Total Synthesis of Benzo[*c*]phenanthridine Alkaloids, Chelerythrine and 12-Methoxydihydrochelerythrine, by a Palladium-Assisted Internal Biaryl Coupling Reaction

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Abstract: A covenient and versatile synthesis of benzo[*c*]phenanthridine alkaloids, chelerythrine (**1**) and 12-methoxydihydrochelerythrine (**5**), was accomplished via an internal aryl-aryl coupling reaction of haloamides **8** and **9** by a palladium-assisted cyclization reaction.

Key words: alkaloids, internal aryl-aryl coupling, ring closure, Heck-type reaction, palladium, haloamides

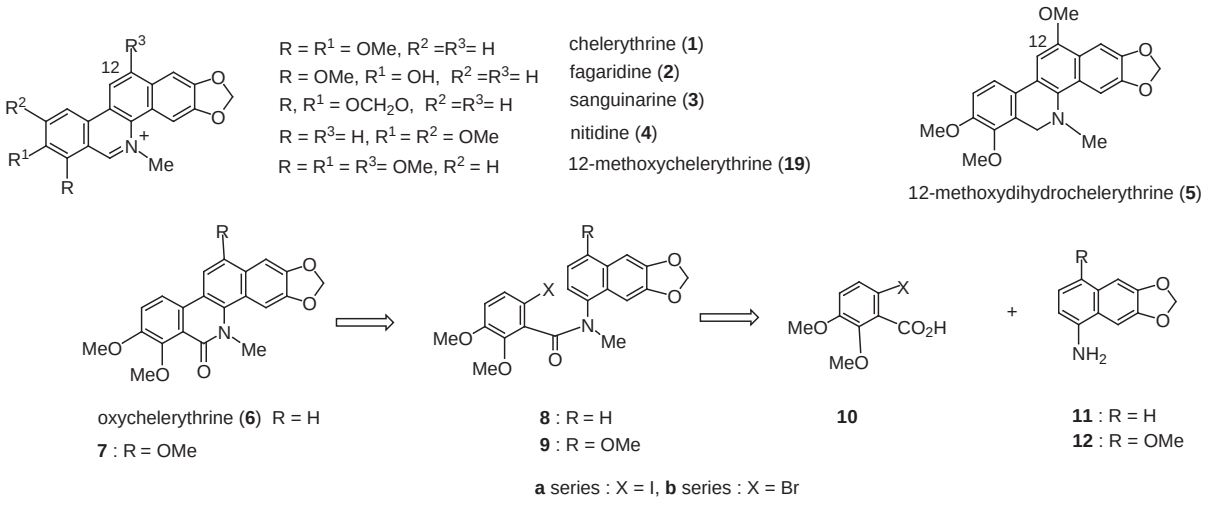
Introduction

Fully aromatized benzo[*c*]phenanthridine alkaloids have attracted much attention because of their potent pharmacological activities.[1] It was recently found that, among these alkaloids, chelerythrine (**1**)[1f] and fagaridine (**2**)[1g,1h] inhibited protein kinase C and DNA topoisomerase 1, respectively, and sanguinarine (**3**)[1i,1j] showed inhibition of lipoxygenase and mediated chemical defense against microorganisms, virus and herbivores in plants. Moreover, nitidine (**4**) and related compounds[1k] including ethoxidine[1l] possessing 12-alkoxy group showed strong antileukemic activity including the inhibition of DNA topoisomerases. Although many reports on the total synthesis of fully aromatized benzo[*c*]phenanthridine alkaloids have been published,[2] the methods had some disadvantages such as excessive number of steps, low yield, and/or absence of generality. Therefore, we endeavored to develop a convenient and versatile method for synthesizing these alkaloids.

Recently, we accomplished the total synthesis of **1** by an internal biaryl coupling reaction of haloamides **8** using a palladium reagent as shown in Scheme 1.[3] Subsequently, in order to examine the generality of this method, we applied it to the synthesis of 12-methoxydihydrochelerythrine (**5**), which was isolated from *Bocconia integrifolia Humb. & Bonpl.* in 1991,[4] and succeeded in the total synthesis of **5**. The details of these results are the subject of this paper.

