TOTAL SYNTHESIS OF AMPHIMEDINE

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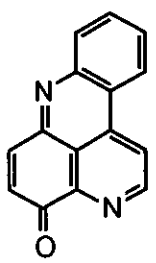
Abstract - The cytotoxic fused pentacyclic aromatic alkaloid, amphimedine (**2**) from a Pacific sponge, was synthesized employing hetero Diels-Alder reactions.

Over the last decade a number of polycyclic fused aromatic alkaloids including 4*H*-pyrido[2,3,4-*kl*]acridone (**1**) have been isolated from marine organisms and more than 40 compounds are now known.[1] Almost all of them are cytotoxic and their regulation of cellular growth and differentiation, their effect on cAMP-mediated processes, inhibition of topoisomerase II, and anti-HIV activity have been reported.[1]
In 1983 Schmitz and co-workers reported the isolation of a novel cytotoxic pentacyclic aromatic alkaloid, named amphimedine (**2**) from an *Amphimedon* sp. of sponge found near the island of Guam.[2] Its structure was assigned on the basis of extensive long-range heterocorrelation and carbon-carbon correlation analyses.



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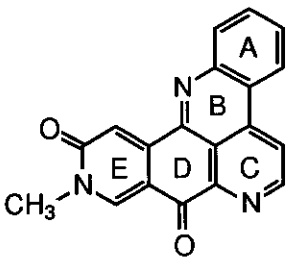
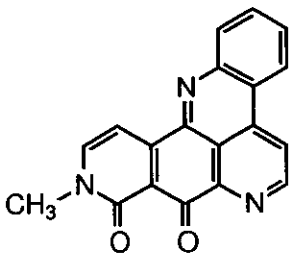
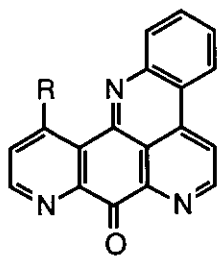


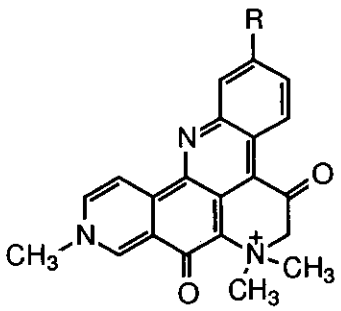
amphimedine (**2**)



neoamphimedine (**3**)



meridine (**4**) R=OH
cystodamine (**5**) R=NH_2

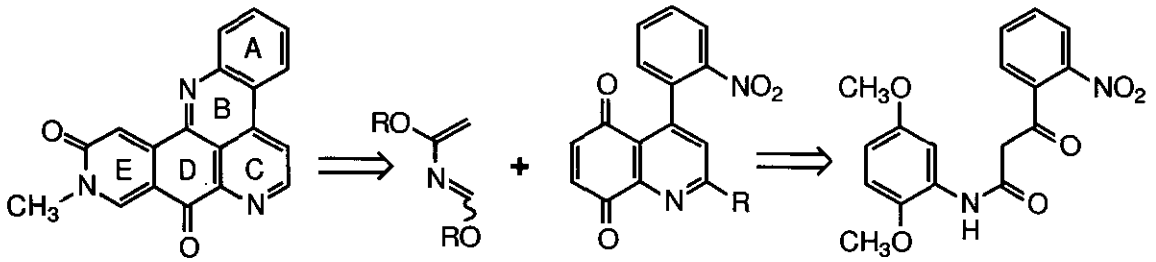


petrosamine (**6**) R=Br
debromopetrosamine (**7**) R=H

Since then, neoamphimedine (**3**) and debromopetrosamine (**7**) from the Micronesian sponge *Xestospongia* cf. *carbonaria*,[1b] meridine (**4**) from the Asidian *Amphicarpa meridiana*,[3] cystodamine (**5**) from the Mediterranean Ascidian *Cystodytes delle chiajei*,[4] and petrosamine (**6**) from the marine sponge *Petrosia*

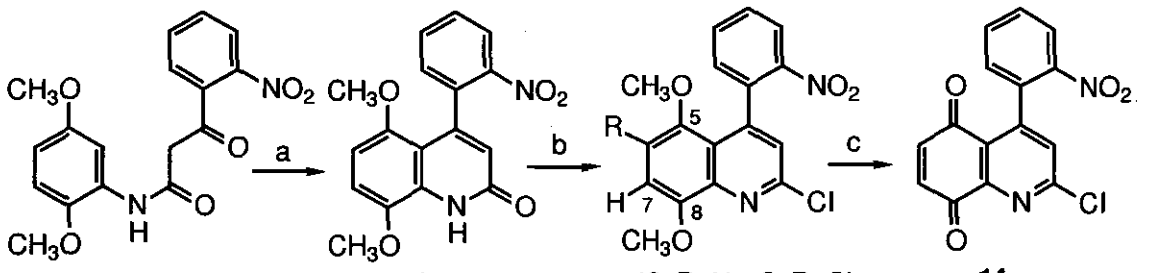
sp.[5] were isolated. All these alkaloids possess the same pentacyclic nuclei including 4*H*-pyrido[2,3,4-*kl*]acridone (**1**). Amphimedine (**2**) and neoamphimedine (**3**) are regioisomers in which a pyridinone moiety and acridinone (**1**) are fused in different positions. Meridine (**4**) and cystodamine (**5**) have the acridinone (**1**) fused with a hydroxy- and aminopyridine moiety, respectively, and petrosamine (**6**) and debromopetrosamine (**7**) contain the acridinone nuclei (**1**) but have a different oxidation level than amphimedine (**2**). In biological activity all six alkaloids are cytotoxic and neoamphimedine (**3**), in particular, was shown to be a potent inhibitor of purified mammalian topoisomerase II.[1b]

In a continued effort to achieve the total synthesis of natural products,[6] interested in their highly fused structures, several biological activities and isolation of **2**, **3**, and **7** from the same marine source stimulated us to synthesize these alkaloids. Six reports of amphimedine synthesis including ours[7] have been published. In this paper, we wish to report the full details of our synthesis of **2**.



