Syntheses of the Acridone Alkaloid Citrusinine-I and Its Derivatives

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Citrusinine-I (1), a naturally occurring acridone alkaloid with potent antiviral activity, was synthesized for the first time, *via* a route involving Ullmann reaction, cyclization, and selective demethylation at the 1-position with boron trifluoride etherate and lithium bromide. 1,5,6-Trihydroxy-3-methoxy-9(10*H*)-acridone (2a) and 1,5,6-trihydroxy-3-methoxy-10-methyl-9(10*H*)-acridone (2b) were also synthesized.

Keywords citrusinine-I; selective demethylation; antiviral activity; acridone alkaloid; *o*-lithiation; Ullmann reaction

Recently, one of the authors reported that naturally occurring acridone alkaloids isolated from Rutaceae had potent antiviral activity against herpes simpex virus.[1] Among them, citrusinine-I (**1**) is one of the most potent derivatives, and has weak cytotoxicity, but no synthesis of **1** has been reported so far.

Preliminary analysis of the quantitative structure–activity relationship of acridone alkaloids by the Free–Wilson method[2] suggested that **2** could have potent activity. Though most potent derivatives of the acridone alkaloids characteristically have two hydroxy groups at the 1- and 5-positions, only a few syntheses of these compounds have been reported.[3] As a part of a synthetic study of 1,5-dihydroxy-9(10*H*)-acridone derivatives, we were interested in synthesizing of **1** and **2a**,**b**.

Our synthetic strategy consisted of *o*-lithiation of **4** or **21c** and subsequent iodination, Ullmann reaction of **5** with **6** or **22c** with **23** followed by cyclization, and regioselective demethylation of the intermediate **11** or **27** at the 1-position, as shown in Chart 1.

Synthesis of Citrusinine-I (1) 2-Iodo-3,4,6-trimethoxy-*N*,*N*-dimethylbenzamide (**5**) was prepared as shown in Chart 2. Amidation of the acid chloride derived from **3** with dimethylamine afforded *N*,*N*-dimethylbenzamide **4** in 58% yield. *o*-Lithiation of **4** with *sec*-butyl lithium (*sec*-BuLi) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) followed by iodination gave **5** in 52% yield.

Ullmann reaction of **5** with **6** in the presence of copper(I) chloride (CuCl) in isopropanol (iso-PrOH) gave **7** in 81% yield, and this product was treated with benzyl chloride to afford **8** in 69% yield. Cyclization of **8** by treatment with phosphorus oxychloride ($POCl_3$) followed by hydrolysis of the intermediate with aqueous hydrochloric acid (HCl) in ethanol (EtOH) gave the acridones **9** and **10** in 50% and 5% yields, respectively. Methylation of **9** with potassium hydroxide (KOH) and dimethyl sulfate in dimethyl sulfoxide

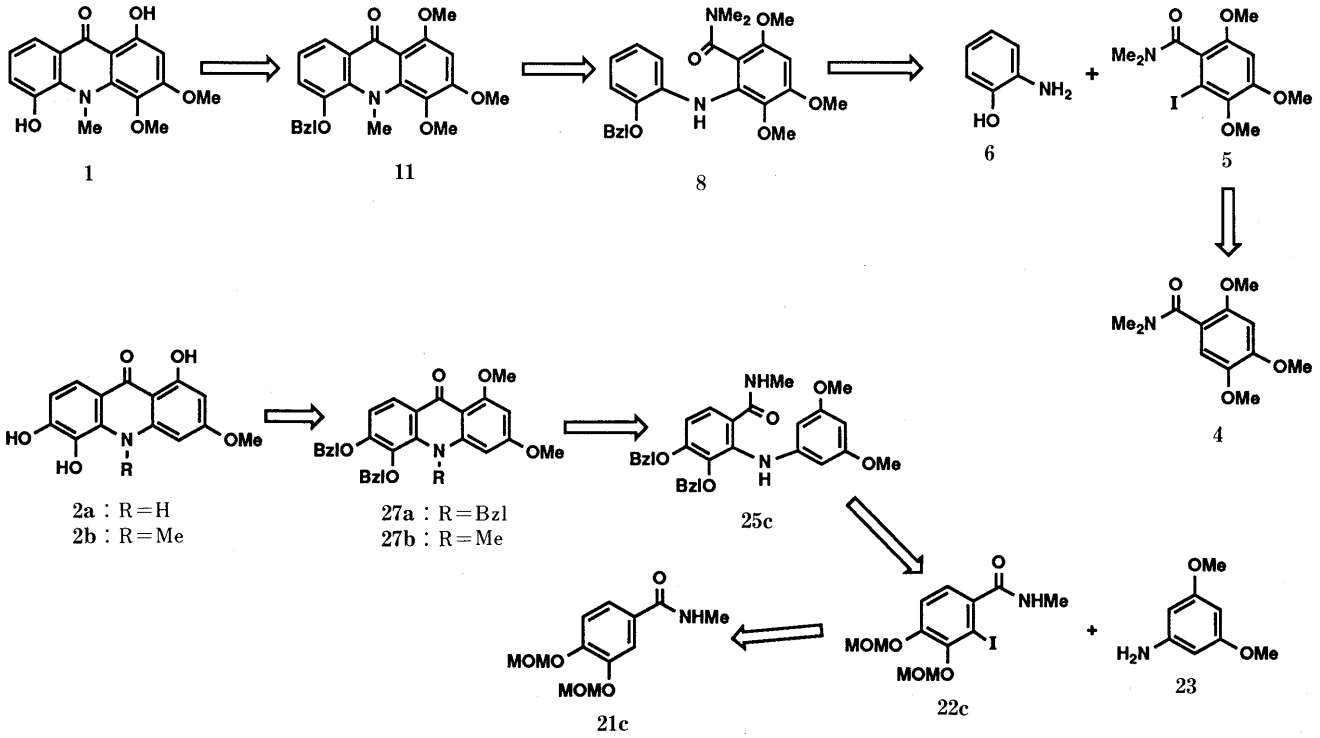

Chart 1

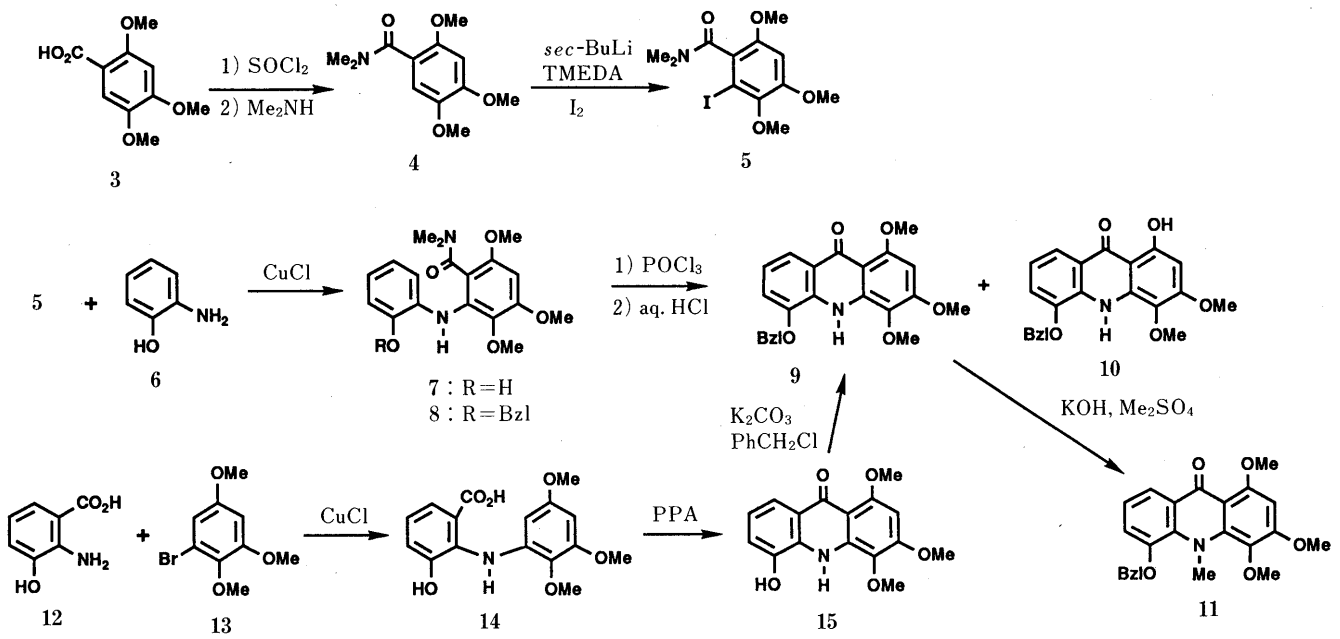

Chart 2

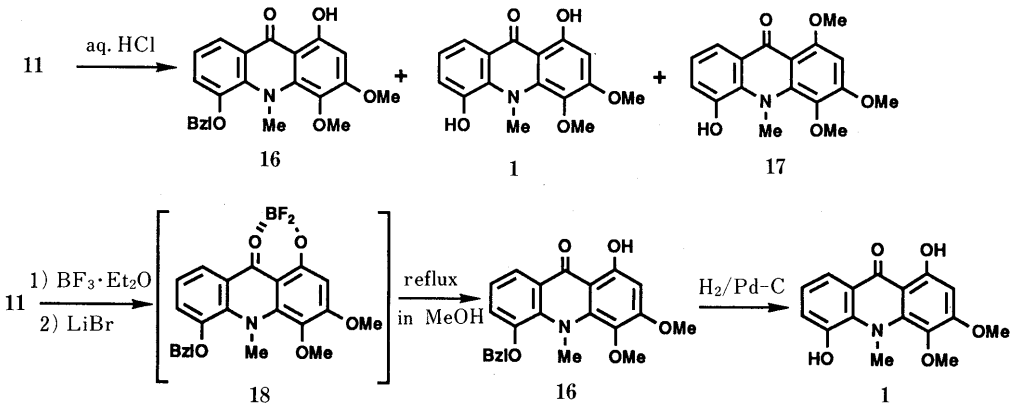

Chart 3

(DMSO) gave **11** in 78% yield.

