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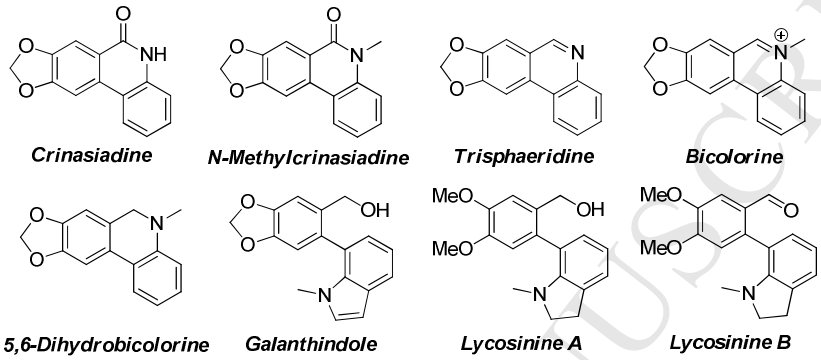

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Synthesis of Phenanthridine Skeletal Amaryllidaceae Alkaloids

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ABSTRACT

Strategies for the synthesis of Amaryllidaceae alkaloids, including crinasiadine, trisphaeridine, bicolorine, *N*-methylcrinasiadine, 5,6-dihydrobicolorine, galanthindole, lycosinine A and lycosinine B were reported. Investigation of optionally synthetic routes to approach bicolorine, 5,6-dihydrobicolorine, trisphaeridine and *N*-methylcrinasiadine were demonstrated as well. In addition, three structurally related alkaloids galanthindole, lycosinine A and lycosinine B were concisely prepared by using Suzuki coupling reaction as the key step.

1. Introduction

Plants of the Amaryllidaceae family, containing *ca.* 85 genera and 1100 species, distribute widely on the tropical to temperate regions around the world. Many of them have been cultivated as ornamental plants for a long time because of their colorful and beautiful flowers; thus, making a big market and great economic values. Not only as ornaments, but Amaryllidaceae plants have also been applied on the pharmaceutical purpose. For example, lycorine[1] (Figure 1), a well-known Amaryllidaceae alkaloid, which can be found in Lycoris' bulb and various Amaryllidaceae species, possesses multi-medicinal functions.

Amaryllidaceae alkaloids, consisted of a nitrogen-containing polycyclic structure, often possess significantly pharmaceutical activities, including antitumor, antimalarial, antivirus, antifungal and antibacterial etc.[2–5] Recent studies have also reported that some derivatives could be used as the treatments for Alzheimer's and Parkinson's diseases.[6, 7] Because of the wide applications, considerable attention have been paid by chemists toward the isolations, preparations and bioactivities of these Amaryllidaceae alkaloids and their analogs.[2–9]

Structures of many Amaryllidaceae alkaloids are with some degree of similarity, generally containing an *o*-dioxygenated aryl group (e.g. benzodioxole) with heterocyclic rings fused on it (Figure 1).[11] This structural similarity can be found in various types of Amaryllidaceae alkaloids, and allows the complicated structures to be afforded through a series of semisyntheses from the simple scaffolds. In our preliminary results,[11] we have shown that the copper catalysis could be applied to be a key step for the synthesis of crinasiadine (**5**).[12] Other two alkaloids, trisphaeridine (**7**)[13] and bicolorine (**8**),[14] can be obtained by subsequent steps (Scheme 1).

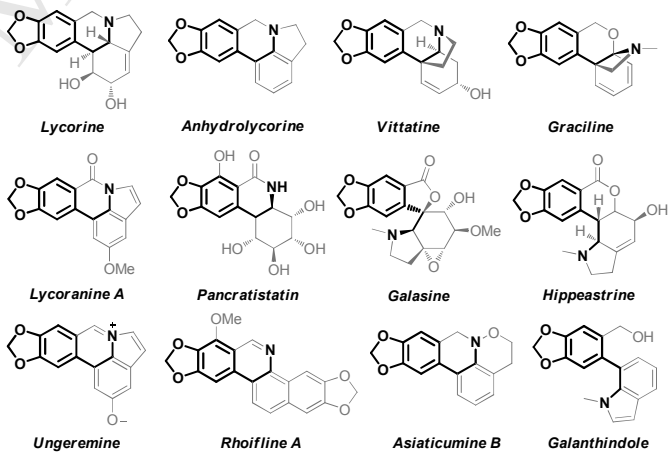

Figure 1. Selected examples of Amaryllidaceae alkaloids

It was reported that bicolorine (**8**) and its derivatives exhibit apparent function to inhibit human DNA topoisomerase I.[15] This important bioactivity makes us explore other possibility to reduce its synthetic steps and to synthesize alkaloids with related structures. Herein, we organize our preliminary studies and report various pathways to approach bicolorine and other structurally related alkaloids.

