Synthesis of trisphaeridine and norchelerythrine through palladium-catalyzed aryl–aryl coupling reactions

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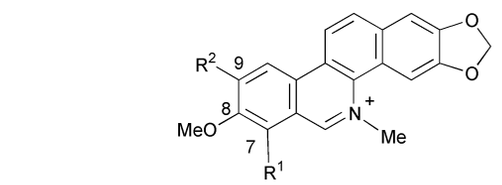
Total syntheses of trisphaeridine (**3**) and norchelerythrine (**4**), fully aromatized phenanthridine and benzo[*c*]phenanthridine alkaloids, were accomplished *via* the internal aryl–aryl coupling reaction of halo amides protected by a methoxymethyl group with the palladium reagent, followed by reduction with lithium aluminium hydride and treatment with hydrochloric acid.

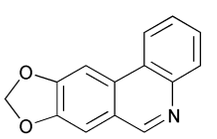
Introduction

Fully aromatized benzo[*c*]phenanthridine alkaloids have a broad range of potent pharmacological activities such as antitumour and antiviral activities, and inhibition of DNA topoisomerase I.[1–12] Therefore, attention is still focused on the development of convenient and effective methods for synthesizing these alkaloids.[1–5,13,14] However, the reported methods have several disadvantages such as numerous steps, low total yield and/or lack of generalizability. We have been studying the development of more rapid and versatile synthetic methods for these alkaloids and recently developed a convenient method for the synthesis of chelerythrine (**1**)[15] and nitidine (**2**),[16] quaternary benzo[*c*]phenanthridine alkaloids, using an internal aryl–aryl coupling reaction assisted by palladium. To examine the general applicability of this method for synthesizing benzo[*c*]phenanthridine alkaloids, we attempted to apply this method to the synthesis of trisphaeridine (**3**)[17,18] and norchelerythrine (**4**),[1] tertiary phenanthridine and benzo[*c*]phenanthridine alkaloids. For the synthesis of these alkaloids, ring closure of secondary amides such as **5a** and **6a** is expected to be a more direct and convenient method. Ames and Opalko reported in 1984 that **5a** possessing a halogen atom on the benzoyl ring did not give rise to a cyclized product, whereas **6a** possessing a halogen atom on the aniline ring provided the expected product (**7a**) in poor to moderate yield.[19] However, we speculated that a tertiary amide (**5b**), which was protected by the methoxymethyl (MOM) group, could be converted to an *N*-MOM lactam (**7b**) with the assistance of a Pd reagent, because the cyclization reaction of a tertiary *N*-methylamide (**5c**) proceeded smoothly and gave the desired product in high yield.[15] Moreover, we supposed that **7b** could be transformed to a fully aromatized tertiary base (**8**) by successive treatment with $LiAlH_4$ and HCl.

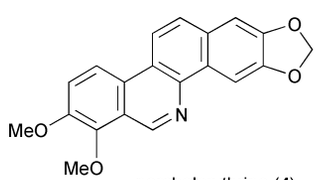


chelerythrine (**1**) R^1=OMe, R^2=H

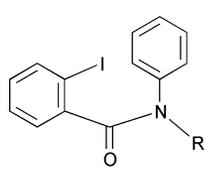
nitidine (**2**) R^1=H, R^2=OMe



trisphaeridine (**3**)



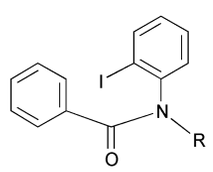
norchelerythrine (**4**)



5a : R = H

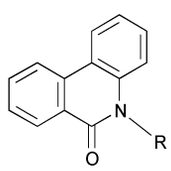
5b : R = MOM

5c : R = Me



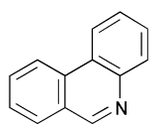
6a : R = H

6b : R = MOM



7a : R = H

7b : R = MOM



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Results and discussion

We began our studies with the biaryl coupling reaction of amides **5b** and **6b** by means of a Pd reagent as a preliminary experiment. These amides were prepared by reaction of secondary amides **5a**[20] and **6a**[21] with dimethoxymethane in the presence of P_2O_5 in yields of 62 and 85%, respectively, and then the cyclization reaction using the Pd reagent was examined. The results are summarized in Table 1. The reaction generally gave the desired product in good to excellent yield, and in the presence or absence of a bidentate ligand provided **7b** in high yield. Reduction of **7b** with $LiAlH_4$ followed by treatment with HCl gave phenanthridine (**8**)[22] in a yield of 54%.

