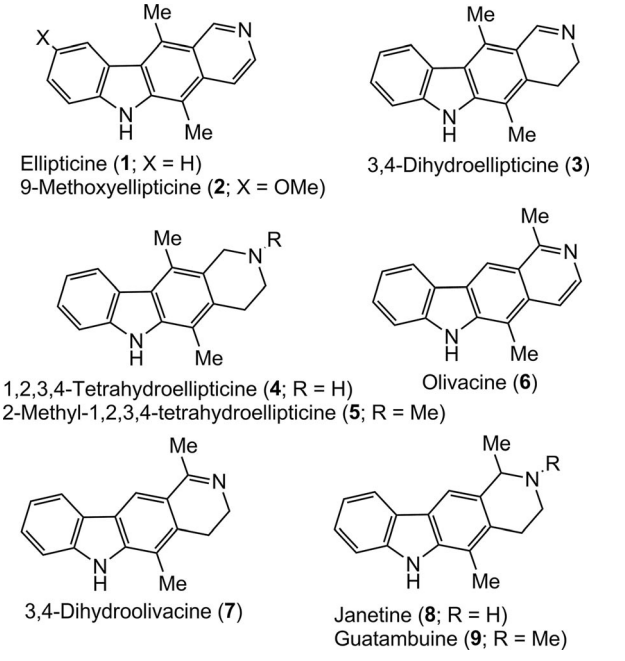
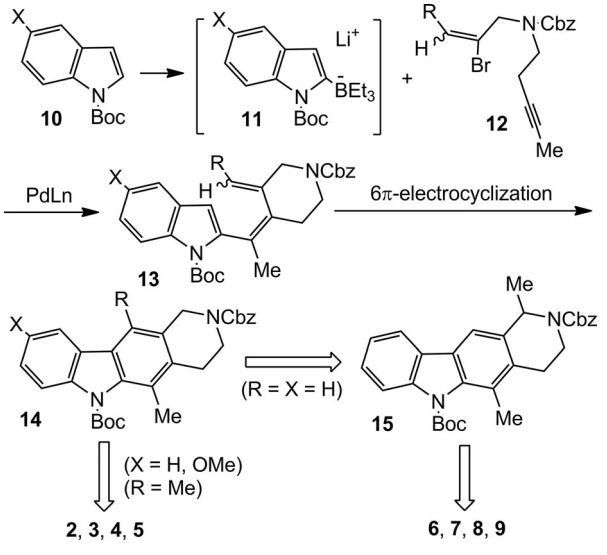


Figure 1. Pyrido[4,3-*b*]carbazole alkaloids.



Scheme 1. Synthetic scheme for generating pyrido[4,3-*b*]carbazole alkaloids.

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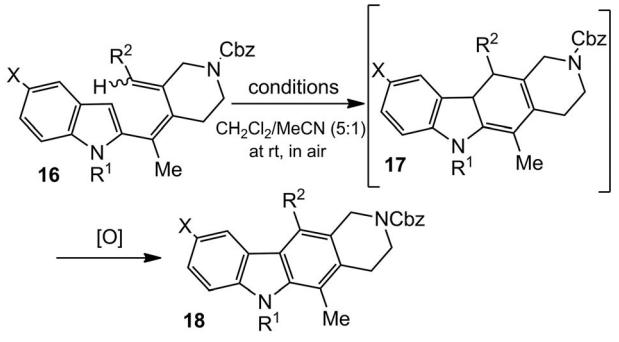
and (±)-gutambuine (**9**) using Cu-mediated 6π-electrocyclization as the key step.

Our synthetic approach is shown in Scheme 1. In our previous reports,[8,9] the conversion of triene **13** to pyridocarbazole **14** was accomplished by a photochemical 6π-electrocyclization, but this reaction provided low yields and was compatible with only small scale reactions. We recently developed a novel Cu-catalyzed 6π-electrocyclization protocol[10] and envisioned that **14** could be successfully synthesized by this reaction. Furthermore, alkaloids **2**–**5** could be obtained from **14**. In addition, carbazole **14** could be transformed into carbazole **15**, which would serve as a diverging intermediate for construction of **6**–**9**.

Results and Discussion

First, Cu-mediated cyclization of triene **16** was investigated (Table 1). Initially, triene **16a**[8] was added to a solution of $(CuOTf)_2$·toluene (1 equiv.) in CH_2Cl_2/MeCN (5:1; v/v) and the mixture was stirred at room temperature in air for 1 h. This readily produced pyridocarbazole **18a**[8] in 85 % yield (Table 1, Entry 1). It is notable that the reversed addition of $(CuOTf)_2$·toluene (1 equiv.) to a solution of **16a** in CH_2Cl_2/MeCN resulted in recovery of **16a**, although the reason for this is presently unclear. Catalytic cyclization was examined next. Simple treatment of **16a** with a catalytic amount of $(CuOTf)_2$·toluene (10 mol-%) required a long reaction time (16 h) to give **18a** in 60 % yield (Table 1, Entry 2). We were delighted to find that the addition of PCC (1.2 equiv.) to accelerate the oxidation of diene intermediate **17** notably increased the yield of **18a** to 84 % (Table 1, Entry 3). The catalytic protocol tolerated **16c**[8] and **16d** bearing the *N*-Me and *N*-OMe groups, respectively, producing **18c**[8] and **18d** in 85 % and 80 % yields (Table 1, Entries 5 and 6). The catalytic cyclization of **16e**[9] bearing no Me group on the vinyl carbon provided **18e**[9] in 83 % yield, and the same treatment of **16f**[9] gave **18f**[9] in 76 % yield, although a long reaction time (16 h) was required (Table 1, Entries 7 and 8). Moreover, increasing the catalyst loading to 30 mol-% gave **18f** in 79 % yield (Table 1, Entry 9).

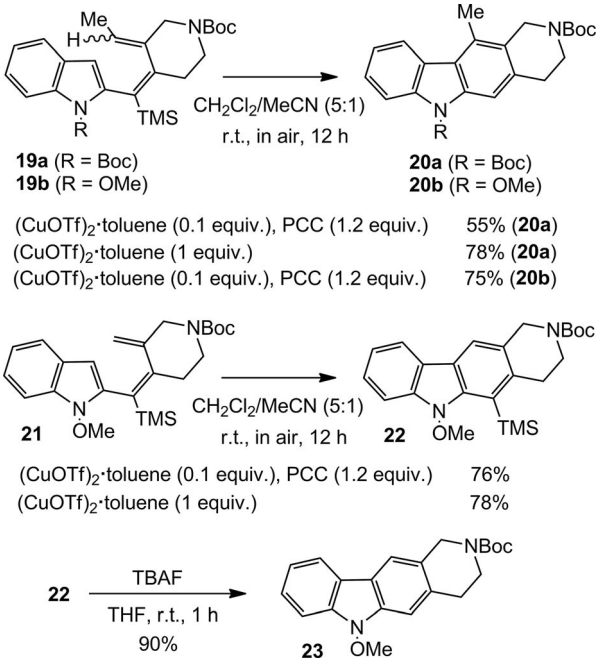
Table 1. Cu-mediated cyclization of indole **16**.



Entry	16	R^1	R^2	X	Conditions	Yield (%)[a]
1	**16a**	Boc	Me	H	condition A,[b] 1 h	85 (**18a**)
2	**16a**	Boc	Me	H	condition B,[c] 16 h	60 (**18a**)
3	**16a**	Boc	Me	H	condition C,[d] 3 h	84 (**18a**)
4	**16b**	Boc	Me	OMe	condition C, 3 h	85 (**18b**)
5	**16c**	Me	Me	H	condition C, 2 h	85 (**18c**)
6	**16d**	OMe	Me	H	condition C, 1 h	80 (**18d**)
7	**16e**	Me	H	H	condition C, 2 h	83 (**18e**)
8	**16f**	Boc	H	H	condition C, 12 h	76 (**18f**)
9	**16f**	Boc	H	H	condition D,[e] 5 h	79 (**18f**)

[a] Isolated yield. [b] $(CuOTf)_2$·toluene (1 equiv.). [c] $(CuOTf)_2$·toluene (0.1 equiv.). [d] $(CuOTf)_2$·toluene (0.1 equiv.), PCC (1.2 equiv.). [e] $(CuOTf)_2$·toluene (0.3 equiv.), PCC (1.2 equiv.).

