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Synthesis of Phenanthro[9,10-*b*]indolizidin-9-ones, Phenanthro[9,10-*b*]quinolizidin-9-one, and Related Benzolactams by $Pd(OAc)_2$-Catalyzed Direct Aromatic Carbonylation

Satoshi Yamashita,[a] Nobuhito Kurono,[b] Hisanori Senboku,[c] Masao Tokuda,[a] and Kazuhiko Orito*[a]

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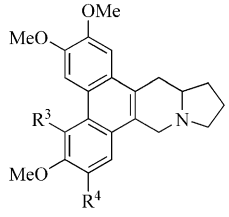
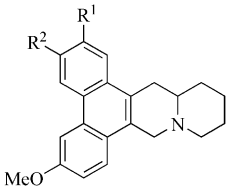
Phenanthro[9,10-*b*]indolizidin-9-ones, phenanthro[9,10-*b*]-quinolizidin-9-one, and related benzolactams were synthesized by benzolactam ring formation using $Pd(OAc)_2$-catalyzed direct aromatic carbonylation. This also constitutes a formal synthesis of the representative phenanthroindolizidine and -quinolizidine alkaloids (±)-tylophorine, (±)-antofine, and (±)-cryptopleurine.

Introduction

Since tylophorine (**1**) was first isolated in 1935,[1] over 60 phenanthroindolizidine and -quinolizidine alkaloids,[2] including their *seco* analogues, have been isolated from plants of the Asclepiadaceae[2b] and Moraceae[2c] families. Because of their interesting biological properties[2d–2h] – including vesicant, mitotic, antitumor, anticancer, and antileukemic, anti-*Candida albicans*, antiinflammatory, selective antifungal, antiamoebic, antibacterial, antiviral, cytotoxic, and antibiotic activities, as well as activities as inhibitors of protein synthesis (peptide bond formation), as insecticides, and as insect antifeedants – many efforts have been made to develop methods for synthesizing these alkaloids and related compounds.[3–8]





tylophorine, $R^3 = H$, $R^4 = OMe$ (**1**) cryptopleurine, $R^1 = R^2 = OMe$ (**3**)
tylocrebrine, $R^3 = OMe$, $R^4 = H$ cryptopleuridine, $R^1 + R^2 = OCH_2O$
antofine, $R^3 = R^4 = H$ (**2**)

[a] Laboratory of Organic Synthesis, Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
Fax: +81-11-761-5383
E-mail: orito@eng.hokudai.ac.jp
[b] Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
E-mail: chrono@eng.hokudai.ac.jp
[c] Division of Chemical Process Engineering, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
E-mail: senboku@eng.hokudai.ac.jp
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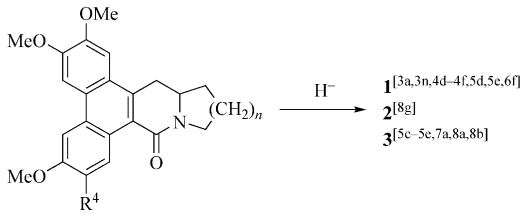
Results and Discussion

Here we report a route to the syntheses of tylophorine (**1**), antofine (**2**), and cryptopleurine (**3**) through the formation of benzolactam rings by $Pd(OAc)_2$-catalyzed direct aromatic carbonylation.[9,10] It has already been reported that the benzolactam target compounds **4a**, **4b**, and **5** in these syntheses are readily transformable into the representative alkaloids **1**, **2**, and **3**, respectively, by hydride reduction (Figure 1).[3a,3n,4d–4f,5c,5e,6f,7a,8a,8b,8g]



4a, $n = 1$, $R^4 = OMe$
4b, $n = 1$, $R^4 = H$
5, $n = 2$, $R^4 = H$

Figure 1. Hydride reduction of benzolactams **4a**, **4b** and **5**.

Several methods for the construction of the phenanthrene ring components in syntheses of the alkaloids[2d–2h] have been developed.[3–8] Direct oxidative cyclizations of stilbenes with VOF_3[3] or $Tl(OAc)_3$,[4] photocyclization of stilbenes in the presence of I_2,[5] or indirect cyclization

either with diazotized stilbenes through Pschorr reactions[6] or with halogenated stilbenes by radical cyclization[7] have been carried out either at the early or at the very last stages of the syntheses. It was reported that the phenanthrenes, **8a**, **8b**, and **10a** were obtained in 75–100% yields by treatment of **7a**, **7b**, and **9a** with the expensive reagent VOF_3 in CF_3COOH,[3a,3d,3e] but this was reported to be unsuccessful for the preparation of less electrophilic substrates such as the trimethoxy derivative **10b**.[3e] It was reported by Herbert et al. that photocyclization of **7a** gave methyl phenanthrene-9-carboxylate **8a** in 31% yield.[5a] We were interested in this method because of its potential economical advantages, and we tried to improve the yield in order also to use it for the preparation of analogous compounds.

The (*Z*)-cinnamic acids **6a** and **6b** (Figure 2) were prepared according to the reported methods,[4b,6b,11] by condensation of (3,4-dimethoxyphenyl)acetic acid with veratraldehyde or 4-methoxybenzaldehyde in the presence of Et_3N and Ac_2O, and their methyl esters **7a** and **7b** were quantitatively obtained by Fischer esterification. A photocyclization of methyl ester **7a** to phenanthrene **8a** based on Herbert's method[5a] was examined in cyclohexane or benzene in the presence of catalytic amounts of iodine, either with air being bubbled or with a limited amount of oxygen in a Pyrex flask open to air, but without agitation or bubbling. The latter method resulted in more efficient formation of phenanthrene **8a** (Figure 2), in 65% yield, together with the regioisomer **8c** (8%). However, this method did

