Collective Total Syntheses of Benzo[*c*]phenanthridine Alkaloids via A Sequential Transition Metal-Catalyzed Pot-Economy Approach

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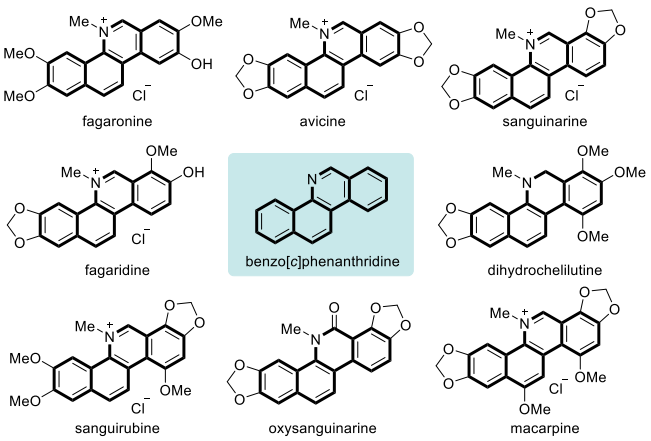
Abstract: The collective total syntheses of a series of benzo[*c*]phenanthridine alkaloids were accomplished via a pot-economy approach. The synthetic strategy was achieved by constructing ring C and ring B on pre-installed ring A and ring D via sequential transition metal-catalyzed reactions and condition-controlled Mannich reactions in a three-pot protocol. A palladium-catalyzed Sonogashira coupling reaction and a following Wittig reaction were utilized to connect ring A and ring D from readily available starting materials to finish the preparation of the 1,5-enyne substrates (the first pot). A gold(I)-catalyzed cycloisomerization and *in situ* iododeauration cascade of 1,5-enyne substrates was developed to form ring C (the second pot). A copper-catalyzed Ullman coupling reaction, followed by a flexible condition-controlled Mannich reaction, was designed to install ring B in the final stage of the synthesis (the third pot). The synthetic naturally occurring alkaloids and related analogues were evaluated in cytotoxic activity against K562, MCF-7 and A549 cells.

Introduction

The efficiency of organic synthesis has become a more and more significant concern since chemists are realizing the environmental issues caused by chemical industry, such as water pollution, environmental accidents, hazardous waste, ozone depletion and soil contamination, etc. To decrease the influence of chemicals on the environments, chemists have been engaged in developing highly efficient synthetic strategies under the guidance of the principle of green chemistry.[1] A number of strategies aiming to improve synthetic efficiency have been developed, such as atom economy,[1a,1b] redox economy,[1f] pot economy,[1d,1h,1j,1l] step economy[1c,1e,1g,1i] and so on. Nowadays, the development of highly efficient and environmentally friendly strategies in the syntheses of natural products and drugs is in urgent need from a sustainability perspective.[1k]

Benzo[*c*]phenanthridine alkaloids, belonging to isoquinoline alkaloids extracted from rutaceae, papaveraceae and other plants, which are widely present in the middle and lower basins of the Yangtze River.[2] Since the first isolation of such alkaloids in 1839, more than 100 alkaloids have been isolated up to date[2a] and the representative structures are shown in Scheme 1. In their structures, the substituents of natural benzo[*c*]phenanthridine alkaloids are mainly alkoxy groups or hydroxyl groups, which are closely related to the particularity of their biosynthetic pathways.[3] These compounds have a variety of important biological activities, including anti-cancer, anti-inflammatory, bactericidal and growth promotion.[4] Numerous *in vivo* and *in vitro* studies signifying the anticancer properties of benzo[*c*]phenanthridines have been disclosed. Most of the anticancer action of these compounds have been attributed to the ability of inducing apoptosis (type I programmed cell death) in a number of different cancers, such as cancers of lung, breast, bladder, colon, cervix and prostate.[5-7]

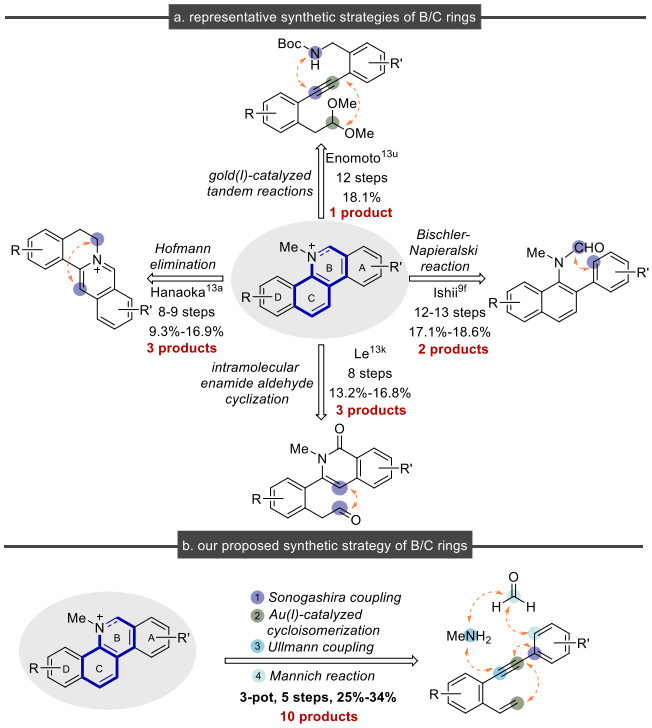


Scheme 1. Representative Benzo[*c*]phenanthridine Alkaloids.

Results and Discussion

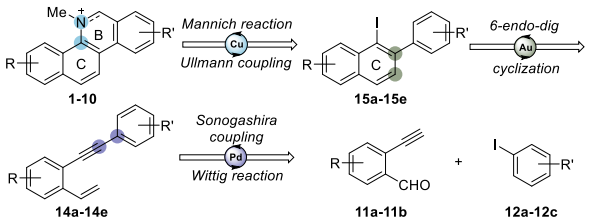
Over the past twenty years, many synthetic methods for the construction of benzo[*c*]phenanthridine alkaloids have been developed,[8-13] among which the construction of ring B and ring C in sequence or in one step on ring A and ring D with pre-installed versatile functional groups in the late stage of synthesis represents the most popular strategy (Scheme 2a). For example, in 1985, Ishii reported a method to construct ring B on the pre-installed rings A/C/D in the final stage of the synthesis.[9f] In 1990, Hanaoka achieved the total syntheses of three benzo[*c*]phenanthridine alkaloids and their analogs using Hofmann elimination to introduce ring C from protoberberine.[13a] In 2004, Le disclosed a 8-step syntheses of three benzo[*c*]phenanthridine alkaloids featured with the construction of ring C via an intramolecular nucleophilic addition.[13k] In 2009, Enomoto completed the total synthesis of nitidine via a gold(I)-

catalyzed tandem cyclization reaction to build up ring C and ring D in one step (Scheme 2a).[13u]



Scheme 2. Representative Strategies and Our Synthetic Strategy.