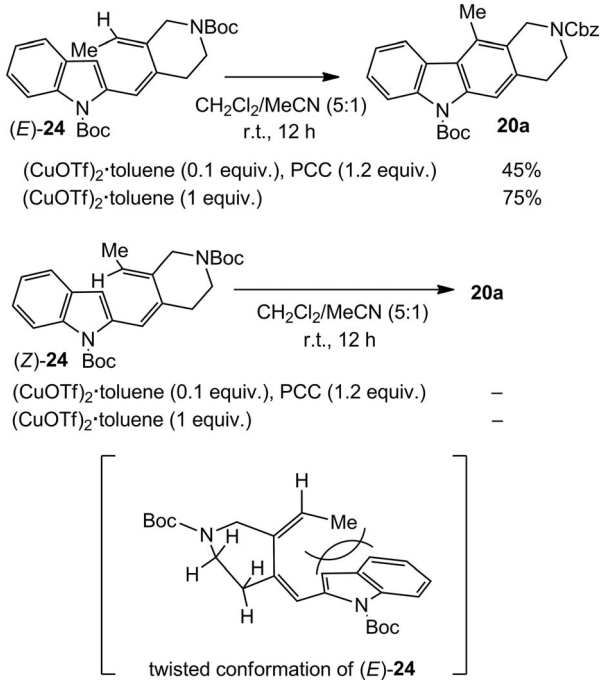
In addition, the cyclization of **19**, with a bulky TMS group on the olefinic carbon, was examined (Scheme 2). Reacting **19a**[11] under the catalytic conditions resulted in formation of **20a** in 55 % yield accompanied by spontaneous elimination of the TMS group. Treating **19a** with 1 equiv. of $(CuOTf)_2$·toluene also afforded **20a** in 78 % yield. The catalytic cyclization of **19b** having the *N*-OMe group provided **20b** in 75 % yield. Moreover, cyclization of **21** lacking a Me group on the vinyl carbon under the catalytic conditions provided carbazole **22** in 76 % yield, and cyclization using 1 equiv. of $(CuOTf)_2$·toluene led to **22** in 78 % yield. The TMS group of **22** was readily removed by treatment with TBAF to give **23** (Scheme 2).



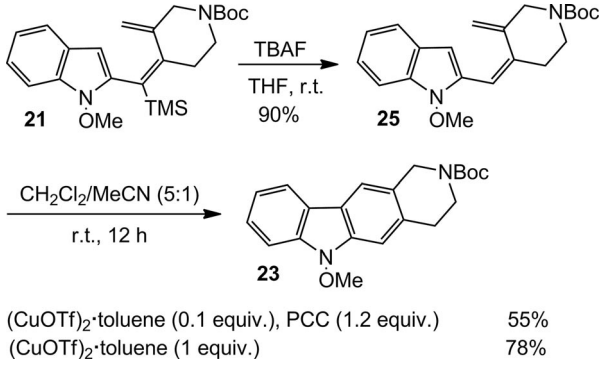
Scheme 2. Cu-promoted cyclization of trienes **19** and **21**.

The cyclization of (*E*)-**24**[11] and (*Z*)-**24**,[11] derived from triene **19a**, was carried out next (Scheme 3). From (*E*)-**24**, carbazole **20a** was obtained in 45 % yield using the identified catalytic conditions and the yield of **20a** increased to 75 % by using 1 equiv. of $(CuOTf)_2$·toluene. In contrast, attempted cyclization of (*Z*)-**24** provided no isolable products, likely due to the twisted conformation of the hexatriene unit[8] (Scheme 3). Repulsive interactions between the Me group on the vinyl carbon and the indole ring of (*E*)-**24** likely restricted the torsion of the triene unit and was advantageous for the cyclization. A high degree of conformational freedom in the twisted conformation of (*Z*)-**24** would hinder cyclization. Moreover, catalytic cycliza-

tion of **25**, derived from **21** by removal of the TMS group, gave **23** in 55 % yield, along with recovery of **25** (20 %); **23** was obtained in 78 % yield when 1 equiv. of $(CuOTf)_2$·toluene was employed (Scheme 4). Even though **25** displays a high degree of conformational flexibility, the less-substituted terminal olefin of the triene unit appears to enable ring-closure.



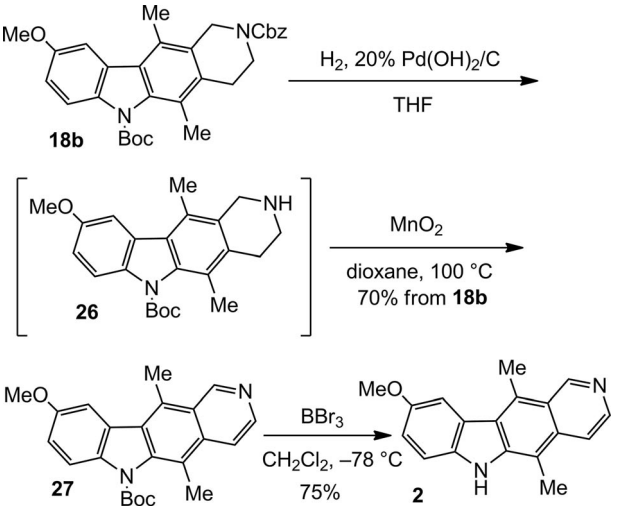
Scheme 3. Cu-promoted cyclization of triene **24**.



Scheme 4. Cu-promoted cyclization of triene **25**.

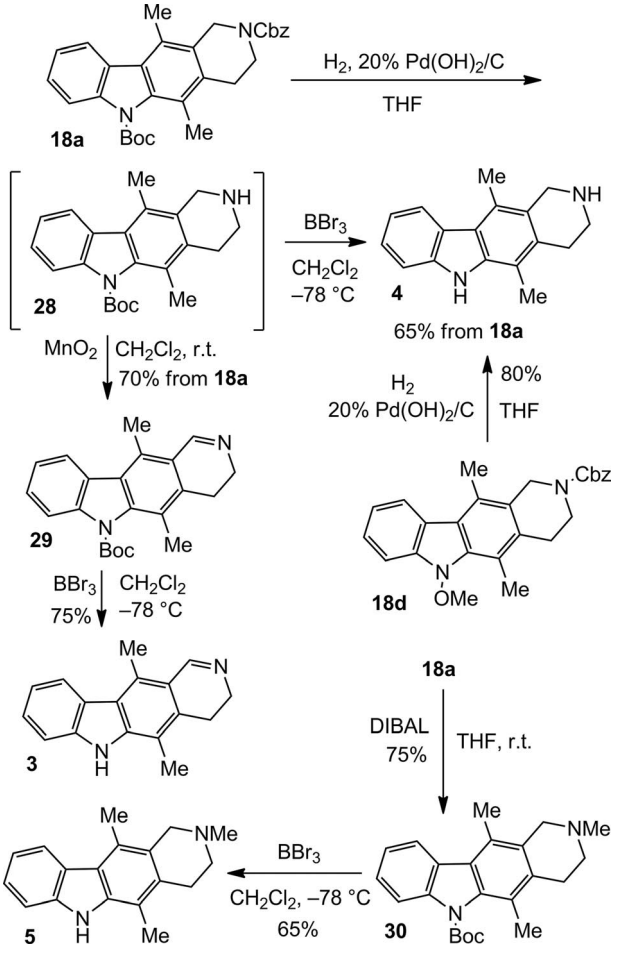
Having succeeded in achieving Cu-catalyzed cyclization of **16**, transformation of carbazoles **18** into pyridocarbazole alkaloids was undertaken next. Initially, 9-methoxyellipticine (**2**)[12] was synthesized starting from carbazole **18b** (Scheme 5). The *N*-Cbz group was removed by catalytic hydrogenation, and resulting amine **26** was subjected, without further purification, to oxidation with MnO_2 in dioxane at 100 °C, to afford **27** in 70 % yield. Removal of the *N*-Boc group with BBr_3 in CH_2Cl_2 at –78 °C afforded **2** in 75 % yield.

Next, carbazole **18a** was converted to 3,4-dihydroellipticine (μ-alkaloid D) (**3**),[13] 1,2,3,4-tetrahydroellipticine (**4**)[14] and 2-methyl-1,2,3,4-tetrahydroellipticine (**5**)[15] (Scheme 6) Removal of the *N*-Cbz group of **18a** by catalytic hydrogenation provided



Scheme 5. Synthesis of 9-methoxyellipticine (**2**).

amine **28**, which was then treated with BBr_3 in CH_2Cl_2 at –78 °C. This sequence of transformations gave 1,2,3,4-tetrahydroellipticine (**4**) in 65 % yield from **18a**. Moreover, catalytic reduction of carbazole **18d** produced **4** in a one-pot reaction. Additionally, amine **28** was oxidized with MnO_2 in CH_2Cl_2 at room temperature to give imine **29**. Treatment of **29** with BBr_3 in CH_2Cl_2

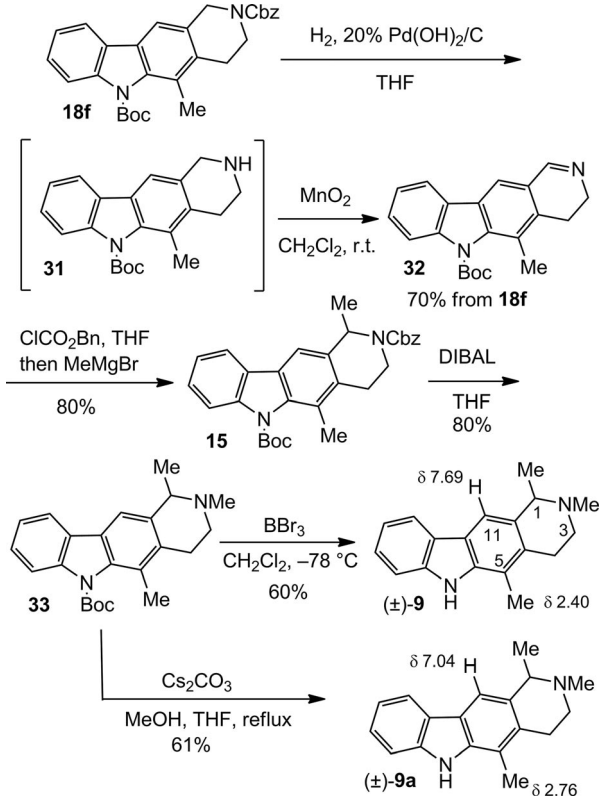


Scheme 6. Synthesis of **4** and **5**.

at –78 °C provided 3,4-dihydroellipticine (**3**) in 75 % yield. The *N*-Cbz group of **18a** was readily reduced to the *N*-Me group with DIBAL in THF at room temperature, leading to compound **30** in 75 % yield. The *N*-Boc group was then removed with BBr_3 in CH_2Cl_2 at –78 °C to give 2-methyl-1,2,3,4-tetrahydroellipticine (**5**).

