HETEROCYCLES, Vol. 53, No. 6, 2000, pp. 1305 - 1316, Received, 17th February, 2000

SYNTHESIS OF BENZACRIDINE AND PYRIDOACRIDINE *VIA* DIELS-ALDER REACTION OF ACRIDONEQUINONE

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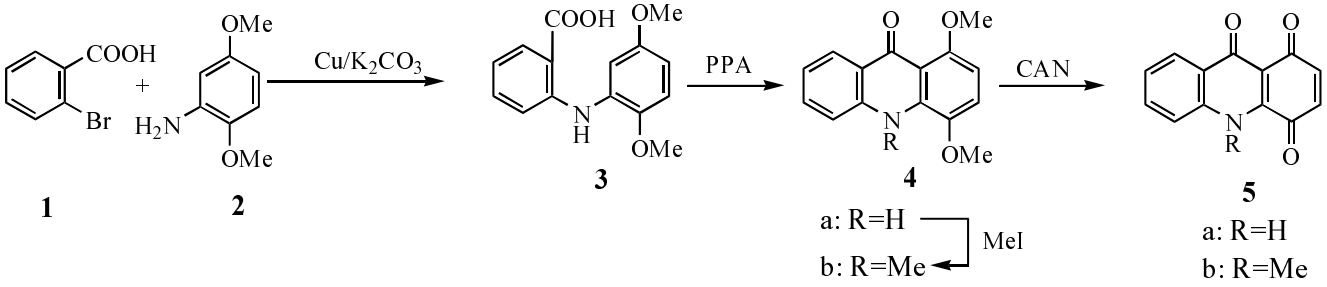
Abstract – Synthesis of benz[*b*]acridones (**8**) and pyrido[3,2-*b*]acridones (**15**) was achieved by Diels-Alder reaction of acridonequinones (**5**) with several activated 1,3-dienes. The addition proceeded in a regioselective manner under mild conditions, thus providing a convenient method for the construction of polycyclic nitrogen heterocycles.

Compounds containing benz[*b*]acridine and pyrido[3,2-*b*]acridine ring systems can be considered to have potential anti-cancer and anti-bacterial activities due to close similar structures with polycyclic nitrogen heterocycles found in sea alkaloids[1] such as ascididemin.[2] Recently, we and many others have demonstrated that the Diels-Alder (D-A) reaction of quinolinequinones (quinoline-5,8-dione) with 1,3-dienes proceeded in a regioselective manner and provided a convenient method constructing 1-aza[3], 1,8-diaza,[4] and 1,5-diazaanthraquinone[5] ring systems. In this paper we describe the D-A reaction of acridonequinone (acridine-1,4,9-trione), an azadienophiles structurally similar to quinolinequinone, and also show that this methodology can be used in the construction of these tetracyclic nitrogen heterocycles.

Preparation of Acridonequinones

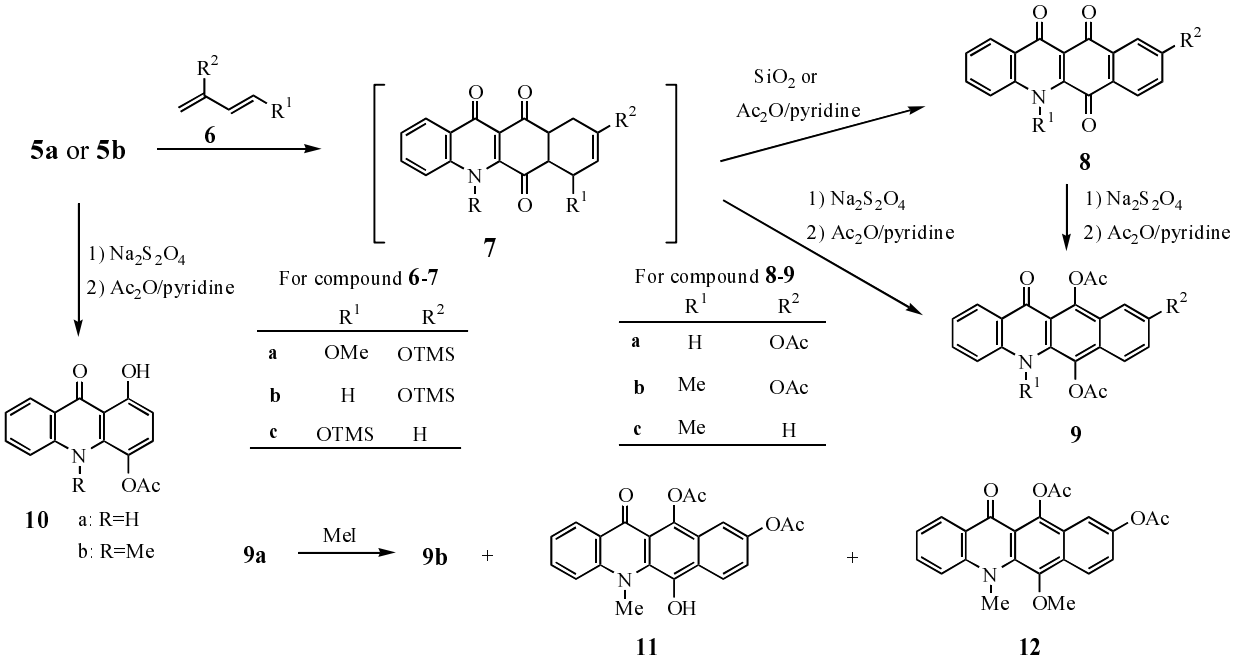
1,4-Dimethoxyacridin-9-one (**4a**) and the *N*-methyl derivative (**4b**) were prepared by the known method[6] with a small modification. Ullmann condensation of 2,5-dimethoxyaniline (**2**) with 2-bromobenzoic acid (**1**) proceeded in the presence of copper catalyst and potassium carbonate under refluxing in *n*-amyl alcohol to give 2-(2,5-dimethoxyphenyl)aminobenzoic acid (**3**) in 79% yield. Heating of **3** in polyphosphoric acid (PPA) at 100°C gave **4a** in 99% yield. Methylation of **4a** with methyl iodide gave **4b** in 96% yield. Oxidation of **4a** and **4b** with cerium ammonium nitrate (CAN) gave acridonequinone (**5a**) and *N*-methyl derivative (**5b**) in 92% and 51% yields, respectively.