2. Results and Discussion

Our strategy started from the preparation of substrate **4** (Scheme 1), which was described in our previously developed method.[11] It started from a cyanation of the commercial available compound **1**, the subsequent Miyaura borylation of compound **2** with diboron converted bromide to boronic ester (**3**).

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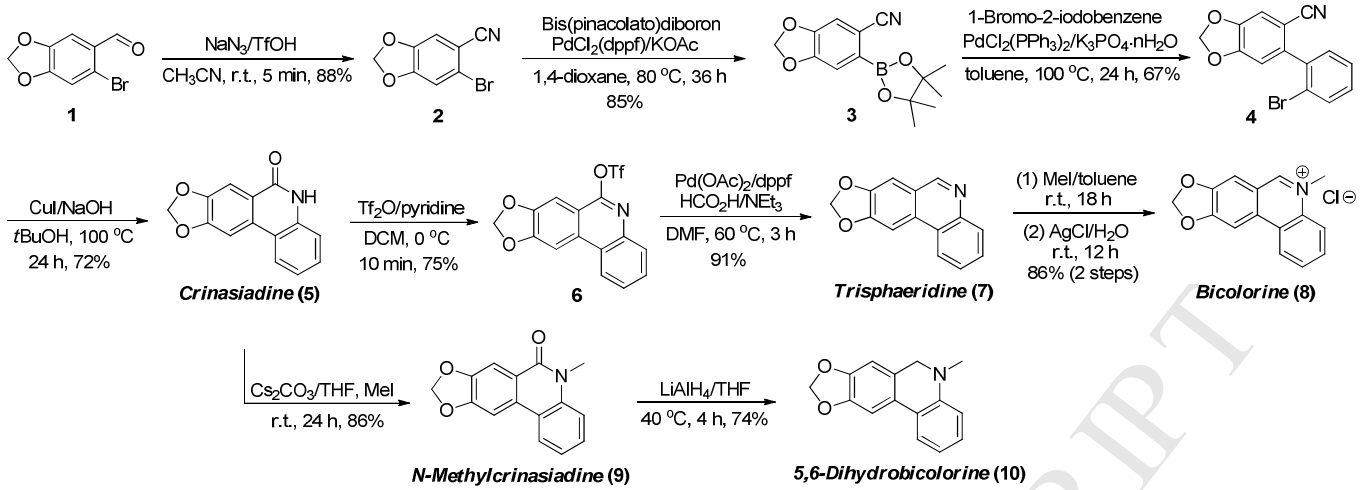
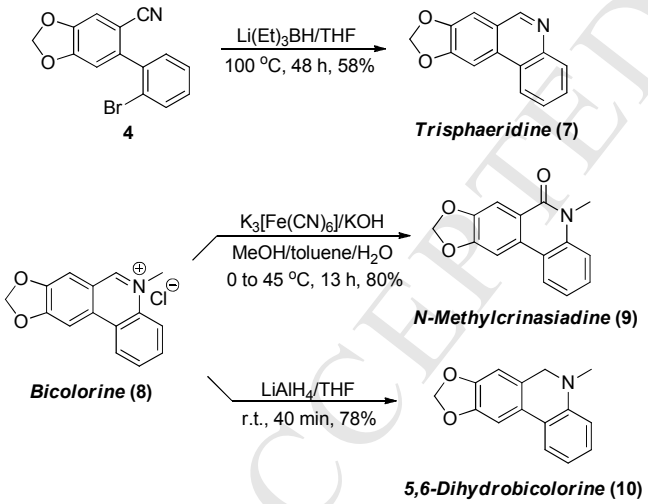


Scheme 1. Synthesis of Amaryllidaceae alkaloids

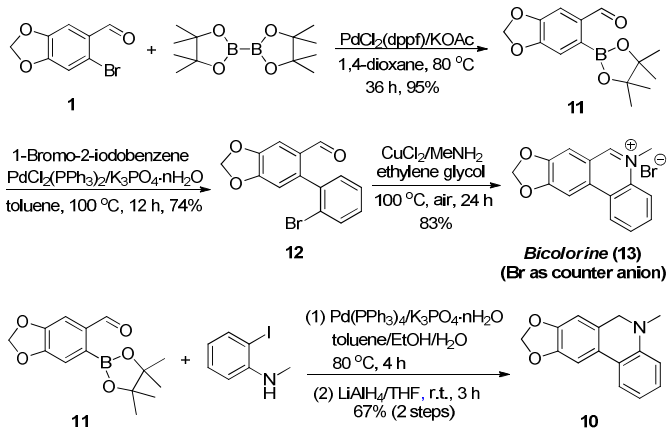
A Suzuki coupling reaction by **3** with 1-bromo-2-iodobenzene afforded compound **4** in 67% yield. Compound **4** was able to be transformed to the crinasiadine (**5**) by our previously developed Cu-catalyzed coupling reaction in 72% yield (36% overall yield, 4 steps).[11a] Crinasiadine is the key intermediate for the further semisyntheses to approach other four alkaloids. Treatment of crinasiadine with Tf_2O and pyridine provided compound **6** in 75% yield with only 10 minutes reaction time. The following Pd-catalyzed hydrogenation provided trisphaeridine (**7**) in 91% yield (25% overall yield, 6 steps). A methylation of trisphaeridine with exchange of the counter anion gave bicolorine (**8**) (chloride as the counter anion) in 86% yield (21% overall yield, 8 steps). Moreover, the alkaloid *N*-methylcrinasiadine (**9**)[16] was obtained in 86% yield simply by a methylation of crinasiadine (**5**). Further reduction of **9** by $LiAlH_4$ afforded alkaloid 5,6-dihydrobicolorine (**10**)[14] in 74% yield.