Internal Coupling Reaction of *N*-Methylbenzanalide Derivatives 13

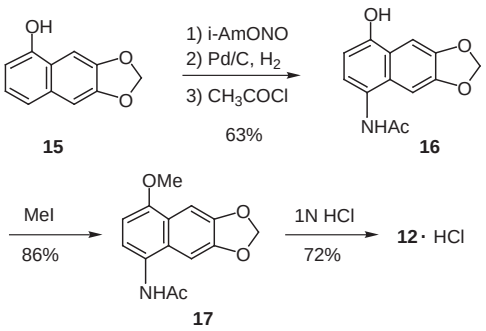
The cross-coupling reaction with a palladium catalyst has been an extremely useful tool in organic synthesis.[5] We designed a synthetic plan for **1** and **5** involving an internal biaryl cyclization by palladium as the key reaction,[6] as shown in Scheme 1. Since the coupling product, oxychelerythrine (**6**), has already been converted into chelerythrine (**1**),[7] the synthesis of **6** indicates a formal synthesis of **1**. It was reported that an internal coupling reaction of bromoamide **13b** with a Pd reagent proceeded in 50% yield.[6a] In order to improve the yield, the cyclization reaction including iodoamide **13a**[7] was re-examined using purified $Pd(OAc)_2$,[9] a phosphine ligand and a base. The



results are summarized in Table 1. By using $Pd(OAc)_2$ (0.2 equivalent) Ph_3P and Ag_2CO_3, the solvent had no crucial effect on the internal coupling reaction of iodoamide **13a**, although Ag_2CO_3 was superior to diisopropylethylamine. Interestingly, good results were obtained when no phosphine ligand was employed (see runs 10 and 11 in Table 1).[5c,5d] On the other hand, the coupling reaction of bromoamide **13b** proceeded slowly even when using a stoichiometric amount of $Pd(OAc)_2$ in the presence of PPh_3 as a ligand in DMF (see run12 in Table 1). However, on using tri(*o*-tolyl)phosphine [(*o*-Tol)$_3$P] as a ligand, the reaction proceeded smoothly with 0.2 equivalent of $Pd(OAc)_2$ and gave phenanthridone **14**[6a,8b] in an excellent yield (see run 13 in Table 1).

Synthesis of Oxychelerythrine (6)

Since the palladium-mediated coupling reaction of benzanilide derivatives **13** was successful as shown in Table 1, we investigated the total synthesis of **1** utilizing this method. Our concise synthetic route is outlined in Scheme 1. Starting materials **8** for the cyclization reaction were prepared from the iodoacid **10a**[10] or bromoacid **10b**[11] and naphthylamine **11**.[12] Thus, successive treatment of **10** with oxalyl chloride and **11** in the presence of triethylamine afforded secondary amides, which were methylated with methyl iodide in the presence of sodium hydride in DMF to give iodoamide **8a** and bromoamide **8b** in 56% and 72% yields, respectively. The coupling reaction of both haloamides **8** with $Pd(OAc)_2$, PPh_3 or (*o*-Tol)$_3$P and Ag_2CO_3 in DMF under reflux afforded oxychelerythrine (**6**)[7] in excellent yield as shown in Table 2, although iodoamide **8a** was more reactive than the bromoamide **8b**. Since the coupling product **6** had already been converted into chelerythrine (**1**),[7] the synthesis of **6** indicates a formal synthesis of **1**.



Scheme 2

Synthesis of 12-Methoxydihydrochelerythrine (5)

We subsequently investigated the total synthesis of **5** utilizing the method according to the synthetic route outlined in Scheme 1. The preparation of the key compound **9a** was realized by condensation between the carboxylic acid **10**[10] and naphthylamine **12**, which was derived from 6,7-methylenedioxy-1-naphthol (**15**)[13] via several steps as shown in Scheme 1. Thus, the basic nitrosation of **15** followed by hydrogenation[14] and acetylation afforded acetyl amide **16** in 63% yield. The methylation of **16** gave **17** in

Table 1 Results of Cyclization Reaction of 2-Halo-*N*-methyl-*N*-phenylbenzamide (**13**)[a]

