# Revision of the Structure of Fagaridine Based on the Comparison of UV and NMR Data of Synthetic Compounds

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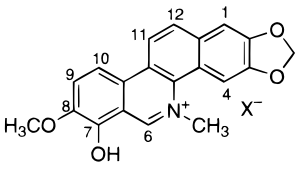
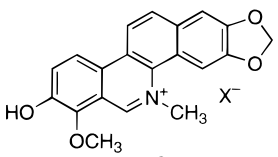
Fagaridine is a quaternary benzo[*c*]phenanthridine alkaloid, originally isolated from *Fagara xanthoxyloides* in 1973. The assigned structure of this alkaloid was 7-hydroxy-8-methoxy-5-methyl-2,3-(methylenedioxy)-benzo[*c*]phenanthridinium (**1**). We have synthesized this compound, coded NK109, aiming at a practical antitumor drug, and during synthetic studies we questioned the original assigned structure. Thus, we synthesized 8-hydroxy-7-methoxy-5-methyl-2,3-(methylenedioxy)benzo[*c*]phenanthridinium (**2**), isomer of the assigned structure, and compared the spectroscopic data of both **1** and **2**. The NMR data of **1** and **2** were very similar, but the UV spectra were completely different. The UV data for fagaridine agreed with these for **2**; consequently, the true structure of fagaridine is **2**, not **1**.

Fagaridine, a benzo[*c*]phenanthridine alkaloid, was isolated from *Fagara xanthoxyloides* by Torto et al. in 1973 and assigned structure **1**.[1] We reported that compound **1** possessed significant antitumor activities in 1989.[2] Also, we had developed a practical synthesis of **1** for a clinical study.[3] During these synthetic studies, we questioned the proposed structure for fagaridine. Torto et al. isolated fagaridine as the hydroxide (X = $OH^-$). Our compound **1** does not convert into the hydroxide under alkaline conditions, but it converts to a ketoamine form (Scheme 1).[2] The keto amine is a characteristic purple solid, but Torto et al. did not mention this property. We also confirmed that the analytical data for our synthetic fagaridine did not agree with those for Torto's fagaridine. They assigned fagaridine on the basis of a comparison of its NMR data with those for similar benzo[*c*]phenanthridiniums, nitidine and chelerythrine, and on the fact that it was methylated with diazomethane to give chelerythrine. Consequently, we considered that the true structure of fagaridine was presumably its isomer **2**. To confirm our assumption, we independently synthesized the compound **2**, called isofagaridine in several papers.[4] In this paper, we present the analytical data for both **1** and **2** and reveal that the true structure of naturally occurring fagaridine is **2**, not **1**. The quaternary benzo[*c*]phenanthridinium **1** ($X^- = HSO_4^- \cdot 2H_2O$), coded NK109, is currently undergoing evaluation in clinical trials in Japan.




