Synthesis of Phenanthridones Using Diels–Alder Reactions of 4-Substituted 2(1*H*)-Quinolones Acting as Dienophiles

Reiko FUJITA,*[,a] Kazuhiro WATANABE,[a] Toshiteru YOSHISUJI,[a] Hisao MATSUZAKI,[a] Yoshihiro HARIGAYA,[b] and Hiroshi HONGO*[,a]

Tohoku Pharmaceutical University,[a] 4–4–1 Komatsushima, Aoba-ku, Sendai, 981–8558, Japan and Kitasato University, School of Pharmaceutical Sciences,[b] Shirokane Minato-ku, Tokyo 108–8642, Japan.
Received October 16, 2000; accepted January 4, 2001

Diels–Alder reactions of 2(1*H*)-quinolones having an electron-withdrawing group at the 4-position with 1,3-butadiene derivatives were carried out to give the phenanthridones richly functionalized under the conditions of atmospheric and high pressure. Furthermore, the reactivities of 4-substituted 2(1*H*)-quinolones acting as a dienophile were examined using MO calculation.

Key words 4-substituted 2(1*H*)-quinolone; Diels–Alder reaction; phenanthridone; MO calculation; high pressure; electron-withdrawing group

2(1*H*)-Quinolones are classified as aromatic heterocycles. With regard to reactions of 2(1*H*)-quinolones, substitution reactions[1)] have been amply reported, but little attention has been focussed on addition reactions. Recently, Nakagawa *et al*. have reported the first example, a Diels–Alder (DA) reaction of 1-methoxylcarbonyl-3-phenylthio-2(1*H*)-quinolone with 2-silyloxy-1,3-butadiene in the presence of Lewis acid to give the intermediate (*cis*-phenanthridone derivative) for the Dynemisine A core (a marine alkaloid) in good yield, but the above thermal reaction with 2-silyloxy-1,3-butadiene or Danishefsky's diene was unsuccessful,[2)] and this is the only report for a DA reaction of 2(1*H*)-quinolones. As a phenanthridine skeleton is commonly found in many alkaloids[3)] of Amarylidaceae, phenanthridones richly functionalized would be expected to be potentially valuable synthetic intermediates for them, and to possess interesting pharmacological activities.[3)] Herein, we wish to report the synthesis of phenanthridones by DA reaction of 1-methyl-2(1*H*)-quinolones having an electron-withdrawing group at the 4-position acting as a dienophlie under the conditions of atmospheric and high pressure (AP and HP) and the examination of the reactivities of the 2(1*H*)-quinolones using MO calculation. It is known that the HP strategy has proven extremely useful to surmount the energy barrier imposed by the steric and electronic effects in cycloaddition reaction, such as DA reaction.[4)]

DA Reactions DA reactions of 1-methyl-2(1*H*)-quinolones (**1a**—**e**) having a methoxycarbonyl,[5)] a cyano,[6)] an acetyl, a benzoyl,[7)] and a formyl[8)] group, respectively, at the 4-position with Danishefsky's diene (**2a**) and 2-trimethylsilyloxy-1,3-butadiene (**2b**) were examined under the conditions of AP as shown in Table 1 and Chart 1. First, DA reaction of **1a** with **2a** was carried out at 180 °C for 3 d and the reaction mixture was treated with trifluoroacetic acid (TFA) to give regio- and stereoselectively the *cis*-enone adduct [**3a** (94%), Entry 1]. On the other hand, the same reaction mixture was treated with H_2O to give **3a** (7%), and the methoxy adducts [**4** (44%) and **5** (42%), Entry 2], both of which were quantitatively converted to **3a** by demethanolation with TFA. Consequently, **4** and **5** were isomeric with each other relating to the stereochemistry of the methoxy group. Next, DA reactions of **1b**—**d** with **2a** were carried out at 180 °C for 3 d and the reaction mixtures were treated with TFA, respectively, to give the corresponding *cis*-enone adducts [**3b** (86%), **3c** (96%), and **3d** (61%), Entries 3—5], whereas in the reaction of **1e** with **2a**, hetero DA reaction proceeded to afford the 2(1*H*)-quinolone [**3e** (54%), Entry 6] having a pyran ring, resulting from 1,4-addition of the formyl group to **2a**.[9)] Furthermore, DA reactions of **1a**—**d** with the diene (**2b**) at 180 °C for 3 d afforded regio- and stereoselectively the corresponding *cis*-ketone adducts [**6a** (35%), **6b** (48%), **6c** (44%), and **6d** (5%), Entries 7—10] (Table 1 and Chart 1). But, the reaction of **1e** and **2b** did not give either the DA adduct or the hetero DA adduct.

Moreover, DA reactions of **1a**—**e** with symmetric 2,3-dimethyl- and 2,3-dimethoxy-1,3-butadienes (**2c**, **d**) were investigated under the conditions of AP (Table 1 and Chart 2). The reactions of **1a**—**e** with **2c** at 180 °C for 3 or 5 d afforded stereoselectively the corresponding *cis*-dimethyl adducts [**7a** (98%), **7b** (98%), **7c** (80%), **7d** (25%), and **7e** (93%), Entries 11—15]. Further, the same reactions with **2d** at 200 °C for 3 or 5 d gave stereoselectively the corresponding *cis*-dimethoxy adducts [**8a** (55%), **8b** (43%), **8c** (41%), **8d** (18%), and **8e** (86%), Entries 16—20].

DA reactions of **1a**, **c**, **d** with **2a**, **c** were performed under the conditions of HP (10 kbar) at 80 or 90 °C (Table 1). The reaction mixtures of **1a**, **c**, **d** with **2a** were worked up by TFA to give **3a** (73%), **3c** (78%), and **3d** (36%), respectively, (Entries 21—23) and the same reactions with **2c** afforded **7a** (62%), **7c** (52%), and **7d** (10%) (Entries 24—26). Unfortunately, the comparison of the yields of the adducts produced under the conditions of AP with those of the corresponding adducts formed under the conditions of HP showed that HPDA reactions did not give fruitful results (Table 1).

