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Synthesis of Pyrrolophenanthridine Alkaloids Based on C(sp^3)–H and C(sp^2)–H Functionalization Reactions

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Abstract: Assoanine, pratosine, hippadine, and dehydroanhydrolycorine belong to the pyrrolophenanthridine family of alkaloids, which are isolated from plants of the *Amaryllidaceae* species. Structurally, these alkaloids are characterized by a tetracyclic skeleton that contains a biaryl moiety and an indole core, and compounds belonging to this class have received considerable interest from researchers in a number of fields because of their biological properties and the challenges associated with their synthesis. Herein, a strategy for the total synthesis of these alkaloids by using C–H activation chemistry is described. The tetracyclic skeleton was constructed in a stepwise manner by C(sp^3)–H functionalization followed by a Catellani reaction, including C(sp^2)–H functionalization. A one-pot reaction involving both C(sp^3)–H and C(sp^2)–H functionalization was also attempted. This newly developed strategy is suitable for the facile preparation of various analogues because it uses simple starting materials and does not require protecting groups.

Keywords: alkaloids · C–H activation · natural products · synthesis design · total synthesis

Introduction

Pyrrolophenanthridine alkaloids, which can be biogenetically produced by the dehydration and aromatization of lycorine, belong to the *Amaryllidaceae* family of alkaloids (Figure 1),[1] and assoanine (**1**), which was originally isolated from *Narcissus pseudonarcissus* by Wildman et al.[2a] in 1956, is representative of this class alkaloid.[2] More than ten congeners, including pratosine (**2**),[3] hippadine (**3**),[4] and dehydroanhydrolycorine (**4**),[5] have been isolated from plants belonging to the *Amaryllidaceae* species. Pyrrolophenanthridine alkaloids exhibit various biological properties, including acetylcholinesterase inhibitory activity,[6] anticancer activity,[7] and anti-tripanosomal activity,[8] and have consequently received considerable attention from both chemists and biological scientists.[1] A variety of total syntheses have been reported, to date, for the preparation of pyrrolophenanthridine alkaloids, and these strategies have generally focused on the use of an indole derivative as the starting material for the construction of the biaryl moiety of the alkaloid.[9] For example, Snieckus and Siddiqui reported the Suzuki coupling reaction of 7-iodoindoline with 2-formylphenyl boronic acid in the presence of a palladium catalyst to give a pyrrolophenanthridine skeleton, which was subsequently converted into hippadine (**3**).[9y] Palladium-catalyzed cross-coupling reactions have also been used to construct the biaryl moiety of pyrrolophenanthridine alkaloids.[9d,e,i,s,t,w] Diels–Alder,[9q,aa] ring expansion,[9t] anion coupling,[9r,u] and radical cyclization[9n,o,s,x] reactions have also been used as key transformations for the construction of the biaryl moiety or the phenanthridine skeleton of pyrrolophenanthridine alkaloids.

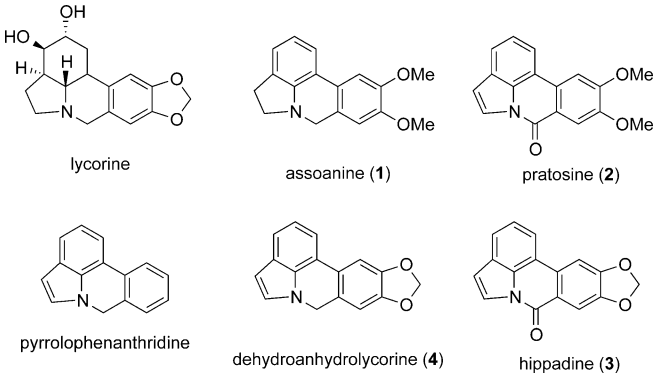

Figure 1. Structures of lycorine and pyrrolophenanthridine alkaloids discussed herein.

C–H functionalization chemistry has received considerable attention as an innovative method in organic chemistry during the last decade, because it has the potential to simplify synthesis by allowing the use of ubiquitous C–H bonds.[10] The popularity of C–H functionalization reactions has grown considerably in recent years, with various groups reporting the concise total syntheses of natural products based on transition-metal-catalyzed C–H functionalization strategies.[11] As part of their work towards the total synthesis of pyrrolophenanthridine alkaloids, Black et al. achieved the