Alternatively, the intermediate **9** was synthesized from **12** and **13** in 3 steps. Ullmann reaction of **12** with **13** gave **14** in 12% yield. The low yield is due to the susceptibility of the product to autooxidation. Cyclization of **14** with polyphosphoric acid (PPA) gave the acridone **15** in 59% yield, and **15** was benzylated to give **9** in 66% yield.

Demethylation of the methoxy group at the 1-position of **11** with aqueous HCl according to a general method[4] gave **16**, **1**, and **17** in 48%, 20%, and 15% yields, respectively, as shown in Chart 3. On the other hand, demethylation with boron trifluoride etherate ($BF_3 \cdot Et_2O$) and lithium bromide (LiBr) gave only **16** in 87% yield over 3 steps, *i.e.*, treatment of **11** with $BF_3 \cdot Et_2O$ in benzene gave a BF_3 complex at the 1-position, then reaction with LiBr in benzene and chloroform ($CHCl_3$) provided the BF_2 complex **18**, and deboration of **18** was accomplished by heating in the presence of sodium methoxide (NaOMe) in methanol (MeOH) to give **16**. Hydrogenolysis of **16** gave **1** in 95% yield. All physical and spectral data of synthetic **1** were identical with those of the natural product.[5]

Synthesis of 2 2-Iodobenzamides **22a**—**c** were synthesized by a similar method to that described for **5**, as shown in Chart 4. Treatment of **19** with methoxymethyl chloride (MOMCl) and triethylamine (Et_3N) in *N*,*N*-dimethylformamide (DMF) followed by hydrolysis of the MOM ester with aqueous sodium hydroxide (NaOH) gave the carboxylic acid **20** in 47% yield from **19**. Amidation of **20** with dimethylamine, diethylamine and methylamine gave **21a**, **21b**, and **21c** in 87%, 64%, and 50% yields, respectively. The *o*-lithiation of **21a**—**c** and subsequent iodination as described for **4** gave **22a**, **22b**, and **22c** in 40%, 61%, and 78% yields, respectively.

The reaction of **22a** or **22b** with **23** in the presence of CuCl did not give the desired Ullmann adduct but only gave a deiodinated product **21a** or **21b**, while the reaction of **22c** with **23** afforded **24c** in 54% yield and a deiodinated product **21c** in 22% yield. The *N*-methylaminocarbonyl group was more favorable than the *N*,*N*-dimethylaminocarbonyl group for this Ullmann reaction. The use of other catalysts such as copper, copper (I) bromide–dimethyl sulfide complex, copper (II) oxide, and copper (II) carbonate, and other solvents such as 2-ethoxyethanol did not improve the yield of **24c**. Treatment of **24c** with

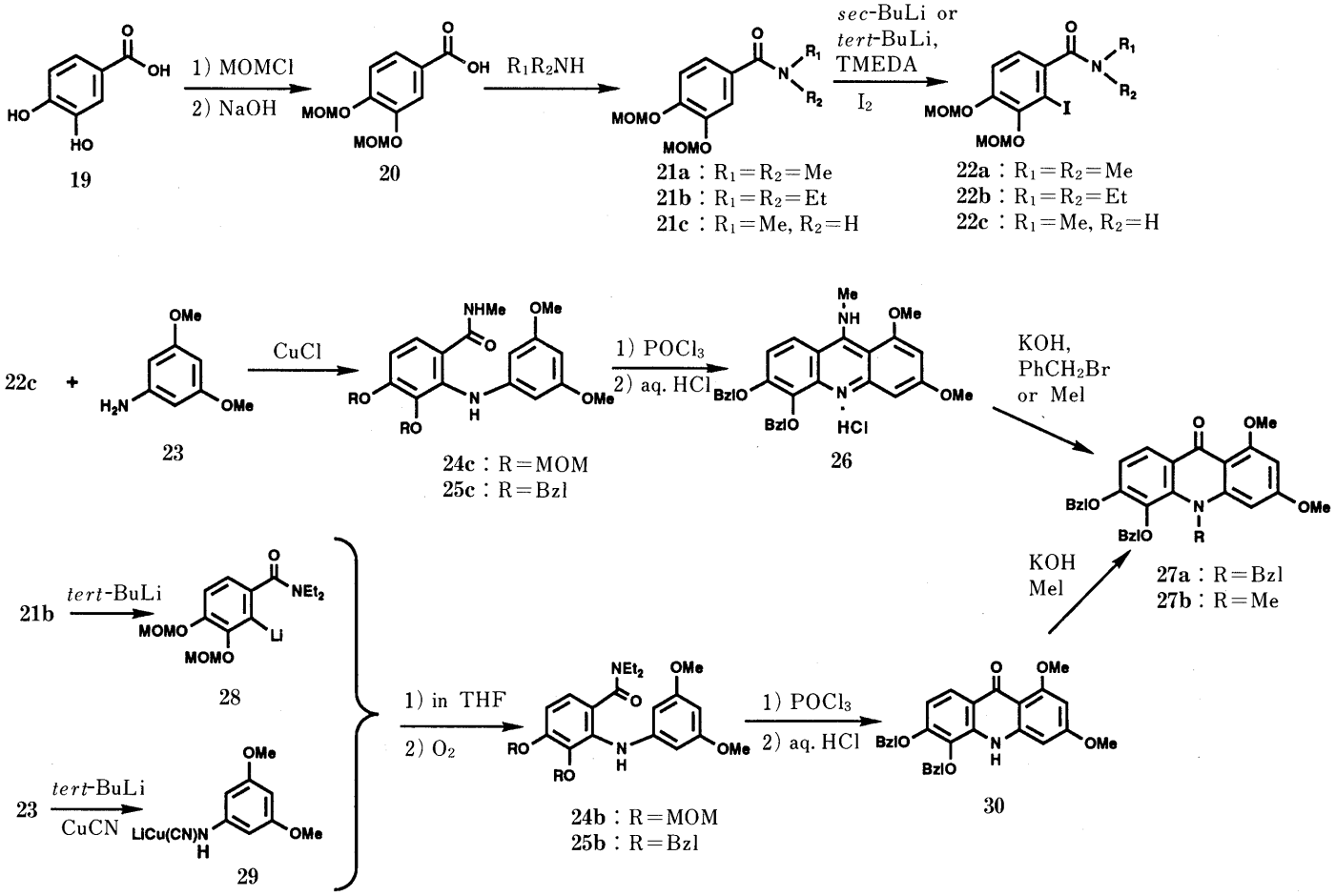

Chart 4

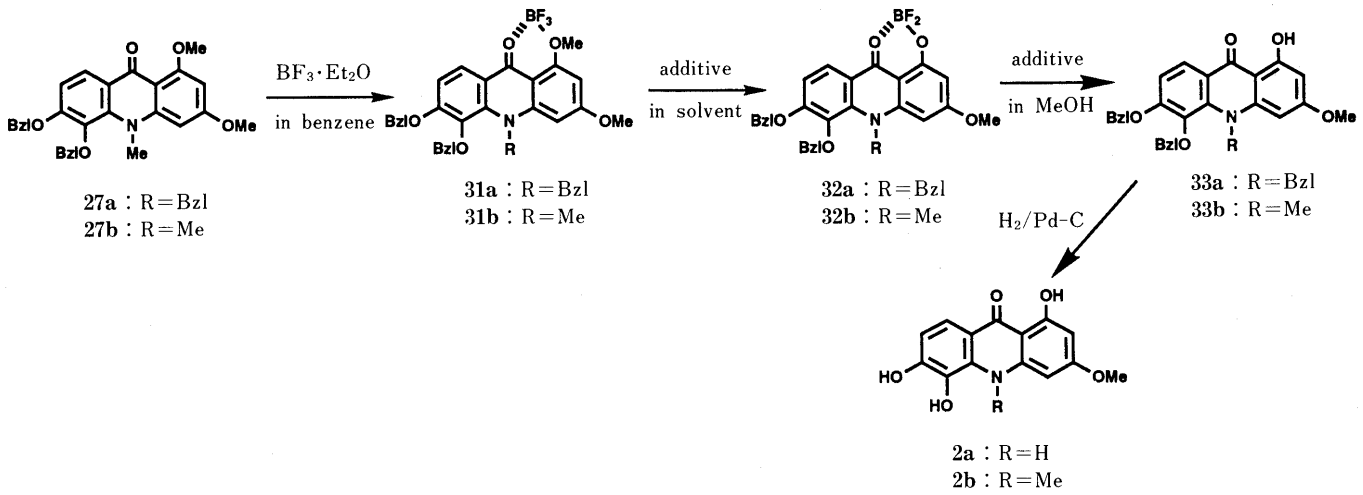

Chart 5

aqueous HCl followed by benzylation gave **25c** in 65% yield from **24c**. Cyclization of **25c** with $POCl_3$ followed by hydrolysis with aqueous HCl afforded 9-(*N*-methylamino)acridine hydrochloride **26** in 96% yield. Alkylation of **26** with benzyl bromide or methyl iodide and KOH in DMSO gave **27a** or **27b** in 71% and 76% yields, respectively.