Scheme 2. Alternative pathways to approach trisphaeridine, *N*-methylcrinasiadine and 5,6-dihydrobicolorine

After achievement of this synthetic strategy, we paid some effort in reducing the synthetic steps for the synthesis of bioactive alkaloid bicolorine. Therefore, a direct synthesis of trisphaeridine from substrate **4** was accessible by treating the super hydride $Li(Et)_3BH$ with **4** (Scheme 2).[9d] This step provided only 58% yield after isolation; however, it reduced two steps from the commercial compound **1** to the trisphaeridine and gave higher overall yield (4 steps, 29% overall yield). Additionally, an alternative route to *N*-methylcrinasiadine (**9**) could be proposed by an addition/oxidation combined step via $K_3[Fe(CN)_6]$ with KOH. And the formation of 5,6-dihydrobicolorine (**10**) could be suggested by a reduction of bicolorine in 78% yield.[9d] Both of the two transformations performed very well, and the purifications could be carried out simply by the filtration of salts.

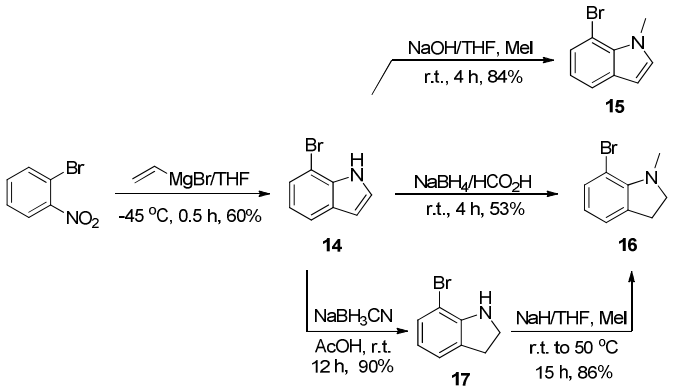
Furthermore, the bicolorine could be also obtained by a synthetic shortcut from the commercial available compound **1** with shorter steps and higher overall yield (Scheme 3).[9e] This strategy starts from a Miyaura borylation of compound **1**. A resulted compound **11** underwent the Suzuki coupling reaction, providing compound **12**. The subsequent Cu-catalyzed annulation reaction converted **12** to bicolorine with bromide as the counter anion (**13**). Through this synthetic sequence, bicolorine (bromide as the counter anion) could be synthesized in 58% overall yield from the commercial compound **1** with only three steps. To the best of our knowledge, this is the shortest way to approach bicolorine and its analogues. In addition, compound **11** could be also utilized to synthesize the 5,6-dihydrobicolorine (**10**) through a combined Suzuki coupling reaction/reduction step in 67% yield (64% overall yield, 3 steps). However, without the second reduction step, we could only detect very few amount of bicolorine in crude NMR spectrum.



Scheme 3. Alternative pathways to approach bicolorine and 5,6-dihydrobicolorine

The Suzuki coupling reaction is able to be utilized in providing galanthindole-type[17] alkaloids with switching the structures of coupling partners. Thus, we prepared substrates **15** and **16** for the synthesis of other three Amaryllidaceae alkaloids galanthindole, lycosinine A and B[18] with similar structures. Compound **14** was prepared according to the Bartoli reaction[19] in the presence of *o*-bromonitrobenzene with vinyl Grignard reagent in THF at -45 °C for only 30 minutes. Longer reaction time was not helpful to improve the reaction yield. Further methylation and reductive

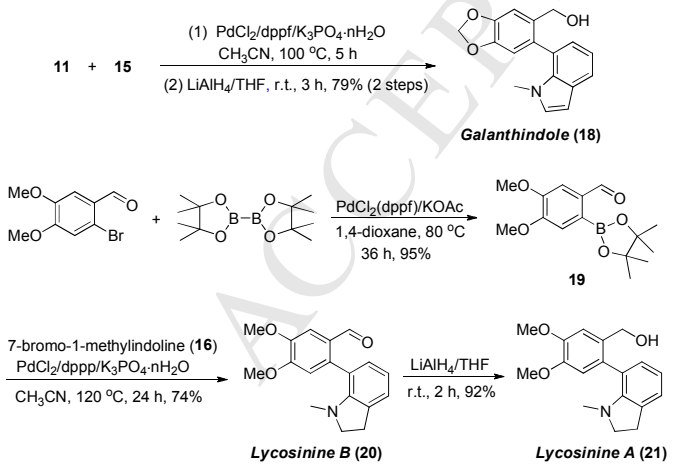
methylation provided substrates **15** and **16** in 84% and 53% yields, respectively (Scheme 4).