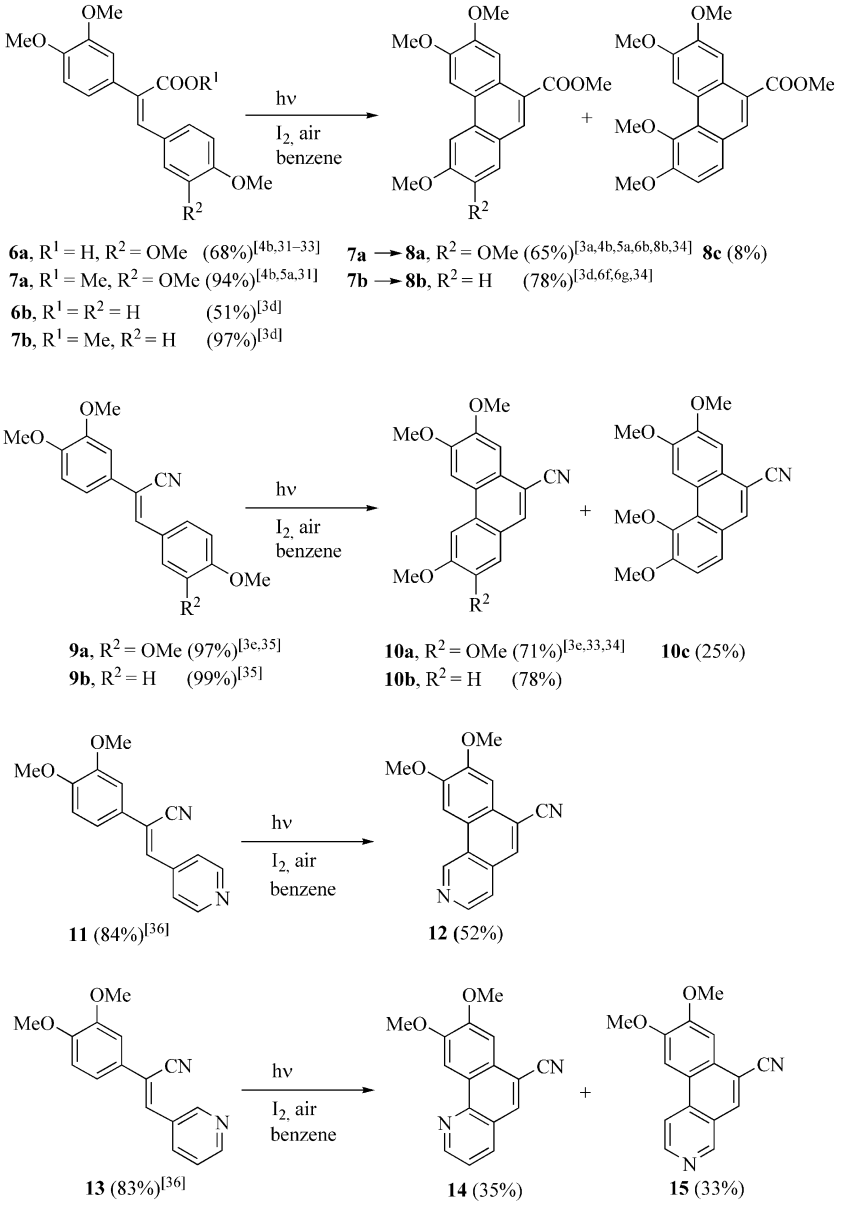


Figure 2. Photocyclization of α-phenylcinnamates and related nitriles.

not work for cyclization of the acids **6a** and **6b**. Attempts to prepare methyl ester **7a** directly by condensation of methyl (3,4-dimethoxyphenyl)acetate with 3,4-dimethoxybenzaldehyde in the presence of Et_3N/Ac_2O[5a] or NaOEt in EtOH[6b] failed. On the other hand, condensation of (3,4-dimethoxyphenyl)acetonitrile with the corresponding aldehydes in the presence of NaOEt in EtOH resulted in exclusive formation of the (*Z*)-cinnamonitriles **9a** and **9b**, photocyclization of which proceeded slowly to give either phenanthronitrile **10a** (71% yield) together with its regioisomer **10c** (25% yield) or **10b** (78% yield).

The pyridine analogues **11** and **13** were also obtained by the same method (NaOEt in EtOH) and were subjected to photocyclization to give azaphenanthrenes **12** in 52% yield and **14** and **15** in 35% and 33% yields, respectively. The regioselectivity of this cyclization seems to be due to steric factors rather than electronic effects.

$LiAlH_4$ reduction of the esters **8a** and **8b**, followed by treatment of the resultant hydroxy groups with PBr_3 at room temperature, afforded bromides **17a**, **17b**, and **17c** in excellent yields, as shown in Figure 3 (see also the Supporting Information). Alcohols **16a**, **16b**, and **16c** were also obtained in excellent yields by treatment of the phenanthronitriles **10a**, **10b**, and **10c** with DIBAL and then aqueous acid, followed by $NaBH_4$ reduction of the resultant aldehyde group.

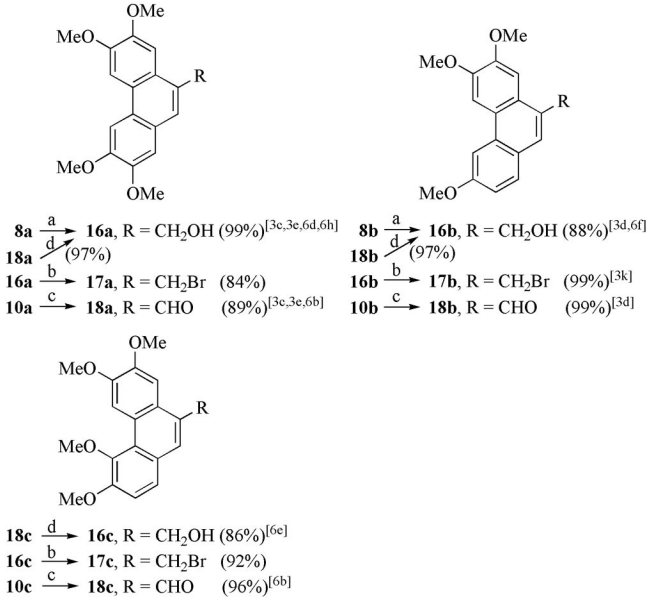


Figure 3. Transformation of phenanthrenes **8a**, **8b**, **10a**, **10b**, and **10c** to bromides **17a**, **17b**, and **17c**. Reaction conditions: (a) $LiAlH_4$ in THF at reflux, 2 h. (b) PBr_3 in $CHCl_3$. (c) (1) DIBAL in CH_2Cl_2; (2) aq. HCl. (d) $NaBH_4$ in $MeOH/CH_2Cl_2$ (1:10).