Alternatively **27b** was prepared by using the oxidative coupling reaction developed by Snieckus *et al.*[6] Reaction of the *o*-lithiated benzamide **28** derived from **21b** with anilido-cyanocuprate **29** derived from **23** and subsequent oxygenation gave **24b** in 49% yield. Treatment of **24b** with aqueous HCl followed by benzylation using the same method as described for **24c** gave **25b** in 67% yield, and this product was cyclized by treatment with $POCl_3$ followed by hydrolysis with aqueous HCl in EtOH, giving **30** in 55% yield. Alkylation of **30** with methyl iodide gave **27b**.

Next, we tried to cleave the methyl ether linkage at the

TABLE I. Demethylation of **31b**

Run	Solvent	Additive	Conditions	Yield of **32b** (%)
1	$CHCl_3$ (1:1)	—	62 °C 3 h	N.R.[a]
2	C_6H_6–$CHCl_3$ (1:1)	—	73 °C 17 h	29[b]
3	$C_6H_5CH_3$–$CHCl_2CHCl_2$ (1:1)	—	127 °C 3 h	42
4	C_6H_6–$CHCl_3$ (1:1)	LiBr (10 eq)	73 °C 15 min	98
5	C_6H_6–$CHCl_3$ (1:1)	$HSCH_2CH_2SH$	73 °C	62

a) N.R.: no reaction. *b*) Recovered yield of **31b**, 68%.

TABLE II. Deboration of **32b**

Run	Solvent	Additive	Conditions	Yield of **33b** (%)
1	MeOH	—	65 °C 18 h	78
2	MeOH	NaOMe (10 eq)	65 °C 2 h	89

1-position of **27b**, as shown in Chart 5. Treatment of **27b** with aqueous HCl in EtOH, boron trichloride (BCl_3),[7] and boron tribromide gave many products, as a result of partial debenzylations as well as the demethylation at 1-position. On the other hand, demethylation of **27b** with $BF_3 \cdot Et_2O$ in benzene proceeded selectively to give a BF_2 complex **31b**. Heating of **31b** in $CHCl_3$ did not afford **32b** at all. In benzene–$CHCl_3$ or toluene–1,1,2,2-tetrachloroethane, **32b** was obtained in 29% or 42% yield, respectively. Addition of LiBr gave **32b** as a sole product in 98% yield. In the case of ethanedithiol,[8] **32b** was obtained in 62% yield together with several other products, as shown in Table I. Heating of **32b** in MeOH gave **33b** in 78% yield. Addition of NaOMe decreased the reaction time and increased the yield to 89%, as shown in Table II. By this method **27a** and **27b** were transformed to **33a** and **33b** in 70% and 81% yields, respectively. In a one-pot reaction, **33b** was obtained in 94% yield from **27b**. Finally catalytic hydrogenation of **33a** and **33b** with palladium on carbon (Pd–C) gave **2a** and **2b** in 87% and 90% yields, respectively.

Conclusion

The intermediates **11** and **27** were synthesized *via* a route involving *o*-lithiation of the benzamides, subsequent iodination, Ullmann reaction, cyclization, and methylation or benzylation.

The regioselective demethylation of the 1-methoxy-substituted-acridones with aqueous HCl or BCl_3 was not effective with **11** and **27**. The use of $BF_3 \cdot Et_2O$ and LiBr successively cleaved the methyl ether at the 1-position without any ether cleavage at other positions. Debenzylation by hydrogenolysis easily proceeded in high yield under mild conditions, and the product was easily purified.

This synthetic method is useful to synthesize acridone derivatives having two hydroxy groups at the 1- and 5-positions.

Experimental

Melting points were taken on a Yamato MP-21 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-302 infrared spectrophotometer. Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were taken with JEOL JNM-PMX 60 and JEOL JNM GSX-400 spectrometers using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference and are given in δ ppm. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured with a Hitachi M-80B mass spectrometer. Elemental analyses were performed with a Yanagimoto MT-3 CHN Corder elemental analyzer. Organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. All solvents used for lithiation reaction were freshly distilled from sodium benzophenone ketyl before use. Chromatography was carried out by flash chromatography on silica gel (Fuji-Davison BW-200MH or BW-300MH).

2,4,5-Trimethoxy-*N*,*N*-dimethylbenzamide (4) A mixture of 2,4,5-trimethoxybenzoic acid (**3**) (81.3 g, 0.383 mol) and thionyl chloride (100 ml) was refluxed for 2 h. The reaction mixture was concentated and the residue was dissolved in a mixture of dry benzene and CH_2Cl_2 (2:1, 300 ml). This solution was added to a solution of dimethylamine hydrochloride (62.5 g, 0.766 mol) in H_2O (100 ml) and 4 N aqueous NaOH (192 ml, 0.766 mol) with vigorous stirring in an ice bath and the mixture was stirred for 1 h at room temperature. The organic layer was washed with H_2O and brine, dried, and concentrated to give crude **4**. This was recrystallized ($CHCl_3$–iso-Pr_2O) to give **4** (52.8 g, 58%) as a pale yellow solid, mp 110—110.9 °C. IR (KBr): 1622, 1466, 1205, 1148, 1026, 811 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.88 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 3.83 (6H, s, $OCH_3 \times 2$), 3.90 (3H, s, OCH_3), 6.48 (1H, s, 3-H), 6.78 (1H, s, 6-H). *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.10; H, 7.31; N, 5.83.

2-Iodo-3,4,6-trimethoxy-*N*,*N*-dimethylbenzamide (5) *n*-BuLi (152 ml, 221 mmol, 1.5 M solution in hexane) was added to a solution of TMEDA (26.8 g, 230 mmol) in tetrahydrofuran (THF) (500 ml) at −78 °C and the mixture was stirred for 20 min at −15 °C. A solution of **4** (45.9 g, 192 mmol) in THF (270 ml) was added to this solution at −78 °C and the mixture was stirred for 1 h, then a solution of iodine (53.6 g, 211 mmol) in THF (60 ml) was added and the resulting mixture was stirred for 10 min at −20 °C. Aqueous sodium hydrosulfite (5%, 200 ml) was added at −40 °C and the mixture was stirred for 30 min at room temperature. The mixture was concentrated, and extracted with AcOEt. The extract was washed with H_2O and brine, dried, and concentrated. The residue was submitted to silica gel column chromatography (AcOEt:$CHCl_3$:hexane = 1:2:1) to give crude **5**. This crude product was recrystallized (benzene–iso-Pr_2O) to afford **5** (36.7 g, 52%) as pale yellow needles, mp 105—108 °C. IR (KBr): 1636, 1316, 1224, 1017 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.80 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.48 (1H, s, 5-H). *Anal.* Calcd for $C_{12}H_{16}INO_4 \cdot 0.1H_2O$: C, 39.28; H, 4.45; N, 3.82. Found: C, 39.00; H, 4.45; N, 3.84.

2-(2-Hydroxyphenylamino)-3,4,6-trimethoxy-*N*,*N*-dimethylbenzamide (7) A mixture of **6** (7.07 g, 64.6 mmol), **5** (13.9 g, 38 mmol), CuCl (3.76 g, 38 mmol), and anhydrous K_2CO_3 (15.8 g, 114 mmol) in iso-PrOH (380 ml) was stirred under reflux for 1.5 h. The precipitated inorganic material was removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel ($CHCl_3$:MeOH = 30:1) to give **7** (14.0 g, 81%) as a pale yellow solid, mp 140—142 °C (iso-Pr_2O–hexane). IR (KBr): 3144, 1589, 1465, 1446, 1242, 1198, 1121 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.70 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 3.50 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.13 (1H, s, OH), 6.30—6.90 (5H, m, aromatic H), 9.00 (1H, br s, NH). HRMS *m/z* (M^+): Calcd for $C_{18}H_{22}N_2O_5$: 346.1527. Found: 346.1521.

2-(2-Benzyloxyphenylamino)-3,4-6-trimethoxy-*N*,*N*-dimethylbenzamide (8) A mixture of **7** (10.7 g, 30.8 mmol), benzyl chloride (7.80 g, 61.6 mmol), and anhydrous K_2CO_3 (8.51 g, 61.6 mmol) in DMF (60 ml) was stirred at room temperature for 2 h, then at 40—45 °C for 1 h. DMF was removed, and the residue was dissolved in $CHCl_3$. This solution was washed with 2 N aqueous HCl, H_2O, and brine and dried. The solvent was removed and the residue was chromatographed on silica gel ($CHCl_3$:MeOH = 100:1) to give **8** (9.30 g, 69%) as a pale yellow solid, mp 122—125 °C ($CHCl_3$–iso-Pr_2O). IR (KBr): 3430, 1646, 1603, 1560, 1494, 1249, 1227, 1115 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.68 (3H, s, NCH_3), 2.88 (3H, s, NCH_3), 3.52 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 5.10 (2H, s, OCH_2Ph), 6.27 (1H, s, 5-H), 6.38 (1H, br s, NH), 6.73 (4H, br s, 3′H—6′H), 7.35 (5H, br s, OCH_2Ph). *Anal.* Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.52; H, 6.52; N, 6.42.