2 **8**: R=TBDMS **9**: R=Cl or H **10**

In the retrosynthetic analysis of **2**, pyridinone ring (E-ring) can be constructed employing hetero Diels-Alder reactions of a substituted 2-azabutadiene (**8**)[8] with 5,8-quinolinequinone (**9**). The B-ring can be constructed by dehydration between a carbonyl group and an amino group, derived by reduction of a nitro group. The desired quinone (**9**) can be prepared by oxidation of the corresponding dimethoxyquinoline which can be derived by classical Knorr cyclization of 2-nitrobenzoylacetanilide (**10**).



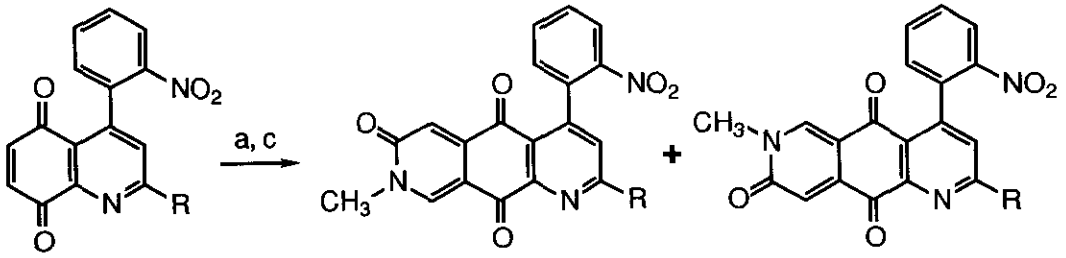
10 **11** **12**: R=H, **13**: R=Cl **14**

(a) 80% H_2SO_4, 75°C, 30 min, 53% (b) PCl_5, $POCl_3$, 70°C, 45 min, **12**: 66%,**13**: 20% or $POCl_3$, DMF, 90°C, 3 h, **12**: 94% (c) CAN, CH_3CN-H_2O, 0°C,15 min, 77%

Our starting material was 2-nitrobenzoylacetanilide (**10**), which was obtained in a quantitative yield by heating 2,5-dimethoxyaniline with ethyl 2-nitrobenzoylacetate in toluene containing a small amount of pyridine at 140°C for 6 h. Knorr cyclization of **10** in 80% H_2SO_4 at 75°C for 30 min gave the 2-quinolinone (**11**) in 53% yield, which gave the 2-chloroquinoline (**12**) and 2,6-dichloroquinoline (**13**) in 66% and 20%

yields, respectively, by heating with PCl_5 in $POCl_3$. Compound (**12**) was also obtained in high yield (94%) by heating at 90°C for 3 h with $POCl_3$ in DMF.

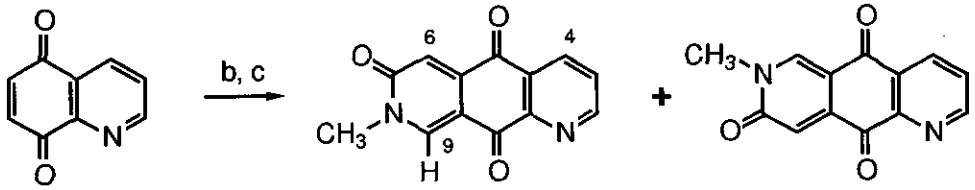
In the ^{1}H-nmr of **13** methoxyl groups of C-5 and C-8 were observed at δ 3.10 (arylshielded) and δ 4.07. The chlorinated position of **13** was decided by observation of a 19% enhancement of the methoxy hydrogen signal δ 4.07 (C-8) in a ^{1}H-DIFNOE experiment involving irradiation of the H-7. Oxidative demethylation of **12** with ceric ammonium nitrate (CAN) in aqueous CH_3CN at 0°C for 15 min, a general and efficient method developed in our laboratory to synthesize heterocyclic quinolinequinone,[9] afforded 2-chloroquinolinequinone (**14**) in 77% yield.



14 R=Cl
16 R=H

15a R=Cl 7%
17a R=H 8%

15b R=Cl 8%
17b R=H 7%



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19a 18%

19b 15%

(a) **8**, $CHCl_3$, 35°C, 8 h, then HCl (b) **8**, $CHCl_3$, 25°C, 3 h, then HCl
(c) CH_3I, K_2CO_3, TDA-1, DMF,25°C, 1 h,

Next, we examined the Diels-Alder reaction of various 5,8-quinolinequinones with azadiene (**8**).

