SYNTHESIS OF 2,3,9,10-TETRAOXYGENATED BENZO[c]PHENANTHRIDINE DERIVATIVES VIA PALLADIUM-MEDIATED ARYL-ARYL COUPLING REACTION

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Abstract – Two 2,3,9,10-tetraoxygenated benzo[c]phenanthridine alkaloids, 1 and 2, originally reported as zanthoxyline and broussonpapyrine, respectively, were synthesized using the Pd-mediated intramolecular aryl-aryl coupling reaction as the key step.

INTRODUCTION
The palladium-mediated aryl-aryl coupling reaction is a powerful method to construct biaryl compounds, and many syntheses of biaryl-type natural products have been accomplished using this technique. 1 Especially, intramolecular coupling is useful for the formation of polyfunctionalized heterocyclic systems. 2 Among such heterocyclic compounds, the benzo[c]phenanthridine alkaloids are recognized as an important class of natural products because of their interesting biological activities such as antitumor and antiviral activities, inhibition of DNA topoisomerase I, etc. 3 In this context, we have reported several syntheses of the benzo[c]phenanthridine natural products via the intramolecular aryl-aryl coupling reaction of the benzonaphthamide derivatives. 4
Recently, two unique natural benzo[c]phenanthridine alkaloids, zanthoxyline (1) 5 and broussonpapyrine (2), 6 were independently isolated, which possess an unusual substituent pattern (Figure). 2 Namely, they contain four oxygen functional groups at positions 2, 3, 9, and 10 on the benzo[c]phenanthridine skeleton. Thereafter, the originally reported structures of both 1 and 2 were revealed to be incorrect based on synthetic studies. 8 From the viewpoint of a structure-bioactivity relationship, even if these compounds are
not natural products, we considered that the establishment of a synthetic method of such unusual benzo[c]phenanthridine derivatives is a meaningful challenge. Thus, in this report, we demonstrate the synthesis of 1 and 2 using the palladium-mediated intramolecular aryl-aryl coupling reaction as the key step.2

![Zanthoxyline (1) and Broussonpapyrine (2)](image)

**Figure. Originally Reported Structures of Zanthoxyline (1) and Broussonpapyrine (2)**

### RESULTS AND DISCUSSION

For the total synthesis of 1, we commenced the preparation of 6,7-methylenedioxy-1-naphthylamine (8) by the reported method (Scheme 1).10 First, 2,3-dihydroxynaphthalene (3) was mesylated to afford 411 followed by regioselective nitration for producing 5.11 Alkaline hydrolysis of 5 and successive methylation of the generated catechol moiety produced the tricyclic compound 7, which was reduced to 812 using the conventional catalytic hydrogenation technique.

![Scheme 1. Preparation of 1-Naphtylamine](image)

Next, we employed 3,4-dihydroxybenzaldehyde (9) as a starting material to prepare the key coupling precursor 15 (Scheme 2). Selective protection of the 4-hydroxy group of 9 with the isopropyl unit and successive iodination afforded 11. The leaving hydroxy group was methylated to form 13 which was further transformed into the benzoic acid 13. Condensation between 8 and 13 for the amide bond formation using the EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) - DMAP system produced 14, leading to the N-protected compound 15 with the MOM group. The intramolecular aryl-aryl coupling reaction (Pd(OAc)2-Ag2CO3-PPh3)4-13 of 15 smoothly proceeded to construct the lactam compound 16. Finally, the synthesis of the target compound 1 was completed by the hydride reduction with LiAlH4 and successive acid treatment involving removal of both the MOM and isopropyl
On the other hand, the second target 2 was synthesized as illustrated in Scheme 3. Isovanillin 17 was regioselectively iodinated to prepare 18 which was converted into the dimethoxy compound 19 using dimethyl sulfate. The formyl group of 19 was oxidized to a carboxylic acid for the formation of 20, which was subjected to the condensation reaction with 8 using EDC-DMAP. Methylation of the amide nitrogen of 21 was also successful to afford the coupling precursor 22. Conditions similar to Scheme 2 were employed for the intramolecular coupling reaction to produce 23. The final reduction using LiAlH4 followed by the treatment with hydrochloric acid succeeded in the synthesis of 2.

CONCLUSION
We demonstrated the synthesis of two benzo[c]phenanthridine alkaloids which possess an unusual substituent pattern, i.e., the 2,3,9,10-tetraoxygenated compounds. The Pd-mediated aryl-aryl coupling reaction was efficiently used as the key step for the construction of the benzo[c]phenanthridine skeleton. Further application of this method for the synthesis of other heterocyclic compounds is currently in progress in our laboratory.

