Pergamon

Tetrahedron, Vol. 53, No. 50, pp. 17029-17038, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10153-3

Synthetic Studies on Pentacyclic Aromatic Alkaloids, Kuanoniamine A, 11-Hydroxyascididemin, and Neocalliactine Acetate

Yoshiyasu Kitahara, Shinsuke Nakahara, Takanobu Yonezawa, Masanori Nagatsu, Yoshikazu Shibano, and Akinori Kubo*

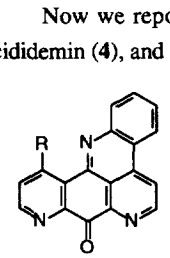
Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

Abstract: A pentacyclic aromatic alkaloid, kuanoniamine A (**6**) was synthesized in three steps from 6-methoxybenzothiazole-4,7-dione (**8**) and 2-aminoacetophenone (**9**). 11-Hydroxyascididemin (**4**) was prepared from 5,8-quinolinedione (**13**, **14**) or 1,4-acridinedione (**20**). The structure of neocalliactine acetate, a derivative of calliactine, was determined to be **5** by total synthesis from 6-methoxy-5,8-quinolinedione (**28**) and 2-amino-5-methoxyacetophenone (**29**). © 1997 Elsevier Science Ltd.

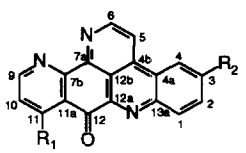
A series of structurally related polycyclic aromatic alkaloids has been isolated from marine organisms.[1] Meridine was isolated from an ascidian *Amphicarpa meridiana* and the structure was determined by X-ray analysis to be 12-hydroxybenzo[*b*]pyrido[4,3,2-*de*][1,7]phenanthrolin-8(8*H*)-one (**1**).[1c] 11-Hydroxyascididemin was obtained from another ascidian a *Leptoclinides* sp. and the structure was estimated by comparison of the ^{1}H- and ^{13}C-NMR spectral data of the alkaloid and ascididemin (**3**)[1d] to be an isomer of meridine (**1**), *i.e.* 10-hydroxyquino[4,3,2-*de*][1,10]phenanthrolin-9(9*H*)-one (**4**).[1c] The alkaloids, **1** and **4**, exhibit cytotoxicity to murine leukemia cells (P388).[1c] Recently cystodamine (**2**) possessing the same skeletone as meridine (**1**) was isolated from a Mediterranean ascidian *Cystodytes delle chiajei* (Polycitoridae).[1e] Kuanoniamine A was isolated from a Micronesian tunicate and its predator, a prosobranch mollusk, *Chelynotus semperi* and the structure was estimated by extensive ^{1}H- and ^{13}C-NMR analysis and correlations to be **6** containing a thiazole ring.[1f]

The structure of neocalliactine acetate obtained as a derivative of calliactine isolated from a sea anemone, *Calliactis parasitica*,[2] was reexamined by Schmitz *et al.* They compared ^{13}C-NMR spectral data of neocalliactine acetate with those of meridine (**1**) and ascididemin (**3**), chose structures **5** and **7** from four proposed structures,[2a] and slightly preferred **5** which has the overall skeletal outline of ascididemin (**3**).[1c]

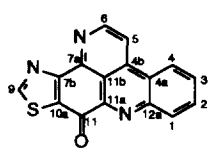
Now we report the synthetic details[3] of pentacyclic alkaloids, kuanoniamine A (**6**) and 11-hydroxyascididemin (**4**), and structure determination of neocalliactine acetate by direct synthesis.



1: R = OH
2: R = NH_2



3: $R_1 = R_2 = H$
4: $R_1 = OH$, $R_2 = H$
5: $R_1 = H$, $R_2 = OCOCH_3$



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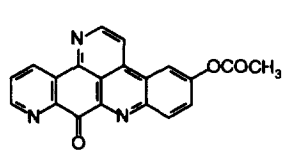

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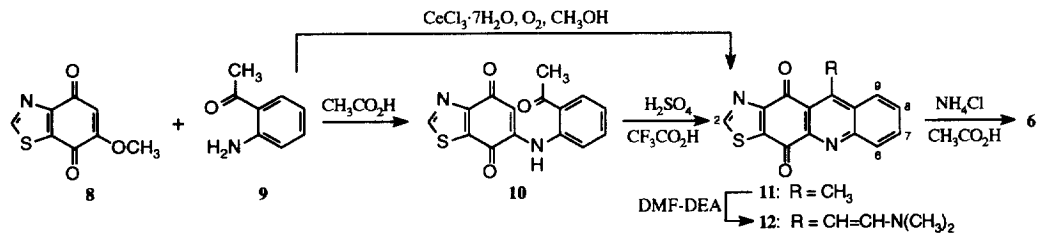
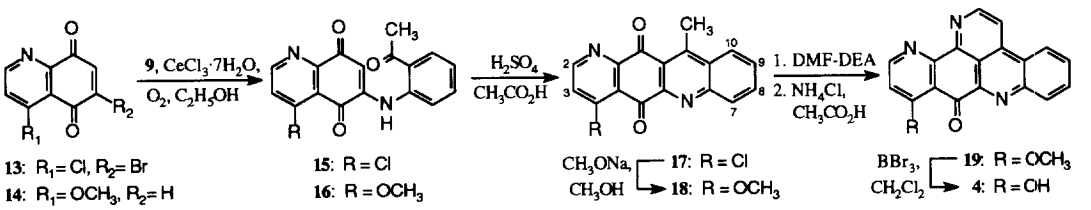
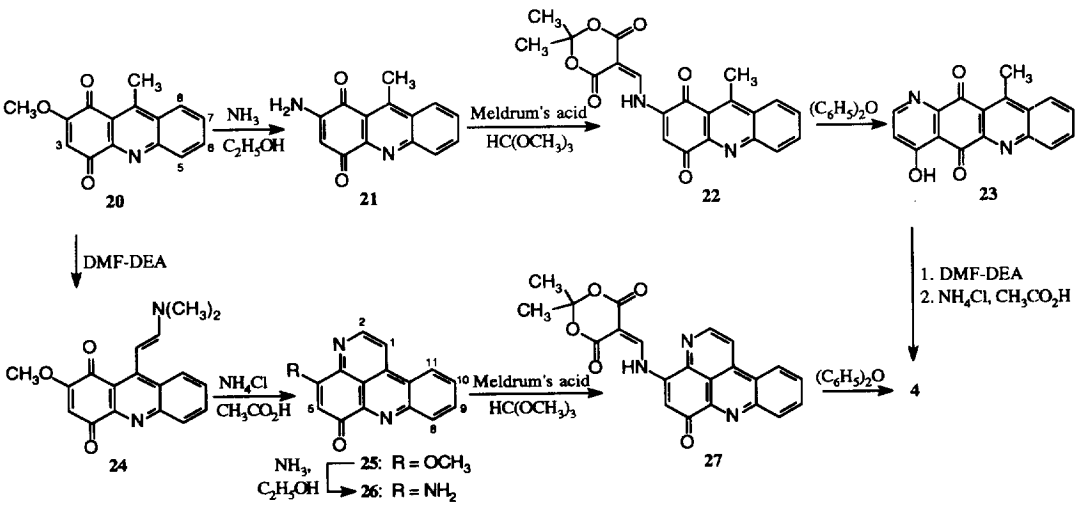
We first synthesized kuanoniamine A (**6**). 6-Methoxybenzothiazole-4,7-dione (**8**)[4] prepared from 6-methoxybenzothiazole, was treated with 2-aminoacetophenone (**9**) in refluxing acetic acid to give **10** in 39% yield. The anilinoquinone (**10**) was refluxed with sulfuric acid–trifluoroacetic acid (1:10) to furnish **11** in 30% yield. When **8** was refluxed with **9** in methanol containing cerium(III) chloride[5] under air, the cyclization product (**11**) was directly obtained in 73% yield. The tetracyclic quinone (**11**) was heated with *N*,*N*-dimethylformamide diethylacetal (DMF-DEA) in *N*,*N*-dimethylformamide (DMF)[6] at 100°C to give **12**. Treatment of **12** with ammonium chloride in acetic acid[6] at 100°C furnished the pentacyclic iminoquinolinequinone (**6**) in 56% yield from **11**. The spectral data of synthetic iminoquinolinequinone (**6**) and kuanoniamine A obtained from the natural resources were identical.