The total syntheses of olivacine (**6**),[16] 3,4-dihydroolivacine (**7**),[17] (±)-janetine (**8**),[18,17a] and (±)-gutambuine (**9**)[19] were undertaken starting from carbazole **18f**. To transform **18f** into carbazole **15**, the *N*-Cbz group of **18f** was removed by catalytic hydrogenation, and resulting amine **31** was subjected, without purification, to oxidation with MnO_2 in CH_2Cl_2 at room temperature, to yield **32** in 70 % yield from **18f**. Next, the Me group was introduced into the C-1 position of **32**. Treatment of **32** with $ClCO_2Bn$ in THF at room temperature, followed by the addition of MeMgBr, readily provided **15** in 80 % yield.

Conversion of **15** to (±)-guatambuine (**9**) was carried out (Scheme 7) by first converting the *N*-Cbz group of **15** to its *N*-Me congener with DIBAL in THF at room temperature; **33** was generated in 80 % yield. Removal of the *N*-Boc group in **33** was effected with BBr_3 in CH_2Cl_2 at –78 °C to provide (±)-guatambuine (**9**) in 60 % yield. The NMR spectroscopic data of **9** were in good agreement with previously reported data.[19c] Additionally, the *N*-Boc group in **33** was cleaved by treatment with Cs_2CO_3 in refluxing MeOH/THF to render **9a**. Importantly, some aspects of the NMR spectroscopic data of **9a** were not consistent with those of **9**. Notably, the ^{1}H NMR spectroscopic data of **9** and **9a** show that the signals of the C5-Me (**9**, δ = 2.40 ppm; **9a**, δ = 2.76 ppm) and the C11-H (**9**, δ = 7.69 ppm; **9a**, δ = 7.04 ppm) had distinctly different chemical shifts, although the ^{1}H NMR spectrum of **9a** closely resembled that of **9**.



Scheme 7. Synthesis of (±)-**9**.

The structure of natural (+)-**9** was unequivocally confirmed by X-ray crystal structure analysis, which showed that the D ring is in a half-chair conformation and that the C1-Me is axial.[20] The NOE effect between the C1-Me (δ = 1.50 ppm) and the C3-H_a (δ = 3.20 ppm) was present in synthetic (±)-**9** (Figure 2). On the other hand, irradiation of the C1-H resonance (δ = 3.90 ppm) for **9a** produced NOE effects on the peaks representative of the C1-Me, N2-Me, C3-H_b, and C11-H moieties. Additionally, irradiation of the N2-Me resonance produced distinct enhancements in the NOE effects noted for C1-Me, C1-H, C3-H_a, and C3-H_b signals. Taken together, these results suggest that the C1-Me group in **9** switched from its axial placement to being equatorial in **9a**; this appears to result from a conformational inversion of the D-ring, accompanied by inversion of the nitrogen at the 2-position.

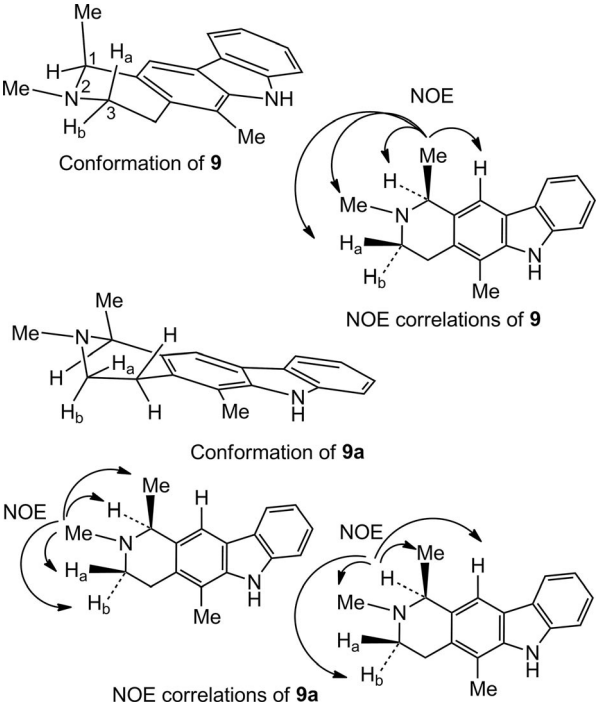
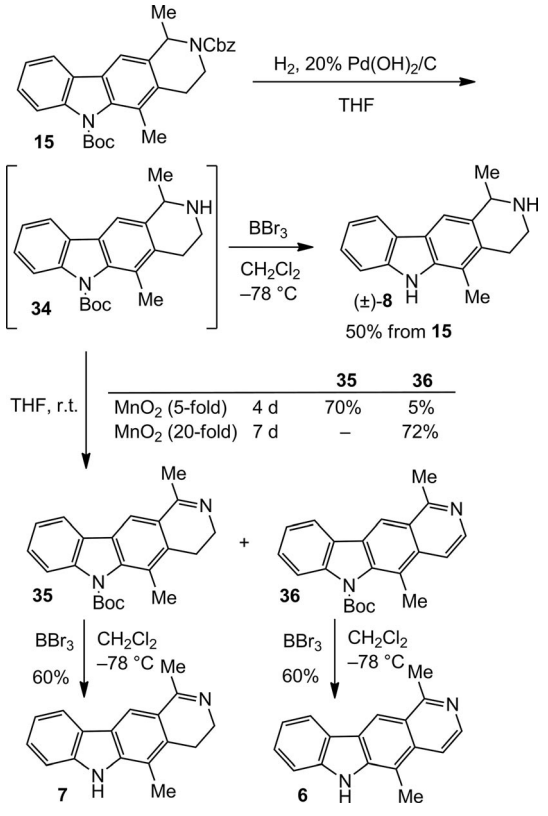


Figure 2. Conformation of **9** and **9a**.

Next, **15** was converted to (±)-janetine (**8**) (Scheme 8) by removal of the *N*-Cbz group using catalytic hydrogenation. Resulting amine **34** was subjected, without purification, to reaction with BBr_3 in CH_2Cl_2 at –78 °C to produce (±)-janetine (**8**)[17b] in 50 % yield. Additionally, amine **34** was oxidized with a five-fold excess of MnO_2, with respect to **15** (w/w), in THF at room temperature for 4 d. This oxidation provided imine **35** in 70 % yield and **36** in 5 % yield from **15**. A 20-fold excess of MnO_2 and prolonged reaction time (7 d) sufficed for the oxidation of **34** at room temperature, affording **36** in 72 % yield from **15**. Removal of the *N*-Boc group in **36** with BBr_3 at –78 °C provided olivacine (**6**) in 60 % yield; the NMR spectroscopic data of this synthetic material were in good agreement with those of natural **6**.[16a] On the other hand, 3,4-dihydroolivacine (**7**) was generated by treatment of **35** with BBr_3 at –78 °C. The ^{1}H NMR spec-

troscopic data of synthetic **7** in [D_6]acetone approximately coincided with the ^{1}H NMR spectroscopic data for **7** in $CDCl_3$ reported in the literature.[17b] Here, synthetic **7** was dissolved in [D_6]acetone because it was insoluble in $CDCl_3$.



Scheme 8. Synthesis of **6**, **7**, and (±)-**8**.

Conclusions

In conclusion, total syntheses of 9-methoxyellipticine (**2**), 3,4-dihydroellipticine (**3**), 1,2,3,4-tetrahydroellipticine (**4**), 2-methyl-1,2,3,4-tetrahydroellipticine (**5**), olivacine (**6**), 3,4-dihydroolivacine (**7**), (±)-janetine (**8**), and (±)-guatambuine (**9**) were achieved using triene **16** as a key intermediate. Most importantly, the cyclization of triene **16** to pyridocarbazole **18** was successfully performed by taking advantage of Cu-mediated 6π-electrocyclization, enabling a gram-scale reaction.