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Table 1 Results of the cyclization reaction of 2-iodo-*N*-methoxymethyl-*N*-phenylbenzamide (**5b**) or *N*-(2-iodophenyl)-*N*-methoxymethylbenzamide (**6b**) to 5-methoxymethylphenanthridin-6(5*H*)-one (**7b**) in DMF under reflux[a]

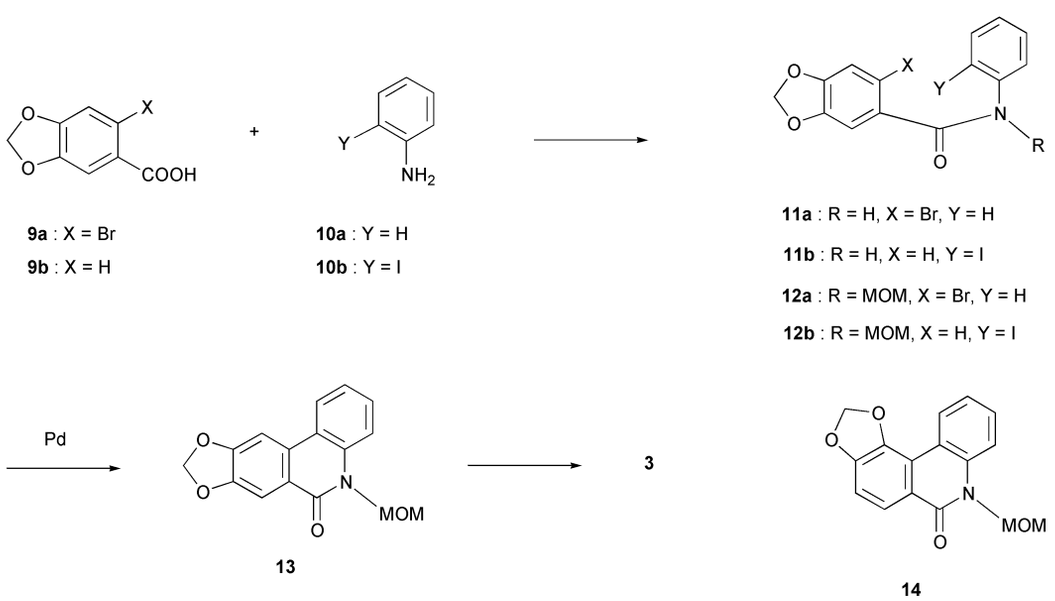
	Run	$Pd(OAc)_2$ (eq.)	Ligand	Base	Time/min	Yield of **7b** (%)
5b	1	0.1	—	Na_2CO_3	60	97
	2[b]	0.1	—	Na_2CO_3	180	88
	3	0.1	—	Ag_2CO_3	40	84
	4	0.1	PPh_3 (2)	Na_2CO_3	40	94
	5	0.1	PPh_3 (2)	Ag_2CO_3	60	91
	6	0.1	PPh_3 (2)	AcONa	20	97
	7	0.1	P(*o*-Tol)$_3$ (2)	Na_2CO_3	90	97
	8	0.1	DPPP[c] (1)	Na_2CO_3	30	94
	9	0.1	DPPP[c] (1)	Ag_2CO_3	40	91
6b	10	0.1	—	Na_2CO_3	60	89
	11	0.1	PPh_3 (2)	Na_2CO_3	40	83
	12	0.1	PPh_3 (2)	Ag_2CO_3	40	82
	13	0.1	DPPP[c] (1)	Na_2CO_3	60	87

[a] All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base. [b] Reaction temperature: 130 °C. [c] DPPP: 1,3-bis(diphenylphosphino)propane.

Table 2 Results of cyclization reactions of 2-bromo-*N*-methoxymethyl-4,5-methylenedioxy-*N*-phenylbenzamide (**12a**) to 5-methoxymethyl-8,9-methylenedioxyphenanthridin-6(5*H*)-one (**13**) in DMF under reflux[a]

					Yield (%)	
Run	$Pd(OAc)_2$ (eq.)	Ligand	Base	Time/h	**13**	S.M.[b]
1	0.1	PPh_3	Ag_2CO_3	3	59	27
2	0.1	P(*o*-Tol)$_3$	Na_2CO_3	6.5	73	—
3	0.1	P(*o*-Tol)$_3$	Ag_2CO_3	2	75	—
4	0.2	P(*o*-Tol)$_3$	Ag_2CO_3	1.5	81	—
5	1.0	P(*o*-Tol)$_3$	Ag_2CO_3	0.5	89	—

[a] All reactions were carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base. [b] S.M. = starting material.