Next, we synthesized 11-hydroxyascididemin (**4**). 6-Bromo-4-chloro-5,8-quinolinedione (**13**) obtained by oxidative demethylation of 6-bromo-4-chloro-5,8-dimethoxyquinoline[7] with cerium(IV) ammonium nitrate (CAN), was condensed with 2-aminoacetophenone (**9**) in ethanol containing cerium(III) chloride under air to give **15** in 74% yield. The cyclization of **15** with sulfuric acid in acetic acid gave tetracyclic quinone (**17**) in 69% yield. When **17** was treated with sodium methoxide in methanol, the chlorine atom in **17** was substituted by

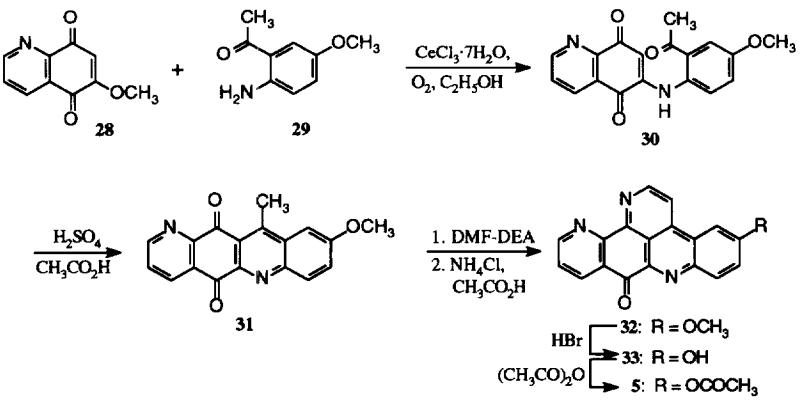




methoxyl group to give **18** in quantitative yield. Alternatively, methoxyquinone (**18**) was obtained from 4-methoxy-5,8-quinolinedione (**14**)[8] *via* **16**. Treatment of **18** with DMF-DEA in DMF followed by ammonium chloride in acetic acid furnished the pentacyclic iminoquinolinequinone (**19**) in 73% yield. The methyl ether in **19** was cleaved with boron tribromide in dichloromethane to furnish **4** in 56% yield. The spectral data of synthetic **4** and 11-hydroxyascididemin obtained from the natural resource were identical.

The iminoquinone (**4**) was synthesized by thermal cyclization[9] of a Meldrum's acid derivative of quinone (**22**). 2-Amino-9-methyl-1,4-acridinedione (**21**) prepared from **20**,[10] was treated with Meldrum's acid in trimethyl orthoformate to give **22** in 20% yield. Thermal cyclization of **22** in diphenyl ether afforded tetracyclic quinone (**23**), which was treated with DMF-DEA in DMF followed by ammonium chloride in acetic acid to furnish **4**. The hydroxyquinone (**23**) was also obtained by reaction of chloroquinone (**17**) with sodium acetate in acetic acid (92% yield). Alternatively, **4** was prepared *via* a Meldrum's acid derivative of iminoquinoline-quinone (**27**) in better yield. 4-Methoxybenzo[*de*][3,6]phenanthrolin-6(6*H*)-one (**25**) obtained from **20** *via* **24** was treated with ammonia in ethanol followed by Meldrum's acid in trimethyl orthoformate to give **27**. The iminoquinolinequinone (**27**) was cyclized in diphenyl ether to furnish **4** in 80% yield.

Finally, we determined the structure of neocalliactine acetate by unambiguous total synthesis. Treatment of 6-methoxy-5,8-quinolinedione (**28**)[11] with 2-amino-5-methoxyacetophenone (**29**, prepared from 3-hydroxy-acetophenone)[12] in ethanol containing cerium(III) chloride under air gave **30** in 53% yield. The anilinoquinone (**30**) was heated with concentrated sulfuric acid in acetic acid to give the cyclization product (**31**) in 94% yield. Treatment of **31** with DMF-DEA in DMF followed by ammonium chloride in acetic acid furnished **32** in 64% yield. The methyl ether (**32**) was refluxed in 48% hydrobromic acid to give **33**. The acetylation of phenol (**33**) with acetic anhydride in pyridine furnished the acetate (**5**) in 39% yield from **32**. The spectral data of synthetic acetate (**5**) and neocalliactine acetate were completely identical. Thus, we determined the structure of neocalliactine acetate to be **5**, *i.e.* 3-acetoxyascididemin.



EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^1H- and ^{13}C-NMR spectra were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ (unless otherwise noted) with tetramethylsilane as an internal standard. Assignments of ^{13}C-NMR spectral data for 11-hydroxy-ascididemin (**4**), kuanoniamine A (**6**), and neocalliactine acetate (**5**) were aided by direct and long-range C-H correlations (HMQC and HMBC experiments). All reactions were run with magnetic stirring. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed with a rotary

evaporator and finally under high vacuum. Column chromatography (flash chromatography) was performed with silica gel 60 (230–400 mesh).

6-Methoxybenzothiazole 2-Amino-6-methoxybenzothiazole (0.90 g, 5 mmol) in tetrahydrofuran (10 ml) was added dropwise to a refluxing solution of pentyl nitrite[13] (1.17 g, 10 mmol) in tetrahydrofuran (20 ml). The solution was refluxed for 3 h, and then the solvent and pentanol were evaporated. The residue was chromatographed (eluting with $CHCl_3$). The crude compound (6-methoxybenzothiazole) was recrystallized from ether–hexane. Yield 0.55 g (67%). mp 70–71.5°C (lit.,[4] mp 69.5–71°C). MS *m/z* (%): 165 (M^+, 100), 150 (53), 122 (32). ^{1}H-NMR δ: 3.89 (3H, s, OCH_3), 7.13 (1H, dd, J = 8.9, 2.6 Hz, C_5-H), 7.40 (1H, d, J = 2.6 Hz, C_7-H), 8.01 (1H, d, J = 8.9 Hz, C_4-H), 8.83 (1H, s, C_2-H). 6-Methoxybenzothiazole-4,7-dione (**8**) was obtained from 6-methoxybenzothiazole as the reported method.[4]

6-(2'-Acetylphenylamino)benzothiazole-4,7-dione (10) A solution of **8** (1.15 g, 5.9 mmol) and 2-aminoacetophenone (**9**) (1.59 g, 11.8 mmol) in acetic acid (15 ml) was refluxed for 2.5 h. The reaction mixture was cooled, diluted with water (200 ml), neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 200 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–methanol, 99:1) to afford **10** (0.68 g, 39%). mp 200°C (violet needles from ethyl acetate–hexane). MS *m/z* (%): 298 (M^+, 100), 280 (87), 269 (28), 256 (65). High-resolution MS Calcd for $C_{15}H_{10}N_2O_3S$: 298.0412. Found: 298.0416. IR (KBr): 1674, 1654, 1636 cm^{-1} (C=O). ^{1}H-NMR δ: 2.70 (3H, s, $COCH_3$), 6.62 (1H, s, C_5-H), 7.2–8.0 (4H, m, C_6H_4-$COCH_3$), 9.16 (1H, s, C_2-H), 11.28 (1H, br, NH).

10-Methylacridino[2,3-*d*]thiazole-4,11-dione (11) (a) A solution of **10** (680 mg, 2.28 mmol) in CF_3CO_2H–H_2SO_4 (10:1, 27.5 ml) was refluxed for 75 min. The reaction mixture was cooled, diluted with water (300 ml), and extracted with CH_2Cl_2 (3 x 300 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–acetone, 19:1) to afford **11** (190 mg, 30%). mp 280–281°C (yellow powder from $CHCl_3$). MS *m/z* (%): 280 (M^+, 100), 252 (26), 224 (15). High-resolution MS Calcd for $C_{15}H_8N_2O_2S$: 280.0306. Found: 280.0305. IR (KBr): 1674 cm^{-1} (C=O). ^{1}H-NMR δ: 3.36 (3H, s, CH_3), 7.82 (1H, ddd, J = 8.6, 6.9, 1.3 Hz, C_8-H), 7.96 (1H, ddd, J = 8.6, 6.9, 1.3 Hz, C_7-H), 8.41 (1H, dd, J = 8.6, 1.3 Hz, C_9-H), 8.47 (1H, dd, J = 8.6, 1.3 Hz, C_6-H), 9.23 (1H, s, C_2-H).

(b) A mixture of **8** (72 mg, 0.37 mmol), $CeCl_3 \cdot 7H_2O$ (138 mg, 0.37 mmol), and methanol (4 ml) was refluxed for 30 min. 2-Aminoacetophenone (**9**) (50 mg, 0.37 mmol) was added to the mixture, and the whole was refluxed for 18 h. The reaction mixture was cooled, diluted with water (15 ml), and extracted with CH_2Cl_2 (3 x 20 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–ethyl acetate, 4:1) to afford **11** (75 mg, 73%).

Kuanoniamine A (6) DMF-DEA (20 mg, 0.14 mmol) was added to a suspension of **11** (28 mg, 0.1 mmol) in DMF (2 ml), and the resulting mixture was heated at 100°C for 30 min under nitrogen. Ammonium chloride (3.0 g) and acetic acid (10 ml) were added, and the whole was heated at 100°C for 30 min. The reaction mixture was cooled, diluted with water (30 ml), and extracted with CH_2Cl_2 (3 x 40 ml). The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–ethyl acetate, 2:1) to afford **6** (16 mg, 56%). mp 258–259°C (decomp.) (yellow powder from $CHCl_3$) (lit.,[1f] mp 255–258°C (decomp.)). MS *m/z* (%): 289 (M^+, 92), 261 (100), 234 (23), 190 (20). *Anal.* Calcd for $C_{16}H_7N_3OS \cdot H_2O$: C, 62.53; H, 2.95; N, 13.67. Found: C, 62.43; H, 2.65; N, 13.45. IR (KBr): 1664 cm^{-1} (C=O). ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.05 (1H, ddd, J = 8.2, 7.9, 1.2 Hz, C_3-H), 8.10 (1H, ddd, J = 8.2, 7.9, 1.2 Hz, C_2-H), 8.46 (1H, dd, J = 8.2, 1.2 Hz, C_1-H), 8.91 (1H, d, J = 5.5 Hz, C_5-H), 9.03 (1H, dd, J = 8.2, 1.2 Hz, C_4-H), 9.14 (1H, d, J = 5.5 Hz, C_6-H), 9.71 (1H,

s, C_9-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 116.64 (C_{12b}), 117.28 (C_5), 123.09 (C_{4a}), 124.09 (C_4), 131.02 (C_3), 131.99 (C_1 or C_2), 132.04 (C_2 or C_1), 136.10 (C_{10a}), 137.25 (C_{4b}), 144.91 (C_{12a}), 147.15 (C_{7a}), 147.30 (C_{11a}), 149.05 (C_6), 157.87 (C_{7b}), 162.71 (C_9), 176.20 (C_{11}).