EXPERIMENTAL
General: Melting points were measured using a Yanagimoto micro-melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 or Shimadzu FTIR-8400 spectrophotometer. The NMR spectra were obtained using a Varian MERCURY-300, JEOL α-400, or JNX-ECX500 instrument with the chemical shifts being reported as δ ppm and the couplings expressed in
Scheme 3. Synthesis of 2 via Pd-mediated Aryl-Aryl Coupling Reaction

Hertz. The elemental analysis was performed using a Yanaco MT-5 or Thermo Scientific FlashEA1112 analyzer. Electron ionization mass spectra (EI-MS) was obtained using a JEOL JMS-700 instrument. Silica gel column chromatography was carried out using Merck 9385 Kieselgel 60 or Wako-gel C-200.

2,3-Bis(methylsulfonyloxy)naphthalene (4)

MsCl (39.3 g, 26.5 mL, 0.343 mol) was added to a solution of 2,3-dihydroxynaphthalene (3) (25 g, 0.156 mol), Et₃N (34.7 g, 47.9 mL, 0.343 mol) in CHCl₃ (500 mL) at 0 °C, then the mixture was allowed to stand at rt. After the resulting precipitates were removed by filtration, water was added to the mother liquid which was extracted with CHCl₃. The organic layer was washed with brine, dried over MgSO₄, and concentrated to give a crude residue. Recrystallization from CHCl₃ gave 4 (48.8 g, 99%) in almost a pure form. Colorless needles, mp 153.9–157.2 °C (CHCl₃) [lit.¹¹ 159-160 °C]. IR (KBr) cm⁻¹: 1360, 1180.

¹H-NMR (300MHz, CDCl₃) δ: 3.29 (6H, s, CH₃), 7.58–7.95 (6H, m, Ar-H).

6,7-Bis(methylsulfonyloxy)-1-nitronaphthalene (5)

To a solution of 4 (18 g, 0.057 mol) in acetic anhydride (180 mL), conc. HNO₃ (42.5 mL) was dropwise added while maintaining the reaction mixture at 35-40 °C. The mixture was then cooled to 5 °C, and stirred for 1 day. After the reaction mixture was poured into ice-water, the resulting precipitates were collected and recrystallized from MeCN to give 5 (16.2 g, 79%). Yellow needles, 198.8-199.8 °C [lit.¹¹ 200-201 °C]. IR (KBr) cm⁻¹: 1520, 1350, 1170. ¹H-NMR (500MHz, CDCl₃) δ: 3.37 (6H, s, CH₃), 7.65 (1H, t, J = 8.0 Hz, C₇-H), 8.11 (1H, s, C₁-H), 8.17 (1H, d, J = 8.5 Hz, C₈-H), 8.43 (1H, d, J = 8.5 Hz C₆-H),
8.78 (1H, s, C₄-H).

6,7-Dihydroxy-1-nitronaphthalene (6)
The mixture of 5 (18.7 g, 0.033 mol) and a 5% NaOH aqueous solution (165 mL) was heated overnight at 100 °C. After acidification with a 10% HCl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, and concentrated to give 6 (10.5 g, 99%). Yellow needles, 206.2-207.0 °C [lit.10 207-209 °C]. IR (KBr) cm⁻¹: 3360 (OH). ¹H-NMR (500MHz, CDCl₃) δ: 5.99 (1H, s, ArOH), 6.31 (1H, s, ArOH), 7.35 (1H, s, C₁-H), 7.36 (1H, t, J = 8.0 Hz, C₇-H), 7.92 (1H, d, J =8.0 Hz, C₈-H), 8.15 (1H, s, C₄-H), 8.17 (1H, d, J =8.0 Hz C₆-H).