**1**
previously accepted structure of fagaridine

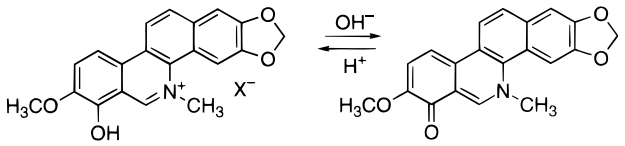



**2**
revised structure of fagaridine

## Results and Discussion

We had previously established the synthetic procedure for **1**.[3] Isomer **2** was synthesized according to a similar procedure (Scheme 2). The appropriate aldehyde unit was prepared from 2,3-dihydroxybenzaldehyde **3**. First, **3** was treated with methyl iodide in the presence of lithium carbonate.[5] **3** was then selectively methylated to 3-hydroxy-2-methoxybenzaldehyde (**4**). Subsequent bromination[6] and benzylation led to 3-(benzyloxy)-6-bromo-2-methoxybenzaldehyde (**6**). The aldehyde unit **6** was identified by NOE between $OCH_3$ and CHO and $OCH_2Ph$ and H-4. On the other hand, 6,7-(methylenedioxy)-1-naphthylamine (**7**) was derived from 2,3-dihydroxynaphthalene.[7] The aldehyde **6** and the amine **7** were condensed to the Schiff base.[8] The imine portion of the Schiff base was reduced to amine with dimethylamineborane to yield the key intermediate **8**.[9] The benzo[*c*]phenanthridine ring system was constructed by radical cyclization, using tri-*n*-octyltin hydride and 2,2′-azobis(2-methylbutyronitrile), and subsequent oxidative aromatization with manganese dioxide. These procedures gave the benzo[*c*]phenanthridine **9**. N-Methylation of **9** was successfully performed by heating with methyl 2-nitrobenzenesulfonate[10] in toluene to give the benzo[*c*]phenanthridinium **10**. Finally **2** was obtained by debenzylation of **10** with hydrochloric acid. Compound **1**, NK109, had been synthesized as the hydrogen sulfate because of long-term stability and handling efficacy for clinical use.[3] In this study, **1** was converted into the chloride for appropriate comparison to the isomer **2**.

**Scheme 1.** Equilibrium of Compound **1**




**1** **1'**

Our synthetic **1** and **2** were identified by NMR experiments. The $^{13}C$ and $^1H$ chemical shifts are listed in Table 1, and HMBC and NOE correlations are shown in Figure 1. HMBC cross-peaks of **2**, observed between $NCH_3$ and C-6, H-6 and C-7, and $OCH_3$ and C-7, supported structure **2**. Also the NOE of **1** between $OCH_3$ and H-9 supported structure **1**.

Next, we compared the additional spectroscopic data for our compounds **1** and **2** with those for Torto's fagaridine.[1] NMR chemical shifts of **1** and **2** in trifluoroacetic acid are given in Table 2. The data similarity indicated closely related structures. The significantly different point was

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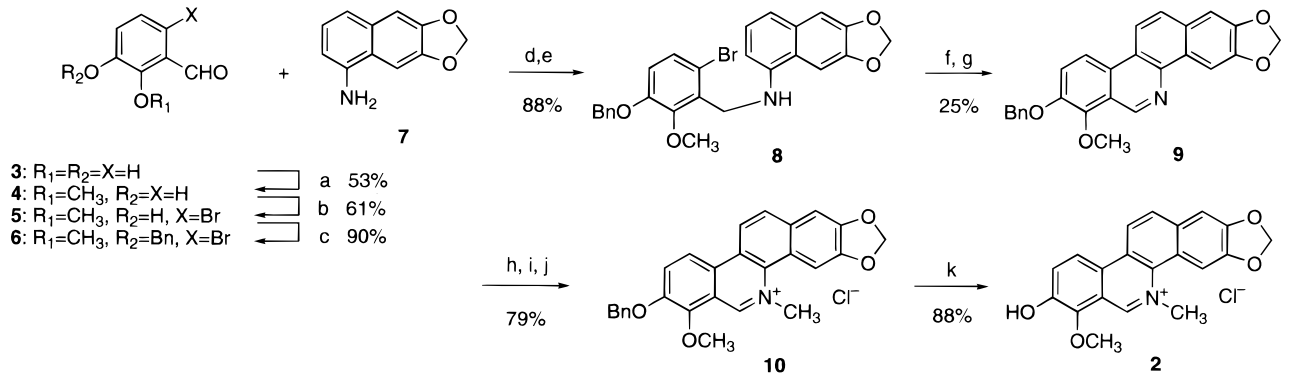
**Scheme 2.** Synthetic Procedure of Compound **2**[a]




[a] Key: (a) MeI, $Li_2CO_3$, DMF, 60 °C, 20 h; (b) NBS, DMF, rt, 2.5 h; (c) BnBr, $K_2CO_3$, DMF, 50 °C, 1.5 h; (d) **6** + **7**, toluene (− $H_2O$), reflux, 1 h; (e) $Me_2NHBH_3$, AcOH, toluene, rt, 1 h; (f) *n*-$Oct_3SnH$, 2,2′-azobis(2-methylbutyronitrile), toluene, 110 °C, 30 min; (g) $MnO_2$, toluene, rt, 1 h; (h) methyl 2-nitrobenzenesulfonate, toluene, 110 °C, 86 h; (i) NaOH aq, EtOH; (j) HCl, aq; (k) concd HCl, AcOH, 60 °C, 5 h.