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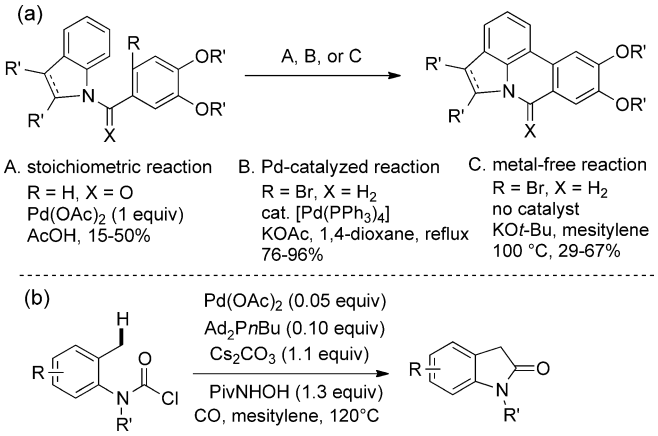
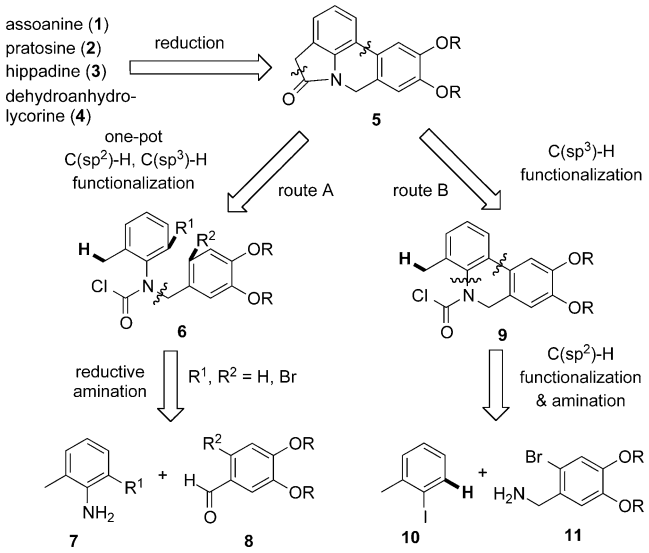


Scheme 1. a) Reported synthesis of biaryl systems obtained by using a C–H functionalization reaction. b) Oxindole formation through a C(sp^3)–H functionalization reaction. Ad = 1-adamantyl, Piv = pivaloyl.



Scheme 2. Retrosynthesis of pyrrolophenanthridine alkaloids based on C-(sp^3)–H and C(sp^2)–H functionalization reactions.

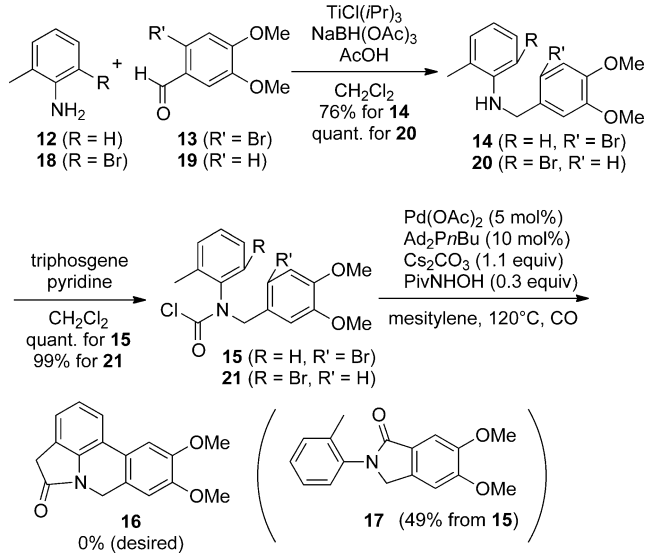
total synthesis of **2** and **3** in 1989 by using a C(sp^2)–H functionalization reaction for the construction of the biaryl moiety in these compounds, although a stoichiometric amount of $Pd(OAc)_2$ was required (Scheme 1 a, A).[9v,z] Ten years later, Miki et al. reported a palladium(0)/palladium(II)-catalyzed C(sp^2)–H functionalization reaction, which started with the oxidative addition of an aryl halide to palladium(0),[9c,l] and several groups went on to adopt this method in their own work (Scheme 1 a, B).[9g,h,k] In 2012, Bisai et al. developed a KO*t*Bu-promoted C(sp^2)–H functionalization reaction for the construction of biaryl compounds, which was applied to total synthesis of several pyrrolophenanthridine alkaloids.[9a,b] There have, however, been no reports in the literature concerning the total synthesis of alkaloids belonging to this class through a C(sp^3)–H functionalization reaction. We recently developed a series of synthetic methods for the construction of several heterocyclic systems, including oxindoles, spirooxindoles, 2-aryl indoles, and benzocarbazoles, by using a C(sp^3)–H functionalization reaction (Scheme 1 b).[12,13] To evaluate the scope and generality of our newly developed C(sp^3)–H functionalization method for the construction of oxindoles, we investigated its application to total synthesis of *Amaryllidaceae* alkaloids.[12a] Herein, we report a concise synthesis of **1**, **2**, **3**, and **4** from simple, commercially available starting materials based on C(sp^3)–H functionalization, which could also be used to prepare various analogues of these compounds.

Synthetic Plan

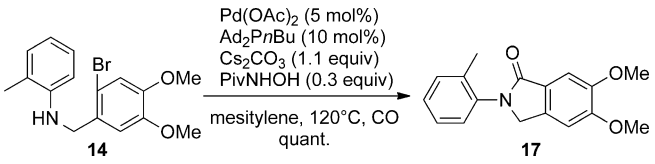
Retrosynthetically, it was envisioned that compound **5** could be used as a common intermediate for the synthesis of pyrrolophenanthridine alkaloids, and that this compound could be synthesized by using C(sp^3)–H and C(sp^2)–H functionalization reactions (Scheme 2). For example, the oxindole and phenanthridine rings could be constructed through C(sp^3)–H and C(sp^2)–H functionalization reactions of the methyl and phenyl groups, respectively. Because both of these reaction require similar conditions in terms of their Pd^0/Pd^{II} catalytic cycles, the tetracyclic skeleton of **5** could be constructed from carbamoyl chloride **6**, according to a one-pot reaction (Scheme 2, route A). In contrast, we could use a stepwise strategy for the construction of the lactam ring and the dihydrophenanthridine skeleton from iodotoluene **10** and benzylaniline **11** through C(sp^2)–H and C(sp^3)–H functionalization reactions. In this case, the lactam ring would have to be constructed during the later stages of the process because the C(sp^3)–H functionalization reaction requires higher temperatures than the C(sp^2)–H reaction.