Substrate	Run	$Pd(OAc)_2$ (equiv)	Ligand	Base	Solvent	Temp.	Time	Yield (%)	
								14	S.M.
13a	1	0.05	PPh_3	Ag_2CO_3	DMF	Refl.	40 min	79	–
	2	0.2	PPh_3	Ag_2CO_3	DMF	Refl.	15 min	93	–
	3	0.2	P(*o*-Tol)$_3$	Ag_2CO_3	DMF	Refl.	15 min	93	–
	4	0.2	PPh_3	Ag_2CO_3	DMF	30–35ºC	35 h	85	–
	5	0.2	PPh_3	Ag_2CO_3	xylene	30–35ºC	23 h	93	–
	6	0.2	PPh_3	Ag_2CO_3	benzene	Refl.	10 min	98	–
	7	0.2	PPh_3	Ag_2CO_3	CH3CN	Refl.	15 min	95	–
	8	0.2	PPh_3	*i*-Pr_2NEt	DMF	Refl.	4.5 h	21	7
	9	0.2	PPh_3	*i*-Pr_2NEt	benzene	Refl.	6 h	45	14
	10	0.2	–	Ag_2CO_3	DMF	Refl.	20 min	90	–
	11	0.2	–	AcONa	DMF	Refl.	25 min	96	–
13b	12	1.0	PPh_3	Ag_2CO_3	DMF	Refl.	60 h	75	7
	13	0.2	P(o-Tol)$_3$	Ag_2CO_3	DMF	Refl.	1.5 h	99	–

[a] All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1:2 and 2 mol equivalent of base.

Table 2 Results of Cyclization Reaction of 6-Halo-2,3-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**8**) to Oxychelerythrine (**6**) in DMF under Reflux[a]

Substrate	Run	$Pd(OAc)_2$ (equiv)	Ligand	Base	Time	Yield (%) **6**
8a	1	0.2	PPh_3	Ag_2CO_3	20 min	85
	2	0.2	P(*o*-Tol)$_3$	Ag_2CO_3	20 min	94
8b	3	0.2	PPh3	Ag_2CO_3	2 h	79
	4	0.2	P(*o*-Tol)$_3$	Ag_2CO_3	3 h	96

[a] All reactions were carried out in the presence of ligand (0.4 equiv) and base (2 equiv).

86% yield, which was hydrolyzed with hydrochloric acid to give naphthylamine **12** as its hydrochloride in 72% yield. Successive treatment of **10** with oxalyl chloride and **12** in the presence of triethylamine afforded a secondary amide, which was methylated with methyl iodide in the presence of sodium hydride in DMF to give the amide **9a** in 76% yield. The coupling reaction of amide **9a** with $Pd(OAc)_2$, a phosphine ligand and Ag_2CO_3 in DMF under reflux afforded 12-methoxyoxychelerythrine (**7**) in excellent yield along with a small amount of benzoazepinone **18**[15] as shown in Table 3 (see runs 2−4 in Table 3). The structures of both the products **7** and **18** were elucidated on the basis of spectral data, especially ^{1}H NMR of **7** which showed three singlet signals due to aromatic protons, whereas **18** showed only one singlet signal for an aromatic proton (see Experimental). Reduction of **7** with $LiAlH_4$ followed by treatment with HCl gave 12-methoxychelerythrine (**19**) in 82% yield, which was reduced with $NaBH_4$ to afford 12-methoxydihydrochelerythrine (**5**) (mp 173−175 °C)[16] in 77% yield. Spectral data of the synthetic material were in good agreement with the reported data of the authentic sample as shown in Table 4.

In conclusion, the biaryl coupling reaction using the Pd reagent is very convenient and effective for preparing benzo[*c*]phenanthridine alkaloids. We are presently investigating the generality of this method.

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a JASCO A-102 or JASCO FT/IR 350 spectrophotometer and ^{1}H and ^{13}C NMR spectra in $CDCl_3$ on a Hitachi R-1500 (60 MHz) or Varian VXR-200 (200 MHz) or 500 (500 MHz) spectrometer unless otherwise stated. NMR data are reported in parts per million downfield from TMS as an internal standard (δ = 0.0) and coupling constants are given in Hertz. Mass spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out on silica gel (Wako gel C-200 or Merck, silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhyd $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filrate was then concentrated to dryness to give purified $Pd(OAc)_2$.[9]