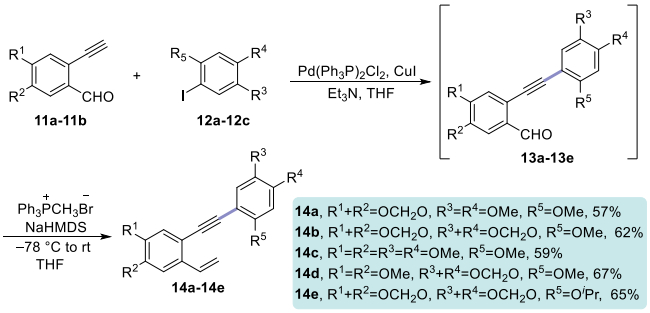
Although strategies for the total synthesis of these compounds are abundant, many of these strategies were developed at a time when the waste minimisation and sustainability were not significant issues. The research aiming for developing highly efficiency and environmentally friendly synthetic strategies to access benzo[*c*]phenanthridine alkaloids is in high demand. Herein, a sequential transition metal-catalyzed pot-economy synthetic strategy for the collective total synthesis of a series of benzo[*c*]phenanthridine alkaloids was developed. The key strategic bonds were constructed via three metal-catalyzed reactions and the syntheses of ten benzo[*c*]phenanthridine alkaloids were achieved in a three-pot protocol (Scheme 2b).



Scheme 3. Retrosynthetic Analysis of Target Molecules.

Retrosynthetically, we envisioned that the construction of ring B in compounds **1-10** could be realized via a Mannich reaction in the late stage, and the C-N bond could be installed by a copper-catalyzed Ullman coupling reaction from intermediates **15a-15e**. The construction of iodo-substituted ring C might be realized via a gold(I)-catalyzed cycloisomerization of 1,5-enyne followed by *in situ* iododeauration with *N*-iodosuccinimide (NIS) starting from 1,5-enynes **14a-14e**. The 1,5-enynes **14a-14e** could be constructed by palladium-catalyzed Sonogashira coupling and Wittig reactions from readily available building blocks **11a-11b** and **12a-12c** (Scheme 3).

The research commenced with the synthesis of the key 1,5-enynes **14a-14e** by a one-pot protocol (Scheme 4). From readily available building blocks **11a-11b**[14] and **12a-12c**,[15] the aldehydes **13a-13e** were prepared smoothly via Sonogashira coupling. After completion of the reaction, methyltriphenylphosphonium bromide and sodium bis(trimethylsilyl)amide were added to the reaction mixture to transform the aldehyde into the olefin via Wittig reaction with 57-67% yields in one pot. Notably, this one-pot reaction could be performed on a decagram scale without loss of efficiency.



Scheme 4. One-Pot Syntheses of 1,5-Enyne Precursors **14a**-**14e**.

The decagram scale synthesis of 1,5-enynes laid the foundation for the construction of ring C through the gold(I)-catalyzed cycloisomerization/*in situ* iododeauration. First, the substrate **14a** was chosen as a model to evaluate the reaction conditions as listed in Table 1. It was found that [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold (I) chloride (IPrAuCl) could realize this transformation, but only in a yield of 11% (Table 1, entry 1). Next, the additives to activate the gold(I) catalyst, such as silver trifluoromethanesulfonate (AgOTf), silver tetrafluoroborate ($AgBF_4$) and silver hexafluoroantimonate ($AgSbF_6$) were screened, which gained an obvious yield improvement, especially the combination of 5 mol% IPrAuCl and 5 mol% $AgSbF_6$ afforded the highest yield (Table 1, entries 2-4). Screening of ligands of the gold(I) catalyst revealed that the catalyst with triphenylphosphine as ligand provided lower yield than that with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (IPr) as ligand (Table 1, entry 5). The screening of solvents such as toluene, 1,2-dichloroethane (DCE) and tetrahydrofuran (THF) showed that DCM was the optimal solvent for this transformation (Table 1, entries 6-8). Temperature screening indicated that either dropping the temperature to 0 °C or elevating the temperature to 40 °C led to a lower yield (Table 1, entries 9-10). An attempt on decreasing the loading of NIS to 0.5 eq. or 1.0 eq. proved unsuccessful, only affording the product in yields of 31% and 46%, respectively (Table 1, entries 11-12). Increasing the loading of NIS to 2.0 eq. did not improve the yield further (Table 1, entry 13). The control experiment utilizing $AgSbF_6$ as the catalyst did not give any product, implied that cationic gold(I)-catalyst was the true reactive species (Table 1, entry 14). Examination of reaction time revealed that prolonging reaction time was not helpful for the yield improvement (Table 1, entry 15). Finally, the optimal reaction conditions were determined as stirring the substrates in the presence of 5 mol% IPrAuCl/$AgSbF_6$ and 1.5 eq. NIS in anhydrous DCM at room temperature for 10 minutes.

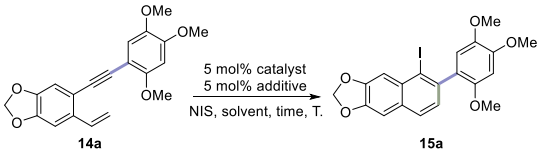


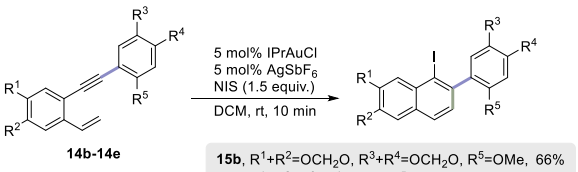
Table 1. Optimization of Reaction Conditions.

Entry	Catalyst	Solvent	Additive	NIS (eq.)	T (°C)	Yield (%)
1	IPrAuCl	DCM	-	1.5	25	11
2	IPrAuCl	DCM	AgOTf	1.5	25	57
3	IPrAuCl	DCM	$AgBF_4$	1.5	25	53
4	**IPrAuCl**	**DCM**	**$AgSbF_6$**	**1.5**	**25**	**73**
5	Ph_3PAuCl	DCM	$AgSbF_6$	1.5	25	68
6	IPrAuCl	Tol.	$AgSbF_6$	1.5	25	41
7	IPrAuCl	THF	$AgSbF_6$	1.5	25	52
8	IPrAuCl	DCE	$AgSbF_6$	1.5	25	66
9	IPrAuCl	DCM	$AgSbF_6$	1.5	0	56[a]
10	IPrAuCl	DCM	$AgSbF_6$	1.5	40	72
11	IPrAuCl	DCM	$AgSbF_6$	0.5	25	31
12	IPrAuCl	DCM	$AgSbF_6$	1.0	25	46
13	IPrAuCl	DCM	$AgSbF_6$	2.0	25	73
14	IPrAuCl	DCM	$AgSbF_6$	1.5	25	0
15	IPrAuCl	DCM	$AgSbF_6$	1.5	25	73[a]

[a] The reaction was run for 0.5 h.