Experimental Section

***tert*-Butyl 2-((1*Z*)-1-{(3*E*,*Z*)-1-[(Benzyloxy)carbonyl]-3-ethylidenepiperidin-4-ylidene}ethyl)-5-methoxy-1*H*-indole-1-carboxylate (16b):** *t*BuLi (1.6 M solution in pentane, 6 mL, 9.6 mmol) was added to a solution of indole **10** (X = OMe, 1.98 g, 8 mmol) in THF (100 mL) at –78 °C under an argon atmosphere, and the mixture was stirred for 1 h. Then, BEt_3 (1 M solution in hexane, 9.6 mL, 9.6 mmol) was added, and the whole mixture was gradually warmed to room temperature over 1 h. Then, $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol) and bromide **12** (R = Me, 1.34 g, 4 mmol) were added, and the mixture was heated at 60 °C for 3 h. The mixture was cooled to 0 °C, and 10 % aqueous NaOH solution (20 mL) and 30 % aqueous H_2O_2 solution (10 mL) were added. After stirring for 20 min, the mixture was diluted with AcOEt (500 mL), washed with brine, and dried with $MgSO_4$. The solvent was removed and the residue was separated by flash column chromatography (AcOEt/hexane, 1:7) to give **16b** (1.3 g, 63 %) as an oil. IR (neat): $\tilde{\nu}$ = 1726, 1699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34–1.46 (m, 3 H), 1.59 (s, 9 H), 1.88 (s, 3 H), 2.24–2.36 (m, 1 H), 2.59–2.70 (m, 1 H), 3.50–3.89 (m, 3 H), 3.83 (s, 3 H), 4.46, 4.49 (two s, 1 H), 5.16 (s, 2 H), 5.12–5.23 (m, 1 H), 5.97, 6.01 (two s, 1 H), 6.84 (dd, *J* = 2.5, 9.0 Hz, 1 H, 1 H), 6.88 (br. s, 1 H), 7.29–7.44 (m, 5 H), 8.01 (d, *J* = 9.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 20.4, 28.1, 30.3, 42.9, 45.6, 55.7, 67.2, 83.3, 103.0, 106.3, 111.9, 116.1, 123.9, 124.3, 125.3, 127.9, 128.0, 128.5, 130.5, 131.2, 133.7, 135.0, 135.2, 136.9, 143.5, 149.9, 155.5, 155.8 ppm. HRMS (ESI): calcd. for $C_{31}H_{36}N_2NaO_5$ [M + Na]$^+$ 539.2521, found 539.2523.

Benzyl (3*E*/*Z*,4*Z*)-3-Ethylidene-4-[1-(1-methoxy-1*H*-indol-2-yl)-ethylidene]piperidine-1-carboxylate (16d): *n*BuLi (1.6 M solution in hexane, 6 mL, 9.6 mmol) was added to a solution of 1-methoxyindole (1.17 g, 8 mmol) in THF (100 mL) at –20 °C under an argon atmosphere, and the mixture was stirred for 0.5 h. Then, BEt_3 (1 M solution in hexane, 9.6 mL, 9.6 mmol) was added, and the whole mixture was gradually warmed to room temperature over 1 h. Then, $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol) and bromide **12** (R = Me, 1.34 g, 4 mmol) were added, and the mixture was heated at 60 °C for 1 h. The mixture was cooled to 0 °C, and 10 % aqueous NaOH solution (20 mL) and 30 % aqueous H_2O_2 solution (10 mL) were added. After stirring for 20 min, the mixture was diluted with AcOEt (500 mL), washed with brine, and dried with $MgSO_4$. The solvent was removed and the residue was separated by flash column chromatography (AcOEt/hexane, 1:7) to give **16d** (1.08 g, 65 %) as an oil. IR (neat): $\tilde{\nu}$ = 1693 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32–1.45 (m, 3 H), 2.08 (s, 3 H), 2.54–2.64 (m, 2 H), 3.60–3.69 (m, 2 H), 3.76 (s, 3 H), 4.24 (br. s, 2 H), 5.02–5.14 (m, 1 H), 5.14 (s, 2 H), 6.14 (s, 1 H), 7.04 (t, *J* = 8.0 Hz, 1 H), 7.10 (t, *J* = 8.5 Hz, 1 H), 7.29–7.40 (m, 6 H), 7.48 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 20.2, 31.1, 31.2, 43.0, 45.2, 45.5, 64.6, 67.1, 97.6, 108.1, 119.4, 119.8, 120.3, 121.7, 123.8, 124.2, 124.6, 128.0, 128.1, 128.6, 132.0, 133.9, 137.0, 138.4, 155.5 ppm. HRMS (ESI): calcd. for $C_{26}H_{28}N_2NaO_3$ [M + Na]$^+$ 439.1998, found 439.1998.

General Procedure for the Cyclization of Triene 16 Using (CuOTf)$_2$·toluene (1.0 equiv.): A solution of **16** (0.5 mmol) in CH_2Cl_2/MeCN (5:1; v/v) (5 mL) was added to a stirred solution of (CuOTf)$_2$·toluene (259 mg, 0.5 mmol) in CH_2Cl_2/MeCN (5:1; v/v) (20 mL) at room temperature in air, and the mixture was stirred (see Table 1 for the reaction time). Then, the mixture was concentrated, and the residue was separated by flash column chromatography with hexane/AcOEt to give pyridocarbazole **18**.

General Procedure for the Catalytic Cyclization of Triene 16 Using (CuOTf)$_2$·toluene (0.1 equiv.) and PCC (1.2 equiv.): To a stirred mixture of (CuOTf)$_2$·toluene (25.9 mg, 0.05 mmol) and PCC (129 mg, 60 mmol) in CH_2Cl_2/MeCN (5:1; v/v) (20 mL), triene **16** (0.5 mmol) was added, and the mixture was stirred at room temperature in air (see Table 1 for the reaction time). Then, the mixture was concentrated, and the residue was separated by flash column chromatography with hexane/AcOEt to give pyridocarbazole **18**.

2-Benzyl 6-*tert*-Butyl 9-Methoxy-5,11-dimethyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]carbazole-2,6-dicarboxylate (18b): Colorless crystals, m.p. 102–103 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1722, 1659 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 2.29 (s, 3 H), 2.65 (s, 3 H), 2.90–3.00 (m, 2 H), 3.73–3.80 (m, 2 H), 3.91 (s, 3 H), 4.72, 4.77 (two s, 2 H), 5.20 (s, 2 H), 7.05 (d, *J* = 9.0 Hz, 1 H), 7.30–7.44 (m, 5 H), 7.62 (s, 1 H), 7.98 (d, *J* = 9.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 15.5, 16.6, 17.3, 26.5, 26.8, 27.1, 27.4, 28.2, 41.1, 41.3, 41.5, 44.6,

45.0, 55.9, 67.2, 83.6, 107.6, 112.5, 115.8, 120.4, 120.8, 122.1, 122.3, 124.4, 124.6, 128.0, 128.1, 128.4, 128.6, 131.3, 131.7, 132.9, 133.2, 135.4, 135.5, 136.9, 138.6, 138.8, 151.5, 151.6, 155.5, 156.0 ppm. HRMS (ESI): calcd. for $C_{31}H_{34}NaN_2O_5$ [M + Na]$^+$ 537.2365, found 537.2349.

Benzyl 6-Methoxy-5,11-dimethyl-1,3,4,6-tetrahydro-2*H*-pyrido[4,3-*b*]carbazole-2-carboxylate (18d): Oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1693 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.64 (s, 3 H), 2.65–2.75 (m, 3 H), 2.92–3.00 (m, 2 H), 3.75–3.82 (m, 2 H), 3.81 (s, 3 H), 4.79 (s, 2 H), 5.20 (s, 2 H), 7.25 (t, *J* = 8.0 Hz, 1 H), 7.29–7.42 (m, 5 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4, 15.3, 26.8, 27.0, 41.3, 41.5, 44.6, 61.8, 67.2, 109.4, 116.8, 117.0, 119.4, 120.9, 121.8, 122.9, 124.8, 125.2, 125.6, 127.1, 127.5, 128.0, 128.4, 132.1, 132.3, 135.9, 137.0, 139.9 155.5 ppm. HRMS (ESI): calcd. for $C_{26}H_{26}N_2NaO_3$ [M + Na]$^+$ 437.1841, found 437.1844.

***tert*-Butyl (3*E*/*Z*,4*E*)-3-Ethylidene-4-[(1-methoxy-1*H*-indol-2-yl)-(trimethylsilyl)methylidene]-piperidine-1-carboxylate (19b):** Oil. IR (neat): $\tilde{\nu}$ = 1693 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.13, 0.21 (two s, 9 H), 1.18, 1.40 (two d, *J* = 7.5 Hz, 3 H), 1.45, 1.46 (two s, 9 H), 2.40–2.82 (m, 2 H), 3.48–3.73 (m, 2 H), 3.86, 3.92 (two s, 3 H), 4.15, 4.18 (two s, 1 H), 5.11–5.19 (m, 1 H), 5.21–5.30 (m, 1 H), 5.83, 5.94 (two s, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 7.10–7.14 (m, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.45 (dd, *J* = 2.3, 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 0.68, 1.35, 13.4, 15.8, 28.5, 35.0, 36.2, 44.6, 45.5, 53.5, 64.5, 65.0, 79.7, 96.7, 97.0, 107.7, 107.8, 119.5, 119.9, 120.0, 120.7, 121.0, 121.7, 123.6, 123.9, 126.9, 131.4, 131.6, 136.4, 137.4, 138.3, 154.5, 154.8 ppm. HRMS (ESI): calcd. for $C_{25}H_{36}N_2NaO_3Si$ [M + Na]$^+$ 463.1393, found 463.2389.

