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Total synthesis of benzo[*c*]phenanthridine alkaloids based on a microwave-assisted electrocyclic reaction of the aza 6π-electron system and structural revision of broussonpapyrine

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ABSTRACT

Total syntheses of the des-*N*-methyl (nor) type of benzo[*c*]phenanthridine alkaloids **1a**–**f** and **19** and benzo[*c*]phenanthridine alkaloids, chelerythrine (**2d**), and broussonpapyrine (**2f**) were achieved. The key step was the construction of tetracyclic 10,11-dihydrobenzo[*c*]phenanthridines using a microwave-assisted electrocyclic reaction of the 2-cycloalkenylbenzaldoxime methyl ether **4** as an aza 6π-electron system, which was derived in two steps from a Suzuki–Miyaura cross-coupling reaction of 2-bromobenzaldehyde **6** with 2-(3,4-dihydro-6,7-methylenedioxynaphthyl)boronic acid pinacol ester **7**. In addition, the exact structure of broussonpapyrine (**2f**) (2,3,9,10-tetraoxygenated type) was determined to be chelerythrine (**2d**).

1. Introduction

Benzo[*c*]phenanthridine alkaloids are a family of tetracyclic aromatic compounds, isolated mainly from the Rutaceae, Papaveraceae, and Fumariaceae plants.[1] The benzo[*c*]phenanthridines are an interesting structure having the isoquinoline part, many of which show a wide range of pharmacological properties including anti-tumor activity.[2,3] Among the benzo[*c*]phenanthridines, nitidine (**2a**) and fagaronine exhibit potential antileukemic activity through the inhibition of topoisomerases,[2–4] while sanguinarine (**2e**) shows antibacterial and antifungal activities.[4d,e] The 7-hydroxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium hydrogen sulfate (NK109) (**2c**), as a topoisomerase II inhibitor, was the promising compounds. However, the activity of NK109 was not exhibited on the clinical trial.[5] NK314, exhibiting significant anti-tumor activity against drug-resistant human tumor cell lines, is a novel synthetic benzo[*c*]phenanthridine fused with pyrrolidine ring at the N5-C6 positions that has entered clinical trials as an anti-tumor agent.[6]

Synthetic studies started in 1937,[7] and since then, they have attracted much attention from the synthetic organic chemists during over the past seventy years.[1,8–10,13,20] Many synthetic approaches to the benzo[*c*]phenanthridine nucleus have been reported, and their routes involve the construction of either B or C ring in the final or semifinal stage. Synthetic methodologies until 1999 were clarified and summarized in an excellent review.[8] Despite the numerous reports on benzo[*c*]phenanthridine alkaloids, to date, highly efficient synthesis remains a challenge.

We are developing the synthesis of the 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.[11] Recently, we reported the total synthesis of furoisoquinoline,[12a] phenanthridine,[12b] β-carboline,[12c] azaanthraquinone,[12d] and benzo[*c*]phenanthridine[13] alkaloids based on a microwave (MW)-assisted electrocyclic reaction of the aza 6π-electron system. We here describes the full detailed synthesis of benzo[*c*]phenanthridines **1a**–**f**, and **2f** as depicted in Fig. 1. The aim of the synthetic plan is to design a synthesis of 11,12-dihydrobenzo[*c*]phenanthridine framework **3**, which would be derived from a 2-cycloalkenylbenzaldoxime methyl ether **4** through a new bond formation between the C4b and N5-positions in the tetracyclic benzo[*c*]phenanthridine by a microwave-assisted electrocyclic reaction as shown in Scheme 1. An appropriate substituted 2-cycloalkenylbenzaldoxime methyl ether **4** and its precursor **5** would be provided by the Suzuki–Miyaura coupling reaction[14] between 2-bromobenzaldehyde **6** and 3,4-dihydro-6,7-methylenedioxynaphthylboronic acid pinacol ester (**7**). This design would be applicable to the preparation of 2,3,8,9-, 2,3,7,8-, and 2,3,9,10-, three types of tetraoxygenated benzo[*c*]phenanthridines **1a**–**f** and **2f** (Scheme 1).

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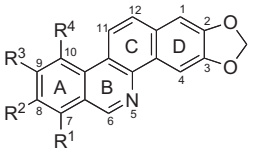
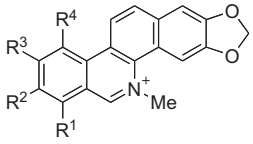


1a : R^1=R^4=H, R^2=R^3=OMe (nornitidine)
1b : R^1=R^4=H, R^2+R^3=OCH_2O (noravicine)
1c : R^1=OH, R^2=OMe, R^3=R^4=H (isodecarine)
1d : R^1=R^2=OMe, R^3=R^4=H (norchelerythrine)
1e : R^1+R^2=OCH_2O, R^3=R^4=H (norsanguinarine)
1f : R^1=R^2=H, R^3=OH, R^4=OMe (zanthoxyline)
1g : R^1=R^2=H, R^3=R^4=OMe (*O*-methylzanthoxyline)
1h : R^1=OMe, R^2=OH, R^3=R^4=H (decarine)

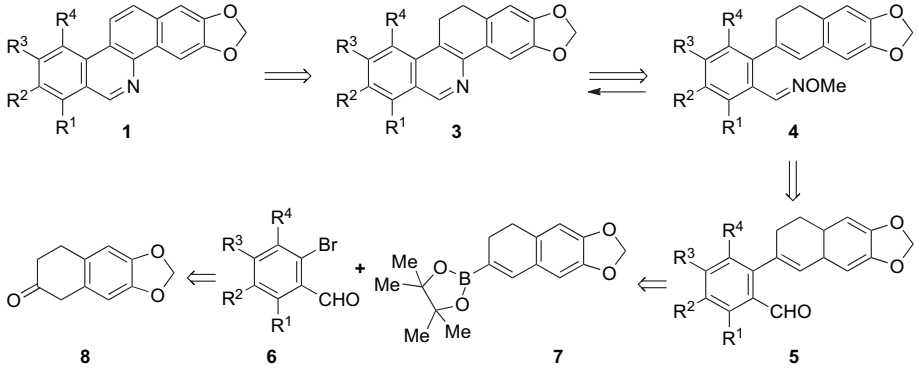


2a : R^1=R^4=H, R^2=R^3=OMe (nitidine)
2b : R^1=R^4=H, R^2+R^3=OCH_2O (avicine)
2c : R^1=OH, R^2=OMe, R^3=R^4=H (NK109)
2d : R^1=R^2=OMe, R^3=R^4=H (chelerythrine)
2e : R^1+R^2=OCH_2O, R^3=R^4=H (sanguinarine)
2f : R^1=R^2=H, R^3=R^4=OMe (broussonpapyrine)

Fig. 1.

O-triflate **10**, which was performed to the Stille reaction with allyl tributyltin in the presence of $PdCl_2(PPh_3)_2$ and LiCl to give the diallylbenzene **11**. Olefin metathesis of diallylbenzene **11** with the Grubbs's 1 catalyst afforded the 1,4-dihydronaphthalene **12**, which was subjected to hydroboration followed by oxidation to yield 2-hydroxytetrahydronaphthalene **13**. The alcohol **13** was subsequently oxidized by pyridinium chlorochromate (PCC) in CH_2Cl_2 to give the known β-tetralone **8**.[16] The unstable β-tetralone was immediately treated with *N*-phenylbis(trifluoromethanesulfonamide) (Tf_2NPh) and LDA to produce the triflate **14**, which was converted to the necessary pinacol borate **7** with bis(pinacolato)diborone and $PdCl_2(dppf)$.[14c] An alternative synthesis of the 6,7-methylenedioxy-β-tetralone (**8**) was achieved in 58% overall yield in a five-step sequence. The pinacol borate **7** was obtained by additional two steps through the triflate **14** (72%).

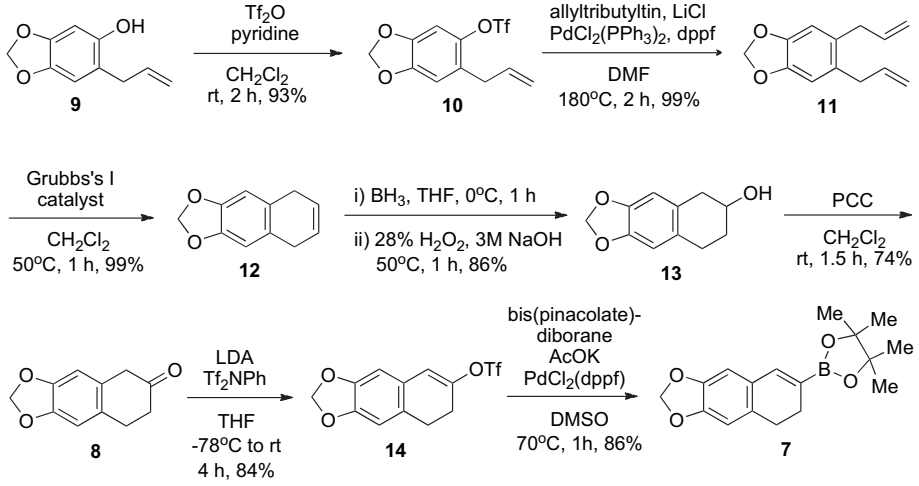
At first, 2,3,8,9-tetraoxygenated benzo[*c*]phenanthridines, nornitidine (**1a**)[1,17] and noravicine (**1b**)[1,17] were chosen as target compounds (Scheme 3). The Suzuki–Miyaura reaction of 2-bromo-4,5-dimethoxybenzaldehyde (**6a**)[18] and 2-bromo-4,5-methylenedioxybenzaldehyde (**6b**)[18] with the pinacol borate **7** smoothly proceeded in the presence of $PdCl_2(PPh_3)_2$ to yield the 2-cyclo-



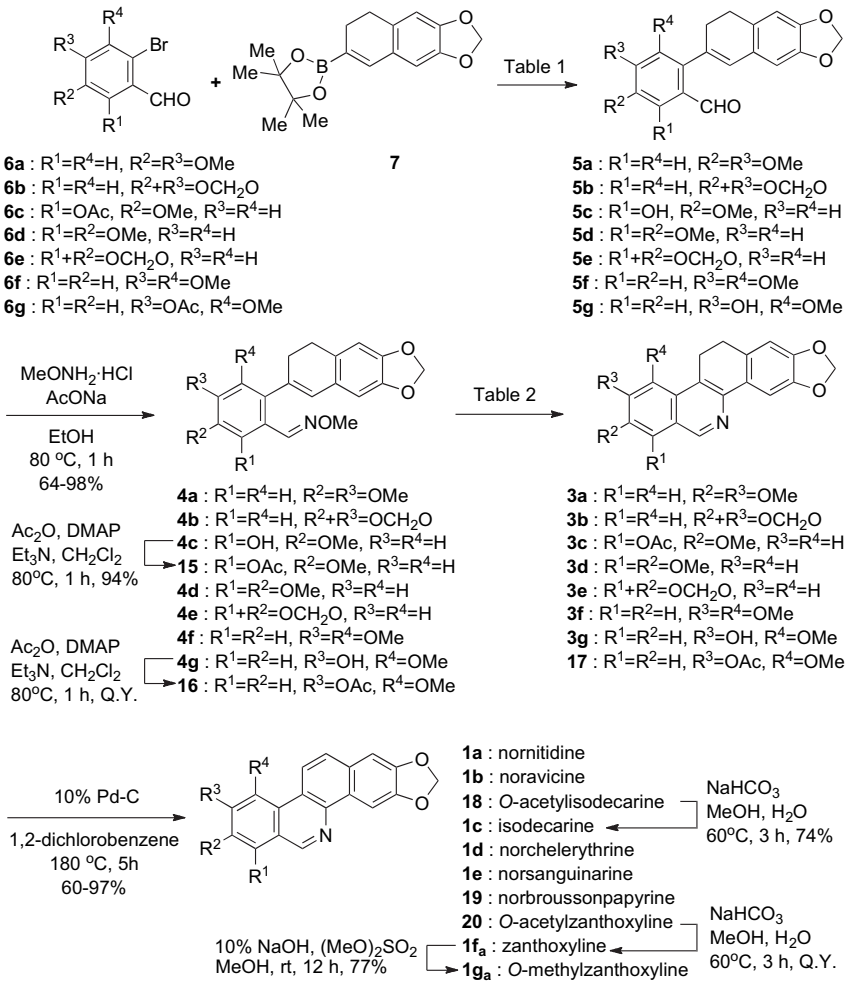
Scheme 1.