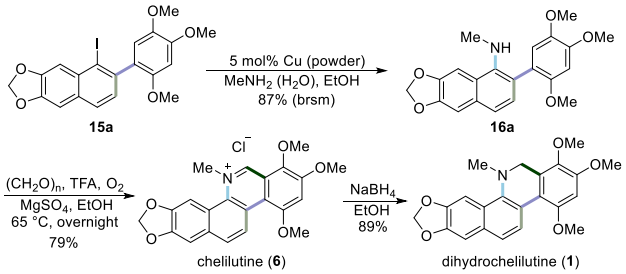
IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]

With the optimal conditions in hand, the scope of gold-catalyzed cycloisomerization/*in situ* iododeauration cascade was examined in the designed substrates **14b**-**14e**, which furnished the 1-iodo-2-phenylnaphthalenes **15b**-**15e** in satisfactory yields (Scheme 5). It is worth mentioning that the facile formation of ring C bearing iodo-substitution set the stage for the following construction of ring B.



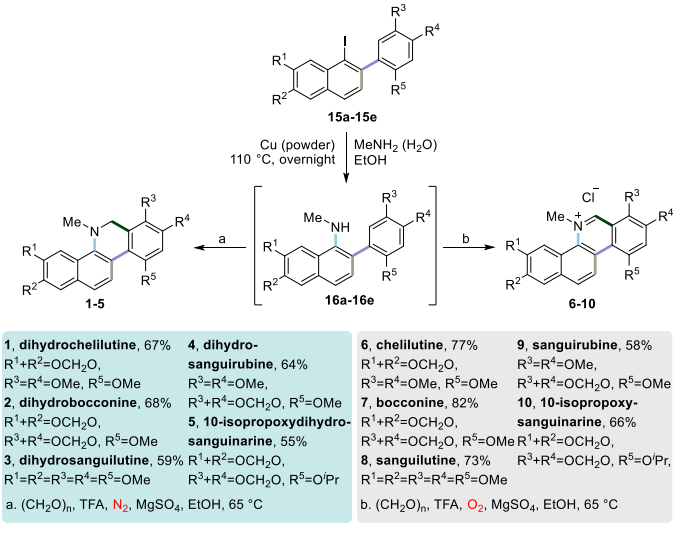
Scheme 5. Au(I)-Catalyzed Cycloisomerization/*in situ* Iododeauration Cascade.

According to the synthetic plan, a metal-catalyzed cross-coupling reaction would be utilized to form the C-N bond. A thorough screening of metal catalysts, including copper(I) iodide (CuI), copper(I) bromide (CuBr), bis(triphenylphosphine)palladium(II) dichloride $[Pd(Ph_3P)_2Cl_2]$, tetrakis(triphenylphosphine)palladium(0) $[Pd(Ph_3P)_4]$, and tris(dibenzylideneacetone)dipalladium(0) $[Pd_2(dba)_3]$ were carried out using model substrate **15a**,[16] however, none of them worked smoothly in catalyzing the C-N bond formation reaction. Finally, treatment of the iodo-substituted substrate **15a** with a catalytic amount of Cu powder in an aqueous solution of methylamine at 110 °C in a sealed tube proved successful in providing the desired product **16a** in 87% yield based on recovering the starting material (Scheme 6).[17]



Scheme 6. Stepwise Total Syntheses of Chelilutine **6** and Dihydrochelilutine **1**.

With the methylamino moiety installed, the closure of ring B was attempted by an intramolecular Mannich/oxidation cascade reaction. The intermediate **16a** was subjected to paraformaldehyde and a catalytic amount of trifluoroacetic acid in the presence of magnesium sulfate under oxygen atmosphere, resulted in the formation of the desired chelilutine (**6**) in 79% yield. A following reduction of iminium of chelilutine (**6**) with sodium borohydride afforded the dihydrochelilutine (**1**) in 89% yield (Scheme 6). Compared with the Bischler-Napieralski reaction involving the utility of reagents like phosphorus oxychloride and phosphorus pentachloride with toxicity and unpleasant irritating odor in precedent synthesis of these alkaloids,[9] the Mannich/oxidation cascade reaction was more environmentally friendly.

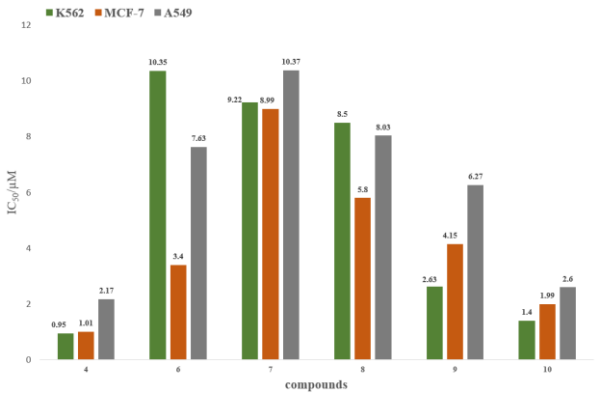


Scheme 7. One-Pot Total Syntheses of Benzo[*c*]phenanthridine Alkaloids **1-10**.

To simplify the synthetic route to benzo[*c*]phenanthridine alkaloids, a pot-economy procedure was developed by

performing the copper-catalyzed Ullmann cross-coupling reaction and Mannich reaction in one pot since both of them could be run in ethanol. It was notable that the oxidative states of the alkaloids could be controlled by the reaction atmosphere. The syntheses of oxidative products **1**-**5** was achieved under an oxygen atmosphere in 55-68% yields and the reductive products **6**-**10** was achieved under a nitrogen atmosphere in 58-82% yields (Scheme 7). Thus, the reduction of sodium borohydride in Scheme 6 was also avoided in the one-pot procedure.

The efficient syntheses of these benzo[*c*]phenanthridines provided great convenience on the research of biological activities of them. Accordingly, the cytotoxic activities of the synthesized benzo[*c*]phenanthridines (**1**-**10**) were evaluated preliminarily against K562, MCF-7 and A549 cell lines using a colorimetric MTT assay. The IC_{50} values of the tested alkaloids on individual cell lines were shown in Scheme 8. It was found that compounds **1** and **2** exhibited weak cytotoxic activities (IC_{50}>100 μM). Compound **4** exhibited the most potent cytotoxic activity against all cells with IC_{50} values of 0.95±0.41 μM, 1.01±0.13 μM and 2.17±0.47 μM, respectively. Compound **10**, which is unnatural product showed similar cytotoxicity in comparison with compound **4**. Compared with compounds **4** and **10**, other compounds showed weaker cytotoxic activities, while compound **5** merely possessed cytotoxic effect against K562 with IC_{50} value of 42±5.68 μM.