***tert*-Butyl (4*E*)-4-[(1-Methoxy-1*H*-indol-2-yl)(trimethylsilyl)-methylidene]-3-methylidenepiperidine-1-carboxylate (21):** Oil. IR (neat): $\tilde{\nu}$ = 1693 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.15 (s, 9 H), 1.48 (s, 9 H), 2.59–2.65 (m, 1 H), 2.66–2.74 (m, 1 H), 3.50–3.57 (m, 1 H), 3.68–3.74 (m, 1 H), 3.95 (s, 3 H), 3.92–4.02 (m, 2 H), 4.64, 4.80 (two s, 2 H), 5.86 (s, 1 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 0.53, 28.5, 34.9, 44.2, 52.0, 65.1, 79.9, 96.5, 107.8, 114.7, 119.7, 120.0, 120.9, 123.9, 127.4, 131.8, 138.0, 142.5, 153.5, 154.7 ppm. HRMS (ESI): calcd. for $C_{24}H_{34}N_2NaO_3Si$ [M + Na]$^+$ 449.2236, found 449.2238.

***tert*-Butyl (4*Z*)-4-[(1-Methoxy-1*H*-indol-2-yl)methylidene]-3-methylidenepiperidine-1-carboxylate (25):** TBAF (1 M solution in THF, 2 mL, 2 mmol) was added to a solution of **21** (500 mg, 1.1 mmol) in THF (50 mL) at room temperature under an argon atmosphere, and the mixture was stirred for 30 min. The mixture was diluted with AcOEt (200 mL), washed with brine, and dried with $MgSO_4$. The solvent was removed, and the residue was separated by flash column chromatography (AcOEt/hexane, 10:1) to give **20** (350 mg, 90 % yield) as an oil. IR (neat): $\tilde{\nu}$ = 1693 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 2.48 (br. s, 1 H), 2.80, 2.89 (two t, *J* = 5.5 Hz, 1 H), 3.55, 3.61 (two t, *J* = 6.3 Hz, 2 H), 4.00, 4.02 (two s, 3 H), 4.09, 4.14 (two s, 2 H), 4.99, 5.24, 5.27, 5.29, 5.34 (five s, 2 H), 6.35, 6.37 (two s, 1 H), 6.62, 6.83 (two s, 1 H), 7.05, 7.09 (two t, *J* = 7.8 Hz, 1 H), 7.17, 7.22 (two t, *J* = 7.8 Hz, 1 H), 7.36, 7.39 (two d, *J* = 8.0 Hz, 1 H), 7.46, 7.55 (two d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.5, 38.1, 44.8, 45.5, 51.2, 52.2, 65.2, 80.0, 97.5, 108.0, 111.5, 114.3, 114.7, 120.4, 120.6, 122.3, 123.8, 131.6, 132.0, 141.2, 154.7 ppm. HRMS (ESI): calcd. for $C_{21}H_{26}N_2NaO_3$ [M + Na]$^+$ 377.1841, found 377.1843.

Di-*tert*-Butyl 11-Methyl-3,4-dihydro-1*H*-pyrido[4,3-*b*]carbazole-2,6-dicarboxylate (20a): Colorless crystals, m.p. 180–181 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1718, 1683 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 9 H), 1.75 (s, 9 H), 2.71 (s, 3 H), 3.01 (t, *J* = 5.7 Hz, 2 H), 3.67 (t, *J* = 5.7 Hz, 2 H), 4.71 (s, 2 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 8.07 (s, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 8.31 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.4, 28.5, 28.6, 30.7, 40.5, 42.1, 43.8, 44.6, 79.9, 84.0, 113.7, 116.1, 122.4, 122.9, 123.0, 126.2, 126.6, 1217.0, 129.5, 134.0, 137.5, 151.2, 155.1 ppm. HRMS (ESI): calcd. for $C_{26}H_{32}N_2NaO_4$ [M + Na]$^+$ 459.2260, found 459.2264.

***tert*-Butyl 6-Methoxy-11-methyl-1,3,4,6-tetrahydro-2*H*-pyrido-[4,3-*b*]carbazole-2-carboxylate (20b):** Colorless crystals, m.p. 178–179 °C. IR (KBr): $\tilde{\nu}$ = 1701 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 9 H), 2.74 (s, 3 H), 3.04 (s, 2 H), 3.68 (s, 2 H), 4.08 (s, 3 H), 4.72 (s, 2 H), 7.16 (s, 1 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5, 28.5, 30.6, 40.7, 41.9, 43.6, 44.3, 63.2, 79.8, 105.5, 108.2, 117.7, 120.1, 120.7, 122.7, 124.1, 125.4, 129.9, 130.3, 133.6, 136.7, 138.1, 155.2 ppm. HRMS (ESI): calcd. for $C_{22}H_{26}N_2NaO_3$ [M + Na]$^+$ 389.1841, found 389.1841.

***tert*-Butyl 6-Methoxy-5-(trimethylsilyl)-1,3,4,6-tetrahydro-2*H*-pyrido[4,3-*b*]carbazole-2-carboxylate (22):** Oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1683 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.49 (s, 9 H), 1.47–1.54 (m, 9 H), 3.09 (t, *J* = 6.2 Hz, 2 H), 3.32 (s, 3 H), 3.53–3.65 (m, 2 H), 4.66 (s, 2 H), 7.25 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.70–7.76 (m, 1 H), 7.91 (d, *J* = 7.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 1.49, 1.89, 28.6, 32.1, 32.4, 41.5, 42.6, 45.5, 46.6, 57.8, 63.4, 79.7, 79.8, 108.5, 112.1, 119.5, 119.8, 120.2, 120.4, 122.0, 122.2, 123.8, 126.1, 126.4, 128.5, 129.2, 134.0, 137.0, 138.2, 141.1, 141.9, 142.1, 144.7, 155.0, 155.1 ppm. HRMS (ESI): calcd. for $C_{24}H_{32}N_2NaO_3Si$: [M + Na]$^+$ 447.2080, found 447.2082.

***tert*-Butyl 6-Methoxy-1,3,4,6-tetrahydro-2*H*-pyrido[4,3-*b*]carbazole-2-carboxylate (23):** TBAF (1 M solution in THF, 1 mL, 1 mmol) was added to a solution of **22** (212 mg, 0.5 mmol) in THF (20 mL) at room temperature under an argon atmosphere, and the mixture was stirred for 30 min. The mixture was diluted with AcOEt (100 mL), washed with brine, and dried with $MgSO_4$. The solvent was removed, and the residue was separated by flash column chromatography (AcOEt/hexane, 1:10) to give **23** (158 mg, 90 % yield) as an oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1681 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 9 H), 3.04 (t, *J* = 6.0 Hz, 2 H), 3.69 (t, *J* = 6.0 Hz, 2 H), 4.10 (s, 3 H), 4.73 (s, 2 H), 7.22 (dt, *J* = 1.1, 7.5 Hz, 1 H), 7.28 (s, 1 H), 7.44 (dt, *J* = 1.1, 8.0 Hz, 1 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 7.77 (s, 1 H), 7.97 (d, *J* = 7.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.6, 30.1, 30.4, 63.4, 79.8, 107.7, 108.5, 118.1, 118.9, 119.9, 120.2, 120.4, 125.6, 126.1, 134.0, 135.8, 137.0, 138.2, 155.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{24}N_2NaO_3$ [M + Na]$^+$ 375.1685, found 375.1684.

***tert*-Butyl 9-Methoxy-5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole-6-carboxylate (27):** A solution of **18b** (500 mg, 0.97 mmol) was stirred in the presence of 20 % $Pd(OH)_2$/C (500 mg) in THF under atmospheric pressure of hydrogen for 1 h, the catalyst and the solvent were removed. The residue **26** and MnO_2 (5 g) were heated in dioxane (100 mL) at 100 °C for 12 h. After cooling, the insoluble materials were removed by filtration, and the filtrate was concentrated and separated by flash column chromatography with AcOEt/hexane (1:1) to give **27** (537 mg, 70 %) as colorless crystals, m.p. 155–156 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1724 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.69 (s, 9 H), 2.83 (s, 3 H), 3.09 (s, 3 H), 3.95 (s, 3 H), 7.14 (dd, *J* = 2.9, 9.1 Hz, 1 H), 7.80 (d, *J* = 2.9 Hz, 1 H), 8.04 (d, *J* = 6.3 Hz, 1 H), 8.07 (d, *J* = 9.1 Hz, 1 H), 8.56 (d, *J* = 6.3 Hz, 1 H), 9.63 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 16.8, 28.2, 56.0, 83.9, 109.2, 114.5, 116.3, 116.8, 119.6, 125.3, 127.5, 127.8, 129.4, 132.7, 137.3, 138.2, 141.1,

149.8, 151.4, 156.2 ppm. HRMS (ESI): calcd. for $C_{23}H_{24}N_2NaO_3$ [M + Na]$^+$ 399.1685, found 399.1687.