6,7-Methylenedioxy-1-nitronaphthalene (7)
CsF (8.51 g, 0.056 mol) was added to a solution of 6 (2.3 g, 0.0112mol) in DMF (23 mL), then the mixture was stirred at rt for 1.5 h. To the mixture, CH₂Br₂ (2.92 g, 1.18 mL, 0.0168 mol) was added, which was heated at 115 °C for 2.5 h. After the mixture was diluted with AcOEt and the insoluble material was removed by filtration, the mixture was washed with a 5% NaOH aqueous solution and brine, dried over MgSO₄, and concentrated. The resulting solid was recrystallized from AcOEt to give 7 (1.5 g, 62%). Yellow needles, mp 159.3-163.0 °C. IR (KBr) cm⁻¹: 1470, 1320. ¹H-NMR (500MHz, CDCl₃) δ: 6.13 (2H, s, O-CH₂-O), 7.20 (1H, s, C₁-H), 7.38 (1H, t, J = 8.0 Hz, C₇-H), 7.91 (1H, d, J =7.5 Hz, C₈-H), 7.98 (1H, s, C₄-H), 8.17 (1H, d, J =7.5 Hz C₆-H).

1-Amino-6,7-methylenedioxyanaphtalene (8)
Under an H₂ atmosphere, the mixture of 7 (2.0 g, 0.0092 mol), EtOH (100 mL), and 10% Pd/C (250 mg) was vigorously stirred at rt for 1.5 h. After filtration, the solvent was evaporated to give a crude residue, and then recrystallization from EtOH gave 8 (1.06 g, 61%). Yellow needles, mp 151.5-154.0 °C [lit.12a 154-155 °C (Et₂O-hexane); lit.12b 152-154 °C (EtOH-H₂O)]. IR (KBr) cm⁻¹: 3210 (NH). ¹H-NMR (500MHz, CDCl₃) δ: 6.03 (2H, s, O-CH₂-O), 6.29-7.21 (5H, m, Ar-H).

3-Hydroxy-4-isopropoxybenzaldehyde (10)
To a suspension of K₂CO₃ (12.5 g, 0.090 mol) in DMF (50 mL), 3,4-dihydroxybenzaldehyde (9, 25 g, 0.28 mol) and 2-iodopropane (18 mL, 0.18 mol) were successively added, then the mixture was stirred at 50 °C for 1 day. The mixture was acidified with a 10% HCl aqueous solution and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:6). The title compound 10 (28.2 g, 86 %) was obtained. Yellow needles, mp 63.7-65.2 °C (AcOEt). IR (KBr) cm⁻¹: 3300 (OH), 1680
(C=O), 1280. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 1.41 (3H, s, ArOCHCH$_3$), 1.42 (3H, s, ArOCHCH$_3$), 4.72 (1H, heptet, $J = 6.3$ Hz, ArOCH(CH$_3$)$_2$), 5.89 (1H, s, ArOH), 6.95 (1H, d, $J = 8.0$ Hz, C$_5$-H), 7.39 (1H, dd, $J = 8.0, 2.5$ Hz, C$_6$-H), 7.43 (1H, d, $J = 2.5$ Hz, C$_2$-H), 9.82 (1H, s, ArCHO). Anal. Calcd for C$_{10}$H$_{12}$O$_3$: C, 66.65; H, 6.71. Found: C, 66.61; H, 6.52.

3-Hydroxy-2-iodo-4-isopropoxybenzaldehyde (11)

To a solution of 10 (12 g, 0.13 mol) in pyridine (80 mL), a solution of ICl (21.9 g, 0.135 mol) in 1,4-dioxane (160 mL) was dropwise added under cooling at 0 °C. The mixture was warmed to rt and allowed to stand for 15 h. After the volatile materials were removed in vacuo, water was added to the mixture. The resulting precipitates were collected, then recrystallization from AcOEt gave 11 (14.27 g, 56%). Pale yellow needles, mp 152.5-156.7 °C (AcOEt). IR (KBr) cm$^{-1}$: 3400 (OH), 1670 (CO), 1280.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 1.41 (3H, s, ArOCHCH$_3$), 1.43 (3H, s, ArOCHCH$_3$), 4.75 (1H, heptet, $J = 6.3$ Hz, ArOCH(CH$_3$)$_2$), 6.36 (1H, s, ArOH), 6.89 (1H, d, $J = 8.7$ Hz, C$_5$-H), 7.53 (1H, d, $J = 8.7$ Hz, C$_6$-H), 10.03 (1H, s, ArCHO). $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$: 194.9, 149.0, 146.4, 128.4, 123.6, 111.6, 88.2, 72.7, 22.1. Anal. Calcd for C$_{10}$H$_{11}$IO$_3$: C, 39.24; H, 3.62. Found: C, 39.23; H, 3.64.