6-Bromo-4-chloro-5,8-quinolinedione (13) A solution of CAN (3.62 g, 6.6 mmol) in water (16 ml) was added dropwise to 6-bromo-4-chloro-5,8-dimethoxyquinoline (200 mg, 0.66 mmol) dissolved in acetonitrile (24 ml) at 0–5°C. The mixture was stirred at 0–5°C for 1 h, diluted with water (200 ml), and extracted with CH_2Cl_2 (3 x 200 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 99:1) to afford **13** (136 mg, 76%). mp 175–177°C (yellow needles from $CHCl_3$). MS *m/z* (%): 275 (M^++4, 27), 273 (M^++2, 100), 271 (M^+, 76), 247 (20), 245 (76), 243 (59). *Anal.* Calcd for $C_9H_3BrClNO_2$: C, 39.67; H, 1.11; N, 5.14. Found: C, 39.72; H, 1.11; N, 5.13. IR (KBr): 1664 cm^{-1} (C=O). ^{1}H-NMR δ: 7.68 (1H, s, C_7-H), 7.73 (1H, d, J = 5.3 Hz, C_3-H), 8.89 (1H, d, J = 5.3 Hz, C_2-H).

6-(2'-Acetylphenylamino)-4-chloro-5,8-quinolinedione (15) A mixture of **13** (54 mg, 0.20 mmol), $CeCl_3 \cdot 7H_2O$ (78 mg, 0.21 mmol), 2-aminoacetophenone (**9**) (28 mg, 0.21 mmol), and ethanol (18 ml) was stirred at 25°C for 4 h. The reaction mixture was diluted with water (40 ml) and extracted with $CHCl_3$ (3 x 15 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate) to afford **15** (48 mg, 74% yield). mp >250°C (decomp.) (red powder from $CHCl_3$-hexane). MS *m/z* (%): 328 (M^++2, 47), 326 (M^+, 100), 284 (38), 186 (44). *Anal.* Calcd for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.24; H, 3.38; N, 8.61. IR (KBr): 1678, 1640 cm^{-1} (C=O). ^{1}H-NMR δ: 2.71 (3H, s, CH_3), 6.91 (1H, s, C_7-H), 7.2–7.7 (3H, m, $C_{4'}$-H, $C_{5'}$-H, $C_{6'}$-H), 7.64 (1H, d, J = 5.3 Hz, C_3-H), 7.98 (1H, dd, J = 7.9, 1.3 Hz, $C_{3'}$-H), 8.86 (1H, d, J = 5.3 Hz, C_2-H), 11.38 (1H, br, NH).

6-(2'-Acetylphenylamino)-4-methoxy-5,8-quinolinedione (16) A mixture of 4-methoxy-5,8-quinolinedione (**14**) (648 mg, 3.43 mmol), $CeCl_3 \cdot 7H_2O$ (1.28 g, 3.43 mmol), **9** (509 mg, 3.77 mmol), and ethanol (50 ml) was stirred at 25°C for 1 h. The reaction mixture was diluted with water (150 ml) and extracted with $CHCl_3$ (3 x 200 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 100:1 – 50:1) to afford **16** (445 mg, 40%). mp 238–245°C (decomp.) (orange needles from CH_2Cl_2). MS *m/z* (%): 322 (M^+, 100), 304 (72), 293 (23), 279 (51), 186 (42). *Anal.* Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.75; H, 4.39; N, 8.47. IR (KBr): 1658, 1638 cm^{-1} (C=O). ^{1}H-NMR δ: 2.68 (3H, s, CH_3), 4.10 (3H, s, OCH_3), 6.84 (1H, s, C_7-H), 7.12 (1H, d, J = 5.9 Hz, C_3-H), 7.20 (1H, ddd, J = 7.9, 6.9, 1.3 Hz, $C_{4'}$-H), 7.57 (1H, ddd, J = 8.3, 6.9, 1.7 Hz, $C_{5'}$-H), 7.64 (1H, dd, J = 8.3, 1.3 Hz, $C_{6'}$-H), 7.96 (1H, dd, J = 7.9, 1.7 Hz, $C_{3'}$-H), 8.84 (1H, d, J = 5.9 Hz, C_2-H), 11.28 (1H, br, NH).

4-Chloro-11-methylpyrido[2,3-*b*]acridine-5,12-dione (17) A solution of **15** (131 mg, 0.4 mmol) in CH_3CO_2H–H_2SO_4 (10:1, 1.6 ml) was heated at 62–63°C for 1 h. The reaction mixture was cooled, diluted with water (30 ml), neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 20 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate–$CHCl_3$, 10:1) to afford **17** (85 mg, 69%). mp >250°C (decomp.) (yellow needles from $CHCl_3$–ether). MS *m/z* (%): 310 (M^++2, 36), 308 (M^+, 100), 282 (17), 280 (49). *Anal.* Calcd for $C_{17}H_9ClN_2O_2$: C, 66.14; H, 2.94; N, 9.07. Found: C, 65.98; H, 2.98; N, 8.82. IR (KBr): 1690 cm^{-1} (C=O). ^{1}H-NMR δ: 3.31 (3H, s, CH_3), 7.76 (1H, d, J = 5.0 Hz, C_3-H), 7.81 (1H, ddd, J = 8.2, 6.9, 1.3 Hz, C_9-H), 7.96 (1H, ddd, J = 8.2, 6.9, 1.3 Hz, C_8-H), 8.39 (1H, dd, J = 8.2, 1.3 Hz, C_{10}-H), 8.46 (1H, dd, J = 8.2, 1.3 Hz, C_7-H), 8.95 (1H, d, J = 5.0 Hz, C_2-H).