Scheme 4. Synthesis of bromoindole and bromoindoline

Although a one-step reductive methylation to afford compound **16** is concise, the low yield of **16** still made us find an alternative pathway to replace this conversion. A two-step synthesis, which contained a sequence of reduction and methylation was carried out. This synthetic sequence performed very well and provided excellent yields for compound **17** and **16**. The combined yield is much higher than the single-step transformation.

After getting substrate **15**, we tried to synthesize galanthindole (**18**) via a Suzuki coupling reaction (Scheme 5). However, the present reaction conditions can not smoothly proceed a coupling reaction with heterocyclic compounds. With further optimization of the conditions, we found that $PdCl_2$ with additional bidentate ligand dppf in acetonitrile at 100 °C is able to carry out this coupling reaction with only 5 h. Thus, we combined this protocol with a further reduction to furnish the galanthindole (**18**) in 79% combined yield. In addition, two other Amaryllidaceae alkaloids lycosinine B (**20**) and lycosinine A (**21**) with related structures to galanthindole could be also obtained by a similar condition with increasing the reaction temperature and modifying the bidentate ligand. Compound **19**, a coupling partner for lycosinine B, was prepared through a Miyaura coupling reaction. The following Suzuki coupling reaction afforded lycosinine B (**20**) in 74% yield. A reduction of the aldehyde to alcohol led to lycosinine A (**21**) in 92% yield.



Scheme 5. Synthesis of galanthindole, lycosinine B and lycosinine A

3. Conclusion

In conclusion, we have developed concisely synthetic pathways for the efficient synthesis of a series of Amaryllidaceae alkaloids, including crinasiadine, *N*-methylcrinasiadine, trisphaeridine, bicolorine, 5,6-dihydrobicolorine, galanthindole, lycosinine A, and lycosinine B. The copper and palladium-mediated coupling reactions were used as the key steps to construct the skeleton of these alkaloids. Further studies for the evaluation of medicinal properties of these alkaloids and their derivatives are currently underway.

4. Experimental Section

4.1. General

All reagents were purchased from Sigma-Aldrich, Alfa-Aesar, TCI and Fisher-Acros, which were used without further purification unless otherwise noted. THF and Et_2O were distilled from sodium, and CH_3CN was distilled from CaH_2. Flash column chromatography was performed using silica gel (230-400 mesh). Analytical thin layer chromatography (TLC) was performed on 60 F_{254} (0.25 mm) plates and visualization was accomplished with UV light (254 and 354 nm) and/or an aqueous alkaline $KMnO_4$ solution followed by heating. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on Bruck 300 or Bruck 600 spectrometer with Me_4Si or solvent resonance as the internal standard (^{1}H NMR, Me_4Si at 0 ppm, $CDCl_3$ at 7.26 ppm, d_6-DMSO at 2.49 ppm; ^{13}C NMR, Me_4Si at 0 ppm, $CDCl_3$ at 77.0 ppm, d_6-DMSO at 39.7 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, br = broad, m = multiplet), coupling constants (Hz), and integration. IR spectral data were recorded on Brucker TENSOR 37 spectrometer. Melting points (mp) were determined using SRS OptiMelt MPA100. High resolution mass spectral data were obtained from MAT-95XL HRMS by using EI method and from Varian 901-MS TQ-FT by using ESI or FAB methods.

4.2. Experimental procedures and data for compounds 2–21

Synthetic procedures and experimental data of compounds **2**–**8**, please check our preliminary results for the detail.[11] Synthetic procedures of compounds **7** (Scheme 2), compounds **9**–**21** as well as the experimental data of compounds **9**–**21** were recorded as below:

Trisphaeridine **(7):** Synthesis from **4** (Scheme 2): 6-(2-Bromophenyl)benzo[*d*][1,3]dioxole-5-carbonitrile (181 mg, 0.6 mmol, 1.0 equiv) was dissolved in dry THF (3 mL) under N_2 and kept stirring at r.t., then $Li(Et)_3BH$ (lithium triethylborohydride, 1.0 M in THF, 0.66 mmol, 1.1 equiv) was slowly injected into the solution. After injection, the reaction temperature was increased to 100 °C and kept stirring for 48 h. Work-up by filtration of slats, then purification through a column chromatography [(R_f = 0.4 (30 % ethyl acetate in hexane)] to afford **7** as a yellow solid (78 mg, 58%).