5-Benzyloxy-1,3,4-trimethoxy-9(10*H*)-acridone (9) and 5-Benzyloxy-1-hydroxy-3,4-dimethoxy-9(10*H*)-acridone (10) A mixture of **8** (8.73 g, 20 mmol) and $POCl_3$ (20 ml) was refluxed for 30 min under a nitrogen atmosphere and the excess $POCl_3$ was evaporated off. The residue was dissolved in EtOH (30 ml) and 1 N aqueous HCl (10 ml), then the mixture was refluxed for 1 h. The reaction mixture was concentrated and diluted with H_2O (150 ml). The precipitate was collected and dried. This precipitate was chromatographed on silica gel ($CHCl_3$ then $CHCl_3$: MeOH = 50 : 1). The first eluate gave **10** (0.35 g, 5%) and the second eluate gave **9** (3.95 g, 50%).

9: mp 158—160 °C ($CHCl_3$–iso-Pr_2O). IR (KBr): 1636, 1618, 1595, 1530, 1480, 1261, 1231, 1139, 961 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.88 (3H, s, OCH_3), 3.96 (6H, s, OCH_3 × 2), 5.23 (2H, s, $OC\underline{H}_2Ph$), 6.25 (1H, s, 2-H), 6.98—7.26 (2H, m, 6-H, and 7-H), 7.40 (br s, $OCH_2\underline{Ph}$), 7.87—8.13 (1H, m, 8-H), 8.85 (1H, br s, NH). *Anal.* Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.26; H, 5.45; H, 3.59.

10: mp 185—187 °C ($CHCl_3$–iso-Pr_2O). IR (KBr): 1646, 1603, 1560, 1494, 1249, 1227, 1115 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.23 (2H, s, $OC\underline{H}_2Ph$), 6.35 (1H, s, 2-H), 6.93—7.60 (2H, m, 6-H and 7-H), 7.38 (5H, s, $OCH_2\underline{Ph}$), 7.73—8.07 (1H, m, 8-H), 8.90 (1H, br s, NH), 13.67 (1H, br s, 1-OH). *Anal.* Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 69.91; H, 4.96; N, 3.77.

5-Benzyloxy-1,3,4-trimethoxy-10-methyl-9(10*H*)-acridone (11) Dimethyl sulfate (4 ml, 42.2 mmol) was added to a solution of **9** (3.18 g, 8.12 mol) and KOH powder (85%, 1.61 g, 24.4 mmol) in DMSO (30 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was decanted into cold H_2O (150 ml), acidified with 6 N aqueous HCl, and extracted with $CHCl_3$. The extract was washed with H_2O and brine, dried, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 100 : 1) to give **11** (2.56 g, 78%) as a dark yellow powder, mp 140—142 °C ($CHCl_3$–iso-Pr_2O). IR (KBr): 1629, 1582, 1456, 1306, 1205, 1191, 1105, 1020 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.65 (3H, s, NCH_3), 3.73 (3H, s, OCH_3), 3.95 (6H, s, OCH_3 × 2), 5.17 (2H, s, $OC\underline{H}_2Ph$), 6.35 (1H, s, 2-H), 7.03—7.63 (7H, m, 6-H, 7-H, and $OCH_2\underline{Ph}$), 7.67—8.07 (1H, m, 8-H). *Anal.* Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.13; H, 5.74, N, 3.49.

3-Hydroxy-2-(2,3,5-trimethoxyphenylamino)benzoic Acid (14) A mixture of **12** (18.4 g, 0.12 mmol), **13**[9] (29.7 g, 0.12 mol), CuCl (11.9 g, 0.12 mol), and anhydrous K_2CO_3 (49.8 g, 0.36 mol) in 2-ethoxyethanol (350 ml) was stirred for 6 h under reflux, then the solvent was removed. The residue was suspended in hot H_2O (800 ml), then the mixture was acidified with concentrated HCl and the precipitate was collected by filtration. The precipitate was dissolved in acetone and the undissolved material was removed by filtration with Hyflo Super-cel. The solvent was removed, and the residue was recrystallized to give **14** (4.54 g, 12%) as a dark green powder. IR (KBr): 3120, 1678, 1580, 1457, 1294, 1213, 1194, 1143, 1081 cm^{-1}. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 3.60 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.65 (1H, d, J = 3 Hz, 6′-H), 6.10 (1H, d, J = 3 Hz, 4′-H), 6.90—7.57 (3H, m, 4-H—6-H), 7.8—8.5 (1H, br s, OH), 9.2—9.8 (1H, br s, NH). HRMS m/z (M^+): Calcd for $C_{16}H_{17}NO_6$: 319.1055. Found: 319.1076.

5-Hydroxy-1,3,4-trimethoxy-9(10*H*)-acridone (15) A mixture of **14** (4.34 g, 13.6 mmol) and PPA (40 ml) was heated for 1 h at 115 °C. The reaction mixture was poured into H_2O (500 ml), triturated, and filtered. The filtrate was recrystallized twice from $CHCl_3$–iso-Pr_2O to give **15** (2.42 g, 59%) as a dark green solid, mp 240 °C (dec.) ($CHCl_3$–iso-Pr_2O). IR (KBr): 3364, 1634, 1202, 1131, 1034, 969 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 6.49 (1H, s, 2-H), 7.01 (1H, dd, J = 8, 8 Hz, 7-H), 7.10 (1H, dd, J = 8, 1 Hz, 6-H), 7.56 (1H, dd, J = 8, 1 Hz, 8-H), 10.71 (1H, s, OH). HRMS m/z (M^+): Calcd for $C_{16}H_{15}NO_5$: 301.0949. Found: 301.0976.

5-Benzyloxy-1,3,4-trimethoxy-9(10*H*)-acridone (9) A mixture of **15** (0.15 g, 0.5 mmol), anhydrous K_2CO_3 (0.35 g, 2.5 mmol), and benzyl chloride (0.32 g, 2.5 mmol) in iso-PrOH (5 ml) was refluxed for 2 h and inorganic material was removed by filtration. The solvent was removed, and the residue was chromatographed on silica gel (AcOEt : benzene = 1 : 1 then 4 : 1) to give **9** (0.13 g, 66%), which was identical with the sample obtained from **8**.

1,5-Dihydroxy-3,4-dimethoxy-10-methyl-9(10*H*)-acridone (1), 5-Benzyloxy-1-hydroxy-3,4-dimethoxy-10-methyl-9(10*H*)-acridone (16), and 5-Hydroxy-1,3,4-trimethoxy-10-methyl-9(10*H*)-acridone (17) Ether Cleavage by Aqueous HCl A solution of **11** (2.11 g, 5.2 mmol) in EtOH (20 ml) and 6 N aqueous HCl (20 ml) was refluxed for 4 h. The precipitate was collected by filtration to give **16** (0.63 g). The filtrate was concentrated and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and brine and dried. The solvent was evaporated off and the residue was chromatographed on silica gel ($CHCl_3$: MeOH = 50 : 1) to give **16** (0.35 g) as a yellow powder from the first eluate. The total yield of **16** was 0.98 g (48%). The second eluate gave **11** (0.14 g, recovered yield 7%), the third eluate gave **1** (0.31 g, 20%) as a yellow solid, and the last eluate gave **17** (0.25 g, 15%) as pale green prisms.

A mixture of **16** (0.81 g, 2.1 mmol) and 5% Pd–C (50 mg) in dry MeOH–acetone (1 : 1, 40 ml) was stirred under hydrogen for 1 h at 50 °C. Pd–C was removed by filtration and the solvent was evaporated off. The residue was chromatographed on silica gel (acetone : $CHCl_3$ = 1 : 2) to give **1** (0.59 g, 95%) as a yellow powder.

1: mp 205—207 °C (acetone) (lit.[3] mp 206—207 °C). UV $\lambda_{max}^{ethanol}$ nm: 222, 265, 319, 331, 416. IR (KBr): 3232, 1591, 1570, 1544, 1487, 1280, 1261, 1242, 1194 cm^{-1}. ^{1}H-NMR (400 MHz, acetone-d_6) δ: 3.77 (3H, s, OCH_3 or NCH_3), 3.84 (3H, s, OCH_3 or NCH_3), 3.98 (3H, s, OCH_3 or NCH_3), 6.41 (1H, s, 2-H), 7.17 (1H, dd, J = 8, 8 Hz, 7-H), 7.30 (1H, dd, J = 8, 2 Hz, 6-H), 7.80 (1H, dd, J = 8, 2 Hz, 8-H), 9.22 (1H, s, 5-OH), 14.16 (1H, s, 1-OH). ^{13}C-NMR (100 MHz, acetone-d_6) δ: 47.3, 57.1, 60.9, 95.1, 107.3, 117.8, 121.4, 124.0, 125.9, 131.6, 138.8, 143.6, 149.3, 161.5, 161.8, 183.6. *Anal.* Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.66; H, 4.93; N, 4.65. All physical data (UV, IR, ^{1}H-NMR, and ^{13}C-NMR of synthetic **1** were identical with those of the natural product.

