Novel Diels–Alder Reaction of 4-Nitro-1(2*H*)-isoquinolones

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A novel Diels–Alder (DA) reaction with 4-nitro-1(2*H*)-isoquinolones acting as the dienophile afforded 5(6*H*)-phenanthridone derivatives. The DA reaction of 4-nitro-1(2*H*)-isoquinolone with 1-methoxy-1,3-butadiene gave biologically active 5(6*H*)-phenanthridone possessing in a high yield. Regioselectivity of 4-nitro-1(2*H*)-isoquinolones with 1-methoxy-3-silyloxy-1,3-butadiene was calculated using molecular orbital (MO) calculations.

Key words 4-nitro-1(2*H*)-isoquinolone; 5(6*H*)-phenanthridone; Diels–Alder reaction; inhibitor; regioselectivity; calculation

1(2*H*)-Isoquinolone derivatives are classified as aromatic heterocycles. Substitution reactions[1,2] of 1(2*H*)-isoquinolone derivatives have been reported, however, little attention has been focused on addition reactions. Dyke *et al.* reported a Diels–Alder (DA) reaction of 2-methyl-1(2*H*)-isoquinolone derivatives as the diene.[3] To the best of our knowledge, however, there have been no reports of a DA reaction of 1(2*H*)-isoquinolones acting as dienophiles. DA reaction of 1(2*H*)-isoquinolone derivatives with dienes afforded phenanthridones. A number of Amaryllidaceae alkaloids contain phenanthridine skeletons, and are thought to be potentially valuable synthetic intermediates. Moreover, these alkaloids may possess novel pharmacological activities.[4—7] Recently, Weltin *et al.* verified the ability of 5(6*H*)-phenanthridones to inhibit PARP [poly(ADP-ribose)polymerase] activity in lymphoma cells.[8] Herein, we report a novel Diels–Alder reaction of 4-nitro-1(2*H*)-isoquinolones acting as the dienophile. This Diels–Alder reaction is a novel synthetic methodology employing the phenanthridine skeleton. Examination of the regioselectivity of 4-nitro-1(2*H*)-isoquinolones[9] with 1-methoxy-3-silyloxy-1,3-butadienes using molecular orbital (MO) calculations is also discussed in the current work.

DA Reaction of 4-Nitro-1(2*H*)-isoquinolones First, DA reactions of 2-methyl- (**1a**)[9] and 2-unsubstituted-1(2*H*)-isoquinolones (**1b**)[9] bearing a nitro group at the 4-position with 1-methoxy-1,3-butadienes (**2a**—**c**) were examined under atmospheric pressure conditions, as shown in Table 1 (entries 1—8) and Chart 1. Reaction of **1a** with 1-methoxy-1,3-butadiene (**2a**) gave the 6-methyl-5(6*H*)-phenanthridone (**4a**[10]: 59%; entry 1 and 26%; entry 2) at 180 °C for 3 d in 1,2-dimethoxyethane (DME) and *o*-xylene (pathway A). Reaction of **1b** with **2a** gave 5(6*H*)-phenanthridone (**4b**[11]: 82%; entry 3) at 160 °C for 3 d in DME in high yield. Reaction of **1a** with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**2b**: TMS) was carried out in *o*-xylene and reaction mixture was treated with trifluoroacetic acid (TFA) to give 8-hydroxy-6-methyl-5(6*H*)-phenanthridone (**5a**[12]: 72%; entry 4) as a single product (pathway B). However, in DME, reaction of **1a** with **2b** (entry 5) gave **5a** (63%) and 8-methoxy-6-methyl-5(6*H*)-phenanthridone (**7a**[13]: 7%). Further, reaction of **1a** with 1-methoxy-3-*t*-butyldimethyl-silyloxy-1,3-butadiene (**2c**: TBS) in DME (entry 6) gave **5a** (52%), **7a** (2%) and 8-*t*-butyldimethylsilyloxy-6-methyl-5(6*H*)-phenanthridone (**6a**: 29%) in total 83% yield. Moreover, reaction of **1b** with **2b** gave 8-hydroxy-5(6*H*)-phenanthridone (**5b**[14]: 75%; entry 7), whereas reaction of **1b** with **2c** gave **5b** (37%) and **6b** (6%) in DME (entry 8). Next, reaction of **1a**, **b** with symmetric dienes (**2d**, **e**) were subsequently investigated as shown in Table 1 (entries 9—12) and Chart 1. The reaction of **1a** with 2,3-dimethyl-1,3-butadiene (**2d**) afforded 6,8,9-trimethyl-5(6*H*)-phenanthridone (**8a**: 18%; entry 9 and 36%; entry 10) at 180 °C for 3 d in *o*-xylene and DME (pathway C). But, the reaction of **1a** with **2d** did not give 8,9-dimethyl-5(6*H*)-phenanthridone (**8b**), and **1b** was recovered. Further, the re-

