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TOTAL SYNTHESIS OF THE BENZO[*c*]PHENANTHRIDINE ALKALOIDS, TERIHANINE AND ISOTERIHANINE, AND THEIR ANTITUMOR ACTIVITY

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This paper is dedicated to Professor Victor Sniekus for his 77th birthday.

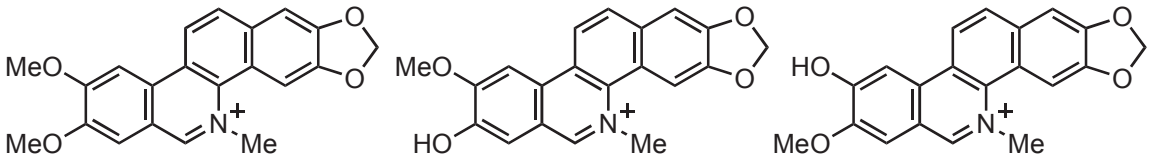
Abstract – A new total synthesis of terihanine (**2a**) and isoterihanine (**2b**) was established by our new bond formation between the C4b and N5 positions of the benzo[*c*]phenanthridine ring based on a microwave-assisted thermal electrocyclic reaction of 2-cycloalkenylbenzaldoxime as an aza 6π-electron system. In addition, the antitumor activity of these synthesized compounds, including nitidine and nornitidine was evaluated in HCT-116 cells.

INTRODUCTION

Fully aromatized quaternary benzo[*c*]phenanthridine alkaloids occur naturally in Rutaceous and Papaveraceous plants.[1] Among these alkaloids, nitidine (**1**), fagaronine, and NK109 (7-hydroxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium hydrogensulfate), have attracted the interest of chemists due to their important pharmacologic properties.[2] NK109, the quarternary base of isodecarine, is a promising topoisomerase inhibitor.[2,3] NK314, exhibiting significant antitumor activity against drug-resistant human tumor cell lines, is a synthetic benzo[*c*]phenanthridine fused with a pyrrolidine ring at the N5-C6 positions that is now in entered clinical trials.[3,4]

Many synthetic approaches to the benzo[*c*]phenanthridine nucleus have been clarified and summarized in excellent reviews.[1,5] In 1984, a new phenolic benzo[*c*]phenanthridine alkaloid, oxyterihanine was isolated from *Xanthoxylum nitidum* (Japanese name: teriha-zansho).[6] To determine the structure of oxyterihanine, the first total synthesis of terihanine (**2a**) and isoterihanine (**2b**) as biogenetic precursors of the

oxy-quaternary base was achieved by Ishikawa and co-workers in 1987 using a Bischler-Napieralski reaction.[7] In 2000, terihanine (**2a**) was isolated from the bark of *Zanthoxylum nitidum* for the first time by the same group.[8] Subsequently, a mixture of terihanine (**2a**) and isoterihanine (**2b**) was discovered in *Zanthoxylum ovalifolium* in 2006 by Waterman and co-workers (Figure 1).[9]



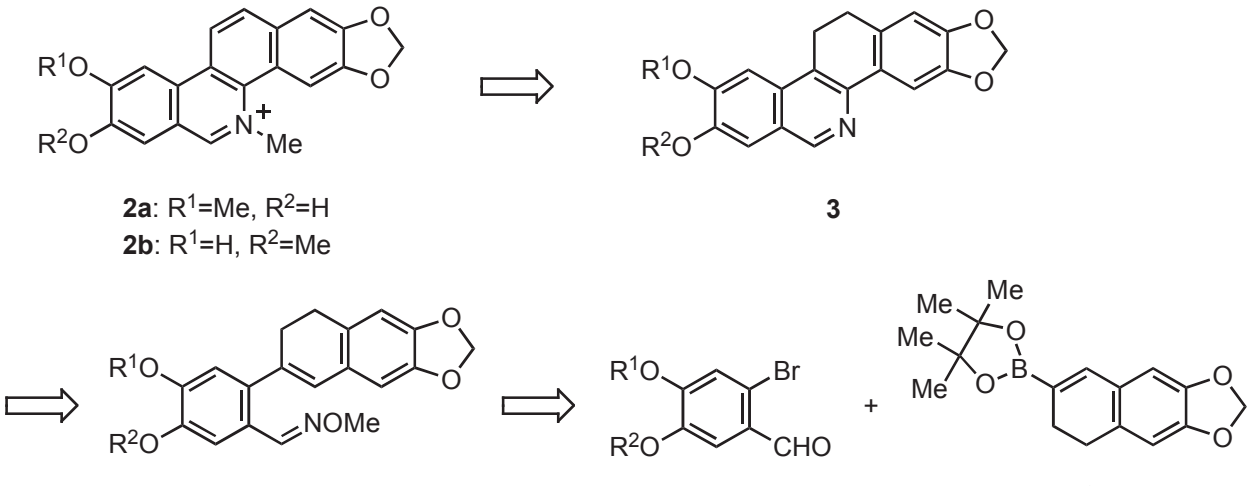
nitidine (**1**)
topoisomerases I/II inhibitor
antimalarial activity

terihanine (**2a**)

isoterihanine (**2b**)