Scheme 1

Next, we applied this methodology to the synthesis of trisphaeridine (**3**),[23] a tertiary phenanthridine alkaloid, which has been isolated from a few plants of *Amaryllidaceae*.[17,18] We planned the synthetic route for **3** as shown in Scheme 1.

Starting materials (**12**) for the cyclization reaction were prepared by methoxymethylation of the corresponding secondary amides (**11**), which were synthesized from 6-bromopiperonylic acid (**9a**)[24] and aniline (**10a**), and from piperonylic acid (**9b**) and 2-iodoaniline (**10b**), respectively (Scheme 1). Thus, successive treatment of the acids with oxalyl chloride and anilines in the presence of triethylamine afforded **11**, which was methoxymethylated with chloromethyl methyl ether in the presence of sodium hydride in DMF to give bromo amide (**12a**) and iodo amide (**12b**) in yields of 62 and 67%, respectively. Subsequently, the cyclization reaction of **12a** and **12b** using the Pd reagent was examined and the results are summarized in Tables 2 and 3, respectively. The reaction of **12a** provided the expected product **13** in good to excellent yield, especially with the use of P(*o*-Tol)$_3$ as a phosphine ligand. On the other hand, **12b**, which possesses an iodo group as a leaving group on the aniline part, gave **14**, which was formed by connection to a more hindered carbon, as a major product along with **13** as a minor product. The influence of oxygen substituent(s) on the cyclization position is now under investigation in our laboratory. Reduction of **13** with $LiAlH_4$ followed by treatment with HCl gave trisphaeridine (**3**)[17,18] in a yield of 54%. The spectral data of the synthetic material were in good agreement with the reported data of an authentic sample.[18,23e]

Table 3 Results of cyclization reactions of *N*-(2-iodophenyl)-*N*-methoxymethyl-3,4-methylenedioxybenzamide (**12b**) in DMF under reflux[a]

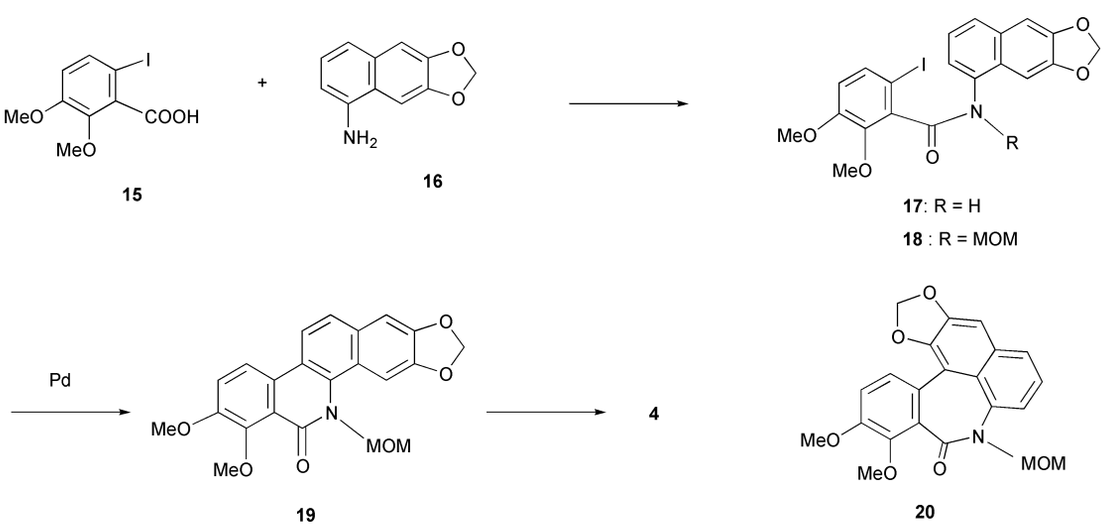
Run	$Pd(OAc)_2$ (eq.)	Ligand	Base	Time/h	Yield (%) of **13** + **14**	**13** : **14**
1	0.1	PPh_3	Na_2CO_3	2	73	1 : 4
2	0.1	PPh_3	Ag_2CO_3	2	72	1 : 4.9

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

Table 4 Results of cyclization reactions of 6-iodo-2,3-dimethoxy-*N*-methoxymethyl-*N*-(6,7-methoxydioxy-1-naphthyl)benzamide (**18**) in DMF under reflux[a]