In order to introduce an α-pyrrolidinomethyl group into the phenanthrene at its 9-position, the reaction behavior of *N*-protected pyrrolidinyl carbanions was examined. As shown in Figure 4, coupling between *N*-Boc-pyrrolidine[12] lithium salt and benzyl bromide in THF gave the 2-benzylpyrrolidine **19** in 73% yield in a modification of the method reported by Beak.[13] However, a similar interaction with phenanthromethyl bromide **17a** gave only a complex mixture, whereas interaction with bromide **17b** gave only a small amount of (phenanthromethyl)pyrrolidine **21b** (6%) after treatment of the reaction mixture containing *N*-Boc product **20b** with TFA. Under the same conditions, the use of aldehydes **18a** or **18b** in place of bromides **17a** or **17b** resulted in complete recovery of **18a** or **18b**. In contrast, an alternative coupling with *N*-nitrosopyrrolidine lithium salt (2 equiv., prepared with LDA in THF, –78 °C) according to Fraser's report[14] based on Seebach's method[15] produced (*N*-nitrosopyrrolidinomethyl)phenanthrenes **21a**, **21b**, and **21c** in 81%, 93%, and 90% yields, respectively. Removal of the nitroso groups by subsequent treatment with HCl gas provided 2-(9-phenanthromethyl)pyrrolidine hydrochlorides **22a**·HCl, **22b**·HCl, and **22c**·HCl.

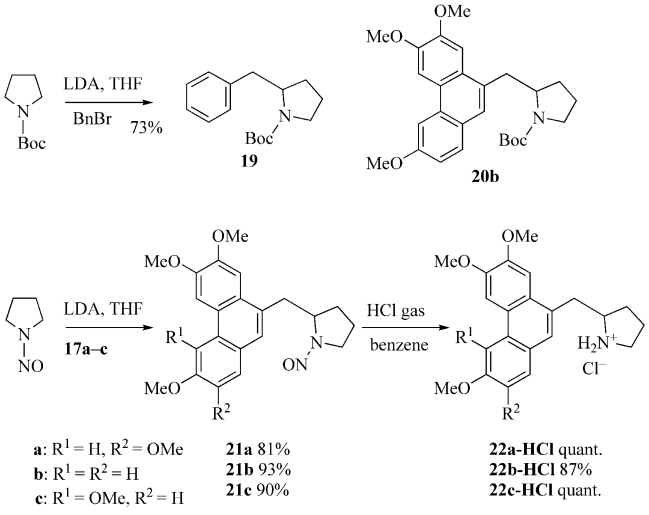


Figure 4. Preparation of 2-(phenanthromethyl)pyrrolidines **22a**, **22b**, and **22c**.

Similar reaction sequences with analogous – or differently *N*-protected – piperidines[16–19] in place of pyrrolidines did not work for the preparation of compounds such as the 2-(9-phenenthromethyl)piperidine **25**. In a modification of Eichen's method,[20] however, Pd^0-catalyzed cross-coupling between 2-bromopyridine (1.2 equiv.) and benzylzinc bromide (1 equiv., prepared from BnBr and Zn) in the presence of $Pd(PPh_3)_4$ afforded 2-benzylpyridine (**23**) in 90% yield (Figure 5). Bromide **17b** under the same conditions, however, failed to give the desired coupling product **26**. Stille coupling[21] with tributyl(2-pyridinyl)stannane[22] (1.1 equiv.) and bromide **17b** (1 equiv.) in the presence of $Pd(PPh_3)_4$ (1 mol-%) (at reflux in THF for 8 h) produced **26** in 58% yield, together with pyridinium salt **27**. The yield of **26** was higher than the yields of couplings performed with other catalytic systems such as $Pd_2dba_3/P(2\text{-furyl})_3$[23] $PdCl_2(PPh_3)_2$,[24] $PdCl_2(dppb)_2/CuO$,[25] and $Pd(OAc)_2/Cu(OAc)_2/K_2CO_3$.[26] In addition, an anionic reaction involving treatment of 2-bromopyridine with *t*BuLi at –78 °C[27] and subsequent trapping of the resultant lithium salt with bromide **17b** or aldehyde **18b** failed to produce the desired **26**. Catalytic hydrogenation of 2-benzylpyridine **23** [PtO_2 (8 mol-%), H_2 (1.5 kg cm^{-2}), concd. HCl/EtOH

(1:20), room temp., 2 h][28] produced the corresponding piperidine **24** quantitatively. Under the same conditions, hydrogenation of hydrochloride **26** never went to completion. After many trials, the use of free amine **26** under hydrogen (25 kg cm^{-2}) with PtO_2 (20 mol-%) in AcOH at 140 °C for 24 h finally led to the quantitative formation of **28**.

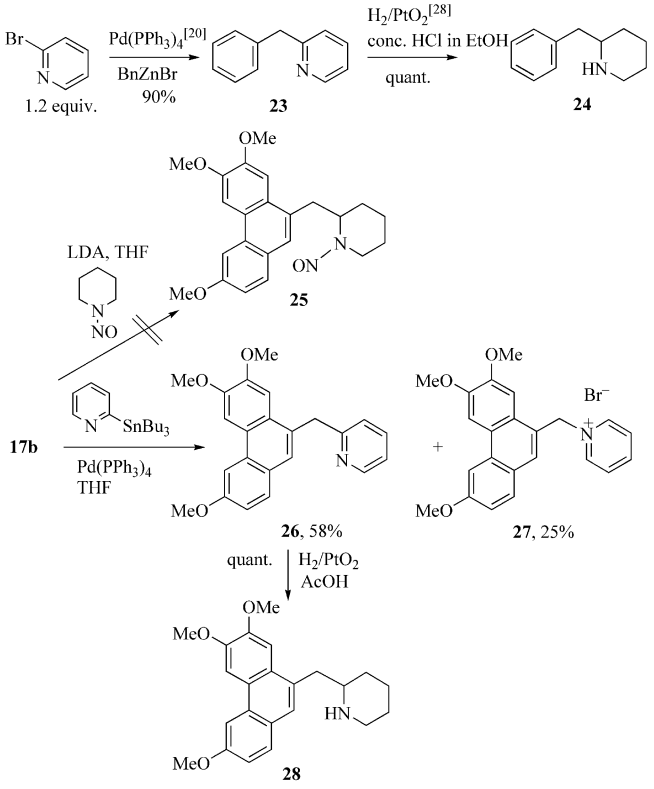


Figure 5. Preparation of 2-(phenanthromethyl)pyrrolidine **28**.