2. Result and discussions

To obtain a necessary pinacol borate **7**, we initially attempted an alternative synthesis of 6,7-methylenedioxy-β-tetralone (**8**) (Scheme 2). Treatment of 2-allyl-4,5-methylenedioxyphenol (**9**)[15] with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine afforded the alkenylbenzaldehydes **5a** (98%) and **5b** (78%) (Table 1: Runs 1 and 2). Treatment of the resulting **5a** and **5b** with hydroxylamine methyl ether gave the oxime methyl ethers **4a** (95%) and **4b** (98%), which were performed to an MW-assisted electrocyclic reaction at 180 °C in 1,2-dichlorobenzene to produce the 10,11-dihydrobenzo[*c*]phenanthridines **3a**[19] (84%) and **3b**[17b,19] (94%), respectively (Table 2:

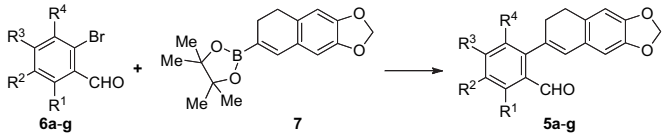


Scheme 2.



Scheme 3.

Table 1
Suzuki–Miyaura reactions between **6a**–**g** and **7**

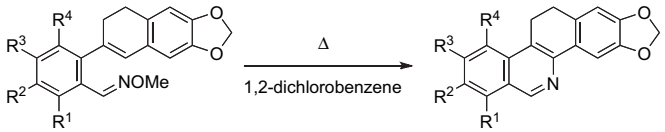


Run	Starting material		Pd Catalyst	Time (h)	Product	
	Compd.	R			Compd.	Yield (%)
1	**6a**	R^1=R^4=H, R^2=R^3=OMe	$PdCl_2(PPh_3)_2$	0.5	**5a**	98
2	**6b**	R^1=R^4=H, R^2+R^3=OCH_2O	$PdCl_2(PPh_3)_2$	0.5	**5b**	78
3	**6c**	R^1=OAc, R^2=OMe, R^3=R^4=H	$PdCl_2(PPh_3)_2$	1	**5c**	96
4	**6d**	R^1=R^2=OMe, R^3=R^4=H	$PdCl_2$(dppf)	1	**5d**	75
5	**6e**	R^1+R^2=OCH_2O, R^3=R^4=H	$PdCl_2$(dppf)	0.5	**5e**	97
6	**6f**	R^1=R^2=H, R^3=R^4=OMe	$PdCl_2(PPh_3)_2$	0.5	**5f**	72
7	**6g**	R^1=R^2=H, R^3=OAc, R^4=OMe	$PdCl_2$(dppf)	1	**5g**	54

Runs 2 and 4). In the case of conventional conditions without MW, the yields of **3a** and **3b** were 45% and 57% (Table 2: Runs 1 and 3). Finally, the dihydrobenzo[*c*]phenanthridines **3a** and **3b** were oxidized by refluxing with 10% Pd–C in 1,2-dichlorobenzene to give nornitidine (**1a**: 97%)[17] and noravicine (**1b**: 74%).[17] The overall yields of **1a** and **1b** were 76% and 53% in a four-step sequence after the Suzuki–Miyaura reaction.

Next, 2,3,7,8-tetraoxygenated benzo[*c*]phenanthridines, isodecarine (**1c**),[1,10d,20] norchelerythrine (**1d**),[1,21] and norsanguinarine (**1e**)[1,22] were synthesized as follows (Scheme 3). Namely, the Suzuki–Miyaura reaction of 2-acetoxy-6-bromo-3-methoxybenzaldehyde (**6c**),[23] 6-bromo-2,3-dimethoxybenzaldehyde (**6d**),[23] and 6-bromo-2,3-methylenedioxybenzaldehyde (**6e**)[24] with the pinacol borate **7** in the presence of $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf) afforded the 2-cycloalkenylbenzaldehydes **5c** (96%), **5d** (75%), and **5e** (97%), respectively (Table 1: Runs 3, 4, and 5). The deacetylated compound **5c** was obtained in the cross-coupling reaction of **6c** with **7**. Three 2-cycloalkenylbenzaldehydes **5c**, **5d**, and **5e** were converted to the

Table 2
Thermal electrocyclic reaction of aza 6π-electron systems



4a-g, **15** and **16** **3a-g**, **17**

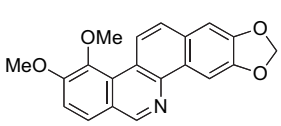
Run	Starting material (S.M.)		Temp (°C)	Time (h)	MW	Product	
	Compd.	R				Compd.	Yield (%)
1	**4a**	R^1=R^4=H, R^2=R^3=OMe	180	12	–	**3a**	45
2	**4a**	R^1=R^4=H, R^2=R^3=OMe	180	2.5	+	**3a**	84
3	**4b**	R^1=R^4=H, R^2+R^3=OCH_2O	180	12	–	**3b**	57
4	**4b**	R^1=R^4=H, R^2+R^3=OCH_2O	180	2	+	**3b**	94
5	**15**	R^1=OAc, R^2=OMe, R^3=R^4=H	180	3	–	**3c**	49
6	**15**	R^1=OAc, R^2=OMe, R^3=R^4=H	180	1	+	**3c**	77
7	**4d**	R^1=R^2=OMe, R^3=R^4=H	180	3	–	**3d**	49
8	**4d**	R^1=R^2=OMe, R^3=R^4=H	180	1	+	**3d**	84
9	**4e**	R^1+R^2=OCH2O, R^3=R^4=H	180	7	–	**3e**	37
10	**4e**	R^1+R^2=OCH2O, R^3=R^4=H	180	4	+	**3e**	95
11	**4f**	R^1=R^2=H, R^3=R^4=OMe	180	7	–	**3f**	S.M. Recover
12	**4f**	R^1=R^2=H, R^3=R^4=OMe	180	4	+	**3f**	80
13	**4g**	R^1=R^2=H, R^3=OH, R^4=OMe	180	6	–	**3g**	S.M. Recover
14	**4g**	R^1=R^2=H, R^3=OH, R^4=OMe	200	4	+	**3g**	75
15	**16**	R^1=R^2=H, R^3=OAc, R^4=OMe	180	7	–	**17**	24
16	**16**	R^1=R^2=H, R^3=OAc, R^4=OMe	200	5	+	**17**	67

corresponding oxime ethers **4c** (95%), **4d** (92%), and **4e** (64%). Acetylation of the oxime ether **4c** with Ac_2O in the presence of 4-*N*,*N*-dimethyaminopyridine (DMAP) and Et_3N in CH_2Cl_2 afforded the *O*-acetyl oxime ether **15** (94%), and then three oximes **15**, **4d**, and **4e** were subjected to an MW-assisted electrocyclic reaction at 180 °C to give the desired 11,12-dihydrobenzo[*c*]phenanthridines **3c** (77%), **3d** (84%), and **3e** (95%), respectively (Table 2: Runs 6, 8, and 10). In the conditions of electrocyclic reaction of **15**, **4d**, and **4e** without MW, good results were not obtained (Table 2: Runs 5, 7, and 9). Oxidation of **3c**, **3d**, and **3e** in a similar way provided the *O*-acetylisodecarine (**18**: 93%), norchelerythrine (**1d**: 91%),[21,22c] and norsanginarine (**1e**: 60%),[22] respectively. *O*-Acetylisodecarine **18** was hydrolyzed with $KHCO_3$ in an aqueous MeOH to produce isodecarine (**1c**: 74%).[10d,20] The overall yields of **1c**, **1d**, and **1e** were 45% (six-steps), 53%, and 35% (four-steps), respectively.

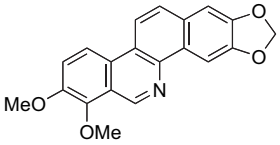
Furthermore, we attempted a synthesis of 2,3,9,10-tetraoxygenated benzo[*c*]phenanthridine, norbroussonpapyrine (**19**), the precursor of broussonpapyrine (**2f**),[25] and zanthoxyline (**1f**)[26] (Scheme 3). The Suzuki–Miyaura reaction of 2-bromo-3,4-dimethoxybenzaldehyde (**6f**)[27] and 4-acetoxy-2-bromo-3-methoxy benzaldehyde (**6g**)[28] with the pinacol borate **7** gave the 2-cycloalkenylbenzaldehyde **5f** (72%) and the deacetylated 2-cycloalkenylbenzaldehyde **5g** (54%). Subsequent treatment of **5f** and **5g** with hydroxylamine methyl ether yielded the oxime ethers **4f** (90%) and **4g** (95%). Acetylation of **4g** with Ac_2O in the presence of DMAP afforded the acetylated **16** (Q.Y.). The oximes **4f**, **4g**, and **16** were performed to an MW-assisted electrocyclic reaction at 200 °C (external) to give the desired tetracyclic dihydrobenzo[*c*]phenanthridines **3f** (80%), **3g** (75%), and acetylated **17** (67%), respectively (Table 2: Runs 12, 14, and 16). Under conventional conditions of Runs 11, 13, and 15 (Table 2) without MW, these reactions produced low yield or resulted in recovery of the starting material. Finally, dihydrobenzo[*c*]phenanthridines **3f**, **3g**, and **17** were converted to norbroussonpapyrine (**19**) (80%), zanthoxyline (**1f$_a$**) (95%), and *O*-acetylzanthoxyline (**20**) (95%), respectively, in a similar manner. Hydrolysis of **20** with an aqueous $NaHCO_3$ in MeOH afforded **1f$_a$** (Q.Y.). The overall yields of **19** and **1f$_a$** were 41% and 35% in four steps. The route of the acetylated **20** through the acetylated **17** provided 31% overall yield in six steps. Based on this result, it was found that there is no necessity for protecting the phenolic group in this ring closure (Table 2: Run 14). O-Methylation of the synthetic zanthoxyline (**1f$_a$**) with dimethyl sulfate and 10% NaOH afforded *O*-methylzanthoxyline (**1g$_a$**) (77%). Thus, the synthesis of 2,3,9,10-tetraoxygenated benzo[*c*]phenanthridines **19** and **1f$_a$** were also established. Our synthetic norbroussonpapyrine (**19**) and synthetic *O*-methylzanthoxyline (**1g$_a$**) should be consistent with *O*-methylzanthoxyline (**1g**) reported by Morel group,[26] but the NMR spectral data of **19** and/or **1g$_a$** was not identical with those of **1g** (Tables 3 and 4). Although, ^{1}H NMR spectral data of the reported *O*-methylzanthoxyline (**1g**) was nearly the same as those of synthetic norchelerythrine (**1d**), ^{13}C NMR spectral data of **1g** and **1d** was extremely superimposed. Therefore, the reported *O*-methylzanthoxyline (**1g**) was estimated to be norchelerythrine (**1d**) (Tables 3 and 4). It was recently reported by Abe group[29] that the correct structure of the reported zanthoxyline (**1f**) by Morel group[26] is 8-hydroxy-7-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (decarine) (**1h**), but not 9-hydroxy-10-methoxy-2,3-methylenedioxybenz[*c*]phenanthridine (**1f$_b$**)[29] or 7-hydroxy-8-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (isodecarine) (**1c**). Our synthetic 9-hydroxy-10-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (**1f$_a$**) was consistent with the reported **1f$_b$** by Abe group[29] on the comparison of the NMR spectral data (Tables 5 and 6).