Figure 1

Our research program is aimed at developing synthetic strategies for bioactive nitrogen-containing fused-heteroaromatic compounds including natural products based on a thermal electrocyclic reaction either a 6π- or an aza 6π-electron system involving an aromatic or heteroaromatic double bond in principle.[10] We recently reported the total synthesis of furoisoquinoline,[11] phenanthridine,[12] β-carboline,[13] azaanthraquinone,[14] benzo[*c*]phenanthridine,[15] and indoloquinoline[16] alkaloids by the construction of fused pyridine ring systems using a microwave-assisted[17] thermal electrocyclic reaction of an aza 6π-electron system. In this report, we describe the new total synthesis of two phenolic benzo[*c*]phenanthridine alkaloids, terihanine (**2a**) and isoterihanine (**2b**), using our methodology,[10-16] and an evaluation of the antitumor activity in HCT-116 cells compared with nitidine (**1**).



2a: R^1=Me, R^2=H
2b: R^1=H, R^2=Me

3

4

5

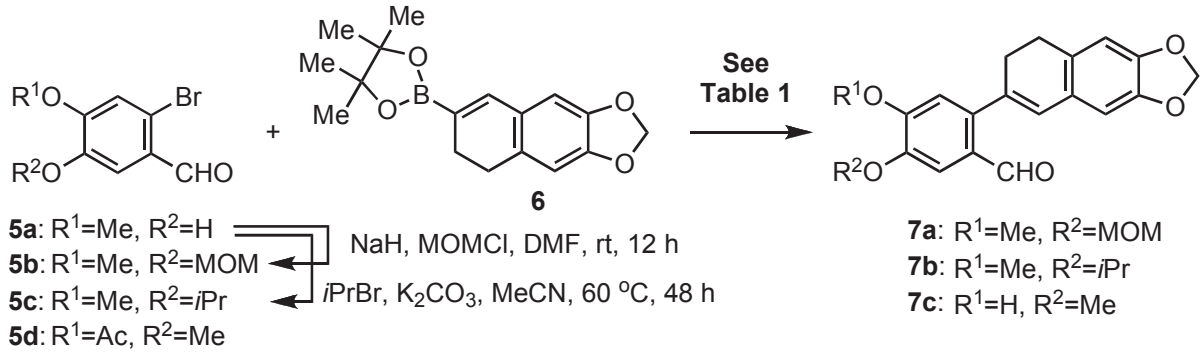
6

Scheme 1

RESULTS AND DISCUSSION

As outlined in Scheme 1, our synthetic plan was to design a 11,12-dihydrobenzophenanthridine

framework **3**, which would be derived from a 2-cycloalkenylbenzaldoxime methyl ether **4** through our new bond formation between the C4b and N5 positions of the benzo[*c*]phenanthridine ring[5] by a microwave-assisted aza-electrocyclic reaction.[15] A 2-cycloalkenylbenzaldoxime methyl ether **4** would be provided by the Suzuki-Miyaura reaction of 2-bromobenzaldehyde **5** with 2-(6,7-methylenedioxy-3,4-dihydronephthyl)boronic acid pinacol ester **6**. After dehydrogenation of **3**, the conversion from norbenzo[*c*]phenanthridine to quaternary base **2** would be performed according to the reported procedures.[7]