The stereochemistries of the adducts were investigated as follows. Previously, we have reported that in the DA reaction of 2(1*H*)-pyridones having an electron-withdrawing group at the 4-position with dienes, the 1(2*H*)-isoquinolone derivatives (A) produced were a *cis*-form according to the Alder–Stein rule (*cis*-principle) and a *trans*-A form as a mixture with the corresponding *cis*-A, and in addition, the signal due to H-8a in the *cis*-A appeared at a lower magnetic field than that in the corresponding *trans*-A in ^{1}H-NMR spectra (Fig. 1).[10)] Considering that the compounds (A) are contained as a main moiety in the adducts, all the adducts obtained as only

* To whom correspondence should be addressed. e-mail: refujita@tohoku-pharm.ac.jp

Table 1. Diels–Alder Reactions of **1a**—**e** with **2a**—**d** in *o*-Xylene

Entry	Compd.	Diene	Pressure (kbar)	Temp. (°C)	Time (d)	Work up (r.t.)	Product	Yield (%)
1	**1a**	**2a**	Atmospheric	180	3	TFA	**3a**	94
2	**1a**	**2a**	Atmospheric	180	3	H_2O	**3a**	7
							4	44
							5	42
3	**1b**	**2a**	Atmospheric	160	3	TFA	**3b**	86
4	**1c**	**2a**	Atmospheric	180	3	TFA	**3c**	96
5	**1d**	**2a**	Atmospheric	180	3	TFA	**3d**	61
6	**1e**	**2a**	Atmospheric	180	2	TFA	**3e**	54
7	**1a**	**2b**	Atmospheric	180	3	TFA	**6a**	35
8	**1b**	**2b**	Atmospheric	180	3	TFA	**6b**	48
9	**1c**	**2b**	Atmospheric	180	3	TFA	**6c**	44
10	**1d**	**2b**	Atmospheric	180	3	TFA	**6d**	5
11	**1a**	**2c**	Atmospheric	180	5	—	**7a**	98
12	**1b**	**2c**	Atmospheric	180	3	—	**7b**	98
13	**1c**	**2c**	Atmospheric	180	3	—	**7c**	80
14	**1d**	**2c**	Atmospheric	180	3	—	**7d**	25
15	**1e**	**2c**	Atmospheric	180	3	—	**7e**	93
16	**1a**	**2d**	Atmospheric	200	5	—	**8a**	55
17	**1b**	**2d**	Atmospheric	200	5	—	**8b**	43
18	**1c**	**2d**	Atmospheric	200	5	—	**8c**	41
19	**1d**	**2d**	Atmospheric	200	5	—	**8d**	18
20	**1e**	**2d**	Atmospheric	200	3	—	**8e**	86
21	**1a**	**2a**	10	90	2	TFA	**3a**	73
22	**1c**	**2a**	10	80	2	TFA	**3c**	78
23	**1d**	**2a**	10	90	2	TFA	**3d**	36
24	**1a**	**2c**	10	80	2	—	**7a**	19
25	**1c**	**2c**	10	80	3	—	**7c**	52
26	**1d**	**2c**	10	90	2	—	**7d**	10

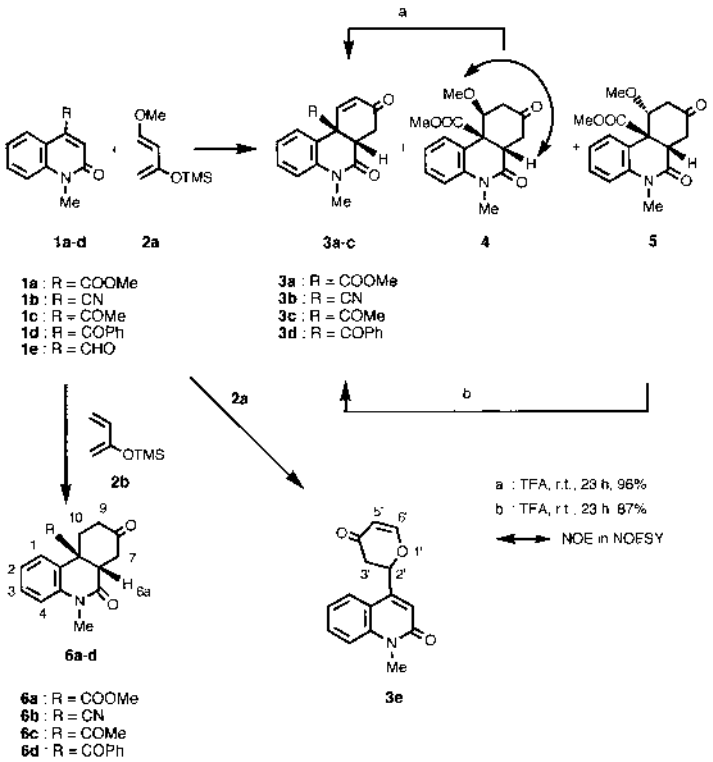
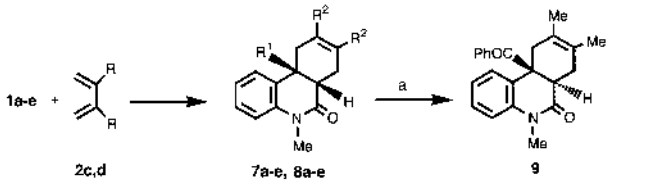


Chart 1

one product may be deduced as a *cis*-form, but the formation of the *trans*-adducts is not completely negligible. The *cis*-stereochemistries of the ring juncture in **3a**, **c** and **7c**, **e** were confirmed by the nuclear Overhauser effect (NOE) measurement of ^{1}H-NMR spectra. Thus, when H-6a was irradiated in these adducts, NOE enhancement was observed between H-6a and the corresponding methoxycarbonyl, acetyl, or formyl group at the 10a-position. Further, **7b** having a cyano group



2c : R = Me
2d : R = OMe

7a : R^1 = COOMe ; R^2 = Me	**8a** : R^1 = COOMe ; R^2 = OMe
7b : R^1 = CN ; R^2 = Me	**8b** : R^1 = CN ; R^2 = OMe
7c : R^1 = COMe ; R^2 = Me	**8c** : R^1 = COMe ; R^2 = OMe
7d : R^1 = COPh ; R^2 = Me	**8d** : R^1 = COPh ; R^2 = OMe
7e : R^1 = CHO ; R^2 = Me	**8e** : R^1 = CHO ; R^2 = OMe

Chart 2

at the 10a-position was determined to be a *cis*-form by X-ray crystallographic analysis (Fig. 2). In addition, the isomer (**9**) of **7d** bearing a benzoyl group at the 10a-position was obtained as shown in Chart 2, and the signal due to H-6a in **7d** and **9** appeared at δ 3.86 and δ 2.56—2.69 in ^{1}H-NMR spectra. Considering the ^{1}H-NMR spectral data of A, **7d** and **9** were deduced as a *cis*- and a *trans*-form. Next, the *cis*-stereochemistries of the ring juncture in **3b**, **d**, **6a**—**d**, **7a**, and **8a**—**e** were deduced by comparing the ^{1}H-NMR spectral data of these adducts with those of the above *cis*- and *trans*-adducts, respectively, and by considering that these adducts were obtained as only one product, similarly to the case of A. Moreover, the stereochemistries of methoxy groups (C-10) in **4** and **5** were determined by NOE in the nuclear and exchange spectroscopy (NOESY) measurement of ^{1}H-NMR spectra. The spectrum of **4** indicated a correlation between the methoxy group and H-6a, but that of **5** did not show a correlation. Consequently, the stereochemistry between the methoxy and methoxycarbonyl group at the 10a-position was confirmed as *cis* in **4** and *trans* in **5**.