**Table 1.** NMR Data[a] for Our Compounds **1** and **2**

| position | $\delta_C$ | $\delta_H$ (no., mult, *J* (Hz)) | HMBC correlations |
|---|---|---|---|
| compound **1** | | | |
| 1 | 106.59 | 7.75 (1H, s) | C-3, C-4a, C-12 |
| 2, 3 | 149.43, 149.46 | | |
| 4 | 105.01 | 8.26 (1H, s) | C-2, C-4b, C-12a |
| 4a | 121.13 | | |
| 4b | 132.18 | | |
| 6 | 151.93 | 10.09 (1H, s) | C-4b, C-6a, C-7, C-10a, $NCH_3$ |
| 6a | 116.10 | | |
| 7 | 146.83 | | |
| 8 | 146.90 | | |
| 9 | 125.48 | 8.15 (1H, d, 9.0) | C-7, C-10a |
| 10 | 114.71 | 8.50 (1H, d, 9.0) | C-6a, C-8, C-10b |
| 10a | 128.33 | | |
| 10b | 126.06 | | |
| 11 | 119.69 | 8.77 (1H, d, 9.0) | C-4b, C-10a, C-10b, C-12a |
| 12 | 131.60 | 8.26 (1H, d, 9.0) | C-1, C-4a, C-10b |
| 12a | 133.02 | | |
| 2,3-O$CH_2$O− | 103.53 | 6.34 (2H, s) | C-2,3 |
| 5-N$CH_3$ | 52.65 | 4.93 (3H, s) | C-4, C-4b, C-6 |
| 7-OH | | 11.40−11.80 (1H, br s) | |
| 8-O$CH_3$ | 57.87 | 4.08 (3H, s) | C-8 |
| compound **2** | | | |
| 1 | 105.82 | 7.79 (1H, s) | C-3, C-4a, C-12 |
| 2, 3 | 148.61, 148.69 | | |
| 4 | 104.33 | 8.32 (1H, s) | C-2, C-4b, C-12a |
| 4a | 120.12 | | |
| 4b | 131.48 | | |
| 6 | 150.09 | 10.04 (1H, s) | C-4b, C-6a, C-7, C-10a, $NCH_3$ |
| 6a | 119.85 | | |
| 7 | 143.32 | | |
| 8 | 149.14 | | |
| 9 | 130.20 | 8.01 (1H, d, 9.0) | C-7, C-10a |
| 10 | 119.31 | 8.73 (1H, d, 9.0) | C-6a, C-8, C-10b |
| 10a | 127.60 | | |
| 10b | 125.45 | | |
| 11 | 118.59 | 8.76 (1H, d, 9.0) | C-4b, C-10a, C-10b, C-12a |
| 12 | 130.95 | 8.30 (1H, d, 9.0) | C-1, C-4a, C-10b |
| 12a | 132.08 | | |
| 2,3-O$CH_2$O− | 102.71 | 6.35 (2H, s) | C-2,3 |
| 5-N$CH_3$ | 52.13 | 4.99 (3H, s) | C-4, C-4b, C-6 |
| 7-O$CH_3$ | 61.69 | 4.16 (3H, s) | C-7 |
| 8-OH | | 11.08 (1H, s) | C-7, C-8, C-9 |

[a] NMR spectra were recorded in DMSO-$d_6$.

that of H-10, which is influenced by the methoxy or hydroxy group of the 7- and 8-positions. Nevertheless, it was difficult to determine which was the true structure of Torto's compound using only chemical shift comparison. The difference was not sufficient to identify the true structure.