Results and Discussion

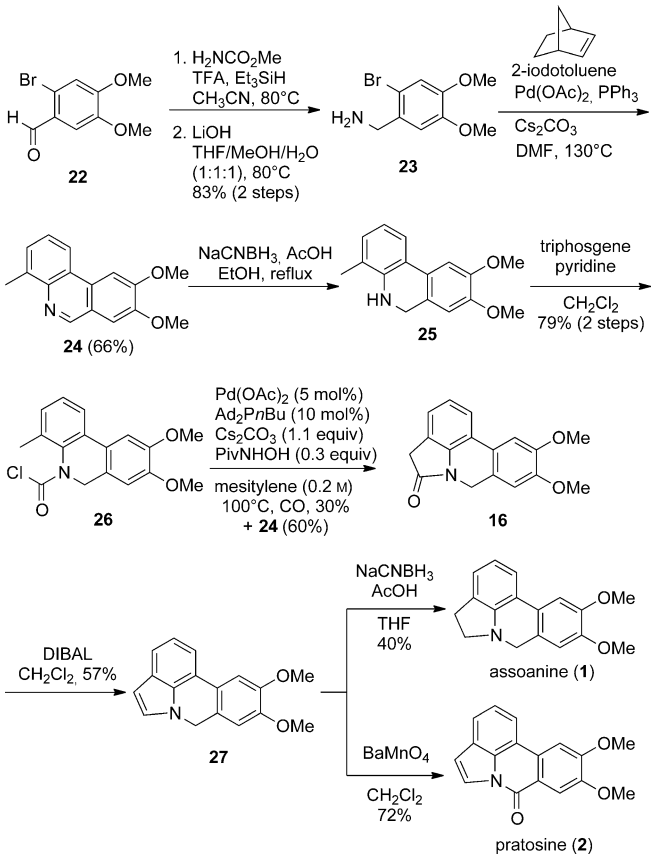
We focused our initial efforts on investigating route A (Scheme 2), which would provide a concise, few-step synthesis involving the challenging double cyclization of carbamoyl chlorides **15** or **21**. *o*-Toluidine (**12**) was coupled with 6-bromoveratraldehyde (**13**), according to McDonald's reductive amination procedure[14] (Scheme 3). The resulting amine **14** was treated with triphosgene and pyridine to give carbamoyl chloride **15**. The other carbamoyl chloride **21** was also prepared by the same two-step sequence from **18** and **19**. The double cyclization reaction involving the C(sp^3)–H and C(sp^2)–H functionalization reactions was attempted by the treatment of **15** with $Pd(OAc)_2$ (5 mol%), Ad_2PnBu (10 mol%), Cs_2CO_3 (1.1 equiv), and PivNHOH (0.3 equiv) in mesitylene (0.2 M) at 120 °C under an atmosphere of carbon monoxide.[12a] Unfortunately, however, this reaction gave lactam **17** in 49% yield instead of the desired product **16**. Byproduct **17** was most likely derived from amine **14**, which would have been produced by the oxidative addition of carbamoyl chloride **15** followed by the elimination of CO. Indeed, treatment of amine **14** under the same conditions



Scheme 3. Attempted one-pot formation of the tetracyclic skeleton.



Scheme 4. Formation of isooxindole **17**.



Scheme 5. Total synthesis of assoanine (**1**) and pratosine (**2**). TFA = trifluoroacetic acid, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide, DIBAL = diisobutylaluminum hydride.

gave compound **17** quantitatively through the oxidative addition of the aryl bromide followed by insertion of CO (Scheme 4). It was assumed that oxidative addition of the aryl bromide would be favorable and that the resulting palladium intermediate would assist in the elimination of CO from the carbamoyl chloride. This sequence would allow for the formation of isooxindole **17** following sequential CO insertion and cyclization reactions.

The carbon–bromide bond was moved from one aryl ring to the other in an attempt to avoid decomposition of the carbamoyl moiety. However, treatment of carbamoyl chloride **21** under the same conditions gave aniline **20** as the major product (31%), which was formed through the elimination of CO, together with small amounts of several unidentified byproducts (Scheme 3). Although compound **21** did not give rise to a four-membered lactam ring, the C-(sp^3)–H functionalization reaction was probably hampered by the oxidative addition of the aryl bromide followed by the elimination of CO. Based on this result, it was concluded that it would be difficult to suppress the undesired reaction because the oxidative addition reactions of the carbamoyl chloride and aryl bromide were competitive, and the activation of the C(sp^3)–H bond would require a higher temperature than those required for the side reactions.