Stabilization Energy and Activation Energy We considered the reactivity of the 4-substituted 2(1*H*)-quinolones (**1a**—**e**) acting as a dienophile using the semi-empirical molecular orbital PM 3 method.[11] We optimized **1a**—**e** and **2c** and calculated the stabilization energy as a reaction index. The stabilization energy (ΔE) considering only HOMO-LUMO interaction is written as follows:

$$\Delta E = \frac{2(C_r C_t \gamma_{rt} + C_s C_u \gamma_{su})^2}{E^L - E^H} \quad (1)$$

Here, E^H and E^L are the HOMO energy of diene and the LUMO energy of dienophile, respectively. C_r and C_s are HOMO amplitudes of atom r and s of the diene, respectively and C_t and C_u are LUMO amplitudes of atom t and u of the dienophile, respectively. γ_{rt} and γ_{su} are the integrals denoting the amplitudes of interaction between atoms (r–t and s–u, respectively) generating a new bond. We assume that they have equal values and write them simply as γ. If the experiments are performed under the same temperature and reaction time, the experimental yields of adducts will reflect the reactivity of the reactions and can be compared with the values of ΔE expressed by Eq. (1). As is shown in Table 2, we can see that the calculated values of ΔE are well correlated with the experimental yields of adducts.

It is very interesting that the DA reaction of **1e** with **2a** produced **3e** having a pyran ring but did not form the phenanthridone. Whereas, the DA reaction of **1e** with **2c**

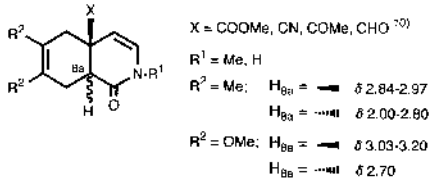


Fig. 1. Chemical Shifts (δ) of A

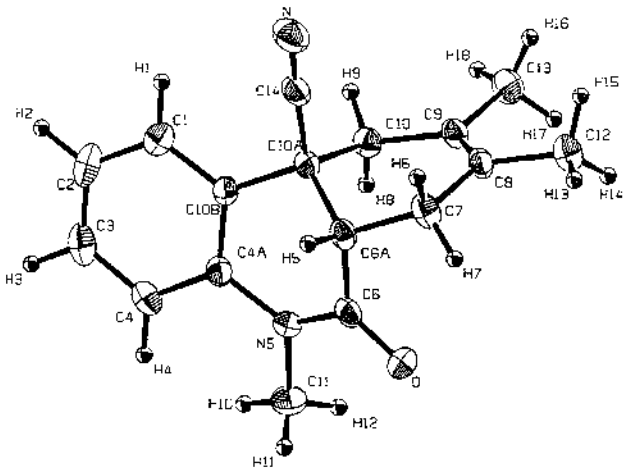


Fig. 2. ORTEP Drawing of **7b**

Table 2. Experimental Yields of Adducts and Calculated Stabilization Energies in Diels–Alder Reactions of **1a**—**e** with **2c**

4-Position R	Stabilization energy $\Delta E/\gamma^2$	Adduct yield (%)	
CN (**1a**)	0.0767	98	High
COOMe (**1b**)	0.0689	98	↑
CHO (**1e**)	0.0655	93	Reaction
COMe (**1c**)	0.0641	80	index
COPh (**1d**)	0.0631	25	|
H [2(1*H*)-quinolone]	0.0552	0	Low

gave the phenanthridone (**7e**) but did not afford the adduct bearing a pyran ring. To study these differences theoretically, we searched and optimized the structures of transition states (TS) of the reactions using the restricted Hartree–Fock (RHF) method with 6-31G (d) basis set in the Gaussian 98 program package.[12] We assumed that the diene and dienophile were far apart in the initial state. We regarded the difference in energy between TS and the initial state as the activation energy (*Ea*). In Table 3, we summarize the calculated activation energies of these four reactions together with the experimental yields of the adducts (**3e**, **7e**). We can see that *Ea* of the 3,4-addition for the reaction with **2c** is smaller than that of the HC=O addition. On the other hand, *Ea* of the HC=O addition for the reaction with **2a** is smaller than that of the 3,4-addition. These results are consistent with the experimental yields of the adducts (**3e**, **7e**).

In conclusion, we have prepared the desired phenanthridones richly functionalized using DA reactions of 2(1*H*)-quinolones having an electron-withdrawing group at the 4-position with symmetric dimethyl- and dimethoxy-1,3-butadienes or unsymmetric silyloxy-1,3-butadienes, and have de-

Table 3. Experimental Yields of Adducts and Calculated Activation Energies for Diels–Alder Reactions of **1e** with **2a** and **2c**

Diene	**1e**			
	3,4-Addition		HC=O addition	
	Ea[a)]	Adduct yield (%)	*Ea*[a)]	Adduct yield (%)
2a	34.60	—	32.81	54
2c	43.03	93	45.36	—

a) Calculated activation energy [RHF/6-31G (d)] in unit of kcal/mol.

veloped a synthetic methodology for phenanthridones. Furthermore, on the reactivities of the 4-substituted 2(1*H*)-quinolones using MO calculation, the calculated stabilization energies (ΔE) are well correlated with the experimental yields of adducts.

Experimental

The following instruments were used to obtain physical data: Melting points, Yanaco micromelting point apparatus (values are uncorrected); IR spectra, Perkin Elmer ET-IR 1725X spectrometer; MS, JEOL JMN-DX 303/JMA-DA5000 spectrometer; NMR spectra, JNM-GSX 400 (^{1}H-NMR; 400 MHz, ^{13}C-NMR; 100 Hz), JNM-EX270 (^{1}H-NMR; 270 MHz, ^{13}C-NMR; 67.5 MHz), JEOL JNM-PMX 60$_{SI}$ spectrometer with tetramethylsilane (TMS) as an internal standard; elemental analyses, PERKINELMER2400 CHN Elemental Analyzer. The following experimental conditions were used for chromatography; column chromatography, Merk Kieselgel silica gel 60 (230—400 mesh); TLC, pre-coated TLC plates with 60F$_{254}$ (2 mm, Merck).

Synthesis of 4-Acetyl-1-methyl-2(1*H*)-quinolone (1c) After a solution of 4-methoxycarbonyl-1-methyl-2(1*H*)-quinolone (**1a**, 2.17 g, 10 mmol) and sodium methoxide (801 mg, 15 mmol) in ethyl acetate 20 ml was stirred for 7 h while refluxing in an oil bath, conc-HCl (30 ml) and water (60 ml) were added. The acidic solution was refluxed for 3 h, neutralized with K_2CO_3 and extracted with chloroform. The chloroform extract was dried over Na_2SO_4, and evaporated to give **1c** (2.0 g, quantitative).