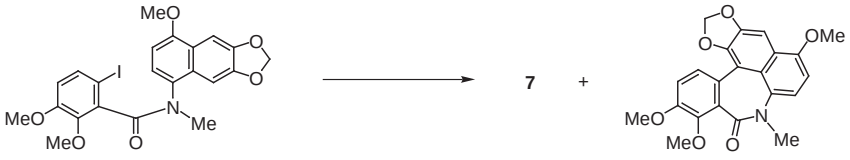
Cyclization Reaction of *N*-Methylbenzanilides 13 by Palladium Reagent; General Procedure

The reaction of **13** (30.8 mg, 62.7 mmol) with $Pd(OAc)_2$, a phosphine ligand, and Ag_2CO_3 (36.4 mg, 125 mmol) in anhyd DMF (3 mL) was carried out under the reaction conditions indicated in Table 1. The reaction mixture was diluted with Et_2O and the precipitate was removed by filtration. The filtrate was washed with brine and the solvent evaporated. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with hexane/EtOAc (4:1) gave phenanthridone (**14**) as colorless needles (from hexane); mp 110−111°C (Lit.,[6a] mp 105−108 °C; Lit.,[8b] mp 108.5 °C).

6-Iodo-2,3-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (8a)

Oxalyl chloride (840 mg, 6.49 mmol) was added to a solution of **10a** (1.02 g, 3.25 mmol) in anhyd CH_2Cl_2 (30 mL) and the stirred mixture was refluxed for 90 min. Then, the mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of **11** (495 mg, 2.60 mmol) in anhyd CH_2Cl_2 (15 mL) and anhyd

Table 3 Results of Cyclization Reaction of 6–Iodo–2,3–dimethoxy–*N*–(4–methoxy–6,7–methylenedioxy–1–naphthyl)–*N*–methylbenzamide (**9a**) to 7,8,12–Trimethoxy–5–methyl–2,3–methylenedioxy–6(5*H*)–benzo[*c*]phenanthridinone (**7**) in DMF under Reflux



9a **18**

Run	$Pd(OAc)_2$ (equiv)	Ligand	L/Pd[a]	Base	Time (min)	Yield (%)	
						7	**18**
1	0.2	P(o-Tol)$_3$	2	Na_2CO_3	180	51	-
2	0.2	PPh_3	2	Ag_2CO_3	30	91	9
3	0.2	DPPP[b]	1	Ag_2CO_3	30	86	6
4	0.2	P(*o*-Tol)$_3$	2	Ag_2CO_3	30	95	5
5	0.2	P(*o*-Tol)$_3$	2	NaOAc	120	20	-

[a] Molar ratio between ligand and $Pd(OAc)_2$.
[b] DPPP:1,3-Bis(diphenylphosphino)propane.

Table 4 Comparison of ^{13}C and ^{1}H NMR Spectral Data Derived from 12–Methoxydihydrochelerythrine (**5**)[a] and Synthetic Sample

Carbon	12–Methoxydihydrochelerythrine (**5**)		Synthetic Sample	
	δ ^{1}H[b] mult; (*J*, Hz)	δ 13C[c]	δ ^{1}H[d] mult; (*J*, Hz)	δ 13C[e]
C–1	7.55 s	99.5	7.55 s	99.5
C–2		148.5		148.4
C–3		147.2		147.2
C–4	7.67 s	100.7	7.65 s	100.7
C–4a		127.5		127.4
C–4b		136.3		135.9
C–6	4.27 s	49.0	4.27 s	49.0
C–6a		126.6		126.4
C–7 ·		146.3		146.2
C–8		152.4		152.3
C–9	6.94 d (8.5)	110.9	6.94 d (8.5)	110.8
C–10	7.48 d (8.5)	118.5	7.48 d (8.5)	118.5
C–10a		126.5		126.4
C–10b		124.2		123.9
C–11	7.05 s	98.7	7.05 s	98.7
C–12		152.4		152.3
C–12a		122.4		122.4
–OCH_2O– (2,3)	6.05 s	101.0	6.05 s	101.0
N–Me	2.53 s	41.3	2.53 s	41.3
7–OMe	3.87 s	61.0	3.87 s	61.1
8–OMe	3.93 s	55.9	3.93 s	55.8
12–OMe	4.03 s	55.7	4.03 s	55.7

[a] See reference 4.
[b] ^{1}H NMR recorded in $CDCl_3$ at 300 MHz; shifts in ppm.
[c] ^{13}C NMR recorded in $CDCl_3$ at 75.5 MHz; shifts in ppm.
[d] ^{1}H NMR recorded in $CDCl_3$ at 500 MHz; shifts in ppm.
[e] ^{13}C NMR recorded in $CDCl_3$ at 125 MHz; shifts in ppm.