Table 1. Diels–Alder Reactions of Isoquinolones (**1a**, **b**) with 1,3-Butadienes (**2a**—**e**)

Entry	Isoquinolone	Diene	Solvent	Temp. (°C)	Time (d)	Product	Yield (%)	
1	**1a**	**2a**	DME	180	3	**4a**	59	
2	**1a**	**2a**	*o*-Xylene	180	3	**4a**	26	
3	**1b**	**2a**	DME	160	3	**4b**	82	
4	**1a**	**2b**	*o*-Xylene	180	3	**5a**	72	
5	**1a**	**2b**	DME	180	3	**5a**	63	T=70%
						7a	7	
6	**1a**	**2c**	DME	180	3	**5a**	52	T=83%
						6a	29	
						7a	2	
7	**1b**	**2b**	DME	180	5	**5b**	75	
8	**1b**	**2c**	DME	180	3	**5b**	37	T=43%
						6b	6	
9	**1a**	**2d**	*o*-Xylene	180	3	**8a**	18	
10	**1a**	**2d**	DME	180	3	**8a**	36	
11	**1a**	**2e**	DME	180	3	**8c**	28	
12	**1b**	**2e**	DME	180	5	**8d**	21	

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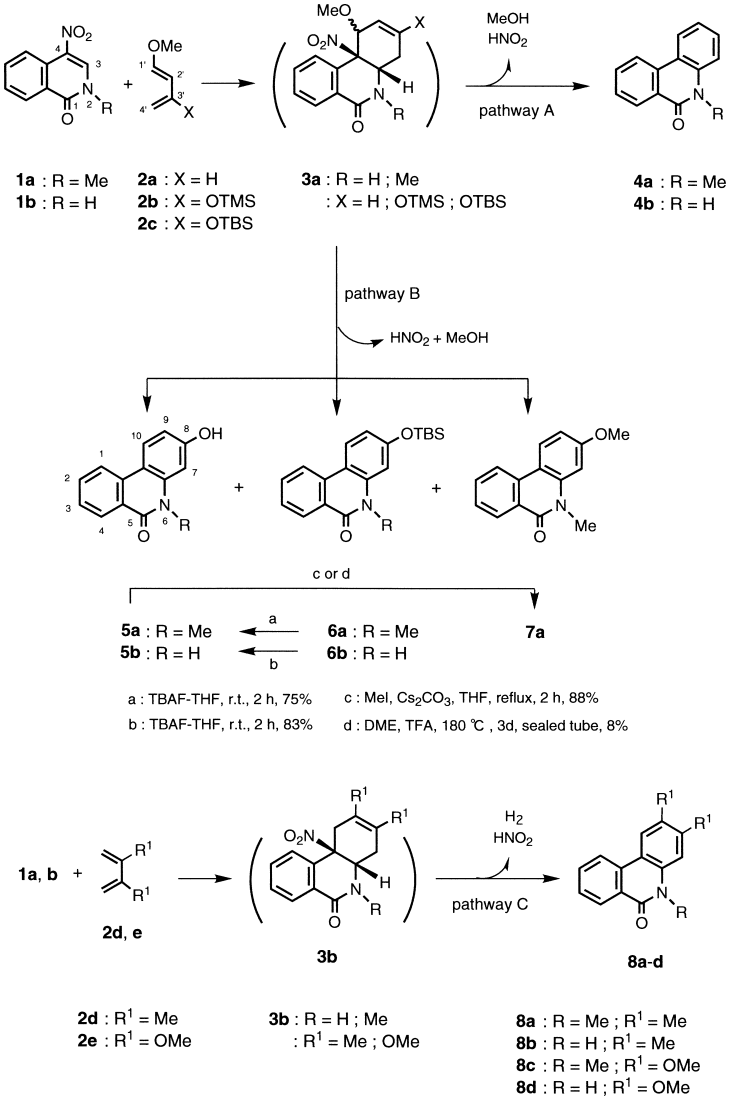

Chart 1

action of **1a** with 2,3-dimethoxy-1,3-butadiene (**2e**) gave 8,9-dimethoxy-6-methyl-5(6*H*)-phenanthridone (**8c**: 28%; entry 11) at 180 °C for 3 d in DME. The reaction of **1b** with **2e** gave 8,9-dimethoxy-5(6*H*)-phenanthridone (**8d**: 21%; entry 12) at 180 °C for 5 d in DME.