1c: Colorless columns (benzene), mp 95 °C. IR (KBr) cm^{-1}: 1689, 1651, 1587. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 3.37 (3H, s), 7.00 (1H, s), 7.10—7.83 (3H, m), 8.07 (1H, d, J=8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 29.8, 29.9, 114.4, 116.5, 121.4, 122.6, 126.9, 131.1, 140.3, 145.8, 161.2, 200.2. MS *m/z*: 201 (M$^+$), 186. HRMS *m/z*: Calcd for $C_{12}H_{11}NO_2$, 201.0790. Found: 201.0789.

General Procedure for DA Reactions of 1a,[5] 4-Cyano-1-methyl-2(1*H*)-quinolone (1b),[6] 1c, 4-Benzoyl-1-methyl-2(1*H*)-quinolone (1d),[7] and 4-Formyl-1-methyl-2(1*H*)-quinolone (1e)[8] with 2a, b (a) A solution of **1a** (217 mg, 1 mmol) and **2a** (860 mg, 5 mmol) in *o*-xylene (3 ml) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was concentrated *in vacuo* and diluted with chloroform. To the reaction mixture, TFA (1 ml) was added with stirring at room temperature for 20 min and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of fraction eluted with acetone–hexane (1 : 2) was evaporated. The crude product was purified by a preparative TLC over silica gel with ether–hexane (4 : 1) to give *cis*-5,6,6a,7,8,10a-hexahydro-10a-methoxycarbonyl-5-methyl-6,8-dioxo-phenanthridine (**3a**).

(b) To the same reaction mixture, water (2 ml) was added with stirring at room temperature for 20 min and extracted with chloroform. The chloroform layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of the fraction eluted with acetone–hexane (1 : 2) was evaporated. The crude product was rechromatographed on a column of silica gel. The solvent of first fraction eluted with ether–hexane (4 : 1) was evaporated to give **3a** and *cis*-5,6,6a,7,8,9,10,10a-octahydro-*r*-10-methoxy-*c*-10a-methoxy-carbonyl-5-methylphenanthridin-6,8-dione (**4**). The second fraction gave *cis*-5,6,6a,7,8,9,10,10a-octahydro-*r*-10-methoxy-*t*-10a-methoxycarbonyl-5-methylphenanthridin-6,8-dione (**5**).

(c) The reactions of **1b**—**e** (1 mmol) with **2a** (5 mmol) were carried out under the conditions listed in Table 1 and the crude products were purified using the same manner as described above to give *cis*-10a-cyano-5,6,6a,7,8,10a-hexahydro-5-methylphenanthridin-6,8-dione (**3b**), *cis*-10a-acetyl-5,6,6a,7,8,10a-hexahydro-5-methylphenanthridin-6,8-dione (**3c**), *cis*-10a-benzoyl-5,6,6a,7,8,10a-hexahydro-5-methylphenanthridin-6,8-dione (**3d**), 4-(2,3-dihydro-4*H*-pyran-4-one-2-yl)-1-methyl-2(1*H*)-quinolone (**3e**), respectively.

(d) The reactions of **1a**—**d** (1 mmol) with **2b** (710 mg, 5 mmol) were carried out using the same procedure as described above to give *cis*-5,6,6a,7,8,9,10,10a-octahydro-10a-methoxy-carbonyl-5-methylphenanthridin-6,8-dione (**6a**), *cis*-10a-cyano-5,6,6a,7,8,9,10,10a-octahydro-5-methylphenanthridin-6,8-dione (**6b**), *cis*-10a-acetyl-5,6,6a,7,8,9,10,10a-octahydro-5-methylphenanthridin-6,8-dione (**6c**), and *cis*-10a-benzoyl-5,6,6a,7,8,9,10,10a-octahydro-5-methylphenanthridin-6,8-dione (**6d**), respectively. The yields of **3a**—**e**, **4**, **5**, and **6a**—**d** are summarized in Table 1.

3a: Colorless columns, mp 134—136 °C (acetone–hexane). IR (KBr) cm^{-1}: 1738, 1682, 1661, 1660. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (1H, dd, J=4.3, 6.9 Hz), 2.77 (1H, dd, J=6.9, 9.3 Hz), 3.38 (3H, s), 3.64 (1H, dd, J=4.3, 9.3 Hz), 3.81 (3H, s), 6.15 (1H, d, J=10.2 Hz), 7.03—7.42 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 29.9, 36.1, 43.7, 50.1, 53.5, 115.3, 123.6, 123.9, 127.7, 129.7, 130.3, 139.3, 146.9, 168.1, 171.4, 194.6. MS *m/z*: 285 (M$^+$), 226. *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.36; H, 5.45; N, 4.81.

3b: Colorless plates (chloroform–ether), mp 210—213 °C. IR (KBr) cm^{-1}: 2241, 1697, 1675, 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.01 (1H, dd, J=4.0, 17.0 Hz), 3.37 (3H, s), 3.42 (1H, ddd, J=1.0, 4.0, 17.0 Hz), 3.53 (1H, ddd, J=2.0, 4.0, 4.0 Hz), 6.19 (1H, dd, J=1.0, 10.0 Hz,), 6.55 (1H, dd, J=2.0, 10.0 Hz), 7.10 (1H, dd, J=1.0, 8.0 Hz), 7.27 (1H, ddd, J=1.0, 8.0, 8.0 Hz), 7.50 (1H, ddd, J=1.0, 8.0, 8.0 Hz), 7.71 (1H, dd, J=1.0, 8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 30.4, 36.2, 40.7, 44.0, 115.9, 117.6, 120.9, 124.6, 127.2, 131.0, 132.8, 138.8, 141.8, 165.7, 192.8. MS *m/z*: 252 (M$^+$), 224, 184. *Anal.* Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.10; H, 5.06; N, 10.85.

3c: Colorless columns (acetone–hexane), mp 142—144 °C. IR (KBr) cm^{-1}: 1709, 1680, 1666, 1599. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 2.59—2.63 (2H, m, J=6.3 Hz), 3.36 (3H, s), 3.61 (1H, dd, J=6.3, 8.6 Hz), 6.22 (1H, d, J=10.2 Hz), 7.05—7.44 (5H, m, J=10.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 26.1, 29.9, 35.8, 42.9, 56.4, 115.5, 123.5, 124.1, 128.2, 129.8, 131.2, 139.6, 146.4, 168.2, 194.4, 204.0. MS *m/z*: 285 (M$^+$), 226. *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.34; H, 5.67; N, 4.93.

3d: Colorless columns (acetone–hexane), mp 175—177 °C. IR (KBr) cm^{-1}: 1683, 1667, 1597. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (1H, dd, J=4.3, 16.8 Hz), 3.03 (1H, dd, J=5.3, 16.8 Hz,), 3.40 (3H, s), 3.86 (1H, dd, J=4.3, 5.3 Hz), 6.16 (1H, d, J=10.2 Hz), 6.88 (1H, d, J=10.2 Hz), 7.08 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 30.2, 35.5, 43.9, 55.8, 115.8, 124.0, 124.4, 128.0, 129.6, 130.0, 130.5, 133.1, 135.1, 139.3, 148.4, 167.8, 194.6, 199.7. MS *m/z*: 331 (M$^+$), 105. *Anal.* Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.15; H, 5.33; N, 4.30.