Conversion of norbroussonpapyrine (**19**) to broussonpapyrine (**2f$_a$** and **2f$_b$**) was achieved by applying the procedures of the Ishikawa[30] and Simanek.[10d] Namely, treatment of **19** with formic acid followed by reduction with $NaBH_4$ gave the *N*-methylated 5,6-dihydrobenzo[*c*]phenanthridine **21**, which was oxidized by Jones reagent followed by treatment with diluted hydrochloric acid to yield broussonpapyrine chloride (**2f$_a$**). *N*-Methylation of **19** with methyl trifluoromethanesulfonate afforded broussonpapyrine trifluoromethanesulfonate (**2f$_b$**) (Scheme 4). The NMR spectral data of synthetic **2f** (Cl), however, were not identical with those of the reported broussonpapyrine (**2f**)[25] (Tables 7 and 8). For a structure analysis of the reported broussonpapyrine (**2f**), our synthetic norchelerythrine (**1d**) was converted to chelerythrine (**2d**) through the dihydro-compound in the same way[30] (Scheme 4). The NMR spectral data of our synthetic chelerythrine (**2d**) was more closely related to the data of reported broussonpapyrine (**2f**), besides the synthetic **2d** was consistent with chelerythrine

Table 3
Comparison of ^{1}H NMR spectral data[a] [δ (ppm), ($\Delta\delta$)[b]]



19 : norbroussonpapyryne
1g : *O*-methylzanthoxyline



1d : norchelerythrine

1g: *O*-Methylzanthoxyline reported by Morel[c],[26]		**1ga**: *O*-Methylzanthoxyline (synthetic compound)[d]		**19**: Norbroussonpapyrine (synthetic compound)[d]		**1d**: Norchelerythrine (synthetic compound)[d]	
4.02, s	(9-OCH_3)	4.00, s	(−0.02)	4.00, s	(−0.02)	4.06, s	(0.04)
4.06, s	(10-OCH_3)	4.09, s	(0.03)	4.09, s	(0.03)	4.13, s	(0.07)
6.05, s	(−O−CH_2−O−)	6.13, s	(0.08)	6.12, s	(0.07)	6.13, s	(0.08)
7.12, s	(C-1)	7.27, s	(0.15)	7.26, s	(0.14)	7.27, s	(0.15)
7.27, d	(C-8)	7.43, d	(0.16)	7.43, d	(0.16)	7.60, d	(0.33)
7.59, d	(C-12)	7.86, d	(0.27)	7.86, d	(0.27)	7.85, d	(0.26)
8.24, d	(C-7)	7.89, d	(−0.35)	7.89, d	(−0.35)	8.36, d	(0.12)
8.24, d	(C-11)	9.33, d	(1.09)	9.33, d	(1.09)	8.37, d	(0.13)
8.65, s	(C-4)	8.75, s	(0.10)	8.75, s	(0.10)	8.72, s	(0.07)
9.67, s	(C-6)	9.24, s	(−0.43)	9.25, s	(−0.42)	9.75, s	(0.08)

[a] NMR spectral data were measured in $CDCl_3$.
[b] Values in parentheses refer to the difference in chemical shift between the synthetic data and the reported data.
[c] 400 MHz ^{1}H NMR.
[d] 300 MHz ^{1}H NMR.

Table 4
Comparison of ^{13}C NMR spectral data[a] [δ (ppm), ($\Delta\delta$)[b]]

1g: *O*-Methylzanthoxyline reported by Morel[c],[26]		**1g$_a$**: *O*-Methylzanthoxyline (synthetic compound)[d]		**19**: Norbroussonpapyrine (synthetic compound)[d]		**1d**: Norchelerythrine (synthetic compound)[d]	
57.0	(9-OCH_3)	56.5	(−0.5)	56.5	(−0.5)	56.8	(−0.2)
61.8	(10-OCH_3)	60.1	(−1.7)	60.1	(−1.7)	61.9	(0.1)
101.3	(−O−CH_2−O−)	101.3	(0)	101.3	(0)	101.3	(0)
102.3	(C-4)	102.6	(0.3)	102.5	(0.2)	102.2	(−0.1)
104.3	(C-1)	103.8	(−0.5)	103.9	(−0.4)	104.4	(0.1)
118.2	(C-7)	113.5	(−4.7)	113.5	(−4.7)	118.2	(0)
118.2	(C-11)	119.6	(1.4)	119.6	(1.4)	118.3	(0.1)
119.2	(C-8)	122.9	(3.7)	122.9	(3.7)	118.7	(−0.5)
120.0	(C-10b)	123.1	(3.1)	123.1	(3.1)	120.0	(0)
121.9	(C-10a)	125.9	(4.0)	126.0	(4.1)	121.9	(0)
127.0	(C-12)	126.4	(−0.6)	126.4	(−0.6)	127.1	(0.1)
128.3	(C-6a)	127.4	(−0.9)	127.4	(−0.9)	128.1	(−0.2)
129.3	(C-4a)	128.8	(−0.5)	128.7	(−0.6)	129.2	(−0.1)
129.8	(C-12a)	130.1	(0.3)	130.1	(0.3)	129.7	(−0.1)
140.2	(C-4b)	141.7	(1.5)	141.5	(1.3)	140.0	(−0.2)
145.6	(C-10)	145.5	(−0.1)	145.5	(−0.1)	145.2	(−0.4)
146.5	(C-6)	148.1	(1.6)	148.1	(1.6)	146.6	(0.1)
148.4	(C-2)	148.5	(0.1)	148.5	(0.1)	148.3	(−0.1)
148.5	(C-3)	151.6	(3.1)	151.5	(3.0)	148.5	(0)
149.4	(C-9)	154.4	(5.0)	154.5	(5.1)	149.4	(0)

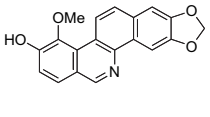
[a] NMR spectral data were measured in $CDCl_3$.
[b] Values in parentheses refer to the difference in chemical shift between the synthetic data and the reported data.
[c] 100 MHz ^{13}C NMR.
[d] 75 MHz ^{13}C NMR.

(**2d**) provided by Ishikawa in all respect (Tables 7 and 8). The structure of synthetic **2f$_b$** (CF_3SO_3) was also confirmed by X-ray single crystallographic analysis (Fig. 2). Consequently, it was found that the exact structure of the reported broussonpapyrine (**2f**) is 7,8-dimethoxy-*N*-methyl-2,3-methylendioxybenzo[*c*]phenanthridinium (chelerythrine) (**2d**). Moreover, the first syntheses of 9,10-dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (**19**) and 9,10-dimethoxy-*N*-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium chloride (**2f$_a$**) (and trifluoromethanesulfonate **2f$_b$**) were achieved.

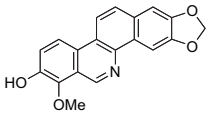
3. Conclusion

A versatile synthesis of benzo[*c*]phenanthridines and benzo[*c*]phenanthridine alkaloids was achieved by the constructing the tetracyclic 10,11-dihydrobenzo[*c*]phenanthridine framework **3a**–**g** and **17** based on the Suzuki–Miyaura reaction between 2-bromobenzaldehydes **6** and 2-(3,4-dihydro-6,7-methylenedioxynaphthyl) boronic acid pinacol ester (**7**), followed by the bond formation between C4b and N5 at the position of the tetracyclic ring using an MW-assisted thermal electrocyclic reaction of the 6π-electron system as a key step. Subsequent dehydrogenation of **3a**–**g** and **17** with 10% Pd–C afforded eight benzo[*c*]phenanthridines **1a**–**b**, **18**, **1d**–**e**, **19**, **20**, and **1f$_a$**. *O*-Acetyl derivatives **18** and **20** were converted to isodecarine **1c** and 9-hydroxy-10-methoxybenzo[*c*]phenanthridine (zanthoxyline) (**1f$_a$**) by hydrolysis. The synthetic zanthoxyline (**1f$_a$**) was converted to *O*-methylzanthoxyline (**1g$_a$**), which was closely superimposed with synthetic norbroussonpapyrine (**19**). Our synthetic zanthoxyline (**1f$_a$**) was consistent with 9-hydroxy-10-methoxybenzo[*c*]phenanthridine (zanthoxyline) (**1f$_b$**) by Abe

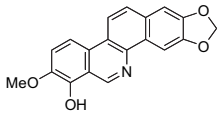
Table 5
Comparison of ^{1}H NMR spectral data[a] [δ (ppm), ($\Delta\delta$)[b]]



1f : zanthoxyline



1h : decarine



1c : isodecarine

1f: Zanthoxyline reported by Morel[c],[26]		**1f$_a$**: Zanthoxyline (synthetic compound)[d]		**1f$_b$**: Zanthoxyline reported by Abe[29]		**1h**: Decarine reported by Abe[29]		**1c**: Isodecarine (synthetic compound)[d]	
4.09, s	(10-OCH_3)	3.88, s	(−0.21)	3.88, s	(−0.21)	4.01, s	(−0.08)	3.98, s	(−0.11)
6.09, s	(−O−CH_2−O−)	6.21, s	(0.12)	6.21, s	(0.12)	6.20, s	(0.11)	6.20, s	(0.11)
7.46, s	(C-1)	7.48, s	(0.02)	7.48, s	(0.02)	7.50, s	(0.04)	7.48, s	(0.02)
7.61, d	(C-8)	7.42, d	(−0.19)	7.43, d	(−0.18)	7.57, d	(−0.04)	7.70, d	(0.09)
7.92, d	(C-12)	7.93, d	(0.01)	7.94, d	(0.02)	7.95, d	(0.03)	7.93, d	(0.01)
8.42, d	(C-7)	7.93, d	(−0.49)	7.94, d	(−0.48)	8.46, d	(0.04)	8.23, d	(−0.19)
8.46, d	(C-11)	9.26, d	(0.80)	9.21, d	(0.81)	8.50, d	(0.04)	8.49, d	(0.03)
8.57, s	(C-4)	8.58, s	(0.01)	8.58, s	(0.01)	8.53, s	(−0.04)	8.51, s	(−0.06)
9.61, s	(C-6)	9.21, s	(−0.40)	9.27, s	(−0.34)	9.57, s	(−0.04)	9.65, s	(0.04)

[a] NMR spectral data were measured in DMSO-d_6.
[b] Values in parentheses refer to the difference in chemical shift between the synthetic data and the reported data.
[c] 400 MHz ^{1}H NMR.
[d] 300 MHz ^{1}H NMR.

Table 6
Comparison of ^{13}C NMR spectral data[a] [δ (ppm), ($\Delta\delta$)[b]]

1f: Zanthoxyline reported by Morel[c],[26]		**1f$_a$**: Zanthoxyline (synthetic compound)[d]		**1f$_b$**: Zanthoxyline reported by Abe[29]		**1h**: Decarine reported by Abe[29]		**1c**: Isodecarine (synthetic compound)[d]	
61.9	(10-OCH_3)	59.5	(-2.4)	59.7	(−2.2)	61.4	(−0.5)	56.9	(−5.0)
102.0	(−O−CH_2−O−)	101.6	(−0.4)	101.7	(−0.3)	100.9	(−1.1)	101.1	(−0.9)
102.4	(C-4)	101.6	(−0.8)	101.7	(−0.7)	102.0	(−0.4)	101.6	(−0.8)
105.1	(C-1)	104.0	(−1.1)	104.2	(−0.9)	105.0	(−0.1)	104.5	(−0.6)
118.9	(C-7)	119.0	(0.1)	119.1	(0.2)	118.7	(−0.2)	118.7	(−0.2)
119.0	(C-11)	119.1	(0.1)	119.3	(0.3)	119.2	(0.2)	118.9	(−0.1)
121.8	(C-10a)	122.1	(0.3)	122.1	(0.3)	121.4	(−0.4)	119.8	(−2.0)
125.6	(C-8)	126.2	(0.6)	126.4	(0.8)	125.6	(0)	127.0	(1.4)
127.4	(C-6a)	126.4	(−1.0)	126.6	(−0.8)	127.2	(−0.2)	127.1	(−0.3)
128.1	(C-12)	126.8	(−1.3)	127.0	(−1.1)	128.2	(0.1)	128.3	(0.2)
129.9	(C-12a)	129.7	(−0.2)	129.9	(0)	129.7	(−0.2)	129.4	(−0.5)
143.2	(C-10)	142.9	(−0.3)	143.1	(−0.1)	142.7	(−0.5)	142.8	(−0.4)
145.5	(C-6)	147.9	(2.4)	148.1	(2.6)	145.1	(−0.4)	144.3	(−1.2)
148.1	(C-9)	148.4	(0.3)	148.5	(0.4)	148.1	(0)	146.7	(−1.4)
148.7	(C-2)	151.9	(3.2)	151.9	(3.2)	148.5	(−0.2)	148.0	(−0.7)
148.9	(C-3)	153.1	(4.2)	153.4	(4.5)	148.8	(−0.1)	148.1	(−0.8)

[a] NMR spectral data were measured in DMSO-d_6.
[b] Values in parentheses refer to the difference in chemical shift between the synthetic data and the reported data.
[c] 100 MHz ^{13}C NMR.
[d] 75 MHz ^{13}C NMR.

