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Synthesis of Benzo[*c*]phenanthridine Alkaloids by $Pd(OAc)_2$-Induced Direct Aromatic Carbonylation

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The $Pd(OAc)_2$-induced carbonylation of alkoxy-substituted 1-amino-2-phenyltetralins and 1-amino-2-phenylnaphthalenes was examined to provide the benzo[*c*]phenanthridine ring system. The carbonylation of substrates containing methylenedioxy groups gave oxysanguinarine and oxyavicine. The tetramethoxy derivatives gave *O*-methyloxyfagaronine. The substrate with a benzyloxy group afforded a known synthetic precursor to the antileukemic alkaloid, fagaronine.

Introduction

Recently we reported the $Pd(OAc)_2$-catalyzed direct aromatic carbonylation reaction of secondary ω-phenylalkylamines, which provided five- or six-membered benzolactams.[1] The site selectivity for the carbonylation was a result of the stability of the cyclopalladation species formed in the transition states.[1a,1b] The *ortho* selectivity increased as a result of the chelation between the *meta*-alkoxy group and Pd^{II}, and was greatly enhanced by the presence of a 3,4-methylenedioxy group (**A**). However, the selectivity decreased as a result of the steric repulsion caused by a bulky substituent, such as a 3,4-dimethoxy group (**B**), and the ligands on the Pd catalyst. Most of the tested *N*-alkylphenethylamines were nucleophilic enough to give the cyclopalladation species, which led to the corresponding benzolactams by subsequent carbonylation. In contrast, *N*-aryl derivatives had some difficulties when subjected to the the carbonylation reaction.[1b] We have been interested in substrates with a 1-amino-2-aryltetralin or 1-amino-2-arylnaphthalene structure (**C**) for the carbonylation reaction, because the products may provide the ring system (**D**) characteristic of the benzo[*c*]phenanthridine alkaloids,[2–4] that is, if the former amino group does not act as a leaving group, and the latter arylamine is not too much less nucleophilic. Some benzo[*c*]phenanthridine alkaloids have interesting biological qualities such as antitumor,[5] antileukemic,[5a,5b,6] anticoagulant and cytotoxic,[7] anticancer,[8] anti-HIV,[9a] antiviral,[9b,9c,9d] antimicrobial,[5d,9c] and antituberculosis activities,[9e] as well as protein kinase C[10] and DNA topoisomerase I and II[11] inhibitory activities. Herein, we report the results of our study of $Pd(OAc)_2$-induced carbonylation reactions leading to the formation of alkoxy-substituted 6-oxobenzo[*c*]phenanthridines, some of which have been transformed into benzo[*c*]phenanthridine alkaloids.[12]

Results and Discussion

First, the carbonylation of substrates containing methylenedioxy groups was examined. Tetrahydronaphthylamine **1** was prepared following the procedure developed by Ishii and Ishikawa,[5e,13,14] and naphthylamine **2** was prepared by dehydrogenation of **1** with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 91%), which involved N-protection with Boc_2O (di-*tert*-butyl dicarbonate, 74%) and deprotection with CF_3COOH (90%).

The direct carbonylation of **1** with a stoichiometric amount of $Pd(OAc)_2$ was carried out under an atmosphere of CO gas in refluxing toluene for 3 h to produce lactams **3** and **4** in a 2:1 ratio (see Table 1, Entry 1). The addition of $Cu(OAc)_2$ gave for **3** and **4** in a 3:1 ratio (Table 1, Entry 3). The carbonylation of **1**·HCl resulted in a complete reversal of the ratio to 1:3, because of an aromatic electrophilic substitution with $Pd(OAc)_2$ (Table 1, Entry 2). Under the conditions for the oxidative carbonylation reaction (Table 1, Entries 4–12) with an atmosphere of CO gas containing air corresponding to 0.5 equiv. of O_2, a catalytic sys-

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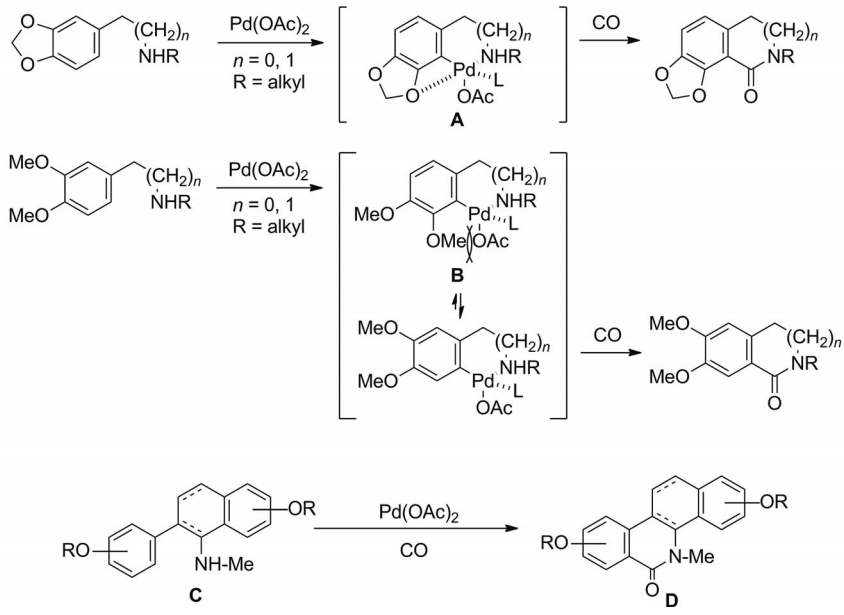


tem with $Pd(OAc)_2$·2PPh_3[15] in refluxing toluene afforded only the desired benzolactam **3** at the beginning of the slow reaction and then a 5:1 mixture of **3** and **4** after 2 d (Table 1, Entry 4). The use of $Pd(OAc)_2$ (5 mol-%)/$Cu(OAc)_2$ (50 mol-%) also afforded a 3:1 selectivity (Table 1, Entry 5). The carbonylation of **1**·HCl using a catalytic amount of $Pd(OAc)_2$/$Cu(OAc)_2$ resulted in the formation of a complex mixture (Table 1, Entry 6). It had been reported that pyridine could act as a smaller but good ligand for a Pd^{II} catalyst.[16,17] The addition of 5 mol-% of pyridine to the reaction mixture formed **3** more selectively in a ratio of 11:1 (Table 1, Entry 7). Using 2,2′-bipyridyl did not exceed the selectivity gained by pyridine (Table 1, Entry 8). DMSO (dimethyl sulfoxide) appeared to be a good solvent for preparation of **3** (Table 1, Entries 9–11), but DMF (dimethylformamide) was not (Table 1, Entry 12). Dehydrogenation of **3** or **4** with DDQ (2 equiv. in refluxing benzene for 2 h) gave oxysanguinarine (**5**)[13] or oxyavicine (**6**)[18,19] in 87% or 71% yields, respectively (see Scheme 1).

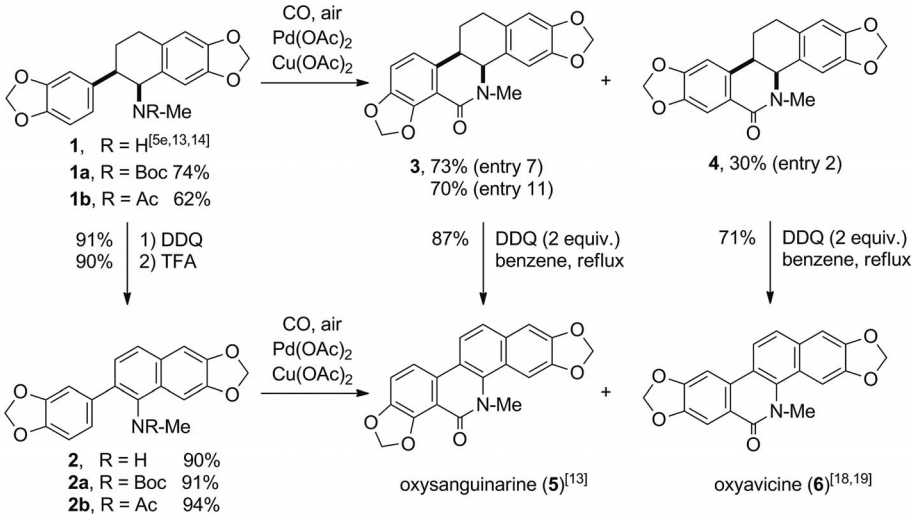
The carbonylation reaction of naphthylamine **2** (see Table 2) proceeded slowly, and the site selectivity was lower, compared with the selectivity observed for the conversion of **1** into **3**. By using a stoichiometric amount of $Pd(OAc)_2$, oxysanguinarine (**5**) and oxyavicine (**6**) were obtained in a 2:3 ratio (Table 2, Entry 1). The catalytic carbonylations (Table 2, Entries 2–5), including that with $Pd(OAc)_2$·2PPh_3, gave the opposite site selectivities (2:1–4:1) in lower yields. Probably, the lower nucleophilicity of the aromatic amino group affected this carbonylation reaction. In fact, acetamide **2b**, corresponding to a byproduct of **1b** produced in carbonylation of **1**, was not formed during the carbonylation of **2**. Thus, the carbonylation of naphthylamine **2** was not superior to that of 1-(*N*-methylamino)tetralin **1**.[20]

To prepare the tetramethoxy analogue of **1** (i.e., **11**), dimethoxy-α-tetralone **7**[21] underwent an arylation reaction to give **9** in 76% yield by using Pinhey's procedure[22] with 3,4-dimethoxyphenyllead triacetate[23] (**8**) in the presence of

Table 1. Carbonylation of tetrahydronaphthylamine **1**.