Scheme 8. IC_{50} (μM) Values of Benzo[*c*]phenanthridines **4**, **6**-**10** Against K562, MCF-7 and A549 Cells.

In addition, to verify the mechanism of anticancer activity of these benzo[*c*]phenanthridines, the preliminary exploration of cell apoptosis in K562 cell caused by dihydrosanguirubine (**4**) was conducted by flow cytometry method. The results implied that dihydrosanguirubine (**4**) could induce late arrest of apoptosis in K562, the human myeloid leukemia cell line (Figure 1a) in a dose-dependent manner (Figure 1b), which was consistent with the results reported previously in lung cancer cells SPC-A1,[6l] colorectal cancer cells HT-29,[6h] epidermoid carcinoma cells KB[18] and so on.

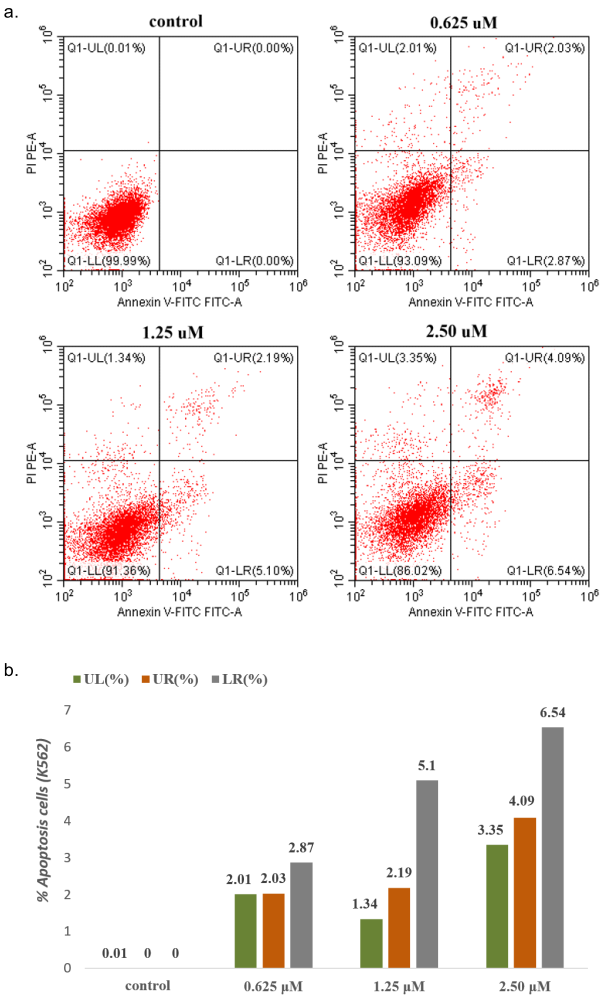


Figure 1. a. Cell Apoptosis Induced by Compound **4** Examined by Flow Cytometer; b. Compound **4** Induced Apoptosis in a Dose-Dependent Manner in K562 Cell Line.

Conclusion

In summary, the collective total syntheses of eight benzo[*c*]phenanthridine alkaloids and two derivatized molecules, including dihydrochelilutine (28% overall yield), dihydrobocconine (28% overall yield), dihydrosanguilutine (26% overall yield), dihydrosanguirubine (33% overall yield), 10-isopropoxydihydrosanguinarine (25% overall yield), chelilutine (32% overall yield), bocconine (34% overall yield), sanguilutine (32% overall yield), sanguirubine (30% overall yield), 10-isopropoxysanguinarine (30% overall yield) were achieved in three pots. This synthetic strategy is featured with the combination of sequential transition metal-catalyzed reactions with flexible condition-controlled Mannich reaction. This pot-economy strategy facilitates the preparation of a string of benzo[*c*]phenanthridine alkaloids and related derivatives and further evaluation of their cytotoxic activities and corresponding mechanism. Further study on benzo[*c*]phenanthridine alkaloids serving as potential anticancer lead compound and the structural optimization of these compounds are currently underway in our laboratory.

Experimental Section

1. General procedures for the preparation of 1,5-enyne precursors **14a**-**14e** and characterization data

A magnetically stirred emulsion of iodobenzenes **12a**-**12c** (2.20 mmol), $Pd(Ph_3P)_2Cl_2$ (80 mg, 0.11 mmol) and CuI (43 mg, 0.23 mmol) in degassed THF (20 mL) at 60 °C under an atmosphere of nitrogen was treated with TEA (1.6 mL, 11.41 mmol) and alkynes **11a**-**11b** (2.50 mmol). The resulting mixture was stirred until the terminal alkynes were completely consumed. After the reaction was completed, the reaction solution containing compounds **13a**-**13e** was is used for the next step directly.

A magnetically stirred emulsion of methyltriphenylphosphonium bromide (1.16 g, 3.30 mmol) in dry THF (25 mL) maintained at –78 °C under an atmosphere of nitrogen was treated with NaHMDS (2 M in THF, 1.7 mL, 3.30 mmol). After being stirred for 30 min sequentially, the resulting mixture was then treated with the compounds **13a**-**13e** (2.20 mmol), prepared by the method described above. The resulting mixture was stirred for 3 h at room temperature then filtered through Celite. The filtrate was purified by a flash column chromatography (EtOAc/petroleum ether) on silica gel to afford the products **14a**-**14e**.

5-((2,4,5-Trimethoxyphenyl)ethynyl)-6-vinylbenzo[*d*][1,3]dioxole (**14a**): Yellow solid (424 mg, 1.25 mmol, 57% for 2 steps) (EtOAc/petroleum ether = 1:20); Mp 93.4 – 94.7 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.32 (s, 1H), 7.26 (dd, *J* = 17.6, 11.1 Hz, 1H), 7.00 (s, 1H), 6.98 (s, 1H), 6.74 (s, 1H), 6.08 (s, 2H), 5.86 (d, *J* = 17.5 Hz, 1H), 5.31 (d, *J* = 11.3 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.24, 150.58, 148.14, 147.08, 142.51, 134.08, 133.39, 115.50, 114.53, 110.34, 104.21, 102.00, 101.69, 97.94, 90.12, 89.94, 56.46, 56.19, 55.81; IR (thin film, cm^{-1}): 3079, 3014, 1876, 1666, 1582, 1477, 1385, 993, 918, 677; HRMS (ESI): *m/z* Calcd. for $C_{20}H_{19}O_5$ $[M+H]^+$ 339.1227, Found 339.1231.