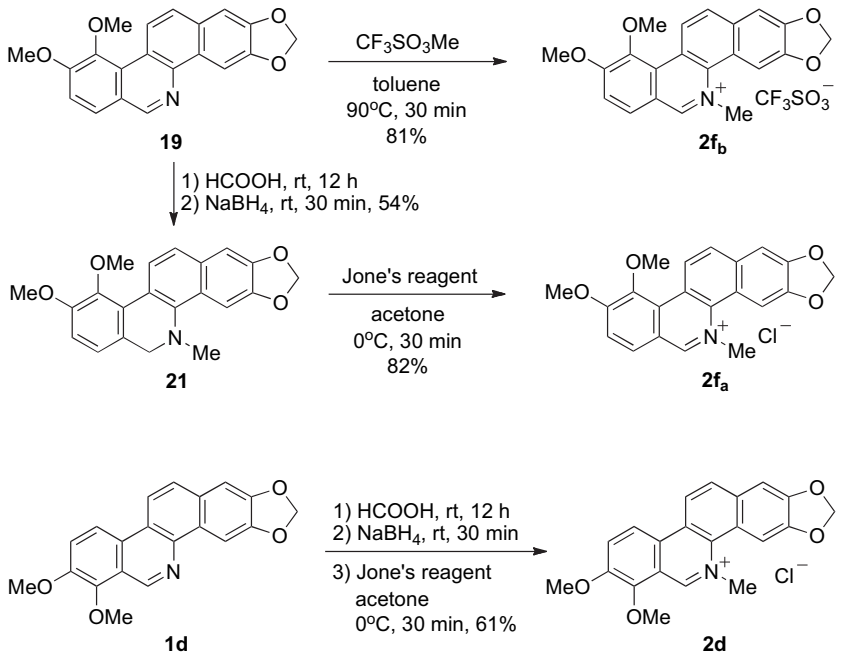
group[29] in all respects. In addition, 9,10-dimethoxy-*N*-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium chloride (broussonpapyrine) (**2f$_a$**) was synthesized from 9,10-dimethoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (norbroussonpapyrine) (**19**). Based on the comparison of NMR spectral data, it was found that the exact structure of the reported broussonpapyrine (**2f**) by Qin group[25] is the known chelerythrine (**2d**). Although, 9,10-dimethoxy-*N*-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium chloride (**2f$_a$**) and 9-hydroxy-10-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (**1f$_a$**) were unnatural compounds, our synthetic methodology was confirmed to be applicable for the synthesis of the 2,3,9,10-tetraoxygenated type of benzo[*c*]phenanthridine.

4. Experimental section

4.1. General

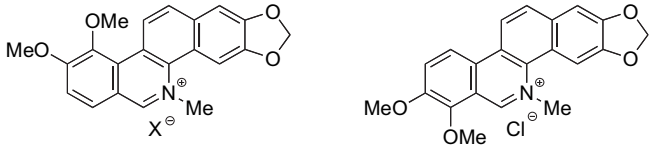
Melting points were determined on a Yanagimoto micro-melting point apparatus MP-500D and are uncorrected. Infrared spectra were recorded with ATR method on a Shimadzu FTIR-8000 spectrometer. Nuclear magnetic resonance spectra were taken with a JEOL JNM AL-300 and JNM-ECA500 instruments using tetramethylsilane as an internal standard. Mass spectra were measured by Shimadzu QP-5050, JEOL JMS-700, and Waters LCT spectrometers by direct inlet system, respectively. The reaction of microwave (MW) irradiation was carried out by Discover of CEM Co. Ltd. with 2450 MHz. Anhydrous THF, CH_2Cl_2, and DMF were used commercially available solvents (Cica reagents) for organic synthesis. 1,2-Dichlorobenzene, using for an MW-assisted electrocyclic reaction, was degassed before use. Silica gel (Merck Art 7744, 60–100 mesh) was used for column chromatography.

*4.1.1. 1-Allyloxy-3,4-methylenedioxy-6-trifluoromethanesulfonyloxybenzene **10**.* A solution of Tf_2O (4 mL, 24 mmol) was added to an ice-cooled solution of phenol **9**[15] (4 g, 20 mmol) and pyridine (2.1 mL, 30 mmol) in CH_2Cl_2 (200 mL) under an N_2 atmosphere. After being stirred at rt for 12 h, the mixture was quenched with water. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column



Scheme 4.

Table 7
Comparison of ^{1}H NMR spectral data[a] [δ (ppm), ($\Delta\delta$)[b]]



2f : broussonpapyrine **2d** : chelerythrine

2f: Broussonpapyrine reported by Qin[c,25]		**2f$_a$**: Broussonpapyrine (Cl:synthetic compound)[d]		**2d**: Chelerythrine (synthetic compound)[d]		**2d**: Chelerythrine (provided by Ishikawa)[c]	
4.15, s	(9-OCH_3)	4.22, s	(0.07)	4.14, s	(−0.01)	4.14, s	(−0.01)
4.25, s	(10-OCH_3)	4.00, s	(−0.25)	4.28, s	(0.03)	4.29, s	(0.04)
5.00, s	(N−CH_3)	4.84, s	(−0.16)	4.99, s	(−0.01)	4.99, s	(−0.01)
6.28, s	(−O−CH_2−O−)	6.26, s	(−0.02)	6.27, s	(0.01)	6.27, s	(−0.01)
7.58, s	(C-1)	7.54, s	(−0.04)	7.55, s	(−0.03)	7.54, s	(−0.04)
8.16, s	(C-4)	8.11, s	(−0.05)	8.18, s	(0.02)	8.17, s	(0.01)
8.20, d	(C-12)	8.17, d	(−0.03)	8.20, d	(0)	8.18, d	(−0.02)
8.21, d	(C-7)	8.37, d	(0.16)	8.20, d	(−0.01)	8.20, d	(−0.01)
8.64, d	(C-11)	9.48, d	(0.84)	8.64, d	(0)	8.62, d	(−0.02)
8.68, d	(C-8)	7.95, d	(−0.73)	8.67, d	(−0.01)	8.65, d	(−0.03)
9.98, s	(C-6)	9.78, s	(−0.20)	9.97, s	(−0.01)	9.96, s	(−0.02)

[a] NMR spectral data were measured in CD_3OD.
[b] Values in parentheses refer to the difference in chemical shift between the synthetic data and the reported data.
[c] 500 MHz ^{1}H NMR.
[d] 300 MHz ^{1}H NMR.

chromatography (silica gel, 50 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily triflate **10** (6.5 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.34–3.42 (2H, m), 5.07–5.21 (2H, m), 5.79–5.96 (1H, m), 6.00 (2H, s), 6.73 (1H, s), 6.74 (1H, s). MS (EI) *m*/*z*: 310 (M^+). HRMS (EI) calcd for $C_{11}H_9F_3O_5S$ 310.0123; found 310.0122.

*4.1.2. 1,2-Diallyloxy-4,5-methylenedioxybenzene **11**.* A solution of allyl tributyltin (21 mL, 80 mmol) was added to a mixture of the *O*-triflate **10** (17.5 g, 60 mmol), LiCl (3.6 g, 80 mmol), $PdCl_2(PPh_3)_2$ (0.5 g, 0.6 mmol), and dppf (0.3 g, 0.6 mmol) in DMF (100 mL) at rt under an argon atmosphere. The stirred mixture was heated for 2 h at 180 °C, which was cooled to rt. After being quenched with an aqueous solution of KF (30%), and then the mixture was stirred at rt for 2 h. The mixture was filtered off through Celite pad and the filtrate 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, 100 g) using hexane as an eluent to give the oily diallylbenzene **11** (11.7 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.29 (4H, d, *J*=5.9 Hz), 4.96–5.06 (4H, m), 5.84–5.98 (4H, m), 6.66 (2H, s). MS (EI) *m*/*z*: 202 (M^+). HRMS (EI) calcd for $C_{13}H_{14}O_2$ 202.0994; found 202.0986.

*4.1.3. 1,4-Dihydro-6,7-methylenedioxynaphthalene **12**.* A stirred mixture of the diallylbenzene **11** (2 g, 9.17 mmol) and Grubbs first (400 mg, 0.49 mmol) in CH_2Cl_2 (40 mL) was heated at 50 °C for 1 h under N_2 atmosphere. After removal of solvent the residue was

Table 8
Comparison of ^{13}C NMR spectral data[a] [δ (ppm), ($\Delta\delta$)[b]]

2f: Broussonpapyrine reported by Qin[c,25]		**2f$_a$**: Broussonpapyrine (Cl:synthetic compound)[d]		**2d**: Chelerythrine (synthetic compound)[d]		**2d**: Chelerythrine (provided by Ishikawa)[c]	
52.94	(N–CH_3)	51.98	(−0.96)	52.94	(0)	52.99	(0.05)
57.6	(9-OCH_3)	57.8	(0.2)	57.6	(0)	57.6	(0)
62.8	(10-OCH_3)	60.9	(−1.9)	62.9	(0.1)	62.9	(0.1)
104.3	(−O–CH_2–O−)	104.2	(−0.1)	104.4	(0.1)	104.4	(0.1)
105.1	(C-4)	105.1	(0)	105.2	(0.1)	105.1	(0)
107.1	(C-1)	106.3	(−0.8)	107.1	(0)	107.1	(0)
119.5	(C-11)	118.3	(−1.2)	119.6	(0.1)	119.5	(0)
119.9	(C-7)	120.7	(0.8)	120.0	(0.1)	119.9	(0)
120.9	(C-6a)	121.5	(0.6)	121.0	(0.1)	120.9	(0)
121.8	(C-4a)	123.3	(1.5)	121.9	(0.1)	121.8	(0)
127.1	(C-12a)	125.8	(−1.3)	127.2	(0.1)	127.1	(0)
127.5	(C-8)	129.5	(2.0)	127.4	(−0.1)	127.4	(−0.1)
130.1	(C-10a)	131.2	(1.1)	130.2	(0.1)	130.1	(0)
132.6	(C-12)	132.0	(−0.6)	132.7	(0.1)	132.6	(0)
133.5	(C-4b)	134.5	(1.0)	133.6	(0.1)	133.5	(0)
134.3	(C-10b)	134.9	(0.6)	134.4	(0.1)	134.3	(0)
147.5	(C-10)	146.3	(−1.2)	147.6	(0.1)	147.5	(0)
150.8	(C-3)	150.3	(−0.5)	150.8	(0)	150.8	(0)
151.0	(C-2)	151.2	(0.2)	151.0	(0)	151.0	(0)
151.8	(C-6)	155.8	(4.0)	151.9	(0.1)	151.8	(0)
152.1	(C-9)	162.4	(10.3)	152.2	(0.1)	152.1	(0)

[a] NMR spectral data were measured in CD_3OD.
[b] Values in parentheses refer to the difference in chemical shift between the synthetic data and the reported data.
[c] 125 MHz ^{13}C NMR.
[d] 75 MHz ^{13}C NMR.

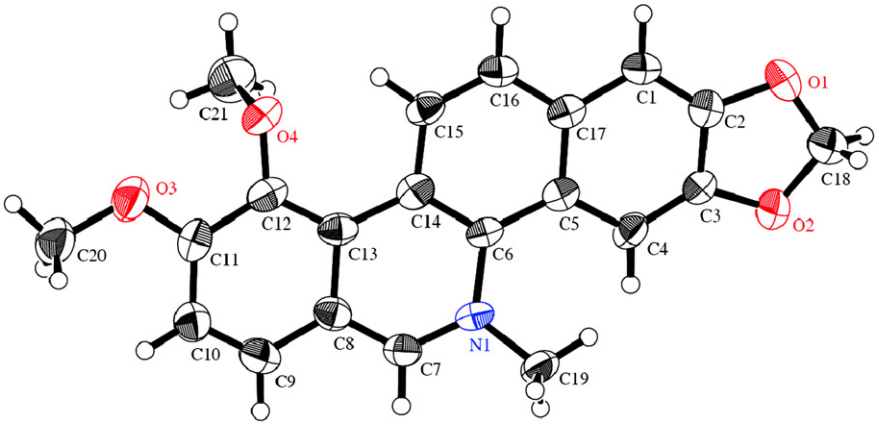


Fig. 2. ORTEP drawing of synthetic **2f$_b$** (trifluoromethanesulfonate).

purified by column chromatography using EtOAc–hexane (1:9 v/v) as an eluent to give the oily dihydronaphthalene **12** (1.8 g, 99%). ^1H NMR(300 MHz, $CDCl_3$) δ: 3.30 (4H, s), 5.80–5.82 (4H, m), 6.57 (2H, s). MS (EI) *m/z*: 174 (M^+). HRMS (EI) calcd for $C_{11}H_{10}O_2$ 174.0681; found 174.0677.