Entry	Reactant	$Pd(OAc)_2$/$Cu(OAc)_2$[a]	Additive (mol-%)	Solvent	*T* [°C]	Time [h]	**3/4/1b**[b]	Product (% yield)[c]
1	**1**	100:0		toluene	reflux	3	32:16:5	
2	**1**·HCl	100:0		toluene	reflux	3	12:35:0	**4** (30)
3	**1**	100:100		toluene	reflux	72	47:16:0	
4	**1**	20:0	PPh_3 (40)	toluene	reflux	48	40:8:5	
5	**1**	5:50		toluene	reflux	12	46:16:7	
6	**1**·HCl	5:50		toluene	reflux	24		complex mixture
7	**1**	5:50	pyridine (5)	toluene	reflux	12	78:7:0	**3** (73)
8	**1**	5:50	2,2′-bipyridyl (5)	toluene	reflux	12	34:8:7	
9	**1**	5:50		toluene/DMSO (1:1)	reflux	12	67:17:0	**3** (64)
10	**1**	5:50		DMSO	120	12	63:13:0	
11	**1**	5:50		DMSO	120	24	73:14:0	**3** (70)
12	**1**	5:50		DMF	120	24	8:2:0	

[a] Mol-% relative to **1**. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

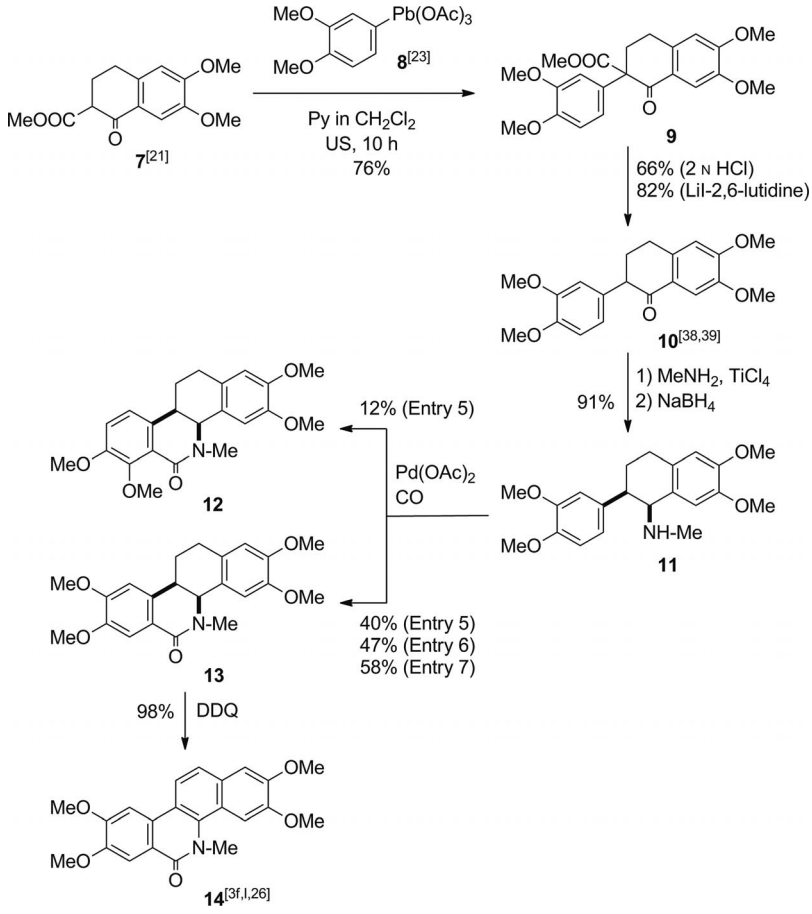


Scheme 1. Carbonylation of substrates with methylenedioxy groups.

Table 2. Carbonylation of naphthylamine **2**.

Entry	$Pd(OAc)_2/Cu(OAc)_2$[a]	Additive (mol-%)	Solvent	*T* [°C]	Time [h]	**5/6**[b]
1	100:0		toluene	reflux	24	34:51
2	20:0	PPh_3 (40)	toluene	reflux	24	30:10
3	5:50		toluene	reflux	24	40:20
4	5:50	pyridine (5)	toluene	reflux	24	40:10
5	5:50		DMSO	120 °C	24	25:12

[a] Mol-% relative to **2**. [b] Determined by ^1H NMR spectroscopy.



Scheme 2. Carbonylation of substrate **11** with tetramethoxy groups.

pyridine. A methoxycarbonyl group of the resultant 3,4-dimethoxyphenylated α-tetralone **9** was removed by an acid-catalyzed hydrolysis in refluxing EtOH and a 2 N HCl solution for 8 h to give α-tetralone **10** in 66% yield (Scheme 2). The decarboxylation of **9** with LiCl/DMSO[24] was unsuccessful, but the use of LiI–2,6-lutidine[25] readily resulted in the formation of **10** in 82% yield. On the basis of a $TiCl_3$-assisted imination of a ketone followed by a $NaBH_4$ reduction, the *N*-methylamination[5e] of **10** was carried out to produce the desired substrate **11** in 91% yield, in preparation for the carbonylation. Using stoichiometric amounts of both $Pd(OAc)_2$ and $Cu(OAc)_2$ in refluxing toluene, the carbonylation of **11** afforded **13** in 86% yield (see Table 3, Entry 3). Using catalytic amounts of $Pd(OAc)_2$ (5 mol-%) and $Cu(OAc)_2$ (50 mol-%), the carbonylation reaction gave **12** and **13** in a 1:6 ratio (Table 3, Entry 4), and the addition of 5 mol-% of pyridine to the reaction mixture gave **12** and **13** in a 1:1.8 ratio, which was the best yield for **12** (Table 3, Entry 5). Increased amounts of pyridine resulted in inhibiting the carbonylation reaction. Changing the solvent to DMSO or a 1:1 mixture of DMSO and toluene gave better results (Table 3, Entries 6 and 7). However, the carbonylation in DMSO of **11**·HCl yielded a complex mixture (Table 3, Entry 8), even under compressed CO gas at 25 atm. In addition, using the more electrophilic catalyst $Pd(OOCCF_3)_2$ in place of $Pd(OAc)_2$ resulted in a complex mixture, and the use of $Cu(OOCCF_3)_2$ in place of $Cu(OAc)_2$ inhibited the carbonylation process completely. The oxidation of **13** by treatment with DDQ quantitatively produced aromatic system **14**, which is named *O*-methyloxyfagaronine.[3f,3l,26]

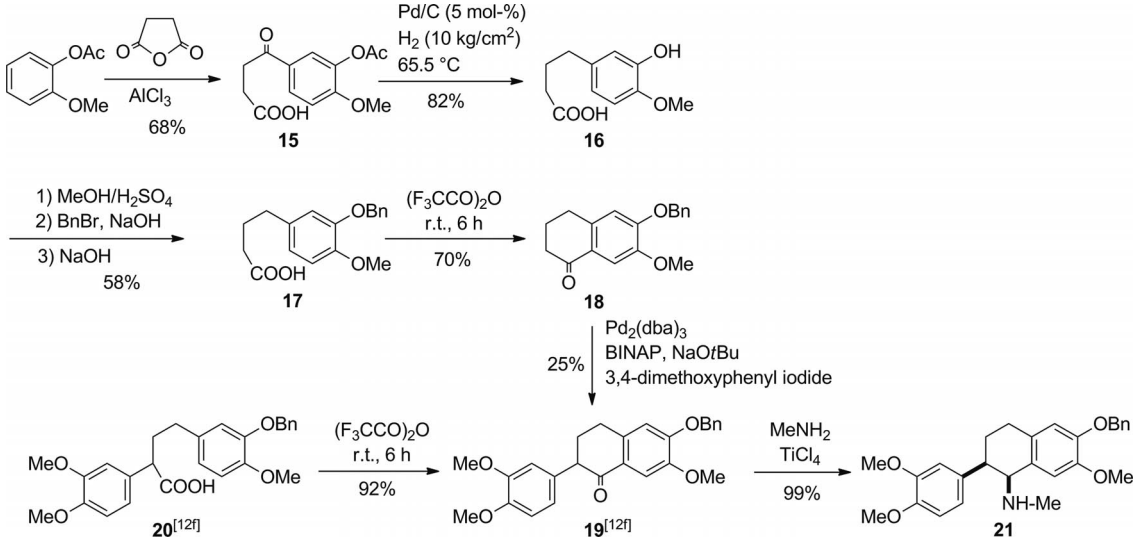
Next, the method was applied to the synthesis of another benzo[*c*]phenanthridine alkaloid, fagaronine (**25**), which was reported to exhibit strong antileukemic activity.[5b] As shown in Scheme 3, the corresponding synthetic intermediate, 2-aryl-α-tetralone **19**, was prepared by a Pd^0-catalyzed arylation reaction of 6-benzyloxy-7-methoxy-α-tetralone (**18**) with 3,4-dimethoxyphenyl iodide, using a modified procedure by Buchwald.[27,28] α-Tetralone **18** was obtained by sequential reactions starting from a regioselective Friedel–Crafts acylation of 2-methoxyphenyl acetate with succinic anhydride and ending with a cyclization of 4-phenylbutanoic acid **17** with $(CF_3CO)_2O$.[29] A similar cyclization of the known acid **20**[12f] also gave **19** in 92% yield. Similar to the method for the preparation of compound **11**, the reductive amination of **19** afforded **21** in an excellent yield (99%), as shown in Scheme 3.

By using a stoichiometric amount of $Pd(OAc)_2$, the carbonylation of amine **21**·HCl afforded benzolactam **23** in 71% yield (see Table 4, Entry 2). In DMSO, the $Pd(OAc)_2$-cata-

Table 3. Carbonylation of tetrahydronaphthylamine **11**.

Entry	Reactant	$Pd(OAc)_2$/ $Cu(OAc)_2$[a]	Additive (mol-%)	Solvent	*T* [°C]	Time [h]	**11/12/13**[b]	Product (% yield)[c]
1	**11**	100:0		toluene	reflux	3	35:0:60	**13** (33)
2	**11**·HCl	100:0		toluene	reflux	3	0:0:100	**13** (70)
3	**11**	100:100		toluene	reflux	3	0:0:100	**13** (86)
4	**11**	5:50		toluene	reflux	24	20:5:30	
5	**11**	5:50	pyridine (5)	toluene	reflux	24	15:25:45	**12** (12), **13** (40)
6	**11**	5:50		DMSO	120	36	3:21:50	**13** (47)
7	**11**	5:50		toluene/DMSO (1:1)	120	24	4:26:64	**13** (58)
8	**11**·HCl	5:50		DMSO	120	24	complex mixture	

[a] Mol-% relative to **11**. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield.



Scheme 3. Preparation of 1-(*N*-methylamino)-α-tetralin **21**.

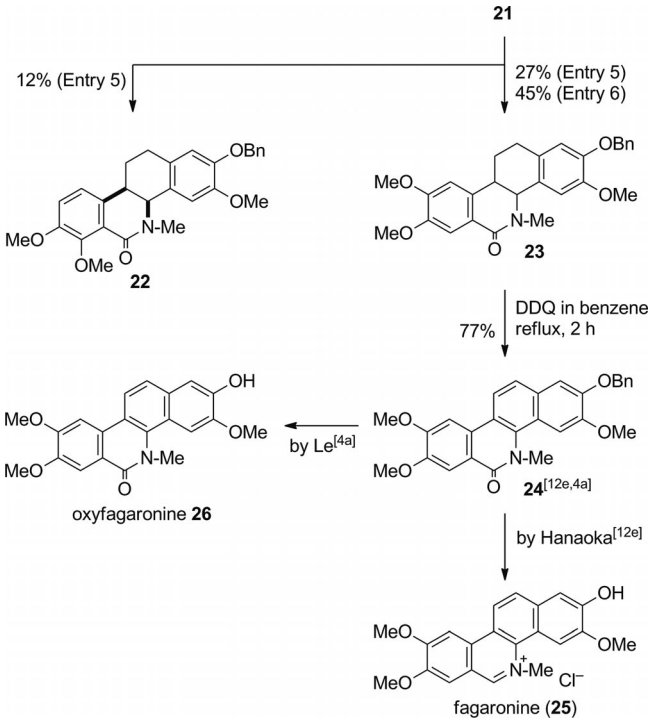
Table 4. Carbonylation of tetrahydronaphthylamine **21**.