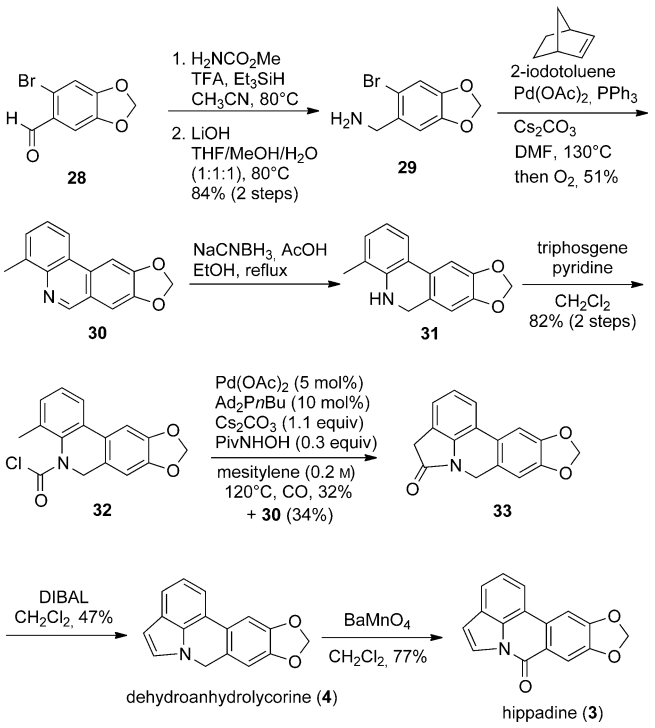
Based on these limitations, we decided to focus our attention on route B, which would avoid possible complications arising from the unfavorable decomposition of the carbamoyl moiety (Scheme 2). This particular synthesis started from the reductive amination of 6-bromoveratraldehyde (**22**), followed by hydrolysis of the resulting carbamate to give benzylamine **23** in 83% yield over two steps (Scheme 5).[15] Compound **23** was then coupled with 2-iodotoluene **12** by using a Catellani reaction with $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Cs_2CO_3 (2.1 equiv), and 2-norbornene (0.5 equiv) in DMF (0.2 M) at 130°C under an argon atmosphere, according to Malacria's procedure.[16,17] Although our initial attempts to isolate dihydrophenathridine **25** resulted in low yields because the material was readily oxidized under the purification conditions, phenanthridine **24** was obtained in 66% yield after purification.[18] Subsequent reduction of compound **24** with $NaCNBH_4$,[19] followed by treatment of the resulting amine with triphosgene, gave carbamoyl chloride **26** in 79% yield over two steps.

We then turned our attention to the cyclization of carbamoyl chloride **26** through the C(sp^3)–H functionalization reaction. Treatment of **26** with $Pd(OAc)_2$ (5 mol%), Ad_2PnBu (10 mol%), Cs_2CO_3 (1.1 equiv), and PivNHOH (0.3 equiv) in mesitylene (0.2 M) under an atmosphere of CO at 100°C gave the desired tetracyclic compound **16** (30%) together with a significant amount of the compound **24** (60%), which was presumably derived from the elimination of CO and aerobic oxidation.[20] Although an extensive period of reac-

tion screening (i.e., palladium sources, ligands, bases, and additives) did not lead to an improvement in the yield of the product, compound **24** could be recycled following its separation from the product by column chromatography on silica gel. Because the carbamoyl moiety was fixed by the rigid tricyclic skeleton, the C–H bond of the methyl group became distant from the palladium center compared with the corresponding derivatives of phenyl carbamoyl chloride, and the elimination of CO consequently became competitive.

With the common intermediate **16** in hand, we investigated the formation of the natural products by adjustment of oxidation level. The reduction of **16** with DIBAL gave dehydroassoanine **27** in 57% yield, which was oxidized with $BaMnO_4$ to give **2** in 72% yield.[9m] In contrast, compound **1** was synthesized in 40% yield by the reduction of **27** with $NaCNBH_3$ in AcOH.[9g] The spectroscopic data for these compounds, including the high-resolution mass spectra of synthetic **1** and **2**, were in agreement with the previously reported data for these compounds.[2,3,9f,h,r,u]

The established synthetic route was applied to the synthesis of **3** and **4**. Commercially available 6-bromopiperonal (**28**) was converted into benzylamine **29** in 84% yield over two steps (Scheme 6). Compound **29** was then coupled to 2-iodotoluene **12** through a Catellani reaction followed by an oxidation reaction to give phenanthridine **30** in 51% yield. Because dihydrophenanthridine **31** was not readily oxidized in the presence of air in the same way as **25**, it was necessary to expose this compound to an oxygen atmosphere to affect the one-pot procedure. Reduction with $NaCNBH_3$ followed by treatment of the resulting amine with triphosgene gave carbamoyl chloride **32** in 82% yield over two steps. In a similar manner to the synthesis of **1**, the cyclization of carbamoyl chloride **32** proceeded smoothly following activation of the C(sp^3)–H bond to give the desired tetracyclic compound **33** and phenanthridine **30**, which was recyclable, in 32 and 34% yield, respectively. Tetracyclic compound **33** was converted into **3** by reduction with DIBAL followed by the oxidation of **4**. The spectroscopic data for the synthetic materials **3** and **4** were in good agreement with the previously reported data for these compound.[4,5,9f,r,s] The established synthetic route, which is short and concise because it does not require the use of protecting groups, could be used to provide facile access to various analogues from simple starting materials.