Et_3N (394 mg, 3.90 mmol) and the mixture was stirred for 50 min at r.t. The mixture was concentrated to dryness and diluted with CH_2Cl_2, then washed with 10% HCl, aq sat. $NaHCO_3$ solution and brine. The residue was dissolved in $CHCl_3$ and the solution was subjected to column chromatography on silica gel. Elution with hexane/EtOAc (3:1) gave 6-iodo-2,3-dimethoxy-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (891 mg, 58%) as colorless needles (from benzene); mp 268−268.5 °C.

IR (KBr): ν = 3250, 1660 cm^{-1}.

^{1}H NMR (60 MHz): δ = 3.86 (6 H, s, 2 × OCH_3), 6.15 (2 H, s, OCH_2O), 6.98 (1 H, d, *J* = 8.8 Hz, C_4- or C_5·-H), 7.35 (1 H, s, C_5-H), 7.45−7.67 (5 H, m, aromatic protons), 10.29 (1 H, br s, NH).

FAB-MS (positive ion mode): *m*/*z* = 478 [M^+ + 1].

Anal. calcd for $C_{20}H_{16}INO_5$: C, 50.33; H, 3.38; N, 2.93. Found : C, 50.58; H, 3.50; N, 2.80.

To a suspension of iodobenzamide prepared as above (500 mg, 1.05 mmol) and NaH (121 mg 63% dispersion in mineral oil, 3.14 mmol) in anhyd DMF (30 mL) was added MeI (164 mg, 1.15 mmol). After stirring for 90 min at r.t., the reaction mixture was diluted with Et_2O and washed with 10% HCl and brine. The residue dissolved in EtOAc/hexane was subjected to column chromatography on silica gel. Elution with hexane/EtOAc (2:1) gave **8a** (496 mg, 96%) as colorless needles (from EtOAc); mp 176−177 °C.

IR (KBr): ν = 1650 cm^{-1}.

^{1}H NMR (60 MHz): δ = 3.19 (3 H, s, NCH_3), 3.56−4.02 (6 H, m, 2 × OCH_3), 6.05 (2 H, s, OCH_2O), 6.68−7.73 (7 H, m, aromatic protons).

FAB-MS (positive ion mode): *m*/*z* = 492 [M^+ + 1].

Anal. calcd for $C_{21}H_{18}INO_5$: C, 51.34; H, 3.69; N, 2.85. Found : C, 51.55; H, 3.82; N, 2.88.

6-Bromo-2,3-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (8b)

A few drops of anhyd DMF and oxalyl chloride (788 mg, 6.13 mmol) were added to a solution of **10b** (1.02 g, 3.25 mmol) in anhyd CH_2Cl_2 (30 mL) and the stirred mixture was refluxed for 80 min. Then the mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of **11** (458 mg, 2.45 mmol) in anhyd CH_2Cl_2 (15 mL) and anhyd Et_3N (372 mg, 3.67 mmol) and the mixture was stirred for 1 h at r.t. The mixture was concentrated to dryness and diluted with CH_2Cl_2, then washed with 10% HCl, aq sat. $NaHCO_3$ solution and brine. The residue was dissolved in $CHCl_3$ and the solution was subjected to column chromatography on silica gel. Elution with hexane/EtOAc (3:1) gave 6-bromo-2,3-dimethoxy-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (1.01 g, 77%) as colorless needles (from benzene/hexane), mp 237.5−239 °C.

IR (KBr): ν = 3250, 1660 cm^{-1}.

^{1}H NMR (60 MHz, DMSO-d_6): δ = 3.87 (6 H, s, 2 × OCH_3), 6.15 (2 H, s, OCH_2O), 6.97 (1 H, d, *J* = 8.8 Hz, C_4- or C_5-H), 7.35 (1 H, s, C_5·-H), 7.45−7.67 (5 H, m, aromatic protons), 10.28 (1 H, br s, NH).

Anal. calcd for $C_{20}H_{16}BrNO_5$: C, 55.83; H, 3.75; N, 3.26. Found : C, 55.89; H, 3.79; N, 3.12.