2-Iodo-4-isopropoxy-3-methoxybenzaldehyde (12)

A mixture of 11 (14 g, 0.045 mol), K$_2$CO$_3$ (12.7 g, 0.092 mol), (MeO)$_2$SO$_2$ (8.66 mL, 0.092 mol), and acetone (50 mL) was heated under reflux for 1 h. The solvent was removed under reduced pressure, then water was added to the mixture which was extracted with Et$_2$O. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated to give a crude solid. Recrystallization from Et$_2$O gave 12 (10.6 g, 73%). Pale yellow prisms, mp 48.1-51.9 °C (Et$_2$O). $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 1.41 (3H, s, ArOCHCH$_3$), 1.42 (3H, s, ArOCHCH$_3$), 3.86 (3H, s, ArOCH$_3$), 4.70 (1H, heptet, $J = 6.0$ Hz, ArOCH), 6.94 (1H, d, $J = 8.5$ Hz, C$_5$-H), 7.68 (1H, d, $J = 8.5$ Hz, C$_6$-H). $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$: 195.1, 156.2, 149.4, 128.6, 127.2, 113.8, 100.9, 71.7, 60.3, 22.0. Anal. Calcd for C$_{11}$H$_{13}$IO$_3$: C, 41.27; H, 4.09. Found: C, 41.50; H, 4.07.

2-Iodo-4-isopropoxy-3-methoxybenzoic acid (13)

To a solution of 12 (150 mg, 0.467 mmol), NaH$_2$PO$_4$•2H$_2$O (18.3 mg, 0.12 mmol), and 30% H$_2$O$_2$ (79.7 mg, 2.34 mmol) in MeCN (15 mL), an 80% aqueous solution of NaClO$_2$ (0.5 mL, 79.5 mg, 0.879 mmol) was added at 0 °C. The mixture was stirred at the same temperature for 5.5 h, then poured into a sat. NaHSO$_3$ aqueous solution. After acidification with 10% HCl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated to give a residue. Recrystallization from AcOEt gave 13 (120 mg, 77%). Colorless needles, mp 152-153 °C.
(AcOEt). IR (KBr) cm\(^{-1}\): 3000 (OH), 1700 (CO), 1280. \(^1\)H-NMR (300MHz, CDCl\(_3\)) \(\delta\): 1.40 (3H, s, ArOCHCH\(_3\)), 1.42 (3H, s, ArOCHCH\(_3\)), 3.84 (3H, s, ArOCH\(_3\)), 4.67 (1H, heptet, \(J = 6.3\) Hz, ArOCH(CH\(_3\))\(_2\)), 6.90 (1H, d, \(J = 8.7\) Hz, C\(_5\)-H), 7.82 (1H, d, \(J = 8.7\) Hz, C\(_6\)-H). \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\): 171.5, 152.2, 150.3, 148.5, 147.8, 135.5, 135.4, 131.6, 125.3, 124.9, 124.4, 121.1, 115.5, 104.7, 101.4, 98.5, 92.5, 71.7, 60.4, 22.1. Anal. Calcd for C\(_{11}\)H\(_{15}\)NO\(_4\): C, 39.31; H, 3.90. Found: C, 39.27; H, 3.86.

2-Iodo-4-isopropoxy-3-methoxy-N-(6,7-methylenedioxy-1-naphthyl)benzamide (14)

A mixture of 13 (100 mg, 0.31 mmol), 8 (67 mg, 0.37 mmol), EDC (98 mg, 0.53 mmol), DMAP (7.9 mg, 0.068 mmol), and CH\(_2\)Cl\(_2\) (10 mL) was heated at 30 °C for 4.5 h. After being poured into water, the mixture was extracted with CH\(_2\)Cl\(_2\). The organic layer was washed with brine, dried over MgSO\(_4\), and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt/hexane (1:4). Recrystallization from CH\(_2\)Cl\(_2\) gave 14 (103 mg, 68%). Colorless needles, mp 226-229 °C (CH\(_2\)Cl\(_2\)). \(^1\)H-NMR (300MHz, CDCl\(_3\)) \(\delta\): 1.40 (3H, s, ArOCHCH\(_3\)), 1.42 (3H, s, ArOCHCH\(_3\)), 3.89 (3H, s, ArOCH\(_3\)), 4.65 (1H, heptet, \(J = 6.3\) Hz, ArOCH(CH\(_3\))\(_2\)), 6.05 (2H, s, OCH\(_2\)O), 6.98 (1H, d, \(J = 8.1\) Hz, C\(_5\)-H), 7.33-7.61 (5H, m, Ar-H), 7.83 (1H, d, \(J = 8.1\) Hz, C\(_6\)-H). \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\): 167.9, 152.2, 150.3, 148.5, 147.8, 135.5, 135.4, 131.6, 125.9, 125.3, 124.9, 124.4, 121.1, 115.5, 104.7, 101.4, 98.5, 92.5, 71.7, 60.4, 22.1. Anal. Calcd for C\(_{22}\)H\(_{20}\)INO\(_5\): C, 52.29; H, 3.99; N, 2.77. Found: C, 52.38; H, 4.10; N, 2.69.