Entry	Reactant	$Pd(OAc)_2$ /$Cu(OAc)_2$[a]	Solvent	*T* [°C]	Time [h]	**21**/**22**/**23**[b]	Product (% yield)[c]
1	**21**	100:0	toluene	reflux	3	20:0:60	**23** (27)
2	**21**·HCl	100:0	toluene	reflux	3	0:0:90	**23** (71)
3	**21**	100:100	toluene	reflux	3	0:0:65	**23** (53)
4	**21**	5:50	toluene	reflux	24	15:10:40	
5	**21**	5:50	DMSO	120	24	0:15:50	**22** (12), **23** (27)
6	**21**	5:50	toluene/DMSO (1:1)	120	24	5:20:55	**23** (45)

[a] Mol-% relative to **21**. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

lyzed carbonylation of **21** produced **23** in 27% and 45% yields, respectively, as shown in Entries 5 and 6 in Table 4. As expected, the selectivity for **22** was low.

Successively, benzolactam **23** was subjected to oxidation by treatment with DDQ (2 equiv.) in refluxing benzene for 2 h to give *O*-benzyloxyfagaronine (**24**)[12e,4a] in 77% yield (Scheme 4). In view of the previous conversions of **24** into fagaronine (**25**)[12e] and oxyfagaronine (**26**),[4a] this constitutes a formal synthesis of both alkaloids.[5a,30,31]



Scheme 4. Carbonylation of **21**.

Conclusions

We have examined the $Pd(OAc)_2$-induced carbonylation of alkoxy-substituted 1-(*N*-methylamino)-2-phenyltetralins and 1-(*N*-methylamino)-2-phenylnaphthalenes to provide the benzo[*c*]phenanthridine ring system. The carbonylation of tetralin **1** with methylenedioxy groups by using a catalytic system of $Pd(OAc)_2$/$Cu(OAc)_2$/pyridine in refluxing toluene predominantly gave tetrahydrooxysanguinarine (**3**, 73% yield). In contrast, the carbonylation of **1**·HCl with a stoichiometric amount of $Pd(OAc)_2$ afforded tetrahydrooxyavicine (**4**, 30% yield). On the basis of these results, similar catalytic carbonylations of the tetramethoxy analogue of the latter reactant afforded *O*-methyloxyfagaronine in solvent systems containing DMSO. A 2-benzyloxy analogue was converted to a synthetic precursor of the antileukemic alkaloid fagaronine (**25**).

Experimental Section

General Remarks: The melting points were measured with a Yanagimoto micro melting point apparatus. The IR spectra were recorded with a JASCO IR-810 spectrometer. The ^{1}H NMR (270 or 400 MHz) and ^{13}C NMR (67.8 or 100.4 MHz) spectra were recorded with a JEOL JNM-JX270 or ECX-400P FT NMR spectrometer, and the samples were prepared with $CDCl_3$ (99.8 atom-% D; containing 0.03% v/v, tetramethylsilane; Aldrich Co.), unless otherwise noted. The chemical shifts were reported in ppm, relative to tetramethylsilane. The LRMS (EI) and HRMS (EI) spectra were performed with a JEOL JMS-HX110, JEOL JMS-FABmate, or JEOL JMS-700TZ mass spectrometer. The mass spectrometric data were obtained by electron ionization at 70 eV. TLC was carried out with Merck silica gel 60 PF_{254}. Elemental analyses were performed with a Yanako MT-6 CHN CORDER and a Dionex DX-500 at the Analytical Laboratory of Faculty of Pharmaceutical Science, Hokkaido University.

***cis*-1-[(*N*-*tert*-Butoxycarbonyl)-*N*-methylamino]-6,7-(methylenedioxy)-2-[3,4-(methylenedioxy)phenyl]-1,2,3,4-tetrahydronaphthalene (1a):** A mixture of **1**[5e,13,14] (143 mg, 0.4 mmol), 4-DMAP [4-(*N*,*N*-dimethylamino)pyridine, 49 mg, 0.4 mmol], Et_3N (81 mg, 0.44 mmol), and $(Boc)_2O$ (96 mg, 0.44 mmol) in CH_2Cl_2 (4 mL) was stirred at room temp. for 11 h, and HCl (0.5 N solution, 10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with HCl (2 N solution, 15 mL) and water (5 mL), dried with Na_2SO_4, and concentrated. The oily residue (129 mg) was subjected to preparative silica gel TLC (1% MeOH/CH_2Cl_2). A band with R_f = 0.7 gave **1a** as colorless crystals (126 mg, 74%), m.p. 154–156 °C (AcOEt/Et_2O). ^{1}H NMR (270 MHz, rotational isomers, 4:3): δ = 1.24, 1.26 (4:3, each s, 9 H, *t*Bu), 1.90, 2.11 (each m, each 1 H, 3-H), 2.94, 2.56 (3:4, each s, 1 H, NMe), 2.70–3.00 (m, 2 H, 4-H), 3.00–3.20 (m, 1 H, 2-H), 5.34, 5.58 (4:3, each d, *J* = 4.2 and 5.9 Hz, 1 H, 1-H), 5.87–5.96 (m, 4 H, OCH_2O), 6.52–6.80 (m, 5 H, Ar) ppm. ^{13}C NMR (67.8 MHz): δ = 24.2, 24.3 (4:3, CH_2), 28.0, 28.1 (4:3, *t*Bu-CH_3), 30.0 (CH_2), 31.9, 32.1 (4:3, CH), 45.3, 45.7 (3:4, CH_3), 54.6, 56.1 (4:3, NCH), 78.9, 79.2 (3:4, CO), 100.6, 100.7 (3:4, OCH_2O), 100.8, 100.9 (3:4, OCH_2O), 107.0, 107.7 (3:4, CH), 107.9, 108.0 (4:3, CH), 108.3, 108.7 (3:4, CH), 108.8, 109.0 (4:3, CH), 120.7, 121.1 (4:3, CH), 127.9, 128.1 (3:4, C), 130.7, 131.0 (4:3, C), 136.5, 136.7 (3:4,

C), 145.8, 146.0 (3:4, C), 146.3 (C), 147.0, 147.1 (3:4, C), 147.1, 147.3 (3:4, C), 155.4, 155.8 (4:3, C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1683 cm^{-1}. MS (EI): *m*/*z* (%) = 425 (1.6) $[M]^+$, 294 (100), 176 (14.6), 162 (10.2), 135 (29.1), 57 (21.1). $C_{24}H_{27}NO_6$ (425.47): calcd. C 67.75, H 6.40, N 3.29; found C 67.65, H 6.48, N 3.28.

***cis*-1-[(*N*-Acetyl)-*N*-methylamino]-6,7-(methylenedioxy)-2-[3,4-(methylenedioxy)phenyl]-1,2,3,4-tetrahydronaphthalene (1b):** A similar treatment of **1**·HCl (32.5 mg, 0.1 mmol) with AcCl (9.5 mg, 0.12 mmol) and Et_3N (12.1 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) afforded **1b** as colorless crystals (22.9 mg, 62%), m.p. 147–149 °C (MeOH/AcOEt/hexane). ^1H NMR (270 MHz, rotational isomers, 5:7): δ = 1.68, 1.80 (5:7, each s, 3 H, OAc), 1.78–2.28 (m, 2 H, 3-H), 2.63, 2.67 (7:5, each s, 3 H, NMe), 2.72–3.05 (m, 2 H, 4-H), 3.05–3.25 (m, 1 H, 2-H), 4.95, 6.14 (5:7, each d, J = 5.1 Hz and 6.4 Hz, 1 H, 1-H), 5.92, 5.93 (5.7, each s, 2 H, OCH_2O), 5.95, 5.96 (5:7, each s, 2 H, OCH_2O), 6.47–6.82 (m, 5 H, Ar) ppm. ^{13}C NMR (67.8 MHz): δ = 21.3, 21.9 (5:7, CH_3), 24.40, 24.43 (7:5, CH_2), 29.7, 29.8 (5:7, CH_2), 32.0, 33.7 (7:5, CH_3), 44.4, 46.6 (7:5, NCH_3), 52.5, 59.2 (5:7, CH), 59.2 (NCH), 100.7, 100.8 (7:5, OCH_2O), 101.0, 101.1 (7:5, OCH_2O), 107.7, 108.0, 108.1, 108.2, 108.3, 108.6 (4 CH), 120.7, 121.2 (7:5, CH), 126.9, 127.7 (5:7, C), 130.9, 131.1 (5:7, C), 135.8, 136.0 (5:7, C), 145.8, 146.5 (7:5, C), 146.4, 146.6 (7:5, C), 147.0, 147.1 (5:7, C), 147.5, 147.8 (5:7, C), 170.9, 171.3 (7:5, C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1625 cm^{-1}. MS (EI): *m*/*z* (%) = 367 (5.5) $[M]^+$, 294 (100), 202 (16.9), 176 (17.5), 162 (11.8), 135 (43.7), 57 (21.1). $C_{21}H_{21}NO_5$ (367.40): calcd. C 68.65, H 5.76, N 3.81; found C 68.44, H 5.95, N 3.76.

1-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-6,7-(methylenedioxy)-2-[(3,4-methylenedioxy)phenyl]naphthalene (2a): A mixture of carbamate **1a** (85 mg, 0.2 mmol) and DDQ (192 mg, 0.8 mmol) in dry benzene (17 mL) was heated to reflux, stirred for 3 h, and then cooled to room temp. After NaOH (2 N solution, 30 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The extracts were washed with water (3 × 20 mL), dried with Na_2SO_4, and concentrated. The oily residue (86 mg) was subjected to preparative silica gel TLC (0.8% MeOH/CH_2Cl_2). A band with R_f = 0.8 gave **2a** as colorless crystals (77 mg, 91%), m.p. 164–165 °C (benzene/hexane). ^1H NMR (270 MHz, rotational isomers, 2:1): δ = 1.27, 1.53 (2:1, each s, 9 H, *t*Bu), 2.83, 2.94 (1:2, each s, 3 H, NMe), 6.00 (s, 2 H, OCH_2O), 6.03, 6.08 (1:2, each d, J = 1.3 Hz, 2/3 H, OCH_2O), 6.06, 6.09 (1:2, each d, each J = 6.6 Hz, 2 H, OCH_2O), 6.82–7.00 (m, 3 H, Ar), 7.08, 7.10 (2:1, each s, 1 H, 5-H), 7.14, 7.15 (1:2, each s, 1 H, 8-H), 7.26, 7.29 (2:1, each d, each J = 8.5 Hz, 1 H, 4-H), 7.61, 7.62 (2:1, each d, each J = 8.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (67.8 MHz): δ = 28.1, 28.4 (2:1, *t*Bu-CH_3), 36.4, 36.8 (2:1, NMe), 79.8, 80.0 (1:2, C), 99.6, 99.6 (2:1, CH), 100.9, 101.0 (2:1, OCH_2O), 101.1, 101.2 (1:2, OCH_2O), 104.0, 104.2 (1:2, CH), 108.0, 108.1 (1:2, CH), 109.1, 109.3 (2:1, CH), 122.2, 122.2 (2:1, CH), 126.3, 126.6 (2:1, CH), 126.6, 126.8 (1:2, CH), 127.9, 128.0 (2:1, C), 130.7, 131.0 (2:1, C), 133.8, 133.8 (2:1, C), 135.2, 135.9 (2:1, C), 136.1, 136.3 (2:1, C), 146.7, 146.7 (1:2, C), 147.4, 147.4 (2:1, C), 147.6, 147.7 (2:1, C), 148.7, 148.9 (2:1, C), 155.4, 155.5 (2:1, CO) ppm. IR (Nujol): $\tilde{\nu}$ = 1684 cm^{-1}. MS (EI): *m*/*z* (%) = 421 (53.1) $[M]^+$, 365 (100), 321 (92.6), 290 (39.0). $C_{24}H_{23}NO_6$ (421.44): calcd. C 68.40, H 5.50, N 3.32; found C 68.35, H 5.39, N 3.32.