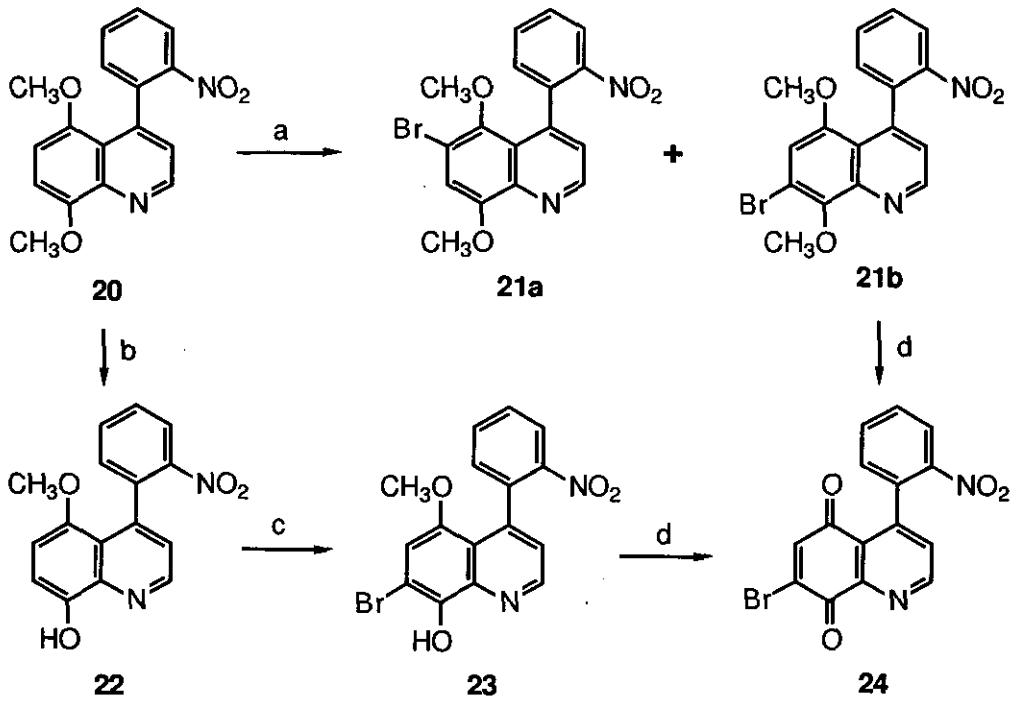
In the Diels-Alder reaction of azanaphthoquinone regiochemical control was exerted by the position of the ring nitrogen atom relative to the carbonyl groups.[10]

2-Chloro-5,8-quinolinequinone (**14**) reacted with azadiene (**8**) in $CHCl_3$ at 35°C for 8 h to yield cycloadducts after acidic workup, methylated with CH_3I/K_2CO_3/tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) in DMF at 25°C for 1 h to afford the corresponding regioisomers, **15a** and **15b** in only 7% and 8% yields, respectively.

In order to improve the yield of the cycloadducts, we examined the Diels-Alder reaction of 2-deschloro-5,8-quinolinequinone (**16**).[11] Diels-Alder reaction of **16** with **8** under the condition applied to **14** above (temperature, time excepted) produced the cycloadducts, **17a** (8%) and **17b** (7%) in very low yields.[12]

We further examined the Diels-Alder reaction of quinone (**18**)[13] with azadiene (**8**). Reaction of simple 5,8-quinolinequinone (**18**) and azadiene (**8**) in $CHCl_3$ at 25°C for 3 h followed by methylation afforded the corresponding **19a** and **19b** in 18% and 15% yields, respectively. The structure of **19a** was determined by a 5.6% enhancement of the hydrogen signal (H-9) in a ^{1}H-DIFNOE experiment involving irradiation of the methyl hydrogen signal on pyridinone ring, and ^{13}C-^{1}H COLOC measurement showed correlations of the signals H-4 (δ 9.43) and H-6 (δ 7.64) with C-5 (δ 177.1).

Since the Diels-Alder reactions of quinolinequinones (**14**,**16**,**18**) with azadiene (**8**) was unsatisfactory, we then turned our attention to 7-bromoquinolinequinone (**24**)[14] as a dienophile.



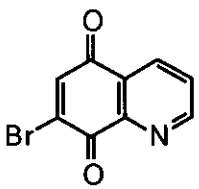
(a) Br_2, K_2CO_3, $CHCl_3$, 25°C, 24 h, **21a**: 32%, **21b**: 36%
(b) BBr_3, CH_2Cl_2, reflux, 15 h, 95% (c) Br_2, $CHCl_3$, 25°C, 1 h, 83%
(d) same procedure as used for **12**, 77% from **21b**, 70% from **23**

Direct bromination of 5,8-dimethoxyquinoline (**20**)[11] with bromine in $CHCl_3$ containing K_2CO_3 at 25°C for 24 h gave **21a** and **21b** in 32% and 36% yields, respectively. The structure of **21b** was assigned in a similar manner to **13**, that is, a 12% enhancement was observed of the methoxy hydrogen signal δ 3.44 (C-5) in a ^{1}H-DIFNOE experiment involving irradiation of the H-6 for **21b**.

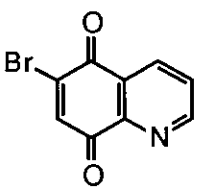
Oxidative demethylation of **21b** afforded 7-bromoquinolinequinone (**24**) in 77% yield. Compound (**24**) was also derived from **20** as follows. Monodemethylation of **20** with BBr_3 in CH_2Cl_2 at refluxing for 15 h gave 8-hydroxyquinoline (**22**) in 95% yield and the position of demethylation occurred at C-8 as methoxy signal was observed at δ 3.41 (arylshielded). Selective bromination of **22** with bromine in $CHCl_3$ at 25°C for 1 h

gave 7-bromoquinoline (**23**) in 83% yield, and the regiochemistry was supported by a ^{1}H-DIFNOE experiment.

Oxidative demethylation of bromoquinoline (**23**) afforded **24** in 70% yield. Diels-Alder reactions of bromoquinones (**25a,b**[15],**24**) with azadiene (**8**) to give regiospecifically the corresponding pyridoquinolinetriones (**19a,b,17a**) as a single regioisomer. These results are summarized in Table I.