4-Methoxy-11-methylpyrido[2,3-*b*]acridine-5,12-dione (18) (a) A solution of **16** (440 mg, 1.37 mmol) in CH_3CO_2H–H_2SO_4 (10:1, 55 ml) was heated at 90°C for 30 min. The reaction mixture was cooled, diluted with water (100 ml), and extracted with CH_2Cl_2 (3 x 50 ml). The extract was washed with 5% $NaHCO_3$ solution and brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–methanol, 100:1–50:1) to afford **18** (230 mg, 55%). mp 260–265°C (decomp.) (yellow needles from $CHCl_3$). MS *m/z* (%): 304 (M^+, 100), 275 (37), 261 (15). *Anal.* Calcd for $C_{18}H_{12}N_2O_3 \cdot 1/2H_2O$: C, 69.00; H, 4.18; N, 8.94. Found: C, 68.88; H, 4.01; N, 8.85. IR (KBr): 1684 cm^{-1} (C=O). ^{1}H-NMR δ: 3.29 (3H, s, CH_3), 4.13 (3H, s, OCH_3), 7.20 (1H, d, J = 5.9 Hz, C_3-H), 7.78 (1H, ddd, J = 8.3, 6.9, 1.3 Hz, C_9-H), 7.92 (1H, ddd, J = 8.3, 6.9, 1.3 Hz, C_8-H), 8.36 (1H, dd, J = 8.3, 1.3 Hz, C_{10}-H), 8.44 (1H, dd, J = 8.3, 1.3 Hz, C_7-H), 8.92 (1H, d, J = 5.9 Hz, C_2-H).

(b) A solution of 28% sodium methoxide in methanol (1.5 ml) was added to **17** (31 mg, 0.1 mmol) in methanol (150 ml). The whole was stirred at 25°C for 30 min, diluted with water (150 ml), and extracted with $CHCl_3$ (3 x 50 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 50:1) to afford **18** (30 mg, 98%).

11-Methoxyascididemin (19) DMF-DEA (220 mg, 1.5 mmol) was added to a suspension of **18** (90 mg, 0.3 mmol) in DMF (3 ml), and the resulting mixture was heated at 110°C for 15 min under nitrogen. Ammonium chloride (300 mg) and acetic acid (1 ml) were added, and the whole was heated at 110°C for 1 h. The reaction mixture was cooled, diluted with water (20 ml), basified with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 50 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 20:1 – 10:1) to afford **19** (68 mg, 73%). mp 270–272°C (decomp.) (yellow powder from CH_2Cl_2–ether). MS *m/z* (%): 313 (M^+, 100), 284 (32), 255 (32). High-resolution MS Calcd for $C_{19}H_{11}N_3O_2$: 313.0851. Found: 313.0860. IR (KBr): 1662 cm^{-1} (C=O). ^{1}H-NMR δ: 4.16 (3H, s, OCH_3), 7.16 (1H, d, J = 5.9 Hz, C_{10}-H), 7.92 (1H, ddd, J = 8.3, 6.9, 1.3 Hz, C_3-H), 8.01 (1H, ddd, J = 8.3, 6.9, 1.3 Hz, C_2-H), 8.54 (1H, d, J = 5.9 Hz, C_5-H), 8.63 (1H, dd, J = 8.3, 1.3 Hz, C_1-H), 8.68 (1H, dd, J = 8.3, 1.3 Hz, C_4-H), 8.98 (1H, d, J = 5.9 Hz, C_9-H), 9.29 (1H, d, J = 5.9 Hz, C_6-H).

2-Amino-9-methylacridine-1,4-dione (21) (a) Ammonia solution (28% in water, 1.9 ml) was added to a solution of 2-methoxy-9-methylacridine-1,4-dione (**20**) (51 mg, 0.2 mmol) in ethanol (10 ml). The whole was heated at 80°C for 3 h, and then evaporated to dryness. The residue was chromatographed (eluting with $CHCl_3$–methanol, 10:1) to afford **21** (21 mg, 44%). mp 245–247°C (decomp.) (dark yellow powder). MS *m/z* (%): 238 (M^+, 100), 210 (72), 182 (33). High-resolution MS Calcd for $C_{14}H_{10}N_2O_2$: 238.0742. Found: 238.0742. IR (KBr): 3440, 3196 cm^{-1} (NH_2); 1730, 1672 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 3.20 (3H, s, CH_3), 6.24 (1H, s, C_3-H), 7.73, 7.89 (each 1H, ddd, J = 8.3, 6.9, 1.3 Hz, C_6-H, C_7-H), 8.31, 8.39 (each 1H, dd, J = 8.3, 1.3 Hz, C_5-H, C_8-H).

(b) Ammonia solution (saturated in methanol, 2.0 ml) was added to **20** (51 mg, 0.2 mmol). The resulting solution was heated at 60°C for 30 min, and then evaporated to dryness. The residue was chromatographed (eluting with $CHCl_3$–methanol, 20:1) to afford **21** (16 mg, 34%).

2,2-Dimethyl-5-[[(9-methyl-1,4-dioxo-1,4-dihydroacridyn-2-yl)amino]methylidene]-1,3-dioxane-4,6-dione (22) A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, 29 mg, 0.2 mmol) and trimethyl orthoformate (1 ml) was refluxed for 2 h, and then a solution of **21** (48 mg, 0.2 mmol) in trimethyl orthoformate (4 ml) was added. The whole was refluxed for 70 min, and then evaporated. The residue was chromatographed (eluting with ethyl acetate–CH_2Cl_2, 2:1) to afford **22** (16 mg, 20%). mp 256–259°C (decomp.) (yellow powder from $CHCl_3$–ether). MS *m/z* (%): 392 (M^+, 11), 34 (100), 288 (20). High-

resolution MS Calcd for $C_{21}H_{16}N_2O_6$: 392.1008. Found: 392.1011. IR (KBr): 1732, 1688, 1666 cm^{-1} (C=O). ^{1}H-NMR δ: 1.79 (6H, s, $C(CH_3)_2$), 3.29 (3H, s, Ar-CH_3), 6.98 (1H, C_3-H), 7.81 (1H, ddd, J = 8.6, 6.9, 1.3 Hz, C_7-H), 7.97 (1H, ddd, J = 8.6, 6.9, 1.3 Hz, C_6-H), 8.39 (1H, dd, J = 8.6, 1.3 Hz, C_8-H), 8.46 (1H, dd, J = 8.6, 1.3 Hz, C_5-H), 8.57 (1H, d, J = 13.9 Hz, =CH–N), 11.73 (1H, d, J = 13.9 Hz, NH).

