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 quaternary 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.5 In 1984, a new phenolic benzo[c]phenanthridine alkaloid, oxyterihanane was isolated from Xanthoxylum nitidum (Japanese name: teriha-zansho).5 To determine the structure of oxyterihanane, 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. In 2000, terihanine (2a) was isolated from the bark of *Zanthoxylum nitidum* for the first time by the same group. Subsequently, a mixture of terihanine (2a) and isoterihanine (2b) was discovered in *Zanthoxylum ovalifolium* in 2006 by Waterman and co-workers (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. We recently reported the total synthesis of furoisoquinoline, phenanthidine, β-carboline, azaanthraquinone, benzo[c]phenanthidine, and indoloquinoline alkaloids by the construction of fused pyridine ring systems using a microwave-assisted thermal electrocyclic reaction of an aza 6π-electron system. In this report, we describe the new total synthesis of two phenolic benzo[c]phenanthidine alkaloids, terihanine (2a) and isoterihanine (2b), using our methodology and an evaluation of the antitumor activity in HCT-116 cells compared with nitidine (1).

RESULTS AND DISCUSSION
As outlined in Scheme 1, our synthetic plan was to design a 11,12-dihydrobenzophenanthidine
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 ring5 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-dihydropinephyl)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](image)

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

<table>
<thead>
<tr>
<th>Run</th>
<th>SM</th>
<th>Pd catalyst</th>
<th>Reagent</th>
<th>MW</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5b</td>
<td>PdCl2(dppf)</td>
<td>K2CO3</td>
<td>−</td>
<td>7a 13</td>
</tr>
<tr>
<td>2</td>
<td>5c</td>
<td>PdCl2(dppf)</td>
<td>K2CO3</td>
<td>−</td>
<td>7b 34 (20)a</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>PdCl2(dppf)</td>
<td>K2CO3</td>
<td>+</td>
<td>7b 22 (22)a</td>
</tr>
<tr>
<td>4</td>
<td>5c</td>
<td>Pd(PPh3)4</td>
<td>Na2CO3</td>
<td>−</td>
<td>7b 27 −a</td>
</tr>
<tr>
<td>5</td>
<td>5c</td>
<td>Pd(PPh3)4</td>
<td>CsF</td>
<td>−</td>
<td>7b 15 (26)a</td>
</tr>
<tr>
<td>6</td>
<td>5c</td>
<td>PdCl2(PPh3)2</td>
<td>NaOMe</td>
<td>−</td>
<td>7b 13 −a</td>
</tr>
<tr>
<td>7</td>
<td>5c</td>
<td>PdCl2(PPh3)2</td>
<td>K2CO3</td>
<td>−</td>
<td>7b 24 (33)a</td>
</tr>
<tr>
<td>8</td>
<td>5c</td>
<td>Pd(OAc)2</td>
<td>AsPh3</td>
<td>−</td>
<td>7b 6 (5)a</td>
</tr>
<tr>
<td>9</td>
<td>5d</td>
<td>PdCl2(dppf)</td>
<td>K2CO3</td>
<td>−</td>
<td>7c 70</td>
</tr>
</tbody>
</table>

a: yield (%) of bisbenzaldehyde 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-dihyronaphthyl)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).

\[
\begin{align*}
7b: R^1 &= \text{Me}, R^2 = \text{iPr} \\
7c: R^1 &= \text{H}, R^2 = \text{Me}
\end{align*}
\]

\[
\begin{align*}
4a: R^1 &= \text{Me}, R^2 = \text{iPr} (88\%) \\
4b: R^1 &= \text{H}, R^2 = \text{Me} (90\%)
\end{align*}
\]

\[
\begin{align*}
3a: R^1 &= \text{Me}, R^2 = \text{iPr} (84\%) \\
3b: R^1 &= \text{H}, R^2 = \text{Me} (96\%)
\end{align*}
\]

\[
\begin{align*}
9: R^1 &= \text{Me}, R^2 = \text{iPr} (75\%) \\
10a: R^1 &= \text{Me}, R^2 = \text{H} (96\%) \\
10b: R^1 &= \text{H}, R^2 = \text{Me} (65\%)
\end{align*}
\]

\[
\begin{align*}
11a: R^1 &= \text{Me}, R^2 = \text{H} (29\%) \\
11b: R^1 &= \text{H}, R^2 = \text{Me} (51\%)
\end{align*}
\]

\[
\begin{align*}
2a: \text{terihanine}: R^1 &= \text{Me}, R^2 = \text{H} (32\%) \\
2b: \text{isoterihanine}: R^1 &= \text{H}, R^2 = \text{Me} (76\%)
\end{align*}
\]

**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 H2SO4 in AcOH at 110 °C 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. Namely, treatment of 10a,b with formic acid followed by reduction with NaBH4 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 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 (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>
<thead>
<tr>
<th>Benzophenanthridines</th>
<th>Cell viability (%) on 10µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>norterihanine (10a)</td>
<td>79.1</td>
</tr>
<tr>
<td>norisoterihanine (10b)</td>
<td>72.7</td>
</tr>
<tr>
<td>nitidine (1)</td>
<td>33.5</td>
</tr>
<tr>
<td>terihanine (2a)</td>
<td>74.7</td>
</tr>
<tr>
<td>isoterihanine (2b)</td>
<td>43.7</td>
</tr>
</tbody>
</table>