25a



25b

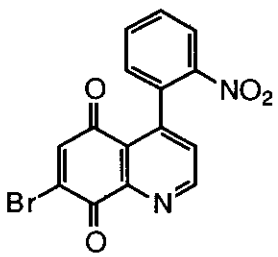


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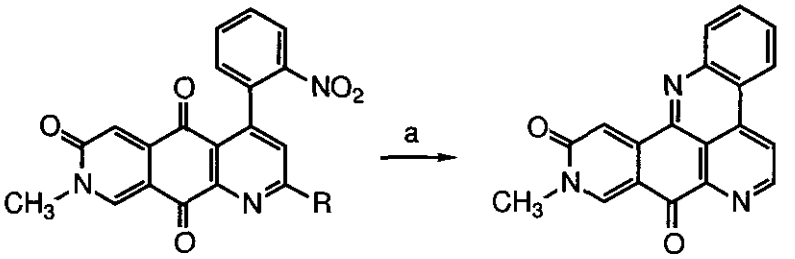
Table I Effect of various conditions in Diels-Alder reactions of bromoquinolinequinones (**25,24**) with azadiene (**8**)

Entry	Quinone	Equiv. of **8**	Solvent	Temp.(°C)	Time (h)	Yield (%)		
						19a	**19b**	**17a**
1	**25a**	2.8	$CHCl_3$	25	1	83.0	---	
2	**25b**	2.8	$CHCl_3$	25	1	---	52.0	
3	**24**	2.8	$CHCl_3$	25	2			20.8
4	**24**	5.6	$CHCl_3$	25	1			27.1
5	**24**	2.8	THF	25	18			17.4

The reactivity of bromoquinones (**25a,b**) with azadiene (**8**) was higher than the quinone (**18**). Although quinone (**18**) gave **19a** in 18% yield, bromoquinone (**25a**) afforded **19a** regiospecifically in 83% yield. Moreover **24** afforded the desired **17a** in 27.1% yield. Therefore **24**, in spite of the presence of nitro substituent, was found to be an more effective dienophile than **14** or **16**.

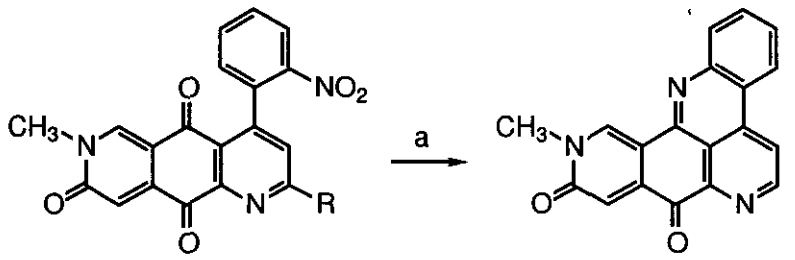
Finally, catalytic hydrogenation of pyridoquinolinetrione (**15a**) with 10% Pd-C in CH_3OH at 25°C afforded amphimedine (**2**) in 13% yield, while the reduction of **17a** afforded **2** in 41% yield. Synthetic amphimedine had spectral properties and hplc mobility identical with those of a natural specimen.

In a similar manner the regioisomer (**26**) was obtained from **15b** and **17b** in 11% and 21% yields, respectively.



15a: R=Cl, **17a**: R=H

2:13% from **15a**, 41% from **17a**



15b: R=Cl, **17b**: R=H

26:11% from **15b**, 21% from **17b**

(a) 10% Pd-C, H_2, CH_3OH

In summary, synthesis of the pentacyclic alkaloid amphimedine (**2**) was accomplished employing hetero Diels-Alder reactions of 2-aza-1,3-bis(*tert*-butyldimethylsilyloxy)-1,3-butadiene (**8**) and quinolinequinones which were prepared by Knorr cyclization followed by the oxidative demethylation reaction. This study confirmed that the hetero Diels-Alder reaction of bromoquinolinequinones proceeded regiospecifically with azadiene (**8**).

ACKNOWLEDGMENTS

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EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-Nmr spectra at 270 MHz and ^{13}C-nmr spectra at 67.5 MHz were measured in $CDCl_3$ or $CDCl_3$-CF_3COOD with tetramethylsilane as an internal standard. 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 (Merck, 230-400 mesh).

2,5-Dimethoxy(2-nitrobenzoyl)acetanilide (10) A solution of 2,5-dimethoxyaniline (765 mg, 5 mmol), ethyl 2-nitrobenzoylacetate (1.42 g, 6 mmol) and pyridine (3 drops) in toluene (13 ml) was refluxed for 6 h. After cooling, the reaction mixture was evaporated and the residue was chromatographed (eluting with benzene-ethyl acetate 20 : 1) to afford **10** (1.72 g, quantitative). mp 93.5-95°C (yellow prisms from $CHCl_3$-hexane). *Anal.* Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.08; H, 4.56; N, 8.10. Ms *m/z* (%): 344 (M^+, 36), 153 (53), 138 (100). Ir (KBr): 3330, 1690, 1685, 1520, 1340 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.78 (3H, s), 3.89 (3H, s), 3.96 (2H, s), 6.60 (1H, dd, *J*=8.9, 3.0 Hz), 6.82 (1H, d, *J*=8.9 Hz), 7.52 (1H, dd, *J*=7.6, 1.3 Hz), 7.66 (1H, td, *J*=7.6, 1.3 Hz), 7.78 (1H, td, *J*=7.6, 1.3 Hz), 8.05 (1H, d, *J*=3.0 Hz), 8.19 (1H, dd, *J*=7.6, 1.3 Hz), 9.03 (1H, br s).

5,8-Dimethoxy-4-(2-nitrophenyl)-2(1*H*)-quinolinone (11) A solution of **10** (2.08 g, 6 mmol) in 80% H_2SO_4 (20 ml) was heated at 75°C for 30 min. The reaction mixture was cooled and poured into ice-water (100 ml). The precipitated crystals of **11** were collected and recrystallized from CH_3OH. Yield 1.05 g (53 %). mp 208-209°C (yellow needles). *Anal.* Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.38; H, 4.19; N, 8.65. Ms *m/z* (%): 326 (M^+, 100), 311 (59). Ir (KBr): 3340, 1650, 1520, 1350 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.33 (3H, s), 3.95 (3H, s), 6.39 (1H, d, *J*=8.9 Hz), 6.43 (1H, s), 6.89 (1H, d, *J*=8.9 Hz), 7.34 (1H, dd, *J*=7.6, 1.3 Hz), 7.55 (1H, td, *J*=7.6, 1.3 Hz), 7.67 (1H, td, *J*=7.6, 1.3 Hz), 8.20 (1H, dd, *J*=7.6, 1.3 Hz), 9.24 (1H, br s).