9-Methoxyellipticine (2): To a solution of **27** (100 mg, 0.26 mmol) in CH_2Cl_2 at –78 °C under an argon atmosphere, BBr_3 (1 M solution in CH_2Cl_2, 0.3 mL) was added. After stirring for 30 min, the reaction was quenched with 10 % aqueous NaOH solution (2 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the extract was dried with Na_2SO_4. The solvent was removed, and the residue was separated by alumina column chromatography with AcOEt to give **2** (68 mg, 70 %) as pale orange colored crystals, m.p. 277–278 °C (ref.[12a] m.p. 276.3–278.5 °C). IR (KBr): $\tilde{\nu}$ = 3437, 3155 cm^{-1}. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 2.78 (s, 3 H), 3.31 (s, 3 H), 7.15 (dd, J = 2.3, 8.6 Hz, 1 H), 7.46 (d, J = 8.6 Hz, 1 H), 7.87 (d, J = 5.7 Hz, 1 H), 7.93 (d, J = 2.3 Hz, 1 H), 8.39 (d, J = 5.7 Hz, 1 H), 9.67 (s, 1 H), 10.20 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_8$]THF): δ = 10.9, 13.6, 55.2, 107.5, 107.8, 110.5, 114.7, 123.9, 124.5, 128.1, 132.9, 137.7, 140.8, 141.6, 149.6, 153.9 ppm. HRMS (ESI): calcd. for $C_{18}H_{17}N_2O$ [M + H]$^+$ 277.1341, found 277.1344.

***tert*-Butyl 5,11-Dimethyl-3,4-dihydro-6*H*-pyrido[4,3-*b*]carbazole-6-carboxylate (29):** A solution of **18a** (1.1 g, 2.3 mmol) was stirred in the presence of 20 % Pd(OH)$_2$/C (500 mg) in THF under atmospheric pressure of hydrogen for 1 h, the catalyst and the solvent were removed. The residue **28** and MnO_2 (5 g) were stirred in CH_2Cl_2 at room temperature for 3 d. The insoluble materials were removed by filtration, and the filtrate was concentrated and separated by alumina column chromatography with hexane/AcOEt (1:1) to give **29** as a pair of conformers (537 mg, 70 %).

Early-Eluting Fraction 29a: Colorless crystals, m.p. 161–162 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1726 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.68 (s, 9 H), 2.57 (s, 3 H), 2.73 (s, 3 H), 2.83 (t, J = 8.0 Hz, 2 H), 3.76 (t, J = 8.0 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.5 Hz, 1 H), 8.10 (d, J = 8.0 Hz, 1 H), 8.15 (d, J = 8.0 Hz, 1 H), 8.80 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.4, 16.5, 22.8, 28.2, 47.1, 82.4, 115.0, 122.4, 123.1, 123.2, 125.6, 126.9, 127.0, 127.1, 128.4, 131.1, 137.9, 141.5, 151.1, 159.1 ppm. HRMS (ESI): calcd. for $C_{22}H_{25}N_2O_2$ [M + H]$^+$ 349.1916, found 349.1915.

Later-Eluting Fraction 29b: Colorless crystals, m.p. 166–167 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1730 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70 (s, 9 H), 2.33 (s, 3 H), 2.85–2.89 (m, 2 H), 2.94 (s, 3 H), 3.74–3.80 (m, 2 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.5 Hz, 1 H), 8.07 (d, J = 8.0 Hz, 1 H), 8.14 (d, J = 8.0 Hz, 1 H), 8.92 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0, 16.9, 23.8, 28.2, 46.6, 84.4, 114.7, 120.7, 122.6, 122.9, 123.3, 124.4, 126.4, 127.0, 129.4, 135.9, 140.5, 140.8, 151.0, 158.4 ppm. HRMS (ESI): calcd. for $C_{22}H_{25}N_2O_2$: [M + H]$^+$ 349.1916, found 349.1914.

3,4-Dihydroellipticine (μ-Alkaloid D) (3): BBr_3 (1 M solution in CH_2Cl_2, 0.4 mL) was added to a solution of **29** (100 mg, 0.287 mmol) in CH_2Cl_2 (10 mL) at –78 °C, and the mixture was stirred for 0.5 h. To the reaction mixture, 10 % aqueous NaOH solution (2 mL) was added, and the mixture was extracte with CH_2Cl_2. The organic layer was washed with brine and dried with Na_2SO_4. The solvent was removed, and the residue was separated by alumina column chromatography with AcOEt/MeOH (100:1) to give **3** (53 mg, 75 %) as colorless crystals, m.p. 276–280 °C dec. (ref.[13a] 281–283 °C dec). IR ($CHCl_3$): $\tilde{\nu}$ = 3650, 1603, 1572 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 2.68 (s, 3 H), 2.75 (s, 3 H), 2.88 (t, J = 7.5 Hz, 2 H), 3.67 (dt, J = 1.7, 7.5 Hz, 2 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 8.20 (d, J = 8.0 Hz, 1 H), 8.77 (s, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 10.6, 14.2, 22.3, 46.6, 110.6, 117.3, 118.7, 122.6, 122.8, 123.4, 124.1, 125.1, 125.5, 126.6, 137.9, 141.5, 159.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_2$ [M + H]$^+$ 249.1392, found 249.1379.

1,2,3,4-Tetrahydroellipticine (4): A solution of **18a** (500 mg, 1.03 mmol) was stirred in the presence of 20 % Pd(OH)$_2$/C (500 mg) in THF under atmospheric pressure of hydrogen for 1 h, the catalyst and the solvent were removed. BBr_3 (1 M solution in CH_2Cl_2, 2 mL) was added to a solution of the residue **28** in CH_2Cl_2 at –78 °C under an argon atmosphere. After the mixture was stirred for 30 min, 10 % aqueous NaOH solution (2 mL) was added. The mixture was diluted with CH_2Cl_2, washed with brine, and dried with Na_2SO_4. The solvent was removed, and the residue was separated by flash column chromatography with AcOEt/MeOH (50:1) to give **4** (167 mg, 65 %) as colorless crystals, m.p. 154–157 °C dec. (ref.[14b] 163–165 °C dec). IR ($CHCl_3$): $\tilde{\nu}$ = 3308 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 2.40 (s, 3 H), 2.66 (s, 3 H), 2.91 (t, J = 6.3 Hz, 2 H), 3.14 (t, J = 6.3 Hz, 2 H), 4.13 (s, 2 H), 7.09 (t, J = 7.5 Hz, 1 H), 7.30 (t, J = 7.5 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 11.3, 13.8, 26.8, 43.0, 46.0, 110.1, 114.7, 118.0, 119.6, 121.9, 123.2, 124.0, 124.1, 125.9, 129.7, 138.4, 140.6 ppm. HRMS (EI): calcd. for $C_{17}H_{18}N_2$ [M]$^+$ 250.1469, found 250.1455.

Preparation of 4 from 18d: A solution of **18d** (100 mg, 0.24 mmol) was stirred in the presence of 20 % Pd(OH)$_2$/C (70 mg) in THF under atmospheric pressure of hydrogen for 1 h, and the solvent and the catalyst was removed to give **4** (48 mg, 80 %).

***tert*-Butyl 2,5,11-Trimethyl-1,2,3,4-tetrahydro-6*H*-pyrido[4,3-*b*]carbazole-6-carboxylate (30):** To a solution of **18a** (200 mg, 0.41 mmol) in THF (30 mL) at room temperature under an argon atmosphere, DIBAL (1 M solution in toluene, 2 mL, 2 mmol) was added. After stirring for 1 h, 10 % aqueous NaOH solution (2 mL) was added to the reaction mixture, and the mixture was diluted with AcOEt (100 mL) and washed with brine. The solvent was removed, and the residue was separated by alumina column chromatography with AcOEt/hexane (1:2) to give **30** (160 mg, 75 %) as colorless crystals, m.p. 158–159 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1728 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 2.26, 2.29 (two s, 3 H), 2.56, 2.57 (two s, 3 H), 2.64, 2.68 (two s, 3 H), 2.79 (t, J = 6.0 Hz, 2 H), 2.97, 3.01 (two t, J = 6.0 Hz, 2 H), 3.68, 3.74 (two s, 2 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 8.10, 8.11 (two d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 15.5, 16.4, 17.1, 27.5, 28.2, 46.1, 52.4, 52.6, 56.6, 57.0, 83.6, 115.0, 119.9, 121.7, 122.4, 122.5, 122.9, 124.0, 124.3, 125.9, 126.3, 127.6, 127.8, 128.1, 132.1, 132.4, 137.6, 137.9, 140.9, 141.0, 151.5, 151.6 ppm. HRMS (ESI): calcd. for $C_{23}H_{29}N_2O_2$ [M + H]$^+$ 365.2229, found 365.2231.