To a suspension of bromobenzamide prepared as above (500 mg, 1.16 mmol) and NaH (134 mg, 63% dispersion in mineral oil, 3.49 mmol) in anhyd DMF (30 mL) was added MeI (165 mg, 1.16 mmol). The reaction mixture was stirred for 5 h at r.t., diluted with Et_2O and then washed with 10% HCl and brine. The residue

was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with EtOAc gave **8b** (478 mg, 93%) as colorless needles (from benzene/hexane), mp 178−179 °C.

IR (KBr): ν = 1650 cm^{-1}.

^1H NMR (60 MHz, DMSO-d_6): δ = 3.13−3.98 (9 H, m, NCH_3 and 2 × OCH_3), 6.18 (2 H, s, OCH_2O), 6.82−7.85 (7 H, m, aromatic protons).

Anal. calcd for $C_{21}H_{18}BrNO_5$: C, 56.77; H, 4.08; N, 3.15. Found : C, 57.01; H, 4.15; N, 3.20.

Oxychelerythrine (6) from Haloamides 8 Catalyzed by Palladium Reagent; General Procedure

Reaction of **8** (62.7 mmol) with $Pd(OAc)_2$, a phosphine ligand, and Ag_2CO_3 (36.4 mg, 125 mmol) in anhyd DMF (3 mL) was carried out under the reaction conditions indicated in Table 2. The reaction mixture was diluted with Et_2O and the precipitate was removed by filtration. The filtrate was washed with brine and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with hexane/EtOAc (2:1) gave oxychelerythrine (**6**) as colorless needles (from benzene); mp 209−211°C (Lit.[7b] mp 199−203 °C). This compound was identical with an authentic sample of oxychelerythrine (**6**).[7]

***N*-(4-Hydroxy-6,7-methylenedioxy-1-naphthyl)acetamide (16)**

To a suspension of **15** (1.73 g, 9.21mmol) and K_2CO_3(12.7 g, 11.1 mmol) in DMF (30 mL) was added isoamyl nitrite (1.49 mL) under ice-cooling and the mixture was stirred for 30 min at 0 °C. After stirring for an additional 90 min at r.t., the mixture was poured into H_2O and extracted with EtOAc. A solution of the residue in THF (50 mL) was hydrogenated at r.t. and at atmospheric pressure in the presence of 10% Pd/C (220 mg). After disappearance of the starting material on TLC, the mixture was filtered. To the filtrate were added pyridine (10 mL) and acetyl chloride (1 mL). The mixture was stirred for 20 min at r.t. and poured into 5% HCl and then extracted with Et_2O. The residue was recrystallized from acetone/hexane to afford **16** (1.43 g, 63%) as colorless needles; mp 254−256 °C.

IR (KBr): ν = 3240, 1620 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.09 (3 H, s, $COCH_3$), 6.12 (2 H, s, OCH_2O), 6.69 (1 H, d, *J* = 8.6 Hz, C_3-H), 7.11 (1 H, d, *J* = 8.5 Hz, C_2-H), 7.19 (1 H, s, C_5-H), 7.39 (1 H, s, C_8-H), 9.47 (1 H, s, NH), 9.89 (1 H, s, OH).

Anal. calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.17. Found : C,63.41; H, 4.79; N, 5.59.

***N*-(4-Methoxy-6,7-methylenedioxy-1-naphthyl)acetamide (17)**

To a suspension of **16** (34.3 mg, 0.14 mmol) and K_2CO_3 (14.5 mg, 0.105 mmol) in anhyd DMF (2 mL) was added MeI (0.013 mL). The reaction mixture was stirred for 20 min at r.t. and poured into 5% HCl and then extracted with EtOAc. The residue was recrystallized from $CHCl_3$/hexane to afford **17** (31.3 mg, 86%) as colorless needles; mp 254−255 °C.

IR (KBr): ν = 3260, 1680 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.11 (3 H, s, $COCH_3$), 3.92 (3 H, s, OCH_3), 6.14 (2 H, s, OCH_2O), 6.82 (1 H, d, *J* = 8.2 Hz, C_3-H), 7.27 (1 H, d, *J* = 8.2 Hz, C_2-H), 7.27 (1 H, s, C_5-H), 7.42 (1 H, s, C_8-H), 9.56 (1 H, s, NH).