Scheme 1

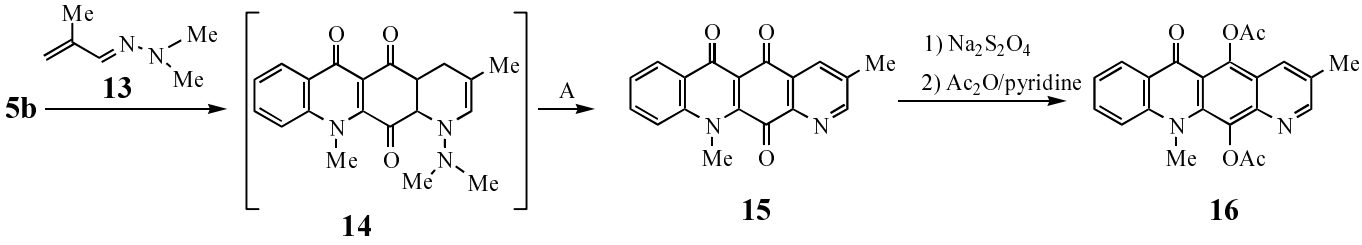
Diels-Alder Reaction of Acridonequinones

The D-A reaction of **5a** and **5b** with several unsymmetrical 1,3-dienes including 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**6a**), 2-trimethylsilyloxy-1,3-butadiene (**6b**), 1-trimethylsilyloxy-1,3-butadiene (**6c**), and 1-dimethylamino-3-methyl-1-aza-1,3-butadiene (azadiene) (**13**) was carried out in benzene at room temperature or at 80°C for appropriate time under argon atmosphere. The products, although the D-A adducts such as **7** and **14** could not be isolated as pure form, were obtained by the procedure of silica gel column chromatography of the reaction mixture (method A), by the purification after acetylation of the products (method B), or by the purification after sodium hydrosulfite reduction of the products followed by acetylation (method C). The fully aromatized compounds (**8**, **9** and **15**) were obtained from each D-A reaction mixture and well characterized by their analytical and spectral data. Thus, the reaction of *N*-methylacridonequinone (**5b**) with the 1,3-dienes proceeded in a regioselective manner to give **8b** (51% from **6a**: method B, and 22% from **6b**: method B), **8c** (6% from **6c**: method B), **9c** (40% from **6c**: method C) and **15** (46% from **13**: method A) as sole adduct, respectively.



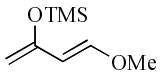
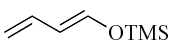
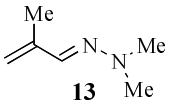
Scheme 2

On the other hand, the acridonequinone (**5a**) only reacted with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**6a**) to give **9a** in 31% yield. In the reactions with the other dienes, the quinone **5a** always yielded hydroquinone monoacetate (**10a**),[8] a reduction product, instead of D-A adducts. This compound was readily obtained by sodium hydrosulfite reduction of **5a** followed by acetylation, proving the structure. The results were summarized in Schemes 2-3, and Table 1.



Scheme 3

Table 1 Diels-Alder Reaction of Acridonequinones (**5**) with 1,3-dienes

Dienes	Dienophiles	Conditions			Isolation procedure*	Yields	
		Solvent	Temp(°C)	Time (h)		D-A adducts	Hydroquinones
 **6a**	**5a**	benzene	rt	20	B	31 (**9a**)	--
	5b	benzene	rt	15	B	51 (**8b**)	--
	5b	benzene	80	1	B	31 (**8b**)	--
 **6b**	**5a**	benzene	80	2	B	--	16 (**10a**)
	5b	benzene	80	2	B	22 (**8b**)	--
 **6c**	**5a**	benzene	80	2	C	--	29 (**10a**)
	5b	benzene	80	1	B	6 (**8c**)	4 (**10b**)
	5b	benzene	80	1	C	40 (**9c**)	--
 **13**	**5a**	benzene	rt	1	C	--	57 (**10a**)
	5b	benzene	rt	1	A	46 (**15**)	--

*A: SiO_2 column chromatography B: Ac_2O/pyridine before SiO_2 column chromatography

C: $Na_2S_2O_4$ and Ac_2O/pyridine before SiO_2 column chromatography

The structures of the D-A adducts were determined as follows. The structure of **8c** as 5-methylbenz[*b*]acridine-6,11,12-trione was deduced from the MS, ^1H- and ^{13}C-NMR spectra. This should be same with the compound prepared by Joule *et al. via* the condensation of 2-lithio-1-methyl-4-quinolone with 2-(chloroformyl)benzoate,[7] although the comparison is difficult since no spectral and physical data including melting point were given in the literature.

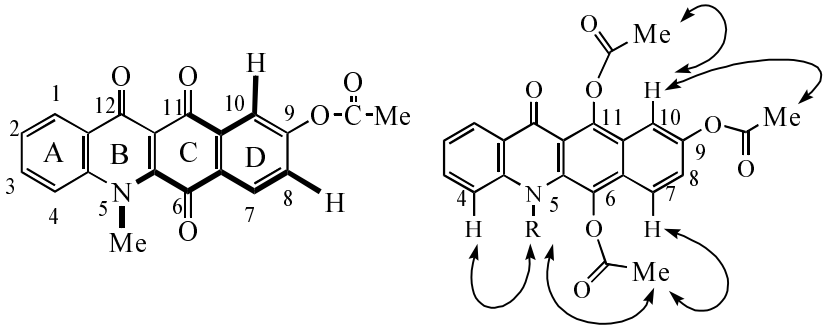
The evidence that the D-A reactions of **5a** and **5b** with the diene (**6a**) proceeded in a same regiochemical manner, was obtained by chemical and spectral means.