N-Methylcrinasiadine (**9**): Synthesis from crinasiadine (Scheme 1): crinasiadine (120 mg, 0.5 mmol, 1.0 equiv), Cs_2CO_3 (815 mg, 2.5 mmol, 5.0 equiv) and CH_3I (1.42 g, 10 mmol, 20 equiv) were stirred in dry THF (5 mL) at r.t. for 24 h. Work-up through an extraction (CH_2Cl_2/H_2O), then purification by wash with hexane and ethyl acetate for several times to afford **9** as a white solid (109 mg, 86%). Synthesis from bicolorine (Scheme 2): bicolorine (71 mg, 0.3 mmol, 1.0 equiv), $K_3[Fe(CN)_6]$ (1.09 g, 3.3 mmol, 11 equiv) and KOH (236 mg, 4.2 mmol, 14 equiv) were stirred in MeOH (3 mL) at 0 °C for 1 h. The co-solvent (6 mL, toluene/H_2O = 1/1) was added into the solution and kept stirring at 45 °C for 12 h. Work-up and purification by filtration of slat to afford **9** as a white solid (61 mg, 80%), mp: 240–242 ℃; IR (KBr): 2976, 2921, 1651, 1467, 1346, 1033, 936, 752 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.90 (s, 1H), 7.60 (s, 1H), 7.50 (td, *J* = 7.8, 1.2 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H),

7.29 (td, *J* = 7.8, 1.2 Hz, 1H), 6.12 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.0, 152.2, 148.4, 137.4, 130.4, 128.9, 122.9, 122.3, 121.3, 119.2, 115.0, 107.0, 101.9, 100.4, 30.0; HRMS [(FAB), M^+]: 253.0741 (cal. for $C_{15}H_{11}NO_3$ 253.0739).

5,6-Dihydrobicolorine (**10**): Synthesis from **9** (Scheme 1): $LiAlH_4$ (lithium aluminum hydride, 76 mg, 2.0 mmol, 4.0 equiv) was added into the solution of **9** (127 mg, 0.5 mmol, 1.0 equiv) in THF (5 mL) at r.t.. The solution was then allowed to stir at 40 °C for 4 h. Work-up by adding excess ethyl acetate to quench the reaction. Extraction (Et_2O/H_2O) then purification through a column chromatography [R_f = 0.75 (10 % ethyl acetate in hexane)] to afford **10** as a yellow solid (89 mg, 74%). Synthesis from **8** (Scheme 2): $LiAlH_4$ (30 mg, 0.8 mmol, 4.0 equiv) was added into the solution of **8** (48 mg, 0.2 mmol, 1.0 equiv) in THF (2 mL) at r.t. and allowed to stir for 40 min. Work-up, extraction then purification to afford **10** as a yellow solid (37 mg, 78%). Synthesis from **11** (Scheme 3): $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 2 mol %), $K_3PO_4 \cdot nH_2O$ (345 mg, 1.5 mmol, 1.5 equiv), compound **11** (276 mg, 1.0 mmol, 1.0 equiv) and 2-iodo-*N*-methylaniline (291 mg, 1.25 mmol, 1.25 equiv) were stirred in co-solvent (6 mL, toluene/EtOH/H_2O = 1/1/1) under N_2 at 80 °C for 4 h. The co-solvent of the reaction mixture was removed under vacuum, and THF (12.5 mL) was added into the residue. $LiAlH_4$ (42 mg, 1.1 mmol, 1.1 equiv) was added into the solution and kept stirring at r.t. for 3 h. Work-up, extraction then purification to afford **10** as a yellow solid (160 mg, 67%), mp: 80–81 °C; IR (KBr): 3452, 2894, 2796, 1510, 1487, 1287, 1236, 1033, 748 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): 7.57 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.24–7.21 (m, 2H), 6.88 (td, *J* = 7.2, 0.6 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.63 (s, 1H), 5.97 (s, 2H), 4.09 (s, 2H), 2.91 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.5, 146.7, 146.4, 128.3, 127.1, 126.2, 123.5, 122.9, 118.6, 112.1, 106.0, 103.1, 100.9, 55.0, 38.5; HRMS [(EI), M^+]: 239.0949 (cal. for $C_{15}H_{13}NO_2$ 239.0946).

