Synthesis of Benzo[*c*]Phenanthridine Alkaloids, Using a Novel Palladium–Phosphine Combination System – $Pd(OAc)_2$, DPPP, and Bu_3P

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Abstract: Total synthesis of several benzo[*c*]phenanthridine alkaloids was accomplished via an aryl-aryl coupling reaction using a novel Pd reagent prepared from $Pd(OAc)_2$, DPPP, and Bu_3P. This is a versatile method for the coupling reactions of not only aryl triflates and arenes but also aryl halides and arenes.

Key words: intramolecular aryl-aryl coupling, ring closure, palladium reagent, halo-amide, triflate-amide

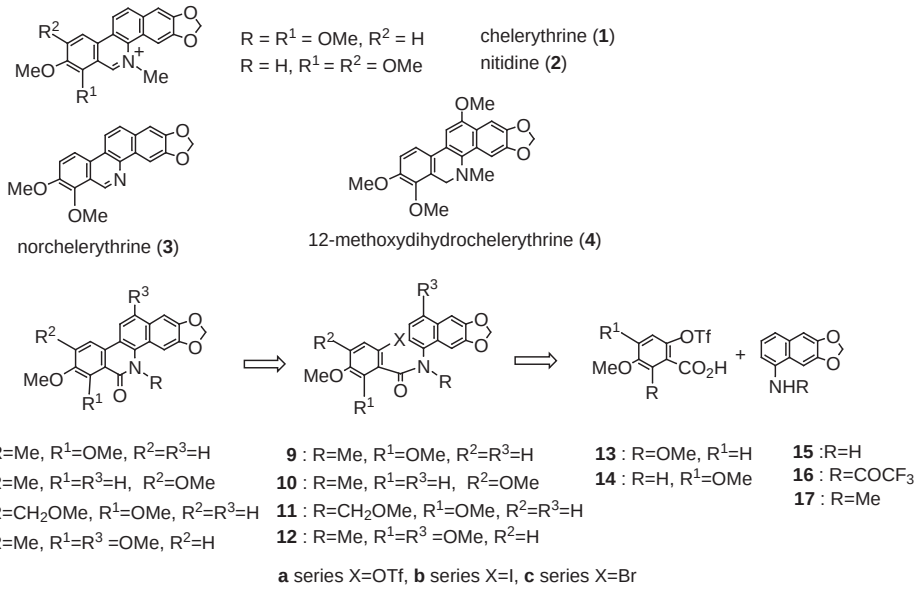
Introduction

Fully aromatized benzo[*c*]phenanthridine alkaloids have a broad range of potent pharmacological activities. They include anti-tumor and antiviral activities, inhibition of DNA topoisomerase I, and so on.[1] Therefore, attention is focused on developing convenient and effective methods for synthesizing these alkaloids and extensive efforts have been directed toward developing a convenient method for synthesizing benzo[*c*]phenanthridine alkaloids.[2] However, the reported methods have several disadvantages, such as numerous steps, low yields, and absence of generality.

Recently, we succeeded in the total synthesis of several benzo[*c*]phenanthridine alkaloids, chelerythrine (**1**),[3a] nitidine (**2**),[3b] norchelerythrine (**3**),[3c] and 12-methoxydihydrochelerythrine (**4**),[3a] using a biaryl coupling reaction of halo amides with palladium as a catalyst. Subsequently, we investigated a biaryl cyclization reaction of amides possessing a triflate group as a leaving group (instead of a halogen group) in order to examine the diversity of leaving groups for a biaryl coupling reaction. We found a novel palladium reagent system prepared from $Pd(OAc)_2$, a bidentate ligand {such as DPPP [1,3-bis-(diphenylphosphino)propane]} and Bu_3P achieves this reaction.[4] Moreover, this method was proven to be effective, not only for triflate leaving groups, but also for halogen groups.[4] Here, we describe the total synthesis of several benzo[*c*]phenanthridine alkaloids using this novel method.