Scheme 6. Total synthesis of hippadine (**3**) and dehydroanhydrolycorine (**4**).

Conclusion

We have accomplished the total synthesis of **1**, **2**, **3**, and **4** through C–H activation chemistry. Tetracyclic skeleton **5** was constructed in a stepwise manner by using a C(sp^3)–H functionalization reaction for the oxindole skeleton and a Catellani reaction, including a C(sp^2)–H functionalization reaction, to complete the system. Our newly developed route is suitable for the facile preparation of related analogues because it uses simple starting materials and does not require the use of protecting groups. Our synthesis is comparable in many ways to those previously reported in this area because it allows for the rapid preparation of analogues related to the target compounds and represents a new area of C(sp^3)–H functionalization chemistry.

Experimental Section

General

All nonaqueous reactions were carried out under a positive atmosphere of argon in oven-dried glassware. Analytical TLC was performed with Silica gel 60 TLC plates (Merck). Column chromatography on silica gel was performed with Kanto silica gel 60 (particle size, 63–210 μm) and Fuji silysia Chromatorex BW-300. ^{1}H NMR spectra were recorded on a JEOL JNM-ECA 500 spectrometer at 500 MHz or a JEOL JNM-AL 400 spectrometer at 400 MHz. Chemical shifts are reported relative to Me_4Si ($\delta = 0.00$ ppm) in $CDCl_3$, and $CHDCl_2$ ($\delta = 5.32$ ppm) in CD_2Cl_2. The multiplicities of the signals are indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 500 at 126 MHz or a JEOL JNM-AL 400 spectrometer at 100 MHz. The chemical shifts are reported relative to residual $CDCl_3$ and CD_2Cl_2 ($\delta = 77.0$ and 53.8 ppm, respectively). IR spectra were recorded on a FT/IR-4100 Fourier-transform infrared ATR attenuated total reflectance spectrometer (JASCO). Low and high-resolution mass spectra were recorded on a JEOL MS700 mass spectrometer.

*Compound **23***

Methyl carbamate (310 mg, 4.12 mmol), TFA (625 μL, 8.16 mmol), triethylsilane (1.65 mL, 10.3 mmol) were added to a solution of 6-bromovaratraldehyde (500 mg, 2.04 mmol) in acetonitrile (20 mL) under an argon atmosphere. The mixture was stirred at 80 °C for 5 h and cooled to room temperature. The mixture was concentrated under reduced pressure and

the residue was dissolved in THF, MeOH, and a 2 M aqueous solution of LiOH (1:1:1; 30 mL). The reaction mixture was stirred at 80 °C for 2 days and cooled to room temperature. The reaction mixture was then diluted with AcOEt and a 1 M aqueous solution of HCl. The organic phase was extracted with a 1 M aqueous solution of HCl. The aqueous extracts were combined and basified with a 1 M aqueous solution of NaOH. The aqueous phase was extracted with AcOEt. The organic extracts were combined, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure afforded **23** as a white solid (419 mg, 83 %, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 1H), 6.92 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.85 ppm (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.4, 148.3, 133.9, 115.5, 113.1, 112.0, 56.1, 55.9, 46.4 ppm; IR (ATR): $\tilde{\nu}$ = 3386, 3323, 3012, 2900, 2842, 1598, 1497, 1382, 1256, 1206, 1150, 1030 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_9H_{13}{}^{81}BrNO_2$: 248.0109 $[M+H]^+$; found: 248.0113.

*Compound **24***

Under an argon atmosphere, Cs_2CO_3 (4.66 g, 14.3 mmol); triphenylphosphine (190 mg, 0.724 mmol); a solution containing 2-iodotoluene (0.92 mL, 7.23 mmol), benzylamine **23** (1.97 g, 6.97 mmol), and 2-norbornene (346 mg, 3.67 mmol) in DMF (20 mL); and $Pd(OAc)_2$ (86.0 mg, 0.383 mmol) were added to a flask. The reaction mixture was stirred at 130 °C for 1 day and cooled to room temperature. The resultant mixture was filtered through Celite and concentrated under reduced pressure. The reaction mixture was diluted with diethyl ether, washed with H_2O, brine, and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the obtained residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give **24** as a yellow solid (1.21 g, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.29 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.85 (s, 1H), 7.55–7.50 (m, 2H), 7.33 (s, 1H), 4.12 (s, 3H), 4.06 (s, 3H), 2.87 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.7, 150.3, 149.8, 142.7, 137.6, 128.5, 128.4, 126.1, 123.6, 121.5, 119.6, 107.6, 101.9, 56.08, 56.06, 18.7 ppm; IR (ATR): $\tilde{\nu}$ = 2990, 2925, 1615, 1593, 1505, 1474, 1442, 1403, 1375, 1263 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{16}NO_2$: 254.1181 $[M+H]^+$; found: 254.1180.