Methylation of **9a** with methyl iodide gave three products, *N*-methyl triacetate (**9b**), *N*-methyl diacetate (**11**)[9] and *N*, *O*-dimethyl diacetate (**12**). The compound (**9b**) thus obtained was found to be identical with the product derived from the D-A product (**8b**) by sodium hydrosulfite reduction followed by acetylation.

All protons and carbons of **8b** were unambiguously assigned by measurement of H-H correlation spectroscopy (COSY), C-H COSY and the high-resolution heteronuclear multiple bond correlation (HR-HMBC) spectra. This HR-HMBC spectrum clearly revealed two connections from 5-N to 8-H and from 11-C to 10-H as shown in bold line (Figure 1), thus suggesting that the acetate on the D ring, which originated from the diene moiety, was positioned at C-9.

This conclusion was confirmed by the cross peaks observed in the 2D-nuclear Overhauser and exchange spectroscopy (NOESY) spectra **9a** and **9b**, which revealed two correlations; one is between the 4- and 7-aromatic protons through the signals for the 5-H or 5-Me and then 6-OAc, the other is between 11-OAc to 9-OAc through the signal of 10-aromatic proton.

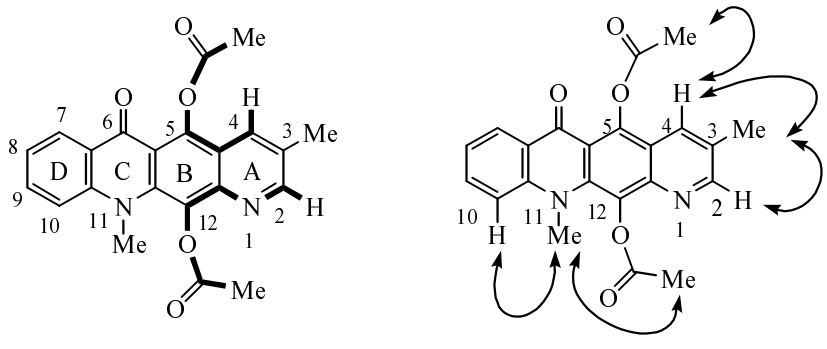
The adduct (**8b**) obtained *via* the cycloaddition of **5b** with **6b** was proved to be identical with the compound through the reaction of **5b** with **6a**, thus proving the regiochemistry of the D-A reaction.



HR-HMBC of **8b** NOESY of **9a** and **9b**

Figure 1

The structure of **15** obtained from the azadiene (**13**) was assigned as pyrido[3,2-*b*]acridone-5,6,12-trione by HR-HMBC and 2D-NOESY spectra of **16** which was prepared by sodium hydrosulfite reduction of **15** followed by acetylation. The spectra clearly showed the correlation



HR-HMBC of **16** NOESY of **16**

Figure 2

depicted in Figure 2, thus clearly revealing the positions of nitrogen and the methyl group introduced from the azadiene moiety.

The dienophile character of acridonequinone as shown above seems to be weak, particularly in the *N*H derivative. The reactivity when compared with that of quinolinequinone, a structurally related azadienophiles, is apparently decreased. However, this decrease in the reactivity is, at least partly, attributable to high sensibility of acridonequinone for a reducing agent since their D-A reaction often accompanied the hydroquinones (**10**) even in the reaction of *N*-Me derivative.

In conclusion these results demonstrate that acridonequinones act as an azadienophiles, although the dienophilic character is deteriorated by its high redox potentiality, and Diels-Alder reaction with electron rich 1,3-dienes provides a convenient method for the construction of such complex heterocycles which, otherwise, is supposed to be difficult to approach.

EXPERIMENTAL

Unless otherwise stated, the following procedures were adopted. All melting points were measured on a Yanagimoto micro hot-stage melting point apparatus (Yanagimoto MP type) and are uncorrected. IR spectra were measured with a JASCO FT/IR-5000 as KBr disks and values are given in cm^{-1}. UV spectra were measured with a Hitachi U-3200 spectrophotometer in dioxane and values are given in λ_{max} nm (ν). NMR spectra were recorded on a JEOL JNM-α500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or a JNM-AL300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) NMR spectrometer in $CDCl_3$ solution using tetramethylsilane (TMS) as an internal standard. The chemical shifts are given in δ values. HR-HMBC spectra were recorded on a JEOL JNM-α500 [Δ_2(delay time of pulse)=300 ms, J=1.7 Hz]. Low-resolution MS spectra (LRMS) and high-resolution MS spectra (HRMS) were determined on a JEOL JMS-HX110A or JMS-D300 spectrometer at 30 eV with a direct inlet system. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. For column chromatography, silica gel (Mallinckrodt type 150A or Wako-Gel C-200) was used. Thin layer chromatography (TLC) was performed on Merck precoated Silica-Gel 60 F254 plates. Medium-pressure liquid chromatography (MPLC) was performed with Kusano CIG pre-packed silica gel columns, and peaks were detected with a Shodex SE-12 RI detector. All organic extracts were washed with 5% HCl, 5% $NaHCO_3$, and water and dried over Na_2SO_4 before concentration *in vacuo*.

Preparation of 2-(2,5-dimethoxyphenyl)aminobenzoic acid (3)

The mixture of 2,5-dimethoxyaniline (1 g, 6.53 mmol), 2-bromobenzoic acid (1.312 g, 6.53 mmol), potassium carbonate (1.083 g, 7.85 mmol) and copper powder (40 mg, 0.63 mmol) in *n*-amyl alcohol (40 mL) was refluxed for 1 h. After acidified by 5% HCl solution the reaction mixture was

extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt:hexane=1:2) and crystallized from $CHCl_3$-Et_2O to give **3** (1.066 g, 79%) as colorless needles, mp 167-168°C (lit.,[6] 162-163°C). IR: 1673, 1657, 1605. UV: 214 (25300), 280 (9600), 312 (9700), 355 (7900). ^{1}H-NMR: 3.77 (3H, s, 2'-OCH_3), 3.85 (3H, 5'-OCH_3), 6.58 (1H, dd, *J*=9, 3 Hz, 4'-H), 6.78 (1H, ddd, *J*=8, 7, 1 Hz, 4-H), 6.88 (1H, d, *J*=9 Hz, 3'-H), 7.05 (1H, d, *J*=3 Hz, 6'-H), 7.35 (1H, dd, *J*=8.5, 1 Hz, 6-H), 7.37 (1H, dd, *J*=8.5, 7, 1.5 Hz, 5-H), 8.07 (1H, dd, *J*=8, 1.5 Hz, 3-H), 9.35 (1H, br s, NH). ^{13}C-NMR: 55.8 (2'-OCH_3), 56.5 (5'-OCH_3), 107.3 (C6'), 107.7 (C4'), 111.7 (C1), 112.3 (C3'), 114.7 (C3), 117.6 (C5), 130.8 (C1'), 132.6 (C6), 135.0 (C4), 146.0 (C2'), 147.7 (C2), 153. 8 (C5'), 173.0 (COOH). LRMS *m/z*: 273 (M^+, BP). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.70; H, 5.57; N, 5.03.