However, the UV spectra of **1** and **2**, shown in Figure 2, were completely different. Compound **1** shows equilibrium based on the 7-position of the hydroxy group as in Scheme 1.[11] Its p$K_a$ value was 5.3; therefore, the keto amine **1′** is a preferable form in dilute solution for UV measurement. The UV absorption of 539 nm reflected from the structure **1′** was strikingly characteristic of compound **1**. The UV data for Torto's fagaridine[12] were obviously different from the data for **1** and were very close to those for **2** except that the peak of 321 nm was the shoulder peak. This minor difference was considered due to the influence of its

**Table 2.** NMR Data[a] for Compounds **1** and **2** and Torto's Fagaridine

| compd **1** | compd **2** | Torto's fagaridine[b] |
|---|---|---|
| 4.23 (s, 8-$OCH_3$) | 4.35 (s, 7-$OCH_3$) | 4.29 (s, $OCH_3$) |
| 5.05 (s, 5-$NCH_3$) | 5.11 (s, 5-$NCH_3$) | 5.05 (s, $NCH_3$) |
| 6.26 (s, 2,3-$OCH_2O$−) | 6.28 (s, 2,3-$OCH_2O$−) | 6.21 (s, $OCH_2O$) |
| 7.52 (s, 1-H) | 7.55 (s, 1-H) | nd[c] |
| 8.06 (s, 4-H) | 8.11 (s, 4-H) | nd[c] |
| 8.08 (d, $J$ = 9.0 Hz, 9-H) | 8.11 (d, $J$ = 9.0 Hz, 9-H) | 8.08 (d, $J$ = 9 Hz) |
| 8.21 (d, $J$ = 9.0 Hz, 12-H) | 8.24 (d, $J$ = 9.0 Hz, 12-H) | 8.21 (d, $J$ = 9 Hz) |
| 8.44 (d, $J$ = 9.0 Hz, 10-H) | 8.60 (d, $J$ = 9.0 Hz, 10-H) | 8.57 (d, $J$ = 9 Hz) |
| 8.58 (d, $J$ = 9.0 Hz, 11-H) | 8.63 (d, $J$ = 9.0 Hz, 11-H) | 8.59 (d, $J$ = 9 Hz) |
| 9.85 (s, 6-H) | 9.78 (s, 6-H) | 9.77 (s) |

[a] NMR spectra were recorded in $CF_3COOD$ solvent. [b] Described in ref 1. [c] Not described.

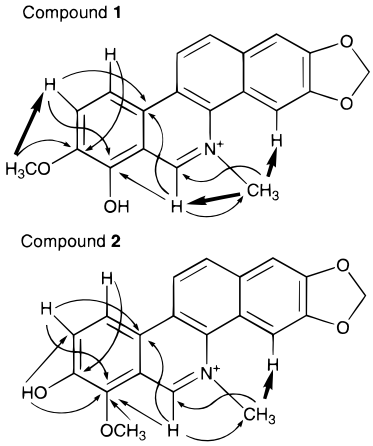



**Figure 1.** HMBC (arrow) and NOE (bold arrow) correlations of compounds **1** and **2**.

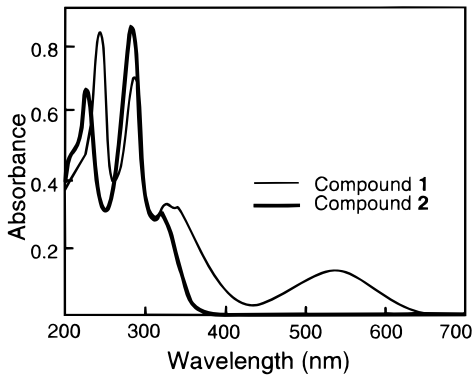



**Figure 2.** UV spectra of compounds **1** and **2** in ethanol solution (20 $\mu$mol/L).

concentration. Thus, we conclude that **2** is the true structure of fagaridine isolated by Torto.

Among other analytical data, TLC was notable in identifying the structures because it easily displayed the equilibrium property of compound **1**. After the development of both compounds in $CH_2Cl_2$−MeOH (9:1) on TLC plates, **1** and **2** were observed as purple and yellow spots, respectively. As in Scheme 1, the color of the quarternary benzo[*c*]phenanthridinium **1** is yellow and the other keto amine **1′** is purple. The compound **1** lost its acid residue on the TLC plate and was developed as structure **1′**, but compound **2** did not show any similar evidence. This is a simple method that distinguishes between them.