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d][1,3]-dioxole-5-carbaldehyde (**11**): Bis(pinacolato)diboron (1.22 g, 4.8 mmol, 1.2 equiv), 6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde (916 mg, 4.0 mmol, 1.0 equiv), $PdCl_2$(dppf) (88 mg, 0.12 mmol, 3 mol %) and KOAc (1.18 g, 12 mmol, 3.0 equiv) were stirred in dry 1,4-dioxane (15 mL) under N_2 at 80 °C for 36 h. Work-up by filtration of salts and extraction (CH_2Cl_2/H_2O). Purification through a column chromatography [R_f = 0.5 (20% ethyl acetate in hexane)] to afford **11** as a white solid (1.05 g, 95%), mp: 105–107 ℃; IR (KBr): 3446, 2978, 2928, 2903, 1684, 1603, 1433, 1252 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.50 (s, 1H), 7.46 (s, 1H), 7.31 (s, 1H), 6.05 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 192.9, 151.7, 150.3, 138.1, 114.7, 106.7, 101.9, 84.4 (2C), 24.8 (4C), C–B signal was not observed due to quadruplolar relaxation; HRMS [(EI), M^+]: 276.1169 (cal. for $C_{14}H_{17}BO_5$ 276.1169).

6-(2-Bromophenyl)benzo[d][1,3]dioxole-5-carbaldehyde (**12**): $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol, 2 mol %), $K_3PO_4 \cdot nH_2O$ (1.04 g, 4.5 mmol, 1.5 equiv), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*][1,3]dioxole-5-carbaldehyde (828 mg, 3.0 mmol, 1.0 equiv) and *o*-bromoiodobenzene (1.06 g, 3.75 mmol, 1.25 equiv) were stirred in dry toluene (10 mL) under N_2 at 100 °C for 12 h. Work-up by filtration of salts, then purification through a column chromatography [R_f = 0.4 (10% ethyl acetate in hexane)] to afford **12** as a yellow solid (677 mg, 74%), mp: 86–88 ℃; IR (KBr): 3059, 2857, 2745, 1683, 1257, 1036, 546 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.30–7.26 (m, 2H), 6.71 (s, 1H), 6.09 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 189.6, 152.0, 148.2, 141.8, 138.3, 132.7, 131.7, 129.8, 128.8, 127.2, 124.1, 110.3, 105.9, 102.2; HRMS [(ESI), $(M+H)^+$]: 304.9815 (cal. for $C_{14}H_{10}BrO_3$ 304.9813).

Bicolorine (bromide as counter anion, **13**): $CuCl_2$ (3 mg, 0.025 mmol, 5 mol %), compound **12** (153 mg, 0.5 mmol, 1.0 equiv) and CH_3NH_2 (19 mg, 0.6 mmol, 1.2 equiv) were stirred in ethylene glycol (5 mL) at 100 °C for 24 h. Work-up by filtration of slats, then purification through a column chromatography [R_f = 0.2 (10% methanol in CH_2Cl_2)] to afford **13** as a yellow solid (99 mg, 83%), mp: 252–254 ℃; IR (KBr): 3434, 2983, 2840, 1643, 1271, 1041, 1010 cm^{-1}; ^{1}H NMR (600 MHz, d_6-DMSO): δ 9.89 (s, 1H), 9.02 (d, *J* = 8.4 Hz, 1H), 8.63 (s, 1H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.07 (t, *J* = 7.2 Hz, 1H), 8.00 (t, *J* = 7.2 Hz, 1H), 7.87 (s, 1H), 6.47 (s, 2H), 4.56 (s, 3H); ^{13}C NMR (150 MHz, d_6-DMSO): δ 157.2, 151.9, 150.0, 134.4, 133.7, 131.5, 129.5, 124.9, 120.4, 119.6, 107.2, 104.2, 101.3, 62.7, 45.2; HRMS [(ESI), $(M-Br)^+$]: 238.0864 (cal. for $C_{15}H_{12}NO_2$ 238.0868).

7-Bromo-1H-indole (**14**): Vinylmagnesium bromide (30 mL, 1.0 M in THF, 30 mmol, 3.0 equiv) was slowly injected into the 1-bromo-2-nitrobenzene/THF solution (2.02 g, 10 mmol, 1.0 equiv in 60 mL) under N_2 at -45 °C. The resulted solution mixture was kept stirring at -45 °C for 30 min. Work-up by adding a saturated brine solution. Extraction (Et_2O/H_2O) then purification through a column chromatography [R_f = 0.6 (10% ethyl acetate in hexane)] to afford **14** as a white solid (1.18 g, 60%), mp: 41–43 ℃; IR (KBr): 3431, 1330, 784, 719, 574 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.34 (br, s, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.27 (dd, *J* = 5.4, 2.4 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.64 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 134.6, 129.0, 124.7, 124.3, 121.0, 119.9, 104.6, 103.9; HRMS [(EI), M^+]: 194.9681 (cal. for C_8H_6BrN 194.9684).