3e: Yellow columns (acetone–hexane), mp 160—161 °C. IR (KBr) cm^{-1}: 1656, 1652, 1595. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (2H, dd, J=9.4, 18.8 Hz), 3.75 (3H, s), 5.62 (1H, d, J=6.1 Hz), 5.87 (1H, dd, J=9.4, 9.4 Hz, 0.6 Hz), 6.97 (1H, d, J=0.6 Hz), 7.28 (1H, ddd, J=1.0, 8.0, 8.0 Hz), 7.47 (1H, dd, J=1.0, 9.3 Hz), 7.57 (1H, d, J=6.1 Hz), 7.60—7.66 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 29.6, 42.2, 76.7, 108.0, 115.2, 117.6 119.1, 122.4, 123.8, 131.2, 140.4, 145.1, 161.7, 162.7, 190.8. MS *m/z*: 255 (M$^+$), 266, 198. *Anal.* Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.35; H, 4.93; N, 5.23.

4: Colorless columns (ether), mp 140—142 °C. IR (KBr) cm^{-1}: 1727, 1678, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (1H, dd, J=15.5, 6.3 Hz), 2.78 (1H, d, J=4.3 Hz), 3.03 (3H, s), 3.16 (1H, dd, J=15.5, 4.3 Hz), 3.35 (3H, s), 3.75 (1H, dd, J=6.3, 4.3 Hz), 3.84 (3H, s), 4.19 (1H, dd, J=4.3 Hz), 7.03—7.11 (2H, m), 7.34—7.40 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 30.1, 38.2, 41.9, 43.1, 53.2, 54.0, 58.3, 84.0, 115.4, 123.0, 123.3, 126.3, 129.1, 141.3, 168.1, 172.5, 204.9. MS *m/z*: 317 (M$^+$), 218. *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.09; H, 6.11; N, 4.18.

5: Colorless columns (acetone–hexane), mp 195—197 °C. IR (KBr) cm^{-1}: 1735, 1678, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (1H, dd, J=14.2, 13.9 Hz), 2.57 (1H, dd, J=5.1, 14.2 Hz), 2.63 (1H, dd, J=3.0, 15.4 Hz), 2.77 (1H, dd, J=3.0, 15.4 Hz), 3.36 (3H, s), 3.39 (3H, s), 3.67 (3H, s), 3.75 (1H, dd, J=5.1, 13.9 Hz), 4.78 (1H, dd, J=3.0, 3.0 Hz), 7.06—7.42 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 29.7, 39.2, 39.5, 41.6, 52.1, 52.9, 57.4, 80.8, 115.7, 120.8, 123.8, 127.3, 129.7, 140.2, 168.8, 171.4, 204.8. MS *m/z*: 317 (M$^+$), 226. *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.09; H, 6.11; N, 4.18.

6a: Colorless columns (ether), mp 120—122 °C. IR (KBr) cm^{-1}: 1729, 1676, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.40—2.53 (5H, m), 2.74 (1H, dd, J=7.9, 15.2 Hz), 3.39 (3H, s), 3.58 (1H, dd, J=5.6, 7.9 Hz), 3.79 (3H, s), 7.04—7.42 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 30.0, 30.1, 37.4, 38.9, 45.0, 48.6, 53.1,

115.7, 123.8, 124.3, 126.4, 129.3, 139.4, 168.4, 162.8, 206.3. MS *m/z*: 287 (M^+), 228. *Anal.* Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.64; H, 5.94; N, 4.59.

6b: Colorless powder (ether), mp 184—186 °C. IR (KBr) cm^{-1}: 2239, 1728, 1670, 1601. ^{1}H-NMR ($CDCl_3$) δ: 2.21—2.26 (2H, m), 2.56 (1H, dddd, J=2.5, 2.5, 5.0, 16.0 Hz), 2.80 (1H, dddd, J=1.0, 6.0, 12.0, 16.0 Hz), 2.88 (1H, ddd, J=1.0, 6.0, 16.0 Hz), 3.35 (1H, ddd, J=2.5, 2.5, 16.0 Hz), 3.41 (3H, s), 3.45 (1H, m), 7.09 (1H, dd, J=1.0, 7.0 Hz), 7.24 (1H, ddd, J=1.0, 7.0, 8.0 Hz), 7.46 (1H, ddd, J=2.0, 7.0, 8.0 Hz), 7.70 (1H, dd, J=2.0, 8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 30.3, 32.5, 37.9, 38.3, 41.1, 45.0, 116.0, 119.9, 122.8, 124.4, 126.7, 130.3, 138.0, 165.8, 203.8. MS *m/z*: 254 (M^+), 184, 156. *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.80; H, 5.84; N, 11.03.

6c: Colorless columns (acetone–hexane), mp 163—164 °C. IR (KBr) cm^{-1}: 1703, 1669, 1598. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 2.10—2.19 (1H, m), 2.33 (1H, dd, J=11.6, 14.6 Hz), 2.46—2.57 (3H, m), 2.68 (1H, dd, J=5.0, 14.2 Hz), 3.35 (3H, s), 3.48 (1H, dd, J=5.0, 11.6 Hz), 7.09—7.47 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 25.1, 29.9, 29.8, 36.7, 38.9, 45.0, 53.7, 115.9, 122.4, 124.0, 127.0, 129.6, 140.4, 168.6, 206.0, 206.1. MS *m/z*: 271 (M^+), 228 (M^+-COMe). HRMS *m/z*: Calcd for $C_{16}H_{17}NO_3$, 271.1208. Found: 271.1227. *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.92; H, 6.36; N, 4.78.

6d: Colorless columns (acetone–hexane), mp 163—164 °C. IR (KBr) cm^{-1}: 1712, 1674, 1598. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.17 (2H, m, J=15.5, 1.9 Hz), 2.45 (1H, ddd, J=1.9, 6.8, 13.7 Hz), 2.56—2.77 (2H, m), 2.90 (1H, ddd, J=1.9, 4.3, 15.5 Hz), 3.43 (3H, s), 3.77 (1H, br d, J=4.3 Hz), 7.04—7.50 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 30.2, 31.0, 37.9, 38.0, 38.9, 45.1, 53.0, 116.0, 123.7, 125.8, 127.3, 128.5, 129.3, 129.4, 132.5, 135.5, 139.0, 168.1, 201.5, 206.7. MS *m/z*: 333 (M^+), 228, 105. *Anal.* Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.44; H, 5.99; N, 4.12.

Demethanolation of 4 and 5 A solution of **4** (51 mg, 0.16 mmol), TFA (1 ml), and benzene (5 ml) was stirred at room temperature for 23 h and concentrated *in vacuo*. The residue was purified by preparative TLC over silica gel with ether–hexane (5 : 1) to give **3a** (44 mg, 96%). Demethanolation of **5** (44 mg, 0.14 mmol) was carried out using the same manner as described above to give **3a** (35 mg, 87%).