					Yield (%)	
Run	$Pd(OAc)_2$ (eq.)	Ligand (L : Pd)	Base	Time/min	**19**	**20**
1	0.2	—	Na_2CO_3	300	10	—
2	0.2	PPh_3 (2)	Na_2CO_3	40	51	13
3	1.0	PPh_3 (2)	Na_2CO_3	30	76	20
4	0.2	PPh_3 (2)	Ag_2CO_3	30	70	18
5	0.2	P(*o*-Tol)$_3$ (2)	Na_2CO_3	60	74	16
6	0.2	P(*o*-Tol)$_3$ (2)	Ag_2CO_3	40	96	1
7	0.2	DPPP (1)	Na_2CO_3	60	61	14

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



Scheme 2

Subsequently, total synthesis of norchelerythrine (**4**)[23b,25] was investigated by applying the synthetic strategy described above. Since *o*-halobenzoic acid is likely to be more accessible than *o*-haloaniline and cyclization reaction of **12b** with a halo group on the aniline part using a Pd reagent yielded two products, we designed a route for the synthesis of **4** through an amide (**18**) that is protected by the MOM group and possesses a halo group on the benzoyl part, as shown in Scheme 2. Methoxymethylation of the amide **17**,[15] which was synthesized from the acid (**15**)[26] and the amine (**16**),[15] with chloromethyl methyl ether in the presence of NaH gave the protected amide **18** in a yield of 87%. The coupling reaction of amide **18** with $Pd(OAc)_2$, a phosphine ligand and a base in DMF under reflux afforded **19** in good to excellent yield, accompanied by a small amount of benzazepinone (**20**)[27] as shown in Table 4 (see runs 3–6). A combination of P(*o*-Tol)$_3$ and Ag_2CO_3 was the most effective combination of additives. The structures of the products **19** and **20** were elucidated on the basis of spectral data, especially ^{1}H-NMR data in which **20** showed two singlet signals due to aromatic protons, whereas **19** showed only one singlet signal due to an aromatic proton (see Experimental). Moreover, in the ^{1}H-NMR spectra the signals attributable to the methylene protons of the MOM group appeared extraordinarily broad in $CDCl_3$ solution, whereas the signal appeared as a broad singlet at δ 5.00 in d_6-DMSO solution at 80 °C. Reduction of **19** with $LiAlH_4$ and subsequent treatment with HCl provided **4** (92%), which was identical with an authentic sample.

Experimental

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are quoted as uncorrected values. IR spectra were recorded for samples in KBr pellets with a JASCO A-102 or JASCO FT/IR 350 spectrophotometer, and ^{1}H- and ^{13}C-NMR spectra were recorded in deuteriochloroform on a Hitachi R-1500 (60 MHz), Varian VXR-200 (200 MHz) or -500 (500 MHz) spectrometer unless otherwise stated. NMR data are reported in ppm downfield from tetramethylsilane 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 (Merck, silica gel 60, No. 9385) or aluminium oxide (Wako, about 300 mesh). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, 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 filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.[28]

2-Iodo-*N*-methoxymethyl-*N*-phenylbenzamide (5b)

To a stirred solution of amide **5a** (200 mg, 0.619 mmol) in dry $CHCl_3$ (12 cm^3) was added dimethoxymethane (14 cm^3, 158 mmol) and phosphorus pentaoxide (2.0 g), and the mixture was stirred for 5 h at rt. The mixture was poured into aqueous 5% Na_2CO_3 solution and extracted with ether. The residue was dissolved in benzene and subjected to column chromatography on alumina. Elution with benzene–hexane (2 : 1) afforded **5b** (141 mg, 62%) as an oil; ν_{max}/cm^{-1} 1670; δ_H (60 MHz) 3.55 (3H, br s, OCH_3), 5.28 (2H, br s, NCH_2O) and 6.96–7.79 (9H, m, aromatic protons); *m*/*z* (FAB) 368 ($M^+ + 1$). Found: C, 49.2; H, 3.9; N, 3.6%. Calcd for $C_{15}H_{14}INO_2$: C, 49.1; H, 3.8; N, 3.8%.