*Compound **26***

AcOH (326 μL, 5.70 mmol) was added to a solution of phenanthridine **24** (1.45 g, 5.70 mmol) in EtOH (10 mL). The mixture was heated at reflux for 1 h and then $NaCNBH_3$ (681 mg, 10.8 mmol) was added. The reaction mixture was stirred for 1.5 h and cooled to room temperature. The reaction mixture was basified with a saturated aqueous solution of $Na_2S_2O_3$ containing 10 % NH_3 and extracted with $CHCl_3$. The organic phases were combined, washed with brine, and dried over Na_2SO_4. The organic residue was filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), cooled to −78 °C under an argon atmosphere, and then triphosgene (861 mg, 2.89 mmol) and pyridine (0.9 mL, 11.1 mmol) were added. The reaction mixture was stirred at room temperature for 3 h, diluted with $CHCl_3$ and H_2O, and extracted with $CHCl_3$. The organic phases were combined, washed with brine, and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the obtained residue was purified by column chromatography on silica gel ($CHCl_3$) to give **26** as a yellow amorphous solid (1.43 g, 79 %, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.2 Hz, 1H), 7.33–7.30 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 6.83 (s, 1H), 5.35–5.30 (m, 1H), 4.38–4.15 (m, 1H), 4.01–3.93 (m, 6H), 2.46–2.35 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.7, 149.4, 149.2, 147.2, 135.8, 134.3, 131.2, 130.4, 129.9, 129.7, 127.8, 127.6, 126.5, 125.0, 124.8, 121.6, 121.5, 109.2, 108.6, 107.4, 56.22, 56.17, 52.2, 50.1, 18.7, 18.5 ppm (mixture of two rotamers); IR (ATR): $\tilde{\nu}$ = 3017, 2960, 2933, 2850, 1728, 1609, 1517, 1470, 1442, 1398, 1348 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{16}NO_3$: 317.0819 $[M]^+$; found: 317.0817.

*Oxindole **16***

Carbamoyl chloride **26** (59.4 mg, 0.19 mmol) was mixed with $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), Ad_2PnBu (6.7 mg, 0.019 mmol), Cs_2CO_3 (67.1 mg, 0.21 mmol), and PivNHOH (6.6 mg, 0.056 mmol), and the resulting mixture was purged under an atmosphere of CO. Mesitylene (1 mL) was then added to the reaction and the resulting mixture was stirred at 100 °C for 1 h. The mixture was then filtered through a pad of Celite and the filtrate was collected and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (hexane/AcOEt = 1/1 (v/v) then CH_2Cl_2/AcOEt = 9/1 to 8/2 (v/v)) to give oxindole **16** (15.7 mg, 30 %) as a white solid and phenanthridine **24** (28.5 mg, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.0 Hz, 1H), 6.63 (s, 1H), 5.01 (s, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.54 ppm (s, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 174.7, 149.9, 149.3, 140.2, 123.7, 123.5, 122.6, 122.0, 121.6, 119.9, 117.3, 110.8, 105.9, 56.3, 56.2, 43.2, 36.6 ppm; IR (ATR): $\tilde{\nu}$ = 3021, 2986, 2836, 1696, 1627, 1521, 1495, 1482, 1467, 1443, 1359, 1242, 1212 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{16}NO_3$: 282.1130 $[M+H]^+$; found: 282.1135.

*Compound **27***

Oxindole **16** (86.4 mg, 0.307 mmol) was dissolved in CH_2Cl_2 (3.6 mL) under an atmosphere of argon and the resulting solution was cooled to 0 °C before being treated with a 1 M solution of DIBAL in toluene (1.95 mL, 1.95 mmol). The reaction mixture was stirred at 0 °C for 2 h and then quenched by the addition of a 2 M aqueous solution of NaOH. The resulting mixture was extracted with $CHCl_3$ and the combined organic layers were washed with brine and dried over Na_2SO_4 before being filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (hexane/$CHCl_3$ = 1/1) to give **27** as a yellow solid (46.1 mg, 57 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 3.6 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.65 (s, 1H), 6.53 (d, *J* = 2.8 Hz, 1H), 5.52 (s, 2H), 3.99 (s, 3H), 3.92 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.9, 148.7, 133.0, 125.9, 125.7, 122.7, 122.5, 120.3, 119.9, 118.6, 112.6, 109.8, 105.5, 102.4, 56.0, 56.0, 47.6 ppm; IR (ATR): $\tilde{\nu}$ = 2933, 2854, 1673, 1608, 1525, 1464, 1392, 1337, 1254, 1212 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{16}NO_2$: 266.1181 $[M+H]^+$; found: 266.1161.

*Pratosine (**2**)*

$BaMnO_4$ (209 mg, 0.814 mmol) was added to a solution of **27** (21.6 mg, 0.0814 mmol) in CH_2Cl_2 (1.9 mL) under an atmosphere of argon and the resulting mixture was stirred at room temperature for 2.5 h. The mixture was then filtered through a pad of Celite and the filtrate was collected and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (CH_2Cl_2 and then CH_2Cl_2/AcOEt = 20/1) to give **2** as a white solid (16.4 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 4.0 Hz, 1H), 8.02 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.67 (s, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 3.2 Hz, 1H), 4.13 (s, 3H), 4.07 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.4, 153.7, 149.7, 131.1, 129.5, 128.5, 123.9, 123.5, 122.4, 120.8, 118.0, 116.7, 110.7, 110.1, 103.8, 56.29, 56.25 ppm; IR (ATR): $\tilde{\nu}$ = 3010, 2837, 1665, 1602, 1526, 1507, 1440, 1362, 1308, 1270, 1216 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{14}NO_3$: 280.0974 $[M+H]^+$; found: 280.0965.