General Procedure for DA Reactions of 1a—e with 2c, d The solution of **1a** (217mg, 1 mmol) and **2c** (410 mg, 5 mmol) in *o*-xylene (3 ml) was heated at 180 °C for 5 d in a sealed tube and the reaction mixture was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of the fraction eluted with acetone–hexane (1 : 2) was evaporated. The crude product was purified by preparative TLC over silica gel with acetone–hexane (1 : 3) to give *cis*-5,6,6a,7,10,10a-hexahydro-10a-methoxycarbonyl-5,8,9-trimethylphenanthridin-6-one (**7a**). The reactions of **1b**—**e** (1 mmol) with **2c** (5 mmol) were carried out under the conditions listed in Table 1 and the reaction mixtures were treated in the same manner as described above to give *cis*-10a-cyano-5,6,6a,7,10,10a-hexahydro-5,8,9-trimethylphenanthridin-6-one (**7b**), *cis*-10a-acetyl-5,6,6a,7,10,10a-hexahydro-5,8,9-trimethylphenanthridin-6-one (**7c**), *cis*-10a-benzoyl-5,6,6a,7,10,10a-hexahydro-5,8,9-trimethylphenanthridin-6-one (**7d**), *cis*-10a-formyl-5,6,6a,7,10,10a-hexahydro-5,8,9-trimethylphenanthridin-6-one (**7e**), respectively. The reactions of **1a**—**e** (1 mmol) with **2d** (570 mg, 5 mmol) were carried out under the conditions listed in Table 1 and the reaction mixtures were treated in the same manner as described above to give *cis*-5,6,6a,7,10,10a-hexahydro-8,9-dimethoxy-10a-methoxycarbonyl-5-methylphenanthridin-6-one (**8a**), *cis*-10a-cyano-5,6,6a,7,10,10a-hexahydro-8,9-dimethoxy-5-methylphenan-thridin-6-one (**8b**), *cis*-10a-acetyl-5,6,6a,7,10,10a-hexahydro-8,9-dimethoxy-5-methylphenanthridin-6-one (**8c**), *cis*-10a-benzoyl-5,6,6a,7,10,10a-hexahydro-8,9-dimethoxy-5-methylphenanthridin-6-one (**8d**), *cis*-10a-formyl-5,6,6a,7,10,10a-hexahydro-8,9-dimethoxy-5-methylphenanthridin-6-one (**8e**), respectively. The yields of **7a**—**e** and **8a**—**e** are summarized in Table 1.

7a: Colorless oil. IR (film) cm^{-1}: 1732, 1676, 1601. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, s), 1.63 (3H, s), 2.14 (1H, d, J=15.5 Hz), 2.31 (1H, d, J=18.0 Hz), 2.47—2.57 (2H, m), 3.28 (1H, dd, J=5.3, 5.3 Hz), 3.37 (3H, s), 3.74 (3H, s), 7.00—7.05 (2H, m), 7.26—7.36 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.7, 18.9, 29.5, 29.9, 35.9, 41.6, 48.8, 52.7, 115.1, 122.8, 123.2, 124.0, 125.5, 127.5, 128.4, 139.2, 170.6, 173.9. MS *m/z*: 299 (M^+), 240, 217. HR MS *m/z*: Calcd for $C_{18}H_{21}NO_3$: 299.1522. Found: 299.1500.

7b: Colorless needles (ether), mp 136—138 °C. IR (KBr) cm^{-1}: 2240, 1676, 1602. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, s), 1.75 (3H, s), 2.25 (1H, d, J=17.8 Hz), 2.37 (1H, d, J=17.8 Hz), 2.57 (1H, d, J=17.8 Hz), 2.94 (1H, d, J=17.8 Hz), 3.04 (1H, d, J=6.0 Hz), 3.38 (3H, s), 7.05 (1H, d, J=8.0 Hz), 7.17 (1H, dd, J=7.6, 8.0 Hz), 7.39 (1H, dd, J=7.6, 8.0 Hz), 7.63 (1H, d, J=7.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.7, 18.8, 28.9, 30.2, 38.5, 39.7, 41.7, 115.5, 120.9, 121.2, 123.7, 124.8, 125.4, 126.1, 129.5, 138.1, 167.5. MS *m/z*: 266 (M^+), 223, 185. *Anal.* Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.73; H, 7.13; N, 10.45. X-Ray analytical data (Fig. 1): 2θ range (20.0—30.7°), crystal system: monoclinic, temperature: 23 °C, space group: $P2_1/n$, D_{calc} (g/cm): 1.235, lattice parameters (Å): a=12.16(1), b=9.49(8), c=12.66(7), V=1433(2) Å^3, β=101.30(5)°. Z=4. μ(Cu$K\alpha$): 5.77 cm^{-1}. Further details have been deposited with the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambrige CB2 1EW, U.K.

7c: Colorless columns (hexane), mp 139—140 °C. IR (KBr) cm^{-1}: 1702, 1672, 1602. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s), 1.65 (3H, s), 2.05 (3H, s), 2.10 (2H, br d, J=18.1 Hz), 2.33 (1H, d, J=17.5 Hz), 2.49 (1H, d, J=17.5 Hz), 3.18 (1H, dd, J=6.6, 7.9 Hz), 3.32 (3H, s), 6.69—7.35 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.6, 19.0, 25.2, 29.6, 30.1, 34.6, 41.5, 53.6, 115.1, 121.9, 123.4, 124.5, 125.7, 126.0, 128.0, 140.1, 171.4, 207.4. MS *m/z*: 283 (M^+), 240. HRMS *m/z*: Calcd for $C_{18}H_{21}NO_2$, 283.1572. Found: 283.1593. *Anal.* Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.29. Found: C, 76.26; H, 7.65; N, 4.79.

7d: Colorless columns (hexane), mp 126—127 °C. IR (KBr) cm^{-1}: 1676, 1658, 1597. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (3H, s), 1.66 (3H, s), 1.75 (1H, br d, J=17.2 Hz), 2.17 (1H, d, J=17.5 Hz), 2.47 (1H, br d, J=17.2 Hz), 2.70 (1H, d, J=17.5 Hz), 3.41 (4H, br s), 6.90—7.52 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.6, 18.8, 28.4, 30.0, 36.6, 42.2, 52.8, 115.5, 122.7, 123.1, 123.1, 126.7, 127.9, 128.1,128.6, 129.3, 131.9, 135.9, 139.1, 170.2, 201.1. MS *m/z*: 345 (M^+), 240, 105. *Anal.* Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.20; H, 6.90; N, 3.85.