5-Methoxy-6-((6-vinylbenzo[*d*][1,3]dioxol-5-yl)ethynyl)benzo[*d*][1,3]dioxole (**14b**): Yellow solid (439 mg, 1.36 mmol, 62% for 2 steps) (EtOAc/petroleum ether = 1:20); Mp 116.8 – 118.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 17.6, 11.0 Hz, 1H), 7.06 (s, 1H), 6.93 (s, 1H), 6.91 (s, 1H), 6.53 (s, 1H), 5.97 (d, *J* = 10.0 Hz, 4H), 5.66 (d, *J* = 17.5 Hz, 1H), 5.26 (d, *J* = 11.1 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.86, 148.92, 148.27, 147.18, 141.08, 134.97, 134.40, 116.41, 113.54, 111.72, 111.25, 104.52, 104.32, 101.73, 101.53, 94.87, 90.86, 89.60, 56.92; IR (thin film, cm^{-1}): 3077, 3021, 1647, 1582, 1461, 1451, 1390, 989, 923, 654; HRMS (ESI): *m/z* Calcd. for $C_{19}H_{15}O_5$ $[M+H]^+$ 323.0914, Found 323.0917.

1-((4,5-Dimethoxy-2-vinylphenyl)ethynyl)-2,4,5-trimethoxybenzene (**14c**): Yellow solid (459 mg, 1.30 mmol, 59% for 2 steps) (EtOAc/petroleum ether = 1:15); Mp 145.6 – 146.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 17.6, 11.0 Hz, 1H), 7.07 (s, 1H), 6.99 (s, 2H), 6.53 (s, 1H), 5.72 (d, *J* = 17.6 Hz, 1H), 5.29 (d, *J* = 11.0 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 6H), 3.90 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.51, 150.41, 149.42, 148.65, 143.05, 135.08, 132.60, 115.70, 115.20, 114.15, 113.26, 106.91, 103.85, 97.45, 90.84, 89.34, 56.98, 56.62, 56.16, 55.97; IR (thin film, cm^{-1}): 3084, 3030, 1873, 1642, 1585, 1449, 1301, 999, 917, 667; HRMS (ESI): *m/z* Calcd. for $C_{21}H_{23}O_5$ $[M+H]^+$ 355.1540, Found 355.1537.

5-((4,5-Dimethoxy-2-vinylphenyl)ethynyl)-6-methoxybenzo[*d*][1,3]dioxole (**14d**): Yellow solid (498 mg, 1.47 mmol, 67% for 2 steps) (EtOAc/petroleum ether = 1:20); Mp 123.1 – 124.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 17.6, 11.0 Hz, 1H), 7.05 (s, 1H), 6.96 (d, *J* = 4.9 Hz, 1H), 6.91 (s, 1H), 6.51 (s, 1H), 5.92 (s, 2H), 5.71 (d, *J* = 17.6 Hz, 1H), 5.26 (d, *J* = 11.2 Hz, 1H), 3.91 (s, 4H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.66, 149.32, 148.78, 148.55, 140.96, 134.93, 132.49, 115.05, 113.97, 113.16, 111.60, 106.81, 104.38, 101.62, 94.69, 90.77, 89.43, 56.74, 55.99, 55.85; IR (thin film, cm^{-1}): 3074, 3021, 1856, 1647, 1600, 1382, 1453, 1382, 979, 656; HRMS (ESI): *m/z* Calcd. for $C_{20}H_{19}O_5$ $[M+H]^+$ 338.1154, Found 338.1159.

5-Isopropoxy-6-((6-vinylbenzo[*d*][1,3]dioxol-5-yl)ethynyl)benzo[*d*][1,3]dioxole (**14e**): Yellow solid (501 mg, 1.43 mmol, 65% for 2 steps) (EtOAc/petroleum ether = 1:20); Mp 182.4 – 184.1 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.29 – 7.22 (m, 2H), 6.89 (d, *J* = 10.6 Hz, 2H), 6.81 (s, 1H), 6.01 (s, 2H), 5.96 (s, 2H), 5.79 (d, *J* = 17.5 Hz, 1H), 5.19 (d, *J* = 11.3 Hz, 1H), 4.54 (m, *J* = 12.0, 6.0 Hz, 1H), 1.22 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.42, 148.50, 147.86, 146.83, 140.62, 133.91, 132.98, 115.35, 113.96, 110.25, 109.95, 104.63, 103.86, 101.40, 98.01, 90.07, 89.68, 71.40, 21.67; IR (thin film, cm^{-1}): 3078, 2341, 1831, 1656, 1591, 1483, 1376, 987, 912, 627; HRMS (ESI): *m/z* Calcd. for $C_{21}H_{19}O_5$ $[M+H]^+$ 351.1227, Found 351.1223.

2. General procedures for the preparation of 1-iodo-2-phenylnaphthalenes **15a**-**15e** and characterization data

A magnetically stirred solution of 1,5-enynes **14a**-**14e** (1.00 mmol) in dry DCM (3 mL) at room temperature under an atmosphere of nitrogen was treated with the gold catalyst, which was generated by stirring the mixture of IPrAuCl (30 mg, 0.05 mmol) and $AgSbF_6$ (17 mg, 0.05 mmol) in dry DCM (2 mL) at room temperature for 30 min. After being stirred for 5 min sequentially, the resulting mixture was then treated with *N*-iodosuccinimide (338 mg, 1.50 mmol), prepared by the method described above, dissolved in dry DCM (1 mL). The resulting mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residues were purified by a flash column chromatography (EtOAc/petroleum ether) on silica gel to afford the products **15a**-**15e**.

5-Iodo-6-(2,4,5-trimethoxyphenyl)naphtho[2,3-*d*][1,3]dioxole (**15a**): Brown oily liquid (339 mg, 0.73 mmol, 73%) (EtOAc/petroleum ether = 1:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.09 (s, 1H), 6.72 (s, 1H), 6.63 (s, 1H), 6.08 (d, *J* = 1.4 Hz, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.68, 149.51, 148.03, 142.89, 141.81, 132.80, 129.99, 127.47, 127.12, 126.80, 114.87, 110.44, 105.14, 103.97, 101.59, 98.09, 56.90, 56.69, 56.23; IR (thin film, cm^{-1}): 3078, 2856, 1670, 1582, 1455, 1387, 990, 864, 782, 653; HRMS (ESI): *m/z* Calcd. for $C_{20}H_{18}IO_5$ $[M+H]^+$ 465.0194, Found 465.0192.