The structures of **5a**, **b** and **6a**, **b** were determined as follows: for **5a** the 8-position of the hydroxy group was confirmed because i) **5a**[12] was a known compound that possesses a hydroxy group at the 8-position; ii) methylation of **5a** with MeI and cesium carbonate produced **7a**[13] in 88% yield, a known compound that possesses a methoxy group at the 8-position. Because desilylation of **6a** using tetra-*n*-butylammonium fluoride (TBAF) results **5a** in 75% yield, the silyloxy group of **6a** occupies the 8-position. Likewise, **5b**[14] was a known compound that possesses a hydroxy group at the 8-position and for **6b**, the 8-position of the hydroxy group was validated because desilylation of **6b** produced **5b**. Moreover, it can be assumed that, for the formation of **7a**, treatment of **5a** and trifluoroacetic acid at 180 °C for 3 d in DME afforded **7a** in 8% yield, so that methylation of **5a** can be a source of DME. Presumably, **4a**, **b**—**6a**, **b**, **7a** were derived from DA adduct (**3a**) *via* elimination of HNO_2 and MeOH. Similarly, the aromatized **8a**, **c**, **d** resulted from release of HNO_2 and dehydrogenation from the DA adduct (**3b**).

Regioselectivity The DA reaction of **1a**, **b** with **2b**, **c** are asymmetric, therefore, regioisomers are formed. However, only products formed by way of (3-4′, 4-1′)-addition reactions were observed in the present experiment. The regioselectivity of the reaction was investigated in terms of the activation energy (*Ea*) calculated using Gaussian 03 at HF/6-31G(d) level.[15] The structures of the transition states (TS) of these DA reactions were first searched and optimized. Two types of TS were obtained, as shown in Fig. 1; TS (A) for (3-4′, 4-1′)-addition, which produces **3a** and TS (B) for (3-1′, 4-4′)-addition, which produces the regioisomer of **3a**. Assuming that the diene and the dienophile were significantly separated at the initial state, *Ea* was calculated as the difference in energy between the TS and the initial state. As shown in Table 2, *Ea*'s for the (3-4′, 4-1′)-addition reactions are much smaller than those for (3-1′, 4-4′)-addition. This result is consistent with the observation that the 8-substituted products (**5a**, **b**, **6a**, **b**, **7a**) were experimentally afforded, but the 9-substituted products were not.

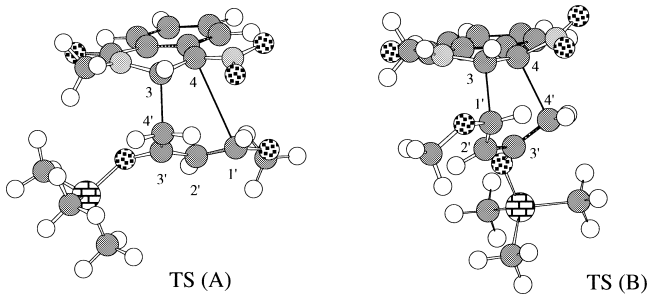

Fig. 1. Structures of TS (A) for (3-4′, 4-1′)-Addition (Left) and TS (B) for (3-1′, 4-4′)-Addition (Right) in the DA Reaction of **1a** with **2c** Optimized at HF/6-31G (d) Level

The calculated relevant interatomic distances are: C3–C4′=1.926 Å, C4–C1′=3.221 Å (left); C3–C1′=2.063 Å, C4–C4′=2.217 Å (right).

Table 2. Regioselectivity Based on Activation Energy (*Ea*) Calculated at HF/6-31G(d) Level

Isoquinolone	Diene	(3-4′, 4-1′)-addition[a]		(3-1′, 4-4′)-addition[a]	
		Ea (kcal/mol)	Adduct	*Ea* (kcal/mol)	Adduct
1a	**2b**	32.10	**5a**, **7a**	58.72	—
1a	**2c**	31.75	**5a**, **6a**, **7a**	58.50	—
1b	**2b**	29.12	**5b**	54.67	—
1b	**2c**	30.46	**5b**, **6b**	55.42	—

a) The numbers of atoms are indicated in Chart 1.

In conclusion, a novel DA reaction with 4-substituted isoquinolones dienophiles has been developed as a new method of synthesizing functionalized 5(6*H*)-phenanthridone derivatives. Regioselectivity of 4-nitro-1(2*H*)-isoquinolones (**1a**, **b**) to **2b**, **c** examined by MO calculations is consistent with the experimental result.