***cis*-1-(*N*-Methylamino)-6,7-(methylenedioxy)-2-(3,4-methylenedioxy)phenylnaphthalene (2):** A mixture of carbamate **2a** (169 mg, 0.4 mmol) and TFA (trifluoroacetic acid, 5 mL) in CH_2Cl_2 (28 mL) was stirred at room temp. for 30 min. After NaOH (2 N solution, 20 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The extracts were washed with NaOH (0.5 N solution, 20 mL) and water (2 × 20 mL), dried with Na_2SO_4, and concentrated. The oily residue (122 mg) was subjected to preparative silica gel TLC (2.4% MeOH/CH_2Cl_2). A fraction with R_f = 0.7 was treated with Et_2O saturated with HCl to give the HCl salt of *N*-methylamine **2** as colorless crystals (128 mg, 90%), m.p. 153–155 °C (MeOH/CH_2Cl_2/Et_2O). Data for **2**·HCl: ^1H NMR (270 MHz): δ = 3.05 (s, 3 H, NMe), 6.08 (s, 2 H, OCH_2O), 6.10 (s, 2 H, OCH_2O), 6.83 (d, J = 7.9 Hz, 6′-H), 6.85 (s, 1 H, 2′-H), 6.96 (d, J = 7.9 Hz, 1 H, 5′-H), 7.19 (d, J = 7.9 Hz, 1 H, 3-H), 7.24 (s, 1 H, 5-H), 7.73 (d, J = 7.9 Hz, 1 H, 4-H), 8.04 (s, 1 H, 8-H), 10.77 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$/[D_6]DMSO): δ = 37.0 (CH_3), 98.5 (CH), 100.4 (OCH_2O), 100.8 (OCH_2O), 103.6 (CH), 107.8 (CH), 108.9 (CH), 122.0 (CH), 125.7 (CH), 127.1 (CH), 128.9 (C), 129.0 (C), 130.5 (2 C), 131.9 (C), 147.1 (C), 147.1 (2 C), 147.4 (C), 148.6 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 1571 cm^{-1}. MS (EI): *m*/*z* (%) = 321 (100) $[M - HCl]^+$, 276 (13.8), 248 (13.2), 103 (17.7). $C_{19}H_{16}ClNO_4$ (357.79): calcd. C 63.78, H 4.51, Cl 9.91, N 3.91; found C 63.93, H 4.57, Cl 10.08, N 3.88. Data for free amine **2**: ^1H NMR (270 MHz): δ = 2.82 (s, 3 H, NMe), 6.03, 6.06 (each s, each 2 H, OCH_2O), 6.85 (dd, J = 7.6, 1.2 Hz, 1 H, 6′-H), 6.89 (d, J = 1.2 Hz, 1 H, 2′-H), 6.91 (d, J = 7.6 Hz, 1 H, 5′-H), 7.11 (s, 1 H, 5-H), 7.13, 7.33 (each d, J = 8.6 Hz, each 1 H, 4- and 3-H), 7.50 (s, 1 H, 8-H) ppm. ^{13}C NMR (67.8 MHz): δ = 37.8 (CH_3), 100.9 (OCH_2O), 101.0 (OCH_2O), 101.1 (CH), 104.3 (CH), 108.5 (CH), 109.8 (CH), 121.3 (CH), 122.5 (CH), 124.6 (C), 126.8 (CH), 129.0 (C), 131.3 (C), 134.0 (C), 143.4 (C), 146.7 (C), 147.3 (C), 147.5 (C), 147.8 (C) ppm. MS (EI): *m*/*z* (%) = 321 (100) $[M]^+$, 290 (10.1).

***cis*-1-[(*N*-Acetyl)-*N*-methylamino]-6,7-(methylenedioxy)-2-[3,4-(methylenedioxy)phenyl]naphthalene (2b):** To a solution of **2** (32.5 mg, 0.1 mmol) and Et_3N (12.1 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) was added AcCl (9.5 mg, 0.12 mmol). The mixture was stirred at room temp. for 6.5 h and then poured into ice water containing HCl (2 N solution, 5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extracts were washed with water (3 × 15 mL), dried with Na_2SO_4, and concentrated. An oily residue (42 mg) was subjected to preparative TLC on silica gel with 3% MeOH/1% Et_3N/CH_2Cl_2. A band with R_f = 0.5 gave **2b** as a colorless oil (38 mg, 94%). ^1H NMR (270 MHz): δ = 1.72 (s, 3 H, NMe), 3.13 (s, 3 H, NAc), 6.02, 6.10 (each s, each 2 H, OCH_2O), 6.78 (each d, J = 7.6 Hz, 6′-H), 6.79 (s, 1 H, 2′-H), 6.87 (each d, J = 7.6 Hz, 5′-H), 7.04, 7.19 (each s, each 1 H, 5- and 6-H), 7.32, 7.69 (each d, J = 8.2 Hz, each 1 H, 4- and 3-H) ppm. ^{13}C NMR (67.8 MHz): δ = 21.8 (CH_3), 36.8 (NMe), 99.2 (OCH_2O), 101.2 (OCH_2O), 101.5 (CH), 104.3 (CH), 108.4 (CH), 108.9 (CH), 122.0 (CH), 127.1 (CH), 127.3 (CH), 127.8 (C), 131.1 (C), 133.0 (C), 135.8 (C), 136.7 (C), 147.1 (C), 147.7 (C), 148.1 (C), 149.6 (C), 171.4 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1626, 1516 cm^{-1}. MS (EI): *m*/*z* (%) = 399 (2.2) $[M]^+$, 326 (100), 311 (17.0), 218 (13.8), 192 (8.6), 178 (7.3), 163 (8.0), 151 (26.8). HRMS (EI): calcd. for $C_{23}H_{29}NO_5$ 399.2045; found 369.2044.

Carbonylation of 1 in a Catalytic System with $Pd(OAc)_2$ and $Cu(OAc)_2$: A General Procedure (Method A)

Preparation of *cis*-2,3,7,8-Bis(methylenedioxy)-5-methyl-4b,5,6,10b,11,12-hexahydro-benzo[*c*]phenanthridin-6-one (3): (Table 1, Entry 7). The HCl salt of naphthylamine **1** [**1**·HCl, 36.2 mg, 0.1 mmol, prepared by Ishii's method as colorless crystals [m.p. 208–209 °C (MeOH/CH_2Cl_2/Et_2O); ref.[5e] m.p. 119.5–121.5 °C for free amine], in $CHCl_3$ (20 mL) was washed with NaOH (2 N solution, 2 × 20 mL) and water (20 mL) and then dried with Na_2SO_4. The solvent was evaporated. A stirred suspension of the residue, $Pd(OAc)_2$ (1.2 mg, 5 mol-%), and $Cu(OAc)_2$ (9.1 mg,

50 mol-%) in toluene (2 mL) containing pyridine (0.395 mg, 5 mol-%) was heated at reflux under CO gas (1 atm, 1.5 L) containing air (6 mL, corresponding to 0.5 equiv. of O_2) delivered by a toy balloon for 12 h. The mixture was filtered through powdered $MgSO_4$, and the precipitates were washed with $CHCl_3$ (15 mL). The filtrate and washings were concentrated, and the residue (39.9 mg, **3/4**, 11:1) was purified by preparative TLC on silica gel developed (2×) with 2% MeOH/CH_2Cl_2. A band with R_f = 0.4 gave **3** as colorless crystals (25.5 mg, 73%), m.p. 235.6–236.9 °C (benzene/hexane). ^{1}H NMR (270 MHz): δ = 1.98 (m, 1 H, 11-H), 2.28 (m, 1 H, 11-H), 2.75–2.96 (m, 2 H, 12-H), 3.10 (s, 3 H, NMe), 3.24 (m, 1 H, 10b-H), 4.59 (d, J = 4.0 Hz, 1 H, 4b-H), 5.91 (s, 2 H, OCH_2O), 6.07, 6.09 (AB type, J = 1.3 Hz, each 1 H, OCH_2O), 6.55, 6.65 (each s, each 1 H, 1- and 4-H), 6.68, 6.83 (each d, J = 7.9 Hz, each 1 H, 10- and 9-H) ppm. ^{13}C NMR (100.4 MHz): δ = 24.3 (CH_2), 26.5 (CH_2), 33.4 (CH), 37.5 (NCH_3), 60.03 (CH), 100.9 (OCH_2O), 102.0 (OCH_2O), 108.6 (CH), 108.8 (CH), 110.7 (CH), 112.51 (C), 118.0 (CH), 127.14 (C), 130.0 (C), 133.8 (C), 145.8 (C), 147.4 (C), 147.6 (C), 147.7 (C), 162.5 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1648 cm^{-1}. MS (EI): *m*/*z* (%) = 351 (100) [M]$^+$, 320 (83.9), 149 (16.1). $C_{20}H_{17}NO_5$ (351.35): calcd. C 68.37, H 4.88, N 3.99; found C 68.10, H 4.91, N 4.01.