Our recently reported[9,29] one-step preparation of five- and six-membered benzolactams by a phosphane-free $Pd(OAc)_2$-catalyzed direct aromatic carbonylation procedure was examined with amine **22b** and its HCl salt in toluene or dioxane (Figure 6). As shown in Table 1, carbonylation of free amine **22b** with $Pd(OAc)_2$ (5 mol-%) and $Cu(OAc)_2$ (50 mol-%) in boiling toluene under CO produced not the benzolactam, but the *N*-acetyl derivative of the reactant (see the Supporting Information). Carbonylation of **22b**·HCl by electrophilic aromatic palladation[29] (5 mol-%) with $Cu(OAc)_2$ (50 mol-%) in boiling toluene under CO also produced no benzolactam but the *N*-acetyl derivative of the reactant (see the Supporting Information). Carbonylation of **22b**·HCl by electrophilic aromatic palladation[29] in the presence of a stoichiometric amount of $Pd(OAc)_2$, however, gave the desired benzolactam – (±)-9-oxoantofine (**4b**) – in 53% yield (Entry 3 in Table 1). Under CO gas (25 kg cm^{-2}), the yield was improved to 70% (Entry 5). A catalytic version of this carbonylation[9a] of **22b**·HCl with $Pd(OAc)_2$ (5 mol-%)/Cu(OAc) (50 mol-%) under air containing CO (corresponding to 0.5 mol-equiv. of O_2) at 25 kg cm^{-2} produced **4b** in 45% yield (Entry 6). Use of a higher or lower pressure of CO decreased the yield. Similar catalytic carbonylations of **22a** and **28** gave (±)-9-oxotylophorine (**4a**) in 26% yield and (±)-9-oxocryptopleurine (**5**) in 31% yield.[30] As described above, it has been reported that hydride reactions converted these compounds into the corresponding alkaloids (Figure 1). (±)-9-Oxotylocrebrine (**4c**) was obtained in 17% yield.

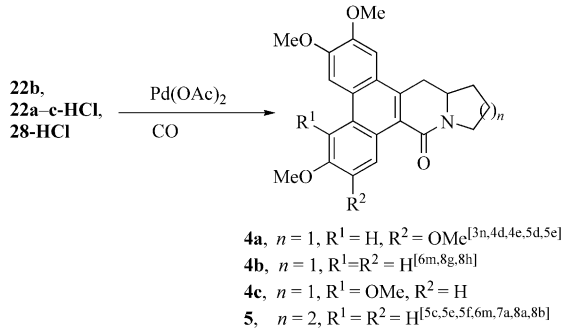


Figure 6. $Pd(OAc)_2$-mediated carbonylation of amines **22a**, **22b**, **22c** and **28**.

Table 1. $Pd(OAc)_2$-mediated carbonylation of amines **22a**, **22b**, **22c**, and **28**.

Entry	Substrate	Solvent	$Pd(OAc)_2$ [mol-%]	$Cu(OAc)_2$ [mol-%]	CO	Time	Yield
1	**22b**	toluene	100	0	1 atm	2 h	0%
2	**22b**	dioxane	5	50	1 atm	2 h	0%
3	**22b**·HCl	toluene	100	0	1 atm	2 h	53% of **4b**
4	**22b**·HCl	toluene	5	50	1 atm	2 h	0%
5	**22b**·HCl	toluene	100	0	25 atm	2 h	70% of **4b**
6	**22b**·HCl	toluene	5	50	25 atm	2 h	45% of **4b**
7	**22b**·HCl	dioxane	5	50	25 atm	24 h	7% of **4b**
8	**22a**·HCl	toluene	100	0	25 atm	24 h	52% of **4a**
9	**22a**·HCl	toluene	5	50	25 atm	24 h	26% of **4a**
10	**22c**·HCl	toluene	5	50	25 atm	24 h	17% of **4c**
11	**28**·HCl	toluene	5	50	25 atm	24 h	31% 5

Similarly, the *N*-propylbenzolactams **32** (26%) and **33** (43%) were obtained by carbonylation of the HCl salts of *N*-propylamines **29** and **31**. Amine **29** was prepared in 92% yield from aldehyde **18b** and propylamine, whereas amine **31** was obtained via nitrosoamine **30**, which was obtained in 90% yield from bromide **16c** and *N*-nitrosopropylamine (Figure 7).

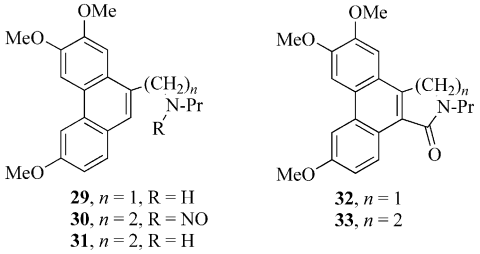


Figure 7. Preparation and carbonylation of amines **29** and **31**.

Conclusions

Phenanthro[9,10-*b*]indolizidin-9-ones, phenanthro[9,10-*b*]quinolizidin-9-one, and related benzolactams were ob-

tained from the corresponding amines by phosphane-free $Pd(OAc)_2$-catalyzed direct aromatic carbonylation. This constitutes a formal synthesis of the representative phenanthroindolizidine and -quinolizidine alkaloids (±)-tylophorine, (±)-antofine, and (±)-cryptopleurine.

Experimental Section

General Remarks: Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IR-810 infrared spectrophotometer. ^{1}H NMR spectra were obtained in $CDCl_3$ (99.8 atom-% D, containing 0.03% v/v TMS, Aldrich) with a JEOL EX-270 high-resolution spectrometer. Mass spectrometric data were recorded with a JEOL JMS-FABmate or JMS-700TZ spectrometer at 70 eV. Preparative TLC was run on Merck silica gel 60 PF-254 plates. Column chromatography was conducted with Cica reagent silica gel 60 (100–210 mm, spherical, Kanto Chemical Co., Inc.). See the Supporting Information for the preparation of compounds **6**–**18**, **23**, and **24**.

1-Nitroso-2-[(2,3,6,7-tetramethoxy-9-phenanthryl)methyl]pyrrolidine (21a). A General Procedure: LDA (1.50 M, THF solution, 0.67 mL, 1.00 mmol) was added under Ar at –78 °C to a stirred solution of *N*-nitrosopyrrolidine (0.091 mL, 1.00 mmol) in dry THF (4 mL). The mixture was stirred at –78 °C for 1 h. A solution of bromide **17a** (195 mg, 0.5 mmol) in dry THF (8 mL) was added. The mixture was stirred at –78 °C for 5 h and was then allowed to warm to room temperature and diluted with CH_2Cl_2 (20 mL). The mixture was washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography with AcOEt/CH_2Cl_2 (1:9) as eluent to give **21a** as colorless crystals (166 mg, 81%), m.p. 176–177 °C (benzene). ^{1}H NMR [rotational isomer A (67%)]: δ = 1.70–2.30 (m, 4 H, 3- and 4-H), 3.18 (dd, J = 13.9, 10.6 Hz, 1 H, benzylic H), 3.60–3.80 (m, 2 H, benzylic H and 5-H), 4.04, 4.05, 4.13, 4.14 (each s, each 3 H, OMe), 4.00–4.20 (m, 1 H, 5-H), 4.90–5.00 (m, 1 H, 2-H), 7.20, 7.46, 7.59, 7.80, 7.86 (each s, each 1 H, Ar-H) ppm; [rotational isomer B (33%)]: δ = 1.70–2.30 (m, 4 H, 3- and 4-H), 2.55 (dd, J = 13.2, 10.9 Hz, 1 H, benzylic H), 3.92 (dd, J = 13.2, 2.6 Hz, 1 H, benzylic H), 4.03, 4.12, 4.14, 4.34 (each s, each 3 H, OMe), 4.30–4.50 (m, 2 H, 5-H), 4.70–4.90 (m, 1 H, 2-H), 7.17, 7.36, 7.78, 7.83, 8.19 (each s, each 1 H, Ar-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1622, 1509 cm^{-1}. EI-MS: m/z (%) = 410 (20.1) $[M]^+$, 380 (23.6), 349 (9.9), 326 (18.7), 311 (100). $C_{23}H_{26}N_2O_5$ (410.46): calcd. C 67.30, H 6.38, N 6.82; found C 67.28, H 6.29, N 6.71.