Preparation of 1,4-dimethoxyacridin-9-one (4a)

The mixture of **3** (1.5 g, 5.49 mmol) and polyphosphoric acid (12 g) was heated at 100°C for 3.5 h and cool down to rt. Water was added to the reaction mixture, which was basified by ammonium solution and extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt:hexane=1:2) and crystallized from EtOH-hexane to give **4a** (1.385 g, 99%) as yellow needles, mp 226-228°C (lit.,[6] 220-221°C). IR: 1630, 1609. UV (EtOH): 216 (6200), 247 (12600), 256 (12100), 317 (2700), 392 (2400). ^{1}H-NMR: 3.95 (3H, s, 4-OCH_3), 3.96 (3H, s, 1-OCH_3), 6.50 (1H, d, *J*=8.5 Hz, 3-H), 6.98 (1H, d, *J*=8.5 Hz, 2-H), 7.23 (1H, ddd, *J*=8, 7, 1 Hz, 6-H), 7.30 (1H, d, *J*=8 Hz, 5-H), 7.59 (1H, ddd, *J*=8.5, 7, 1.5 Hz, 7-H), 8.45 (1H, dd, *J*=8.5, 1 Hz, 8-H), 8.58 (1H, br s, NH). ^{13}C-NMR: 56.2 (C4-OCH_3), 56.3 (C1-OCH_3), 100.5 (C2), 112.0 (C5), 112.5 (C9a), 116.1 (C7), 121.7 (C3), 123.3 (C8a), 127.5 (C8), 132.9 (C6), 133.6 (C4a), 138.8 (C10a), 140.4 (C4), 154.6 (C1), 177.8 (C9). LRMS *m/z*: 255 (M^+), 240 (BP). *Anal.* Calcd for $C_{15}H_{13}NO_3 \cdot H_2O$: C, 65.93; H, 5.53; N, 5.13. Found: C, 65.73; H, 4.97; N, 5.05.

Methylation of 4a

The mixture of **4a** (1 g, 3.92 mmol) and potassium hydroxide (1.5 g, 26.8 mmol) in acetone (80 mL) was refluxed for 10 min. MeI (25 mL) in acetone (30 mL) was added to the reaction mixture and refluxed for 30 min. After acidified by 5% HCl solution, the reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt) to give 1,4-dimethoxy-10-methylacridin-9-one (**4b**) (1.015 g, 96%) as yellow powder (lit.,[6] 88-89°C). IR: 1635, 1601, 1498. UV: 256 (30700), 312 (7900), 394 (6800). ^{1}H-NMR: 3.88 (3H, s, 4-OCH_3), 3.89 (3H, s, 1-OCH_3), 3.97 (3H, s, NCH_3), 6.66 (1H, d, *J*=9 Hz, 3-H), 7.14 (1H, d, *J*=9 Hz, 2-H), 7.22 (1H, ddd, *J*=8, 7, 1 Hz, 7-H), 7.41 (1H, d, *J*=8.5 Hz, 5-H), 7.63 (1H, ddd, *J*= 8.5, 7, 1.5 Hz, 6-H), 8.35 (1H, dd, *J*= 8, 1.5 Hz, 8-H). ^{13}C-NMR: 42.2 (NCH_3), 56.6 (C4-OCH_3), 57.3 (C1-OCH_3), 103.4 (C2), 115.7 (C5), 116.4 (C9a), 117.5 (C7), 121.4 (C3), 125.3 (C8a), 127.1 (C8), 132.9 (C6), 138. 3 (C4a), 143.7

(10a), 145.0 (C4), 154.9 (C1), 178.7 (C9). LRMS *m/z*: 269 (M^+), 254 (BP). HRMS *m/z* (M^+): Calcd for $C_{16}H_{15}NO_3$: 269.1052. Found: 269.1052.

Preparation of Acridonequinones (5) (General Procedure)

CAN (4.11g, 7.5 mmol) in MeCN-H_2O (2:1, 30 mL) was added to the solution of **4** (2 mmol) in MeCN-H_2O (2:1, 30 mL) with stirring at 0 °C for 20 min. The reaction mixture was poured into brine and extracted with $CHCl_3$. The residue was purified by column chromatography ($CHCl_3$) to give **5**.

Acridine-1,4,9-trione (5a): Yield 92%, red prisms crystallized from $CHCl_3$, mp 180°C (decomp). IR: 1678, 1665, 1609. UV: 231 (21900), 286 (5800), 421 (1800). ^{1}H-NMR: 7.08 (1H, d, *J*=10 Hz, 3-H), 7.14 (1H, d, *J*=10 Hz, 2-H), 7.70 (1H, ddd, *J*=8, 7, 1 Hz, 7-H), 7.91 (1H, ddd, *J*=8, 7, 1.5 Hz, 6-H), 8.22 (1H, br d, *J*=8 Hz, 5-H), 8.45 (1H, dd, *J*=8, 1.5 Hz, 8-H). LRMS *m/z*: 225 (M^+, BP).