As mentioned above, the natural fagaridine should be described as structure **2**, which was reported previously by Fang and co-workers in 1993.[4a] They isolated compound **2** as an inhibitor of DNA topoisomerase I from *Zanthoxylum nitidum* and named it isofagaridine. They determined the structure on the basis of NMR experiments and several spectral methods. Also, their UV data[13] were identical with those of our compound **2**. The presented structure of **2** was correct, but their compound was not exactly a new benzo[*c*]phenanthridinium. They isolated the natural fagaridine and assigned it correctly for the first time.

After Torto and co-workers had reported the isolation of fagaridine from *F. xanthoxyloides*, many researchers isolated fagaridine from several Rutaceae plants.[14] All of them were identical with Torto's fagaridine; therefore, they are compound **2** as well. As far as we know, compound **1** was never isolated from plants; only synthetic approaches were achieved by Hanaoka in 1985[15] and our laboratory in 1990.[16] Accordingly, compound **1** is not a natural product but a completely synthetic one.

In conclusion, natural fagaridine was isolated by Torto and co-workers for the first time; however, its true structure has not been recognized until now. Both fagaridine and isofagaridine isolated from plants are the same product, that is, compound **2**. From now on, compound **2** should be called "fagaridine". Also, compound **1**, not yet known as a natural product, should be called "isofagaridine".

## Experimental Section

**General Experimental Procedures.** 2,2′-Azobis(2-methylbutyronitrile) and tri-*n*-octyltin hydride were purchased from Japan Hydrazine Co., Inc., and Sankyo Organic Chemicals Co., Ltd., respectively. Other materials were obtained from commercial suppliers. DMF was dehydrated by molecular sieves 4A, and others were used without further purifications. Melting points were determined on a Büchi 535 melting point apparatus. UV and IR spectra were recorded on a Shimadzu UV-2200 and a Hitachi 260-10 spectrometer, respectively. NMR spectra were obtained on a Varian Gemini-200 and a JEOL JNM-GX400 spectrometer. All chemical shifts are reported in ppm relative to the internal standard tetramethylsilane (TMS, $\delta$ 0.00). Coupling constants are reported in Hz. HMBC and GOESY spectra of compounds **1** and **2** were obtained on a BRUKER AVANCE DRX 400. Mass spectra were recorded on a Micromass Limited Auto Spec-Q spectrometer. Elemental analyses were performed on a Yanako CHN Corder (C, H, N analysis) and a Yokogawa IC-7000D (Br analysis). TLC for **1** and **2** were carried out on silica gel 60 $F_{254}$ (0.25 mm-thick plates) using $CH_2Cl_2$−MeOH (9:1) as solvent.

**3-Hydroxy-2-methoxybenzaldehyde (4).** To a mixture of 2,3-dihydroxybenzaldehyde (**3**) (3.84 g, 27.8 mmol) and lithium carbonate (5.14 g, 69.5 mmol) in DMF (70 mL) was added 2.60 mL of methyl iodide (41.7 mmol) and the mixture heated at 60 °C for 20 h. The mixture was condensed in vacuo, and the resulting residue was diluted with water, acidified with concentrated HCl, and then extracted with diisopropyl ether. The organic layer was washed with water, dried over $Na_2SO_4$, filtered, and evaporated. The crude residue was chromatographed on silica gel (hexanes−ethyl acetate 4:1) to give **4** (2.23 g, 53%) as a white solid: mp 115 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.98 (3H, s), 5.96 (1H, s), 7.15 (1H, dd, $J$ = 8.2, 7.4), 7.24 (1H, dd, $J$ = 8.2, 2.0), 7.38 (1H, dd, $J$ = 7.4,

2.0), 10.27 (1H, s); ESIMS *m/z* 151 [$M^-$ − H]; *anal.* C 63.02%, H 5.29%, calcd for $C_8H_8O_3$, C 63.15%, H 5.30%.