*Assoanine (**1**)*

AcOH (0.3 mL) and $NaCNBH_3$ (0.72 mmol) were added to a solution of **27** (20.7 mg, 0.078 mmol) in THF (1.0 mL) and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was then neutralized with a 1 M aqueous solution of NaOH and extracted with AcOEt. The combined organic phases were washed with brine and dried over Na_2SO_4 before being filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (hexane/AcOEt = 5/1) to give **1** as a yellow solid (8.4 mg, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.66 (s, 1H), 4.12 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.35 (t, *J* = 8.2 Hz, 2H), 3.03 ppm (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.6, 148.6, 148.4, 128.5, 124.7, 124.3, 123.3, 119.6, 119.3, 119.0, 110.3, 105.4, 56.03, 56.01, 55.4, 53.2, 29.0 ppm; IR (ATR): $\tilde{\nu}$ = 2924, 1609, 1520, 1472, 1406, 1346, 1250 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{18}NO_2$: 268.1338 $[M+H]^+$; found: 268.1329.

*Compound **29***

Methyl carbamate (1.33 g, 17.8 mmol), TFA (2 mL, 26.2 mmol), and triethylsilane (4.2 mL, 26.2 mmol) were added to a solution of 6-bromopiperonal (2.01 g, 8.78 mmol) in acetonitrile (80 mL) under an argon atmosphere. The mixture was stirred at 80 °C for 12 h and then cooled to room temperature. The mixture was concentrated under reduced pressure and the residue was dissolved in THF, MeOH, and a 2 M aqueous solution of LiOH (1:1:1; 150 mL). The reaction mixture was stirred at 80 °C for 1 day and then cooled to room temperature. The reaction mixture was diluted with AcOEt and a 1 M aqueous solution of HCl. The organic phase was extracted with a 1 M aqueous solution of HCl. The aqueous extracts were combined and basified with a 1 M aqueous solution of NaOH. The aqueous phase was extracted with AcOEt. The organic extracts were combined, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure afforded **29** as a white solid (1.69 g, 84%, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.00$ (s, 1H), 6.89 (s, 1H), 5.96 (s, 2H), 3.81 ppm (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 147.3$, 147.1, 135.3, 113.4, 112.7, 109.0, 101.5, 46.6 ppm; IR (ATR): $\tilde{\nu} = 3318$, 3037, 2907, 1587, 1503, 1474, 1415, 1347, 1244 cm^{-1}; HRMS (FAB): m/z calcd for $C_8H_9BrNO_2$: 229.9817 $[M+H]^+$; found: 229.9815.

*Compound **30***

Cs_2CO_3 (493 mg, 1.51 mmol); triphenylphosphine (37.7 mg, 0.144 mmol); a solution containing 2-iodotoluene (92 μL, 0.723 mmol), benzylamine **29** (166 mg, 0.719 mmol), and 2-norbornene (34.3 mg, 0.364 mmol) in DMF (3.6 mL); and $Pd(OAc)_2$ (16.3 mg, 0.0726 mmol) were added to a flask under an argon atmosphere. The reaction mixture was stirred at 130 °C for 1 day. Oxygen was added to the reaction mixture through a balloon for 1 h, and then cooled to room temperature. The resultant mixture was filtered through Celite and concentrated under reduced pressure. After the reaction mixture was diluted with AcOEt, the organic layer was washed with a saturated aqueous solution of K_2CO_3 and brine and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the obtained residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give **30** as a red solid (87.2 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.13$ (s, 1H), 8.25 (d, $J = 7.6$ Hz, 1H), 7.93 (s, 1H), 7.56–7.52 (m, 2H), 7.35 (s, 1H), 6.17 (s, 2H), 2.86 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 151.2$, 150.4, 148.0, 142.9, 137.6, 130.5, 128.7, 126.2, 124.1, 122.8, 119.9, 105.2, 101.8, 100.0, 18.7 ppm; IR (ATR): $\tilde{\nu} = 2918$, 1463, 1257, 1220, 1036 cm^{-1}; HRMS (FAB): m/z calcd for $C_{15}H_{12}NO_2$: 238.0868 $[M+H]^+$; found: 238.0872.

*Compound **32***

AcOH (68 μL, 1.18 mmol) was added to a solution of phenanthridine **30** (280 mg, 1.18 mmol) in EtOH (2.4 mL). The mixture was heated at reflux for 1 h and then $NaCNBH_3$ (142 mg, 2.25 mmol) was added. The reaction mixture was stirred for 2 h and cooled to room temperature. The reaction mixture was basified with a saturated aqueous solution of $Na_2S_2O_3$ containing 10% NH_3 and extracted with $CHCl_3$. The organic phases were combined, washed with brine, and dried over Na_2SO_4. The organic residue was filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (6 mL), cooled to −78 °C under an argon atmosphere, and then triphosgene (177 mg, 0.593 mmol) and pyridine (190 μL, 2.36 mmol) were added. The reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with $CHCl_3$ and H_2O, and extracted with $CHCl_3$. The organic phases were combined, washed with brine, and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the obtained residue was purified by column chromatography on silica gel ($CHCl_3$) to give **32** as a yellow oil (290 mg, 82%, 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.47$ (d, $J = 7.6$ Hz, 1H), 7. 30 (d, $J = 7.2$ Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 6.80 (s, 1H), 6.00 (s, 2H), 5.30–5.24 (m, 1H), 4.31–4.08 (m, 1H), 2.44–2.33 ppm (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 149.6$, 148.2, 147.5, 147.2, 135.7, 135.4, 135.0, 134.2, 131.1, 130.4, 130.0, 129.8, 128.9, 127.9, 127.7, 126.5, 126.3, 121.8, 121.6, 106.7, 106.1, 104.7, 101.4, 52.4, 50.7, 50.3, 18.6, 18.4 ppm (mixture of two rotamers); IR (ATR): $\tilde{\nu} = 2902$, 1739, 1503, 1469, 1348, 1247, 1221 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{13}ClNO_3$: 302.0584 $[M+H]^+$; found: 302.0574.