2-Iodo-4-isopropoxy-3-methoxy-N-(methoxymethyl)-N-(6,7-methylenedioxy-1-naphthyl)benzamide (15)

NaH (50% in mineral oil, 28 mg, 0.59 mmol) was washed with hexane before use. To a mixture of the prepared base and DMF (10 mL), 14 (100 mg, 0.198 mmol) was added and stirred at rt for 30 min. MOMCl (24 mg, 0.023 mL, 0.30 mmol) was added to the mixture, then stirred at rt for 5 h. The mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO\(_4\), and concentrated to give a residue. Silica gel column chromatography with AcOEt/hexane (1:3) gave 15 (88.7 mg, 82%) as an amorphous solid. \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.17-1.42 (6H, m, ArOCH(CH\(_3\))\(_2\)), 3.69-3.89 (6H, m, N-CH\(_2\)OCH\(_3\)), ArOCH\(_3\)), 4.29-4.68 (1H, m, ArOCH(CH\(_3\))\(_2\)), 4.86, 5.75 (2H, d, \(J = 9.9\), NCH\(_2\)OCH\(_3\)), 6.32-6.37 (1H, m, C\(_5\)-H), 6.56-6.64 (1H, m, C\(_6\)-H), 7.06-7.50 (5H, m, Ar-H). \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) (selected peaks) \(\delta\): 171.6, 150.5, 150.1, 148.9, 147.9, 136.7, 131.6, 127.7, 126.2, 124.1, 114.4, 104.6, 101.5, 99.3, 93.4, 78.7, 71.3, 60.2, 57.9, 22.1, 21.7. Anal. Calcd for C\(_{24}\)H\(_{24}\)INO\(_6\): C, 52.47; H, 4.40; N, 2.55. Found: C, 52.71; H, 4.51; N, 2.37.

9-Isopropoxy-10-methoxy-N-methoxymethyl-2,3-methylenedioxybenzo[c]phenanthridin-6(5\(\overline{H}\))-
A mixture of 15 (100 mg, 0.18 mmol), PPh₃ (19.2 mg, 0.072 mmol), Ag₂CO₃ (101 mg, 0.36 mmol) Pd(OAc)₂ (8.2 mg, 0.036 mmol), and DMF (2 mL) was heated under reflux for 1 h. After the mixture was diluted with AcOEt, any undissolved materials were filtered off. The mother liquid was washed with brine, dried over MgSO₄, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:4). The title compound 16 (52 mg, 67%) was obtained, which was recrystallized from AcOEt for use as an analytical sample. Yellow needles, mp 175.7-177.7 °C (AcOEt). IR (KBr) cm⁻¹: 1660 (CO). ¹H-NMR (300 MHz, CDCl₃) δ: 1.46 (3H, s, ArOCHCH₃), 1.48 (3H, s, ArOCHCH₃), 3.72 (3H, s, ArOCHCH₃), 3.87 (3H, s, ArOCH₃), 4.77 (1H, heptet, J = 6.3 Hz, ArOCH(CH₃)₃), 5.37 (2H, s, NCH₂OCH₃), 6.09 (2H, s, OCH₂O), 7.15-7.56 (4H, m, Ar-H), 8.35 (1H, d, J = 9.0, C7-H), 9.12 (1H, d, J = 9.0, C8-H). ¹³C-NMR (75 MHz, CDCl₃) δ: 165.1, 155.6, 147.8, 147.6, 146.3, 136.3, 132.0, 128.7, 125.8, 123.2, 122.9, 121.2, 119.5, 116.7, 114.6, 104.0, 102.7, 101.3, 82.1, 71.1, 60.0, 57.1, 22.1. Anal. Calcd for C₂₄H₂₃NO₆·0.5 H₂O: C, 66.97; H, 5.62; N, 3.25. Found C, 66.93, H, 5.56; N, 3.34.