4-Hydroxy-11-methylpyrido[2,3-*b*]acridine-5,12-dione (23) (a) A mixture of **17** (401 mg, 1.3 mmol), acetic acid (22 ml), and sodium acetate (1.1 g) was heated at 90°C for 6.5 h. The reaction mixture was cooled and diluted with water (100 ml). The precipitated crystals were collected by filtration, washed with water, and dried to afford **23** (346 mg, 92%) as a yellow solid, which was used without further purification. mp >300°C. MS *m/z* (%): 290 (M^+, 100), 262 (18). High-resolution MS Calcd for $C_{17}H_{10}N_2O_3$: 290.0691. Found: 290.0691. IR (KBr): 1684, 1630 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$–CF_3CO_2D) δ: 3.54 (3H, s, CH_3), 7.70 (1H, d, J = 6.9 Hz, C_3-H), 8.21, 8.39 (each 1H, dd, J = 8.9, 7.6 Hz, C_8-H, C_9-H), 8.62, 8.73 (each 1H, d, J = 8.9 Hz, C_7-H, C_{10}-H), 8.91 (1H, d, J = 6.9 Hz, C_2-H).

(b) A mixture of **22** (10 mg, 0.025 mmol) and diphenyl ether (2 ml) was heated at 190°C for 1 h. After cooling the mixture was chromatographed. Elution with hexane was discarded, and further elution with $CHCl_3$–methanol (9:1–4:1) afforded **23** (4.2 mg, 57%) as a yellow solid.

4-Methoxybenzo[*de*][3,6]phenanthrolin-6(6*H*)-one (25) (a) DMF-DEA (113 mg, 0.77 mmol) was added to a suspension of **20** (51 mg, 0.2 mmol) in dry DMF (0.9 ml), and the resulting mixture was heated at 120°C for 20 min under nitrogen. Ammonium chloride (210 mg, 3.93 mmol) and acetic acid (3 ml) were added, and the whole was heated at 70°C for 2 h. The reaction mixture was cooled, diluted with water (50 ml), basified with ammonia solution, and extracted with $CHCl_3$ (3 x 50 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–ethyl acetate–methanol, 8:8:1) to afford **25** (11mg, 21%). mp 275°C (decomp.) (dark yellow powder from methanol–acetone). MS *m/z* (%): 262 (M^+, 100), 261 (35), 233 (50), 205 (66), 204 (46). High-resolution MS Calcd for $C_{16}H_{10}N_2O_2$: 262.0742. Found: 262.0744. ^{1}H-NMR δ: 4.16 (3H, s, OCH_3), 6.43 (1H, s, C_5-H), 7.92 (1H, ddd, J = 7.9, 7.2, 1.3 Hz, C_{10}-H), 8.00 (1H, ddd, J = 7.9, 7.2, 1.3 Hz, C_9-H), 8.51 (1H, d, J = 5.9 Hz, C_1-H), 8.62 (1H, dd, J = 7.9, 1.3 Hz, C_8-H), 8.65 (1H, dd, J = 7.9, 1.3 Hz, C_{11}-H), 9.11 (1H, d, J = 5.9 Hz, C_2-H).

(b) DMF-DEA (66 mg, 0.45 mmol) was added to a suspension of **20** (38 mg, 0.15 mmol) in dry toluene (1.0 ml). The resulting mixture was heated at 120°C for 20 min under nitrogen, and then evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 100:3) to afford **24** (23 mg, 50%). ^{1}H-NMR δ: 3.13 (6H, s, $N(CH_3)_2$), 3.93 (3H, s, OCH_3), 6.28 (1H, s, C_3-H), 7.18, 7.38 (each 1H, d, J = 12.9 Hz, CH=CH), 7.51, 7.75 (each 1H, ddd, J = 7.3, 6.9, 1.3 Hz, C_6-H, C_7-H), 8.23, 8.25 (each 1H, dd, J = 7.3, 1.3 Hz, C_5-H, C_8-H). Ammonium chloride (120 mg, 2.25 mmol) and acetic acid (2 ml) were added to a solution of **24** (21 mg, 0.067 mmol) in dry toluene (1.0 ml), and the whole was heated at 120°C for 20 min under nitrogen. The reaction mixture was cooled, diluted with water (20 ml), basified with saturated aqueous Na_2CO_3 solution, and extracted with $CHCl_3$ (3 x 40 ml). The extract was dried and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 10:1) to afford **25** (17 mg, 99%).

(c) DMF-DEA (66 mg, 0.45 mmol) was added to a suspension of **20** (31 mg, 0.12 mmol) in dry toluene (1.0 ml), and the resulting mixture was heated at 120°C for 20 min under nitrogen. Ammonium chloride (120 mg, 2.25 mmol) and acetic acid (2 ml)were added, and the whole was heated at 120°C for 15 min. The reaction mixture was cooled, diluted with water (20 ml), basified with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (containing 3% methanol, 3 x 40 ml). The extract was dried and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 100:3) to afford **25** (24 mg, 75%).

4-Aminobenzo[*de*][3,6]phenanthrolin-6(6*H*)-one (26) Ammonia solution (28% in water, 30 ml) was added to a solution of **25** (161 mg, 0.62 mmol) in ethanol (30 ml). The whole was heated at 80°C for 1.5 h, and then evaporated to dryness. The residue was chromatographed (eluting with $CHCl_3$–methanol, 10:1) to afford **26** (107 mg, 70%). mp 285°C (decomp.) (dark red powder from $CHCl_3$–acetone). MS *m/z* (%): 247 (M^+, 100), 219 (71). High-resolution MS Calcd for $C_{15}H_9N_3O$: 247.0746. Found: 247.0746. IR (KBr): 1642 cm^{-1} (C=O). ^{1}H-NMR (DMSO-d_6) δ: 6.03 (1H, s, C_5-H), 7.63 (2H, br, NH_2), 7.92, 8.01 (each 1H, t, J = 7.9 Hz, C_9-H, C_{10}-H), 8.35, 8.90 (each 1H, d, J = 7.9 Hz, C_8-H, C_{11}-H), 8.85 (1H, d, J = 5.9 Hz, C_1-H), 9.03 (1H, d, J = 5.9 Hz, C_2-H).