1-Nitroso-2-[(2,3,6-trimethoxy-10-phenanthryl)methyl]pyrrolidine (21b): Colorless crystals (93%) from bromide **17b**, m.p. 165–167 °C (benzene). ^{1}H NMR [rotational isomer A (60%)]: δ = 1.70–2.30 (m, 4 H, 3- and 4-H), 3.13 (dd, J = 13.9, 10.6 Hz, 1 H, benzylic H), 3.60–3.80 (m, 2 H, 2- and 5-H), 4.02, 4.05, 4.12 (each s, each 3 H, OMe), 4.00–4.20 (m, 1 H, benzylic H), 4.88–5.00 (m, 1 H, 5-H), 7.20 (dd, J = 8.9, 2.3 Hz, 1 H, 7′-H), 7.46 (s, 1 H, 1′-H), 7.57 (s, 1 H, 9′-H), 7.74 (d, J = 8.9 Hz, 1 H, 8′-H), 7.84 (d, J = 2.3 Hz, 1 H, 5′-H), 7.93 (s, 1 H, 4′-H) ppm; [rotational isomer B (40%)]: δ = 1.70–2.30 (m, 4 H, 3- and 4-H), 2.51 (dd, J = 13.2, 10.9 Hz, 1 H, benzylic H), 3.88 (dd, J = 13.2, 2.6 Hz, 1 H, benzylic H), 4.01, 4.12, 4.35 (each s, each 3 H, OMe), 4.30–4.45 (br. s, 2 H, 5-H), 4.70–4.85 (br. s, 1 H, 5-H), 7.17 (dd, J = 8.9, 2.3 Hz, 1 H, 7′-H), 7.36 (s, 1 H, 1′-H), 7.71 (d, J = 8.9 Hz, 1 H, 8′-H), 7.83 (d, J = 2.3 Hz, 1 H, 5′-H), 7.90 (s, 1 H, 9′-H), 8.22 (s, 1 H, 4′-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1611, 1525 cm^{-1}. EI-MS: m/z (%) = 380 (33.0) $[M]^+$, 350 (29.9), 281 (100). $C_{22}H_{24}N_2O_4$ (380.44): calcd. C 69.46, H 6.36, N 7.36; found C 69.55, H 6.41, N 7.30.

1-Nitroso-2-[(2,3,5,6-tetramethoxy-10-phenanthryl)methy]pyrrolidine (21c): Colorless crystals (90%) from bromide **17c**, m.p. 124–137 °C (EtOH). ^{1}H NMR [rotational isomer A (60%)]: δ = 1.70–2.30 (m, 4 H, 3- and 4-H), 3.13 (dd, J = 13.9, 10.6 Hz, 1 H, benzylic H), 3.60–3.80 (m, 2 H, 5-H), 3.90–4.50 (m, 14 H, OMe, benzylic H and 5-H), 4.95 (m, 1 H, 5-H), 7.20–7.65 (m, 3 H, Ar-H), 9.36 (s, 1 H, 4′-H) ppm; [rotational isomer B (40%)]: δ = 1.70–2.30 (m, 4 H, 3- and 4-H), 2.50 (dd, J = 13.2, 10.9 Hz, 1 H, benzylic H), 3.60–3.80 (m, 1 H, 5-H), 3.90–4.50 (m, 14 H, OMe, benzylic H and 5-H), 4.74 (m, 1 H, 2-H), 7.20–7.65 (m, 3 H, Ar-H), 8.20 (s, 1 H, 9′-H), 9.32 (s, 1 H, 4′-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1602, 1528, 1509 cm^{-1}. EI-MS: m/z (%) = 410 (33.3) $[M]^+$, 380 (28.2), 311 (100). $C_{23}H_{26}N_2O_5$ (410.46): calcd. C 67.30, H 6.38, N 6.82; found C 67.17, H 6.52, N 6.88.

2-[(2,3,6,7-Tetramethoxy-9-phenanthryl)methyl]pyrrolidine Hydrochloride (22a·HCl). A General Procedure: HCl gas (generated from NaCl and H_2SO_4) was introduced into a solution of nitrosoamine **21a** (141.5 mg, 0.35 mmol) in benzene (25 mL) at reflux over 1 h, and the mixture was then heated under N_2 gas for 30 min. The solvent was evaporated. Crystallization of the residue from CH_2Cl_2 gave **22a**·HCl as colorless crystals (144 mg, 99%), m.p. 159–162 °C (free amine: ref.[6d] m.p. 152 °C).

2-[(2,3,6-Trimethoxy-10-phenanthryl)methyl]pyrrolidine Hydrochloride (22b·HCl): This compound was obtained as colorless crystals (87%) from nitrosoamine **21b**; m.p. 257–259 °C (dec. $CHCl_3$) [free amine: ref.[3q] m.p. 144–145 °C; ref.[6o] m.p. 145–146 °C; (*R*) form: ref.[3l] m.p. 144–148 °C; picrate: ref.[6f] m.p. 229 °C].

2-[(2,3,5,6-Tetramethoxy-10-phenanthryl)methyl]pyrrolidine Hydrochloride (22c·HCl): This compound was obtained as a colorless oil (99%) from nitrosoamine **21c** (picrate: ref.[6e] m.p. 247–249 °C). It was used for carbonylation without further purification.