7e: Pale yellow powder (acetone–ether), mp 93—96 °C. IR (KBr) cm^{-1}: 1720, 1665, 1599, 1665, 1422. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, s), 1.662 (3H, s), 2.06 (1H, br d, J=17.0 Hz), 2.22 (1H, d, J=17.0 Hz), 2.40 (1H, d, J=17.0 Hz), 2.55 (1H, br d, J=17.0 Hz), 3.07 (1H, dd, J=5.5, 5.5 Hz), 3.38 (3H, s), 6.96 (1H, dd, J=1.0, 7.6 Hz), 6.98—7.11 (2H, m), 7.34 (1H, dd, J=7.6, 8.0 Hz), 9.56 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 18.7, 19.0, 29.0, 29.9, 32.9, 39.2, 51.4, 115.5, 122.3, 123.3, 124.3, 124.5, 125.9, 128.9, 140.0, 169.8, 199.3. MS *m/z*: 269 (M^+), 240, 212, 187. *Anal.* Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.59; H, 7.39; N, 5.09.

8a: Yellow oil. IR (film) cm^{-1}: 1735, 1679, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.30—2.47 (2H, m, J=16.0 Hz), 2.82 (1H, d, J=16.0 Hz), 2.87 (1H, d, J=16.0 Hz), 3.34 (1H, dd, J=4.3, 9.3 Hz), 3.40 (3H, s), 3.60 (6H, s), 3.80 (3H, s), 7.02—7.09 (3H, m), 7.30 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 23.4, 30.1, 30.7, 41.4, 49.1, 52.9, 57.4, 57.5, 115.4, 123.4, 125.3, 126.7, 128.8, 135.0, 136.5, 139.0, 169.3, 173.0. MS *m/z*: 331 (M^+), 217. HRMS *m/z*: Calcd for $C_{18}H_{21}NO_5$, 331.1420. Found: 331.1403.

8b: Pale yellow columns (ether), mp 99—100 °C. IR (KBr) cm^{-1}: 2239, 1679, 1601. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (2H, m). 2.73 (1H, m), 3.07 (1H, d, J=6.1 Hz), 3.30 (1H, d, J=18.0 Hz), 3.40 (3H, s), 3.60 (3H, s), 3.71 (3H, s), 7.07 (1H, d, J=8.0 Hz), 7.19 (1H, dd, J=7.6, 8.0 Hz), 7.42 (1H, dd, J=7.6, 8.0 Hz), 7.65 (1H, d, J=7.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 23.4, 30.3, 33.9, 39.9, 41.9, 57.4, 58.1, 115.7, 120.3, 123.8, 123.9, 126.1, 123.0, 133.3, 137.3, 138.0, 166.3. MS *m/z*: 298 (M^+), 269, 184. HRMS *m/z*: Calcd for $C_{17}H_{18}N_2O_2$, 298.1317. Found: 293.1318. *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.59; H, 6.45; N, 9.13.

8c: Pale yellow oil. IR (film) cm^{-1}: 1709, 1680, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.31 (2H, d, J=7.0 Hz), 2.62 (2H, dd, J=1.9, 1.9 Hz), 3.22 (1H, dd, J=7.0, 7.0 Hz), 3.34 (3H, s), 3.51 (6H, s), 3.66 (3H, s), 7.02—7.35 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 24.1, 25.2, 29.7, 41.2, 53.6, 57.3, 58.0, 115.3, 123.7, 124.8, 125.8, 129.0, 134.4, 136.4, 140.0, 168.9, 206.0. MS *m/z*: 315 (M^+), 272, 201. HRMS *m/z*: Calcd for $C_{18}H_{21}NO_5$, 315.1471. Found: 315.1453.

8d: Yellow oil. IR (film) cm^{-1}: 1720, 1680, 1599. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (1H, dd, J=2.7, 15.5 Hz), 2.26 (1H, d, J=12.5 Hz), 2.76 (1H, dd, J=1.5, 15.5 Hz), 3.08 (1H, d, J=12.5 Hz), 3.39—3.43 (4H, br d, J=2.5 Hz), 3.57 (3H, s), 3.65 (3H, s), 7.03—7.13 (3H, m), 7.36—7.50 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 22.7, 30.2, 31.3, 42.2, 52.9, 57.4, 57.6, 115.7, 123.4, 126.7, 126.9, 128.3 (C2), 129.0, 129.3 (C2), 132.2, 135.1, 135.3, 135.7, 139.0, 168.9, 200.0. MS *m/z*: 377 (M^+), 272, 263, 240. HRMS *m/z*: Calcd for $C_{23}H_{23}NO_4$, 377.1627. Found: 377.1647.

8e: Pale yellow oil. IR ($CHCl_3$) cm^{-1}: 1728, 1674, 1601, 1213, 1053, 667. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (1H, ddd, J=3.0, 6.0, 16.0 Hz), 2.37 (1H, d, J=16.0 Hz), 2.68 (1H, d, J=16.0 Hz), 2.88 (1H, ddd, J=2.0, 4.0, 16.0 Hz), 3.11 (1H, dd, J=4.0, 6.0 Hz), 3.41 (3H, s), 3.59 (6H, s), 3.63 (3H, s), 6.98 (1H, dd, J=1.4, 7.9 Hz), 7.09—7.13 (2H, m), 7.38 (1H, m), 9.60 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 23.1, 28.2, 39.0, 57.4, 57.8, 115.8, 123.6, 123.8, 125.8, 129.2, 134.6, 136.4, 139.7, 168.5, 198.2. MS *m/z*: 301 (M^+), 240,

187. HRMS *m/z*: Calcd for $C_{17}H_{19}NO_4$, 301.1314. Found: 301.1322.

Isomerization of 7d A solution of **7d** (86 mg, 0.287 mmol), aqueous 10% NaOH (3 ml), and EtOH (5 ml) was refluxed for 1.5 h and the reaction mixture was extracted with chloroform. The chloroform extract was washed with saturated aqueous NaCl (5 ml), dried over Na_2SO_4, and evaporated. The residue was purified by preparative TLC (ether–hexane=1 : 1) to give *trans*-10a-benzoyl-5,6,6a,7,10,10a-hexahydro-5,8,9-trimethylphenanthridin-6-one [**9**, *Rf*=0.43, 11 mg, (13%)] and the recovery of **7d** [*Rf*=0.55, 52 mg (60%)].

9: Colorless needles (hexane), mp 137—138 °C. IR (KBr) cm^{-1}: 1683, 1669, 1597. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, s), 1.70 (3H, s), 2.47 (1H, d, *J*=17.0 Hz), 2.56—2.69 (3H, m), 2.76 (1H, d, *J*=17.0 Hz), 3.37 (3H, s), 6.87—7.39 (9H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.7, 19.1, 29.7, 31.2, 39.8, 42.5, 52.5, 115.5, 120.0, 122.5, 125.8, 126.4 (C2), 126.9, 127.7 (C2), 127.8, 129.2, 129.9, 139.3, 141.0, 171.4, 203.7. MS *m/z*: 345 (M^+), 240, 105. *Anal.* Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.19; H, 6.63; N, 3.83.