16: mp 159—160 °C (MeOH–iso-Pr_2O). IR (KBr): 1590, 1564, 1490, 1323, 1300, 1259, 1187, 1144, 1082, 1046 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.75 (6H, s, OCH_3 or NCH_3), 3.95 (3H, s, OCH_3 or NCH_3), 5.18 (2H, s, $OC\underline{H}_2Ph$), 6.33 (1H, s, 2-H), 7.12—7.63 (7H, m, $OCH_2\underline{Ph}$, 6-H and 7-H), 7.93 (1H, dd, J = 6, 3 Hz, 8-H), 14.5 (1H, s, 1-OH). *Anal.* Calcd for $C_{23}H_{21}NO_5 \cdot 0.2H_2O$: C, 69.93; H, 5.46; N, 3.55. Found: C, 69.83; H, 5.33; N, 3.48.

17: mp 210—212 °C ($CHCl_3$–iso-Pr_2O). IR (KBr): 3370, 2920, 1590, 1458, 1389, 1324, 1192 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.70 (3H, s, OCH_3 or NCH_3), 3.78 (3H, s, OCH_3 or NCH_3), 3.93 (3H, s, OCH_3 or NCH_3), 4.00 (3H, s, OCH_3 or NCH_3), 6.47 (1H, s, 2-H), 6.80—7.23 (2H, m, 6-H and 7-H), 7.57 (1H, dd, J = 8, 2 Hz, 8-H), 9.68 (1H, s, 5-OH). *Anal.* Calcd for $C_{22}H_{19}NO_5 \cdot 0.2H_2O$: C, 64.02; H, 5.50; N, 4.44. Found: C, 63.93; H, 5.39; N, 4.42.

Ether Cleavage Using $BF_3 \cdot Et_2O$ and LiBr A solution of $BF_3 \cdot Et_2O$ (75 mg, 0.53 mmol) in dry benzene (2 ml) was added to a solution of **11** (0.20 g, 0.5 mmol) in dry benzene (8 ml), and the mixture was stirred for 1 h at room temperature under nitrogen atmosphere. A dark red oil was separated. $CHCl_3$ (10 ml) and LiBr (0.32 g, 3.4 mmol) were added to the mixture, and the resulting mixture was refluxed for 15 min. LiBr was removed by filtration and the solvent was evaporated off. A mixture of this residue and NaOMe (286 mg, 5.3 mmol) in MeOH (100 ml) was refluxed for 2 h, then acetic acid (0.3 ml) was added and refluxing was continued for 10 min. The solvent was removed and the residue was chromatographed on silica gel (benzene then hexane : benzene : AcOEt = 2 : 7 : 1) to give **16** (0.17 g, 87%) as a yellow powder.

3,4-Bis(methoxymethoxy)benzoic Acid (20) Under a nitrogen atmosphere, MOMCl (49 ml, 648 mmol) was added to a solution of **19** (25.0 g, 162 mmol) in Et_3N (230 ml) and dry DMF (150 ml) at below 0 °C, and the mixture was stirred for 15 h at room temperature. The reaction mixture was diluted with AcOEt, washed with H_2O and brine, and dried, then the solvent was removed. The residue was chromatographed on silica gel (benzene : hexane = 1 : 1 then benzene) to give methoxymethyl 3,4-bis(methoxymethoxy) benzoate (26.9 g, 58%) as a colorless oil. A solution of this oil (23.8 g, 83.2 mmol) in EtOH (50 ml) and 1 N aqueous NaOH (125 ml) was stirred for 2 h at 50 °C. The reaction mixture was cooled in an ice bath and acidified to pH 5 with concentrated HCl, and the solvent was removed. The residue was dissolved in $CHCl_3$–EtOH (3 : 1, 400 ml) and the precipitate (NaCl) was removed by filtration. The filtrate was dried and concentrated. The residue was recrystallized from EtOH–iso-Pr_2O to give **20** (18.1 g, 90%) as colorless needles, mp 125—129 °C. IR (KBr): 2900, 1672, 1288, 1269, 1158, 1150, 1080, 982 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.47 (6H, s, OCH_3 × 2), 5.20 (2H, s, OCH_2O), 5.23 (2H, s, OCH_2O), 7.08 (1H, d, J = 8 Hz, 5-H), 7.70 (1H, d, J = 8 Hz, 6-H), 7.77 (1H, s, 2-H), 9.13 (1H, br s, CO_2H). *Anal.* Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.73; H, 5.81.

3,4-Bis(methoxymethoxy)-*N*,*N*-dimethylbenzamide (21a) Under a nitrogen atmosphere, a solution of dimethylamine hydrochloride (1.03 g, 12.6 mmol) in DMF (4 ml) and Et_3N (3.5 ml) was stirred for 10 min at room temperature. The precipitate was removed by filtration. Diethyl cyanophosphate (1.26 g, 6.93 mmol) in DMF (4 ml) was added to a mixture of **20** (1.02 g, 4.2 mmol) and the resulting dimethylamine in DMF solution

in an ice bath and the mixture was stirred at that temperature for 1 h and then for 16 h at room temperature. DMF was removed and the residue was chromatographed on silica gel ($CHCl_3$: hexane = 1 : 1, $CHCl_3$: AcOEt = 4 : 1) to give **21a** (0.98 g, 87%) as a colorless oil. IR (film): 1634, 1468, 1393, 1260, 1150, 1077, 981, 923 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.03 (3H, s, NCH_3), 3.07 (3H, s, NCH_3), 3.51 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 5.25 (2H, s, OCH_2O), 5.26 (2H, s, OCH_2O), 7.05 (1H, dd, J = 8, 2 Hz, 6-H), 7.17 (1H, d, J = 8 Hz, 5-H), 7.27 (1H, d, J = 2 Hz, 2-H). HRMS m/z (M^+): Calcd for $C_{13}H_{19}NO_5$: 269.1262. Found: 269.1273.

3,4-Bis(methoxymethoxy)-*N*,*N*-diethylbenzamide (21b) The reaction was carried out in the same way as described for **21a**. The crude product was chromatographed on silica gel (AcOE : benzene = 1 : 5) to give **21b** (1.57 g, 64%) as a colorless oil. IR (film): 1625, 1467, 1457, 1429, 1290, 1252, 1153, 1127, 1073, 984, 921 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.18 (6H, t, J = 7 Hz, CH_2CH_3 × 2), 3.40 (4H, q, J = 7 Hz, CH_2CH_3 × 2), 3.50 (6H, s, OCH_3 × 2), 5.20 (4H, s, OCH_2O × 2), 6.92 (1H, dd, J = 8, 2 Hz, 6-H), 7.07 (1H, s, J = 2 Hz, 2-H), 8.02 (1H, d, J = 8 Hz, 5-H). HRMS m/z (M^+): Calcd for $C_{12}H_{17}NO_4$: 297.1575. Found: 297.1555.

3,4-Bis(methoxymethoxy)-*N*-methylbenzamide (21c) Under a nitrogen atmosphere, isobutoxycarbonyl chloride (10 g, 70.4 mmol) was added to a solution of **20** (16.9 g, 70 mmol) in Et_3N (20 ml) and DMF (50 ml) at 10 °C, and the mixture was stirred for 30 min in an ice bath. A mixture of methylamine hydrochloride (14.2 g, 210 mmol) in H_2O (10 ml), Et_3N (59 ml), and DMF (30 ml) was added to the above solution in an ice bath and the resulting mixture was stirred for 15 h at room temperature. The solvent was removed and the residue was diluted with AcOEt, then the AcOEt solution was washed with H_2O, saturated $NaHCO_3$, and brine, and dried. The solvent was removed and the residue was chromatographed on silica gel ($CHCl_3$ then $CHCl_3$: MeOH = 50 : 1) to give **21c** (8.95 g, 50%). The saturated $NaHCO_3$ layer was acidified with aqueous HCl (10%) to pH 3—4 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine and dried. The solvent was removed to provide **20** (3.73 g, 22%) as white crystals. **21c**: mp 98—99 °C (iso-Pr_2O–hexane). IR (KBr): 1628, 1491, 1261, 1154, 1073, 986 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.93 (3H, d, J = 5 Hz, NCH_3), 3.24 (6H, s, OCH_3 × 2), 5.23 (4H, s, OCH_2O × 2), 6.45 (1H, br s, NH), 7.08 (1H, d, J = 9 Hz, 5-H), 7.37 (1H, dd, J = 9, 2 Hz, 6-H), 7.57 (1H, d, J = 2 Hz, 2-H). *Anal.* Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.46; H, 6.84; N, 5.50.