5-Iodo-6-(6-methoxybenzo[*d*][1,3]dioxol-5-yl)naphtho[2,3-*d*][1,3]dioxole (**15b**): Yellow oily liquid (295 mg, 0.66 mmol, 66%) (EtOAc/petroleum ether = 1:5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.08 (s, 1H), 6.66 – 6.61 (m, 2H), 6.08 (s, 2H), 6.00 (dd, *J* = 11.5, 1.3 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.78, 149.53, 148.04, 141.83, 140.96, 132.74, 129.98, 127.87, 127.52, 126.70, 110.73, 110.42, 105.24, 103.97, 101.54, 95.34, 56.84; IR (thin film, cm^{-1}): 3075, 2861, 1668, 1588, 1453, 1381, 980, 863, 742, 651; HRMS (ESI): *m/z* Calcd. for $C_{19}H_{14}IO_5$ $[M+H]^+$ 448.9881, Found 448.9885.

1-Iodo-6,7-dimethoxy-2-(2,4,5-trimethoxyphenyl)naphthalene (**15c**): Yellow oily liquid (360 mg, 0.75 mmol, 75%) (EtOAc/petroleum ether = 1:5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.13 (s, 1H), 6.73 (s, 1H), 6.63 (s, 1H), 4.07 (s, 3H), 4.03 (s, 3H), 3.97 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.01, 150.71, 149.90, 149.43, 142.87, 141.43, 131.17, 128.32, 127.14, 126.71, 114.89, 112.77, 106.57, 104.73, 98.10, 56.91, 56.67, 56.18; IR (thin film, cm^{-1}): 3072, 3015, 1700, 1585, 1450, 1388, 1377, 992, 747, 663; HRMS (ESI): *m/z* Calcd. for $C_{21}H_{22}IO_5$ $[M+H]^+$ 481.0507, Found 481.0503.

5-(1-Iodo-6,7-dimethoxynaphthalen-2-yl)-6-methoxybenzo[*d*][1,3]dioxole (**15d**): Yellow oily liquid (362 mg, 0.78 mmol, 78%) (EtOAc/petroleum ether = 1:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 1H), 7.64 (s, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.12 (s, 1H), 6.66 (s, 1H), 6.64 (s, 1H), 6.03 – 5.98 (m, 2H), 4.07 (s, 3H), 4.03 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.83, 149.93, 148.01, 141.46, 131.12, 128.32, 126.86, 126.69, 112.74, 110.79, 106.58, 101.49, 95.36, 56.85, 56.19, 29.85; IR (thin film, cm^{-1}): 3089, 3021, 1698, 1587, 1463, 1382, 987, 756, 673; HRMS (ESI): *m/z* Calcd. for $C_{20}H_{18}IO_5$ $[M+H]^+$ 465.0194, Found 465.0190.

5-Iodo-6-(6-isopropoxybenzo[*d*][1,3]dioxol-5-yl)naphtho[2,3-*d*][1,3]dioxole (**15e**): Yellow oily liquid (362 mg, 0.70 mmol, 70%) (EtOAc/petroleum ether = 1:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.08 (s, 1H), 6.66 (s, 1H), 6.61 (s, 1H), 6.08 (dd, *J* = 4.7, 1.1 Hz, 2H), 6.00 (dd, *J* = 14.5, 1.3 Hz, 2H), 4.11 (m, *J* = 12.2, 6.1 Hz, 1H), 1.06 (dd, *J* = 8.2, 6.1 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.31, 149.33, 148.21, 144.58, 140.90, 132.10, 130.63, 129.01, 125.14, 119.27, 112.39, 106.09, 104.45, 101.24, 97.33, 76.17, 22.07; IR (thin film, cm^{-1}): 3089, 3021, 1698, 1587, 1463, 1382, 987, 756, 673; HRMS (ESI): *m/z* Calcd. for $C_{20}H_{18}IO_5$ $[M+H]^+$ 465.0194, Found 465.0190.

3. General procedures for the preparation of benzo[*c*]phenanthridine alkaloids **1**-**5** and characterization data

A mixture of compounds **15a**-**15e** (1.00 mmol), 30% aqueous methylamine solution (0.6 mL, 5.00 mmol), copper powder (3.2 mg, 0.05 mmol), EtOH (0.1 mL), and a stirring bar were sealed in a 30 mL screwed tube and stirred electromagnetically in an oil bath at 110 °C. During the reaction, most of the copper powder was dissolved. After the reaction was completed, the reaction solution was used for the next step directly.

A mixture of the products obtained above (1.00 mmol), paraformaldehyde (150 mg, 5.00 mmol), trifluoroacetic acid (0.2 mL, 2.4 mmol), $MgSO_4$ (600 mg, 5.00 mmol) and EtOH (1.0 mL) under an atmosphere of nitrogen and a stirring bar were sealed in a 30 mL screwed tube and stirred electromagnetically in an oil bath at 65 °C. After the reaction was completed, the reaction mixture was cooled to room temperature and DCM (3 mL) was added. The organic layer was separated and the aqueous layer was extracted by DCM (3×2 mL). The combined extracts were dried by anhydrous sodium sulfate and the solvent was removed under reduced pressure to give the crude product that was purified by a flash column chromatography (EtOAc/petroleum ether) on silica gel to afford the products **1**-**5**.

Dihydrochelilutine (**1**): White solid (254 mg, 0.67 mmol, 67% for 2 steps) (EtOAc/petroleum ether = 1:25); Mp 145.2 – 146.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.7 Hz, 1H), 7.69 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.11 (s, 1H), 6.57 (s, 1H), 6.04 (s, 2H), 4.21 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.82 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.40, 152.47, 147.84, 147.53, 143.40, 140.29, 130.42, 129.12, 126.31, 124.87, 123.60, 122.81, 114.22, 104.18, 101.03, 100.72, 96.83, 61.46, 56.27, 56.07, 49.20, 40.61; IR (thin film, cm^{-1}): 3023, 2865, 2402, 1604, 1587, 1263, 861, 852, 743, 654; HRMS (ESI): *m/z* Calcd. for $C_{22}H_{22}NO_5$ $[M+H]^+$ 380.1313, Found 380.1318.

Dihydrobocconine (**2**): White solid (247 mg, 0.68 mmol, 68% for 2 steps) (EtOAc/petroleum ether = 1:30); Mp 189.9 – 191.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.7 Hz, 1H), 7.69 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.10 (s, 1H), 6.61 (s, 1H), 6.04 (s, 2H), 6.00 (s, 2H), 4.10 (s, 2H), 3.87 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.07, 147.80, 147.58, 147.35, 130.18, 124.65, 123.68, 122.77, 103.95, 101.30, 100.83, 100.51, 94.24, 56.49, 48.80, 40.62; IR (thin film, cm^{-1}): 3101, 2874, 2392, 1673, 1598, 1581, 1447, 854, 759, 637; HRMS (ESI): *m/z* Calcd. for $C_{21}H_{18}NO_5$ $[M+H]^+$ 364.1180, Found 364.1177.