ACPI-MS (positive ion mode): *m*/*z* = 260 $[M + 1]^+$.

Anal. calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found : C, 64.22; H, 5.04; N, 5.40.

4-Methoxy-6,7-methylenedioxy-1-naphthylamine (12) Hydrochloride

A solution of **17** (101 mg, 0.39 mmol) in 1 N HCl (5 mL) and MeOH (5 mL) was refluxed for 7.5 h and evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH/Et_2O to give **12**·HCl (71 mg, 72%) as colorless prisms; mp 201−205 °C.

IR (KBr): ν = 2900 (br), 2560 cm^{-1}.

^1H NMR (60 MHz): δ = 3.91 (3 H, s, OCH_3), 6.04 (2 H, s, OCH_2O), 6.60 (2 H, C_2 and C_3-H), 7.14 (1 H, s, C_5-H), 7.55 (1 H, s, C_8-H).

FAB-MS (positive ion mode): *m*/*z* = 218 $[M + 1]^+$.

Anal. calcd for $C_{12}H_{12}NO_3$.1/9H_2O : C, 56.37; H, 4.82; N, 5.48. Found : C, 56.30; H, 4.77; N, 5.40.

6-Iodo-2,3-dimethoxy-*N*-(4-methoxy-6,7-methylenedioxy-1-naphthyl)-*N*-methylbenzamide (9a)

A few drops of anhyd DMF and oxalyl chloride (951 mg, 7.49 mmol) were added to a solution of **10a** (961 mg, 3.12 mmol) in anhyd CH_2Cl_2 (40 mL) under ice-cooling and the mixture was refluxed for 3 h. Then the mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of **12** (660 mg, 2.60 mmol) in anhyd CH_2Cl_2 (20 mL) and anhyd Et_3N (757 mg, 7.49 mmol) and the mixture was stirred for 30 min at r.t. The mixture was concentrated to dryness and diluted with CH_2Cl_2, then washed with 10% HCl, aq sat. $NaHCO_3$ solution and brine. The residue was recrystallized from $CHCl_3$/hexane to give 6-iodo-2,3-dimethoxy-*N*-(4-methoxy-6,7-methylenedioxy-1-naphthyl)benzamide (1.11 g, 84%) as colorless needles; mp 284−285.5 °C.

IR (KBr): ν = 3240, 1655 cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 3.86 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 6.16 (2 H, s, OCH_2O), 6.90 (1 H, d, *J* = 8.3 Hz, C_9-H), 6.98 (1 H, d, *J* = 8.6 Hz, C_4-H), 7.33 (1 H, d, *J* = 8.3 Hz, C_8-H), 7.45 (1 H, s, C_{11} or C_{14}-H), 7.59 (1 H, d, *J* = 8.6 Hz, C_5-H), 10.13 (1 H, br s, NH).

FAB-MS (positive ion mode): *m*/*z* = 507 $[M^+ + 1]$.

Anal. calcd for $C_{21}H_{18}INO_6$: C, 49.72; H, 3.58; N, 2.76. Found: C, 49.31; H, 3.78; N, 2.94.

To a suspension of the iodobenzamide prepared as above (122 mg, 0.24 mmol) and NaH (48 mg 63% dispersion in mineral oil, 1.2 mmol) in anhyd DMF (10 mL) was added MeI (102 mg, 0.72 mmol). After stirring for 20 h at r.t., the reaction mixture was diluted with EtOAc and washed with 10% HCl and brine. The residue was dissolved in EtOAc/hexane and subjected to column chromatography on silica gel. Elution with $CHCl_3$ gave **9a** (115 mg, 91%) as colorless prisms; mp 186−187 °C.

IR (KBr): ν = 1645 cm^{-1}.

^1H NMR (200 MHz): δ = 3.17−4.01 (12 H, m, 3 × OCH_3 and NCH_3 rotamer), 6.05 (2 H, m, OCH_2O, rotamer), 6.36−7.67 (6 H, m, aromatic protons, rotamer).

Anal. calcd for $C_{22}H_{20}INO_6$: C, 50.69 H, 3.87; N, 2.69. Found: C, 50.89; H, 4.08; N, 2.58.