10-Methylacridine-1,4,9-trione (5b): Yield 51%, brown prisms crystallized from $CHCl_3$, mp 180°C (decomp). IR: 1678, 1665, 1599. UV: 235 (29000), 300 (6700), 451 (4300). ^{1}H-NMR: 4.06 (3H, s, NCH_3), 6.81 (1H, d, *J*=10 Hz, 3-H), 6.85 (1H, d, *J*=10 Hz, 2-H), 7.49 (1H, t, *J*=7 Hz, 7-H), 7.69 (1H, d, *J*=8.5 Hz, 5-H), 7.78 (1H, ddd, *J*=8.5, 7, 1.5 Hz, 6-H), 8.49 (1H, dd, *J*=8, 1.5 Hz, 8-H). ^{13}C-NMR: 39.6 (NCH_3), 114.7 (C8a), 117.5 (C5), 126.0 (C7), 127.5 (C8), 130.3 (C9a), 133.9 (C6), 134.7 (C3), 138.7 (C2), 141.7 (C5a), 145.9 (C10a), 174.9 (C9), 182.8 (C4), 184.9 (C1). LRMS *m/z*: 239 (M^+, BP). HRMS *m/z* (M^+): Calcd for $C_{14}H_{19}NO_3$: 239.0583. Found: 239.0613.

Diels-Alder Reaction of 5 (General Procedure)

The suspension of **5** (0.42 mmol) and 1,3-diene (**6** or **13**) (1.26 mmol) in benzene (20 mL) was stirred at rt or heated at 80 °C for appropriated times (see Table 1) under Ar atmosphere.

Method A: The residue obtained by evaporation of the solvent of the reaction mixture *in vacuo* was purified by column chromatography (AcOEt:hexane=1:2) and crystallized from $CHCl_3$-Et_2O.

Method B: The reaction mixture obtained from D-A reaction was evaporated the solvent *in vacuo*, and the residue was treated with acetic anhydride-pyridine (1:2, 3 mL) at rt for 15 h. The reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt:hexane=1:2) and crystallized from $CHCl_3$-Et_2O.

Method C: After removal of the solvent of the D-A reaction mixture, the residue was dissolved in dioxane (15 mL) and the solution of $Na_2S_2O_4$ (139 mg, 0.8 mmol) in H_2O (15 mL) was added to the mixture at 0°C. The mixture was stirred for 10 min and extracted with $CHCl_3$. The residue was treated with acetic anhydride-pyridine (2:1, 3 mL) at rt for 15 h. The reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt:hexane=2:1) and crystallized from $CHCl_3$-Et_2O. The results were given in Table 1.

9-Acetoxy-5-methylbenz[*b*]acridine-6,11,12-trione (8b): Yield 51% from **5b** with **6a**, 22% from **5b**

with **6b**, orange prisms crystallized from $CHCl_3$-Et_2O, mp 250-252°C. IR: 1686, 1671, 1655, 1649. UV: 235 (21000), 265 (14600), 308 (7800), 433 (3500). ^{1}H-NMR: 2.37 (3H, s, 9-$OCOCH_3$), 4.11 (3H, s, NCH_3), 7.41 (1H, t, *J*=8 Hz, 2-H), 7.44 (1H, dd, *J*=8.5, 2 Hz, 8-H), 7.68 (1H, d, *J*=8.5 Hz, 4-H), 7.74 (1H, td, *J*=8.5, 1.5 Hz, 3-H), 7.83 (1H, d, *J*=2 Hz, 10-H), 8.06 (1H, d, *J*=8.5 Hz, 7-H), 8.40 (1H, dd, *J*=8, 1.5 Hz, 1-H). ^{13}C-NMR: 21.1 (C9-OCO<u>C</u>H_3), 40.5 (NCH_3), 115.8 (C11a), 117.6 (C4), 119.5 (C10), 126.1 (C2), 126.7 (C8), 127.3 (C1), 128.6 (C7), 129.4 (C12a), 130.2 (C6a), 134.1 (C3), 134.5 (C10a), 142.0 (C4a), 148.5 (C5a), 156.0 (C9), 168.4 (C9-O<u>C</u>OCH_3), 175.3 (C12), 179.9 (C11), 182.3 (C6). LRMS *m/z*: 347 (M^+), 222 (BP). HRMS *m/z* (M^+): Calcd for $C_{20}H_{13}NO_5$: 347.0791. Found: 347.0766. *Anal.* Calcd for $C_{20}H_{13}NO_5 \cdot 1/2H_2O$: C, 67.42; H, 3.93; N, 3.93. Found: C, 67.32; H, 3.95; N, 3.80.

5-Methylbenz[*b*]acridine-6,11,12-trione (8c): Yield 6%, brown prisms crystallized from $CHCl_3$-Et_2O, mp 210°C (decomp). IR: 1688, 1671, 1601. UV: 237 (18900), 262 (15700), 308 (8100), 4 19 (3400). ^{1}H-NMR: 4.10 (3H, s, NCH_3), 7.47 (1H, t, *J*=8 Hz, 3-H), 7.69 (1H, d, *J*=8 Hz, 4-H), 7.72 (1H, t, *J*=8 Hz, 9-H), 7.77 (1H, ddd, *J*=8, 7, 1.5 Hz, 2-H), 7.80 (1H, t, *J*=7 Hz, 8-H), 8.03 (1H, d, *J*=7 Hz, 7-H), 8.20 (1H, d, *J*=8 Hz, 10-H), 8.50 (1H, dd, *J*=8, 1 Hz, 1-H). ^{13}C-NMR: 40.1 (NCH_3), 116.4 (C11a), 117.3 (C4), 125.8 (C3), 126.2 (C7), 126.7 (C10), 127.6 (C1), 130.1 (C12a), 132.5 (C10a), 132.96 (C9), 132.99 (C6a), 133.8 (C2), 135.2 (C8), 142.0 (C4a), 148.3 (C5a), 175.7 (C12), 180.7 (C11), 184.2 (C6). LRMS *m/z*: 289 (M^+, BP). HRMS *m/z* (M^+): Calcd for $C_{18}H_{11}NO_3$: 289.0736. Found: 289.0725.