3,4-Bis(methoxymethoxy)-2-iodo-*N*,*N*-dimethylbenzamide (22a) Under a nitrogen atmosphere, *sec*-BuLi (3.5 ml, 2.42 mmol, 0.7 M solution in hexane) was added to a solution of TMEDA (0.28 g, 3.3 mmol) in THF (4 ml) at −70 °C and the mixture was stirred for 20 min. A solution of **21a** (0.59 g, 2.2 mmol) in THF (2 ml) was added slowly and the mixture was stirred for 1 h. A solution of iodine (0.84 g, 3.3 mmol) in THF (5 ml) was further added and the resulting mixture was stirred for 1 h at −70 °C. Then aqueous sodium hydrosulfite (5%, 10 ml) was added. The whole was concentrated and extracted with AcOEt, then the extract was washed with H_2O and brine, dried, and concentrated. The residue was chromatographed on silica gel ($CHCl_3$, $CHCl_3$: CH_3CN = 30 : 1, then 10 : 1) to give **22a** (0.35 g, 40%) as a pale yellow oil. IR (film): 1634, 1468, 1393, 1260, 1150, 1077, 981, 923 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.82 (3H, s, NCH_3), 3.08 (3H, s, NCH_3), 3.47 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.17 (4H, s, OCH_2O × 2), 6.85 (1H, d, J = 8 Hz, 5-H), 7.15 (1H, d, J = 8 Hz, 6-H). HRMS m/z (M^+): Calcd for $C_{13}H_{18}INO_5$: 395.0230. Found: 395.0260.

3,4-Bis(methoxymethoxy)-*N*,*N*-diethyl-2-iodobenzamide (22b) The reaction was carried out in the same way as described for **22a**. The crude product was chromatographed on silica gel (AcOEt : $CHCl_3$: hexane = 1 : 1 : 2) to give **22b** (2.44 g, 61%) as a pale yellow oil. IR (film): 1625, 1454, 1428, 1288, 1257, 1154, 1077, 969, 941 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.08 (3H, t, J = 7 Hz, CH_3), 1.28 (3H, t, J = 7 Hz, CH_3), 3.12 (4H, q, J = 7 Hz, NCH_2 × 2), 3.47 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 5.17 (4H, s, OCH_2O × 2), 6.85 (1H, d, J = 8 Hz, 5-H), 7.13 (1H, d, J = 8 Hz, 6-H). HRMS m/z (M^+): Calcd for $C_{15}H_{22}INO_5$: 423.0543. Found: 423.0515.

3,4-Bis(methoxymethoxy)-2-iodo-*N*-methylbenzamide (22c) The reaction was carried out in the same way as described for **22a** using *tert*-BuLi (2 eq for **21c**, 1.2 M solution in hexane). The crude product was chromatographed on silica gel (AcOEt : $CHCl_3$: hexane = 4 : 5 : 3) to give **22c** (10.1 g, 78%) as a white solid, mp 111—112 °C (MeOH–iso-Pr_2O–hexane). IR (KBr): 3244, 1635, 1542, 1459, 1150, 988, 963 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.00 (3H, d, J = 5 Hz, $NHCH_3$), 3.48 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 5.18 (2H, s, OCH_2O), 5.21 (2H, s, OCH_2O), 5.80 (1H, br s, NH), 7.09 (1H, d, J = 9 Hz, 5-H), 7.14 (1H, d, J = 9 Hz, 6-H). *Anal.* Calcd for $C_{12}H_{16}INO_5$: C, 37.81; H, 4.23; N, 3.67. Found: C, 37.73; H, 4.24; N, 3.67.

3,4-Bis(methoxymethoxy)-2-(3,5-dimethoxyphenylamino)-*N*-methylbenzamide (24c) Under a nitrogen atmosphere, a mixture of **22c** (2.00 g, 5.24 mmol), **23** (1.61 g, 10.5 mmol), CuCl (0.52 g, 5.24 mmol), anhydrous K_2CO_3 (1.45 g, 10.5 mmol), and iso-PrOH (25 ml) was stirred for 2 h under reflux. Then CuCl (0.23 g, 2.36 mmol) was added and the resulting mixture was stirred for 12 h under reflux. The precipitated inorganic materials were removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel ($CHCl_3$: hexane = 1 : 1 then $CHCl_3$) to give **24c** (1.15 g, 54%) as a greenish solid and **21c** (0.29 g, 22%) as a pale brown solid. **24c**: mp 96.0—98.0 °C (MeOH–iso-Pr_2O–hexane). IR (KBr): 1648, 1596, 1481, 1449, 1151, 1062, 1029, 962, 926 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.76 (3H, d, J = 5 Hz, $NHCH_3$), 3.43 (3H, s, OCH_2OCH_3), 3.50 (3H, s, OCH_2OCH_3), 3.70 (6H, s, OCH_3 × 2), 4.99 (2H, s, OCH_2O), 5.24 (2H, s, OCH_2O), 5.97 (2H, d, J = 2 Hz, 2′-H and 6′-H), 6.03 (1H, dd, J = 2, 2 Hz, 4′-H), 6.96 (1H, d, J = 9 Hz, 5-H), 7.26 (1H, br s, NH), 7.58 (1H, d, J = 9 Hz, 6-H). *Anal.* Calcd for $C_{20}H_{26}N_2O_7$: C, 59.10; H, 6.45; N, 6.89. Found: C, 58.87; H, 6.44; N, 6.86.

3,4-Dibenzyloxy-2-(3,5-dimethoxyphenylamino)-*N*-methylbenzamide (25c) A solution of **24c** (3.89 g, 9.6 mmol) and 1 N HCl in MeOH (30 ml) was stirred for 1 h and the solvent was removed. A mixture of this residue, benzyl chloride (4.86 g, 38.4 mmol), and anhydrous K_2CO_3 (5.31 g, 38.4 mmol) in iso-PrOH (50 ml) was stirred for 2 h under reflux. The precipitate was removed by filtration and washed with $CHCl_3$, then the filtrate and washing were combined and concentrated. The residue was chromatographed on silica gel ($CHCl_3$: hexane = 1 : 1 then $CHCl_3$) to give **25c** (3.12 g, 65%) as pale gray needles, mp 90—93 °C (iso-Pr_2O–hexane). IR (KBr): 3268, 1593, 1474, 1449, 1283, 1193, 1148 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.73 (3H, d, J = 5 Hz, $NHCH_3$), 3.69 (6H, s, OCH_3 × 2), 4.85 (2H, s, OCH_2Ph), 5.19 (2H, s, OCH_2Ph), 5.87 (2H, d, J = 2 Hz, 2′-H and 6′-H), 6.04 (1H, dd, J = 2, 2 Hz, 4′-H), 6.38 (1H, s, NH), 6.89 (1H, d, J = 9 Hz, 5-H), 7.13—7.47 (10H, m, OCH_2Ph × 2), 7.75 (1H, d, J = 9 Hz, 6-H). *Anal.* Calcd for $C_{30}H_{30}N_2O_5 \cdot 0.2H_2O$: C, 71.75; H, 6.10; N, 5.58. Found: C, 71.66; H, 6.11; N, 5.51.

5,6-Dibenzyloxy-1,3-dimethoxy-9-(*N*-methylamino)acridine Hydrochloride (26) A mixture of **25c** (2.88 g, 5.8 mmol) and excess $POCl_3$ (15 ml) was stirred for 8 min under reflux and $POCl_3$ was removed. The residue was dissolved in $CHCl_3$–EtOH (1 : 1, 20 ml) and the solution was filtered and evaporated. The residue was dissolved in MeOH (60 ml) and 1 N aqueous HCl (20 ml), and this solution was stirred for 30 min at 60 °C. The mixture was neutralized by addition of 1 N aqueous NaOH and concentrated. The precipitate was collected by filtration and dried to give **26** (2.88 g, 96%) as a pale yellow solid, mp 179—193 °C (MeOH–iso-Pr_2O–hexane). IR (KBr): 3248, 1619, 1593, 1492, 1447, 1275, 1203, 1161, 1104 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.56 (3H, d, J = 4 Hz, $NHCH_3$), 3.93 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 5.22 (2H, s, OCH_2Ph), 5.44 (2H, s, OCH_2Ph), 6.59 (1H, d, J = 1 Hz, 2-H), 7.23—7.56 (12H, m, OCH_2Ph × 2, 4-H, 7-H), 8.21 (1H, d, J = 9 Hz, 8-H), 10.08 (1H, br m, NH), 11.78 (1H, s, HCl). HRMS m/z (M^+): Calcd for $C_{30}H_{28}N_2O_4 \cdot HCl$: 480.2047. Found: 480.2022.