2,2-Dimethyl-5-[[(6-oxo-6*H*-benzo[*de*][3,6]phenanthrolin-4-yl)amino]methylidene]-1,3-dioxane-4,6-dione (27) (a) A mixture of Meldrum's acid (43 mg, 0.3 mmol) and trimethyl orthoformate (1 ml) was refluxed for 2 h, and then a solution of **26** (50 mg, 0.2 mmol) in trimethyl orthoformate (4 ml) was added. The whole was refluxed for 1 h, then cooled, and diluted with ether (20 ml). The precipitated crystals of **27** were collected by filtration. Yield 46 mg (57%). mp 257°C (decomp.) (dark yellow powder from toluene–ether). MS *m/z* (%): 401 (M^+, 2), 343 (37), 299 (47), 271 (100), 243 (39). High-resolution MS Calcd for $C_{22}H_{15}N_3O_5$: 401.1012. Found: 401.1010. ^{1}H-NMR δ: 1.81 (6H, s, $C(CH_3)_2$), 6.93 (1H, s, C_5-H), 7.97 (1H, td, J = 7.9, 1.7 Hz, C_{10}-H), 8.05 (1H, td, J = 7.9, 1.7 Hz, C_9-H), 8.60 (1H, d, J = 5.9 Hz, C_1-H), 8.65 (1H, dd, J = 7.9, 1.7 Hz, C_8-H), 8.68 (1H, dd, J = 7.9, 1.7 Hz, C_{11}-H), 8.78 (1H, d, J = 14.2 Hz, =CH-N), 9.15 (1H, d, J = 5.9 Hz, C_2-H), 12.62 (1H, d, J = 14.2 Hz, NH).

(b) A mixture of Meldrum's acid (43 mg, 0.3 mmol) and trimethyl orthoformate (1 ml) was refluxed for 2 h, and then a solution of **26** (43 mg, 0.17 mmol) in toluene (4 ml) was added. The whole was refluxed for 1 h, then cooled, and diluted with ether (20 ml). The precipitated crystals of **27** were collected by filtration. Yield 62 mg (89%).

11-Hydroxyascididemin (4) (a) Boron tribromide (0.4 ml) was added dropwise to a solution of **19** (30 mg, 0.1 mmol) in dry CH_2Cl_2 (12 ml) at –20°C. The whole was stirred at –30 – –10°C for 1 h, poured into water (150 ml), neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (containing 3% methanol, 3 x 100 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 20:1–10:1) to afford **4** (16 mg, 56%) as a yellow solid. mp >260°C (decomp.) (lit.,[1c] mp >250°C). MS *m/z* (%): 299 (M^+, 84), 271 (100), 243 (41). High-resolution MS Calcd for $C_{18}H_9N_3O_2$: 299.0695. Found: 299.0695. IR (KBr): 3071 cm^{-1} (OH); 1674 cm^{-1} (C=O). ^{1}H-NMR (500 MHz) δ: 7.15 (1H, d, J = 5.6 Hz, C_{10}-H), 8.00 (1H, ddd, J = 8.2, 7.0, 1.4 Hz, C_3-H), 8.06 (1H, ddd, J = 8.2, 7.0, 1.4 Hz, C_2-H), 8.59 (1H, d, J = 5.6 Hz, C_5-H), 8.66 (1H, dd, J = 8.2, 1.4 Hz, C_1-H), 8.73 (1H, dd, J = 8.2, 1.4 Hz, C_4-H), 8.90 (1H, d, J = 5.6 Hz, C_9-H), 9.32 (1H, d, J = 5.6 Hz, C_6-H), 13.06 (1H, s, OH). ^{13}C-NMR (125 MHz) δ: 114.81 (C_{10}), 115.59 (C_{11a}), 117.16 (C_5), 117.74 (C_{12b}), 123.07 (C_4), 123.76 (C_{4a}), 131.40 (C_3), 132.10 (C_2), 133.35 (C_1), 137.80 (C_{4b}), 145.63 (C_{12a}), 145.76 (C_{13a}), 149.30 (C_{7a}), 150.07 (C_6), 154.09 (C_{7b}), 156.70 (C_9), 169.47 (C_{11}), 187.37 (C_{12}).

(b) DMF-DEA (588 mg, 4.0 mmol) was added to a suspension of **23** (290 mg, 1.0 mmol) in DMF (4 ml), and the resulting mixture was heated at 100–105°C for 1 h under nitrogen. Ammonium chloride (952 mg) and acetic acid (10 ml) were added, and the whole was heated at 70–80°C for 1 h. The reaction mixture was cooled, diluted with ice–water (70 ml), neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (8 x 40 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 2:1) to afford **4** (108 mg, 36%).

(c) A solution of **27** (32 mg, 0.08 mmol) in diphenyl ether (3 ml) was heated at 190°C for 1 h. After cooling the mixture was chromatographed. Elution with hexane was discarded, and further elution with $CHCl_3$–methanol (9:1) afforded **4** (19 mg, 80%).

6-(2'-Acetyl-4'-methoxyphenylamino)-5,8-quinolinedione (30) A mixture of 6-methoxy-5,8-quinolinedione (**28**) (276 mg, 1.46 mmol), $CeCl_3 \cdot 7H_2O$ (596 mg, 1.60 mmol), 2-amino-5-methoxyacetophenone (**29**) (264 mg, 1.60 mmol), and ethanol (30 ml) was stirred at 25°C for 1 h. The reaction mixture was diluted with water (50 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate–methanol, 100:1) to afford **30** (251 mg, 53%). mp 203–205°C (dark red needles from CH_2Cl_2-ether). MS *m/z* (%): 322 (M^+, 49), 304 (100), 261 (28). *Anal.* Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.00; H, 4.42; N, 8.68. IR (KBr): 1680, 1645, 1634 cm^{-1} (C=O). ^{1}H-NMR δ: 2.68 (3H, s, $COCH_3$), 3.90 (3H, s, OCH_3), 6.79 (1H, s, C_7-H), 7.15 (1H, dd, J = 8.9, 3.0 Hz, $C_{5'}$-H), 7.45 (1H, d, J = 3.0 Hz, $C_{3'}$-H), 7.58 (1H, d, J = 8.9 Hz, $C_{6'}$-H), 7.64 (1H, dd, J = 7.9, 4.6 Hz, C_3-H), 8.49 (1H, dd, J = 7.9, 1.3 Hz, C_4-H), 9.05 (1H, dd, J = 4.6, 1.3 Hz, C_2-H), 10.81 (1H, br, NH).