2-Chloro-5,8-dimethoxy-4-(2-nitrophenyl)quinoline (12) and 2,6-Dichloro-5,8-dimethoxy-4-(2-nitrophenyl)quinoline (13) Method A: Quinolinone (**11**)(3.22 g, 9.86 mmol) was added to a mixture of PCl_5 (5.0 g, 24 mmol) and $POCl_3$ (4.47 ml, 17.7 mmol). The whole was heated at 70°C for 45 min. The reaction mixture was cooled and poured into ice-water (100 ml). The precipitated crystals were collected and chromatographed. Elution with benzene-ethyl acetate (30 : 1) afforded the less polar 2-chloroquinoline (**12**)(2.42 g, 66%) and further elution with benzene-ethyl acetate (20 : 1) afforded the more polar 2,6-dichloroquinoline (**13**)(0.75 g, 20%). Method B: Quinoline (**11**) (33 mg, 0.1 mmol) was added to $POCl_3$ (0.15 ml, 0.59 mmol) in DMF (0.25 ml). The whole was heated at 90°C for 3 h. Treatment of the reaction mixture as Method A afforded **12** (32 mg, 94%). **12**: mp 225-226°C (yellow prisms from benzene). *Anal.* Calcd for $C_{17}H_{13}N_2O_4Cl$: C, 59.22; H, 3.80; N, 8.13. Found: C, 59.18; H, 3.59; N, 8.07. Ms *m/z* (%): 346 (M^++2, 35), 344 (M^+, 100), 329 (56). Ir (KBr): 1515, 1345 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.40 (3H, s), 4.04 (3H, s), 6.70 (1H, d, *J*=8.9 Hz), 7.01 (1H, d, *J*=8.9 Hz), 7.21 (1H, s), 7.32 (1H, dd, *J*=7.6, 1.3 Hz), 7.58 (1H, td, *J*=7.6, 1.3 Hz), 7.68 (1H, td, *J*=7.6, 1.3 Hz), 8.21 (1H, dd, *J*=7.6, 1.3 Hz). **13**: mp 218-219°C (yellow needles from benzene). *Anal.* Calcd for $C_{17}H_{12}N_2O_4Cl_2$: C, 53.84; H, 3.19; N, 7.39. Found: C, 53.81; H, 2.97; N, 7.35. Ms *m/z* (%): 380 (M^++2, 54), 378 (M^+, 84), 363 (100). Ir (KBr): 1520, 1350 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.10 (3H, s), 4.07 (3H, s), 7.07 (1H, s), 7.23 (1H, s), 7.42 (1H, dd, *J*=7.6, 1.3 Hz), 7.64 (1H, td, *J*=7.6, 1.3 Hz), 7.73 (1H, td, *J*=7.6, 1.3 Hz), 8.30 (1H, dd, *J*=7.6, 1.3 Hz).

2-Chloro-4-(2-nitrophenyl)quinoline-5,8-dione (14) A solution of CAN (2.3 g, 4.2 mmol) in water (2.8 ml) was added dropwise to **12** (288 mg, 0.84 mmol) dissolved in acetonitrile-water (4 : 1, 70 ml) at 0°C. The mixture was left at 0°C for 15 min, poured into water (210 ml) and extracted with $CHCl_3$ (3 x 200

ml). The extract was washed with brine, dried and concentrated. The residue was recrystallized from $CHCl_3$. Yield 204 mg (77 %). mp 188-190°C(decomp.) (yellow prisms). *Anal.* Calcd for $C_{15}H_7N_2O_4Cl$: C, 57.25; H, 2.24; N, 8.90. Found: C, 57.18; H, 1.94; N, 8.60. Ms *m/z* (%): 316 (M^++2, 1), 314 (M^+, 4), 269 (35), 267 (100), 240 (42). Ir (KBr): 1670, 1520, 1350 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 6.86 (1H, d, *J*=10.6 Hz), 7.13 (1H, d, *J*=10.6 Hz), 7.25 (1H, dd, *J*=7.6, 1.3 Hz), 7.48 (1H, s) 7.70 (1H, td, *J*=7.6, 1.3 Hz), 7.77 (1H, td, *J*=7.6, 1.3 Hz), 8.35 (1H, dd, *J*=7.6, 1.3 Hz).