*Oxindole **33***

Carbamoyl chloride **32** (179 mg, 0.59 mmol) was mixed with $Pd(OAc)_2$ (6.6 mg, 0.029 mmol), Ad_2PnBu (21 mg, 0.059 mmol), Cs_2CO_3 (213 mg, 0.65 mmol), and PivNHOH (21 mg, 0.18 mmol), and the resulting mixture was purged under an atmosphere of CO. Mesitylene (3 mL) was then added to the reaction and the resulting mixture was stirred at 120 °C for 1.5 h before being filtered through a pad of Celite. The filtrate was collected and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (hexane/AcOEt = 3/1 then CH_2Cl_2/AcOEt = 9/1) to give oxindole **33** (49.9 mg, 32%) as a yellow solid and phenanthridine **30** (53.8 mg, 34%). ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta = 7.41$ (d, $J = 7.0$ Hz, 1H), 7.22 (s, 1H), 7.07 (d, $J = 7.0$ Hz, 1H), 6.96 (t, $J = 7.7$ Hz, 1H), 6.64 (s, 1H), 5.99 (s, 2H), 4.92 (s, 2H), 3.47 ppm (s, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2): $\delta = 174.6$, 148.4, 148.3, 140.2, 123.7, 123.6, 123.4, 123.2, 122.7, 120.1, 117.3, 107.9, 102.8, 102.1, 43.7, 36.6 ppm; IR (ATR): $\tilde{\nu} = 3042$, 2922, 1698, 1632, 1510, 1474, 1351, 1255, 1231, 1209 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{12}NO_3$: 266.0817 $[M+H]^+$; found: 266.0817.

*Dehydroanhydrolycorine (**4**)*

Oxindole **33** (43.8 mg, 0.165 mmol) was dissolved in CH_2Cl_2 (2 mL) under an atmosphere of argon, and the resulting solution was cooled to 0 °C before being treated with a 1 M solution of DIBAL in toluene (0.99 mL, 0.99 mmol). The reaction mixture was then stirred at 0 °C for 3 h before being quenched by the addition of a 2 M aqueous solution of NaOH. The residue was extracted with $CHCl_3$ and the combined organics were washed with brine and dried over Na_2SO_4, before being filtered and concentration under reduced pressure to give a residue that was purified by column chromatography on silica gel (hexane/$CHCl_3$ = 1/1) to give **4** as a red solid (19.9 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 8.0$ Hz, 1H), 7.37 (s, 1H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.12 (d, $J = 3.2$ Hz, 1H), 7.05 (t, $J = 7.4$ Hz, 1H), 6.65 (s, 1H), 6.52 (d, $J = 3.2$ Hz, 1H), 6.00 (s, 2H), 5.50 ppm (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 147.6$, 147.5, 133.0, 125.9, 125.7, 124.2, 123.8, 120.4, 120.0, 118.6, 112.9, 107.1, 102.9, 102.5, 101.3, 48.1 ppm; IR (ATR): $\tilde{\nu} = 2902$, 1730, 1657, 1502, 1485, 1461, 1339, 1242 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{12}NO_2$: 250.0868 $[M+H]^+$; found: 250.0855.

*Hippadine (**3**)*

$BaMnO_4$ (126 mg, 0.493 mmol) was added to a solution of oxindole **33** (12.3 mg, 0.0493 mmol) in CH_2Cl_2 (1.4 mL) under an atmosphere of argon, and the resulting mixture was stirred at room temperature for 2.5 h. The reaction mixture was then filtered through a pad of Celite and the filtrate was collected and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (hexane/CH_2Cl_2 2/1) to give **3** as a white solid (10.0 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (d, $J = 3.6$ Hz, 1H), 7.99 (s, 1H), 7.93 (d, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.67 (s, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 6.90 (d, $J = 3.2$ Hz, 1H), 6.17 ppm (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 158.2$, 152.6, 148.5, 131.6, 130.9, 128.4, 124.0, 123.5, 122.6, 122.5, 118.4, 116.7, 110.8, 108.0, 102.3, 101.7 ppm; IR (ATR): $\tilde{\nu} = 3152$, 2922, 1670, 1618, 1526, 1477, 1457, 1392, 1366, 1347, 1310, 1286, 1244 cm^{-1}; HRMS (FAB): m/z calcd for $C_{16}H_{10}NO_3$: 264.0661 $[M+H]^+$; found: 264.0647.

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