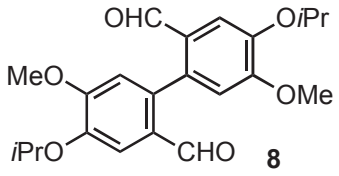


Scheme 2

Table 1. Synthesis of 2-cycloalkenylbenzaldehydes 7a-c

Run	SM	Pd catalyst	Reagent	MW	Products	
					No.	Yield (%)
1	**5b**	$PdCl_2$(dppf)	K_2CO_3	–	**7a**	13
2	**5c**	$PdCl_2$(dppf)	K_2CO_3	–	**7b**	34 (20)[a]
3	**5c**	$PdCl_2$(dppf)	K_2CO_3	+	**7b**	22 (22)[a]
4	**5c**	$Pd(PPh_3)_4$	Na_2CO_3	–	**7b**	27 –[a]
5	**5c**	$Pd(PPh_3)_4$	CsF	–	**7b**	15 (26)[a]
6	**5c**	$PdCl_2(PPh_3)_2$	NaOMe	–	**7b**	13 –[a]
7	**5c**	$PdCl_2(PPh_3)_2$	K_2CO_3	–	**7b**	24 (33)[a]
8	**5c**	$Pd(OAc)_2$	$AsPh_3$	–	**7b**	6 (5)[a]
9	**5d**	$PdCl_2$(dppf)	K_2CO_3	–	**7c**	70

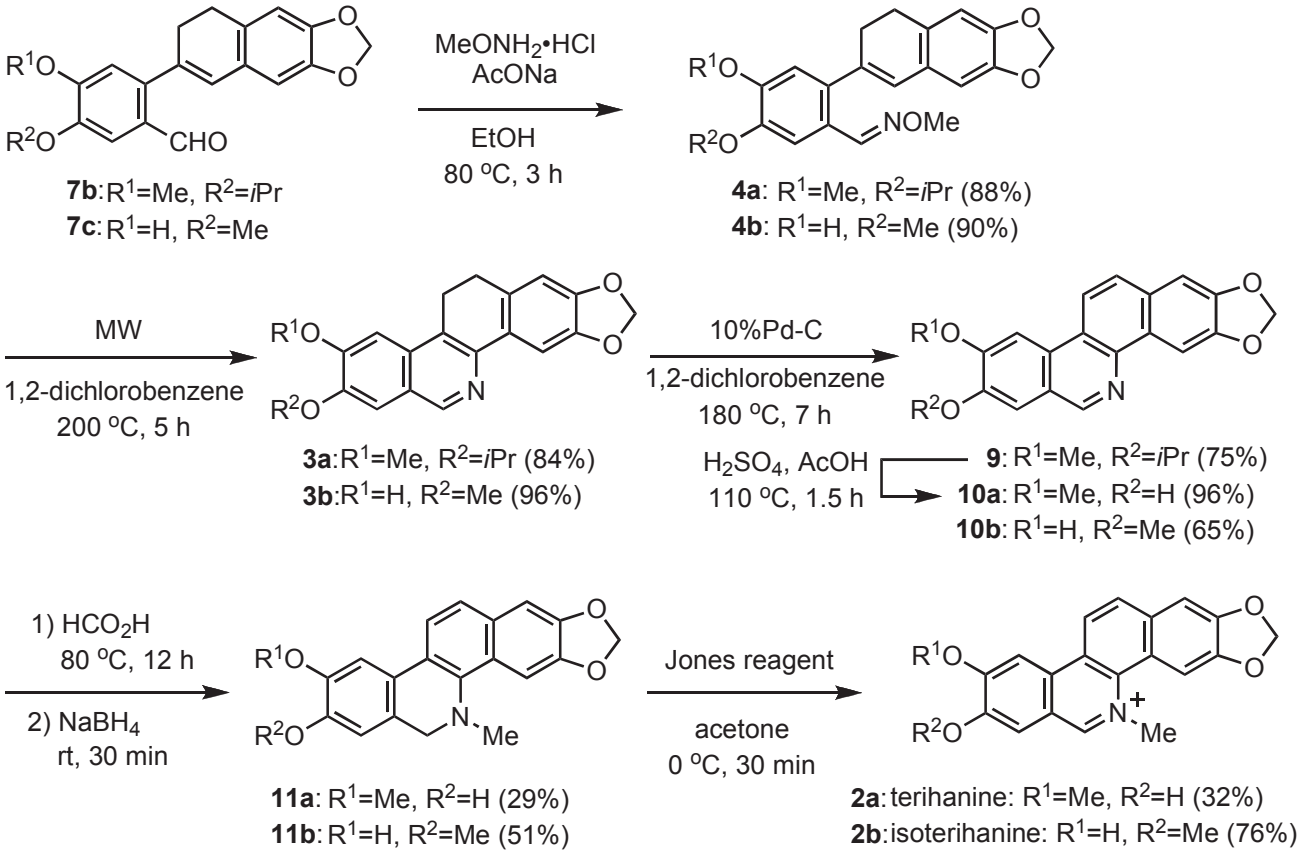
a: yield (%) of bisbenzaldehyde **8**



8

To synthesize the required 2-cycloalkenylbenzaldoxime methyl ether **4**, we initially attempted a synthesis