2-Methyl-1,2,3,4-tetrahydroellipticine (5): To a solution of **30** (100 mg, 0.27 mmol) in CH_2Cl_2 at –78 °C under an argon atmosphere, BBr_3 (1 M solution in CH_2Cl_2, 0.4 mL) was added. After stirring for 30 min, the reaction was quenched with 10 % aqueous NaOH solution (2 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the extract was dried with Na_2SO_4. The solvent was removed, and the residue was separated by alumina column chromatography with AcOEt/hexane (3:1) to give **5** (46 mg, 65 %) as colorless crystals, m.p. 221–225 °C (ref.[15] m.p. 218–223 °C). IR ($CHCl_3$): $\tilde{\nu}$ = 3474 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.57 (s, 3 H), 2.66 (s, 3 H), 2.76 (t, J = 6.3 Hz, 2 H), 2.99 (t, J = 6.3 Hz, 2 H), 3.73 (s, 2 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.36 (t, J = 7.5 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.97 (br. s, 1 H), 8.18 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 15.1, 28.2, 46.6, 52.8, 57.0, 110.4, 114.3, 119.1, 120.0, 122.6, 124.6, 124.7, 126.6, 130.0, 137.8, 139.9 ppm. ^{1}H NMR (500 MHz, CD_3OD): δ = 2.37 (s, 3 H), 2.52 (s, 3 H), 2.64 (s, 3 H), 2.77 (t, J = 6.3 Hz, 2 H), 2.98 (t, J = 6.3 Hz, 2 H), 3.73 (s, 2 H), 7.08 (t, J = 7.5 Hz, 1 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.42 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 11.4, 13.9, 27.2, 44.9, 52.3, 56.2, 110.7, 114.5, 118.0, 119.7, 121.9, 122.3,

123.9, 124.1, 125.8, 128.6, 138.4, 140.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}N_2$ [M + H]$^+$ 265.1705; found 265.1677.

***tert*-Butyl 5-Methyl-3,4-dihydro-6*H*-pyrido[4,3-*b*]carbazole-6-carboxylate (32):** A solution of **18f** (1.1 g, 2.3 mmol) was stirred in the presence of 20 % $Pd(OH)_2$/C (500 mg) in THF under atmospheric pressure of hydrogen for 1 h, the catalyst and the solvent were removed. The residue **31** and MnO_2 (5 g) were stirred in dioxane at room temperature for 3 d. The insoluble materials were removed by filtration, and the filtrate was concentrated and separated by flash column chromatography with AcOEt/hexane (1:1) to give **32**[13] (537 mg, 70 %).

2-Benzyl 6-*tert*-Butyl 1,5-Dimethyl-3,4-dihydro-1*H*-pyrido-[4,3-*b*]carbazole-2,6-dicarboxylate (15): Benzyl chloroformate (0.33 mL, 2.3 mmol) was added to a solution of **32** (600 mg, 1.8 mmol) in THF (50 mL) at 0 °C under an argon atmosphere, and the mixture was stirred for 30 min at 0 °C. Then, MeMgBr (1.4 M solution in THF, 1.6 mL) was added to the mixture at 0 °C, and the whole mixture was stirred at 0 °C for 30 min. Then, ice-cold water was (20 mL) added, and the mixture was extracted with AcOEt (200 mL). The organic layer was washed with brine, and dried with $MgSO_4$. The solvent was removed, and the residue was separated by flash column chromatography with hexane/AcOEt (1:1) to give **15** (700 mg, 80 %) as an oil. IR (neat): $\tilde{\nu}$ = 1722, 1697 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.52–1.60 (m, 3 H), 1.68, 1.75 (two s, 9 H), 2.32, 2.72 (two s, 3 H), 2.82–3.04 (m, 2 H), 3.30–3.49 (m, 1 H), 4.15–4.39 (m, 1 H), 5.12–5.28 (m, 2 H), 5.38–5.50 (m, 1 H), 7.29–7.46 (m, 7 H), 7.53–7.59, 7.86–7.91 (two m, 0.6 H), 8.00, 8.01 (two s, 0.4 H), 8.03–8.08, 8.27–8.32 (two m, 1 H), 8.13–8.18, 8.36–8.41 (two m, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 16.0, 17.5, 22.6, 23.0, 23.2, 26.2, 26.3, 27.0, 27.1, 28.3, 28.5, 37.4, 37.8, 38.2, 51.1, 51.7, 67.1, 67.2, 83.8, 84.0, 112.2, 112.4, 115.5, 116.1, 119.6, 119.7, 122.5, 122.9, 123.1, 123.2, 124.7, 124.9, 125.8, 126.3, 126.5, 126.9, 127.1, 127.4, 127.9, 128.0, 128.6, 130.7, 130.9, 132.3, 132.6, 134.3, 134.7, 137.0, 137.2, 137.3, 137.4, 137.7, 138.0, 138.9, 139.1, 140.8, 151.1, 151.4, 154.9, 155.2 ppm. HRMS (ESI): calcd. for $C_{30}H_{32}N_2O_4Na$ [M + Na]$^+$ 507.2260, found 507.2261.

***tert*-Butyl 1,2,5-Trimethyl-1,2,3,4-tetrahydro-6*H*-pyrido[4,3-*b*]-carbazole-6-carboxylate (33):** To a solution of **15** (190 mg, 0.39 mmol) in THF (30 mL), DIBAL (1 M solution in toluene, 5 mL) was added at 0 °C, and then stirred at room temperature for 3 h. Ice-cold water (10 mL) was added to the mixture, and the mixture was extracted with AcOEt (100 mL). The organic layer was washed with brine and dried with $MgSO_4$. The solvent was removed, and the residue was separated by flash column chromatography with hexane/AcOEt (1:1) to give **33** (114 mg, 80 %) as an oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1716 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 6.9 Hz, 3 H), 1.75 (s, 9 H), 2.52 (s, 3 H), 2.71 (s, 3 H), 2.74–2.80 (m, 1 H), 2.86–3.00 (m, 2 H), 3.14–3.22 (m, 1 H), 3.84 (q, *J* = 6.9 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 8.05 (s, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 8.34 (d, *J* = 8.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 17.3, 20.0, 20.4, 25.5, 26.3, 28.3, 28.5, 42.9, 48.4, 48.7, 59.6, 60.3, 83.6, 83.7, 112.3, 115.3, 115.5, 116.1, 119.4, 122.3, 122.7, 122.8, 123.0, 124.4, 125.5, 126.1, 126.7, 126.8, 127.3, 130.5, 132.6, 135.8, 137.2, 137.7, 139.0, 139.1, 140.8, 151.2, 151.5 ppm. HRMS (ESI): calcd. for $C_{23}H_{29}N_2O_2$ [M + H]$^+$ 365.2229, found 365.2243.

(±)-Guatambuine (9): To a solution of **33** (50 mg, 0.13 mmol) in CH_2Cl_2 (15 mL) at –78 °C under an argon atmosphere, BBr_3 (1 M solution in CH_2Cl_2, 0.26 mL) was added. Then, the whole mixture was stirred at –78 °C for 30 min, and the reaction was quenched with 10 % aqueous NaOH solution (2 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the extract was dried with Na_2SO_4. The solvent was removed, and the residue was separated on TLC plate (Aluminium oxide 60 F_{254} basic, Merck) with hexane/AcOEt (2:1) to give (±)-**9** (20 mg, 60 %) as colorless crystals, m.p. 248–250 °C (ref.[19a] m.p. 245–248 °C). IR (KBr): $\tilde{\nu}$ = 3136, 1600 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.9 Hz, 3 H), 2.40 (s, 3 H), 2.52 (s, 3 H), 2.72–2.80 (m, 1 H), 2.88–2.98 (m, 2 H), 3.12–3.20 (m, 1 H), 3.86 (q, *J* = 6.9 Hz, 1 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.69 (s, 1 H), 7.81 (s, 1 H), 8.00 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.0, 20.5, 25.9, 42.8, 48.6, 59.7, 110.6, 116.0, 116.7, 119.3, 120.2, 121.2, 123.9, 125.5, 130.0, 131.7, 137.9, 139.8 ppm. ^{1}H NMR (500 MHz, CD_3OD): δ = 1.48 (d, *J* = 6.9 Hz, 3 H), 2.42 (s, 3 H), 2.48 (s, 3 H), 2.74–2.80 (m, 1 H), 2.90–3.00 (m, 2 H), 3.14–3.20 (m, 1 H), 3.89 (q, *J* = 6.5 Hz, 1 H), 7.07 (t, *J* = 7.5 Hz, 1 H), 7.28 (t, *J* = 7.5 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.68 (s, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 11.6, 18.5, 22.8, 39.4, 47.3, 60.1, 110.5, 115.7, 117.5, 118.5, 119.5, 121.7, 123.0, 125.3, 125.4, 125.8, 139.1, 140.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}N_2$ [M + H]$^+$ 265.1705, found 265.1705.