6,11-Diacethoxy-5-methylbenz[*b*]acridin-12-one (9c): Yield 40%, yellow prisms crystallized from $CHCl_3$-Et_2O, mp 233-235°C (decomp). IR: 1773, 1644, 1620, 1605. UV: 274 (2890 0), 298 (11300), 314 (5000), 456 (2300). ^{1}H-NMR: 2.57 (3H, s, 6-$OCOCH_3$), 2.68 (3H, s, 11-$OCOCH_3$), 3.88 (3H, s, NCH_3), 7.21 (1H, ddd, *J*=8, 7, 1 Hz, 2-H), 7.33 (1H, d, *J*=8.5 Hz, 4-H), 7.51 (1H, ddd, *J*=8, 7, 1 Hz, 9-H), 7.65 (1H, ddd, *J*=8, 7, 1 Hz, C8-H), 7.68 (1H, ddd, *J*=8.5, 7, 2 Hz, 3-H), 7.81 (1H, d, *J*=8 Hz, 7-H), 8.13 (1H, d, *J*=8 Hz, 10-H), 8.29 (1H, dd, *J*=8, 2 Hz, 1-H). ^{13}C-NMR: 20.8 (C6-OCO<u>C</u>H_3), 21.4 (C11-OCO<u>C</u>H_3), 41.9 (NCH_3), 115.6 (C4), 116.3 (C11a), 120.2 (C7), 121.4 (C2), 123.2 (C6a), 123.3 (C10a), 123.5 (C10), 125.5 (C9), 127.3 (C1), 130.0 (C8), 130.5 (C12a), 130.9 (C5a), 134.4 (C3), 135.0 (C4a), 145.5 (C11), 145.6 (C6), 168.1 (2C, C6-O<u>C</u>OCH_3 and C11-O<u>C</u>OCH_3), 178.5 (C12). LRMS *m/z*: 375 (M^+), 241 (BP). HRMS *m/z* (M^+): Calcd for $C_{22}H_{17}NO_5$: 375.1104. Found: 375.1084.

3,11-Dimethylpyrido[3,2-*b*]acridine-5,6,12-trione (15): Yield 46%, orange prisms crystallized from $CHCl_3$-Et_2O, mp 270°C (decomp). IR: 1731, 1698, 1671, 1601. UV: 241 (12700), 270 (6400), 305 (4700), 428 (1700). ^{1}H-NMR: 2.56 (3H, s, 3-CH_3), 4.15 (3H, s, NCH_3), 7.52 (1H, ddd, *J*=8, 7, 1 Hz, 8-H), 7.73 (1H, d, *J*=8.5 Hz, 10-H), 7.81 (1H, ddd, *J*=8.5, 7, 2 Hz, 9-H), 8.33 (1H, d, *J*=2 Hz, 4-H), 8.53 (1H, dd, *J*=8, 2 Hz, 7-H), 8.83 (1H, d, *J*=2 Hz, 2-H). ^{13}C-NMR: 19.1 (C3-CH_3), 40.2 (NCH_3),

117.4 (C10), 127.7 (C7), 129.4 (C6a), 130.2 (C5a), 130.9 (C4a and C8), 132.4 (C3), 134.0 (C9), 134.6 (C4), 140.2 (C10a), 141.9 (C11a), 155.1 (C2), 167.8 (C12a), 175.5 (C6), 179.9 (C12), 182.6 (C5). LRMS *m/z*: 304 (M^+, BP). HRMS *m/z* (M^+): Calcd for $C_{18}H_{12}N_2O_3$: 304.0846. Found: 304.0831.

6,9,11-Triacetoxybenz[*b*]acridin-12-one (9a): Yield 31%, yellow prisms crystallized from $CHCl_3$-Et_2O, mp 260°C (decomp.). IR: 1758, 1655, 1651, 1630. UV: 271 (56900), 295 (24900), 320 (6800), 438 (3800), 458 (3800). ^{1}H-NMR: 2.37 (3H, s, 6-$OCOCH_3$), 2.41 (3H, s, 9-$OCOCH_3$), 2.81 (3H, 11-$OCOCH_3$), 6.59 (1H, d, *J*=8 Hz, 4-H), 6.86 (1H, t, *J*=7 Hz, 2-H), 6.98 (1H, d, *J*=9 Hz, 7-H), 7.09 (1H, dd, *J*=9, 2 Hz, 8-H), 7.19 (1H, ddd, *J*=8, 7, 2 Hz, 3-H), 7.73 (1H, d, *J*=2 Hz, 10-H), 7.95 (1H, d, *J*=7 Hz, 1-H), 8.15 (1H, br s, NH). ^{13}C-NMR: 20.3 (C11-OCO<u>C</u>H_3), 21.2 (C6-OCO<u>C</u>H_3), 21.8 (C9-OCO<u>C</u>H_3), 113.2 (C10), 113.4 (C11a), 116.3 (C4), 120.1 (C6a), 121.4 (C2), 121.9 (C10a), 122.2 (C8), 125.1 (C7), 126.1 (C1), 126.5 (C12a), 129.1 (C5a), 129.7 (C4a), 133.8 (C3), 139.6 (C 11), 144.5 (C6), 147.6 (C9), 168.7 (C11-O<u>C</u>OCH_3), 169.4 (C6-O<u>C</u>OCH_3), 171.6 (s, C9-O<u>C</u>OCH_3), 177.4 (s, C12). LRMS *m/z*: 419 (M^+), 292 (BP). HRMS *m/z* (M^+): Calcd for $C_{23}H_{12}NO_7$: 419.1002. Found: 419.0825. *Anal.* Calcd for $C_{23}H_{17}NO_7 \cdot 3/4H_2O$: C, 63.81; H, 4.28; N, 3 .24. Found: C, 63.82; H, 4.11; N, 3.19.