**6-Bromo-3-hydroxy-2-methoxybenzaldehyde (5).** To a solution of **4** (2.23 g, 14.7 mmol) in DMF (73 mL) was added dropwise *N*-bromosuccinimide (3.92 g, 22.0 mmol) in DMF (100 mL). After **4** disappeared, the solution was concentrated in vacuo. The resulting residue was partitioned between diisopropyl ether and water. The organic layer was washed with water, dried over $Na_2SO_4$, filtered, and evaporated. The crude residue was chromatographed on silica gel ($CH_2Cl_2$) to give **5** (2.07 g, 61%) as a pale yellow powder: mp 135 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.93 (3H, s), 6.03 (1H, s), 7.07 (1H, d, $J$ = 8.7), 7.34 (1H, d, $J$ = 8.7), 10.35 (1H, s); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 63.4, 115.9, 121.4, 126.7, 130.0, 148.3, 149.4, 191.1; FABMS *m/z* 230, 232 [$M^{\bullet+}$], 231, 233 [$M^+$ + H]; *anal.* C 41.37%, H 3.05%, Br 34.52%, calcd for $C_8H_7BrO_3$, C 41.59%, H 3.05%, Br 34.58%.

**3-(Benzyloxy)-6-bromo-2-methoxybenzaldehyde (6).** To a mixture of **5** (1.94 g, 8.39 mmol) and potassium carbonate (1.16 g, 12.6 mmol) in DMF (40 mL) was added 1.2 mL of benzyl bromide (10.1 mmol), and the mixture was heated at 50 °C for 1.5 h. The mixture was concentrated in vacuo and partitioned between toluene and water. The organic layer was washed with water, dried over $Na_2SO_4$, filtered, and evaporated. The crude residue was chromatographed on silica gel (hexanes−ethyl acetate 92:8) to give **6** (2.44 g, 90%) as a white solid: mp 76 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.97 (3H, s), 5.14 (2H, s), 6.99 (1H, d, $J$ = 8.8), 7.30 (1H, d, $J$ = 8.8), 7.33−7.46 (5H, m), 10.35 (1H, s); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 62.4, 71.3, 113.5, 119.6, 127.3 × 2, 128.3, 128.7 × 2, 128.9, 129.3, 136.0, 151.8, 152.7, 190.5; FABMS *m/z* 320, 322 [$M^{\bullet+}$], 321, 323 [$M^+$ + H]; *anal.* C 56.01%, H 3.94%, Br 24.48%, calcd for $C_{15}H_{13}BrO_3$, C 56.10%, H 4.08%, Br 24.88%.

***N*-[3′-(Benzyloxy)-6′-bromo-2′-methoxybenzyl]-6,7-(methylenedioxy)-1-naphthylamine (8).** The solution of **6** (2.44 g, 7.59 mmol) and 6,7-(methylenedioxy)-1-naphthylamine **7** (1.42 g, 7.59 mmol) in toluene (77 mL) was refluxed for 1 h, and the toluene was distilled in atmospheric pressure to give a Schiff base as an oil. This was dissolved in toluene (77 mL), 447 mg of dimethylamineborane (7.59 mmol) was added, and then acetic acid (10.3 mL, 179.9 mmol) was added to the solution and the mixture stirred for 1 h. When the reduction was completed, the reaction mixture was quenched with 1 N HCl (38.5 mL). After 1 h, the mixture was neutralized with 6 N NaOH. The organic layer was separated, washed with water, dried over $Na_2SO_4$, filtered, and evaporated. The resulting residue was recrystallized with ethyl acetate−ethanol to give **8** (3.28 g, 88%) as a white powder: mp 160 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 3.89 (3H, s), 4.48 (1H, br s), 4.57 (2H, s), 5.11 (2H, s), 5.99 (2H, s), 6.82 (1H, d, $J$ = 8.9), 6.83 (1H, dd, $J$ = 7.0, 1.1), 7.07 (1H, s), 7.12 (1H, dd, $J$ = 7.6, 1.1), 7.14 (1H, s), 8.83 (1H, d, $J$ = 8.9), 7.21−7.47 (6H, m); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 43.8, 61.8, 71.0, 97.5, 100.9, 104.7, 105.5, 115.0, 116.0, 117.8, 120.3, 125.1, 127.3 × 2, 128.0, 128.1, 128.7 × 2, 131.3, 132.7, 136.5, 143.1, 147.1, 147.3, 149.5, 151.4; FABMS *m/z* 491, 493 [$M^{\bullet+}$], 492, 494 [$M^+$ + H]; *anal.* C 63.00%, H 4.35%, N 2.33%, Br 15.22%, calcd for $C_{26}H_{22}BrNO_4$·0.3AcOEt, C 62.97%, H 4.74%, N 2.70%, Br 15.40%.