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 60SI spectrometer with tetra-methylsilane (TMS) as an internal standard; and elemental analysis, PERKINELMER 2400 CHN Elemental Analyzer. Chromatography was carried out under the following experimental conditions: column chromatography, Merk Kieselgel silica gel 60 (230—400 mesh); TLC, pre-coated TLC plates with $60F_{254}$ (2 mm, Merck).

Typical Procedure for DA Reaction of 1a, b with 2a a) A solution of **1a** (100 mg, 0.49 mmol) and **2a** (0.3 ml, 2.45 mmol) in DME (3 ml) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 1) was evaporated to give **4a**[10] [mp 105 °C ($CHCl_3$); lit.[10] mp 105—108 °C, 60 mg, 59%]. The solvent of second fraction was evaporated to give **1a** (18 mg, 18%). b) A solution of **1b** (100 mg, 0.526 mmol) and **2a** (0.26 ml, 2.63 mmol) in DME (3 ml) was heated at 160 °C for 3 d in a sealed tube. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of fraction eluted with ethyl acetate was evaporated, and the residure was diluted with chloroform (20 ml). The chloroform was washed with saturated aqueous NaCl (10 ml) and was evaporated. The residue was rechromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 2) was evaporated to give **4b**[11] [mp 300 °C (acetone); lit.[11] mp 292 °C, 84 mg, 82%]. The respective yields of **4a**, **b** are summarized in Table 1.

Typical Procedure for DA Reaction of 1a, b with 2b a) A solution of **1a** (100 mg, 0.49 mmol) and **2b** (0.48 ml, 2.5 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 was diluted with chloroform (20 ml). To the reaction mixture, TFA (0.75 ml) was added with stirring at room temperature for 20 min and chloroform solition concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 1) was evaporated to give **5a**[12] [mp 250 °C (acetone), lit.[12] mp 251 °C, 79 mg, 72%]. b) A solution of **1a** (100 mg, 0.49 mmol) and **2b** (0.48 ml, 2.5 mmol) in DME (3 ml) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture were treated as described above, and the residue was chromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 1) was evaporated to give **5a** (69 mg, 63%). The solvent of second fraction was evaporated to give **7a**[13] (7 mg, 7%). c) A solution of **1b** (100 mg, 0.526 mmol) and **2b** (0.26 ml, 2.63 mmol) in DME (3 ml) was heated at 160 °C for 5 d in a sealed tube. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of fraction eluted with ethyl acetate was evaporated, and the residure was diluted with chloroform (20 ml). The chloroform was washed with saturated aqueous NaCl (10 ml) and was evaporated. The residue was rechromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 1) was evaporated to give **5b**[14] [mp 298 °C (acetone); lit.[14] mp 290 °C, 83 mg, 75%]. The respective yields of **5a**, **b**, **7a** are summarized in Table 1.

7a: Pale yellow powder ($CHCl_3$), mp 131—132 °C (lit.[13] mp 134—134.5 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.78 (3H, s, OMe), 3.99 (3H, s, OMe), 7.14 (1H, dd, J=2.3, 8.8 Hz, H-9), 7.26—7.57 (3H, m, H-1,2,3), 7.63 (1H, d, J=2.3 Hz, H-7), 8.19 (1H, dd, J=1.0, 8.1 Hz, H-4), 8.47 (1H, d, J=8.8 Hz, H-10). MS *m*/*z*: 239 (M^+). HR-MS *m*/*z*: Calcd for $C_{15}H_{13}NO_2$, 239.0946. Found: 239.0921.

Typical Procedure for DA Reaction of 1a, b with 2c a) A solution of **1a** (100 mg, 0.49 mmol) and **2c** (0.49 ml, 2.45 mmol) in DME (3 ml) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was concentrated *in vacuo* and was diluted with chloroform (20 ml). To the reaction mixture, TFA (0.75 ml) was added with stirring at room temperature for 20 min and chloroform solution concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 3) was evaporated to give 8-*tert*-butylmethylsilyloxy-5-methyl-5(6*H*)-phenanthridone (**6a**; 47 mg, 29%). The solvent of second fraction was evaporated to give **7a** (2 mg, 2%). The solvent of third fraction was evaporated to give **5a** (57 mg, 52%). b) A solution of **1b** (200 mg, 1.052 mmol) and **2c** (0.98 ml, 5.26 mmol) in DME (6 ml) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was concentrated *in vacuo* and was diluted with chloroform (20 ml). To the reaction mixture, TFA (1.5 ml) was added with stirring at room temperature for 20 min and chloroform solution concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 1) was evaporated to give **6b** (18 mg, 6%). The solvent of second fraction was evaporated to give **5b** (83 mg, 37%). The respective yields of **5a**, **b**, **6a**, **b**, **7a** are summarized in Table 1.