of 2-cycloalkenylbenzaldehyde **7** by the Suzuki-Miyaura reaction[18] of *O*-protected benzaldehyde **5** with 2-(6,7-methylenedioxy-3,4-dihydronaphthyl)boronic acid pinacol ester (**6**) in the presence of a palladium catalyst (Scheme 2, Table 1). Using *O*-methoxymethyl (MOM) 2-bromobenzaldehyde **5b** gave the 2-cycloalkenylbenzaldehyde **7a** in only a low yield (run 1). The benzaldehyde **5c**, which was converted from the MOM group into the isopropyl group, was treated with pinacol ester **6** under the same conditions. As a result, product **7b** along with bisbenzaldehyde **8** (20%) was obtained in a 34% yield (run 2). Despite performing this reaction under microwave irradiation conditions[12] the yield of **7b** was not increased (run 3). Although we attempted other conditions (palladium catalysts and additive parameters) in further detail, the yield of **7b** was not improved (runs 4-8). The cross-coupling reaction of 4-acetoxy-2-bromobenzaldehyde **5d** with pinacol ester **6** afforded the deacetylated 2-cycloalkenylbenzaldehyde **7c** in moderate yield without byproducts (run 9). A reason for the low reactivity of **5c** with **6** on the Suzuki-Miyaura reaction is unclear (Table 1).



Scheme 3

Treatment of the obtained 2-cycloalkenylbenzaldehyde **7b** and **7c** with hydroxylamine methyl ether gave benzaldoxime **4a** (88%) and **4b** (90%), which was subjected to the microwave-assisted thermal aza-electrocylic reaction[11-16] in 1,2-dichlorobenzene to yield the 11,12-dihydrobenzophenanthridine **3a**

(84%) and **3b** (96%), respectively. Subsequently, the 11,12-dihydrobenzophenanthridine **3a** and **3b** were oxidized by refluxing with 10% Pd-C in 1,2-dichrolobenzene to give *O*-isopropyl norterihanine (**9**: 75%) and norisoterihanine (**10b**: 65%). The *O*-isopropyl group of **9** was cleaved with H_2SO_4 in AcOH at 110 ºC to produce norterihanine (**10a**: 96%). Finally, conversion of norterihanine (**10a**) and norisoterihanine (**10b**) to terihanine (**2a**) and isoterihanine (**2b**), respectively, was achieved according to the procedures of the Ishikawa group.[19] Namely, treatment of **10a**,**b** with formic acid followed by reduction with $NaBH_4$ gave the *N*-methylated 5,6-dihydrobenzophenanthridines **11a**,**b**, which were oxidized by Jones reagent followed by treatment with diluted hydrochloric acid to yield terihanine (**2a**) and isoterihanine (**2b**). Physical and spectroscopic data of our synthetic terihanine (**2a**) and isoterihanine (**2b**) were identical with those of authentic samples provided by Ishikawa[7] in all respects.

The antitumor activity of the synthesized benzophenanthridines (nitidine (**1**), terihanine (**2a**), isoterihanine (**2b**), and three compounds of their nor-type was assessed in HCT-116 cells[20] (Table 2). At a dose of 10 μM, nitidine (**1**) and isoterihanine (**2b**) inhibited the tumor cell viability to 33.5% and 43.7%, respectively, whereas the other benzophenanthridines had weak antitumor activity at the same dose. The correlation between the structure and antitumor activity will be reported elsewhere in due course.

Table 2. Effect of benzo[*c*]phenanthridines on HCT-116 cells viability

Benzophenanthridines	Cell viability (%) on 10μM
nornitidine	81.4
norterihanine (**10a**)	79.1
norisoterihanine (**10b**)	72.7
nitidine (**1**)	33.5
terihanine (**2a**)	74.7
isoterihanine (**2b**)	43.7

CONCLUSION

In conclusion, a new total synthesis of the phenolic 8,9-disubstituted benzo[*c*]phenanthridine alkaloids terihanine (**2a**) and isoterihanine (**2b**) was achieved by our new bond formation between the C4b and N5 positions of the tetracyclic ring based on the microwave-assisted thermal azaelectrocyclic reaction. These synthesized compounds including nitidine and nornitidine were evaluated for antitumor activity on HCT-116 cells. Nitidine and isoterihanine at a dose of 10 μM inhibited tumor cell viability to 33.5% and 43.7% of the tumor cells viability, respectively.