Conformer 9a: A mixture of **33** (50 mg) and Cs_2CO_3 (100 mg) in MeOH (10 mL) and THF (10 mL) was heated under reflux for 3 h, and then, the solvent was removed. The residue was diluted with CH_2Cl_2 (100 mL), washed with brine, and dried with Na_2SO_4. The solvent was removed, and the residue was separated on TLC plate (Aluminium oxide 60 F_{254} basic, Merck) with hexane/AcOEt (2:1) to give **9a** (22 mg, 61 %) as colorless crystals, m.p. 240–241 °C. IR (KBr): $\tilde{\nu}$ = 3138, 1610 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.3 Hz, 3 H), 2.52 (s, 3 H), 2.76 (s, 3 H), 2.74–2.84 (m, 1 H), 2.90–3.00 (m, 2 H), 3.06–3.24 (m, 1 H), 3.83 (q, *J* = 6.3 Hz, 1 H), 7.04 (s, 1 H), 7.20 (dt, *J* = 1.1, 7.5 Hz, 1 H), 7.37 (dt, *J* = 1.1, 7.5 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.94 (br. s, 1 H), 8.20 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 20.5, 25.3, 42.8, 49.2, 60.1, 106.2, 110.3, 119.2, 121.2, 122.7, 124.0, 125.1, 131.1, 138.2, 140.1 ppm. ^{1}H NMR (500 MHz, CD_3OD): δ = 1.51 (d, *J* = 6.3 Hz, 3 H), 2.55 (s, 3 H), 2.73 (s, 3 H), 2.84–2.92 (m, 1 H), 2.96–3.04 (m, 2 H), 3.24–3.30 (m, 1 H), 3.98 (q, *J* = 6.5 Hz, 1 H), 7.09 (s, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 14.6, 18.5, 24.2, 41.1, 58.5, 106.0, 110.0, 118.0, 120.7, 121.2, 122.0, 123.4, 124.4, 130.2, 136.4, 138.9, 140.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}N_2$ [M + H]$^+$ 265.1705, found 265.1700.

(±)-Janetine (8): A solution of **15** (100 mg, 0.2 mmol) was stirred in the presence of 20 % $Pd(OH)_2$/C (100 mg) in THF under atmospheric pressure of hydrogen for 1 h, the catalyst and the solvent were removed. The residue **34** was dissolved in CH_2Cl_2, and cooled to –78 °C under an argon atmosphere. Then, BBr_3 (1 M solution in CH_2Cl_2, 0.26 mL) was added. After stirring for 30 min, the reaction was quenched with 10 % aqueous NaOH solution (2 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the extract was dried with Na_2SO_4. The solvent was removed, and the residue was separated on TLC plate (Aluminium oxide 60 F_{254} basic, Merck) with hexane/AcOEt (1:1) to give (±)-**8** (25 mg, 50 %) as colorless crystals, m.p. > 300 °C. (ref.[17a] 290–295 °C). IR (KBr): $\tilde{\nu}$ = 3431, 3286, 1606 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 1.77 (d, *J* = 6.8 Hz, 3 H), 2.48 (s, 3 H), 3.09–3.24 (m, 2 H), 3.40–3.48 (m, 1 H), 3.57–3.63 (m, 1 H), 4.70 (q, *J* = 6.8 Hz, 1 H), 7.12 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.34 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.84 (s, 1 H), 8.00 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 11.8, 19.0, 23.3, 39.4, 52.0, 110.6, 114.8, 117.7, 118.6, 119.6, 121.8, 122.9, 124.1, 125.5, 126.2, 139.3, 140.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{19}N_2$ [M + H]$^+$ 251.1548, found 251.1554.

***tert*-Butyl 1,5-Dimethyl-6*H*-pyrido[4,3-*b*]carbazole-6-carboxylate (36):** A solution of **24** (300 mg, 0.62 mmol) was stirred in the

presence of 20 % $Pd(OH)_2/C$ (300 mg) in THF under atmospheric pressure of hydrogen for 1 h, and then, the catalyst and the solvent were removed. The residue **34** was stirred with MnO_2 (6 g) in CH_2Cl_2 (100 mL) at room temperature for 7 d. The insoluble materials were removed by filtration, and the filtrate was concentrated and separated by flash column chromatography with AcOEt to give **36** (154 mg, 72 %) as colorless crystals, m.p. 183–184 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.71, 1.83 (two s, 9 H), 2.75, 3.16 (two s, 6 H), 7.40–7.49 (m, 1 H), 7.54, 7.60 (two dt, J = 1.1, 7.5 Hz, 1 H), 7.89, 7.98 (two d, J = 6.3 Hz, 1 H), 8.10, 8.48 (two d, J = 8.5 Hz, 1 H), 8.12, 8.36 (two d, J = 7.9 Hz, 1 H), 8.40 (d, J = 6.3 Hz, 1 H), 8.58, 9.00 (two s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.2, 17.3, 22.8, 23.0, 28.2, 28.5, 84.3, 84.4, 109.2, 113.9, 115.4, 115.6, 116.1, 116.3, 120.2, 120.5, 123.4, 123.7, 123.9, 124.9, 125.6, 126.0, 126.5, 127.5, 128.1, 128.4, 128.5, 128.6, 131.4, 135.6, 137.3, 139.0, 139.7, 140.2, 140.9, 142.2, 151.0, 151.1, 158.8, 159.0 ppm. HRMS (ESI): calcd. for $C_{22}H_{23}N_2O_2$ $[M + H]^+$ 347.1760, found 347.1766.

***tert*-Butyl 1,5-Dimethyl-3,4-dihydro-6*H*-pyrido[4,3-*b*]carbazole-6-carboxylate (35):** A solution of **15** (300 mg, 0.62 mmol) was stirred in the presence of 20 % $Pd(OH)_2/C$ (300 mg) in THF (30 mL) under atmospheric pressure of hydrogen for 1 h, and then, the catalyst and the solvent were removed. The residue **34** was stirred with MnO_2 (1.5 g) in THF (50 mL) at room temperature for 4 d. The insoluble materials were removed by filtration, and the filtrate was concentrated and separated by flash column chromatography with AcOEt to give **35** (151 mg, 70 %) as an oil and **36** (10 mg, 5 %). IR ($CHCl_3$): $\tilde{\nu}$ = 1722 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.79 (s, 9 H), 2.61 (s, 3 H), 2.79 (s, 3 H), 2.90–2.97, 3.09–3.14 (two m, 2 H), 3.76–3.80, 4.08–4.14 (two m, 2 H), 7.37, 7.39 (two t, J = 7.5 Hz, 1 H), 7.48, 7.52 (two t, J = 7.5 Hz, 1 H), 8.16, 8.22 (two d, J = 7.9 Hz, 1 H), 8.39, 8.42 (two d, J = 7.5 Hz, 1 H), 8.53, 8.58 (two s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 22.7, 23.3, 28.5, 46.1, 84.4, 112.6, 116.3, 123.0, 123.1, 123.3, 125.9, 127.3, 127.6, 129.7, 130.5, 137.0, 139.8, 150.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.1916, found 349.1919.

3,4-Dihydroolivacine (7): To a solution of **35** (100 mg, 0.26 mmol) in CH_2Cl_2 (20 mL) at –78 °C under an argon atmosphere, BBr_3 (1 M solution in CH_2Cl_2, 0.5 mL) was added. Then, the whole mixture was stirred at –78 °C for 30 min, and the reaction was quenched with 10 % aqueous NaOH solution (2 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the extract was dried with Na_2SO_4. The solvent was removed, and the residue was separated on TLC plate (aluminum oxide 60 F_{254} basic, Merck) with hexane/AcOEt (2:1) to give **7** (42 mg, 60 %) as pale yellow crystals, m.p. > 300 °C. (ref.[17a] 307–318 °C). IR (KBr): $\tilde{\nu}$ = 3300, 1627 cm^{-1}. ^1H NMR (500 MHz, [D_6]acetone): δ = 2.42 (s, 3 H), 2.52 (s, 3 H), 2.75–2.85 (m, 2 H), 3.56 (t, J = 7.5 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.35 (t, J = 7.5 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 8.24 (s, 1 H), 10.4 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, [D_6]acetone): δ = 12.0, 23.2, 23.4, 46.9, 111.1, 115.7, 116.3, 119.3, 120.0, 120.5, 122.4, 124.0, 125.5, 133.4, 140.4, 140.9, 163.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}N_2$ $[M + H]^+$ 249.1392, found 249.1398.

Olivacine (6): To a solution of **36** (50 mg, 0.13 mmol) in CH_2Cl_2 (15 mL) at –78 °C under an argon atmosphere, BBr_3 (1 M solution in CH_2Cl_2, 0.26 mL) was added. Then, the whole mixture was stirred at –78 °C for 30 min, and the reaction was quenched with 10 % aqueous NaOH solution (2 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the extract was dried with Na_2SO_4. The solvent was removed, and the residue was separated on TLC plate (aluminum oxide 60 F_{254} basic, Merck) with hexane/AcOEt (2:1) to give **6** (20 mg, 60 %) as colorless crystals, m.p. > 300 °C (ref.[16a] > 300 °C). ^1H NMR (500 MHz, CD_3OD): δ = 2.82 (s, 3 H), 3.06 (s, 3 H), 7.23 (dt, J = 1.1, 7.5 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.87 (d, J = 6.3 Hz, 1 H), 8.15 (d, J = 6.3 Hz, 1 H), 8.26 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 11.0, 21.0, 110.5, 111.2, 114.6, 115.2, 119.2, 120.7, 127.3, 123.1, 125.8, 127.5, 133.0, 137.6, 141.6, 143.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N_2$ $[M + H]^+$ 247.1235, found 247.1233.

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