2-[(2,3,6-Trimethoxy-10-phenanthryl)methyl]pyridine (26) and 1-[(2,3,6-Trimethoxy-10-phenanthryl)methyl]pyridinium Bromide (27): A solution of bromide **17b** (360 mg, 1 mmol) and $Pd(PPh_3)_4$ (12 mg, 1 mol-%) in dry THF was stirred under N_2 at room temp. for 5 min. Tributyl(2-pyridyl)stannane [0.343 mL, 1.1 mmol, prepared according to the reported method[22a] in 96% yield, b.p. 122 °C/0.4 Torr (ref.[22b] b.p. 140–145 °C/0.3 Torr)] was then added, and the mixture was heated at reflux for 8 h. The solvent was evaporated, and the residue was dissolved in hot AcOEt (20 mL). An insoluble product was collected by suction filtration and recrystallized from EtOH/CH_2Cl_2 to give **27** (110.8 mg, 25%), as colorless crystals, m.p. 216 °C (dec.). ^{1}H NMR: δ = 4.02, 4.03, 4.07 (each s, each 3 H, OMe), 6.93 (s, 2 H, CH_2), 7.18 (dd, J = 8.9, 2.3 Hz, 1 H, 7′-H), 7.34 (s, 1 H, 1′-H), 7.67–7.70 (m, 2 H, 5′- and 9′-H), 7.78 (d, J = 8.9 Hz, 1 H, 8′-H), 7.90 (t, J = 7.3 Hz, 2 H, 3- and 5-H), 8.00 (s, 1 H, 4′-H), 8.29 (t, J = 7.6 Hz, 1 H, 4-H), 9.58 (d, J = 5.6 Hz, 2 H, 2- and 6-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1612, 1524, 1511 cm^{-1}. EI-MS: m/z (%) = 360 (8.6) $[M – Br]^+$, 281 (100). $C_{23}H_{22}BrNO_3$ (440.33): calcd. C 62.74, H 5.04, Br 18.15, N 3.90; found C 62.55, H 5.16, Br 18.43, N 3.75. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel with AcOEt as eluent to give **26** (207.6 mg, 58%), m.p. 166–167 °C (EtOH) as colorless crystals. ^{1}H NMR: δ = 3.87, 4.04, 4.08 (each s, each 3 H, OMe), 4.61 (s, 2 H, CH_2), 7.00–7.20 (m, 2 H, 3- and 5-H), 7.21 (dd, J = 8.6, 2.3 Hz, 1 H, 7′-H), 7.42 (s, 1 H, 1′-H), 7.47 (dt, J = 7.9, 2.0 Hz, 1 H, 4-H), 7.60 (s, 1 H, 9′-H), 7.79 (d, J = 8.6 Hz, 1 H, 8′-H), 7.86 (d, J = 2.3 Hz, 1 H, 5′-H), 7.90 (s, 1 H, 4′-H), 8.50–8.70 (m, 1 H, 6-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1611, 1591, 1567, 1509 cm^{-1}. EI-MS: m/z (%) = 359 (100) $[M]^+$, 344

(41.7). $C_{23}H_{21}NO_3$ (359.42): calcd. C 76.86, H 5.89, N 3.90; found C 76.75, H 6.03, N 4.11.

2-[(2,3,6-Trimethoxy-10-phenanthryl)methyl]piperidine (28): A solution of **26** (71.9 mg, 0.2 mmol) and PtO_2 (9 mg, 20 mol-%) in AcOH (1 mL) was stirred at 140 °C under H_2 (25 kg cm^{-2}) for 24 h. The mixture was filtered through Celite to remove precipitates by washing with CH_2Cl_2 (15 mL). The combined solution and washings were washed with Na_2CO_3 solution (5%) and H_2O (2 × 10 mL) and dried (Na_2SO_4). The solvents were evaporated. Crystallization of the residue from EtOH gave **28** as colorless crystals (73.0 mg, 99%), m.p. 110–116 °C [ref.[6o] m.p. 122–123 °C; ref.[3q] m.p. 136–137 °C; (*R*) form: ref.[3l] m.p. 147–148 °C]. Its hydrochloride was prepared as follows. A solution of **28** (36.5 mg, 0.1 mmol) in $CHCl_3$ was treated with an HCl solution (2 N), dried, and concentrated. Crystallization of the residue from $CHCl_3$ gave **28**·HCl as colorless crystals (40.1 mg, 99%), m.p. 205–208 °C. ^{1}H NMR: δ = 1.65–2.15 (m, 6 H, 3-, 4- and 5-H), 2.80–3.00 (m, 1 H, 6-H), 3.25–3.45 (m, 2 H, benzyl H), 3.60 (m, 1 H, 6-H), 3.99 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 4.15–4.30 (m, 1 H, 2-H), 4.19 (s, 3 H, OMe), 7.14 (dd, J = 8.9, 2.3 Hz, 1 H, 7′-H), 7.40 (s, 1 H, 1′-H), 7.58 (s, 1 H, 9′-H), 7.66 (d, J = 8.9 Hz, 1 H, 8′-H), 7.74 (d, J = 2.3 Hz, 1 H, 5′-H), 7.82 (s, 1 H, 4′-H), 9.67, 10.40 (each br. s, each 1 H, NH and HCl) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3650, 1610, 1526, 1511 cm^{-1}. EI-MS: *m*/*z* (%) = 365 (0.5) [M – HCl]$^+$, 282 (28.3), 84 (100). $C_{23}H_{28}ClNO_3$ (401.93): calcd. C 68.73, H 7.02, Cl 8.82, N 3.48; found C 68.79, H 6.85, Cl 8.46, N 3.48.

***N*-[(2,3,6-Trimethoxy-10-phenanthryl)methyl]propylamine (29):** A mixture of aldehyde **18b** (444 mg, 1.5 mmol), propylamine (0.25 mL, 3 mmol), and Na_2SO_4 (50 mg) in CH_2Cl_2 (15 mL) was stirred at room temperature for 19 h. A solution of $NaBH_4$ (121.6 mg, 3 mmol) in MeOH (15 mL) was added. After 1 h, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with H_2O (2 × 100 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was crystallized from EtOH to give **29** as colorless crystals (467 mg, 92%), m.p. 142–143 °C. ^{1}H NMR: δ = 0.97 (t, J = 7.3 Hz, 1 H, Pr-CH_3), 1.60, 2.68 (each sext, J = 7.3 Hz, each 2 H, Pr-CH_2), 4.02, 4.06, 4.12 (each s, each 3 H, OMe), 4.20 (s, 2 H, benzylic H), 7.19 (dd, J = 8.6, 2.3 Hz, 1 H, 7′-H), 7.58 (s, 2 H, 1- and 9′-H), 7.77 (d, J = 8.6 Hz, 1 H, 8′-H), 7.85 (d, J = 2.3 Hz, 1 H, 5′-H), 7.92 (s, 1 H, 4′-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2926, 1656, 1611, 1561, 1523, 1509 cm^{-1}. EI-MS: *m*/*z* (%) = 339 (33.4) [M]$^+$, 282 (87.2), 281 (100). $C_{21}H_{25}NO_3$ (339.43): calcd. C 74.31, H 7.42, N 4.13; found C 74.04, H 7.48, N 3.96.