Synthesis of Starting Materials 9–12

We designed a common plan for synthesizing benzo[*c*]phenanthridine alkaloids, as shown in Scheme 1.



Scheme 1 Retrosynthetic plan for the synthesis of benzo[*c*]phenanthridine alkaloids

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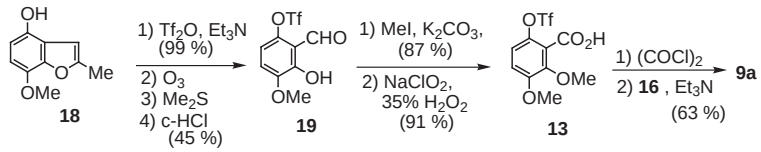
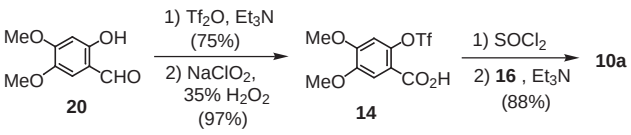


Scheme 2 Synthesis of precursor **9a** for the biaryl coupling reaction

Triflate-amides **9a** and **10a**, the starting materials for the coupling reaction, were synthesized as follows. First, the monomethylnaphthylamine **17** was synthesized from 6,7-methylenedioxy-1-naphthylamine (**15**)[3b] via trifluoroacetylation, N-methylation, and hydrolysis. Thus, **15** was treated with trifluoroacetic anhydride to afford *N*-(6,7-methylenedioxy-1-naphthyl)-2,2,2-trifluoroacetamide **16**, which was methylated with methyl iodide in the presence of sodium hydride, and hydrolyzed with alkali to produce **17** in 76% total yield. Triflate-benzoic acid **13** for the synthesis of **9a** was prepared as shown in Scheme 2. The reaction of benzofuran **18**[5] with triflic anhydride and successive treatment with ozone, dimethyl sulfide, and hydrochloric acid provided salicylaldehyde **19** in 45% total yield. Methylation of **19**, followed by oxidation with sodium chlorite and 35% hydrogen peroxide afforded **13** in 77% yield. Finally, reaction of the acid chloride of **13** with **17** provided triflate-amide **9a** in 63% yield.

Next, triflate-benzoic acid **14** for synthesis of **10** was prepared as shown in Scheme 3. The reaction of salicylaldehyde **20**[6] with triflic anhydride followed by oxidation gave **14**, which was treated with oxalyl chloride, followed by **16**, to afford triflate-amide **10a** in 85% total yield.

Halo-amides **9b**,[3b] **9c**,[3a] **10b**,[3b] **11b**,[3c] and **12b**[3a] were synthesized using reported literature procedures.



Scheme 3 Synthesis of precursor **10a** for the biaryl coupling reaction

Biaryl Coupling Reactions of Triflate-amides and Halo-amides in the Presence of Palladium Reagent

The biaryl coupling reaction of **9**–**12** by our novel palladium-phosphine combination system[4] was examined. As seen in the Table, small amounts of naphthobenzoazepinones **21**–**24** were obtained with phenanthridones **5**–**8** in each reaction. The synthetic samples **23**[3b] and **24**[3a] were identical to the authentic sample. The structures of the products **21** and **22** were elucidated on the basis of ^{1}H NMR spectral data, in which **21** showed only one singlet signal due to an aromatic proton and **22** showed three singlet signals due to aromatic protons in addition to signals due to other aromatic protons (see Experimental). On using diisopropylethyl amine as the base, the coupling reaction of **9a** proceeded quickly and in a higher yield to give oxychelerythrine (**5**)[3a] (see runs 1 and 2). Moreover, on applying the novel method to halo-amides **9b** and **9c**,[3a] both amides gave **5** in excellent yields (see runs 3–6 in Table). Using this procedure, the coupling reaction of **10a** provided oxynitidine (**6**)[3b] in excellent yield (see run 7 in Table) and **10b**[3b] provided **6** in high yield (see runs 8 and 9 in Table).