***N*-(2-Iodophenyl)-*N*-methoxymethylbenzamide (6b)**

To a stirred solution of amide **6a** (200 mg, 0.619 mmol) in dry $CHCl_3$ (12 cm^3) was added dimethoxymethane (14 cm^3, 158 mmol) and phosphorus pentaoxide (2.0 g), and the reaction mixture was stirred for 46 h at rt. The mixture was poured into aqueous 5% Na_2CO_3 solution and extracted with ether. The residue dissolved in benzene was subjected to column chromatography on alumina. Elution with benzene afforded **6b** (194 mg, 85%) as colorless prisms, mp 70–71.5 °C (from hexane); ν_{max}/cm^{-1} 1650; δ_H (60 MHz) 3.46 (3H, s, OCH_3), 4.63 (1H, d, *J* 10.0, NCH_AH_BO), 5.70 (1H, br d, *J* 10.0, NCH_AH_BO) and 6.95–7.90 (9H, m, aromatic protons); *m*/*z* (EI) 367 (M^+). Found: C, 49.0; H, 4.2; N, 3.8%. Calcd for $C_{15}H_{14}INO_2$: C, 49.1; H, 3.8; N, 3.8%.

General procedure for the cyclization reaction of *N*-methoxymethylbenzanilides 5b and 6b by palladium reagent

Reaction of benzanilide (36.7 mg, 0.1 mmol) with $Pd(OAc)_2$, a phosphine ligand, and a base in dry DMF (4 cm^3) was carried out using $Pd(OAc)_2$ and the ligand in a ratio of 1 : 2 and 2 mol equivalents of base under reflux and under the reaction conditions indicated in Table 1. The reaction mixture was diluted with benzene and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in benzene was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (4 : 1) gave 5-methoxymethylphenanthridin-6(5*H*)-one (**7b**) as colorless prisms, mp 93–94 °C (from ether); ν_{max}/cm^{-1} 1670; δ_H (60 MHz) 3.48 (3H, s, OCH_3), 5.83 (2H, s, NCH_2O) and 7.27–8.62 (8H, m, aromatic protons). Found: C, 75.5; H,5.5; N, 5.8%. Calcd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.5; N, 5.9%.

Phenanthridine (8)

$LiAlH_4$ (68.3 mg, 1.80 mmol) was added to a solution of **7b** (144 mg, 0.60 mmol) in dry THF (7 cm^3) and the mixture was stirred for 2 h at rt. Excess hydride was decomposed with wet ether and the organic layer was decanted. The residue in THF (3 cm^3) was treated with 6 M HCl (3 cm^3) for 1 h under reflux. The reaction mixture was poured into aqueous sat. Na_2CO_3 solution and extracted with $CHCl_3$. The residue in $CHCl_3$ was subjected to chromatography on silica gel. Elution with hexane–AcOEt (6 : 1) gave **8** (58 mg, 54%) as colorless prisms, mp 103–105 °C (from EtOH–hexane) (lit.[22] mp 104–105 °C); *m*/*z* (EI) 170 (M^+). Found: C, 87.1; H, 5.4; N, 7.8%. Calcd for $C_{13}H_9N$: C, 87.1; H, 5.1; N, 7.8%.

2-Bromo-4,5-methylenedioxy-*N*-phenylbenzamide (11a)

Oxalyl chloride (3.33 g, 26.3 mmol) was added to a solution of 6-bromopiperonylic acid (**9a**) (3.0 g, 13.1 mmol) in dry THF (120 cm^3) containing twenty drops of dry DMF at 10 °C. The stirred mixture was refluxed for 3 h, and then concentrated to dryness under reduced pressure. To this residue was added a solution of aniline (**10a**) (1.21 g,13.1 mmol) in dry THF (60 cm^3) and dry NEt_3 (2.18 cm^3, 15.7 mmol) and the mixture was stirred for 3 h at rt. The reaction mixture was concentrated to dryness and diluted with $CHCl_3$, then washed with 10% HCl, aqueous 5% NaOH solution and brine. The residue was dissolved in benzene and the solution was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (6 : 1) gave **11a** (3.12 g, 74%) as colorless needles, mp 149–152 °C (from ether); ν_{max}/cm^{-1} 3280 and 1660; δ_H (200 MHz) 6.04 (2H, s, OCH_2O), 7.03 (1H, s, 3-H), 7.13 (1H, s, 6-H), 7.16 (1H, t, *J* 7.8, 4′-H), 7.37 (2H, t, *J* 7.8, 3′-H and 5′-H), 7.62 (2H, d, *J* 7.8, 2′-H and 6′-H) and 7.78 (1H, br s, NH). Found: C, 52.3; H, 3.2; N, 4.3%. Calcd for $C_{14}H_{10}BrNO_3$: C, 52.5; H, 3.2; N, 4.4%.