2-Chloro-8-methyl-4-(2-nitrophenyl)pyrido[4,3-*g*]quinoline-5,7,10(8*H*)-trione (15a) and 2-chloro-7-methyl-4-(2-nitrophenyl)pyrido[3,4-*g*]quinoline-5,8,10(7*H*)-trione (15b) A mixture of *p*-quinone (**14**) (189 mg, 0.6 mmol) and 2-aza-1,3-bis(*tert*-butyldimethylsilyloxy)-1,3-butadiene (**8**) (284 mg, 0.9 mmol) in $CHCl_3$ (2 ml) was warmed at 35°C for 8 h. The reaction mixture was cooled and concentrated HCl (0.6 ml) was added. The whole was stirred at room temperature for 5 min and concentrated. Water (30 ml) was added to the residue and the mixture was extracted with ethyl acetate (3 x 20 ml). The extract was washed with brine, dried and evaporated. To the residue, K_2CO_3 (124 mg, 0.9 mmol), methyl iodide (1.4 ml, 4.3 mmol), and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1)(3 drops) in DMF (2.5 ml) were added and a mixture was stirred at 25°C for 1 h. The mixture was diluted with water (30 ml) and extracted with $CHCl_3$ (3 x 20 ml). The extract was washed with brine, dried and concentrated. The residue was chromatographed (eluting with benzene-ethyl acetate 3 : 1) to afford **15a** (15 mg, 7 %) and **15b** (18 mg, 8 %). **15a**: mp 286-288°C (yellow powder from $CHCl_3$). High-resolution Ms Calcd for $C_{19}H_{10}N_3O_5Cl$: 395.0309. Found: 395.0337. Ms *m/z* (%): 397(M^++2, 4), 395 (M^+, 11), 351 (34), 349 (100). Ir (KBr): 1694, 1644, 1526, 1302cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.73 (3H, s), 7.03 (1H, s), 7.26 (1H, dd, *J*=7.6, 1.3 Hz), 7.48 (1H, s), 7.72 (1H, td, *J*=7.6, 1.3 Hz), 7.80 (1H, td, *J*= 7.6, 1.3 Hz), 8.38 (1H, dd, *J*=7.6, 1.3 Hz), 8.67 (1H, s). **15b**: mp > 300°C (yellow powder from $CHCl_3$-benzene). High-resolution Ms Calcd for $C_{19}H_{10}N_3O_5Cl$: 395.0309. Found: 395.0316. Ms *m/z* (%): 397(M^++2, 1), 395 (M^+, 3), 351 (37), 349 (100). Ir (KBr): 1686, 1648, 1526, 1306 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.64 (3H, s), 7.29 (1H, dd, *J*=7.6, 1.3 Hz), 7.35 (1H, s), 7.51 (1H, s), 7.70 (1H, td, *J*=7.6, 1.3 Hz), 7.79 (1H, td, *J*=7.6, 1.3 Hz), 8.32 (1H, s), 8.35 (1H, dd, *J*=7.6, 1.3 Hz).

Typical procedure for preparation of pyridinoquinolinetriones (17,19) from 16,18, and from 25,24 (Table I) A mixture of *p*-quinone (**25a**) (71 mg, 0.3 mmol) and azadiene (**8**) (265 mg, 0.84 mmol) in $CHCl_3$ (0.6 ml) was stirred at 25°C for 1 h and concentrated HCl (0.6 ml) was added. The whole was stirred at room temperature for 5 min and concentrated. To the residue, K_2CO_3 (83 mg, 0.6 mmol), methyl iodide (1.5 ml, 4.6 mmol), and TDA-1 (3 drops) in DMF (3 ml) were added and a mixture was stirred at room temperature for 1 h. The mixture was diluted with water (9 ml) and extracted with $CHCl_3$ (3 x 4 ml). The extract was washed with brine, dried and concentrated. The residue was chromatographed (eluting with ethyl acetate) to afford **19a** (60 mg, 83 %).

8-Methyl-4-(2-nitrophenyl)pyrido[4,3-*g*]quinoline-5,7,10(8*H*)-trione (17a) mp 178-179°C (decomp.) (yellow powder from $CHCl_3$-CH_3OH). High-resolution Ms Calcd for $C_{19}H_{11}N_3O_5$: 361.0699. Found: 361.0692. Ms *m/z* (%): 361 (M^+, 12), 315 (100), 287 (27). Ir (KBr): 1692, 1644, 1522, 1384 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.73 (3H, s), 7.06 (1H, s), 7.24 (1H, dd, *J*=7.6, 1.3 Hz), 7.46 (1H, d, *J*=4.6 Hz), 7.70 (1H, td, *J*=7.6, 1.3 Hz), 7.78 (1H, td, *J*= 7.6, 1.3 Hz), 8.36 (1H, dd, *J*=7.6, 1.3 Hz), 8.70 (1H, s), 9.16 (1H, d, *J*=4.6 Hz).

7-Methyl-4-(2-nitrophenyl)pyrido[3,4-*g*]quinoline-5,8,10(7*H*)-trione (17b) mp 250-251°C (decomp.) (yellow powder from $CHCl_3$-CH_3OH). High-resolution Ms Calcd for $C_{19}H_{11}N_3O_5$: 361.0699. Found: 361.0690. Ms *m/z* (%): 361 (M^+, 3), 315 (100), 287 (31). Ir (KBr): 1694, 1682, 1522, 1378 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.64 (3H, s), 7.24 (1H, dd, *J*=7.6, 1.3 Hz), 7.38 (1H, s), 7.49 (1H, d, *J*=4.6 Hz), 7.68 (1H, td, *J*=7.6, 1.3 Hz), 7.77 (1H, td, *J*=7.6, 1.3 Hz), 8.33 (1H, dd, *J*=7.6, 1.3 Hz), 8.34 (1H, s), 9.14 (1H, d, *J*=4.6 Hz).

8-Methylpyrido[4,3-*g*]quinoline-5,7,10(8*H*)-trione (19a) mp>300°C (yellow powder from $CHCl_3$-CH_3OH). High-resolution Ms Calcd for $C_{13}H_8N_2O_3$: 240.0535. Found: 240.0535. Ms *m/z* (%): 240 (M^+, 100), 225 (20), 212 (8), 171 (28). Ir (KBr): 1704, 1674, 1660 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.76 (3H, s), 7.34 (1H, s), 7.77 (1H, dd, *J*=7.9, 4.6 Hz), 8.64 (1H, dd, *J*=7.9, 1.5 Hz), 8.71 (1H, s), 9.16 (1H, dd, *J*=4.6, 1.5 Hz). ^{1}H-Nmr ($CDCl_3$-CF_3COOD) δ: 3.91 (3H, s), 7.64 (1H, s), 8.54 (1H, dd, *J*=7.9, 5.3 Hz), 8.94 (1H, s), 9.38 (1H, d, *J*=5.3 Hz), 9.43 (1H, d, *J*=7.9 Hz). ^{13}C-Nmr ($CDCl_3$-CF_3COOD) δ: 40.03, 112.91, 119.38, 132.72, 139.76, 142.10, 147.06, 147.59, 148.63, 165.45, 172.09, 177.09.