EXPERIMENTAL

All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer

chromatography was performed with Silica gel $60PF_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60N (63-210 μm, KANTO CHEMICAL Co. Ltd.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). NMR spectra was measured with $CDCl_3$ unless otherwise noted. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.7). Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and technologies DuraScop. Low and high resolution mass spectra (HRMS) were recorded on JEOL JMS-700 spectrometers by direct inlet system.

2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-5-isopropoxy-4-methoxybenzaldehyde (7b)

A mixture of 2-bromobenzaldehyde **5c** (50 mg, 0.18 mmol), naphthylboronic acid pinacol ester **6**[15] (82 mg, 0.28 mmol), K_2CO_3 (76 mg, 0.55 mmol), and $PdCl_2(PPh_3)_2$ (11 mg, 0.014 mmol) in anhyd. MeOH (8 mL) and DMF (2 mL) was stirred at 80 ºC for 1 h under N_2 atmosphere. The reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc-hexane (1:19 v/v) as an eluent to give the 2-naphthylbenzaldehyde **7b** (23 mg, 34%), mp 108–109 ºC (EtOAc-hexane). IR (ATR) ν: 1673 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.41 (6H, d, *J*=6.0 Hz), 2.66 (2H, t, *J*=8.0 Hz), 2.91 (2H, t, *J*=8.0 Hz), 3.94 (3H, s), 4.67 (1H, sept, *J*=6.0 Hz), 5.93 (2H, s), 6.29 (1H, s), 6.62 (1H, s), 6.70 (1H, s), 6.81 (1H, s), 7.48 (1H, s), 10.08 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.9 (2C), 28.4, 29.8, 56.2, 71.3, 100.9, 107.3, 108.4, 110.5, 112.4, 127.1, 127.8, 128.7, 130.5, 133.8, 142.1, 146.2, 146.8, 154.7, 190.7. MS (EI) *m/z*: 366 (M^+). HRMS (EI) calcd for $C_{22}H_{22}O_5$ 366.1467; found 366.1478.

2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-4-hydroxy-5-methoxybenzaldehyde (7c)

4-Acetoxy-2-bromo-5-methoxybenzaldehyde (**5d**) (167 mg, 0.61 mmol), naphthylboronic acid pinacol ester **6**[15] (200 mg, 0.67 mmol), K_2CO_3 (276 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (24 mg, 0.03 mmol) in anhyd. MeOH (8 mL) and DMF (2 mL) were used in the same procedure as above to give the 2-naphthylbenzaldehyde **7c** (138 mg, 70%), mp 225-228 ºC (EtOAc-hexane). IR (ATR) ν: 3143, 1654 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.64 (2H, t, *J*=7.9 Hz), 2.90 (2H, t, *J*=7.9 Hz), 3.98 (3H, s), 5.94 (2H, s), 6.12 (1H, s), 6.26 (1H, s), 6.62 (1H, s), 6.70 (1H, s), 6.92 (1H, s), 7.48 (1H, s), 10.07 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.3, 29.5, 56.2, 100.9, 107.3, 108.4, 108.9, 113.7, 127.0, 127.8, 128.7, 130.8, 133.3, 143.0, 146.0, 146.2, 146.8, 150.6, 190.7. MS (EI) *m/z*: 324 (M^+). HRMS (EI) calcd for $C_{19}H_{16}O_5$ 324.0998; found 324.0978.

2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-5-isopropoxy-4-methoxybenzaldehyde *O*-methyloxime (4a)

A mixture of 2-naphthylbenzaldehydes **7b** (194 mg, 0.53 mmol), $MeONH_2$•HCl (80 mg, 0.95 mmol), and AcONa (78 mg, 0.95 mmol) in EtOH (10 mL) was stirred at 80 ºC for 3 h. After removal of solvent, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using EtOAc-hexane (1:19 v/v) as an eluent to give the oxime ether **4a** (185 mg, 88%), mp 86-87 ºC (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.41 (6H, d, *J*=6.0 Hz), 2.55 (2H, t, *J*=8.1 Hz), 2.86 (2H, t, *J*=8.1 Hz), 3.88 (3H, s), 3.94 (3H, s), 4.66 (1H, sep, *J*=6.0 Hz), 5.92 (2H, s), 6.24 (1H, s), 6.61 (1H, s), 6.68 (1H, s), 6.72 (1H, s), 7.41 (1H, s), 8.23 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.0 (2C), 28.4, 29.6, 55.9, 61.8, 71.2, 100.8, 107.1, 108.3, 110.8, 111.9, 121.7, 128.1, 128.4, 128.5, 135.7, 136.8, 146.0, 146.3, 146.4, 147.9, 151.4. MS (EI) *m*/*z*: 395 (M^+). HRMS (EI) calcd for $C_{23}H_{25}NO_5$ 395.1733; found 395.1740.