9-Hydroxy-10-methoxy-2,3-methylenedioxybenzo[c]phenanthidine (1)

To a solution of 16 (120 mg, 0.285 mmol) in THF (5 mL), LiAlH₄ (32 mg, 0.855 mmol) was added at 0 °C, then the mixture was vigorously stirred for 1 h. After quenching with ice water, a NaOH aqueous solution was added as the mixture was adjusted to pH 12-13. After extraction with Et₂O, the organic layer was washed with brine, dried over K₂CO₃, and concentrated. To the resulting solid, a conc. HCl aqueous solution (10 mL) was added, then the mixture was stirred for 24 h. After adjusting to pH 9 by adding a sat. NH₄Cl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:2). The title compound 1 (63 mg, 83 %) was obtained, which was recrystallized from CHCl₃ for use as an analytical sample. Brown needles, mp 226-228 °C (CHCl₃) [lit. ⁵ 220-222 °C (originally reported zanthoxyline); lit. ¹⁰ 226-227 °C (synthesized by Hibino)]. IR (KBr) cm⁻¹: 3400 (OH), 1480. ¹H-NMR (300 MHz, DMSO-d₆) δ: 3.88 (3H, s, ArOCH₃), 6.21 (2H, s, OCH₂O), 7.43 (1H, d, J = 9.0 Hz, C8-H), 7.48 (1H, d, C1-H) 7.94 (2H, d, J = 9.0 Hz, C7,12-H), 8.58 (1H, s, C4-H), 9.21 (1H, d, J = 9.0 Hz, C11-H), 9.27 (1H, s, C6-H), 10.46 (1H, br, OH). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 153.43, 151.88, 148.52, 148.10, 143.05, 129.86, 127.03, 126.57, 126.36, 122.12, 119.27, 119.14, 104.16, 101.72, 101.66, 59.65. Anal. Calcd for C₁₉H₁₃NO₄·0.5 H₂O: C, 69.51; H, 4.30; N, 4.27. Found: C, 69.70; H, 4.26; N, 4.26. FAB-MS m/z: 320 (M+1)+.

3-Hydroxy-2-iodo-4-methoxybenzaldehyde (18)
To a solution of isovanillin (17) (10.0 g, 65.7 mmol) in pyridine (40 mL), a solution of ICl (12.1 g, 74.5 mmol) in 1,4-dioxane (80 mL) was dropwise added under cooling at 0 °C. The mixture was warmed to rt and allowed to stand for 3 h. After water was added to the mixture, the resulting precipitates were collected, then recrystallization from AcOEt gave 18 (13.4 g, 74%). Yellow needles, mp 162.3-163.6 °C (AcOEt) [lit.14 169-171.5 °C]. 1H-NMR (500 MHz, CDCl3) δ: 10.03 (1H, s, ArCHO), 7.56 (1H, d, J = 8.3 Hz, C5-H), 6.93 (1H, d, J = 8.3 Hz, C6-H), 6.31 (1H, s, ArOH), 4.00 (3H, s, ArOCH3).

2-Iodo-3,4-dimethoxybenzaldehyde (19)

A mixture of 11 (10.0 g, 36.0 mmol), K2CO3 (9.40 g, 68.0 mmol), (MeO)2SO2 (6.80 mL, 70.1 mmol), and acetone (50 mL) was heated under reflux for 1 h. The solvent was removed under reduced pressure, and then water was added to the mixture which was extracted with Et2O. The organic layer was washed with brine, dried over MgSO4, and concentrated to give a crude solid. Recrystallization from Et2O gave 19 (8.78 g, 84%). Colorless needles, mp 80.5-82.0 ºC (AcOEt) [lit.15a 82 ºC]. 1H-NMR (500 MHz, CDCl3) δ: 9.93 (1H, s, ArCHO), 7.63 (1H, d, J = 8.5 Hz, C6-H), 6.92 (1H, d, J = 8.5 Hz, C5-H), 3.91 (3H, s, ArOCH3), 3.80 (3H, s, ArOCH3).