7-Methylpyrido[3,4-*g*]quinoline-5,8,10(7*H*)-trione (19b) mp 269-270°C (yellow powder from $CHCl_3$-CH_3OH). High-resolution Ms Calcd for $C_{13}H_8N_2O_3$: 240.0535. Found: 240.0539. Ms *m/z* (%): 240 (M^+,100), 225 (8), 212 (9), 171 (24). Ir (KBr): 1698, 1678, 1630 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.76 (3H, s), 7.41 (1H, s), 7.78 (1H, dd, *J*=7.9, 4.6 Hz), 8.60 (1H, s), 8.66 (1H, dd, *J*=7.9, 1.8 Hz), 9.13 (1H, dd, *J*=4.6, 1.8 Hz).

6-Bromo-5,8-dimethoxy-4-(2-nitrophenyl)quinoline (21a) and 7-bromo-5,8-dimethoxy-4-(2-nitrophenyl)quinoline (21b) A solution of bromine (63.9 mg, 0.4 mmol) in CCl_4 (0.4 ml) was added dropwise to a stirring solution of 5,8-dimethoxyquinoline (**20**)(62 mg, 0.2 mmol) in $CHCl_3$ (3.2 ml) containing K_2CO_3 (55.3 mg, 0.4 mmol) at 0°C. The solution was stirred at room temperature for 24 h, poured into 1% aqueous $NaHCO_3$ (10 ml), and extracted with $CHCl_3$ (3 x 5 ml). The extract was washed with 1% aqueous sodium hydrogen sulfite, brine, dried and concentrated. The residue was chromatographed (eluting with hexane-ethyl acetate 1 : 1) to afford 6-bromoquinoline (**21a**)(25.2 mg, 32 %) and 7-bromoquinoline (**21b**)(27.8 mg, 36 %). **21a**: mp 205-206°C (yellow needles from $CHCl_3$-hexane). *Anal.* Calcd for $C_{17}H_{13}N_2O_4Br$: C, 52.46; H, 3.37; N, 7.20. Found: C, 52.57; H, 3.38; N, 7.15. Ms *m/z* (%): 390 (M^++2, 71), 388 (M^+, 71), 375 (97), 373 (100), 329 (50), 328 (51), 327 (51), 326 (48). Ir (KBr): 1518, 1344 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.10 (3H, s), 4.10 (3H, s), 7.19 (1H, s), 7.23 (1H, d, *J*=4.6 Hz), 7.43 (1H, dd, *J*=7.6, 1.3 Hz), 7.61 (1H, td, *J*=7.6, 1.3 Hz), 7.71 (1H, td, *J*=7.6, 1.3 Hz), 8.26 (1H, dd, *J*=7.6, 1.3 Hz), 8.95 (1H, d, *J*=4.6 Hz). **21b**: mp 170-171°C (colorless plates from $CHCl_3$-hexane). *Anal.* Calcd for $C_{17}H_{13}N_2O_4Br$: C, 52.46; H, 3.37; N, 7.20. Found: C, 52.46; H, 3.37; N, 7.17. Ms *m/z* (%): 390 (M^++2, 98), 388 (M^+, 100), 375(88), 373 (94), 361 (46), 359 (48), 329 (52), 328 (44), 327 (52), 326 (43). Ir (KBr): 1520, 1354 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.44 (3H, s), 4.12 (3H, s), 6.87 (1H, s), 7.19 (1H, d, *J*=4.3 Hz), 7.29 (1H, dd, *J*=7.6, 1.3 Hz), 7.57 (1H, td, *J*=7.6, 1.3 Hz), 7.67 (1H, td, *J*=7.6, 1.3 Hz), 8.19 (1H, dd, *J*=7.6, 1.3 Hz), 8.98 (1H, d, *J*=4.3 Hz).

8-Hydroxy-5-methoxy-4-(2-nitrophenyl)quinoline (22) To a solution of **20** (31 mg, 0.1 mmol) in CH_2Cl_2 (3 ml) was added dropwise boron tribromide (125 mg, 0.5 mmol) in CH_2Cl_2 (0.5 ml) at room temperature. The solution was refluxed for 15 h, poured into ice-water (10 ml), basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 ml). The extract was washed with brine, dried and

concentrated. The residue was chromatographed (eluting with hexane-ethyl acetate 4 : 1) to afford 8-hydroxyquinoline (**22**)(28.4 mg, 95 %). mp 194-195°C (yellow plate from $CHCl_3$-ether). *Anal.* Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.85; H, 4.08; N, 9.41. Ms *m/z* (%): 296 (M^+, 100), 281 (69), 235 (68). Ir (KBr): 3332, 1516, 1342 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.41 (3H, s), 6.71 (1H, d, *J*=8.3 Hz), 7.09 (1H, d, *J*=8.3 Hz), 7.23 (1H, d, *J*=4.6 Hz), 7.32 (1H, dd, *J*=7.6, 1.3 Hz), 7.57 (1H, td, *J*=7.6, 1.3 Hz), 7.67 (1H, td, *J*=7.6, 1.3 Hz), 8.05 (1H, brs), 8.20 (1H, dd, *J*=7.6, 1.3 Hz), 8.82 (1H, d, *J*=4.6 Hz).