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 (1H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me₄Si (δ 0.00). NMR spectra was measured with CDCl₃ 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 (13C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to CDCl₃ (δ 77.0) and DMSO-d₆ (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 6¹⁵ (82 mg, 0.28 mmol), K₂CO₃ (76 mg, 0.55 mmol), and PdCl₂(PPh₃)₂ (11 mg, 0.014 mmol) in anhyd. MeOH (8 mL) and DMF (2 mL) was stirred at 80 °C for 1 h under N₂ 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 Na₂SO₄, 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 °C (EtOAc-hexane). IR (ATR) v: 1673 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃) 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). ¹³C-NMR (75 MHz, CDCl₃) δ: 21.9 (2C), 28.4, 29.5, 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 C₂₂H₂₂O₅ 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 6¹⁵ (200 mg, 0.67 mmol), K₂CO₃ (276 mg, 2.0 mmol) and PdCl₂(PPh₃)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 °C (EtOAc-hexane). IR (ATR) v: 3143, 1654 cm⁻¹. ¹H-NMR (300 MHz, CDCl₃) 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). ¹³C-NMR (75 MHz, CDCl₃) 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 C₁₉H₁₆O₅ 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), MeONH₂•HCl (80 mg, 0.95 mmol), and AcONa (78 mg, 0.95 mmol) in EtOH (10 mL) was stirred at 80 °C for 3 h. After removal of solvent, the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na₂SO₄, 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 °C (EtOAc-hexane). ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): δ: 22.0 (2C), 28.4, 29.6, 55.9, 61.8, 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 C₂₃H₂₅NO₅ 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), MeONH₂•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 °C (EtOAc-hexane). ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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, 135.3, 137.5, 145.8, 146.0, 146.4, 147.0, 148.2. MS (EI) m/z: 353 (M⁺). HRMS (EI) calcd for C₂₂H₁₉NO₅ 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 °C for 5 h with MW-irradiation under N₂ atmosphere. After removal of solvent, the residue was purified by column chromatography (silica gel) using EtOAc-hexane (1:19 v/v) as an eluent to give the 11,12-dihydrobenzophenanthridine 3a (40 mg, 84%), mp 201-202 °C (EtOAc-hexane). ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, CDCl₃): 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 C₂₂H₂₁NO₄ 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
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 °C (CHCl₃-hexane). ¹H-NMR (300 MHz, CDCl₃): 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). ¹³C-NMR (75 MHz, DMSO-d₆): 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 C₂₂H₁₉NO₄ 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 H₂SO₄ (20 µL, 0.38 µmol) in AcOH (10 mL) was stirred at 110 °C 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 Na₂SO₄, 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 °C (CHCl₃-hexane). ¹H-NMR (300 MHz, DMSO-d₆): 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). ¹³C-NMR (75 MHz, DMSO-d₆): δ: 55.8, 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 C₁₉H₁₉NO₄ 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 °C 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 °C (CHCl₃-hexane). ¹H-NMR (300 MHz, DMSO-d₆): 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). ¹³C-NMR (75 MHz, DMSO-d₆): 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,
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 HCO₂H (2.5 mL) was stirred for 12 h at 80 °C, and then NaBH₄ (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 CHCl₃. The CHCl₃ layer was washed with water and brine, dried over K₂CO₃, 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. ¹H-NMR (300 MHz, CDCl₃): 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), HCO₂H (3 mL) and NaBH₄ (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 °C (EtOAc-hexane) (Lit., mp 235-242 °C). ¹H-NMR (300 MHz, CDCl₃): 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 C₂₀H₁₇NO₄ 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 CHCl₃. The CHCl₃ layer was washed with water and brine, dried over K₂CO₃, and concentrated under reduced pressure. The residue was dissolved in a small amount of CHCl₃, 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 °C (MeOH-Et₂O) (Lit., mp 280 °C, melted at 240-245 °C and then solidified again) (Lit., mp 271-278 °C, melted at 242-245 °C and then solidified again). ¹H-NMR (300 MHz, CF₃COOD): 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). ¹H-NMR (300 MHz, DMSO-d₆): 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). ¹³C-NMR (75 MHz, DMSO-d₆): 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 C₂₀H₁₆NO₄ 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 °C (MeOH-Et₂O) (Lit., mp 243-247 °C). 

\[\begin{align*}
\text{1H-NMR (300 MHz, CF₃COOD)} & : 4.23 (3H, s), 4.97 (3H, s), 6.23 (2H, s), 7.50 (1H, s), 7.69 (1H, s), 8.07 (1H, s), 8.17 (1H, d, J=8.6 Hz), 8.30 (1H, s), 8.47 (1H, d, J=8.6 Hz), 9.30 (1H, s). \\
\text{1H-NMR (300 MHz, DMSO-d₆)} & : 4.03 (3H, s), 4.82 (3H, s), 6.30 (2H, s), 7.70 (1H, s), 7.86 (1H, s), 8.18 (1H, s), 8.19 (1H, d, J=9.2 Hz), 8.24 (1H, s), 8.51 (1H, d, J=9.2 Hz), 9.71 (1H, s). \\
\text{13C-NMR (75 MHz, DMSO-d₆)} & : 51.3, 56.5, 102.9, 104.6, 105.9, 106.5, 109.7, 118.8, 118.9, 120.2, 123.6, 130.2, 132.4, 132.5, 132.5, 148.6, 148.9, 151.3, 151.4, 158.1. \\
\text{TOFMS (ESI) calcd for C₂₀H₁₆NO₄} & : 334.0 \text{ found 334.1088.}
\end{align*}\]

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REFERENCES AND NOTES