Carbonylation of 1 with a Stoichiometric Amount of $Pd(OAc)_2$: A General Procedure (Method B)

Preparation of *cis*-2,3,8,9-Bis(methylenedioxy)-5-methyl-4b,5,6,10b,11,12-hexahydro-benzo[*c*]phenanthridin-6-one (4): (Table 1, Entry 2). A stirred suspension of **1**·HCl (38.3 mg, 0.107 mmol) and $Pd(OAc)_2$ (24 mg, 100 mol-%) in toluene (2.2 mL) was heated at reflux under CO (1 atm) for 3 h. The mixture was filtered through $MgSO_4$, and the precipitates were washed with $CHCl_3$ (15 mL). The filtrate was concentrated, and the residue (32.1 mg, **3/4**, 1:3) was subjected to preparative TLC on silica gel developed (2×) with 2% MeOH/CH_2Cl_2. A band with R_f = 0.5 gave lactam **4** as colorless crystals (10.9 mg, 30%), m.p. 258–259 °C (benzene/hexane). ^{1}H NMR (400 MHz): δ = 2.00 (m, 1 H, 11-H), 2.21 (m, 1 H, 11-H), 2.83 (m, 2 H, 12-H), 3.08 (s, 3 H, NMe), 3.18 (m. 1 H, 10b-H), 4.60 (d, J = 3.8 Hz, 1 H, 4b-H), 5.91, 5.92 (AB type, J = 1.3 Hz, each 1 H, OCH_2O), 5.97, 6.00 (AB type, J = 1.3 Hz, each 1 H, OCH_2O), 6.56, 6.65, 6.68, 7.51 (each s, each 1 H, Ar) ppm. ^{13}C NMR (67.8 MHz): δ = 24.3 (CH_2), 26.9 (CH_2), 33.7 (CH), 37.6 (NCH_3), 59.6 (CH), 100.9 (OCH_2O), 101.4 (OCH_2O), 105.6 (CH), 108.5 (CH), 108.6 (CH), 109.0 (CH), 123.1 (C), 127.1 (C), 130.1 (C), 136.4 (C), 145.8 (C), 146.7 (C), 147.5 (C), 150.5 (C), 164.3 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1646 cm^{-1}. MS (EI): *m*/*z* (%) = 351 (90.9) [M]$^+$, 320 (100), 294 (33.8), 203 (50.0). $C_{20}H_{17}NO_5$ (351.35): calcd. C 68.37, H 4.88, N 3.99; found C 68.10, H 4.94, N 4.14.

Oxysanguinarine (5): A mixture of **3** (11.5 mg, 0.033 mmol) and DDQ (98% active, 23.5 mg, 0.1 mmol) in benzene (2 mL) was heated at reflux for 3.5 h. The resulting precipitate was removed by suction filtration, and the filtrate was concentrated. The residue was dissolved in $CHCl_3$ (30 mL), and the resulting solution was washed with NaOH (2 N solution, 2×10 mL) and brine (10 mL) and then dried with anhydrous Na_2SO_4. Evaporation of the solvent and crystallization from AcOEt afforded oxysanguinarine (**5**) as colorless crystals (9.9 mg, 87%), m.p. > 300 °C (ref.[18c] m.p. 300 °C; ref.[32] m.p. 346–348 °C; ref.[33] m.p. 347–349 °C; ref.[34] m.p. 356–358 °C; ref.[35] m.p. 360 °C; ref.[3o,4a] m.p. 360–362 °C; ref.[36] m.p. 366–368 °C). This was also obtained by preparative silica gel TLC (developed 2× with 2% MeOH/CH_2Cl_2, R_f = 0.4) of the crude products that formed from $Pd(OAc)_2$-catalyzed carbonylation of amine **2** (see Table 2).

Oxyavicine (6) − DDQ Oxidation of 4: Similar treatment of **4** (10.5 mg, 0.03 mmol) with DDQ (98% active, 21 mg, 0.09 mmol) in refluxing benzene (2 mL) for 3.5 h gave **6** as colorless crystals (7.4 mg, 71%), m.p. 275–276 °C (MeOH; ref.[19b] m.p. 257–258 °C; ref.[19a] m.p. 276–277 °C; ref.[19c] m.p. 278–283 °C; ref.[3o,4a] m.p. 279–282 °C; ref.[18c] m.p. 281.5–282 °C). This was also obtained by preparative silica gel TLC (developed 2× with 2% MeOH/CH_2Cl_2, R_f = 0.5) of the crude products that formed from the carbonylation of amine **2** (see Table 2).

Methyl 6,7-Dimethoxy-2-(3,4-dimethoxyphenyl)-1-tetralone-2-carboxylate (9): According to Pinhey's arylation,[22,23] a stirred suspension of methyl 6,7-dimethoxy-1-tetralone-2-carboxylate[37] [**7**, 497 mg, 2 mmol, m.p. 134–136 °C (MeOH, ref.[37] m.p. 140–141 °C)], 3,4-dimethoxyphenyllead triacetate[23] (**8**, 1.147 mg, 2.2 mmol), and pyridine (174 mg, 2.2 mmol) in CH_2Cl_2 (13 mL) was heated at reflux in an ultrasonic apparatus for 10 h. H_2SO_4 (2 N solution, 10 mL) was added, and the resulting precipitate was removed by suction filtration. The filtrate was extracted with CH_2Cl_2 (3×20 mL). The extracts were washed with water (3×30 mL), dried with Na_2SO_4, and concentrated. The oily residue (816 mg) was purified by crystallization from MeOH to give **9** as colorless crystals (610 mg, 76%), m.p. 158–160 °C. ^{1}H NMR (270 MHz): δ = 2.63–3.01 (m, 4 H, 3- and 4-H), 3.76, 3.83, 3.85, 3.91, 3.93 (each s, each 3 H, OMe), 6.58 (s, 1 H, 5-H), 6.74–6.83 (m, 3 H, 2′-, 5′-, and 6′-H), 7.60 (s, 1 H, 8-H) ppm. ^{13}C NMR (67.8 MHz): δ = 25.6 (CH_2), 32.8 (CH_2), 52.7 (OMe), 55.7 (OMe), 55.8 (OMe), 55.9 (OMe), 56.0 (OMe), 62.4 (OMe) 109.1 (CH), 109.9 (CH), 110.7 (CH), 111.3 (CH), 120.0 (CH), 124.9 (C), 128.5 (C), 137.9 (C), 148.1 (C), 148.4 (C), 148.6 (C), 153.8 (C), 172.3 (C=O), 193.3 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1734, 1686, 1599, 1561, 1508 cm^{-1}. MS (EI): *m*/*z* (%) = 400 (97.8) [M]$^+$, 341 (40.8), 340 (100), 313 (22.5), 178 (49.9), 150 (52.3). $C_{22}H_{24}O_7$ (400.42): calcd. C 70.16, H 6.48; found C 69.95, H 6.51.

6,7-Dimethoxy-2-(3,4-dimethoxyphenyl)-1-tetralone (10): A solution of methyl ester **9** (400 mg) in a mixture of HCl (2 N solution, 10 mL) and AcOH (28 mL) was heated at reflux for 8 h. The product was extracted with CH_2Cl_2 (3×20 mL), and the combined extracts were washed with water (3×30 mL), dried with Na_2SO_4, and concentrated. The oily residue (350 mg) was crystallized from MeOH to give **10** as colorless crystals (226 mg, 66%), m.p. 148–150 °C (ref.[38] m.p. 144–146 °C; ref.[39] m.p. 147–149 °C). ^{1}H NMR (400 MHz): δ = 2.39 (m, 2 H, 3-H), 2.99 (m, 2 H, 4-H), 3.70 (dd, J = 7.9, 7.6 Hz, 1 H, 2-H), 3.86, 3.87, 3.93, 3.96 (each s, each 3 H, OMe), 6.69 (s, 1 H, 5-H), 6.72 (d, J = 1.9 Hz, 1 H, 1′-H), 6.73 (dd, J = 8.5, 1.9 Hz, 1 H, 6′-H), 6.84 (d, J = 8.5 Hz, 1 H, 5′-H), 7.58 (s, 1 H, 8-H) ppm. ^{13}C NMR (67.8 MHz): δ = 28.3 (CH_2), 31.6 (CH_2), 53.1 (CH), 55.7 (OMe), 55.8 (OMe), 55.9 (OMe), 60.0 (OMe), 108.8 (CH), 110.0 (CH), 111.1 (CH), 111.7 (CH), 120.2 (CH), 125.9 (C), 132.5 (C), 138.8 (C), 147.8 (C), 147.9 (C), 148.7 (C), 153.4 (C), 197.1 (C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1669, 1599, 1511 cm^{-1}. MS (EI): *m*/*z* (%) = 342 (8.3) [M]$^+$, 204 (29.3), 191 (93.6), 178 (73.7), 151 (63.0), 150 (100.0).

6,7-Dimethoxy-2-(3,4-dimethoxyphenyl)-1-(*N*-methylamino)-1,2,3,4-tetrahydronaphthalene Hydrochloride (11·HCl): According to Ishii's method,[5e] tetralone **10** (514 mg, 1.5 mmol) in $CHCl_3$ (39 mL) was treated with $MeNH_2$ in $CHCl_3$ (7 mL), prepared from 40% $MeNH_2$/water solution (4.8 mL, 90 mmol) and NaOH (5.45 g, 90 mmol). The mixture was then added dropwise to $TiCl_4$ (0.173 mL, 1.05 mmol) in $CHCl_3$ (5.6 mL), and the resulting mixture was stirred at –5 to 0 °C for 30 min, at room temp. for 30 min, and at reflux for 30 min. Then, the precipitate was removed by suction filtration. The filtrate was concentrated, and the residue

was dissolved in MeOH (75 mL). The solution was treated with $NaBH_4$ (153 mg, 2.7 equiv.) in three portions at room temp. for 1 h. After the evaporation of the MeOH, HCl (6 N solution, 10 mL) was added to the residue. The mixture was stirred for 30 min and then basified with NaOH (6 N solution, 20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined extracts were washed with water (3 × 40 mL), dried with Na_2SO_4, and concentrated. The residue (516 mg) was treated with Et_2O containing HCl, and the resulting solid was recrystallized from MeOH to give **11**·HCl as colorless crystals (513 mg, 91%), m.p. 179–183 °C. ^{1}H NMR (400 MHz): δ = 1.91 (br. s, 3 H, NMe), 2.18 (m, 1 H, 3-H), 2.70–2.90 (m, 2 H, 4-H), 3.03 (m, 1 H, 3-H), 3.32 (d, J = 11.8 Hz, 1 H, 2 H), 3.84, 3.89, 3.94, 3.95 (each s, each 3 H, OMe), 4.25 (s, 1 H, 1-H), 6.57 (s, 1 H, 2′-H), 6.95, 6.88 (AB type, J = 7.8 Hz, each 1 H, 5′- and 6′-H), 6.98, 7.03 (each s, each 1 H, 5- and 6-H), 8.76, 8.98 (each br. s, each 1 H, NH_2) ppm. ^{13}C NMR (67.8 MHz): δ = 22.5 (CH_2), 28.5 (CH_2), 33.2 (CH), 42.1 (NMe), 55.7 (OMe), 55.8 (OMe), 56.1 (OMe), 56.2 (OMe), 63.3 (NCH), 111.1 (CH), 111.1 (CH), 111.6 (CH), 113.5 (CH), 120.0 (C), 129.7 (C), 132.0 (C), 147.2 (C), 148.5 (C), 149.4 (C), 149.7 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 3498, 3434, 1608, 1586, 1522 cm^{-1}. MS (EI): m/z (%) = 357 (1.7) [M – HCl]$^+$, 311 (42.6), 193 (30.5), 178 (20.9), 151 (23.8), 327 (22.0), 126 (100). $C_{21}H_{28}ClNO_4$ (393.90): calcd. C 64.03, H 7.16, Cl 9.00, N 3.56; found C 64.90, H 7.26, Cl 8.74, N 3.49. Data for free amine **11**: ^{1}H NMR (270 MHz): δ = 1.98 (m, 1 H, 3-H), 2.23 (s, 3 H, NMe), 2.32–2.54 (m, 1 H, 3-H), 2.73–3.2 (m, 2 H, 4-H), 3.14–3.2 (m, 1 H, 2-H), 3.63 (d, J = 4.0 Hz, 1 H, 1-H), 3.87, 3.88 (each s, each 3 H, OMe), 3.89 (s, 6 H, OMe), 6.66, 6.79 (each s, each 1 H, 5- and 8-H), 6.82–6.87 (m, 3 H, 2′-, 5′- and 6′-H) ppm.