**8-(Benzyloxy)-7-methoxy-2,3-(methylenedioxy)benzo[*c*]phenanthridine (9).** The solution of **8** (2.78 g, 5.64 mmol) and tri-*n*-octyltin hydride (6.48 g, 14.1 mmol) in toluene (278 mL) was heated at 110 °C and then azobis(2-methylbutyronitrile) (1.63 g, 8.46 mol) in toluene (5 mL) was added. After 30 min, the solution was cooled to room temperature, and manganese dioxide (2.78 g) was added. After being stirred for 1 h, the reaction mixture was filtered through Celite, and the solvent was evaporated. The residue was recrystallized with $CHCl_3$−hexane to give **9** (567 mg, 25%) as a white powder: mp 212 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 4.17 (3H, s), 5.32 (2H, s), 6.13 (2H, s), 7.26 (1H, s), 7.34−7.47 (3H, m), 7.48−7.56 (2H, m), 7.59 (1H d, $J$ = 9.0), 7.83 (1H, d, $J$ = 9.0), 8.30 (1H, d, $J$ = 9.0), 8.32 (1H, d, $J$ = 9.0), 8.72 (1H, s), 9.76 (1H, s); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 62.0, 72.0, 101.3, 102.2, 104.4, 118.16, 118.22, 120.0, 120.9, 122.0, 127.0, 127.5 × 2, 128.2, 128.6, 128.7 × 2, 129.1, 129.8, 136.8, 140.1, 146.0, 146.5, 148.3, 148.4, 148.5; FAB-MS *m/z* 410 [$M^+$ + H]; *anal.* C 75.99%, H 4.59%, N 3.16%, calcd for $C_{26}H_{19}NO_4$, C 76.27%, H 4.68%, N 3.42%.

**8-(Benzyloxy)-7-methoxy-5-methyl-2,3-(methylenedioxy)benzo[*c*]phenanthridinium Chloride (10).** The solution of **9** (282 mg, 0.69 mmol) and methyl 2-nitrobenzenesulfonate (299 mg, 1.38 mmol) in toluene (5.6 mL) was heated at 110 °C for 86 h to yield a yellow suspension. It was filtered, and the residue was neutralized with ethanol (13.8 mL) and 0.1 N NaOH (13.8 mL). The resulting white suspension was partitioned between $CH_2Cl_2$ and water. The organic layer was washed with saturated NaCl, dried over $Na_2SO_4$, filtered, and evaporated. The crude residue was chromatographed on silica gel (toluene−ethyl acetate) to give the pure pseudobase.[3,17] It was dissolved in acetone (10 mL), and then 1 N HCl (1.38 mL) was added. The resulting precipitate was filtered, washed with acetone, and dried in vacuo to give **10** (250 mg, 79%) as a yellow powder: mp 174−175 °C dec; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 4.21 (3H, s), 5.00 (3H, s), 5.50 (2H, s), 6.35 (2H, s), 7.36−7.51 (3H, m), 7.54−7.62 (2H, m), 7.78 (1H, s), 8.30 (1H, d, $J$ = 8.8 H), 8.31 (1H, s), 8.37 (1H, d, $J$ = 9.4 H), 8.82 (1H, d, $J$ = 8.8 H), 8.82 (1H, d, $J$ = 9.4 H), 10.12 (1H, s); $^{13}$C NMR (DMSO-$d_6$, 50 MHz) $\delta$ 52.1, 62.2, 70.9, 102.7, 104.2, 105.7, 118.7, 119.1, 119.3, 120.0, 125.1, 127.2, 127.8 × 2, 128.2, 128.6 × 2, 130.9, 131.7, 132.2, 136.1, 145.7, 148.6, 148.7, 149.4, 150.7; FABMS *m/z* 424 [$M^+$ + H]; *anal.* C 62.59%, H 5.20%, N 2.58%, calcd for $C_{27}H_{22}ClNO_4$·1.5HCl·0.15$H_2O$, C 62.40%, H 5.08%, N 2.70%.