***N*-(2-Iodophenyl)-3,4-methylenedioxybenzamide (11b)**

Oxalyl chloride (3.05 g, 24.1 mmol) was added to a solution of piperonylic acid (**9b**) (2.0 g, 12.0 mmol) in dry THF (100 cm^3) containing ten drops of dry DMF at 10 °C. The stirred mixture was refluxed for 2.5 h, and concentrated to dryness under reduced pressure. To this residue was added a solution of 2-iodoaniline (**10b**) (2.63 g, 12.0 mmol) in dry THF (50 cm^3) and dry NEt_3 (2.01 cm^3, 14.4 mmol) and the mixture was stirred for 3 h at rt. The reaction mixture was concentrated to dryness and diluted with AcOEt, then washed with 10% HCl, aqueous 5% NaOH solution and brine. The residue was dissolved in benzene and subjected to column chromatography on silica gel. Elution with hexane–AcOEt (5 : 1) gave **11b** (3.53 g, 80%) as colorless needles, mp 122–124.5 °C (from ether); ν_{max}/cm^{-1} 3260 and 1650; δ_H (200 MHz) 6.08 (2H, s, OCH_2O), 6.88 (1H, ddd, *J* 7.9, 7.8 and 1.6, 4′-H), 6.92 (1H, d, *J* 8.2, 5-H), 7.40 (1H, ddd, *J* 7.8, 7.8 and 1.6, 5′-H), 7.45 (2H, d, *J* 1.8, 2-H), 7.52 (1H, dd, *J* 8.2 and 1.8, 6-H), 7.81 (1H, dd, *J* 7.8 and 1.6, 6′-H), 8.16 (1H, br s, NH) and 8.42 (1H, dd, *J* 7.9 and 1.6, 3′-H). Found: C, 45.7; H, 3.0; N, 3.7%. Calcd for $C_{14}H_{10}INO_3$: C, 45.8; H, 2.7; N, 3.8%.

2-Bromo-*N*-methoxymethyl-4,5-methylenedioxy-*N*-phenylbenzamide (12a)

To a suspension of **11a** (1.0 g, 3.12 mmol) and NaH (360 mg, 63% dispersion in mineral oil, 9.37 mmol) in dry DMF (50 cm^3) was added chloromethyl methyl ether (378 mg, 4.69 mmol). After stirring for 5 h at rt, the reaction mixture was diluted with ether and washed with aqueous sat. $NaHCO_3$ solution and brine. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on alumina. Elution with hexane–AcOEt (4 : 1) gave **12a** (955 mg, 84%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1640; δ_H (60 MHz) 3.52 (3H, s, OCH_3), 5.20 (2H, s, NCH_2O), 5.91 (2H, s, OCH_2O), 6.63 (1H, s, 3-H), 6.87 (1H, s, 6-H) and 7.26 (5H, br s, aromatic protons); *m*/*z* (FAB) 364 ($M^+ + 1$).

***N*-(2-Iodophenyl)-*N*-methoxymethyl-3,4-methylenedioxbenzamide (12b)**

To a suspension of **11b** (300 mg, 0.82 mmol) and NaH (94 mg, 63% dispersion in mineral oil, 2.45 mmol) in dry THF (12 cm^3) was added chloromethyl methyl ether (99 mg, 1.23 mmol). After stirring for 1.5 h at rt, the reaction mixture was diluted with ether and washed with aqueous sat. $NaHCO_3$ solution and brine. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on alumina. Elution with hexane–AcOEt (4 : 1) gave **12b** (283 mg, 84%) as pale yellow prisms, mp 77–79 °C (from ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 1640; δ_H (60 MHz) 3.45 (3H, s, OCH_3), 4.63 (1H, d, *J* 10.0, NCH_AH_BO), 5.60 (1H, br d, *J* 10.0, NCH_AH_BO), 5.92 (2H, s, OCH_2O) and 6.55–7.92 (7H, m, aromatic protons). Found: C, 47.0; H, 3.3; N, 3.3%. Calcd for $C_{16}H_{14}INO_4$: C, 46.7; H, 3.4; N, 3.4%.