The synthetic samples **5**–**8** were identical to authentic samples, which had already been converted to the corresponding natural products **1**–**4**,[3] by successive treatment with $LiAlH_4$ and HCl.

Consequently, the novel combination system consisting of $Pd(OAc)_2$, DPPP, Bu_3P, and base is a very efficient and powerful method for intramolecular aryl-aryl coupling reactions involving either a triflate or halogen as the leaving group. We are now investigating the catalytic ability of this method.

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

***N*-Methyl-6,7-methylenedioxy-1-naphthylamine (17)**

To a solution of **15** (100 mg, 0.53 mmol) in anhyd pyridine (3 mL), Tf_2O (0.11 mL, 0.80 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min and poured into 10% HCl (10 mL) and then extracted with Et_2O. The residue was recrystallized from Et_2O–hexanes to afford **16** (140 mg, 93%) as colorless needles, mp 172–174 °C.

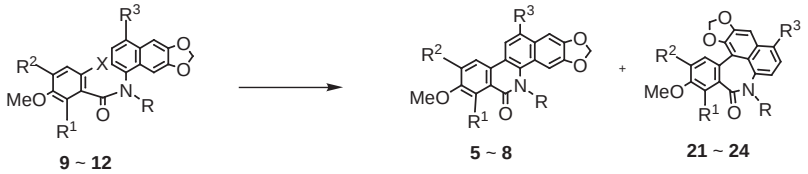
IR (KBr): 3300, 1715 cm^{-1}.

^{1}H NMR (60 MHz): δ = 6.07 (2 H, s, OCH_2O), 7.03–7.74 (5 H, m, ArH), 8.07 (1 H, br s, NH).

MS-FAB: *m/z* $[M + H]^+$ calcd for $C_{13}H_8F_3NO_3$, 284; found, 284.

To a solution of **16** (105 mg, 0.37 mmol) prepared above and MeI (205 mg, 1.48 mmol) in anhyd acetone (10 mL) was added solid KOH (82.2 mg). The reaction mixture was refluxed for 20 min and solvent removed under reduced pressure. The residue was dissolved in EtOH (5 mL) and aq 5% NaOH solution (5 mL) and refluxed for 10 min. The reaction mixture was diluted with H_2O (40 mL) and ex-

Table Results of Coupling Reaction of Amides (**9**–**12**) to Benzo[*c*]phenanthridones (**5**–**8**) and naphthobenzoazepinones (**21**–**24**) in DMF under Reflux[a]



9 ~ **12** **5** ~ **8** **21** ~ **24**

9 : R=Me, R^1=OMe, R^2=R^3=H
10 : R=Me, R^1=R^3=H, R^2=OMe
11 : R=CH_2OMe, R^1=OMe, R^2=R^3=H
12 : R=Me, R^1=R^3 =OMe, R^2=H

5 and **21** : R=Me, R^1=OMe, R^2=R^3=H
6 and **22** : R=Me, R^1=R^3=H, R^2=OMe
7 and **23** : R=CH_2OMe, R^1=OMe, R^2=R^3=H
8 and **24** : R=Me, R^1=R^3 =OMe, R^2=H

a series X=OTf, **b** series X=I, **c** series X=Br

Run	Starting Material	$Pd(OAc)_2$ (eq)	Ligand	Bu_3P (eq)	Base	Time	Products (Yield, %)			
1	**9a**	1.0	DPPP	1.0	*i*Pr_2Net	30 min	**5**	(81)	**21**	(~ 5)
2		1.0	DPPP	1.0	Ag_2CO_3	4 h		(62)		(~ 3)
3	**9b**	1.0	DPPP	1.0	*i*Pr_2Net	15 min		(85)		(~ 3)
4		1.0	DPPP	1.0	Ag_2CO_3	15 min		(95)		(~ 3)
5	**9c**	1.0	DPPP	1.0	*i*Pr_2Net	30 min		(79)		(~ 3)
6		1.0	DPPP	1.0	Ag_2CO_3	30 min		(89)		(~ 2)
7	**10a**	1.0	DPPP	1.0	*i*Pr_2NEt	30 min	**6**	(93)	**22**	(~ 5)
8	**10b**	1.0	DPPP	1.0	*i*Pr_2Net	30 min		(94)		(~ 2)
9		1.0	DPPP	1.0	Ag_2CO_3	30 min		(88)		(~ 3)
10	**11b**	1.0	DPPP	1.0	*i*Pr_2NEt	40 min	**7**	(83)	**23**	(16)
11	**12b**	1.0	DPPP	1.0	*i*Pr_2NEt	30 min	**8**	(90)	**24**	(9)