Carbonylation of 11 (Method B)

Preparation of *cis*-2,3,8,9-Tetramethoxy-5-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridin-6-one (13): (Table 3, Entry 3). A solution of **11**·HCl (19.7 mg, 0.05 mmol) in $CHCl_3$ (20 mL) was washed with NaOH (2 N solution, 20 mL) and water (20 mL) and then dried with Na_2SO_4. The solvent was evaporated. A stirred suspension of the residue, $Pd(OAc)_2$ (11.3 mg, 100 mol-%), and $Cu(OAc)_2$ (9.1 mg, 100 mol-%) in toluene (1 mL) was heated at reflux under CO (1 atm) for 6.5 h. The mixture was filtered through $MgSO_4$, and the precipitate was washed with $CHCl_3$. The filtrate and washings were combined and concentrated, and the residue (21.4 mg) was purified by preparative TLC on silica gel developed (2×) with 2% MeOH/CH_2Cl_2. A band with R_f = 0.5 gave **13** as colorless crystals (16.4 mg, 86%), m.p. 186–188 °C (EtOH). ^{1}H NMR (270 MHz): δ = 1.93–2.04 (m, 1 H, 11-H), 2.20–2.34 (m, 1 H, 11-H), 2.78–2.96 (m, 2 H, 12-H), 3.04 (s, 3 H, NMe), 3.10–3.20 (m, 1 H, 10b-H), 3.86 (s, 6 H, OMe), 3.92 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.70 (d, J = 4.0 Hz, 1 H, 4b-H), 6.61 (s, 1 H, 1-H), 6.68 (s, 1 H, 4-H), 6.71 (s, 1 H, 10-H), 7.59 (s, 1 H, 7-H) ppm. ^{13}C NMR (67.8 MHz): δ = 24.5 (CH_2), 26.9 (CH_2), 33.2 (CH), 37.7 (NCH_3), 55.7 (OMe), 56.0 (3 OMe), 59.2 (NCH), 108.0 (CH), 110.7 (CH), 111.3 (CH), 112.7 (CH), 121.4 (C), 125.7 (C), 129.0 (C), 134.8 (C), 147.0 (C), 148.9 (C), 151.9 (C), 164.7 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1635, 1603 cm^{-1}. MS (EI): m/z (%) = 383 (57.6) [M]$^+$, 353 (23.7), 352 (100), 351 (25.0), 337 (16.7). $C_{22}H_{25}NO_5$ (383.44): calcd. C 68.91, H 6.57, N 3.65; found C 68.98, H 6.59, N 3.66.

Carbonylation of 11 (Method A)

Preparation of *cis*-2,3,7,8-Tetramethoxy-5-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]-phenanthridin-6-one (12): (Table 3, Entry 5). A solution of **11**·HCl (19.7 mg, 0.05 mmol) in $CHCl_3$ (20 mL) was washed with NaOH (2 N solution, 20 mL) and water (20 mL) and then dried with Na_2SO_4. The solvent was evaporated. A stirred suspension of the residue, $Pd(OAc)_2$ (0.6 mg, 5 mol-%), and $Cu(OAc)_2$ (4.6 mg, 50 mol-%) in toluene (1 mL) containing pyridine (0.198 mg, 5 mol-%) was heated at reflux under CO gas (1 atm, 1.5 L) containing air (3 mL) for 24 h. The mixture was filtered through $MgSO_4$, and the precipitate was washed with $CHCl_3$. The filtrate was washed with water (4 × 20 mL) and concentrated to give an oil (19.2 mg, **11/12/13**, 3:5:9) that was subjected to preparative TLC on silica gel developed (2×) with 2% MeOH/CH_2Cl_2. A band with R_f = 0.4 gave benzolactam **12** as colorless crystals (2.3 mg, 12%), m.p. 185–190 °C (EtOH). ^{1}H NMR (270 MHz): δ = 2.01 (s, 1 H, 11-H), 2.28 (s, 1 H, 11-H), 2.76–2.87 (m, 2 H, 12-H), 3.10 (s, 3 H, NMe), 3.21 (t, J = 4.3 Hz, 1 H, 10b-H), 3.84 (s, 6 H, OMe), 3.85 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.63 (d, J = 3.6 Hz, 1 H, 4b-H), 6.55 (s, 1 H, 1-H), 6.66 (s, 1 H, 4-H), 6.97 (s, 2 H, 9- and 10-H) ppm. ^{13}C NMR (100.4 MHz): δ = 24.1 (CH_2), 26.2 (CH_2), 33.6 (CH), 37.9 (NCH_3), 55.8 (OMe), 55.0 (OMe), 56.0 (OMe), 56.1 (OMe), 59.2 (NCH), 61.5 (OMe), 111.4 (CH), 111.8 (CH), 115.0 (CH), 120.9 (CH), 123.4 (C), 126.2 (C), 128.6 (C), 134.3 (C), 147.1 (s), 148.8 (C), 150.0 (C), 152.6 (C), 163.0 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1646 cm^{-1}. MS (EI): m/z (%) = 383 (100) [M]$^+$, 352 (88). $C_{22}H_{25}NO_5$ (383.44): calcd. C 68.91, H 6.57, N 3.65; found C 68.76, H 6.51, N 3.57. A band with R_f = 0.5 gave benzolactam **13** (7.7 mg, 40%).

2,3,8,9-Tetramethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridin-6-one (14): A solution of DDQ (95% active, 59.3 mg, 0.248 mmol) in dry benzene (1.4 mL) was added to a solution of lactam **13** (30.7 mg, 0.08 mmol) in dry benzene (0.25 mL). The mixture was heated at reflux for 2 h. The resulting precipitate was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (30 mL), and the resulting solution was washed with NaOH (2 N solution, 2 × 10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated. The crude crystalline product (29.8 mg, 98%) was recrystallized from MeOH to give **14** as colorless crystals (24.2 mg, 80%), m.p. 253–254 °C (ref.[3f] m.p. 220–250 °C; ref.[26] m.p. 245–247 °C).

4-(3-Acetoxy-4-methoxyphenyl)-4-oxobutyric Acid (15): To a stirred suspension of powdered succinic anhydride (9.009 g, 90 mmol) in dry CH_2Cl_2 (150 mL) was added powdered $AlCl_3$ (24.001 g, 180 mmol) over a period of 10 min. The mixture was stirred at room temp. for 12 h, and then 2-methoxyphenyl acetate (9.966 g, 60 mmol) was added. The mixture was vigorously stirred at 0–5 °C for 5 h, and then ice (50 g) and HCl (2 N solution, 50 mL) were added. The mixture was extracted with CH_2Cl_2 (60, 30, and 30 mL). The combined extracts were washed with water, dried with Na_2SO_4, and concentrated. The residue (19.307 g) was crystallized from CH_2Cl_2 to give keto acid **15** as colorless crystals (10.824 g, 68%), m.p. 132–134 °C. ^{1}H NMR (270 MHz): δ = 2.33 (s, 3 H, OAc), 2.80 (t, J = 6.6 Hz, 2 H, 3-H), 3.27 (t, J = 6.6 Hz, 2 H, 2-H), 3.91 (s, 3 H, OMe), 7.01 (d, J = 8.7 Hz, 1 H, 5′-H), 7.69 (s, J = 2 Hz, 1 H, 2′-H), 7.90 (d, J = 8.7, 2.0 Hz, 1 H, 6′-H) ppm. IR (Nujol): $\tilde{\nu}$ = 1771, 1699, 1670, 1610 cm^{-1}. ^{13}C NMR (67.8 MHz): δ = 20.5 (CH_3), 28.0 (CH_2), 32.7 (CH_2), 56.0 (OMe), 111.6 (CH), 122.8 (CH), 129.5 (CH), 139.5 (C), 155.3 (C), 168.8 (C), 178.5 (C=O), 195.6 (C=O) ppm. MS (EI): m/z (%) = 266 (3.2) [M]$^+$, 249 (0.8), 224 (32.2), 151 (100). $C_{13}H_{14}O_6$ (266.25): calcd. C 58.65, H 5.30; found C 58.44, H 5.29.

4-(4-Methoxy-3-hydroxyphenyl)butyric Acid (16): A mixture of keto acid **15** (1.019 g, 4.50 mmol) and 5% Pd-C (135.1 mg) in AcOH (6 mL) in an autoclave in an oil bath at 120 °C was stirred under hydrogen (9 kg/cm^2) for 12 h. The precipitate was removed by suction filtration through a pad of Celite. The filtrate was concentrated to give the acetate of **16** [4-(3-acetoxy-4-methoxyphenyl)butyric

acid] as a colorless oil (962 mg). ^{1}H NMR (270 MHz): δ = 1.93 (quint. J = 7.6 Hz, 2 H, 3-H), 2.31 (s, 3 H, OAc), 2.36, 2.59 (each t, J = 7.6 Hz, each 2 H, 4- and 2-H), 3.87 (s, 3 H, OMe), 6.65 (d, J = 8.3, 2.0 Hz, 1 H, 6′-H), 6.76 (d, J = 2.0 Hz, 1 H, 2′-H), 6.77 (dd, J = 8.3 Hz, 1 H, 5′-H) ppm. The acetate of **16** was dissolved in NaOH (6 N solution, 10 mL), and the resulting solution was heated at reflux for 3 h. The mixture was then acidified with HCl (6 N solution, 11 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The CH_2Cl_2 layers were combined, washed with water (20 mL), dried with Na_2SO_4, and concentrated. Crystallization of the residue (770 mg) from benzene gave acid **16** as colorless crystals (654 mg, 82%), m.p. 114 °C. ^{1}H NMR (270 MHz): δ = 1.93 (m, 2 H, 3-H), 2.36 (t, J = 7.6 Hz, 1 H, 4-H), 2.59 (t, J = 7.6 Hz, 2 H, 2-H), 3.87 (s, 3 H, OMe), 6.65 (dd, J = 8.3, 2.0 Hz, 1 H, 6′-H), 6.76 (d, J = 2.0 Hz, 1 H, 2′-H), 6.77 (d, J = 8.3 Hz, 2 H, 5′-H) ppm. ^{13}C NMR (67.8 MHz): δ = 26.1 (CH_2), 33.1 (CH_2), 34.2 (CH_2), 55.9 (OMe), 110.6 (CH), 114.6 (CH), 119.8 (CH), 134.4 (C), 144.8 (C), 145.4 (C), 179.9 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 3434, 1697, 1588, 1516 cm^{-1}. MS (EI): m/z (%) = 210 (48.0) [M]$^+$, 150 (7.4), 137 (100). $C_{11}H_{14}O_4$ (210.23): calcd. C 62.85, H 6.71; found C 62.68, H 6.75.