General procedure for the cyclization reaction of bromo-*N*-methoxymethylbenzanilide (12a) by palladium reagent

Reaction of **12a** (180 mg, 0.5 mmol) with $Pd(OAc)_2$, a phos-

phine ligand, and a base in dry DMF (12 cm^3) was carried out using $Pd(OAc)_2$ and ligand in a ratio of 1 : 2 and 2 mol equivalents of base under reflux and under the reaction conditions indicated in Table 2. The reaction mixture was diluted with ether–AcOEt (1 : 1) and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in benzene and subjected to column chromatography on silica gel. Elution with hexane–AcOEt (6 : 1) gave 5-methoxymethyl-8,9-methylenedioxyphenanthridin-6(5*H*)-one (**13**) as colorless needles, mp 180–182 °C (from AcOEt); ν_{max}/cm^{-1} 1640; δ_H (200 MHz) 3.46 (3H, s, OCH_3), 5.82 (2H, s, NCH_2O), 6.12 (2H, s, OCH_2O), 7.30 (1H, ddd, *J* 8.2, 7.0 and 1.4, 2-H), 7.48 (1H, ddd, *J* 8.1, 7.0 and 1.4, 3-H), 7.59 (1H, s, 10-H), 7.60 (1H, dd, *J* 8.1 and 1.4, 4-H), 7.87 (1H, s, 7-H) and 8.04 (1H, dd, *J* 8.2 and 1.4, 1-H). Found: C, 67.6; H, 4.4; N, 4.9%. Calcd for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6; N, 5.0%.

General procedure for the cyclization reaction of iodo-*N*-methoxymethylbenzanilide (12b) by palladium reagent

Reaction of **12b** (100 mg, 0.24 mmol) with $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), triphenylphosphine (12.9 mg, 0.05 mmol), and two mol equivalents of base as indicated in Table 3 in dry DMF (3 cm^3) was carried out for 2 h. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on alumina. Elution with hexane–$^i Pr_2O$ (2 : 1) gave **13**, mp 178–179 °C and successive elution with the same solvent gave 5-methoxymethyl-9,10-methylenedioxyphenanthridin-6(5*H*)-one (**14**) as colorless needles, mp 183–185 °C (from $CHCl_3$–hexane); $\nu_{max}(CHCl_3)/cm^{-1}$ 1600; δ_H (500 MHz) 3.47 (3H, s, OCH_3), 5.81 (2H, br s, NCH_2O), 6.27 (2H, s, OCH_2O), 7.09 (1H, d, *J* 8.5, 8-H), 7.30 (1H, ddd, *J* 8.2, 8.2 and 1.3, 2-H), 7.50 (1H, ddd, *J* 8.2, 8.2 and 1.4, 3-H), 7.59 (1H, dd, *J* 8.2 and 1.3, 4-H), 8.19 (1H, d, *J* 8.5, 7-H) and 8.62 (1H, dd, *J* 8.2 and 1.4, 1-H). Found: C, 67.9; H, 4.8; N, 4.9%. Calcd for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6; N, 5.0%.

The ratio of products was determined by HPLC (column, chemosorb 5Si; eluent, hexane–AcOEt (1 : 3); flow rate, 1.0 ml min^{-1}; wavelength, 254 nm; t_R for **13** = 7.2 min; t_R for **14** = 6.4 min).

Trisphaeridine (3)

$LiAlH_4$ (59.4 mg, 1.57 mmol) was added to a solution of **13** (89 mg, 0.31 mmol) in dry THF (9 cm^3) and the mixture was stirred for 3 h at rt. Excess hydride was decomposed with wet ether and the organic layer was decanted. A solution of the residue in 10% HCl (3 cm^3) was stirred for 1 h at 80 °C. The reaction mixture was poured into aqueous 5% NaOH solution and extracted with $CHCl_3$. The organic layer was washed with brine. The residue in $CHCl_3$ was subjected to chromatography on alumina. Elution with $CHCl_3$ gave **3** (38 mg, 54%) as colorless prisms, mp 142.5–144 °C (from hexane) (lit.[23e] mp 144.5–145 °C); *m*/*z* (FAB) 224 (M^+ + 1). Found: C, 69.6; H, 4.7; N, 5.8%. Calcd for $C_{14}H_9NO_2 \cdot H_2O$: C, 69.7; H, 4.6; N, 5.8%.