*4.1.4. 1,2,3,4-Tetrahydro-6,7-methylenedioxy-2-naphthol **13**.* An ice-cooled solution of BH_3·THF (1.4 mL, 1.6 mmol) was added to a solution of the dihydronaphthalene **12** (560 mg, 3.2 mmol) in THF (25 mL) under N_2 atmosphere. After being stirred at the same temperature for 1 h, an aqueous 3 M NaOH (0.52 mL, 1.6 mmol) followed by an aqueous 30% H_2O_2 (0.52 mL, 4.6 mmol) were added to the mixture, and then the resulting mixture was stirred at the same temperature for 1 h. After quenched with water, 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, 10 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the tetrahydronaphthol **13** (530 mg, 86%), mp 78–79 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.56–2.07 (2H, m), 2.62–3.03 (4H, m), 4.08–4.19 (1H, m), 5.88 (2H, s), 6.54 (1H, s), 6.56 (1H, s). MS (EI) *m/z*: 192 (M^+). HRMS (EI) calcd for $C_{11}H_{12}O_3$ 192.0786; found 192.0813.

*4.1.5. 6,7-Methylenedioxy-β-tetralone **8**.* A mixture of the 2-naphthol **13** (430 mg, 2.24 mmol), PCC (2.4 g, 11.20 mmol), and Celite (2.4 g) was stirred at rt for 1.5 h under N_2 atmosphere. After diluted with Et_2O, the mixture was filtered off through Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the β-tetralone **8** (314 mg, 74%), mp 93–94 °C (EtOAc–hexane) (lit.[16a] mp 91–92 °C and lit.[16b] mp 97–98 °C). IR (ATR) ν: 1699 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.50–2.54 (2H, m), 2.94–2.99 (2H, m), 3.48 (2H, s), 5.93 (2H, s), 6.60 (1H, s), 6.71 (1H, s). MS (EI) *m/z*: 190 (M^+). HRMS (EI) calcd for $C_{11}H_{10}O_3$ 190.0629; found 190.0624.

*4.1.6. 3,4-Dihydro-6,7-methylenedioxy-2-trifluoromethanesulfonyloxynaphthalene **14**.* A solution of β-tetralone **8** (360 mg, 1.89 mmol) in THF (5 mL) was added to a solution of LDA [prepared from *i*-Pr_2NH (0.36 mL, 2.84 mmol) and *n*-BuLi (2.6 M in hexane, 0.9 mL, 2.84 mmol)] at −78 °C under N_2 atmosphere. The mixture was stirred

at the same temperature at 30 min, and then Tf_2NPh (675 mg, 1.89 mmol) in THF (5 mL) was added to the mixture. The reaction temperature was gradually raised up to rt for 4 h. The mixture was quenched with water, and then the mixture was extracted with Et_2O. The Et_2O layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, 10 g) using EtOAc–hexane (1:19 v/v) as an eluent to give the oily triflate **14** (490 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.61–2.67 (2H, m), 2.93–2.99 (2H, m), 5.94 (2H, s), 6.35 (1H, s), 6.58 (1H, s), 6.64 (1H, s). MS (EI) *m*/*z*: 322 (M^+). HRMS (EI) calcd for $C_{12}H_9F_3O_5S$ 322.0123; found 322.0133.

4.1.7. 3,4-Dihydro-6,7-methylendioxynaphthylboronic acid pinacol ester ***7***. A mixture of the triflate **14** (250 mg, 0.78 mmol), bis(pinacolato)diborone, AcOK, and $PdCl_2$(dppf) (7 mg, 0.008 mmol) in DMSO (20 mL) was stirred at 80 °C for 1 h. 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 (silica gel, 10 g) using EtOAc–hexane (1:19 v/v) as an eluent to give the naphthylboronic acid pinacol ester **7** (200 mg, 86%), mp 92–94 °C (EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (12H, s), 2.30–2.36 (2H, m), 2.63–2.68 (2H, m), 5.91 (2H, s), 6.62 (2H, s), 7.08 (1H, s). MS (EI) *m*/*z*: 300 (M^+). HRMS (EI) calcd for $C_{17}H_{21}BO_4$ 300.1533; found 300.1534.

4.2. General procedure of Suzuki–Miyaura reaction between 2-bromobenzaldehyde 6 and 3,4-dihydro-6,7-methylenedioxynaphthylboronic acid pinacol ester 7

A mixture of bromobenzaldehyde **6**, the naphthylboronic acid pinacol ester **7**, K_2CO_3, and $PdCl_2(PPh_3)_2$ in anhyd MeOH and DMF was stirred at 80 °C for 0.5–1 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 naphthylbenzaldehyde **5**.

4.2.1. 2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-4,5-dimethoxybenzaldehyde ***5a***. 2-Bromo-4,5-dimethoxybenzaldehyde (**6a**)[18] (50 mg, 0.20 mmol), naphthylboronic acid pinacol ester **7** (200 mg, 0.62 mmol), K_2CO_3 (83 mg, 0.6 mmol), and $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) in anhyd MeOH (8 mL) and DMF (2 mL) were used to give the 2-naphthylbenzaldehyde **5a** (68 mg, 98%), mp 145–147 °C (EtOAc–hexane). IR (ATR) ν: 1660 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.64–2.70 (2H, m), 2.89–2.94 (2H, m), 3.96 (3H, s), 3.97 (3H, s), 5.94 (2H, s), 6.30 (1H, s), 6.63 (1H, s), 6.71 (1H, s), 6.81 (1H, s), 7.47 (1H, s), 10.09 (1H, s). MS (EI) *m*/*z*: 338 (M^+). HRMS (EI) calcd for $C_{20}H_{18}O_5$ 338.1154; found 338.1158.

4.2.2. 2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-4,5-methylenedioxybenzaldehyde ***5b***. 2-Bromopiperonal (**6b**)[18] (40 mg, 0.17 mmol), naphthylboronic acid pinacol ester **7** (80 mg, 0.26 mmol), K_2CO_3 (36 mg, 0.26 mmol), and $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) in anhyd MeOH (4 mL) and DMF (1 mL) were used to give the naphthylbenzaldehyde **5b** (44 mg, 78%), mp 182–184 °C (EtOAc–hexane). IR (ATR) ν: 1670 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.60–2.65 (2H, m), 2.90 (2H, t, *J*=8.1 Hz), 5.94 (2H, s), 6.06 (2H, s), 6.26 (1H, s), 6.61 (1H, s), 6.70 (1H, s), 6.82 (1H, s), 7.41 (1H, s), 10.04 (1H, s). MS (EI) *m*/*z*: 322 (M^+). HRMS (EI) calcd for $C_{19}H_{14}O_5$ 322.0841; found 322.0843.

4.2.3. 6-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-2-hydroxy-3-methoxybenzaldehyde ***5c***. 2-Acetoxy-6-bromo-3-methoxybenzaldehyde (**6c**)[23] (30 mg, 0.1 mmol), naphthylboronic acid pinacol ester **7** (45 mg, 0.15 mmol), K_2CO_3 (41 mg, 0.3 mmol), and $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) in anhyd MeOH (4 mL) and DMF (1 mL) were used to give the naphthylbenzaldehyde **5c** (31 mg, 96%), mp 180–181 °C (EtOAc–hexane). IR (ATR) ν: 1635 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.61–2.66 (2H, m), 2.86–2.91 (2H, m), 3.93 (3H, s), 5.94 (2H, s), 6.27 (1H, s), 6.62 (1H, s), 6.70 (1H, s), 6.84 (1H, d, *J*=8.1 Hz), 7.09 (1H, d, *J*=8.1 Hz), 10.13 (1H, s), 12.08 (1H, s). MS (EI) *m*/*z*: 324 (M^+). HRMS (EI) calcd for $C_{19}H_{16}O_5$ 324.0998; found 324.1025.

4.2.4. 6-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-2,3-dimethoxybenzaldehyde ***5d***. 6-Bromo-2,3-dimethoxybenzaldehyde (**6d**)[23] (30 mg, 0.12 mmol), naphthylboronic acid pinacol ester **7** (55 mg, 0.18 mmol), K_2CO_3 (51 mg, 0.37 mmol), and $PdCl_2$(dppf) (7 mg, 0.01 mmol) in anhyd MeOH (6 mL) and DMF (2 mL) were used to give the naphthylbenzaldehyde **5d** (31 mg, 75%), mp 148–149 °C (EtOAc–hexane). IR (ATR) ν: 1685 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.44–2.49 (2H, m), 2.88–2.93 (2H, m), 3.92 (3H, s), 3.96 (3H, s), 5.92 (2H, s), 6.22 (1H, s), 6.59 (1H, s), 6.67 (1H, s), 7.03 (1H, d, *J*=8.4 Hz), 7.10 (1H, d, *J*=8.4 Hz), 10.38 (1H, s). MS (EI) *m*/*z*: 338 (M^+). HRMS (EI) calcd for $C_{20}H_{18}O_5$ 338.1154; found 338.1157.

4.2.5. 6-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-2,3-methylenedioxybenzaldehyde ***5e***. 6-Bromo-2,3-methylenedioxybenzaldehyde (**6e**)[24] (20 mg, 0.09 mmol), naphthylboronic acid pinacol ester **7** (52 mg, 0.18 mmol), K_2CO_3 (36 mg, 0.26 mmol), and $PdCl_2$(dppf) (7 mg, 0.01 mol) in anhyd MeOH (4 mL) and DMF (1 mL) were used to give the naphthylbenzaldehyde **5e** (28 mg, 97%), mp 153–155 °C (EtOAc–hexane). IR (ATR) ν: 1679 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.58–2.63 (2H, m), 2.86–2.92 (2H, m), 5.93 (2H, s), 6.16 (2H, s), 6.27 (1H, s), 6.61 (1H, s), 6.69 (1H, s), 6.87 (1H, d, *J*=8.1 Hz), 6.99 (1H, d, *J*=8.1 Hz), 10.13 (1H, s). MS (EI) *m*/*z*: 322 (M^+). HRMS (EI) calcd for $C_{19}H_{14}O_5$ 322.0841; found 322.0843.

4.2.6. 2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-3,4-dimethoxybenzaldehyde ***5f***. 2-Bromo-3,4-dimethoxybenzaldehyde (**6f**)[27] (50 mg, 0.20 mmol), the naphthylboronic acid pinacol ester **7** (93 mg, 0.31 mmol), K_2CO_3 (87 mg, 0.62 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) in anhyd MeOH (8 mL) and DMF (2 mL) were used to give the oily naphthylbenzaldehyde **5f** (50 mg, 72%). IR (ATR) ν: 1676 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.89–2.94 (2H, m), 3.79 (3H, s), 3.96–3.98 (5H, m), 5.94 (2H, s), 6.28 (1H, s), 6.61 (1H, s), 6.72 (1H, s), 6.98 (1H, d, *J*=8.8 Hz), 7.79 (1H, d, *J*=8.8 Hz), 10.03 (1H, s). MS (EI) *m*/*z*: 338 (M^+). HRMS (EI) calcd for $C_{20}H_{18}O_5$ 338.1154; found 338.1149.