2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-4-hydroxy-5-methoxybenzaldehyde *O*-methyloxime (4b)

2-Naphthylbenzaldehyde **7c** (163 mg, 0.50 mmol), $MeONH_2$•HCl (65 mg, 0.78 mmol), and AcONa (64 mg, 0.78 mmol) in EtOH (10 mL) were used in the same procedure as above to give the oxime ether **4b** (160 mg, 90%), mp 133-134 ºC (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.52 (2H, t, *J*=8.3 Hz), 2.84 (2H, t, *J*=8.3 Hz), 3.94 (3H, s), 3.97 (3H, s), 5.78 (1H, s), 5.92 (2H, s), 6.21(1H, s), 6.60 (1H, s), 6.67 (1H, s), 6.82 (1H, s), 7.38 (1H, s), 8.25 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.4, 29.4, 56.1, 61.8, 100.8, 107.2, 107.7, 108.3, 113.6, 121.3, 128.1, 128.5, 128.8, 135.3, 137.5, 145.8, 146.0, 146.4, 147.0, 148.2. MS (EI) *m*/*z*: 353 (M^+). HRMS (EI) calcd for $C_{20}H_{19}NO_5$ 353.1263; found 353.1234.

11,12-Dihydro-8-isopropoxy-9-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (3a)

A mixture of oxime ether **4a** (52 mg, 0.13 mmol) in 1,2-dichlorobenzene (1.5 mL) was stirred at 200 ºC for 5 h with MW-irradiation under N_2 atmosphere. After removal of solvent, the residue was purified by column chromatography (silica gel) using EtOAc (1:19 v/v) as an eluent to give the 11,12-dihydrobenzophenanthridine **3a** (40 mg, 84%), mp 201-202 ºC (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.48 (6H, d, *J*=6.1 Hz), 2.95 (2H, t, *J*=7.7 Hz), 3.19 (2H, d, *J*=7.7 Hz), 4.03 (3H, s), 4.76 (sep, *J*=6.1 Hz), 5.98 (2H, s), 6.75 (1H, s), 7.21 (1H, s), 7.89 (1H, s), 8.92 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.8 (2C), 23.5, 28.0, 56.0, 71.1, 100.9, 101.4, 105.6, 107.9, 108.9, 122.8, 123.8, 126.5, 130.9, 131.0, 147.0, 147.3, 147.8, 147.9, 150.5, 154.1. MS (EI) *m*/*z*: 363 (M^+). HRMS (EI) calcd for $C_{22}H_{21}NO_4$ 363.1471; found 363.1480.

11,12-Dihydro-9-hydroxy-8-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (3b)

Oxime ether **4b** (80 mg, 0.23 mmol) in 1,2-dichlorobenzene (2.5 mL) with MW-irradiation were used in the same procedure as above to give the 11,12-dihydrobenzophenanthridine **3b** (70 mg, 96%), mp

246-248 ºC (EtOAc-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.93 (2H, t, *J*=7.5 Hz), 3.16 (2H, t, *J*=7.5 Hz), 4.08 (3H, s), 5.98 (2H, s), 6.24 (1H, br s), 6.74 (1H, s), 7.21 (1H, s), 7.41 (1H, s), 7.88 (1H, s), 8.95 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 23.4, 28.0, 56.1, 100.9, 104.8, 105.6, 105.7, 107.9, 122.8, 123.6, 129.7, 131.2, 131.6, 144.7, 147.0, 147.2, 147.3, 148.3, 149.5. MS (EI) *m/z*: 321 (M^+). HRMS (EI) calcd for $C_{19}H_{15}NO_4$ 321.1001; found 321.1014.