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

tracted with Et_2O (100 mL). The residue was recrystallized from EtOH (10 mL) to afford **17** (60 mg, 82%) as pale yellow prisms, mp 105.5–106.5 °C.

IR (KBr): 3450 cm^{-1}.

^{1}H NMR (60 MHz): δ = 2.96 (3 H, s, NCH_3), 3.33 (1 H, br s, NH), 5.99 (2 H, s, OCH_2O), 6.52 (1 H, dd, *J* = 7.0, 2.1 Hz, C_2-H), 7.02–7.40 (5 H, m, ArH).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.65; H, 5.37; N, 6.85.

6-[(Trifluoromethanesulfonyl)oxy]-2-hydroxy-3-methoxybenzaldehyde (19)

To a mixture of **18** (2 g, 1.2 mmol) and anhyd NEt_3 (3.13 mL, 22.4 mmol) in anhyd CH_2Cl_2 (40 mL) at 0 °C was added Tf_2O (2.83 mL, 16.8 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 20 min at 0 °C. The mixture was diluted with CH_2Cl_2 (300 mL) and washed with 1 N HCl (50 mL), sat. $NaHCO_3$ (50 mL) and brine (80 mL). The organic layer was dried over anhyd $MgSO_4$. The residue dissolved in hexanes–EtOAc (2:1) and was subjected to column chromatography on silica gel. Elution with hexanes–EtOAc (2:1) afforded 4-[(trifluoromethanesulfonyl)oxy]-7-methoxy-2-methylbenzo[*b*]furan (3.46 g, 99%) as colorless oil.

IR ($CHCl_3$): 1145 cm^{-1}.

^{1}H NMR (60 MHz): δ = 2.50 (3 H, d, *J* = 0.9 Hz, CH_3), 4.01 (3 H, s, OCH_3), 6.48 (1 H, q, *J* = 0.9 Hz, C_3-H), 6.68 (1 H, d, *J* = 8.8 Hz, C_6-H), 7.07 (1 H, d, *J* = 8.8 Hz, C_5-H).

MS-FAB: *m/z* $[M + H]^+$ calcd for $C_{11}H_9F_3O_5S$, 311; found, 311.

The triflate–benzofuran prepared above (3.46 g, 11.2 mmol) was dissolved in anhyd CH_2Cl_2 (200 mL) and cooled to –78 °C. Ozone was bubbled through the solution for 30 min with stirring. The pale–blue reaction mixture was stirred at the same temperature further for 30 min. Excess ozone was removed by bubbling argon through the solution for 15 min at –78 °C. DMS (2.0 mL, 27 mmol) was added and the reaction mixture was stirred at r.t. for 1 h followed by concentration under reduced pressure. The residue was diluted with H_2O and extracted with EtOAc (300 mL). To the residue dissolved in EtOH (60 mL) was added concd HCl (10 mL). The reaction mixture was refluxed for 1 h, poured into H_2O (100 mL), and extracted with EtOAc (500 mL). The residue dissolved in hexanes–EtOAc (5:1) and subjected to column chromatography on silica gel. Elution with hexanes–EtOAc (5:1) afforded **19** (1.51 g, 45%) as colorless plates (from hexanes) mp 75.5–76.5 °C.