4-(3-Benzyloxy-4-methoxyphenyl)butyric Acid (17): A mixture of acid **16** (105 mg, 0.5 mmol) and 1 drop of H_2SO_4 (conc.) in MeOH (3 mL) was heated at reflux for 3 h and then extracted with CH_2Cl_2 (3 × 20 mL). The extracts were combined, washed with water (3 × 20 mL), dried with Na_2SO_4, and concentrated to give the methyl ester of **16** as a colorless oil (125 mg). ^{1}H NMR (270 MHz): δ = 1.91 (quint. J = 7.6 Hz, 2 H, 3-H), 2.31, 2.56 (each t, J = 7.6 Hz, each 2 H, 4-H and 2-H), 3.66 (s, 3 H, COOMe), 3.86 (s, each 3 H), 5.56 (s, 1 H), 6.64 (dd, J = 8.3, 2.0 Hz, 1 H), 6.76 (br. s, 1 H), 6.77 (d, J = 8.3 Hz, 1 H) ppm. The methyl ester of **16** was dissolved in DMF (5 mL) containing K_2CO_3 (154 mg, 0.837 mmol) and benzyl bromide (96 mg, 0.837 mmol), and the mixture was heated at 60 °C for 10 h. The reaction mixture was cooled and diluted with water (20 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with water (20 mL), dried with Na_2SO_4, and concentrated. The crude benzyl ether (149 mg) was purified by preparative TLC (CH_2Cl_2), and a band with R_f = 0.4 gave the methyl ester of **17** as a colorless oil (113 mg, 76% in 2 steps). ^{1}H NMR (270 MHz): δ = 1.87 (quint, J = 7.6 Hz, 2 H, 3-H), 2.26 (t, J = 7.6 Hz, 2 H, 4-H), 2.54 (t, J = 7.6 Hz, 2 H, 2-H), 3.66 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 5.13 (s, 2 H, benzyl H), 6.72 (d, J = 6.0 Hz, 1 H, 5′-H), 6.72 (br. s, 1 H, 2′-H), 6.82 (dd, J = 6.0, 3.0 Hz, 1 H, 6′-H), 7.29–7.46 (m, 5 H, phenyl H) ppm. IR (neat): $\tilde{\nu}$ = 1735 cm^{-1}. The methyl ester of **17** was heated at reflux in a mixture of THF (1 mL) and NaOH (6 N solution, 3 mL) under nitrogen for 1.5 h. The mixture was acidified with HCl (2 N solution, 6 mL), and the resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with water (20 mL), dried with Na_2SO_4, and concentrated to give a solid, which was recrystallized from Et_2O/hexane to give acid **17** as colorless crystals (82 mg, 58% yield in 3 steps), m.p. 80–82 °C. ^{1}H NMR (270 MHz): δ = 1.89 (quint, J = 7.3 Hz, 2 H, 3-H), 2.29 (t, J = 7.3 Hz, 2 H, 4-H), 2.57 (t, J = 7.3 Hz, 2 H, 2-H), 3.87 (s, 3 H, OMe), 5.14 (s, 2 H, benzyl H), 6.73 (s, 1 H, 2′-H), 6.75 (d, J = 8.6 Hz, hiding 1 H, 5′-H), 6.82 (d, J = 8.6 Hz, 1 H, 6′-H), 7.28–7.46 (m, 5 H, phenyl H) ppm. ^{13}C NMR (67.8 MHz): δ = 26.2 (CH_2), 33.0 (CH_2), 34.3 (CH_2), 56.0 (OMe), 71.0 (CH_2), 111.9 (CH), 114.7 (CH), 121.0 (CH), 127.3 (2 CH), 127.7 (CH), 128.2 (CH), 128.4 (2 CH), 133.6 (C), 137.1 (C), 147.9 (C), 148.0 (C), 179.7 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1698, 1602, 1588, 1519 cm^{-1}. MS (EI): m/z (%) = 300 (5.6) [M]$^+$, 210 (18.6), 150 (25.4), 138 (6.6), 91 (100). $C_{18}H_{20}O_4$ (300.14): calcd. C 71.98, H 6.71; found C 72.21, H 6.81.

6-Benzyloxy-7-methoxy-1-tetralone (18): A mixture of butanoic acid **17** (3.11 g, 10.3 mmol) and $(CF_3CO)_2O$ (4.35 g, 20.7 mmol) in dry $ClCH_2CH_2Cl$ (20 mL) was stirred at room temp. for 6 h and then poured into ice water (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were washed with water (3 × 30 mL), dried with Na_2SO_4, and concentrated. The crystalline residue (3.477 g) was recrystallized from Et_2O/CH_2Cl_2/hexane to give α-tetralone **18** as colorless crystals (2.04 g, 70%), m.p. 134–136 °C. ^{1}H NMR (270 MHz): δ = 2.09 (quint, J = 6.3 Hz, 2 H, 3-H), 2.59 (t, J = 6.3 Hz, 2 H, 4-H), 2.83 (t, J = 6.3 Hz, 2 H, 2-H), 3.92 (s, 3 H, OMe), 5.20 (s, 2 H, benzylic H), 6.70 (s, 1 H, 5-H), 7.28–7.45 (m, 5 H, benzyl H), 7.54 (s, 1 H, 8-H) ppm. ^{13}C NMR (67.8 MHz): δ = 23.5 (CH_2), 29.3 (CH_2), 38.5 (CH_2), 56.0 (OMe), 70.6 (CH_2), 108.8 (CH), 112.0 (CH), 126.0 (C), 127.1 (2 CH), 128.0 (CH), 128.6 (2 CH), 128.2 (CH), 128.4 (2 CH), 133.6 (C), 139.0 (C), 148.3 (C), 152.6 (C), 197.2 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1666, 1560, 1541 cm^{-1}. MS (EI): m/z (%) = 282 (15.3) [M]$^+$, 91 (100). $C_{18}H_{18}O_3$ (282.33): calcd. C 76.57, H 6.43; found C 76.42, H 6.54.

2-(3,4-Dimethoxyphenyl)-6-benzyloxy-7-methoxy-1-tetralone (19): To a stirred suspension of $Pd_2(dba)_3$ (30.2 mg, 0.126 mmol), BINAP [2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, 78.5 mg, 0.126 mmol], and NaO*t*Bu (442 mg, 4.6 mmol) in dry THF (14 mL) under argon were added 3,4-dimethoxyiodobenzene[40] (1.85 mg, 7 mmol) and **18** (988 mg, 3.5 mmol) in dry THF (7 mL). The mixture was heated at reflux for 20 h. The insoluble materials were removed by suction filtration, and the THF was evaporated. The residue was dissolved in water (10 mL) and CH_2Cl_2 (10 mL). The organic layer was washed with water (10 mL), dried with Na_2SO_4, and concentrated. The residue (2.45 g) was subjected to preparative TLC (2% MeOH/CH_2Cl_2). A band with R_f = 0.5 afforded **19** as colorless crystals (369 mg, 25%), m.p. 149–151 °C (MeOH; ref.[12f] m.p. 140 °C).

Friedel–Crafts-Type Cyclization of 20: A mixture of **20** (655 g, 1.5 mmol, m.p. 118–119 °C, prepared by Bisagni's method[12f]) and $(CF_3CO)_2O$ (420 mg, 3.0 mmol) in dry $ClCH_2CH_2Cl$ (11 mL) was stirred at 0 °C for 20 min and then at room temp. for 1 h. The reaction mixture was poured into ice water (10 mL), and the resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with water (3 × 30 mL), dried with Na_2SO_4, and concentrated. The crystalline residue (685 mg) was recrystallized from MeOH to give **19** as colorless crystals (576 mg, 92%), m.p. 144–145 °C.

***cis*-6-Benzyloxy-2-(3,4-dimethoxyphenyl)-7-methoxy-1-(methylamino)-1,2,3,4-tetrahydronaphthalene (21):** A dry $CHCl_3$ solution (5 mL) containing $MeNH_2$ (see below) was added to a solution of α-tetralone **19** (92.1 mg, 0.22 mmol) in dry $CHCl_3$ (2 mL). [The $MeNH_2$ was prepared from a solution of 40% $MeNH_2$/water (1.4 mL, 1.26 g, 39.6 mmol) and NaOH (1.6 g, 39.6 mmol) and was dried by passing it through a NaOH drying tube.] The resulting solution was added to a stirred solution of $TiCl_4$ (0.027 mL, 46.7 mg, 0.242 mmol) in dry $CHCl_3$ (3 mL) at –5 to 0 °C for 20 min. After the mixture was stirred at 0 °C for 30 min, at room temp. for 30 min, and at reflux for 30 min, the precipitate was removed by suction filtration. The filtrate was concentrated, and the residue was dissolved in MeOH (15 mL). The solution was treated with $NaBH_4$ (22.6 mg, 0.594 mmol, 2.7 equiv.) in three portions at room temp. for 1 h. After evaporation of the MeOH, the residue was treated with HCl (6 N solution, 10 mL), and the mixture was stirred for 30 min and then basified with NaOH (6 N solution). The resulting solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with water (3 × 15 mL), dried with

Na_2SO_4, and concentrated. The residue (127.5 mg) was treated with Et_2O containing HCl, and the resulting solid was recrystallized from CH_2Cl_2/petroleum ether to give the *N*-methylamine hydrochloride of **21** (**21**·HCl) as colorless crystals (103.1 mg, 99%), m.p. 111–112 °C (CH_2Cl_2/petroleum ether). ^{1}H NMR (400 MHz): δ = 1.97 (s, 3 H, NMe), 2.15 (m, 1 H, 4-H), 2.71–2.80 (m, 2 H, 3- and 4-H), 2.97 (m, 1 H, 3-H), 3.31 (d, J = 8.0 Hz, 1 H, 2-H), 3.87, 3.93, 3.96 (each s, each 3 H, OMe), 4.27 (s, 1 H, 1-H), 5.12 (s, 2 H, benzylic H), 6.62 (s, 1 H, 2′-H), 6.88, 6.95 (AB type, J = 8.1 Hz, each 1 H, 5′- and 6′-H), 6.96 (s, 1 H, 5-H), 7.10 (s, 1 H, 8-H), 7.29–7.42 (m, 5 H) ppm. ^{13}C NMR (67.8 MHz): δ = 22.4 (CH_2), 28.3 (CH_2), 33.3 (CH_2), 42.0 (NMe), 55.8 (OMe), 56.0 (OMe), 56.2 (OMe), 63.3 (NCH), 70.6 (OCH_2), 111.1 (CH), 111.5 (CH), 113.4 (CH), 114.0 (CH), 120.0 (CH), 122.1 (C), 127.1 (2 CH), (CH), 127.8 (CH), 128.4 (2 CH), 129.6 (C), 131.9 (C), 136.6 (C), 147.7 (C), 148.4 (C), 148.9 (C), 149.3 (C) ppm. IR (Nujol): $\tilde{\nu}$ = 1589, 1517 cm^{-1}. MS (EI): *m*/*z* (%) = 433 (3.4) [M – HCl]$^+$ 402 (29.3), 311 (100), 178 (14.4), 151 (22.3), 145 (21.5), 91 (27.8). $C_{27}H_{31}NO_4$·HCl (470.00): calcd. C 69.00, H 6.86, Cl 7.54, N 2.98; found C 68.80, H 6.73, Cl 7.31, N 2.92. Data for free amine **21**: Colorless crystals, m.p. 136–139 °C (MeOH). ^{1}H NMR (270 MHz): δ = 1.91–2.00 (m, 1 H, 4-H), 2.23 (s, 3 H, NMe), 2.34–2.47 (m, 1 H, 4-H), 2.77–2.95 (m, 2 H, 3-H), 3.15 (dt, J = 11.9, 3.3 Hz, 1 H, 2-H), 3.61 (d, J = 3.6 Hz, 1 H, 1-H), 3.85, 3.88 and 3.89 (each s, each 3 H, OMe), 5.14 (s, 2 H, benzylic H), 6.70 (s, 1 H, 5-H), 6.77–6.84 (m, 4 H, 8-, 2′-, 5′-, and 6′-H), 7.27–7.47 (m, 5 H, benzyl H) ppm. IR (Nujol): $\tilde{\nu}$ = 1605, 1587, 1515 cm^{-1}. MS (EI): *m*/*z* (%) = 433 (3.3) [M]$^+$, 403 (11.3), 311 (100), 91 (61.5). $C_{27}H_{31}NO_4$ (433.54): calcd. C 74.80, H 7.21, N 3.23; found C 74.61, H 7.25, N 3.24.