8-Isopropoxy-9-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (9)

A stirred mixture of 11,12-dihydrobenzophenanthridine **3a** (40 mg, 0.11 mmol) and 10% Pd-C (60 mg) in 1,2-dichlorobenzene (3 mL) were heated at reflux for 7 h. After removal of solvent, the residue was purified by column chromatography using the EtOAc-hexane (1:9 v/v) as an eluent to give the benzophenanthridine **9** (30 mg, 75%), mp 220-222 ºC ($CHCl_3$-hexane). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.52 (6H, d, *J*=5.8 Hz), 4.14 (3H, s), 4.82 (1H, sep, *J*=5.8 Hz), 6.13 (2H, s), 7.26 (1H, s), 7.42 (1H, s), 7.84 (1H, d, *J*=8.2 Hz), 7.90 (1H, s), 8.31 (1H, d, *J*=8.2 Hz), 8.71 (1H, s), 9.21 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 21.9 (2C), 56.2, 71.3, 101.3, 102.0, 102.2, 104.4, 110.2, 118.2, 119.9, 122.2, 126.4, 128.6, 129.2, 129.5, 140.5, 148.0, 148.2, 148.4, 149.7, 153.9. MS (EI) *m/z*: 361 (M^+). HRMS (EI) calcd for $C_{22}H_{19}NO_4$ 361.1314; found 361.1301.

8-Hydroxy-9-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (10a)

A mixture of benzophenanthridine **9** (20 mg, 0.055 mmol) and H_2SO_4 (20 μL, 0.38 μmol) in AcOH (10 mL) was stirred at 110 ºC for 1.5 h. The mixture was diluted with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc-hexane (1:9 v/v) as an eluent to give norterihanine (**10a**) (17 mg, 96%), mp 286-288 ºC ($CHCl_3$-hexane). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.08 (3H, s), 6.19 (2H, s), 7.47 (1H, s), 7.49 (1H, s), 7.93 (1H, d, *J*=8.6 Hz), 8.14 (1H, s), 8.52 (1H, s), 8.60 (1H, d, *J*=8.6 Hz), 9.19 (1H, s), 10.00 (1H, br s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 57.3, 80.3, 102.1, 102.6, 103.7, 105.7, 112.0, 120.3, 121.1, 123.4, 127.4, 128.5, 129.5, 130.2, 140.2, 148.9, 149.1, 150.8, 154.0. MS (EI) *m/z*: 319 (M^+); HRMS (EI) calcd for $C_{19}H_{13}NO_4$ 319.0845; found 319.0819.

9-Hydroxy-8-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (10b)

A mixture of 11,12-dihydrobenzophenanthridines **3b** (80 mg, 0.25 mmol) in the presence of 10% Pd-C (120 mg) in 1,2-dichlorobenzene (3 mL) was stirred at 180 ºC for 7 h. After removal of solvent, the residue was purified by column chromatography using EtOAc-hexane (1:9 v/v) as an eluent to give norisoterihanine **10b** (51 mg, 65%), mp 271-273 ºC ($CHCl_3$-hexane). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.99 (3H, s), 6.20 (2H, s), 7.49 (1H, s), 7.68 (1H, s), 7.91 (1H, d, *J*=8.9 Hz), 8.01 (1H, s), 8.32 (1H, d, *J*=8.9 Hz), 8.52 (1H, s), 9.25 (1H, s), 10.33 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 55.8, 101.1, 101.5, 104.5, 105.6, 108.2, 118.7, 119.3, 121.5, 126.3, 128.4, 128.4, 129.2, 139.5, 147.9, 148.0, 149.2, 150.1,

151.5. MS (EI) *m/z*: 319 (M^+). HRMS (EI) calcd for $C_{19}H_{13}NO_4$ 319.0845; found 319.0856.

5,6-Dihydro-8-hydroxy-9-methoxy-*N*-methyl-2,3-methylenedioxybenzo[*c*]phenanthridine (11a)

A mixture of norterihanine (**10a**) (26 mg, 0.081 mmol) in HCO_2H (2.5 mL) was stirred for 12 h at 80 ºC, and then $NaBH_4$ (288 mg, 7.61 mmol) was added to the solution at rt. After being stirred at rt for 30 min, the mixture was adjusted to weakly alkaline with aqueous 10% NaOH solution, and then the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and brine, dried over K_2CO_3, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5 g) using EtOAc-hexane (1:9, v/v) as an eluent to give the 5,6-dihydro-*N*-methylbenzophenanthridine **11a** (8 mg, 29%), which was used without any further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.59 (3H, s), 4.00 (3H, s), 4.10 (3H, s), 5.68 (1H, br s), 6.05 (2H, s), 6.85 (1H, s), 7.11 (1H, s), 7.28 (1H, s), 7.49 (1H, d, *J*=8.6 Hz), 7.66 (1H, s), 7.68 (1H, d, *J*=8.6 Hz). MS (EI) *m/z*: 335 (M^+).