7-Bromo-8-hydroxy-5-methoxy-4-(2-nitrophenyl)quinoline (23) A solution of bromine (159.8 mg, 1 mmol) in CCl_4 (1 ml) was added dropwise to a stirring solution of **22** (296 mg, 1 mmol) in $CHCl_3$ (16 ml) at 10°C. The solution was stirred at room temperature for 1 h, poured into water (30 ml), basified with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3 x 20 ml). The extract was washed with brine, dried and concentrated. The residue was chromatographed (eluting with hexane-ethyl acetate 1 : 1) to afford 7-bromoquinoline (**23**) (311.4 mg, 83 %). mp 165-166°C (orange needles from ether). *Anal.* Calcd for $C_{16}H_{11}N_2O_4Br$: C, 51.22; H, 2.96; N, 7.47. Found: C, 51.21; H, 2.97; N, 7.35. Ms *m/z* (%): 376 (M^++2, 99), 374 (M^+, 100), 361 (72), 359 (74), 315 (89), 313 (86). Ir (KBr): 3312, 1524, 1354 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.42 (3H, s), 6.85 (1H, s), 7.24 (1H, d, *J*=4.6 Hz), 7.31 (1H, dd, *J*=7.6, 1.3 Hz), 7.59 (1H, td, *J*=7.6, 1.3 Hz), 7.68 (1H, td, *J*=7.6, 1.3 Hz), 8.20 (1H, dd, *J*=7.6, 1.3 Hz), 8.25-8.50 (1H, br), 8.82 (1H, d, *J*=4.6 Hz).

7-Bromo-4-(2-nitrophenyl)-5,8-quinolinedione (24) Oxidation of **21b** or **23** was carried out by the same procedure as used for **12**. Yield 77 % from **21b**, 70 % from **23**. mp 170-171°C (yellow powder from ether). *Anal.* Calcd for $C_{15}H_7N_2O_4Br \cdot 1/2H_2O$: C, 48.94; H, 2.19; N, 7.61. Found: C, 48.92; H, 2.01; N, 7.34. Ms *m/z* (%): 362 (M^++4, 1), 360 (M^++2, 1), 314 (99), 312 (100). Ir (KBr): 1692, 1656, 1518, 1350 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 7.22 (1H, dd, *J*=7.6, 1.3 Hz), 7.39 (1H, s), 7.46 (1H, d, *J*=4.6 Hz), 7.68 (1H, td, *J*=7.6, 1.3 Hz), 7.76 (1H, td, *J*=7.6, 1.3 Hz), 8.33 (1H, dd, *J*=7.6, 1.3 Hz), 9.09 (1H, d, *J*=4.6 Hz).

Amphimedine (2) Entry A: The compound (**15a**) (15.8 mg, 0.04 mmol) in CH_3OH (16 ml) and pyridine (8 drops) was hydrogenated at 1 atm for 20 h using 10 % palladium on carbon (21 mg) as a catalyst. The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed (eluting with $CHCl_3$-CH_3OH 50 : 1) to afford amphimedine (**2**)(1.6 mg, 13 %). Entry B: The compound (**17a**) (36.1 mg, 0.1 mmol) in CH_3OH (15 ml) was hydrogenated at 1 atm for 1.5 h using 10 % palladium on carbon (20 mg) as a catalyst. Treatment of the reaction mixture as used for **15a** afforded **2** (12.8 mg, 41 %). mp>300°C (yellow powder from $CHCl_3$-CH_3OH). High-resolution Ms Calcd for $C_{19}H_{11}N_3O_2$: 313.0851. Found: 313.0857. Uv (EtOH): λ_{max} nm (ε) 235 (38000), 281 (10000), 340 (7000). Ms *m/z* (%): 313 (M^+, 100), 298 (41). Ir (KBr): 1680, 1642 cm^{-1}. ^{1}H-Nmr (CF_3COOD-$CDCl_3$, 2:1) δ: 4.09 (3H, s), 8.21 (1H, t-like), 8.38 (1H, t, like), 8.49 (1H, s), 8.69 (1H, d, *J*=8.1 Hz), 8.97 (1H, d, *J*=8.1 Hz) 9.19 (1H, s), 9.32 (1H, d, *J*=6.5 Hz), 9.51 (1H, d, *J*=6.5 Hz). ^{1}H-Nmr ($CDCl_3$) δ: 3.86 (3H, s), 7.57 (1H, s), 7.77 (1H, s), 7.93 (1H, dd, *J*=7.6, 1.3 Hz), 8.19 (1H, td, *J*=7.6, 1.3 Hz), 8.59 (1H, dd, *J*=7.6, 1.3 Hz), 8.65 (1H, d, *J*=4.6 Hz), 9.14 (1H, s) 9.31 (1H, d, *J*=4.6 Hz). ^{13}C-Nmr (CF_3COOD-$CDCl_3$, 2:1) δ: 40.03, 114.36, 115.08, 119.16, 120.85, 125.38, 125.58, 133.28, 133.65, 137.72, 139.64, 139.94, 144.41, 145.62, 146.47, 147.76, 148.11, 166.34, 173.58.

11-Methyl-8*H*-benzo[*b*]pyrido[4,3,2-*de*][1,9]phenanthroline-8,10(11*H*)-dione (26) Hydrogenation of **15b**, **17b** was carried out by the same procedure as used for amphimedine (**2**) (Entry A and B). Yields 11

% from **15b** and 21 % from **17b**. mp>300°C (red orange powder from $CHCl_3$-MeOH). High-resolution Ms Calcd for $C_{19}H_{11}N_3O_2$: 313.0851. Found: 313.0851. Ms *m/z* (%): 313 (M^+, 100), 298 (69), 285 (23). Ir (KBr): 1692, 1662 cm^{-1}. ^{1}H-Nmr (CF_3COOD:$CDCl_3$=2:1) δ: 4.10 (3H, s), 7.92 (1H, s), 8.15 (1H, t-like), 8.34 (1H, t-like), 8.53 (1H, d, *J*=8.5 Hz), 8.91 (1H, d, *J*=8.1 Hz), 9.45 (2H, s like), 9.68 (1H, s). ^{1}H-Nmr ($CDCl_3$) δ: 3.86 (3H, s), 7.57 (1H, s), 7.77 (1H, t, *J*=7.8 Hz), 7.93 (1H, t, *J*=7.8 Hz), 8.20 (1H, d, *J*=7.8 Hz), 8.59 (1H, d, *J*=7.8 Hz), 8.65 (1H, d, *J*=5.3 Hz), 9.14 (1H, s), 9.31 (1H, d, *J*=5.3 Hz).

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