6-Iodo-2,3-dimethoxy-*N*-methoxymethyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (18)

A suspension of **17** (1.0 g, 2.1 mmol) and NaH (380 mg, 63% dispersion in mineral oil, 6.3 mmol) in dry DMF (30 cm^3) was stirred for 2 h at rt and then chloromethyl methyl ether (254 mg, 3.2 mmol) was added to the reaction mixture. After stirring for 2 h at rt, the reaction mixture was diluted with ether and washed with brine. The residue was dissolved in benzene and subjected to column chromatography on silica gel. Elution with hexane–AcOEt (2 : 1) gave **18** (951 mg, 87%) as colorless prisms, mp 152–153 °C (from ether–hexane); ν_{max}/cm^{-1} 1660; δ_H (60 MHz) 3.19–4.89 (11H, m, 3 × OCH_3 and NCH_2O, rotamer), 6.05 (2H, s, OCH_2O), 6.76 (1H, d, *J* 8.5, 4-H), 7.58 (1H, d, *J* 8.5, 5-H) and 7.03–7.65 (5H, m, aromatic protons); *m*/*z* (FAB) 522 (M^+ + 1). Found: C, 50.7; H, 3.8; N, 2.7%. Calcd for $C_{22}H_{20}INO_6$: C, 50.7; H, 3.9; N, 2.7%.

General procedure for the cyclization reaction of iodo-*N*-methoxymethylbenzanilide (18) by palladium reagent

Reaction of **18** (260 mg, 0.5 mmol) with $Pd(OAc)_2$, a phosphine ligand, and a base in dry DMF (15 cm^3) was carried out using $Pd(OAc)_2$ and ligand in a ratio 1 : 2 and 2 mol equivalents of base under reflux and under the reaction conditions indicated in Table 4. The reaction mixture was diluted with benzene and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in benzene and subjected to column chromatography on silica gel. Elution with hexane–AcOEt (2 : 1) gave 9,10-dimethoxy-7-methoxymethyl-1,2-methylenedioxynaphtho[1,8-*cd*][2]benzazepin-8(7*H*)-one (**20**) and successive elution with the same solvent gave 7,8-dimethoxy-5-methoxymethyl-2,3-methylenedioxybenzo[*c*]phenanthridin-6(5*H*)-one (**19**).

Compound **20**: mp 178–179 °C (from ether–hexane) as colorless prisms; ν_{max}/cm^{-1} 1660; δ_H (200 MHz) 3.47 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 6.12 (2H, br s, OCH_2O), 6.94 (1H, d, *J* 8.8, 11-H), 6.98 (1H, s, 3-H), 7.25 (1H, dd, *J* 7.6 and 7. 4, 5-H), 7.38 (1H, d, *J* 8.8, 12-H), 7.38 (1H, dd, *J* 7.4 and 1.4, 4-H) and 7.56 (1H, dd, *J* 7.6 and 1.4, 6-H); (500 MHz, d_6-DMSO, 80 °C) 3.21 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.00 (2H, br s, NCH_2O), 6.23 (2H, br s, OCH_2O), 7.13 (1H, d, *J* 9.0, 11-H), 7.19 (1H, s, 3-H), 7.29 (1H, dd, *J* 8.0 and 7.5, 5-H), 7.41 (1H, d, *J* 9.0, 12-H), 7.47 (1H, dd, *J* 7. 5 and 1.0, 4-H) and 7.49 (1H, dd, *J* 8.0 and 1.0, 6-H). Found: C, 67.2; H, 5.0; N, 3.5%. Calcd for $C_{22}H_{19}NO_6$: C, 67.2; H, 4.9; N, 3.6%.

Compound **19**: mp 199–200 °C (from ether–hexane) as colorless prisms; ν_{max}/cm^{-1} 1665; δ_H (500 MHz) 3.75 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 5.35 (2H, s, NCH_2O), 6.09 (2H, s, OCH_2O), 7.12 (1H, s, 1-H), 7.38 (1H, d, *J* 8.5, 9-H), 7.50 (1H, d, *J* 8.5, 12-H), 7.95 (1H, d, *J* 8.5, 9-H) and 8.38 (1H, s, 4-H). Found: C, 67.2; H, 5.1; N, 3.6%. Calcd for $C_{22}H_{19}NO_6$: C, 67.2; H, 4.9; N, 3.6%.

Norchelerythrine (4)

$LiAlH_4$ (43.4 mg, 1.14 mmol) was added to a solution of **19** (149 mg, 0.38 mmol) in dry THF (15 cm^3) and the mixture was stirred for 30 min at rt. Excess hydride was decomposed with wet ether and the organic layer was decanted. A solution of residue in THF (10 cm^3) and 10% HCl (25 cm^3) was stirred for 1 h at rt. The reaction mixture was poured into aqueous sat. $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with brine. The residue was recrystallized from benzene–hexane to provide **4** (116 mg, 92%) as pale yellow prisms, mp 217–219 °C (from hexane) (lit.[25a] mp 212–214 °C, lit.[25c] mp 213–215 °C).

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