Hydrochloride 29·HCl: Colorless crystals (92%) from **29**, m.p. 110 °C. ^{1}H NMR: δ = 0.87 (t, J = 7.6 Hz, 3 H, Pr-CH_3), 1.86 (sext, J = 7.6 Hz, 2 H, Pr-H), 2.65–2.85 (m, 2 H, Pr-CH_2), 3.87, 3.94 (each s, each 3 H, OMe), 4.10–4.20 (m, 2 H, benzylic H), 4.15 (s, 3 H, OMe), 7.13 (dd, J = 8.9, 2.3 Hz, 1 H, 7′-H), 7.20 (s, 1 H, 1′-H), 7.51 (d, J = 2.3 Hz, 1 H, 5′-H), 7.65, 7.69 (each s, each 1 H, 9′- and 4′-H), 7.75 (d, J = 8.9 Hz, 1 H, 8′-H), 9.76 (br. s, 2 H, $^+NH_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 1527, 1510 cm^{-1}. EI-MS: *m*/*z* (%) = 339 [M – HCl]$^+$ (52.3), 282 (87.5), 281 (100). $C_{21}H_{26}ClNO_3$ (375.89): calcd. C 67.10, H 6.97, Cl 9.43, N 3.73; found C 66.99, H 7.16, Cl 9.18, N 3.77.

***N*-Nitroso-*N*-[2-(2,3,6-trimethoxy-10-phenanthryl)ethyl]propylamine (30):** BuLi (1.58 M, hexane solution, 1.26 mL, 2 mmol) was added under Ar at –78 °C to a stirred solution of *N*-nitrosopropylamine (0.21 mL, 2 mmol) in dry THF (4 mL). The mixture was stirred at –78 °C for 1 h. A solution of bromide **17b** (360 mg, 1 mmol) in dry THF (8 mL) was added dropwise, and the mixture was stirred at –78 °C for 5 h. The mixture was allowed to warm to room temperature, and CH_2Cl_2 (20 mL) was added. The CH_2Cl_2 layer was washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography with AcOEt/CH_2Cl_2 (1:9) as eluent to give **30** (315 mg, 82%), which was treated with EtOH to give colorless crystals, m.p. 108–111 °C. ^{1}H NMR [rotational isomer A (73%)]: δ = 0.96 (t, J = 7.6 Hz, 3 H, Pr-CH_3), 1.78 (sext, J = 7.6 Hz, 2 H, Pr-CH_2), 3.14 (t, J = 5.6 Hz, 2 H, N-CH_2), 3.81 (t, J = 5.6 Hz, 2 H, benzylic H), 3.95–4.10 (overlapping, 2 H, Pr-CH_2N), 3.99, 4.10, 4.27 (each s, each 3 H, OMe), 7.10–7.95 (m, 6 H, Ar-H) ppm; [rotational isomer B (27%)]: δ = 0.85 (t, J = 7.6 Hz, 3 H, Pr-CH_3), 1.52 (sext, J = 7.6 Hz, 2 H, Pr-CH_2), 3.44 (m, 2 H, benzylic H), 3.52 (m, 2 H, Pr-CH_2N), 3.99, 4.00, 4.10, (each s, each 3 H, OMe), 4.43 (t, J = 5.6 Hz, 2 H, N-CH_2), 7.10–7.95 (m, 6 H, Ar-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1612, 1527, 1510 cm^{-1}. EI-MS: *m*/*z* (%) = 382 (27.3) [M]$^+$, 394 (20.6), 281 (100). $C_{22}H_{26}N_2O_4$ (382.45): calcd. C 69.09, H 6.85, N 6.32; found C 69.20, H 6.63, N 6.54.

***N*-[2-(2,3,6-Trimethoxy-10-phenanthryl)ethyl]propylamine (31):** This compound was obtained as a colorless oil (95%) from **30**. ^{1}H NMR: δ = 0.90 (t, J = 7.2 Hz, 3 H, Pr-CH_3), 1.53 (q, J = 7.2 Hz, 2 H, Pr-CH_2), 2.65 (t, J = 7.2 Hz, 2 H, benzylic H), 3.09, 3.29 (each t, J = 7.2 Hz, each 2 H, CH_2NCH_2), 4.02, 4.06, 4.12 (each s, each 3 H, OMe), 7.19 (dd, J = 8.8, 2.3 Hz, 1 H, 7′-H), 7.45, 7.48 (each s, each 1 H, 1′- and 9′-H), 7.75 (d, J = 8.8 Hz, 1 H, 8′-H), 7.85 (d, J = 2.3 Hz, 1 H, 5′-H), 7.93 (s, 1 H, 4′-H) ppm.

Hydrochloride 31·HCl: ^{1}H NMR: δ = 1.03 (t, J = 7.6 Hz, 3 H, Pr-CH_3), 2.00 (m, 2 H, Pr-CH_2), 2.99, 3.30, 3.87 (each br. s, each 2 H, CH_2NCH_2), 3.99, 4.06, 4.15 (each s, each 3 H, OMe), 7.16 (dd, J = 8.9, 2.3 Hz, 1 H, 7′-H), 7.47, 7.53 (each s, each 1 H, 1′- and 9′-H), 7.68 (d, J = 8.9 Hz, 1 H, 8′-H), 7.75 (d, J = 2.3 Hz, 1 H, 5′-H), 7.82 (s, 1 H, 4′-H), 10.05 (br. s, 2 H, $^+NH_2$) ppm. This was used for the carbonylation without further purification.

(±)-9-Oxotylophorine (4a): A mixture of **22a** (21 mg, 0.05 mmol), $Pd(OAc)_2$ (0.6 mg, 5 mol-%), and $Cu(OAc)_2$ (4.6 mg, 50 mol-%) in toluene (2.5 mL) was stirred at 140 °C under air (3 mL) containing CO (25 kg cm^{-2}) for 25 h. The reaction mixture was filtered through a pad of powdered $MgSO_4$. The precipitates were washed with $CHCl_3$ (10 mL). The combined organic layers were washed with NaOH solution (0.5 N, 1 mL) and H_2O (10 mL), dried (Na_2SO_4), and concentrated. The residue (18 mg) was purified by preparative TLC on silica gel with AcOEt and crystallized from EtOH to give **4a** (5.3 mg, 26%) as colorless crystals, which melted at 200 °C, then solidified, and remelted at 283–289 °C [ref.[5d] m.p. 237–238 °C; ref.[5e] m.p. 280–281 °C; ref.[4d] m.p. 282–283 °C; ref.[3n] m.p. 284–286 °C; (*R*) form: ref.[4e] m.p. 286–289 °C].