IR (KBr): 3150, 1680, 1140 cm^{-1}.

^{1}H NMR (60 MHz): δ = 3.94 (3 H, s, OCH_3), 6.85 (1 H, d, *J* = 9.1 Hz, C_4-H), 7.10 (1 H, d, *J* = 9.1 Hz, C_5-H), 10.22 (1 H, s, CHO), 11.96 (1 H, s, OH).

MS-FAB: *m/z* $[M + H]^+$ calcd for $C_9H_7F_3O_6S$, 301; found, 301.

Anal. Calcd for $C_9H_7F_3O_6S$: C, 36.01; H, 2.35. Found: C, 36.31; H, 2.65.

6-[(Trifluoromethanesulfonyl)oxy]-2,3-dimethoxybenzoic Acid (13)

To a mixture of **19** (1.43 g, 4.76 mmol) and K_2CO_3 (0.49 mg, 3.57 mmol) in anhyd DMF (50 mL) was added MeI (0.36 mL, 5.72 mmol) and the solution was stirred at r.t. for 2 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (300 mL). The residue dissolved in $CHCl_3$ (20 mL) was subjected to column chromatography on silica gel. Elution with $CHCl_3$ afforded 6-[(trifluoromethanesulfonyl)oxy]-2,3-dimethoxybenzaldehyde (1.30 g, 87%) as colorless needles (from benzene–hexanes) mp 86–87 °C.

IR (KBr): 1700, 1145 cm^{-1}.

^1H NMR (60 MHz): δ = 3.94 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 7.08 (2 H, m, C_4-H, C_5-H), 10.42 (1 H, s, CHO).

Anal. Calcd for $C_{10}H_9F_3O_6S$: C, 38.22; H, 2.89. Found: C, 38.38; H, 3.11.

To a stirred mixture of the benzaldehyde (500 mg, 1.59 mmol) prepared above, monobasic $NaHSO_3$ (62 mg, 0.40 mmol) and 35% H_2O_2 (0.20 mL, 2.39 mmol) in CH_3CN (20 mL) and H_2O (1 mL) were added. A solution of $NaClO_2$ (80%; 270 mg, 2.39 mmol) in H_2O (1 mL) was added and the mixture was stirred at 10 °C for 6 h. After the decomposition of excess H_2O_2 with 10% aq $NaHSO_3$ solution (20 mL), the mixture was poured into H_2O (100 mL) and extracted with Et_2O (300 mL). The crystalline residue was recrystallized from Et_2O–hexanes (20 mL) to afford **13** (480 mg, 91%) as colorless needles; mp 75–76.5 °C.

IR (KBr): 2920, 1715, 1140 cm^{-1}.

^1H NMR (60 MHz): δ = 3.93 (3 H, s, OCH_3), 3.98 (3 H, s, OCH_3), 6.43 (1 H, bs, COOH), 7.07 (2 H, m, C_4-H, C_5-H).

Anal. Calcd for $C_{10}H_9F_3O_7S$: C, 36.37; H, 2.75. Found: C, 36.43; H, 2.92.

6-[(Trifluoromethanesulfonyl)oxy]-2,3-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (9a)

A few drops of anhyd DMF and oxalyl chloride (232 mg, 1.82 mmol) were added to a solution of **13** (300 mg, 0.91 mmol) in anhyd CH_2Cl_2 (15 mL) under ice-cooling and the mixture was refluxed for 1.5 h. Then the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of **16** (210 mg, 1.0 mmol) in anhyd CH_2Cl_2 (2 mL) and anhyd Et_3N (0.16 mL, 1.14 mmol) and this mixture was stirred for 30 min at r.t. The reaction mixture was concentrated to dryness and diluted with CH_2Cl_2 (100 mL), then washed with 10% HCl (20 mL), sat. $NaHCO_3$ solution (20 mL) and brine (50 mL). The residue was dissolved in $CHCl_3$ (10 mL) and subjected to column chromatography on silica gel. Elution with $CHCl_3$ afforded **9a** (293 mg, 63%) as colorless needles (from benzene–hexanes) mp 213–213.5 °C.