Dihydrosanguilutine (**3**): White solid (233 mg, 0.59 mmol, 59% for 2 steps) (EtOAc/petroleum ether = 1:30); Mp 152.4 – 154.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 1H), 7.68 (s, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.12 (s, 1H), 6.58 (s, 1H), 4.24 (s, 2H), 4.07 (s, 3H), 4.01 (s, 3H), 3.95 (s, 4H), 3.93 (s, 3H), 3.83 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.39, 152.41, 149.56, 142.81, 140.35, 129.26, 128.99, 124.78, 123.27, 122.11, 114.46, 106.73, 102.90, 97.00, 61.47, 56.32, 56.10, 56.08, 56.01, 49.29, 40.43; IR (thin film, cm^{-1}): 3096, 2861, 2226, 1618, 1587, 1492, 1431, 864, 747, 621; HRMS (ESI): *m/z* Calcd. for $C_{23}H_{26}NO_5$ $[M+H]^+$ 396.1806, Found 396.1810.

Dihydrosanguirubine (**4**): White solid (243 mg, 0.65 mmol, 65% for 2 steps) (EtOAc/petroleum ether = 1:25); Mp 148.7 – 149.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.7 Hz, 1H), 7.68 (s, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.11 (s, 1H), 6.61 (s, 1H), 6.01 (s, 2H), 4.12 (s, 2H), 4.07 (s, 3H), 4.01 (s, 3H), 3.88 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.26, 149.61, 147.22, 124.95, 124.78, 122.29, 115.73, 106.70, 102.92, 101.51, 94.55, 56.76, 56.08, 56.02, 49.11, 40.68; IR (thin film, cm^{-1}): 3111, 2865, 1613, 1590, 1454, 1261, 1024, 751, 693; HRMS (ESI): *m/z* Calcd. for $C_{22}H_{22}NO_5$ $[M+H]^+$ 380.1493, Found 380.1497.

10-Isopropoxydihydrosanguinarine (**5**): White solid (215 mg, 0.55 mmol, 55% for 2 steps) (EtOAc/petroleum ether = 1:30); Mp 169.3 – 171.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.10 (s, 1H), 6.59 (s, 1H), 6.03 (s, 2H), 6.00 (s, 2H), 4.40 – 4.36 (m, 1H), 4.09 (s, 2H), 2.59 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.12, 147.88, 147.54, 147.09, 143.07, 139.21, 130.34, 126.48, 125.27, 124.32, 122.77, 116.37, 115.72, 104.16, 101.48, 101.03, 100.77, 98.53, 73.02, 49.10, 40.86, 22.31; IR (thin film, cm^{-1}): 3090, 2871, 1632, 1586, 1481, 1272, 1113, 861, 765; HRMS (ESI): *m/z* Calcd. for $C_{23}H_{22}NO_5$ $[M+H]^+$ 392.1493, Found 392.1495.

4. General procedures for the preparation of benzo[*c*]phenanthridine alkaloids **6**-**10** and characterization data

A mixture of compounds **15a**-**15e** (1.00 mmol), 30% aqueous methylamine solution (0.6 mL, 5.00 mmol), copper powder (3.2 mg, 0.05 mmol), EtOH (0.1 mL), and a stirring bar were sealed in a 30 mL screwed tube and stirred electromagnetically in an oil bath at 110 °C. During the reaction, most of the copper powder was dissolved. After the reaction was completed, the reaction solution was used for the next step directly.

A mixture of the products obtained above (1.00 mmol), paraformaldehyde (150 mg, 5.00 mmol), trifluoroacetic acid (0.2 mL, 2.4 mmol), $MgSO_4$ (600 mg, 5.00 mmol) and EtOH (1.0 mL) under an atmosphere of oxygen and a stirring bar were sealed in a 30 mL screwed tube and stirred electromagnetically in an oil bath at 65 °C. After the reaction was completed, the reaction mixture was cooled to room temperature and DCM (3 mL) was added. The organic layer was separated and the aqueous layer was extracted by DCM (3×2 mL). The combined extracts were dried by anhydrous sodium sulfate and the solvent was removed under reduced pressure to give the crude product that was purified by a flash column chromatography (EtOAc/petroleum ether) on silica gel to afford the products **6**-**10**.

Chelilutine (**6**): Orange solid (318 mg, 0.77 mmol, 77% for 2 steps) (MeOH/DCM = 1:50); Mp 197.4 – 198.9 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.02 (s, 1H), 9.39 (d, *J* = 9.1 Hz, 1H), 8.22 (d, *J* = 9.3 Hz, 1H), 8.20 (s, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 6.34 (s, 2H), 4.93 (s, 3H), 4.26 (s, 3H), 4.16 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.27, 152.34, 147.71, 147.40, 143.27, 140.16, 130.29, 128.99, 126.18, 124.74, 123.47, 122.68, 114.09, 104.05, 100.90, 100.59, 96.70, 61.33, 56.14, 55.94, 49.07, 40.48; IR (thin film, cm^{-1}): 3114, 2902, 2867, 1642, 1521, 1470, 841, 832, 699; HRMS (ESI): *m/z* Calcd. for $C_{22}H_{20}NO_5$ $[M-Cl]^+$378.1341, Found 378.1344.

Bocconine (**7**): Red solid (326 mg, 0.82 mmol, 82% for 2 steps) (MeOH/DCM = 1:50); Mp 280.2 – 281.7 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.06 (s, 1H), 9.36 (d, *J* = 9.2 Hz, 1H), 8.22 (d, *J* = 9.2 Hz, 1H), 8.17 (s, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 6.56 (s, 2H), 6.33 (s, 2H), 4.86 (s, 3H), 4.17 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.26, 149.99, 149.11, 148.67, 148.15, 139.95, 131.73, 131.59, 130.65, 130.03, 126.44, 122.24, 120.37, 114.76, 109.69, 105.40, 105.16, 105.00, 104.57, 103.03, 58.15, 52.37; IR (thin film, cm^{-1}): 3062, 2892, 2887, 1653, 1542, 1463, 856, 848, 753; HRMS (ESI): *m/z* Calcd. for $C_{21}H_{16}NO_5$ $[M-Cl]^+$362.1028, Found 362.1032.

Sanguilutine (**8**): Red solid (313 mg, 0.73 mmol, 73% for 2 steps) (MeOH/DCM = 1:40); Mp 250.3 – 251.9 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.05 (s, 1H), 9.42 (d, *J* = 9.1 Hz, 1H), 8.27 (d, *J* = 9.2 Hz, 1H), 8.06 (s, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 5.01 (s, 3H), 4.27 (s, 3H), 4.17 (s, 3H), 4.08 (s, 3H), 4.07 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.33, 150.77, 150.23, 149.77, 148.68, 138.58, 130.80, 129.64, 129.59, 124.96,

121.26, 119.58, 118.07, 116.42, 107.92, 107.65, 107.19, 62.06, 57.07, 56.81, 55.77, 55.63, 52.01; IR (thin film, cm^{-1}): 3096, 2903, 2886, 1621, 1592, 1470, 853, 811, 762; HRMS (ESI): *m/z* Calcd. for $C_{23}H_{24}NO_5$ [M-Cl]$^+$394.1654, Found 394.1651.