10-Benzyl-5,6-dibenzyloxy-1,3-dimethoxy-9(10*H*)-acridone (27a) KOH powder (85%; 1.94 g, 29.4 mmol) was added to a solution of **26** (0.76 g, 1.47 mmol) in DMSO (15 ml) at room temperature and the mixture was stirred for 30 min. A solution of benzyl bromide (5.03 g, 29.4 mmol) in DMSO (3 ml) was added and the resulting mixture was stirred at 50 °C for 1 h. The reaction mixture was decanted into cold H_2O (20 ml), acidified with 6 N aqueous HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and brine, dried, and removed. The residue was chromatographed on silica gel (benzene then benzene : AcOEt = 1 : 1) to give **27a** (0.58 g, 71%) as a pale brown powder, mp 151—153 °C (AcOEt–iso-Pr_2O). IR (KBr): 2924, 1598, 1453, 1424, 1284, 1202, 1168, 1143, 1113, 698 cm^{-1}. ^{1}H-NMR: (400 MHz, $CDCl_3$) δ: 3.62 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.74 (2H, s, OCH_2Ph), 5.19 (2H, s, OCH_2Ph), 5.64 (2H, s, 10-CH_2Ph), 6.23 (1H, s, 2-H or 4-H), 6.24 (1H, s, 2-H or 4-H), 6.80 (2H, d, J = 7 Hz, 2-H and 6-H of 5-OCH_2Ph), 7.02—7.40 (14H, m, NCH_2Ph, 6-OCH_2Ph, 3-H—5-H of 5-OCH_2Ph, and 7-H), 8.27 (1H, d, J = 9 Hz, 8-H). *Anal.* Calcd for $C_{36}H_{31}NO_5$: C, 77.54; H, 5.60; N, 2.51. Found: C, 77.55; H, 5.53; N, 2.50.

5,6-Dibenzyloxy-1,3-dimethoxy-10-methyl-9(10*H*)-acridone (27b) The reaction was carried out in the same way as described for **27a** by using methyl iodide (15 eq for **26**) as the methylating agent. The crude product was chromatographed on silica gel (benzene and benzene : AcOEt = 1 : 1) to give **27b** (1.19 g, 76%) as a pale brown powder, mp 111.4—113.4 °C (AcOEt–iso-Pr_2O). IR (KBr): 1628, 1591, 1453, 1422, 1282, 1265, 1238, 1206, 1157, 1072, 1057 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.81 (3H, s, OCH_3 or NCH_3), 3.92 (3H, s, OCH_3 or NCH_3), 3.98 (3H, s, OCH_3 or

NCH_3), 4.91 (2H, s, $OC\underline{H}_2Ph$), 5.23 (2H, s, $OC\underline{H}_2Ph$), 6.27 (2H, s, 2-H and 4-H), 7.00 (1H, d, J=9 Hz, 7-H), 7.26—7.48 (10H, m, $OCH_2\underline{Ph}$ × 2), 8.19 (1H, d, J=9 Hz, 8-H). *Anal.* Calcd for $C_{30}H_{27}NO_5$: C, 74.50; H, 5.39; N, 3.00. Found: C, 74.43; H, 5.29; N, 2.98.

3,4-Bis(methoxymethoxy)-*N*,*N*-diethyl-2-(3,5-dimethoxyphenylamino)-benzamide (24b) *tert*-BuLi (1.71 ml, 2.1 mmol, 1.2 M solution in hexane) was added to a solution of TMEDA (0.28 g, 2.4 mmol) in anhydrous THF (30 ml) at −78 °C under a nitrogen atmosphere and the mixture was stirred for 20 min. A solution of **21b** (0.30 g, 1.0 mmol) in anhydrous THF (2 ml) was added slowly to this solution and the resulting yellow solution of the lithiated benzamide was stirred for 1 h. In a different vessel, *tert*-BuLi (5.8 ml, 6.9 mmol, 1.2 M solution in pentane) was added to a solution of **23** (0.92 g, 6.0 mmol) in anhydrous THF (20 ml) at −20 °C with stirring, then CuCN (1.08 g, 12 mmol) was added and the mixture was stirred for 1 h at room temperature. This solution was added to the previous solution at −78 °C, and then CuCN (0.54 g, 6.0 mmol) was added (the color of the solution changed to dark brown) and the mixture was stirred for 40 min at −78 °C. Oxygen gas was bubbled into this reaction mixture with stirring for 20 min at −78 °C. The color of the solution was changed to dark black. Then aqueous NH_4OH (28%, 15 ml) was added to this solution, the precipitate was removed by filtration, and the solution was concentrated. This solution was extracted with CH_2Cl_2 and the CH_2Cl_2 layer was washed with aqueous NH_4OH (28%), H_2O, and brine, dried, and removed. The residue was chromatographed on silica gel (AcOEt : benzene = 1 : 9 then iso-Pr_2O–benzene = 4 : 1) to give **24b** (0.22 g, 49%) as a black oil. IR ($CDCl_3$) δ: 3018, 1598, 1154, 1063, 666 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.92 (6H, br s, $CH_2C\underline{H}_3$ × 2), 3.19 (2H, br s, $C\underline{H}_2CH_3$), 3.35 (2H, br s, $C\underline{H}_2CH_3$), 3.43 (3H, s, $OCH_2OC\underline{H}_3$), 3.53 (3H, s, $OCH_2OC\underline{H}_3$), 3.72 (6H, s, OCH_3 × 2), 5.03 (2H, s, OCH_2O), 5.24 (2H, s, OCH_2O), 5.97 (2H, d, J=2 Hz, 2′-H and 6′-H), 5.98 (1H, dd, J=2, 2 Hz, 4′-H), 6.37 (1H, br s, NH), 6.93 (1H, d, J=9 Hz, 5-H), 7.00 (1H, d, J=9 Hz, 6-H). HRMS m/z (M^+): Calcd for $C_{23}H_{32}N_2O_7$: 448.2208. Found: 448.2232.

3,4-Dibenzyloxy-*N*,*N*-diethyl-2-(3,5-dimethoxyphenylamino)benzamide (25b) A solution of **24b** (0.21 g, 0.47 mmol) in 4 N aqueous HCl (10 ml) and EtOH (10 ml) was stirred at 45 °C for 10 min and the solvent was removed. A mixture of the residual oil, benzyl chloride (0.24 g, 1.88 mmol), and anhydrous K_2CO_3 (0.26 g, 1.88 mmol) in iso-PrOH (5 ml) was stirred under reflux for 3 h. Inorganic material was removed by filtration and solvent was removed. The residue was chromatographed on silica gel (AcOEt : benzene = 1 : 9) to give **25b** (0.17 g, 67%) as a pale brown oil. IR ($CHCl_3$): 3019, 1600, 1460, 1153, 668 cm^{-1}. ^{1}H-MMR (400 MHz, $CDCl_3$) δ: 0.80 (3H, br s, $CH_2C\underline{H}_3$), 0.93 (3H, br s, $CH_2C\underline{H}_3$), 3.12 (2H, br s, $C\underline{H}_2CH_3$), 3.26 (2H, br s, $C\underline{H}_2CH_3$), 3.71 (6H, s, OCH_3 × 2), 4.97 (2H, s, $OC\underline{H}_2Ph$), 5.16 (2H, s, $OC\underline{H}_2Ph$), 5.94 (2H, d, J=2 Hz, 2′-H and 6′-H), 5.99 (1H, dd, J=2, 2 Hz, 4′-H), 6.18 (1H, br s, NH), 6.75 (1H, d, J=8 Hz, 5-H), 7.03 (1H, d, J=8 Hz, 6-H), 7.19—7.46 (10H, m, $OCH_2\underline{Ph}$ × 2). HRMS m/z (M^+): Calcd for $C_{33}H_{36}N_2O_5$: 540.2622. Found: 540.2624.

5,6-Dibenzyloxy-1,3-dimethoxy-9(10*H*)-acridone (30) A mixture of **25b** (80 mg, 0.31 mmol) and $POCl_3$ (2 ml) was stirred for 10 min under reflux and excess $POCl_3$ was removed. EtOH (10 ml) and 1 N aqueous HCl (5 ml) were added to the residue and the mixture was stirred for 30 min at 60 °C. The aqueous layer was extracted with $CHCl_3$, and the extract was washed with H_2O and brine, and dried. The solvent was removed and the residue was chromatographed on silica gel ($CHCl_3$: MeOH = 20 : 1) to give **30** (80 mg, 55%) as a pale brown solid, mp 109—114 °C (dec.). IR (KBr): 1605, 1567, 1455, 1275, 1209, 1158, 1137, 1089 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.85 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.19 (2H, s, $OC\underline{H}_2Ph$), 5.29 (2H, s, $OC\underline{H}_2Ph$), 5.93 (1H, d, J=2 Hz, 2-H), 6.17 (1H, d, J=2 Hz, 4-H), 6.95 (1H, d, J=9 Hz, 7-H), 7.34—7.51 (10H, m, $OCH_2\underline{Ph}$ × 2), 7.89 (1H, s, NH), 8.11 (1H, d, J=9 Hz, 8-H). HRMS m/z (M^+): Calcd for $C_{29}H_{25}NO_5$: 467.1731. Found: 467.1690.

5,6-Dibenzyloxy-1,3-dimethoxy-10-methyl-9(10*H*)-acridone (27b) The reaction was carried out in the same way as described for the preparation of **27b** from **26**, using **30** as a starting material. The yield of **27b** was 76% and the product was identical with the sample obtained from **26**.