**8-Hydroxy-7-methoxy-5-methyl-2,3-(methylenedioxy)-benzo[*c*]phenanthridinium Chloride (2).** The mixture of **10** (217 mg, 0.47 mmol), acetic acid (4.34 mL), and concentrated HCl (2.17 mL) was warmed at 60 °C for 5 h. When the reaction was completed, the solution was cooled to room temperature and diluted with acetone (26 mL). The resulting orange suspension was filtered, washed with acetone, and dried in vacuo to give **2** (154 mg, 88%) as an orange powder: mp 231−233 °C dec; UV (EtOH) $\lambda_{max}$ (log $\epsilon$) 227 (4.52), 283 (4.63), 321 (4.18), $\lambda_{min}$ (log $\epsilon$) 251 (4.19), 311 (4.16); IR (KBr) $\nu_{max}$ 3440, 3072, 1606, 1547, 1483, 1475, 1404, 1385, 1321, 1284, 1257, 1203, 1161, 1126, 1082, 1039, 976, 935, 879, 827 cm$^{-1}$; FABMS *m/z* 334 [$M^+$]; TLC $R_f$ 0.40 (as a yellow spot); $^1$H and $^{13}$C NMR see Tables 1 and 2.

**7-Hydroxy-8-methoxy-5-methyl-2,3-(methylenedioxy)-benzo[*c*]phenanthridinium Chloride (1).** 7-Hydroxy-8-methoxy-5-methyl-2,3-(methylenedioxy)benzo[*c*]phenanthridinium hydrogensulfate dihydrate[3] (467 mg, 1.00 mmol) was dissolved with water, neutralized with 0.1 N NaOH, and extracted with $CH_2Cl_2$. The organic layer was washed with water, dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The resulting violet solid was suspended with acetone (8 mL), and 1 N HCl (2 mL) was added to yield an orange suspension. It was filtered, washed with acetone, and dried in vacuo to give **1** (347 mg, 94%) as an orange powder: mp 224−226 °C dec; UV (EtOH) $\lambda_{max}$ (log $\epsilon$) 245 (4.63), 286 (4.55), 328 (4.22), 539 (3.81), $\lambda_{min}$ (log $\epsilon$) 261 (4.30), 312 (4.16), 433 (3.16); IR (KBr) $\nu_{max}$ 3400, 1603, 1550, 1492, 1481, 1379, 1352, 1301, 1277, 1260, 1211, 1157, 1117, 1099, 1037, 969, 934, 863, 823 cm$^{-1}$; FABMS *m/z* 334 [$M^+$]; TLC $R_f$ 0.32 (as a purple spot); $^1$H and $^{13}$C NMR see Tables 1 and 2.

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**Supporting Information Available:** Copies of the $^1$H NMR, $^{13}$C NMR, and HMBC spectra of compounds **1** and **2** (6 pages). Ordering information is given on any current masthead page.

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(11) Manuscript in preparation.
(12) Described in ref 1: UV (EtOH) $\lambda_{max}$ (log $\epsilon$) 228 (4.55), 284 (4.65), 322 (sh) (4.14), $\lambda_{min}$ (log $\epsilon$) 252 (4.16) nm.
(13) Described in ref 4a: UV (MeOH) $\lambda_{max}$ (log $\epsilon$) 228 (4.20), 284 (4.29), 322 (sh) (3.82), $\lambda_{min}$ (log $\epsilon$) 252 (3.85) nm.
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