IR (KBr): 1660, 1145 cm^{-1}.

^1H NMR (500 MHz): δ = 3.27–4.10 (9 H, m, NCH_3, 2 × OCH_3, rotamer), 6.06 (2 H, s, OCH_2O), 6.63–7.68 (7 H, m, ArH, rotamer).

Anal. Calcd for $C_{22}H_{18}F_3NO_8S$: C, 51.46; H, 3.53; N, 2.73. Found: C, 51.30; H, 3.61; N, 2.85.

2-[(Trifluoromethanesulfonyl)oxy]-4,5-Dimethoxybenzoic Acid (14)

To a mixture of **20**[6] (1 g, 5.50 mmol) and anhyd Et_3N (1.11 g, 11.0 mmol) in anhyd CH_2Cl_2 (40 mL) at 0 °C was added Tf_2O (2.33 g, 8.25 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h at 0 °C. The mixture was diluted with CH_2Cl_2 (300 mL) and washed with 1 N HCl (50 mL), sat. $NaHCO_3$ (50 mL) and brine (80 mL). The organic layer was dried over anhyd $MgSO_4$. The residue was dissolved in CH_2Cl_2–hexanes (1:1) and was subjected to column chromatography on silica gel. Elution with CH_2Cl_2–hexanes (1:1) afforded 2-[(trifluoromethanesulfonyl)oxy]-4,5-dimethoxybenzaldehyde (1.29 g, 75%) as colorless needles (from hexanes) mp 76.5–78 °C

IR (KBr): 1700, 1140 cm^{-1}.

^1H NMR (60 MHz): δ = 3.96 (3 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 6.84 (1 H, s, C_3-H), 7.42 (1 H, s, C_6-H), 10.17 (1 H, s, CHO).

Anal. Calcd for $C_{10}H_9F_3O_6S$: C, 38.22; H, 2.89. Found: C, 38.30; H, 2.88.

To a stirred mixture of triflate-benzaldehyde (934 mg, 2.97 mmol) prepared above, monobasic sodium phosphate dihydrate (105 mg, 0.67 mmol) and 35% H_2O_2 (0.39 mL, 4.46 mmol) in CH_3CN (30 mL) and H_2O (3 mL) was added. A solution of $NaClO_2$ (80%; 487 mg, 4.31 mmol) in H_2O (3 mL) was added to the reaction mixture and then solution was stirred at 10 °C for 3 h. After the decomposition of excess H_2O_2 with 10% aq $NaHSO_3$ solution (20 mL), the mixture was poured into H_2O (100 mL) and extracted with EtOAc (300 mL). The residue dissolved in hexanes–EtOAc (2:1) was subjected to column chromatography on silica gel. Elution with hexanes–EtOAc (2:1) afforded **14** (954 mg, 97%) as colorless needles (from benzene) mp 168–170 °C.

IR (KBr): 2950, 1700, 1140 cm^{-1}.

^1H NMR (60 MHz): δ = 3.97 (6 H, s, 2 × OCH_3), 6.74 (1 H, s, C_3-H), 7.62 (1 H, s, C_6-H), 8.81 (1 H, s, COOH).

Anal. Calcd for $C_{10}H_9F_3O_7S$: C, 36.37; H, 2.75. Found: C,36.53; H, 2.87.

2-[(Trifluoromethanesulfonyl)oxy]-4,5-dimethoxy-*N*-methyl-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (10a)

A solution of **14** (420 mg, 127 mmol) and thionyl chloride (167 mg, 1.40 mmol) in anhyd CH_2Cl_2 (10 mL) and anhyd pyridine (0.2 mL) was refluxed for 1.5 h. Then the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of **16** (256 mg, 1.27 mmol) in anhyd $CHCl_3$ (10 mL) and anhyd Et_3N (0.2 mL, 1.53 mmol) and the mixture was stirred for 12 h at r.t. The reaction mixture was concentrated to dryness and diluted with CH_2Cl_2 (300 mL), then washed with 10% HCl (50 mL), sat. $NaHCO_3$ soln (50 mL) and brine (80 mL). The residue dissolved in $CHCl_3$ (10 mL) was subjected to column chromatography on silica gel. Elution with $CHCl_3$ afforded **10a** (578 mg, 88%) as colorless prisms (from benzene–hexanes) mp 184–185 °C.