4.2.7. 2-(3,4-Dihydro-6.7-methylenedioxy-2-naphthyl)-4-hydroxy-3-methoxybenzaldehyde ***5g***. 4-Acetoxy-2-bromo-3-methoxybenzaldehyde (**6g**)[28] (220 mg, 0.81 mmol), the naphthylboronic acid pinacol ester 7 (267 mg, 0.89 mmol), K_2CO_3 (336 mg, 2.43 mmol), $PdCl_2$(dppf) (24 mg, 0.03 mmol) in anhyd MeOH (12 mL) and DMF (3 mL) were used to give the naphthylbenzaldehyde **5g** (130 mg, 54%), mp 153–155 °C (EtOAc–hexane). IR (ATR) ν: 1666 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.64 (2H, br s), 2.91–2.96 (2H, m), 3.80 (3H, s), 5.95 (2H, s), 6.38 (2H, s), 6.62 (1H, s), 6.72 (1H, s), 7.15 (1H, d, *J*=8.4 Hz), 7.74 (1H, d, *J*=8.4 Hz), 10.01 (1H, s). MS (EI) *m*/*z*: 324 (M^+). HRMS (EI) calcd for $C_{19}H_{16}O_5$ 324.0998; found 324.1127.

4.3. General procedure of benzaldehyde *O*-methyl oximes 4

A mixture of the naphthylbenzaldehydes **5**, $MeONH_2 \cdot HCl$, and AcONa in EtOH was stirred at 80 °C for 1 h. After removal of solvent followed by addition of water, 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 benzaldoxime *O*-methyl ethers **4**.

*4.3.1. 2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-4,5-dimethoxybenzaldehyde O-methyloxime **4a**.* The naphthylbenzaldehyde **5a** (100 mg, 0.30 mmol), $MeONH_2 \cdot HCl$ (37 mg, 0.44 mmol), and AcONa (37 mg, 0.44 mmol) in EtOH (10 mL) were used to give the oxime ether **4a** (103 mg, 95%), mp 119–120 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.52–2.57 (2H, m), 2.83–2.89 (2H, m), 3.90 (3H, s), 3.95 (3H, s), 5.93 (3H, s), 6.24 (1H, s), 6.61(1H, s), 6.68 (1H, s), 6.72 (1H, s), 7.39 (1H, s), 8.25 (1H, s). MS (EI) *m*/*z*: 367 (M^+). HRMS (EI) calcd for $C_{21}H_{21}NO_5$ 367.1420; found 367.1433.

*4.3.2. 2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-4,5-methylenedioxybenzaldehyde O-methyloxime **4b**.* The naphthylbenzaldehyde **5b** (42 mg, 0.13 mmol), $MeONH_2 \cdot HCl$ (19 mg, 0.20 mmol), and AcONa (19 mg, 0.20 mmol) in EtOH (5 mL) were used to give the oxime ether **4b** (45 mg, 98%), mp 178–180 °C (EtOAc-hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.47–2.53 (2H, m), 2.82–2.87 (2H, m), 3.93 (3H, s), 5.92 (2H, s), 5.99 (2H, s), 6.21 (1H, s), 6.60 (1H, s), 6.67 (1H, s), 6.71 (1H, s), 7.36 (1H, s), 8.22 (1H, s). MS (EI) *m*/*z*: 351 (M^+). HRMS (EI) calcd for $C_{20}H_{17}NO_5$ 351.1107; found 351.1126.

*4.3.3. 6-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-2-hydroxy-3-methoxybenzaldehyde O-methyloxime **4c**.* The naphthylbenzaldehyde **5c** (55 mg, 0.17 mmol), $MeONH_2 \cdot HCl$ (21 mg, 0.25 mmol), and AcONa (21 mg, 0.25 mmol) in EtOH (10 mL) were used to give the oxime ether **4c** (57 mg, 95%), mp 189–190 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.49–2.55 (2H, m), 2.83–2.88 (2H, m), 3.92 (3H, s), 3.98 (3H, s), 5.93 (2H, s), 6.23 (1H, s), 6.60 (1H, s), 6.68 (1H, s), 6.76 (1H, d, *J*=8.3 Hz), 6.90 (1H, d, *J*=8.3 Hz), 8.44 (1H, s), 10.59 (1H, s). MS (EI) *m*/*z*: 353 (M^+). HRMS (EI) calcd for $C_{20}H_{19}NO_5$ 353.1263; found 353.1273.

*4.3.4. 6-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-2,3-dimethoxybenzaldehyde O-methyloxime **4d**.* The naphthylbenzaldehyde **5d** (116 mg, 0.34 mmol), $MeONH_2 \cdot HCl$ (50 mg, 0.60 mmol), and AcONa (49 mg, 0.60 mmol) in EtOH (5 mL) were used to give the oxime ether **4d** (115 mg, 92%), mp 73–75 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.44–2.50 (2H, m), 2.81–2.86 (2H, m) 3.84 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 5.91 (2H, s), 6.32 (1H, s), 6.60 (1H, s), 6.66 (1H, s), 6.90 (1H, d, *J*=8.8 Hz), 7.01 (1H, d, *J*=8.8 Hz), 8.35 (1H, s). MS (EI) *m*/*z*: 367 (M^+). HRMS (EI) calcd for $C_{21}H_{21}NO_5$ 367.1420; found 367.1436.

*4.3.5. 6-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-2,3-methylenedioxybenzaldehyde O-methyloxime **4e**.* The naphthylbenzaldehyde **5e** (130 mg, 0.40 mmol), $MeONH_2 \cdot HCl$ (51 mg, 0.61 mmol), and AcONa (51 mg, 0.61 mmol) in EtOH (10 mL) were used to give the oxime ether **4e** (90 mg, 64%), mp 137–138 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.48–2.53 (2H, m), 2.82–2.87 (2H, m), 3.99 (3H, s), 5.92 (2H, s), 6.10 (2H, s), 6.26 (1H, s), 6.60 (1H, s), 6.67 (1H, s), 6.77 (1H, s, *J*=8.1 Hz), 6.81 (1H, d, *J*=8.1 Hz), 8.21 (1H, s). MS (EI) *m*/*z*: 351 (M^+). HRMS (EI) calcd for $C_{21}H_{17}NO_5$ 351.1107; found 351.1089.

*4.3.6. 2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-3,4-dimethoxybenzaldehyde O-methyloxime **4f**.* The naphthylbenzaldehyde **5f** (68 mg, 0.20 mmol), $MeONH_2 \cdot HCl$ (24 mg, 0.30 mmol), AcONa (24 mg, 0.30 mmol) in EtOH (10 mL) were used to give the oily oxime ether **4f** (70 mg, 90%). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.84–2.89 (2H, m), 3.76 (3H, s), 3.89–3.97 (8H, m), 5.92 (2H, s), 6.20 (1H, s), 6.60 (1H, s), 6.69 (1H, s), 6.88 (1H, d, *J*=8.8 Hz), 7.66 (1H, d, *J*=8.8 Hz), 8.16 (1H, s). MS (EI) *m*/*z*: 367 (M^+). HRMS (EI) calcd for $C_{21}H_{21}NO_5$ 367.1120; found 367.1145.

*4.3.7. 2-(3,4-Dihydro-6,7-methylenedioxy-2-naphthyl)-4-hydroxy-3-methoxybenzaldehyde O-methyloxime **4g**.* The naphthylbenzaldehyde **5g** (194 mg, 0.60 mmol), $MeONH_2 \cdot HCl$ (88 mg, 1.05 mmol), AcONa (86 mg, 1.05 mmol) in EtOH (10 mL) were used to give the oxime ether **4g** (203 mg, 95%), mp 152–153 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.53 (2H, br s), 2.86–2.91 (2H, m), 3.75 (3H, s), 3.92 (3H, s), 5.88 (1H, s), 5.94 (2H, s), 6.30 (1H, s), 6.62 (1H, s), 6.70 (1H, s), 6.92 (1H, d, *J*=8.6 Hz), 7.63 (1H, d, *J*=8.6 Hz), 8.15 (1H, s). MS (EI) *m*/*z*: 353 (M^+). HRMS (EI) calcd for $C_{20}H_{19}NO_5$ 353.1263; found 353.1278.

*4.3.8. 2-Acetoxy-6-(3,4-dihydro-6,7-methylenedioxy-2-naphthyl)-3-methoxybenzaldehyde O-methyloxime **15**.* A solution of the oxime ether **4c** (41 mg, 0.12 mmol) and Ac_2O (0.03 mL, 0.17 mmol) in the presence of DMAP (12 mg, 0.10 mmol) and Et_3N (0.03 mL, 0.17 mmol) in CH_2Cl_2 (5 mL) was stirred at 80 °C for 1 h. The reaction mixture was quenched with water, and then the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 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, 10 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the acetate (43 mg, 94%), mp 141–143 °C (EtOAc–hexane). IR (ATR) ν: 1768 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.34 (3H, s), 2.48–2.53 (2H, m), 2.81–2.86 (2H, m), 3.85 (3H, s), 3.93 (3H, s), 5.92 (2H, s), 6.28 (1H, s), 6.60 (1H, s), 6.67 (1H, s), 6.97 (1H, d, *J*=8.6 Hz), 7.15 (1H, d, *J*=8.6 Hz), 8.10 (1H, s). MS (EI) *m*/*z*: 395 (M^+). HRMS (EI) calcd for $C_{22}H_{21}NO_6$ 395.1369; found 395.1360.

*4.3.9. 4-Acetoxy-2-(3,4-dihydro-6,7-methylenedioxy-2-naphthyl)-3-methoxybenzaldehyde O-methyloxime **16**.* A solution of the oxime ether **4g** (58 mg, 0.16 mmol) and Ac_2O (0.03 mL, 0.17 mmol) in the presence of DMAP (20 mg, 0.16 mmol) and Et_3N (0.03 mL, 0.17 mmol) in CH_2Cl_2 (5 mL) was stirred at 80 °C for 1 h. The reaction mixture was quenched with water, and then the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 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, 10 g) using EtOAc–hexane (1:9 v/v) as an eluent to give the oily acetate (60 mg, 100%). IR(ATR) ν:1766 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.26 (3H, s), 2.44 (2H, br s), 2.76–2.81 (2H, m), 3.65 (3H, s), 3.85 (3H, s), 5.84 (2H, s), 6.18 (1H, s), 6.53 (1H, s), 6.61 (1H, s), 6.95 (1H, d, *J*=8.6 Hz), 7.61 (1H, d, *J*=8.6 Hz), 8.10 (1H, s). MS (EI) *m*/*z*: 395 (M^+). HRMS (EI) calcd for $C_{22}H_{21}NO_6$ 395.1369; found 395.1352.

4.4. General procedure of thermal electrocyclic reaction with MW irradiation

An each mixture of the oxime ethers **4a**–**g**, **15**, and **16** in 1,2-dichlorobenzene was stirred at 180–200 °C (external) under N_2 atmosphere under microwave irradiation. 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 corresponding 11,12-dihydrobenzo[*c*]phenanthridines **3a**–**g**, and **17**, respectively (Table 2). All thermal electrocyclic reactions without MW irradiation were carried out by the same procedure except MW, and the results were also shown in Table 2.

*4.4.1. 11,12-Dihydro-8,9-dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine **3a**.* The oxime ether **4a** (13 mg, 0.04 mmol) in 1,2-dichlorobenzene (1.5 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **3a** (10 mg, 84%), mp 230–232 °C (EtOAc–hexane) (lit.[19] mp 218–220 °C). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.93–2.98 (2H, m), 3.17–3.23 (2H, m), 4.05 (3H, s), 4.06 (3H, s), 5.98 (2H, s), 6.75 (1H, s), 7.21 (2H, d, *J*=2.2 Hz), 7.90 (1H, s), 8.96 (1H, s). MS (EI) *m*/*z*: 335 (M^+). HRMS (EI) calcd for $C_{20}H_{17}NO_4$ 335.1158; found 335.1161.

*4.4.2. 11,12-Dihydro-2,3,8,9-bismethylenedioxybenzo[c]phenanthridine **3b**.* The oxime ether **4b** (20 mg, 0.06 mmol) in 1,2-dichlorobenzene (1.5 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **3b** (17 mg, 94%), mp 296–298 °C (EtOAc–hexane) (lit.[17b] mp >300 °C and lit.[19] mp 288 °C). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.91–2.96 (2H, m), 3.12–3.17 (2H, m), 5.98 (2H, s), 6.10 (2H, s), 6.74

(1H, s), 7.19 (1H, s), 7.29 (1H, s), 7.88 (1H, s), 8.90 (1H, s). MS (EI) *m/z*: 319 (M^+). HRMS (EI) calcd for $C_{19}H_{13}NO_4$ 319.0845; found 319.0861.