Sanguirubine (**9**): Red solid (250 mg, 0.58 mmol, 58% for 2 steps) (MeOH/DCM = 1:50); Mp 285.5 – 286.7 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.40 (d, *J* = 9.1 Hz, 1H), 8.26 (d, *J* = 9.2 Hz, 1H), 8.01 (s, 1H), 7.98 (s, 1H), 7.73 (s, 1H), 6.56 (s, 2H), 4.94 (s, 3H), 4.19 (s, 3H), 4.06 (s, 3H), 4.01 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.60, 150.15, 148.73, 147.31, 139.13, 130.47, 129.70, 129.50, 125.57, 121.29, 118.23, 114.36, 109.23, 109.09, 107.59, 107.10, 104.44, 104.30, 57.46, 55.80, 55.62, 51.83; IR (thin film, cm^{-1}): 3079, 2894, 2866, 1671, 1587, 1463, 865, 820, 753; HRMS (ESI): *m/z* Calcd. for $C_{22}H_{20}NO_5$ [M-Cl]$^+$378.1341, Found 378.1343.

10-Isopropoxysanguinarine (**10**): Red solid (274 mg, 0.66 mmol, 66% for 2 steps) (MeOH/DCM = 1:60); Mp 272.3 – 274.1 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.44 (d, *J* = 9.2 Hz, 1H), 8.17 (d, *J* = 9.3 Hz, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.66 (s, 1H), 6.55 (s, 2H), 6.32 (s, 2H), 5.06 – 4.98 (m, 1H), 4.83 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.25, 149.25, 148.29, 147.88, 147.41, 139.59, 130.85, 130.72, 129.63, 125.76, 121.25, 119.57, 114.86, 108.94, 106.98, 104.58, 104.28, 103.74, 102.28, 73.33, 51.54, 21.33; IR (thin film, cm^{-1}): 3112, 2906, 2870, 1644, 1535, 1432, 1352, 811, 749; HRMS (ESI): *m/z* Calcd. for $C_{23}H_{20}NO_5$ [M-Cl]$^+$390.1341, Found 390.1346.

5. Protocols for screening of cytotoxic activities

MCF-7:

Cell culture conditions (10% FBS+89% MEM+1% double antibody)

Prepare the cell suspension, according to the cell 4000/100 μL/well, seed it in a 96-well clear-bottom cell culture plate, place it in an incubator (incubator environment: 37 °C, 5% CO_2), and culture it for 24 hours. Placed in an incubator for 24 h after administration, added MTT, and read the absorbance value in a microplate reader after 4 h. Detection wavelength 570 nm, reference wavelength 630 nm. Inhibition rate% = [1-(570 nm OD value of administration group-630 nm OD value)/(570 nm OD value of Control group - 630 nm OD value of Control group)] × 100%.

A549:

Cell culture conditions (10% FBS+89% RPMI1640+1% double antibody)

Prepare the cell suspension, according to the cell 3000/100 μL/well, seed it in a 96-well clear-bottom cell culture plate, place it in an incubator (incubator environment: 37 °C, 5% CO_2), and culture it for 24 hours. Placed in an incubator for 24 h after administration, added MTT, and read the absorbance value in a microplate reader after 4 h. Detection wavelength 570 nm, reference wavelength 630 nm. Inhibition rate% = [1-(570 nm OD value of administration group-630nmOD value)/(570 nm OD value of Control group – 630 nm OD value of Control group)] × 100%.

K562:

Cell culture conditions (10% FBS+89% IMDM+1% double antibody)

Prepare the cell suspension, according to the cell 3000/100 μL/well, seed it in a 96-well clear-bottom cell culture plate, place it in an incubator (incubator environment: 37° C, 5% CO_2), and culture it for 24 hours. Placed in an incubator for 24h after administration, added MTT, and read the absorbance value in a microplate reader after 4 h. Detection wavelength 450 nm. Inhibition rate%=[(Ac-As)/(Ac-Ab)] × 100%

6. Detection of apoptosis by Annexin-V FITC/PI double staining

Material: the culture conditions of K562 cells were RPMI-1640 + 10% FBS, cultured in an incubator at 37 °C, 5% CO_2, and saturated humidity.

Main reagents and consumables: 6 well cell culture plate (Corning Incorporated 3516, USA); Annexin V-FITC/PI Apoptosis Detection Kit (KGA105, Jiangsu KGI Biotechnology Co., Ltd., China)

Main instruments and equipment: flow cytometer (BECKMAN COULTER CytoFLEX)

Method:

1. Digest and inoculate the cells in the logarithmic growth phase into 6-well plates, add the corresponding transfection medium according to the group settings, and set up a negative control group at the same time; 2. Digest and collect cells with 0.25% trypsin (without EDTA); 3. Wash the cells twice with PBS (centrifugation at 1000 rpm, 5 min) to collect 5 ×105 cells; 4. Add 500 μL of Binding Buffer to suspend the cells; 5. After adding 5 μL Annexin V-FITC and mixing, add 5 μL Propidium Iodide and mix well; 6. At room temperature, in the dark, react for 5–15 min; use flow cytometry to detect cell apoptosis.

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Keywords: collective total synthesis • benzo[*c*]phenanthridine alkaloids • transition metal catalysis • pot economy • cytotoxic activity

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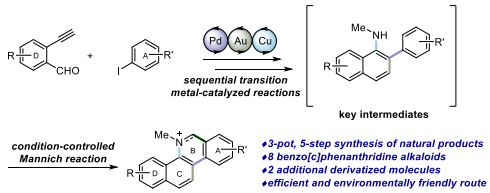
Collective Total Syntheses of Benzo[*c*]phenanthridine Alkaloids via A Sequential Transition Metal-Catalyzed Pot-Economy Approach



Collective total syntheses of ten benzo[*c*]phenanthridines were achieved based on construction of rings C and B through sequential transition metal-catalyzed reactions and flexible condition-controlled Mannich reaction via 3 pots in 25-34% yields, which provided an efficient route to benzo[*c*]phenanthridines in a pot-economy approach. The exploration of the cytotoxic activity and the verification of the mechanism indicated that benzo[*c*]phenanthridines may serve as the potential anticancer lead compounds.

Institute and/or researcher Twitter usernames: ((optional))