Cyclization of Iodoamide (9a) by Palladium Reagent; General Procedure

Reaction of **9a** (52.1 mg, 0.10 mmol) with $Pd(OAc)_2$ (4.5 mg, 0.02mmol), a phosphine ligand, and a base in anhyd DMF (3 mL) was carried out under the reaction conditions indicated in Table 3. The reaction mixture was diluted with Et_2O and the precipitate was removed by filtering. The filtrate was washed with brine and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with $CHCl_3$ gave 4,9,10-trimethoxy-7-methyl-1,2-methylenedioxy-8(7*H*)ben-

zo[*e*]naphth[1,8-*bc*]azepinone (**18**) and successive elution with the same solvent gave 7,8,12-trimethoxy-5-methyl-2,3-methylenedioxy-6(5*H*)-benzo[*c*]phenenthridone (12-methoxyoxychelerythrine) (**7**).

18

Mp 251−253°C; colorless prisms (from EtOAc).

IR (KBr): ν = 1645 cm^{-1}.

^{1}H NMR (200 MHz): δ = 3.36 (3 H, s, NCH_3), 3.87 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 6.12 (2 H, s, OCH_2O), 6.66 (1 H, d, *J* = 8.4 Hz, C_5-H), 6.91 (1 H, d, *J* = 9.0 Hz, C_{11}-H), 7.09 (1 H, d, *J* = 8.4 Hz, C_6-H), 7.37 (1 H, d, *J* = 9.0 Hz, C_{12}-H), 7.42 (1 H, s, C_3-H).

Anal. calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.15; H, 5.09; N, 3.54.

7

Mp 168−170°C; colorless needles (from EtOH) (Lit.[17] mp 108−110°C).

IR (KBr): ν = 1645 cm^{-1}.

^{1}H NMR (60 MHz): δ = 3.86 (3 H, s, NCH_3), 3.98 (3 H, s, OCH_3), 4.08 (6 H, s, 2 × OCH_3), 6.08 (2 H, s, OCH_2O), 7.28 (1 H, s, C_{11}-H), 7.35 (1 H, d, *J* = 9.1 Hz, C_9-H), 7.49 (1 H, s, C_1-H), 7.61 (1 H, s, C_4-H), 7.91 (1 H, d, *J* = 9.1 Hz, C_{10}-H).

High Resolution FAB-MS: Calcd for $C_{22}H_{19}NO_6$: 393.1212. Found: 393.1270.

12-Methoxychelerythrine Chloride (19)

$LiAlH_4$ (6.8 mg, 0.3 mmol) was added to a solution of **7** (39.4 mg, 0.10 mmol) in anhyd THF (2 mL) and the mixture was stirred for 20 min at r.t. Excess hydride was decomposed with wet Et_2O and the organic layer was decanted. The residue was treated with 10% HCl (2 mL) at r.t. to produce **19** (20.4 mg, 82%) as yellow needles (from EtOH/Et_2O), mp 175 °C.

^{1}H NMR (200 MHz, CD_3OD): δ = 4.12 (3 H, s, OCH_3), 4.25 (3 H, s, OCH_3), 4.26 (3 H, s, OCH_3), 4.91 (3 H, s, NCH_3), 6.26 (2 H, s, OCH_2O), 7.73 (1 H, s, C_{11}-H), 7.79 (1 H, C_1-H), 8.06 (1 H, C_4-H), 8.12 (1 H, d, *J* = 9.5 Hz, C_9-H), 8.62 (1 H, d, *J* = 9.1 Hz, C_{10}-H), 9.72 (1 H, s, C_6-H).

Anal. calcd for $C_{22}H_{20}ClNO_5 \bullet H_2O$: C, 61.19; H, 5.14; N, 3.24. Found: C, 61.42; H, 4.85; N, 3.22.

12-Methoxydihydrochelerythrine (5)

A solution of **19** (26.6 mg, 0.07 mmol) and $NaBH_4$ (19.0 mg, 0.50 mmol) in absolute MeOH (2.5 mL) was stirred at r.t. for 30 min. The mixture was diluted with H_2O and extracted with $CHCl_3$. The residue was subjected to column chromatography on Al_2O_3 with benzene to afford **5** (18.7 mg, 77%) as pale yellow needles (from benzene/MeOH); mp 173−174.5°C.

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data are given in Table 4.

Anal. calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.62; H, 5.79; N, 3.61.

The NMR data of the synthetic sample were identical with the reported data of the authentic sample.[4]

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