*4.4.3. 7-Acetoxy-11,12-dihydro-8-methoxy-2,3-methylenedioxybenzo[c]phenanthridine **3c**.* The oxime ether **15** (24 mg, 0.06 mmol) in 1,2-dichlorobenzene (1.5 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **3c** (17 mg, 77%), mp 191–194 °C (EtOAc–hexane). IR (ATR) *ν*: 1768 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 2.48 (3H, s), 2.92–2.97 (2H, m), 3.22–3.28 (2H, m), 3.98 (3H, s), 5.98 (2H, s), 6.75 (1H, s), 7.54 (1H, d, *J*=9.2 Hz), 7.89 (1H, s), 7.94 (1H, d, *J*=9.2 Hz), 9.19 (1H, s). MS (EI) *m/z*: 363 (M^+). HRMS (EI) calcd for $C_{21}H_{17}NO_5$ 363.1107; found 363.1103.

*4.4.4. 11,12-Dihydro-7,8-dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine **3d**.* The oxime ether **4d** (41 mg, 0.11 mmol) in 1,2-dichlorobenzene (1.5 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **3d** (30 mg, 84%), mp 172–174 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 2.91–2.97 (2H, m), 3.21–3.26 (2H, m), 4.02 (3H, s), 4.07 (3H, s), 5.98 (2H, s), 6.75 (1H, s), 7.50 (1H, d, *J*=9.5 Hz), 7.77 (1H, d, *J*=9.5 Hz), 7.93 (1H, s), 9.48 (1H, s). MS (EI) *m/z*: 335 (M^+). HRMS (EI) calcd for $C_{20}H_{17}NO_4$ 335.1158; found 335.1155.

*4.4.5. 11,12-Dihydro-2,3,7,8-bismethylendioxybenzo[c]phenanthridine **3e**.* The oxime ether **4e** (21 mg, 0.06 mmol) in 1,2-dichlorobenzene (1 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **3e** (20 mg, 95%), mp 237–238 °C ($CHCl_3$–hexane). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 2.91–2.96 (2H, m), 3.21–3.25 (2H, m), 5.98 (2H, s), 6.24 (2H, s), 6.75 (1H, s), 7.38 (1H, d, *J*=8.8 Hz), 7.58 (1H, d, *J*=8.8 Hz), 7.90 (1H, s), 9.24 (1H, s). MS (EI) *m/z*: 319 (M^+). HRMS (EI) calcd for $C_{19}H_{13}NO_4$ 319.0845; found 319.0861.

*4.4.6. 11,12-Dihydro-9,10-dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine **3f**.* The oxime ether **4f** (44 mg, 0.12 mmol) in 1,2-dichlorobenzene (1.5 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **3f** (32 mg, 80%), mp 161 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 2.83–2.89 (2H, m), 3.71–3.76 (2H, m), 3.86 (3H, s), 4.04 (3H, s), 5.98 (2H, s), 6.75 (1H, s), 7.33 (1H, d, *J*=8.8 Hz), 7.73 (1H, d, *J*=8.8 Hz), 7.87 (1H, s), 9.02 (1H, s). MS (EI) *m/z*: 335 (M^+). HRMS (EI) calcd for $C_{20}H_{17}NO_4$ 335.1158; found 335.1144.

*4.4.7. 11,12-Dihydro-9-hydroxy-10-methoxy-2,3-methylenedioxybenzo[c]phenanthridine **3g**.* The oxime ether **4g** (180 mg, 0.51 mmol) in 1,2-dichlorobenzene (3 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **3g** (123 mg, 75%), mp 230–232 °C (EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 2.83–2.88 (2H, m), 3.65–3.70 (2H, m), 3.79 (3H, s), 5.99 (2H, s), 6.51 (1H, s), 6.75 (1H, s), 7.27 (1H, d, *J*=8.8 Hz), 7.68 (1H, d, *J*=8.8 Hz), 7.88 (1H, s), 9.00 (1H, s). MS (EI) *m/z*: 321 (M^+). HRMS (EI) calcd for $C_{19}H_{15}NO_4$ 321.1001; found 321.0997.

*4.4.8. 9-Acetoxy-11,12-dihydro-10-methoxy-2,3-methylenedioxybenzo[c]phenanthridine **17**.* The oxime ether **16** (34 mg, 0.09 mmol) in 1,2-dichlorobenzene (3 mL) with MW was used to give the dihydrobenzo[*c*]phenanthridine **17** (21 mg, 67%), mp 182–184 °C (EtOAc–hexane). IR (ATR) *ν*: 1749 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 2.43 (3H, s), 2.83–2.88 (2H, m), 3.68–3.73 (2H, m), 3.83 (3H, s), 5.99 (2H, s), 6.75 (1H, s), 7.27 (1H, d, *J*=8.8 Hz), 7.73 (1H, d, *J*=8.8 Hz), 7.88 (1H, s), 9.09 (1H, s). MS (EI) *m/z*: 363 (M^+). HRMS (EI) calcd for $C_{21}H_{17}NO_5$ 363.1107; found 363.1104.

4.5. General procedure of benzo[c]phenanthridines 1a,b, 18, 1c from 18, 1d,e, 19, and 20 from 11,12-dihydrobenzo[c] phenanthridines 3a–g, and 17

An each mixture of 11,12-dihydrobenzo[*c*]phenanthridines **3a**–**g**, and **17** in the presence of 10% Pd–C in 1,2-dichlorobenzene was stirred at 180 °C for 5–7 h. After removal of solvent, the residue was purified by column chromatography using EtOAc–hexane (1:9 v/v) as an eluent to give the corresponding benzo[*c*]phenanthridines **1a**,**b**, **18**, **1d**,**e**, **19**, and **20**, respectively. Compound **1c** was obtained from **18** by hydrolysis.

*4.5.1. 8,9-Dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine (nornitidine) **1a**.* The 11,12-dihydrobenzo[*c*]phenanthridine **3a** (30 mg, 0.03 mmol) and 10% Pd–C (30 mg) in 1,2-dichlorobenzene (5 mL) were used to give nornitidine (**1a**) (29 mg, 97%), mp 278–281 °C (EtOAc–hexane) (lit.[17a] mp 281–282 °C and lit.[17b] mp 281–282 °C). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 4.10 (3H, s), 4.17 (3H, s), 6.14 (2H, s), 7.28 (1H, s), 7.41 (1H, s), 7.84 (1H, d, *J*=9.2 Hz), 7.91 (1H, s), 8.31 (1H, d, *J*=9.2 Hz), 8.72 (1H, s), 9.25 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6) *δ*: 55.8, 56.2, 101.1, 101.5, 102.5, 104.6, 107.8, 119.3, 119.8, 122.0, 126.4, 128.3, 128.4, 129.4, 139.7, 148.0, 148.1, 149.8, 150.1, 153.2. MS (EI) *m/z*: 333 (M^+). HRMS (EI) calcd for $C_{20}H_{15}NO_4$ 333.1001; found 333.1021.

*4.5.2. 2,3,8,9-Bismethylenedioxybenzo[c]phenanthridine (noravicine) **1b**.* The 11,12-dihydrobenzo[*c*]phenanthridine **3b** (16 mg, 0.05 mmol) and 10% Pd–C (16 mg) in 1,2-dichlorobenzene (5 mL) were used to give noravicine (**1b**) (12 mg, 75%), mp 312 °C (EtOAc–hexane) (lit.[17a] mp 325 °C and lit.[17b] mp >300 °C). ^1H NMR (300 MHz, DMSO-d_6) *δ*: 6.20 (2H, s), 6.27 (2H, s), 7.50 (1H, s), 7.67 (1H, s), 7.92 (1H, d, *J*=8.8 Hz), 8.31 (1H, s), 8.51 (1H, d, *J*=8.8 Hz), 8.52 (1H, s), 9.25 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6) *δ*: 100.1, 101.1, 101.5, 102.2, 104.6, 104.9, 119.2, 120.3, 123.2, 123.3, 126.6, 128.2, 129.4, 130.3, 139.9, 147.9, 148.1, 150.1, 151.6. MS (EI) *m/z*: 317 (M^+). HRMS (EI) calcd for $C_{19}H_{11}NO_4$ 317.0668; found 317.0674.

*4.5.3. 7-Acetoxy-8-methoxy-2,3-methylenedioxybenzo[c]phenanthridine (O-acetylisodecarine) **18**.* The 11,12-dihydrobenzo[*c*]phenanthridine **3c** (28 mg, 0.08 mmol) and 10% Pd–C (20 mg) in 1, 2-dichlorobenzene (5 mL) were used to give acetylisodecarine **18** (26 mg, 93%), mp 261–262 °C ($CHCl_3$–hexane). IR (ATR) *ν*: 1743 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 2.54 (3H, s), 4.03 (3H, s), 6.14 (2H, s), 7.28 (1H, s), 7.65 (1H, *J*=9.2 Hz), 7.88 (1H, d, *J*=9.2 Hz), 8.37 (1H, d, *J*=9.0 Hz), 8.54 (1H, d, *J*=9.0 Hz), 8.69 (1H, s), 9.46 (1H, s). MS (EI) *m/z*: 361 (M^+). HRMS (EI) calcd for $C_{21}H_{15}NO_5$ 361.0950; found 361.0956.

*4.5.4. 7-Hydroxy-8-methoxy-2,3-methylenedioxybenzo[c]phenanthridine (isodecarine) **1c**.* A mixture of the *O*-acetylisodecarine **18** (12 mg, 0.03 mmol) and $NaHCO_3$ (6 mg, 0.07 mmol) in MeOH (10 mL) and H_2O (2 mL) was stirred at 60 °C for 3 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 general procedure described above to give isodecarine (**1c**) (8 mg, 74%), mp 239–241 °C ($CHCl_3$–hexane) (lit.[20] mp 225–227 °C and lit.[10d] mp 265–268 °C). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 4.08 (3H, s), 6.13 (2H, s), 6.24 (1H, br s), 7.27 (1H, s), 7.54 (1H, d, *J*=9.0 Hz), 7.85 (1H, d, *J*=8.8 Hz), 8.16 (1H, d, *J*=9.0 Hz), 8.35 (1H, d, *J*=8.8 Hz), 8.73 (1H, s), 9.79 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6) *δ*: 56.9, 101.1, 101.6, 104.5, 113.3, 117.4, 118.7, 118.9, 119.8, 127.0, 127.1, 128.3, 129.4, 138.9, 142.8, 144.3, 146.7, 148.0, 148.1. MS (EI) *m/z*: 319 (M^+). HRMS (EI) calcd for $C_{19}H_{13}NO_4$ 319.0845; found 319.0819.

*4.5.5. 7,8-Dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine (norchelerythrine) **1d**.* The 11,12-dihydrobenzo[*c*]phenanthridine **3d** (30 mg, 0.09 mmol) and 10% Pd–C (30 mg) in 1,2-dichlorobenzene (5 mL) were used to give norchelerythrine (**1d**) (27 mg, 91%), mp 210–212 °C ($CHCl_3$–hexane) (lit.[21a] mp 210–217 °C, lit.[21b] mp 210–212 °C, and lit.[17a,22a] mp 215–216 °C). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 4.06 (3H, s), 4.13 (3H, s), 6.13 (2H, s), 7.27

(1H, s), 7.60 (1H, d, *J*=9.0 Hz), 7.85 (1H, d, *J*=8.8 Hz), 8.36 (1H, d, *J*=9.0 Hz), 8.37 (1H, d, *J*=8.8 Hz), 8.72 (1H, s), 9.75 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.8, 61.9, 101.3, 102.2, 104.4, 118.2, 118.3, 118.7, 120.0, 121.9, 127.1, 128.1, 129.2, 129.7, 140.0, 145.2, 146.6, 148.3, 148.5, 149.4. MS (EI) *m*/*z*: 333 (M^+). HRMS (EI) for $C_{20}H_{15}NO_4$ calcd for 333.1001; found 333.0999.