2-Iodo-3,4-dimethoxybenzoic acid (20)

To a solution of 19 (1.00 g, 3.42 mmol), NaH2PO4·2H2O (137 mg, 0.878 mmol), and 30% H2O2 (600 mg, 5.29 mmol) in MeCN (15 mL), an 80% aqueous solution of NaClO2 (1.5 mL, 385 mg, 5.34 mmol) was added at 0 ºC. The mixture was stirred at the same temperature for 4 h, then poured into a 10% Na2S2O3 aqueous solution. After acidification with a 10% HCl aqueous solution, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO4, and concentrated to give a residue. Recrystallization from AcOEt gave 20 (1.01 g, 96%). Colorless needles, mp 203.8-204.5 ºC (AcOEt) [lit.16 204.5-205 ºC]. 1H-NMR (500 MHz, CDCl3) δ: 7.85 (1H, d, J = 8.5 Hz, C6-H), 6.93 (1H, d, J = 8.5 Hz, C5-H), 3.94 (3H, s, ArOCH3), 3.85 (3H, s, ArOCH3).

2-Iodo-3,4-dimethoxy-N-(6,7-methylenedioxy-1-naphthyl)benzamide (21)

A mixture of 20 (197 mg, 0.641 mmol), 8 (100 mg, 0.534 mmol), EDC (246 mg, 1.28 mmol), DMAP (7.3 mg, 0.059 mmol), and CH2Cl2 (10 mL) was stirred at rt overnight. After being poured into water, the mixture was extracted with CH2Cl2. The organic layer was washed with brine, dried over MgSO4, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt/hexane (1:4). Recrystallization from CHCl3-MeOH gave 21 (173 mg, 68%). Colorless needles, mp 124.6-125.8 ºC (CHCl3-MeOH). IR (KBr) cm⁻¹: 1654 (CO), 1468 (C-N), 1289, 1250 (COC). 1H-NMR (500 MHz, DMSO-d6) δ: 10.18 (1H, s), 7.65 (1H, d, J = 8.3Hz, C6-H), 7.54 (1H, d, J = 7.5Hz,
naphC₂-H), 7.49 (1H, s, naphC₃-H), 7.31 (3H, m, naphC₂, C₄, C₅-H), 7.19 (1H, d, J = 8.3 Hz, C₆-H), 6.14 (2H, s, OCH₂O), 3.88 (3H, s, OCH₃), 3.76 (1H, s, OCH₃). ¹³C-NMR (125 MHz, DMSO-d₆) δ: 168.3, 153.0, 148.4, 147.7, 147.5, 136.7, 133.0, 131.3, 125.8, 125.3, 124.4, 124.0, 121.7, 112.9, 104.0, 101.5, 99.9, 93.0, 60.0, 56.4. Anal. Calcd for C₂₀H₁₆NO₄·0.1H₂O: C, 50.14; H, 3.41; N, 2.92. Found: C, 49.84; H, 3.11; N, 2.97.

2-Iodo-3,4-dimethoxy-N-methyl-N-(6,7-methylenedioxy-1-naphthyl)benzamide (22)
To a mixture of NaH (60% in mineral oil, 76 mg, 1.89 mmol) and DMF (10 mL), 21 (300 mg, 0.629 mmol) was added and stirred at rt for 30 min. MeI (1.57 mL, 0.30 mmol) was added to the mixture, then stirred at 70 °C overnight. The mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, and concentrated to give a residue. Silica gel column chromatography with AcOEt/hexane (1:4) gave 22 (235 mg, 76%). Colorless prisms, mp 189.9-190.4 °C (AcOEt-hexane). IR (KBr) cm⁻¹: 1654 (CO), 1463(C=N), 1246 (COC). ¹H-NMR (500 MHz, CDCl₃) δ: 7.68 (0.15H, d, J = 8.5 Hz, C₆-H), 7.47 (1H, d, J = 7.7 Hz, naphC₆-H) 7.35 (1H, d, J = 7.7 Hz, naphC₅-H), 7.29 (1H, s, naphC₁-H) 7.10 (1H, t, J = 7.7 Hz, naphC₇-H), 7.19, 7.08 (0.15, 0.8H, s, naphC₄-H), 7.03 (0.15H, d, J = 8 Hz, C₅-H), 6.61 (0.85H, d, J = 8.5 Hz, C₆-H), 6.36 (0.85H, d, J = 8.5 Hz, C₅-H), 6.11, 6.09 (1.7H, d, J = 1.5 Hz, OCH₂O), 6.08, 6.05 (0.3H, d, J = 1.5 Hz, OCH₂O) 3.93, 3.90 (0.45H, s, OCH₃), 3.73, 3.64 (2.55H, s, OCH₃), 3.51 (2.55H, s, NCH₃), 3.21 (0.45H, s, NCH₃). ¹³C-NMR (125 MHz, CDCl₃) δ: 170.8, 153.0, 148.4, 147.7, 147.5, 136.7, 133.0, 131.6, 127.3, 127.1, 124.4, 124.2, 122.4, 111.3, 104.5, 101.5, 99.3, 93.3, 60.3, 55.7, 37.3. Anal. Calcd for C₂₁H₁₈NO₅: C, 51.34; H, 3.69; N, 2.85. Found: C, 51.58; H, 3.66; N, 2.92.