4-Acetoxy-1-hydroxyacridin-9-one (10a): Yellow needles crystallized from $CHCl_3$, mp 265-266 °C. IR: 1773, 1636, 1605. UV: 249 (30800), 293 (2600), 305 (3500), 372 (5500), 389 (6300). ^{1}H-NMR: 2.47 (3H, s, 4-$OCOCH_3$), 6.62 (1H, d, *J*=8.5 Hz, 3-H), 7.30 (1H, ddd, *J*=8, 7, 1 Hz, 7-H), 7.31 (1H, d, *J*=8.5 Hz, 5-H), 7.39 (1H, d, *J*=8.5 Hz, 2-H), 7.67 (1H, ddd, *J*=8.5, 7, 1 Hz, 6-H), 8.17 (1H, br s, NH), 8.38 (1H, dd, *J*=8, 1 Hz, 8-H), 13.52 (1H, s, 1-OH). ^{13}C-NMR: 21.1 (C4-OCO<u>C</u>H_3), 106.0 (C2), 109.4 (C9a), 114.1 (C5), 120.3 (C8a), 122.5 (C7), 126.5 (C3), 128.1 (C4a), 128.3 (C8), 132.8 (C4), 134.5 (C6), 147.2 (C10a), 160.1 (C1), 168.9 (C4-O<u>C</u>OCH_3), 182.5 (C9). LRMS *m/z*: 269 (M^+), 226 (BP). HRMS *m/z* (M^+): Calcd for $C_{15}H_{11}NO_4$: 269.0688. Found: 269.0723.

4-Acetoxy-1-hydroxy-5-methylacridin-9-one (10b): Yield 4%, yellow prisms crystallized from $CHCl_3$, mp 100-102°C. IR: 1763, 1636, 1599. UV: 256 (33100), 312 (8300), 410 (6500). ^{1}H-NMR 2.40 (3H, s, 4-$OCOCH_3$), 3.91 (3H, NCH_3), 6.70 (1H, d, *J*=8.5 Hz, 3-H), 7.26 (1H, d, *J*=8.5 Hz, 2-H), 7.32 (1H, t, *J*=8 Hz, 7-H), 7.43 (1H, d, *J*=8.5 Hz, 5-H), 7.75 (1H, ddd, *J*=8.5, 7, 1.5 Hz, 6-H), 8.41 (1H, dd, *J*=8, 1.5 Hz, 8-H), 14.28 (1H, s, 1-OH). ^{13}C-NMR: 21.1 (C4-OCO<u>C</u>H_3), 40.4 (NCH_3), 108.2 (C2), 111.5 (C9a), 115.7 (C5), 121.6 (C8a), 122.1 (C7), 126.6 (C3), 129.3 (C4a), 131.4 (C8), 134.7 (C6), 137.6 (C4), 144.8 (C10a), 161.4 (C1), 169.3 (C4-O<u>C</u>OCH_3), 182.6 (C9). LRMS *m/z*: 283 (M^+), 241 (BP).

Reduction and acetylation of 5a and 5b

A solution of $Na_2S_2O_4$ (90 mg, 0. 50 mmol) in H_2O (15 mL) was added to the dioxane (15 mL) solution of **5a** or **5b** (0.1 mmol) at 0°C and the mixture was stirred for 10 min and extracted with $CHCl_3$. The residue was treated with acetic anhydride-pyridine (2:1, 3 mL) at rt for 15 h. The

reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt) and crystallized from $CHCl_3$ to give **10a** (yield 53% form **5a**) or **10b** (yield 33% from **5b**).

Methylation of 9a

The mixture of **9a** (20 mg, 0.048 mmol), MeI (54 mg, 0. 24 mmol) and K_2CO_3 (26 mg, 0.12 mmol) in acetone (20 mL) was refluxed for 2 h under Ar atmosphere. The reaction mixture was acidified by 5% HCl solution, and extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt) and MPLC (AcOEt:hexane=2:1) to give **9b** (10 mg, 45%), **11** (3 mg, 16%) and **12** (3 mg, 16%), respectively

6,9,11-Triacetoxy-5-methylbenz[*b*]acridin-12-one (9b): Orange prisms crystallized from $CHCl_3$-Et_2O, mp 210-212°C. IR: 1765, 1657, 1649, 1638, 1607. UV: 277 (39000), 299 (1270 0), 461 (2700). ^{1}H-NMR: 2.37 (3H, s, 9-$OCOCH_3$), 2.56 (3H, s, 6-$OCOCH_3$), 2.67 (3H, s, 11-$OCOCH_3$), 3.87 (3H, s, NCH_3), 7.22 (1H, ddd, *J*=8, 7, 1 Hz, 2-H), 7.32 (1H, d, *J*=8 Hz, C4-H), 7.42 (1H, dd, *J*=9.5, 2 Hz, 8-H), 7.68 (1H, ddd, *J*=8, 7, 1.5 Hz, 3-H), 7.82 (1H, d, *J*=2 Hz, 10-H), 7.83 (1H, d, *J*=9.5 Hz, 7-H), 8.29 (1H, dd, *J*= 8, 1.5 Hz, 1-H). ^{13}C-NMR: 20.8 (C6-OCO<u>C</u>H_3), 21.2 (C9-OCO<u>C</u>H_3), 21.4 (C11-OCO<u>C</u>H_3), 41.9 (NCH_3), 114.1 (C10), 115.7 (C4), 116.9 (C11a), 121.5 (C2), 122.1 (C8), 123.3 (C6a), 123.6 (C10a), 125.9 (C7), 127.3 (C1), 128.5 (C12a), 131.1 (C5a), 134.5 (C3), 135.0 (C4a), 145.1 (C11), 145.5 (C6), 148.3 (C9), 167.9 (C6-O<u>C</u>OCH3 and C11-O<u>C</u>OCH_3), 169.3 (C9-O<u>C</u>OCH_3), 178.3 (C12). LRMS *m/z*: 433 (M^+), 348 (BP). HRMS *m/z* (M^+): Calcd for $C_{24}H_{19}NO_7$: 433.1162. Found: 433.1189. *Anal.* Calcd for $C_{24}H_{19}NO_7 \cdot 5/4H_2O$: C, 63.23; H, 4.72; N, 3.07. Found: C, 63.21; H, 4.44; N, 3.07.