4.5.6. 2,3,7,8-Bismethylenedioxybenzo[c]phenanthridine (norsanguinarine) ***1e****.* The 11,12-dihydrobenzo[*c*]phenanthridine **3e** (25 mg, 0.08 mmol) and 10% Pd–C (10 mg) in 1,2-dichlorobenzene (5 mL) were used to give norsanguinarine (**1e**) (15 mg, 60%), mp 282–283 °C ($CHCl_3$–hexane) (lit.[22a] mp 278–280 °C, lit.[22b] mp 280–281 °C, and lit.[22c] mp 285–287 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.21 (2H, s), 6.38 (2H, s), 7.52 (1H, s), 7.69 (1H, d, *J*=8.8 Hz), 7.99 (1H, d, *J*=8.8 Hz), 8.40 (1H, d, *J*=8.8 Hz), 8.50 (1H, s), 8.55 (1H, d, *J*=8.8 Hz), 9.40(1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 101.0, 101.6, 102.9, 104.5, 111.9, 114.3, 116.3, 118.9, 120.1, 127.2, 127.6. 128.4, 129.5, 138.8, 143.1, 144.6, 145.2, 148.1, 148.3. MS (EI) *m*/*z*: 317 (M^+). HRMS (EI) calcd for $C_{19}H_{11}NO_4$ 317.0668; found 317.0674.

4.5.7. 9,10-Dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine (norbroussonpapyrine) ***19****.* The 11,12-dihydrobenzo[*c*]phenanthridine **3f** (92 mg, 0.27 mmol) and 10% Pd–C (138 mg) in 1,2-dichlorobenzene (10 mL) were used to give norbroussonpapyrine (**19**) (72 mg, 80%), mp 206–208 °C (EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.00 (3H, s), 4.09 (3H, s), 6.12 (2H, s), 7.26 (1H, s), 7.43 (1H, d, *J*=8.8 Hz), 7.86 (1H, d, *J*=9.2 Hz), 7.89 (1H, d, *J*=8.8 Hz), 8.75 (1H, s), 9.25 (1H, s), 9.33 (1H, d, *J*=9.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.5, 60.1, 101.3, 102.5, 103.9, 113.5, 119.6, 122.9, 123.1, 126.0, 126.4, 127.4, 128.7, 130.1, 141.5, 145.5, 148.1, 148.5, 151.5, 154.5. MS (EI) *m*/*z*: 333 (M^+). HRMS (EI) calcd for $C_{20}H_{15}NO_4$ 333.1001; found 333.0997.

4.5.8. 9-Acetoxy-10-methoxy-2,3-methylenedioxybenzo[c]phenanthridine (O-acetylzanthoxyline) ***20****.* The 11,12-dihydrobenzo[*c*]phenanthridine **17** (18 mg, 0.05 mmol) and 10% Pd–C (27 mg) in 1, 2-dichlorobenzene (3 mL) were used to give *O*-acetylzanthoxyline **20** (17 mg, 95%), mp 212–213 °C (EtOAc–hexane). IR (ATR) ν: 1749 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.48 (3H, s), 3.97 (3H, s), 6.14 (2H, s), 7.28 (1H, s), 7.47 (1H, d, *J*=8.6 Hz), 7.88 (1H, d, *J*=9.2 Hz), 7.92 (1H, d, *J*=8.6 Hz), 8.76 (1H, s), 9.21 (1H, d, *J*=9.2 Hz), 9.33 (1H, s). MS (EI) *m*/*z*: 361 (M^+). HRMS (EI) calcd for $C_{21}H_{15}NO_5$ 361.0950; found 361.0928.

4.5.9. 9-Hydroxy-10-methoxy-2,3-methylenedioxybenzo[c]phenanthridine (zanthoxyline) ***1f$_a$****.* The 11,12-dihydrobenzo[*c*]phenanthridine **3g** (18 mg, 0.05 mmol) and 10% Pd–C (27 mg) in 1,2-dichlorobenzene (2 mL) were used to give 9-hydroxy-10-methoxy-2,3-methylenedioxy-benzo[*c*]phenanthridine (zanthoxyline) (**1f$_a$**) (17 mg, 95%), mp 226–227 °C (EtOAc–hexane) (lit.[26] mp 220–222°°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.93 (3H, s), 6.14 (2H, s), 7.28 (1H, d, *J*=8.6 Hz), 7.43 (1H, s), 7.86 (1H, d, *J*=8.6 Hz), 7.87 (1H, d, *J*=9.2 Hz), 8.75 (1H, s), 9.06 (1H, d, *J*=9.2 Hz), 9.24 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 60.8, 101.3, 102.6, 104.0, 117.1, 118.6, 122.0, 123.1, 126.6, 126.7, 126.8, 128.8, 130.2, 141.9, 142.1, 148.3, 148.7, 151.4, 151.5. MS (EI) *m*/*z*: 319 (M^+). HRMS (EI) calcd for $C_{19}H_{13}NO_4$ 319.0845; found 319.0838.

4.5.10. Hydrolysis of 9-acetoxy-10-methoxy-2,3-methylenedioxybenzo[c]phenanthridine (O-acetylzanthoxyline) ***20****.* The 9-acetoxybenzo[*c*]phenanthridine **20** (17 mg, 0.05 mmol) was treated with an aqueous $NaHCO_3$ in MeOH (10 mL) at 60 °C for 3 h, and then the mixture was diluted with water. 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 9-hydroxy-10-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (zanthoxyline) (**1f$_a$**) (16 mg, 100%), mp 226–227 °C (EtOAc–hexane). The NMR data were identical with those of above data (Section 4.5.9).

4.5.11. O-Methylation of 9-hydroxy-10-methoxy-2,3-methylenedioxybemzo[c]phenanthridine (zanthoxyline) ***1f$_a$*** *(O-methylzanthoxyline* ***1g$_a$****).* A solution of zanthoxyline (**1f$_a$**) (20 mg, 0.062 mmol) in MeOH (5 mL) and an aqueous 10% NaOH (0.118 mL, 0.29 mmol) was stirred at rt for 1 h. Dimethyl sulfate (0.024 mL, 0.26 mmol) was added to the solution. After being stirred at rt for 12 h, the mixture was quenched with water and extracted with 10% MeOH–$CHCl_3$. 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) to give the *O*-methylzanthoxyline (**1g$_a$**) (16 mg, 77%), mp 206–208 °C, which was consistent with the synthetic norbroussonpapyrine (**19**) in all respects.

4.5.12. 5,6-Dihydro-9,10-dimethoxy-N-methyl-2,3-methylenedioxybenzo[c]phenanthridine ***21*** *from 9,10-dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine (norbroussonpapyrine)* ***19****.* Norbroussonpapyrine (**19**) (15 mg, 0.05 mmol) in HCO_2H (2 mL) was stirred for 12 h at rt, and then $NaBH_4$ (168 mg, 4.4 mmol) was added portionwise to the solution at rt. After being stirred at rt for 30 min, the mixture was adjusted to weakly alkaline with an aqueous 10% NaOH and 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 (1:19, v/v) as an eluent to give the 5,6-dihydro-*N*-methylbenzo[*c*]phenanthridine **21** (8 mg, 54%), mp 168–170 °C (EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.59 (3H, s), 3.73 (3H, s), 3.93 (3H, s), 4.06 (2H, s), 6.05 (2H, s), 6.90 (1H, d, *J*=8.1 Hz), 6.99 (1H, d, *J*=8.1 Hz), 7.13 (1H, s), 7.50 (1H, d, *J*=8.8 Hz), 7.70 (1H, s), 8.44 (1H, d, *J*=8.8 Hz). MS (EI) *m*/*z*: 349 (M^+). HRMS (EI) calcd for $C_{21}H_{19}NO_4$ 349.1314; found 349.1324.

4.5.13. 9,10-Dimethoxy-N-methyl-2,3-methylenedioxybenzo[c]phenanthridinium chloride (broussonpapyrine chloride) ***2f$_a$*** *from* ***21****.* The Jones reagent (0.042 mL) was added to a stirred solution of the resulting 5,6-dihydro-*N*-methylbenzo[*c*]phenanthridine **21** in acetone (2 mL) under ice-cooling. The mixture was stirred at the same temperature for 30 min, and basified with an aqueous 10% NaOH, which 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 ice-cooling. The resulting precipitates were collected by filtration (9 mg, 82%) to give broussonpapyrine chloride (**2f$_a$**), mp 152–153 °C ($CHCl_3$–MeOH) (lit.[25] mp 201–205 °C). ^{1}H NMR and ^{13}C NMR spectra of synthetic **2f$_a$** were shown in Tables 7 and 8. TOFMS (ESI) calcd for $C_{21}H_{18}NO_4$ 348.1236; found 348.1220 (M^+).

4.5.14. 9,10-Dimethoxy-2,3-methylenedioxybenzo[c]phenanthridinium trifluoromethanesulfonate (broussonpapyrine trifluoromethanesulfonate) ***2f$_b$*** *from 9,10-dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine (norbroussonpapyrine)* ***19****.* A mixture of norbroussonpapyrine (**19**) (20 mg, 0.06 mmol) and methyl trifluoromethanesulfonate (39 mg, 0.24 mmol) in dry toluene (4 mL) was stirred in a sealed tube at 90 °C for 0.5 h. After being cooled to rt, the precipitated solid was filtered off, washed with heated toluene, which was recrystallized from $CHCl_3$–MeOH to give **2f$_b$** (24 mg, 81%), mp 216–218 °C ($CHCl_3$–MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ: 3.99 (3H, s), 4.21 (3H, s), 4.83 (3H, s), 6.26 (2H, s), 7.52 (1H, s), 7.94 (1H, d, *J*=9.2 Hz), 8.09 (1H, s), 8.14 (1H, d, *J*=9.2 Hz),

8.36 (1H, d, J=8.8 Hz), 9.44 (1H, d, J=8.8 Hz), 9.75 (1H, s). ^{13}C NMR (75 MHz, CD_3OD) δ: 52.0, 57.8, 60.9, 104.2, 105.0, 106.2, 118.2, 120.7, 121.4, 123.2, 125.7, 129.4, 131.1, 132.0, 134.4, 134.8, 146.3, 150.3, 151.2, 155.8, 162.4. ^{19}F NMR (500 MHz, CD_3OD) δ: −78.4 (s). TOFMS (ESI) calcd for $C_{21}H_{18}NO_4$ 348.1236; found 348.1226 (M^+).

4.5.15. X-ray crystal structure determination for ***2f$_b$***. A single crystal of **2f$_b$**, which was crystallized from $CHCl_3$–MeOH, was determined by a Rigaku RAXIS RAPID II. The structure was solved by direct methods using SIR2004 and expanded using Fourier techniques. All calculations were performed using the Crystal Structure crystallographic software package except for refinement, which was performed using SHELXL-97. The crystal data of **2f$_b$** have been deposited in CCDC with number 776,353. Crystal data of **2f$_b$**: $2C_{21}H_{18}NO_4\cdot 2CF_3SO_3\cdot CHCl_3$; orthorhombic, space group $Pna2_1$, a=14.3231(3) Å, b=17.7869(3) Å, c=18.3620(3) Å, V=4677.95 (15) Å^3; Z=4; D_c=1.582 g cm^{-3}; R=0.0967, R_w=0.3161, GOF=1.191. The ORTEP drawing is illustrated in Fig. 2.

4.5.16. 7,8-Dimethoxy-N-methyl-2,3-methylenedioxybenzo[c]phenanthridinium chloride (chelerythrine chloride) ***2d*** *from 7,8-dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine (norchelerythrine)* ***1d***. A solution of norchelerythrine (**1d**) (10 mg, 0.03 mmol) in HCO_2H (2 mL) was stirred for 12 h, and then $NaBH_4$ (111 mg, 2.93 mmol) was added to the solution at rt. After being stirred at rt for 30 min, the mixture was adjusted to weakly alkaline with an aqueous 10% NaOH and 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 (1:19, v/v) as an eluent to give the 5,6-dihydrochelerythrine (7 mg, 67%), mp 221–224 °C (lit.[30] mp 220–224 °C), which was used to the oxidation step. The Jones reagent (0.063 mL) was added to a stirred solution of the resulting 5,6-dihydrochelerythrine in acetone (10 mL) under ice-cooling. The mixture was stirred at the same temperature for 30 min, and basified with an aqueous NaOH, which 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 10% HCl was added dropwise to the solution under ice-cooling. The resulting precipitates were collected by filtration to give chelerythrine chloride **2d** (7 mg, 91%), mp 194–195 °C (MeOH–acetone) (lit.[30a] mp 192–193 °C and lit.[30b] mp 203–206 °C). ^{1}H NMR and ^{13}C NMR spectra of synthetic **2d** were shown in Tables 7 and 8.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.066. These data include MOL files and InChIKeys of the most important compounds described in this article.

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