9-Methoxy-11-methylpyrido[2,3-*b*]acridine-5,12-dione (31) A solution of **30** (188 mg, 0.58 mmol) in CH_3CO_2H–H_2SO_4 (10:1, 22 ml) was heated at 90°C for 30 min. The reaction mixture was cooled, diluted with water (50 ml), neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 x 50 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–methanol, 100:1) to afford **31** (166 mg, 94%). mp 287–290°C (decomp.) (yellow needles from CH_2Cl_2). MS *m/z* (%): 304 (M^+, 100), 289 (11), 275 (10), 261 (21). *Anal.* Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21. Found: C, 70.78; H, 3.97; N, 9.10. IR (KBr): 1682 cm^{-1} (C=O). ^{1}H-NMR δ: 3.29 (3H, s, CH_3), 4.06 (3H, s, OCH_3), 7.54 (1H, d, J = 2.6 Hz, C_{10}-H), 7.61 (1H, dd, J = 9.2, 2.6 Hz, C_8-H), 7.78 (1H, dd, J = 7.9, 5.0 Hz, C_3-H), 8.43 (1H, d, J = 9.2 Hz, C_7-H), 8.75 (1H, dd, J = 7.9, 1.7 Hz, C_4-H), 9.16 (1H, dd, J = 5.0, 1.7 Hz, C_2-H).

Neocalliactine Methyl Ether (32) DMF-DEA (120 mg, 0.82 mmol) was added to a suspension of **31** (40 mg, 0.13 mmol) in DMF (1.5 ml), and the resulting mixture was heated at 120°C for 30 min under nitrogen. Ammonium chloride (600 mg) and acetic acid (2 ml) were added, and the whole was heated at 120°C for 30 min. The reaction mixture was cooled, diluted with water (50 ml), and extracted with CH_2Cl_2 (3 x 40 ml). The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–methanol, 20:1 – 10:1) to afford **32** (26 mg, 64%). mp >280°C (decomp.) (yellow powder from CH_2Cl_2–ether). MS *m/z* (%): 313 (M^+, 100), 285 (22), 270 (17), 242 (20). High-resolution MS Calcd for $C_{19}H_{11}N_3O_2$: 313.0851. Found: 313.0852. IR (KBr): 1672, 1612, 1578, 1508, 1484, 1400, 1364, 1240, 1090, 1070, 1034, 1008, 944, 856, 834, 806, 738, 548 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 4.15 (3H, s, OCH_3), 7.68 (1H, dd, J = 9.2, 2.6 Hz, C_2-H), 7.76 (1H, dd, J = 7.9, 4.6 Hz, C_{10}-H), 8.06 (1H, d, J = 2.6 Hz, C_4-H), 8.66 (1H, d, J = 5.9 Hz, C_5-H), 8.55 (1H, d, J = 9.2 Hz, C_1-H), 8.85 (1H, dd, J = 7.9, 1.3 Hz, C_{11}-H), 9.20 (1H, dd, J = 4.6, 1.3 Hz, C_9-H), 9.29 (1H, d, J = 5.9 Hz, C_6-H).

Neocalliactine Acetate (5) A solution of **32** (50 mg, 0.16 mmol) in 48% hydrobromic acid (4 ml) was refluxed for 18 h, and then evaporated to dryness. Pyridine (10 ml) and acetic anhydride (2 ml) were added to the residue, and the whole was stirred at 25°C for 10 h. The reaction mixture was diluted with water (50 ml), and extracted with CH_2Cl_2 (3 x 50 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with $CHCl_3$–methanol, 50:1) to afford **5** (21 mg, 39%). mp >270°C (decomp.) (yellow powder from $CHCl_3$) (lit.,[2a] no mp was given). MS *m/z* (%): 341 (M^+, 13), 313 (22), 299

(100), 271 (41). High-resolution MS Calcd for $C_{20}H_{11}N_3O_3$: 341.0800. Found: 341.0800. IR (KBr): 1756, 1678, 1614, 1576, 1508, 1474, 1412, 1372, 1262, 1176, 1082, 1068, 810 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 2.48 (3H, s, $COCH_3$), 7.78 (1H, dd, J = 7.9, 4.6 Hz, C_{10}-H), 7.83 (1H, dd, J = 8.9, 2.6 Hz, C_2-H), 8.52 (1H, d, J = 2.6 Hz, C_4-H), 8.60 (1H, d, J = 5.6 Hz, C_5-H), 8.67 (1H, d, J = 8.9 Hz, C_1-H), 8.85 (1H, dd, J = 7.9, 1.6 Hz, C_{11}-H), 9.21 (1H, dd, J = 4.6, 1.6 Hz, C_9-H), 9.32 (1H, d, J = 5.6 Hz, C_6-H). ^{13}C-NMR (100 MHz, $CDCl_3$–CD_3OD) δ: 20.80 (q, J = 130.5 Hz, CH_3), 115.03 (dd, J = 164.0, 4.6 Hz, C_4), 117.18 (dd, J = 166.3, 8.4 Hz, C_5), 117.72 (d, J = 6.1 Hz, C_{12b}), 124.42 (m, C_{4a}), 125.82 (dd, J = 167.9, 8.4 Hz, C_{10}), 126.71 (dd, J = 166.3, 5.3 Hz, C_2), 128.81 (d, J = 6.1 Hz, C_{11a}), 133.99 (d, J = 167.1 Hz, C_1), 136.54 (dd, J = 167.9, 6.1 Hz, C_{11}), 137.68 (m, C_{4b}), 143.20 (m, C_{13a}), 145.25 (s, C_{12a}), 149.24 (m, C_{7a}), 149.31 (d, J = 183.1 Hz, C_6), 151.67 (m, C_{7b}), 152.24 (m, C_3), 155.15 (ddd, J = 181.6, 7.6, 3.1 Hz, C_9), 169.05 (q, J = 7.6 Hz, CH_3CO), 181.33 (d, J = 3.8 Hz, C_{12}).

Acknowledgement This work was partly supported by a Grant-in-Aid for Scientific Research (No. 03671018) from the Ministry of Education, Science and Culture, Japan, and a Special Grant from Meiji College of Pharmacy. We thank Mr. N. Eguchi, Ms. S. Yoshioka, and Ms. T. Koseki in the Analytical Center of our College for measurement of spectral data (NMR and MS) and microanalytical data.

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(*Received in Japan* 20 *August* 1997; *accepted* 6 *October* 1997)