Carbonylation of 21 (Method B)

Preparation of *cis*-2-Benzyloxy-3,8,9-trimethoxy-5-methyl-4a,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridin-6-one (23)

Entry 3 in Table 4: **21**·HCl (13.2 mg, 0.028 mmol) in $CHCl_3$ (20 mL) was washed with NaOH (2 N solution, 2 × 20 mL) and water (20 mL) and then dried with Na_2SO_4. The solvent was evaporated. A stirred suspension of the residue, $Pd(OAc)_2$ (6.4 mg, 100 mol-%), and $Cu(OAc)_2$ (5.2 mg, 100 mol-%.) in toluene (1 mL) was heated at reflux under CO (1 atm) for 3 h. The mixture was filtered through $MgSO_4$, and the precipitate was washed with $CHCl_3$ (15 mL). The filtrate and washings were combined and concentrated to give a residue (9.1 mg). An analytical sample was purified by preparative TLC on silica gel developed with 3% MeOH/CH_2Cl_2. Upon crystallization from MeOH, a band with R_f = 0.5 gave lactam **23** as colorless crystals (6.8 mg, 53%), m.p. 167–168 °C. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.94 (m, 1 H, 11-H), 2.23 (m, 1 H, 11-H), 2.74–2.90 (m, 2 H, 12-H), 3.04 (s, 3 H, NMe), 3.15 (dt, J = 10.0, 3.9, 3.9 Hz, 1 H, 10b-H), 3.86, 3.92, 3.93 (each s, each 3 H), 4.69 (d, J = 3.9 Hz, 1 H, 4b-H), 5.12 (s, 2 H, benzylic H), 6.65, 6.69, 6.71 (each s, each 1 H, 1-, 4-, and 10-H), 7.29–7.45 (m, 5 H, benzyl H), 7.59 (s, 1 H, 7-H) ppm. ^{13}C NMR (67.8 MHz): δ = 24.5 (CH_2), 26.9 (CH_2), 33.2 (CH), 37.7 (NCH_3), 56.0 (OMe), 56.2 (3 OMe), 59.3 (NCH), 70.8 (OCH_2), 108.1 (CH), 110.7 (CH), 113.4 (CH), 113.9 (CH), 121.4 (C), 126.3 (C), 127.3 (2 CH), 127.8 (CH), 128.5 (2 CH), 129.0 (C), 134.9 (C), 136.8 (C), 147.6 (C), 147.9 (C), 158.2 (C), 151.9 (C), 164.7 (C=O) ppm. IR (Nujol): $\tilde{\nu}$ = 1647, 1600 1515, 1506 cm^{-1}. MS (EI): *m*/*z* (%) = 459 (43.3) [M]$^+$, 368 (72.6), 337 (44.6), 232 (13.2), 91 (100). $C_{28}H_{29}NO_5$ (459.53): calcd. C 73.18, H 6.36, N 3.05; found C 73.40, H 6.23, N 2.97.

Entry 1 in Table 4: A stirred mixture of **21** (43.3 mg, 0.1 mmol) and $Pd(OAc)_2$ (22.5 mg, 0.1 mmol) in toluene (2 mL) was heated at reflux in an atmosphere of CO for 3 h. To the cooled reaction mixture was added HCl (2 N solution, 10 mL). The mixture was stirred for 30 min, and the resultant precipitate was removed by suction filtration. The filtrate was diluted with water (50 mL), and the solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (50 mL), dried with anhydrous Na_2SO_4, and concentrated. The residue (34 mg) was subjected to preparative TLC on silica gel (4% MeOH/CH_2Cl_2). Upon crystallization from MeOH, a band with R_f = 0.8 gave lactam **23** (17.3 mg, 27%), m.p. 167–168 °C.

Entry 2 in Table 4: Similarly, a stirred mixture of **21**·HCl (23.5 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 100 mol-%) in toluene (1 mL) was heated at reflux in an atmosphere of CO for 3 h. Workup and crystallization from MeOH afforded **23** (16.3 mg, 71%), m.p. 167–168 °C (MeOH).

Carbonylation of 21 (Method A)

Preparation of *cis*-2-Benzyloxy-3,7,8-trimethoxy-4-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridin-6-one (22)

Entry 5 in Table 4: Freshly prepared amine **21** (21.7 mg, 0.05 mmol), $Pd(OAc)_2$ (0.6 mg, 5 mol-%), and $Cu(OAc)_2$ (4.6 mg, 50 mol-%) in DMSO (1 mL) was heated to 120 °C under CO (1 atm, 1.5 mL) containing air (3 mL) for 24 h. The mixture was filtered through powdered $MgSO_4$, and the filtrate was washed with water (4 × 20 mL) and concentrated to give a brown oil (23 mg, **22**/**23**, 3:10), which was subjected to preparative silica gel TLC developed (2×) with 2% MeOH/CH_2Cl_2. A band with R_f = 0.4 gave **22** as a colorless oil (2.8 mg, 12%). ^{1}H NMR (270 MHz): δ = 2.01 (m, 1 H, 11-H), 2.27 (m, 1 H, 11-H), 2.77 (q, J = 7.6 Hz, 2 H, 12-H), 3.11 (s, 3 H, NMe), 3.18 (m, 1 H, 10b-H), 3.84, 3.85, 3.96 (each s, each 3 H, OMe), 4.61 (d, J = 4.0 Hz, 1 H, 4b-H), 5.09 (s, 2 H, benzylic H), 6.59, 6.69 (each s, each 1 H, 1- and 4-H), 6.95 (s, 2 H, 9- and 10-H), 7.30–7.44 (m, 5 H, benzyl H) ppm. IR (Nujol): $\tilde{\nu}$ = 1648, 1514, 1252 cm^{-1}. MS (EI): *m*/*z* (%) = 459 (38.7) [M]$^+$, 368 (49.9), 337 (21.6) 320 (13.4), 91 (100). HRMS (EI): calcd. for $C_{28}H_{29}NO_5$ 459.2045; found 459.2055. A band with R_f = 0.6 gave **23** as colorless crystals (6.2 mg, 27%), m.p. 167–168 °C (MeOH).

Entry 6 in Table 4: A similar catalytic carbonylation in a 1:1 mixture of toluene and DMSO afforded a mixture of **21**, **22**, and **23** in 1:4:11 ratio. A band with R_f = 0.6 gave **23** as colorless crystals (10.4 mg, 45%), m.p. 167–168 °C (MeOH).

2-Benzyloxy-3,8,9-trimethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridin-6-one (24): A mixture of lactam **23** (49.2 mg, 0.107 mmol) and DDQ (98% active, 77.6 mg, 0.332 mmol) in dry benzene (11 mL) was heated at reflux for 2 h. The resulting precipitate was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (30 mL), and the resulting solution was washed with NaOH (2 N solution, 2 × 15 mL) and brine (10 mL) and then dried with anhydrous Na_2SO_4. The solvent was evaporated. Crystallization of the residue from MeOH afforded benzolactam **24** as colorless crystals (37.7 mg, 77%), m.p. 227–229 °C (ref.[4a] m.p. 219–221 °C; ref.[12e] m.p. 227–229 °C).

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra of new and related compounds.

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[20] In connection with these carbonylative cyclizations, it should be added that the Bischler–Napieralski cyclization is useful for the preparation of **6**. The treatment of **2a** with Tf_2O and 4-DMAP in CH_2Cl_2 at 0 °C to room temperature for 24 h, see: (M. G. Banwell, B. D. Bissett, S. Busato, C. J. Vowden, D. C. R. Hockless, J. W. Holman, R. W. Read, A. W. Wu, *J. Chem. Soc., Chem. Commun.* **1995**, 2551–2553), afforded **6** in 92% yield, and an alternative treatment of **2a** with P_2O_5 in refluxing $POCl_3$ for 2 h, see: (X. Wang, J. Tan, K. Grozinger, *Tetrahedron Lett.* **1998**, *39*, 6609–6612), gave **6** in 65% yield. The classical conditions using $POCl_3$ in refluxing toluene for 2 h, see (W. M. Whaley, T. R. Govindachari in *Organic Reactions* (Ed.: Roger Adams), John Wiley & Sons, Inc., London, **1951**, vol. 6, pp. 74–155), could not start the cyclization at all. Tetralin carbamate **1a** failed to give any lactams like **4** under those conditions, probably because the *N*-acylamino group at the benzyl position was lost under the acidic and thermal conditions.
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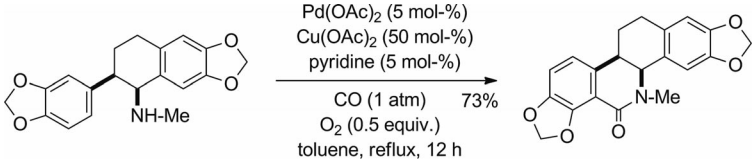

A study of the syntheses of benzo[*c*]phenanthridine alkaloids based on a $Pd(OAc)_2$-induced direct aromatic carbonylation was carried out, starting with preparing the substrates for the carbonylation, exploring site selectivities for the cyclopalladation, and investigating efficient additives and solvents. Oxysanguinarine, oxyavicine, *O*-methyloxyfagaronine, and *O*-benzyloxyfagaronine were obtained.

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Synthesis of Benzo[*c*]phenanthridine Alkaloids by $Pd(OAc)_2$-Induced Direct Aromatic Carbonylation

Keywords: Alkaloids / Synthetic methods / Nitrogen heterocycles / Carbonylation / Palladium