9,10-Dimethoxy-N-methyl-2,3-methylenedioxybenzo[c]phenanthridin-6(5H)-one (23)
A mixture of 22 (500 mg, 1.02 mmol), PPh₃ (107.4 mg, 0.408 mmol), Ag₂CO₃ (563 mg, 2.04 mmol) Pd(OAc)₂ (45.8 mg, 0.036 mmol), and DMF (5 mL) was heated under reflux for 1 h. After the mixture was diluted with AcOEt, any undissolved materials were filtered off. The mother liquid was washed with brine, dried over MgSO₄, and concentrated to give a residue which was subjected to silica gel column chromatography with AcOEt-hexane (1:3). The title compound 23 (337 mg, 91%) was obtained, which was recrystallized from AcOEt for use as an analytical sample. Colorless needles, mp 261.6-262.4 °C (AcOEt). IR (KBr) cm⁻¹: 1644 (CO), 1464 (CN), 1321, 1040 (COC). ¹H-NMR (500MHz, CDCl₃) δ: 9.10 (1H, d, J = 8.8 Hz, C₁₁-H), 8.38 (1H, d, J = 8.8 Hz, C₇-H), 7.538 (1H, d, J = 8.8 Hz, C₁₂-H), 7.535 (1H, s, C₄-H), 7.20 (1H, d, J = 8.8 Hz, C₅-H), 7.15 (1H, s, C₁-H), 6.08 (2H, s, OCH₂O), 4.02 (3H, s, NCH₃), 3.89 (6H, s, OCH₃). ¹³C-NMR (125 MHz, CDCl₃) δ: 164.7, 156.8, 147.9, 146.7, 145.6, 136.9, 132.1, 128.0, 125.8, 123.1, 122.8, 120.8, 120.1, 117.1, 112.2, 104.3, 102.8, 101.5, 60.3, 56.2, 41.7. HRMS (El) m/z: calcd for 363.1107, found: 363.1109.
9,10-Dimethoxy-N-methyl-2,3-methylenedioxybenzo[c]phenanthridinium chloride (2)

To a solution of 23 (100 mg, 0.275 mmol) in THF (5 mL), LiAlH₄ (31.3 mg, 0.825 mmol) was added at 0 °C, then the mixture was vigorously stirred for 30 min. After quenching with ice water, any undissolved materials were filtered off. To the mother liquid, a 10% HCl aqueous solution was added to leave yellow precipitates which were recrystallized from MeOH. The title compound 2 (78 mg, 74%) was obtained as yellow needles, mp 195.6-196.1 °C (MeOH) [lit. 152-153 °C (CHCl₃-MeOH)]. IR (KBr) cm⁻¹: 1619 (C=N), 1495 (CN), 1285, 1259 (COC).

¹H-NMR (500 MHz, CD₃OD) δ: 9.77 (1H, s, C₆-H), 9.16 (1H, d, J = 9.3 Hz, C₁₁-H), 8.33 (1H, d, J = 9.3 Hz, C₇-H), 8.00 (1H, s, C₄-H), 7.95 (1H, d, J = 9.3 Hz, C₁₂-H), 7.88 (1H, d, J = 9.3 Hz, C₈-H), 7.36 (1H, s, C₁-H), 6.24 (2H, s, OCH₂O), 4.81 (3H, s, NCH₃), 4.18 (3H, s, OCH₃), 3.93 (3H, s, OCH₃).

¹³C-NMR (125 MHz, CD₃OD) δ: 162.2, 155.7, 151.0, 150.1, 145.9, 134.4, 134.1, 132.1, 130.9, 129.1, 125.4, 122.9, 121.2, 120.5, 118.1, 106.1, 105.0, 104.2, 60.9, 57.8, 52.1.

Anal. Calcld for C₂₁H₁₈ClNO₄·0.8H₂O: C, 63.34; H, 4.96; N, 3.52. Found: C, 63.38; H, 5.10; N, 3.59.

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REFERENCES AND NOTES


9. For a preliminary communication of a part of this work, see: ref. 8a.