7-Bromo-1-methyl-1H-indole (**15**): 7-Bromo-1*H*-indole (196 mg, 1.0 mmol, 1.0 equiv), NaOH (224 mg, 5.6 mmol, 5.6 equiv) and CH_3I (284 mg, 2.0 mmol, 2.0 equiv) were stirred in THF (12.5 mL) at r.t. for 4 h. Work-up by filtration of salts and extraction (Et_2O/H_2O). Purification through a column chromatography [R_f = 0.8 (10% ethyl acetate in hexane)] to afford **15** as a white solid (176 mg, 84%), mp: 52–54 ℃; IR (KBr): 3101, 3061, 2949, 2919, 1607, 1557, 1487, 1445, 1381, 1297, 1103, 918, 781, 711, 577 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 3.0 Hz, 1H), 4.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 133.1, 131.7, 131.7, 126.5, 120.5, 120.3, 103.9, 101.2, 36.8; HRMS [(EI), M^+]: 208.9839 (cal. for C_9H_8BrN 208.9840).

7-Bromo-1-methylindoline (**16**): Synthesis form **14**: 7-Bromo-1*H*-indole (980 mg, 5.0 mmol, 1.0 equiv) dissolved in formic acid (HCO_2H, 20 mL) at r.t.. The resulted solution was then allowed to stir at 0 °C. $NaBH_4$ (sodium borohydride, 3.78 g, 100 mmol, 20 equiv) was slowly added into the solution and kept stirring at r.t. for 4 h. Work-up by extraction (ethyl acetate/H_2O), then purification through a column chromatography [(R_f = 0.8 (10 % ethyl acetate in hexane)] to afford **16** as a yellow liquid (562 mg, 53%). Synthesis from **17**: 7-Bromoindoline (99 mg, 0.5 mmol, 1.0 equiv) and NaH (95%, 38 mg, 1.5 mmol, 3.0 equiv) were stirred in THF (6 mL) at r.t. for 1 h. CH_3I (142 mg, 1.0 mmol, 2.0 equiv) was injected into the solution and kept stirring at 50 °C for 15 h. Work-up by filtration of salts, then purification through a column chromatography to afford **16** as a yellow liquid (91 mg, 86%). IR (KBr): 3448, 2949, 1633, 1414, 1268, 1086, 1050, 562 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, *J* = 7.8 Hz, 1H), 7.00 (dd, *J* = 7.2, 0.6 Hz, 1H), 6.55 (t, *J* = 7.8 Hz, 1H), 3.38 (t, *J* = 8.4 Hz, 2H), 3.11 (s, 3H), 2.95 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 149.8, 133.9, 132.7, 123.4, 120.1,

103.2, 57.2, 39.4, 28.5; HRMS [(EI), M^+]: 210.9994 (cal. for $C_9H_{10}BrN$ 210.9997).

7-Bromoindoline (**17**): 7-Bromo-1*H*-indole (980 mg, 5.0 mmol 1.0 equiv) and $NaBH_3CN$ (Sodium cyanoborohydride, 471 mg, 7.5 mmol, 1.5 equiv) were stirred in AcOH (10 mL) under N_2 from 0 °C to r.t. for 12 h. Work-up by adding excess ethyl acetate to quench the reaction. Extraction (Et_2O/H_2O) then purification through a column chromatography [(R_f = 0.6 (10 % ethyl acetate in hexane)] to afford **17** as a yellow liquid (891 mg, 90%), IR (KBr): 3382, 3070, 2956, 2845, 1461, 1054, 573 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.17 (d, *J* = 7.8 Hz, 1H), 7.03 (dd, *J* = 7.2, 1.2 Hz, 1H)), 6.57 (t, *J* = 7.8 Hz, 1H), 3.98 (br, s, 1H), 3.61 (t, *J* = 9.0 Hz, 2H), 3.15 (t, *J* = 9.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.1, 130.4, 129.7, 123.3, 119.5, 103.1, 46.6, 30.8; HRMS [(EI), M^+]: 196.9844 (cal. for C_8H_8BrN 196.9840).

Galanthindole (**18**): $PdCl_2$ (18 mg, 0.1 mmol, 10 mol %), dppf (6 mg, 0.1 mmol, 10 mol %), $K_3PO_4 \cdot nH_2O$ (691 mg, 3.0 mmol, 3.0 equiv), compound **11** (483 mg, 1.75 mmol, 1.75 equiv) and compound **15** (210 mg, 1.0 mmol, 1.0 equiv) were stirred in dry CH_3CN (6 mL) under N_2 at 100 °C for 5 h. After completion of the reaction, the solvent was removed under vacuum, and THF (12.5 mL) was added into the residue. $LiAlH_4$ (42 mg, 1.1 mmol, 1.1 equiv) was then added into the solution and kept stirring at r.t. for 3 h. Work-up by adding excess ethyl acetate to quench the reaction. Extraction (CH_2Cl_2/H_2O) then purification through a column chromatography [R_f = 0.5 (30 % ethyl acetate in hexane)] to afford **18** as a white solid (222 mg, 79%), mp: 127–129 ℃; IR (KBr): 3353, 2917, 1482, 1227, 1042 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.04 (s, 1H), 6.95 (d, *J* = 3.0 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.82 (s, 1H), 6.52 (d, *J* = 3.0 Hz, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 6.02 (d, *J* = 1.2 Hz, 1H), 4.30 (s, 2H), 3.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.4, 146.3, 134.1, 133.7, 132.1, 130.8, 129.7, 123.8, 123.7, 120.6, 119.1, 110.9, 107.9, 101.2, 101.1, 63.1, 35.8; HRMS [(EI), M^+]: 281.1055 (cal. for $C_{17}H_{15}NO_3$ 281.1052).