5,6-Dihydro-9-hydroxy-8-methoxy-*N*-methyl-2,3-methylenedioxybenzo[*c*]phenanthridine (11b)

Norisoterihanine (**10b)** (15 mg, 0.09 mmol), HCO_2H (3 mL) and $NaBH_4$ (314 mg, 8.3 mmol) were used in the same procedure as above to give the 5,6-dihydro-*N*-methylbenzophenanthridine **11b** (15 mg, 51%), mp 221-223 ºC (EtOAc-hexane) (Lit.,[7] mp 235-242 ºC). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.60 (3H, s), 3.96 (3H, s), 4.12 (2H, s), 5.60 (1H, br s), 6.05 (2H, s), 6.78 (1H, s), 7.11 (1H, s), 7.38 (1H, s), 7.49 (1H, d, *J*=8.6 Hz), 7.65 (1H, s), 7.66 (1H, d, *J*=8.6 Hz). MS (EI) *m/z*: 335 (M^+). HRMS (EI) calcd for $C_{20}H_{17}NO_4$ 335.1158; found 335.1163.

Terihanine (2a) chloride

Jones reagent (50 μL) was added to a stirred solution of 5,6-dihydro-*N*-methylbenzophenanthridine **11a** (12 mg, 0.036 mmol) in acetone (9 mL) under cooling with ice. The mixture was stirred at the same temperature for 30 min, and basified with aqueous 10% NaOH solution, and then the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and brine, dried over K_2CO_3, and concentrated under reduced pressure. The residue was dissolved in a small amount of $CHCl_3$, and then diluted HCl was added dropwise to the solution under cooling with ice. The resulting precipitates were collected by filtration to give terihanine (**2a**) chloride (4 mg, 32%), mp 246-248 ºC (MeOH-Et_2O) (Lit.,[7] mp 280 ºC, melted at 240-245 ºC and then solidified again) (Lit.,[8] mp 271-278 ºC, melted at 242-245 ºC and then solidified again). ^{1}H-NMR (300 MHz, CF_3COOD) δ: 4.47 (3H, s), 5.07 (3H, s), 6.34 (2H, s), 7.61 (1H, s), 7.93 (1H, s), 8.17 (1H, s), 8.19 (1H, d, *J*=8.6 Hz), 8.31 (1H, s), 9.39 (1H, s). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.21 (3H, s), 4.85 (3H, s), 6.32 (2H, s), 7.75 (2H, s), 8.25 (1H, d, *J*=8.6 Hz), 8.28 (1H, s), 8.33 (1H, s), 8.86 (2H, d, *J*=8.6 Hz), 9.86 (1H, s), 11.11 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 51.3, 57.2, 102.7, 103.5, 104.6, 105.8, 119.3, 119.8, 120.1, 124.3, 130.0, 131.0, 132.1, 132.3, 148.4, 148.7, 150.3, 151.4, 158.4. TOFMS (ESI) calcd for $C_{20}H_{16}NO_4$ 334.1074; found 334.1057.

Isoterihanine (2b) chloride

5,6-Dihydro-*N*-methylbenzophenanthridine **11b** (18 mg, 0.054 mmol), and Jones reagent (80 μL) in acetone (13 mL) were used in the same procedure as above to give isoterihanine (**2b**) chloride (15 mg, 76%), mp 230-232 ºC (MeOH-Et_2O) (Lit.,[7] mp 243-247 ºC). ^{1}H-NMR (300 MHz, CF_3COOD) δ: 4.23 (3H, s), 4.97 (3H, s), 6.23 (2H, s), 7.50 (1H, s), 7.69 (1H, s), 8.07 (1H, s), 8.17 (1H, d, *J*=8.6 Hz), 8.30 (1H, s), 8.47 (1H, d, *J*=8.6 Hz), 9.30 (1H, s). ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 4.03 (3H, s), 4.82 (3H, s), 6.30 (2H, s), 7.70 (1H, s), 7.86 (1H, s), 8.18 (1H, s), 8.19 (1H, d, *J*=9.2 Hz), 8.24 (1H, s), 8.51 (1H, d, *J*=9.2 Hz), 9.71 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 51.3, 56.5, 102.9, 104.6, 105.9, 106.5, 109.7, 118.8, 118.9, 120.2, 123.6, 130.2, 132.4, 132.5, 132.5, 148.6, 148.9, 151.3, 151.4, 158.1. TOFMS (ESI) calcd for $C_{20}H_{16}NO_4$ 334.1074; found 334.1088.

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