(±)-9-Oxoantofine (4b): Colorless crystals (45%) from **22b**·HCl, m.p. 262–264 °C (benzene) (ref.[8g] m.p. 183–184 °C; ref.[6m] m.p. 254–256 °C; ref.[8h] m.p. 265–270 °C).

(±)-9-Oxotylocrebrine (4c): Colorless crystals (6%) from **22c**·HCl, m.p. 231–235 °C (EtOH) (ref.[5d,5e] dec. 207 °C). ^{1}H NMR: δ = 1.85–2.05 (m, 2 H, 12- and 13-H), 220–2.50, 2.40–2.55 (each m, each 1 H, 12- and 13-H), 2.92 (dd, J = 15.8, 13.3 Hz, 1 H, 15-H), 3.55 (dd, J = 15.8, 4.0 Hz, 1 H, 15-H), 3.70–4.20 (m, 3 H, 11- and 14-H), 3.88, 4.05, 4.07, 4.09 (each s, each 3 H, OMe), 7.33 (dd, J = 9.3 Hz, 1 H), 7.36 (s, 1 H, 1-H), 7.33 (d, J = 9.3 Hz, 1 H, 7-H), 7.36 (s, 1 H, 1-H), 9.10 (d, J = 9.3 Hz, 1 H, 8-H), 9.37 (s, 1 H, 4-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1635, 1603, 1524, 1512 cm^{-1}. EI-MS: *m*/*z* (%) = 407 (100) [M]$^+$, 392 (40.8), 339 (36.4).

(±)-9-Oxocryptopleurinone (5): Colorless crystals (30%) from **28**·HCl, m.p. 190–192 °C (benzene) [ref.[5c,8a,8b] m.p. 194–195 °C; ref.[5e] m.p. 194–196 °C; ref.[6m] m.p. 197–198.5 °C; (*R*) form: ref.[7a] m.p. 194–195.5 °C; (*R*) form: ref.[5f] m.p. 196–197 °C].

2,3,6-Trimethoxy-*N*-propylphenanthro[9,10-*c*]pyrrolidin-9-one (32): Colorless crystals (26%) from **29**, m.p. 205–206 °C (EtOH). ^{1}H NMR: δ = 1.02 (t, J = 7.3 Hz, 3 H, Pr-CH_3), 1.79 (sext, J = 7.3 Hz, 2 H, Pr-CH_2), 3.68 (t, J = 7.3 Hz, 2 H, Pr-CH_2), 4.02, 4.04, 4.12 (each s, each 3 H, OMe), 4.56 (s, 2 H, 11-H), 7.03 (s, 1 H, 1-H), 7.32 (dd, J = 8.9, 2.3 Hz, 1 H, 7-H), 7.83 (d, J = 2.3 Hz, 1 H, 5-H), 7.85 (s, 1 H, 4-H), 9.29 (d, J = 8.9 Hz, 1 H, 8-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1675, 1606, 1526 cm^{-1}. EI-MS: *m*/*z* (%) = 365 (86) [M]$^+$, 336 (100). $C_{22}H_{23}NO_4$ (365.42): calcd. C 72.31, H 6.34, N 3.83; found C 72.18, H 6.25, N 3.78.

2,3,6-Trimethoxy-*N*-propylphenanthro[9,10-*c*]piperidin-9-one (33): Colorless crystals (43%) from **31**·HCl, m.p. 67–71 °C (EtOH). ^{1}H NMR: δ = 1.03 (t, J = 7.3 Hz, 3 H, Pr-CH_3), 1.75 (sext, J = 7.3 Hz, 2 H, Pr-CH_2), 3.28 (t, J = 6.6 Hz, 2 H, 12-H), 3.60–3.75 (m, 4 H, Pr-CH_2 and 3-CH_2), 4.01, 4.05, 4.13 (each s, each 3 H, OMe), 7.25 (dd, J = 9.2, 2.6 Hz, 1 H, 7-H), 7.32 (s, 1 H, 1-H), 7.86 (d, J = 2.6 Hz, 1 H, 5-H), 7.96 (s, 1 H, 4-H), 9.26 (d, J = 9.2 Hz, 1 H, 8-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1633, 1619, 1510 cm^{-1}. EI-MS: *m*/*z* (%) = 379 (84) [M]$^+$, 350 (100). $C_{23}H_{25}NO_4$ (379.45): calcd. C 72.80, H 6.64, N 3.59; found C 72.72, H 6.77, N 3.60.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures for compounds **6a**–**18c**, **23**, and **24** and ^{1}H NMR spectra for compounds **4**–**18**, **21**–**24**, **26**–**33**, and carbamates of amines **22a**, **22b**, and **28**.

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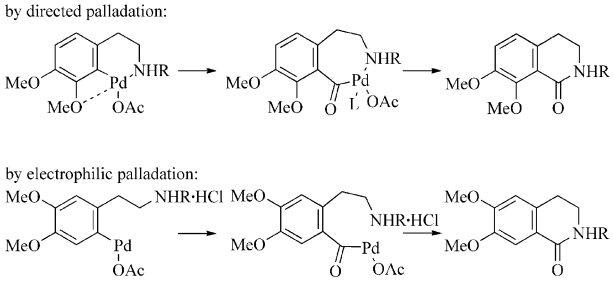
[29] Palladium-catalyzed direct aromatic carbonylation of (3,4-dimethoxyphenethyl)amine is depicted below:



[30] In a two-step approach to **4** based on Bischler–Napieralski cyclization, methyl carbamates of **22** were stable under classical conditions on treatment with excess $POCl_3$ in boiling toluene or xylene. Wang's modification (excess P_2O_5 in boiling $POCl_3$: X. Wang, J. Tan, K. Grozinger, *Tetrahedron Lett.* **1998**, *39*, 6609–6612) effectively produced **4a**, **4b** and **5** (see Supporting Information). It was reported by Herndon[8h] that Banwell's procedure (Tf_2O/DMAP: M. G. Banwell, B. D. Bissett, S. Busato, C. J. Cowden, D. C. R. Hockless, J. W. Holman, R. W. Read, A. W. Wu, *J. Chem. Soc., Chem. Commun.* **1995**, 2551–2553) also gave **4b** in good yield.

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