4,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzaldehyde (**19**): Bis(pinacolato)diboron (1.22 g, 4.8 mmol, 1.2 equiv), 2-bromo-4,5-dimethoxybenzaldehyde (980 mg, 4.0 mmol, 1.0 equiv), $PdCl_2$(dppf) (88 mg, 0.12 mmol, 3 mol %) and KOAc (1.18 g, 12 mmol, 3.0 equiv) were stirred in dry 1,4-dioxane (15 mL) under N_2 at 80 °C for 36 h. Work-up by filtration of salts and extraction (CH_2Cl_2/H_2O). Purification through a column chromatography [R_f = 0.4 (20% ethyl acetate in hexane)] to afford **19** as a white solid (1.11 g, 95%), mp: 107–109 ℃; IR (KBr): 3493, 2978, 2936, 2845, 1681, 1586, 1514, 1269 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 10.58 (s, 1H), 7.55 (s, 1H), 7.35 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 1.37 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.7, 152.8, 151.2, 136.3, 117.2, 108.6, 84.3 (2C), 56.1, 56.0, 24.9 (4C), C–B signal was not observed due to quadruplolar relaxation; HRMS [(ESI), $(M+H)^+$]: 293.1562 (cal. for $C_{15}H_{22}BO_5$ 293.1560).

Lycosinine B (**20**): $PdCl_2$ (18 mg, 0.1 mmol, 10 mol %), dppp (4 mg, 0.1 mmol, 10 mol %), $K_3PO_4 \cdot nH_2O$ (691 mg, 3.0 mmol, 3.0 equiv), compound **19** (511 mg, 1.75 mmol, 1.75 equiv) and compound **16** (212 mg, 1.0 mmol, 1.0 equiv) were stirred in dry CH_3CN (6 mL) under N_2 at 120 °C for 24 h. Work-up by filtration of salts, then purification through a column chromatography [R_f = 0.4 (30% ethyl acetate in hexane)] to afford **20** as a yellow liquid (220 mg, 74%), IR (KBr): 3457, 2927, 2849, 1683, 1596, 1509, 1353, 1266, 1137, 1061 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 9.77(s, 1H), 7.48 (s, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.87 (s, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.35 (dd, *J* = 16.2, 8.4 Hz, 1H), 3.25 (dd, *J* = 17.4, 9.0 Hz, 1H), 3.05–2.96 (m, 2H) , 2.25(s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 191.6, 153.5, 151.2, 148.7, 139.8, 131.6, 130.8, 127.6, 124.3, 119.0, 118.2, 113.1, 108.0, 56.9, 56.3, 56.1, 39.1, 28.6; HRMS [(EI), M^+]: 297.1368 (cal. for $C_{18}H_{19}NO_3$ 297.1365).

Lycosinine A (**21**): $LiAlH_4$ (21 mg, 0.55 mmol, 1.1 equiv) was added into the solution of **20** (149 mg, 0.5 mmol, 1.0 equiv) in THF (6 mL) at r.t. and kept stirring for 2 h. Work-up by adding excess ethyl acetate to quench the reaction, then purification through a column chromatography [R_f = 0.2 (30 % ethyl acetate in hexane)] to afford **21** as a colorless liquid (138 mg, 92%), IR (KBr): 3454, 2935, 2843, 1635, 1515, 1243, 1148, 1061 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.00 (s, 1H), 6.94 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.90 (t, *J* = 7.2 Hz, 1H), 6.85 (s, 1H), 4.22 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.60 (td, *J* = 7.8, 2.4 Hz, 1H), 3.13–3.08 (m, 1H), 3.01–2.91 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 151.0, 148.6, 148.5, 132.2, 132.1, 131.8, 129.7, 126.2, 123.9, 120.9, 112.9, 112.6, 64.6, 56.7, 56.0, 55.9, 41.0, 28.9; HRMS [(EI), M^+]: 299.1525 (cal. for $C_{18}H_{21}NO_3$ 299.1521).

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Supplementary data

Experimental procedure, ^1H and ^{13}C NMR spectra and spectral data for all compounds are available in the online version.

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