10-Benzyl-5,6-dibenzyloxy-1-hydroxy-3-methoxy-9(10*H*)-acridone (33a) Under a nitrogen atmosphere, a solution of $BF_3 \cdot Et_2O$ (0.17 g, 1.2 mmol) in dry benzene (12 ml) was added to a solution of **27a** (0.56 g, 1.0 mmol) in dry benzene (3 ml). The mixture was stirred for 2 h at room temperature then the yellow precipitate (**31a**) was collected by filtration and dried. A mixture of this powder (0.61 g), and LiBr (0.52 g, 6 mmol) in dry benzene–$CHCl_3$ (1 : 1, 30 ml) was refluxed for 15 min. Insoluble materials were removed by filtration and the solvent was removed. The residue (**32a**) was dissolved in MeOH (700 ml) and the solution was refluxed for 24 h. The solvent was removed and the residue was chromatographed on silica gel (benzene after benzene : AcOEt = 10 : 1) to give **33a** (0.38 g, 70%) as a yellow powder, mp 169—171 °C (AcOEt–hexane). IR (KBr): 1638, 1585, 1496, 1432, 1276, 1216, 1202, 1164, 1142, 1102 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.69 (3H, s, OCH_3), 4.62 (2H, s, 5-$OC\underline{H}_2Ph$), 5.23 (2H, s, 6-$OC\underline{H}_2Ph$), 5.72 (2H, s, 10-$C\underline{H}_2Ph$), 6.11 (1H, d, J=2 Hz, 4-H), 6.26 (1H, d, J=2 Hz, 2-H), 6.66 (2H, d, J=7 Hz, 2-H and 6-H of 5-$OCH_2\underline{Ph}$), 7.04 (2H, dd, J=7, 7 Hz, 3-H and 5-H of 5-$OCH_2\underline{Ph}$), 7.11 (1H, d, J=9 Hz, 7-H), 7.14—7.16 (3H, m, 2-H and 6-H of 10-$CH_2\underline{Ph}$ and 4-H of 5-$OCH_2\underline{Ph}$), 7.23—7.30 (3H, m, 3-H—5-H of 10-$CH_2\underline{Ph}$), 7.35—7.36 (3H, m, 3-H—5-H of 6-$OCH_2\underline{Ph}$), 7.40—7.43 (2H, m, 2-H and 6-H of 6-$OCH_2\underline{Ph}$), 8.30 (1H, d, J=9 Hz, 8-H), 14.68 (1H, s, OH). *Anal.* Calcd for $C_{35}H_{29}NO_5 \cdot 0.2H_2O$: C, 76.82; H, 5.42; N, 2.56. Found: C, 76.91; H, 5.32; N, 2.54.

5,6-Dibenzyloxy-1-hydroxy-3-methoxy-10-methyl-9(10*H*)-acridone (33b) Under a nitrogen atmosphere, a solution of $BF_3 \cdot Et_2O$ (0.39 g, 0.80 mmol) in dry benzene (13 ml) was added to a solution of **27b** (0.56 g, 1.0 mmol) in dry benzene (3 ml). The mixture was stirred for 2 h at room temperature, then the yellow precipitate was collected by filtration to give **31b**. A mixture of part of this powder (55 mg, 0.1 mmol) and LiBr (87 mg, 1 mmol) in dry benzene–$CHCl_3$ (1 : 1, 6 ml) was refluxed for 15 min, then insoluble materials were removed by filtration and the solvent was evaporated off. The residue was chromatographed on silica gel (benzene then benzene : AcOEt = 10 : 1) to give **32b** (50.5 mg, 98%) as yellow needles. A mixture of the crystals (50.5 mg, 0.098 mmol) and NaOMe (52 mg, 0.98 mmol) in dry MeOH (100 ml) was refluxed for 2 h. Then three drops of acetic acid were added, and the reaction mixture was refluxed for 5 min. The solvent was removed and the residue was chromatographed on silica gel (benzene then benzene : AcOEt = 10 : 1) to give **33b** (41.0 mg, 89%) as a yellow powder.

31b: mp 165 °C (dec.). IR (KBr): 1626, 1607, 1469, 1275, 1219, 1074 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.82 (3H, s, OCH_3 or NCH_3), 3.82 (3H, s, OCH_3 or NCH_3), 3.92 (3H, s, OCH_3 or NCH_3), 4.89 (2H, s, $OC\underline{H}_2Ph$), 5.28 (2H, s, $OC\underline{H}_2Ph$), 6.36 (1H, d, J=2 Hz, 4-H), 6.51 (1H, d, J=2 Hz, 2-H), 7.21 (1H, d, J=9 Hz, 7-H), 7.27—7.54 (10H, m, $OCH_2\underline{Ph}$ × 2), 7.89 (1H, d, J=9 Hz, 8-H).

32b: mp 240 °C (dec.). IR (KBr): 1633, 1584, 1270, 1214, 1073, 1037 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 4.01 (3H, s, OCH_3 or NCH_3), 4.18 (3H, s, OCH_3 or NCH_3), 4.96 (2H, s, $OC\underline{H}_2Ph$), 5.45 (2H, s, $OC\underline{H}_2Ph$), 6.51 (1H, d, J=2 Hz, 4-H), 6.71 (1H, d, J=2 Hz, 2-H), 7.27—7.59 (10H, m, $OCH_2\underline{Ph}$ × 2), 7.68 (1H, d, J=9 Hz, 7-H), 8.28 (1H, d, J=9 Hz, 8-H).

33b: mp 155—156 °C (AcOEt–hexane). IR (KBr): 1639, 1591, 1443, 1331, 1271, 1235, 1204, 1188, 1151, 1134, 806, 736 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.87 (3H, s, OCH_3 or NCH_3), 3.89 (3H, s, OCH_3 or NCH_3), 4.89 (2H, s, $OC\underline{H}_2Ph$), 5.26 (2H, s, $OC\underline{H}_2Ph$), 6.19 (1H, d, J=2 Hz, 4-H), 6.28 (1H, d, J=2 Hz, 2-H), 6.61 (1H, d, J=9 Hz, 7-H), 7.26—7.49 (10H, m, $OCH_2\underline{Ph}$ × 2), 8.20 (1H, d, J=9 Hz, 8-H), 14.5 (1H, s, 1-OH). *Anal.* Calcd for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.39; N, 3.00. Found: C, 74.47; H, 5.38; N, 2.95.

One-Pot Procedure Under a nitrogen atmosphere, a solution of $BF_3 \cdot Et_2O$ (45 mg, 3.2 mmol) in dry benzene (2 ml) was added to a solution of **27b** (144 mg, 0.30 mmol) in dry benzene (5 ml) and the mixture was stirred for 1.5 h at room temperature. A yellow powder (**31b**) was precipitated. LiBr (261 mg, 30 mmol), dry benzene (8 ml), and $CHCl_3$ (15 ml) were added to this reaction mixture and the mixture was refluxed for 15 min. LiBr was removed by decantation and the solvent was evaporated off. A mixture of this residue (**32b**) and NaOMe (0.162 g, 3 mmol) in MeOH (100 ml) was refluxed for 2 h and, after addition of acetic acid (0.5 ml), additionally refluxed for 5 min. The solvent was removed and the residue was chromatographed on silica gel to give **33b** (132 mg, 94%).

1,5,6-Trihydroxy-3-methoxy-9(10*H*)-acridone (2a) A suspension of Pd black (50 mg) was suspended in dry MeOH–acetone (1 : 1, 30 ml) was stirred for 10 min under hydrogen, then a solution of **33a** (0.29 g, 0.53 mmol) in dry MeOH–acetone (1 : 1, 70 ml) was added and the mixture wsa stirred at 40 °C for 2 h under hydrogen. The Pd black was removed by filtration and the solvent was evaporated off. The residue was recrystallized from acetone–MeOH to afford **2b** (0.126 g, 87%) as a pale yellow powder, mp 290 °C (dec.) (acetone–MeOH). IR (KBr): 3377, 1648, 1589, 1324, 1286, 1230 cm^{-1}. ^{1}H-NMR (400 MHz, acetone-d_6) δ: 3.87 (3H, s, OCH_3), 5.5 (2H, br s, 5-OH and 6-OH), 6.11 (1H, d, J=2 Hz, 4-H), 6.80 (1H, d, J=2 Hz, 2-H), 6.89 (1H, d, J=9 Hz, 7-H), 7.70 (1H, d, J=9 Hz, 8-H), 10.15 (1H, s, NH), 14.45 (1H, s, 1-OH). *Anal.* Calcd for $C_{14}H_{11}NO_5 \cdot 1/3H_2O$: C, 60.22; H, 4.21, N, 5.02. Found: C, 60.40; H, 4.14; N, 4.82.

1,5,6-Trihydroxy-3-methoxy-10-methyl-9(10*H*)-acridone (2b) The reaction was carried out in the same manner as described for the preparation

of **2a** from **33a** using **33b** as the starting material to give **2b** (0.31 g, 90%) as a pale yellow powder, mp 245—248 °C (acetone–MeOH). IR (KBr): 3260, 1628, 1586, 1561, 1328, 1280, 1228 cm^{-1}. ^1H-NMR (400 MHz, acetone-d_6) δ: 3.94 (3H, s, OCH_3 or NCH_3), 4.11 (3H, s, OCH_3 or NCH_3), 6.19 (1H, d, $J=2$ Hz, 4-H), 6.45 (1H, d, $J=2$ Hz, 2-H), 6.98 (1H, d, $J=9$ Hz, 7-H), 7.17 (1H, d, $J=9$ Hz, 8-H), 7.89 (1H, br s, 5-OH or 6-OH), 9.58 (1H, br s, 5-OH or 6-OH), 14.83 (1H, s, 1-OH). HRMS m/z (M^+): Calcd for $C_{15}H_{13}NO_5$: 287.0793. Found: 287.0775.

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