IR (KBr): 1655, 1140 cm^{-1}.

^1H NMR (500 MHz): δ = 3.29 (3 H, s, NCH_3), 3.51 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 6.08 (2 H, s, OCH_2O), 6.52 (1 H, s, ArH), 6.53 (1 H, s, ArH), 7.11–7.17 (3 H, m, ArH), 7.26 (1 H, s, ArH), 7.42 (1 H, dd, *J* = 6.5, 3.0 Hz, ArH).

Anal. Calcd for $C_{22}H_{18}F_3NO_8S$: C, 51.46; H, 3.53; N, 2.73. Found: C, 51.74; H, 3.73; N, 2.66.

Coupling Reaction of Amides 9–12 by the Pd Reagent; General Procedure

The reaction of amides **9**–**12** (0.3 mmol) in anhyd DMF (8 mL) was carried out using $Pd(OAc)_2$ and DPPP in a molar ratio of 1:1 and one equiv of Bu_3P, and 2 mol equiv of base under reflux. The reaction mixture was diluted with Et_2O (200 mL) and the precipitate was removed by filtration. The filtrate was washed with 1 N HCl (20 mL), sat. $NaHCO_3$ solution (20 mL) and brine (30 mL). The residue was dissolved in hexanes–EtOAc (4:1) and subjected to column chromatography on silica gel. Elution with hexanes–EtOAc (2:1) gave naphthobenzoazepinones **21**–**24** and successive elution with the same solvent afforded the phenanthridones **5**–**8**.

9,10-Dimethoxy-7-methyl-1,2-methylenedioxynaphtho[1,8-*cd*][2]benzazepin-8(7*H*)-one (21)
Mp 202–204 °C, pale yellow needles (from hexanes–EtOAc).

IR (KBr): 1660 cm^{-1}.

^1H NMR (200 MHz): δ = 3.40 (3 H, s, NCH_3), 3.87 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 6.11 (2 H, s, OCH_2O), 6.92 (1 H, d, *J* = 9.0 Hz, C_{11}-H), 6.97 (1 H, s, C_3-H), 7.16 (1 H, dd, *J* = 7.1, 1.6 Hz, C_6-H), 7.27 (1 H, dd, *J* = 7.9, 7.1 Hz, C_5-H), 7.34 (1 H, dd, *J* = 7.9, 1.61 Hz, C_4-H), 7.39 (1 H, d, *J* = 9.0 Hz, C_{12}-H),

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}NO_5$: 364.1185. Found: 364.1138.

10,11-Dimethoxy-7-methyl-1,2-methylenedioxynaphtho[1,8-*cd*][2]benzazepin-8(7*H*)-one (22)
Mp 232.5–236 °C, colorless needles (from hexanes–EtOAc).

IR (KBr): 1630 cm^{-1}.

^1H NMR (500 MHz): δ = 3.45 (3 H, s, NCH_3), 3.87 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 6.12 (2 H, s, OCH_2O), 7.02 (1 H, s, C_3-H), 7.12 (1 H, dd, *J* = 7.5, 1.0 Hz, C_6-H), 7.20 (1 H, s, C_9-H or C_{12}- H), 7.29 (1 H, dd, *J* = 7.5, 7.5 Hz, C_5-H), 7.36 (1 H, d, *J* = 7.5 Hz, C_4-H), 7.61 (1 H, s, C_{12}-H or C_9- H)

MS-FAB: *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}NO_5$: 364.1185. Found: 364.1214.

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