General Procedure for HPDA Reactions of 1a, c, d with 2a, c (a) A mixture of **1a** (108 mg, 0.5 mmole) and **2a** (430 mg, 2.5 mmol) in dichloromethane (3 ml) was placed in a Teflon tube. The tube was placed in a high pressure reactor and pressurized to 10 kbar, followed by heating at 90 °C for 48 h. The pressure was released and the reaction mixture was treated with TFA, concentrated *in vacuo*. The residue was purified by column chromatography and preparative TLC as described above to give **3a**. The reactions of **1c**, **d** (0.5 mmol) with **2a** (430 mg, 2.5 mmol) carried out under the reaction conditions listed in Table 1 and the reaction mixtures were treated in the same way as described above to give **3c**, **d**.

(b) A mixture of **1a**, **c**, **d** (0.5 mmole) and **2c** (205 mg, 2.5 mmol) in dichloromethane (3 ml) was placed in a Teflon tube, and treated under the reaction conditions listed in Table 1. The reaction mixture was concentrated *in vavuo* and the residue was chromatographed on a column of silica gel to give **7a**, **c**, **d**. The yields of **3a**, **c**, **d** and **7a**, **c**, **d** are summarized in Table 1.

Calculation of Activation Energy We optimized the structures of the initial and the transition states using RHF/6-31G (d) in Gaussian 98 program package.[12] The effect of a solvent was not considered. Assuming that the diene and the dienophile were far apart at the initial state, we calculated the activation energy (*Ea*) as a difference in energy between the TS and the initial state. After optimizing the TS structure, we performed the vibrational calculation and confirmed that the TS had exactly one imaginary vibrational frequency. We also carried out the intrinsic reaction coordinate (IRC) calculation to make sure that the TS connects the initial with the intended final state.

References

1) *a*) Mittasch A., *J. Prakt. Chem*., **68**, 103—105 (1903); *b*) Cook D. J., Bowen R. E., Sorter P., Daniels E., *J. Org. Chem*., **26**, 4949—4955 (1961); *c*) Tomisawa H., Watanabe M., Fujita R., Hongo H., *Chem. Pharm. Bull.*, **18**, 919—924 (1970); *d*) Tomisawa H., Kobayashi Y., Hongo H., Fujita R., *ibid*., **18**, 923—936 (1970); *e*) Tomisawa H., Fujita R., Hongo H., Kato H., *ibid*., **22**, 2091—2096 (1974); *f*) Tomisawa H., Fujita R., Hongo H., *ibid*., **23**, 592—596 (1975); *g*) Nishiwaki N., Tanaka A., Uchida M., Tohda Y., Ariga M., *Bull. Chem. Soc. Jpn*., **69**, 1377—1381 (1996); *h*) Nishiwaki N., Tanaka C., Asahara M., Asaka N., Tohda Y., Ariga M., *Heterocycles*, **51**, 567—574 (1999).

2) Nagata T., Koide Y., Nara K., Itoh E., Arisawa M., Naruto S., Torisawa Y., Hino T., Nakagawa M., *Chem. Pharm. Bull*., **44**, 451—453 (1996).

3) For biological properties of phenanthridine alkaloids, see: *a*) Okamoto T., Torii Y., Isogai Y., *Chem. Pharm. Bull*., **16**, 1860—1864 (1968); *b*) Ceriotti G G., *Nature* (London), **213**, 595—596 (1967); *c*) Mondon A., Krohn K., *Chem. Ber.*, **108**, 445—463 (1975).

4) *a*) Matsumoto K., Sera A., Uchida T., *Synthesis*, **1985**, 1—26; *b*) Matsumoto K., Sera A., *ibid.*, **1985**, 999—1027.

5) Kaneko C., Naito T., Hashiba M., *Chem. Pharm. Bull.*, **27**, 1813—1819 (1979).

6) *a*) Bailey A. S., Morris T., Rashid Z., *J. Chem. Soc*., *Perkin Trans. 1*, **1975**, 420—424; *b*) Fujita R., Watanabe K., Hongo H., Annual Report of Tohoku College of Pharmacy, **44**, 105—109 (1997) [*Chem. Abstr*., **130**, 13911 (1999)].

7) Fujita R., Yasugahira H., Tomisawa H., *Annual Report of Tohoku College of Pharmacy*, **39**, 91—99 (1992) [*Chem. Abstr*., **120**, 217224 (1994)].

8) *a*) Cook D. J., Stamper M., *J. Am. Chem. Soc*., **69**, 1467—1468 (1947); *b*) Forbis R. M., Reinehart K. L., Jr., *ibid*., **95**, 5003—5013 (1973).

9) Trost B. M., "Comprehensive Organic Synthesis," Vol. 2, Pergamon Press, Oxford, 1991, pp. 661—706.

10) *a*) Fujita R., Hoshino M., Tomisawa H., Hongo H., *Chem. Pharm. Bull*., **48**, 1814—1817 (1999); *b*) Kato H., Fujita R., Hongo H., Tomisawa H., *Heterocycles*, **12**, 1—4 (1979); *c*) Tomisawa H., Kato H., Fujita R., Hongo H., *Chem. Pharm. Bull*., **27**, 810—812 (1979); *d*) Kato H., Fujita R., Hongo H., Tomisawa H., *Annual Report of Tohoku College of Pharmacy*, **25**, 51—55 (1978) [*Chem. Abstr*., **91**, 56790 (1979)]; *e*) Tomisawa H., Fujita R., Kato H., Hayasaka K., Kamimura T., Hongo H., *Chem. Pharm. Bull*., **36**, 1882—1885 (1988); *f*) Fujita R., Watanabe K., Masuyama T., Matsuzaki H., Nakano H., Okuyama Y., Hongo H., *J. Tohoku Pharmaceutical University*, **46**, 77—81 (1999).

11) *a*) Mopac 93 release 2, Stewart J. J. P., Fujitsu Limited, Tokyo, Japan, 1994; *b*) Stewart J. J. P., *J. Comp. Chem*., **10**, 209—220 (1989); *c*) *Idem*, *ibid.*, **10**, 221—264 (1989).

12) Gaussian 98, Revision A.9, Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Zakrzewski V. G., Montgomery J. A., Jr., Stratmann R. E., Burant J. C., Dapprich S., Millam J. M., Daniels A. D., Kudin K. N., Strain M. C., Farkas O., Tomasi J., Barone V., Cossi M., Cammi R., Mennucci B., Pomelli C., Adamo C., Clifford S., Ochterski J., Petersson G. A., Ayala P. Y., Cui Q., Morokuma K., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Cioslowski J., Ortiz J. V., Baboul A. G., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Gomperts R., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Andres J. L., Gonzalez C., Head-Gordon M., Replogle E. S., Pople J. A., Gaussian, Inc., Pittsburgh PA, 1998.