9,11-Diacetoxy-6-hydroxy-5-methylbenz[*b*]acridin-12-one (11): Orange prisms, crystallized from $CHCl_3$-Et_2O, mp 250-252 °C. IR: 1758, 1649, 1622, 1601. UV: 275 (21800), 340 (3200), 449 (2 800), 472 (2700). ^{1}H-NMR: 2.38 (3H, s, 11-$OCOCH_3$), 2.70 (3H, s, 9-$OCOCH_3$), 4.05 (3H, s, NCH_3), 7.18 (1H, ddd, *J*=8, 7, 1 Hz, 2-H), 7.22 (1H, d, *J*= 8 Hz, C4-H), 7.36 (1H, dd, *J*=9, 2 Hz, C8-H), 7.59 (1H, ddd, *J*=8, 7, 1.5 Hz, 3-H), 7.79 (1H, d, *J*=2 Hz, 10-H), 8.01 (1H, d, *J*=9 Hz, 7-H), 8.35 (1H, d, *J*=8 Hz, 1-H). LRMS *m/z*: 391 (M^+), 292 (BP). HRMS *m/z* (M^+): Calcd for $C_{22}H_{17}NO_6$: 391.1054. Found: 391.1049.

9,11-Diacetoxy-6-methoxy-5-methylbenz[*b*]acridin-12-one (12): Orange prisms, crystallized from $CHCl_3$-Et_2O, mp 52-53°C. IR: 1767, 1649, 1607. UV: 278 (18000), 303 (13500), 455 (2800). ^{1}H-NMR: 2.38 (3H, s, 9-$OCOCH_3$), 2.66 (3H, s, 11-$OCOCH_3$), 3.84 (3H, 6-OCH_3), 4.00 (3H, NCH_3), 7.22 (1H, ddd, *J*=8, 7, 1 Hz, 2-H), 7.41 (1H, dd, *J*=9, 2 Hz, 8-H), 7.43 (1H, d, *J*=8.5 Hz, 4-H), 7.70 (1H, ddd, *J*=8.5, 7, 1.5 Hz, 3-H), 7.78 (1H, d, *J*=2 Hz, 10-H), 8.22 (1H, d, *J*=9 Hz, 7-H), 8.32 (1H, dd, *J*=8, 1.5 Hz, 1-H). ^{13}C-NMR: 21.2 (C11-OCO<u>C</u>H_3), 21.4 (C9-OCO<u>C</u>H_3), 41.7 (NCH_3), 61.6 (C6-OCH_3), 113.9 (C10), 115.7 (C4), 117.1 (C11a), 121.1 (C2), 123.2 (C8), 123.8 (C6a), 125.1 (C7),

127.1 (C10a), 127.4 (C1), 129.4 (C12a), 134.2 (C4a), 134.4 (C3), 141.7 (C5a), 142.8 (C11), 145.9 (C9), 148.3 (C6), 169.5 (C11-O<u>C</u>OCH$_3$), 169.9 (C9-O<u>C</u>OCH$_3$), 178.8 (C12). LRMS *m/z*: 405 (M^+), 205 (BP).

Preparation of 6,9,11-triacetoxy-5-methylbenz[*b*]acridin-12-one (9b) from 8b

To a solution of **8b** (20 mg, 0.057 mmol) in dioxane (15 mL) $Na_2S_2O_4$ (50 mg, 0.29 mmol) in H_2O (15 mL) solution was added with stirring at 0 °C and the mixture was stirred for 15 min. and extracted with $CHCl_3$. The residue was treated with acetic anhydride-pyridine (2:1, 3 mL) at rt for 15 h. The reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt:hexane=1:2) and crystallized from $CHCl_3$-Et_2O to give **9b** (10 mg, 40%).

Preparation of 5,12-diacetoxy-3,11-dimethylpyrido[3,2-*b*]acridin-6-one (16)

To a solution of **15** (30 mg, 0.1 mmol) in dioxane (15 mL) $Na_2S_2O_4$ (66 mg, 0.5 mmol) in H_2O (15 mL) solution was added with stirring at 0 °C and the mixture was stirred for 15 min. and extracted with $CHCl_3$. The residue was treated with acetic anhydride-pyridine (2:1, 3 mL) at rt for 15 h. The reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography (AcOEt) and crystallized from $CHCl_3$-Et_2O to give **16** (21 mg, 58%) as orange prisms, mp 213-215°C. IR: 1760, 1657, 1605. UV: 278 (50300), 301 (17400), 319 (11500), 450 (4200). ^{1}H-NMR: 2.54 (3H, s, 3-CH_3), 2.60 (3H, s, 12-OCOCH$_3$), 2.68 (3H, s, 5-OCOCH$_3$), 3.95 (3H, s, NCH$_3$), 7.22 (1H, ddd, *J*=8, 7, 1 Hz, 8-H), 7.37 (1H, d, *J*=8 Hz, 10-H), 7.69 (1H, ddd, *J*=8, 7, 1.5 Hz, 9-H), 8.13 (1H, d, *J*=2 Hz, 4-H), 8.28 (1H, dd, *J*=8, 1.5 Hz, 7-H), 8.83 (1H, d, *J*=2 Hz, 2-H). ^{13}C-NMR: 18.9 (C3-CH_3), 21.2 (C12-OCO<u>C</u>H$_3$), 21.4 (C5-OCO<u>C</u>H$_3$), 41.9 (N-CH_3), 115.7 (C10), 116.5 (C5a), 118.4 (C4a), 121.6 (C8), 123.1 (C6a), 127.2 (C7), 129. 9 (C4), 130.4 (C3), 132.3 (C12), 134.5 (C9), 136.6 (C11a), 141.1 (C12a), 144.3 (C5), 145.6 (C10a), 156.1 (C2), 169.4 (C12 -O<u>C</u>OCH$_3$), 169.8 (C5-O<u>C</u>OCH$_3$), 178.3 (s, C6). LRMS *m/z*: 390 (M^+), 306 (BP). HRMS *m/z* (M^+): Calcd for $C_{22}H_{18}N_2O_5$: 390.1216. Found: 390.1242.

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8. Observation of strong intramolecular hydrogen bonding in the ^{1}H-NMR spectrum suggested that acetylation occurred selectively at C_4-OH group.
9. Absence of intramolecular hydrogen bonding in the ^{1}H-NMR spectrum suggested that hydrolysis occurred selectively at C_6-OAc group.