6a: Pale yellow powder ($CHCl_3$), mp 68 °C. IR (KBr) cm^{-1}: 1649, 1608, 781, 713. ^{1}H-NMR ($CDCl_3$) δ: 0.28 (6H, s, $SiMe_2$), 1.03 (9H, s, CMe_3), 3.75 (3H, s, NMe), 6.81 (1H, dd, J=2.3, 8.6 Hz, H-9), 6.85 (1H, d, J=2.3 Hz, H-7), 7.49 (1H, ddd, J=1.3, 7.9, 8.3 Hz, H-3), 7.69 (1H, ddd, J=1.5, 7.9, 8.3 Hz, H-2), 8.09—8.14 (2H, m, H-1, 10), 8.50 (1H, dd, J=1.5, 7.9 Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ: −4.34 (C2), 18.25, 25.63 (C3), 29.91, 106.26, 113.32, 114.87, 121.03, 124.38, 126.81, 128.79, 132.68 (C2), 133.68, 139.39, 157.07, 161.89. MS *m*/*z*: 339 (M^+). HR-MS *m*/*z*: Calcd for $C_{20}H_{25}NO_2Si$, 339.1655. Found: 339.1651.

6b: Pale brown powder (acetone), mp 167 °C. IR (KBr) cm^{-1}: 1674, 1610, 838, 769. ^{1}H-NMR ($CDCl_3$) δ: 0.30(6H, s, $SiMe_2$), 1.03 (9H, s, CMe_3), 6.81 (1H, dd, J=2.3, 8.7 Hz, H-9), 6.86 (1H, d, J=2.3 Hz, H-7), 7.54 (1H, ddd, J=1.3, 8.1, 8.3 Hz, H-3), 7.75 (1H, ddd, J=1.5, 8.1, 8.3 Hz, H-2), 8.07 (1H, d, J=8.7 Hz, H-10), 8.17 (1H, dd, J=1.3, 8.1 Hz, H-1), 8.51 (1H, dd J=1.5, 8.1 Hz, H-4), 10.81 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: −4.30 (C2), 18.29, 25.66 (C3), 106.79, 112.77, 116.01, 121.51, 124.14, 124.58, 126.74, 128.19, 132.79, 135.08, 137.32, 157.10, 163.13. LMS *m*/*z*: 325 (M^+), 268. HR-MS *m*/*z*: Calcd for $C_{19}H_{23}NO_2Si$, 325.1498. Found: 325.1517.

Treatment of 6a, b with TBAF a) To a solution of **6a** (40 mg, 0.118 mmol) in THF (1 ml) was added 1 mol/THF TBAF (0.59 ml, 0.59 mmol) and the reaction solution was stirred at 30 °C for 2 h. The reaction mixture was evaporated *in vacuo* and was diluted with chloroform (20 ml). The organic layer was washed with saturated aqueous NH_4Cl (10 ml), dried over $MgSO_4$, then concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The soluvent of first fraction

with eluted acetone–hexane (2 : 1) was evaporated in *in vacuo* to give **5a** (20 mg, 75%). b) To a solution of **6b** (28 mg, 0.086 mmol) in THF (3 ml) was added 1 mol/THF TBAF (0.43 ml, 0.43 mmol) and the reaction solution was stirred at 30 °C for 2 h. The reaction mixture was treated as described above to gave **5b** (15 mg, 83%).

Methylation of 5a a) To a suspention of cesium carbonate (391 mg, 1.2 mmol) and **5a** (65 mg, 0.3 mmol) in THF (4 ml) was added MeI (175 mg, 1.2 mmol) at room temperature under N_2. The mixture was refluxed for 2 h. The reaction mixture was concentrated *in vacuo*, quenched with H_2O (10 ml) and extacted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. The ethyl acetate was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel. The solvent of first fraction eluted with ethyl acetate–hexane (1 : 1) was evaporated to give **7a** (63 mg, 88%). b) A DME solution of **5a** (50 mg, 0.22 mmol) and TFA (0.09 ml, 0.12 mmol) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography. The first fraction eluted with ethyl acetate–hexane (1 : 1) was concentrated to give **7a** (5 mg, 8%). The second fraction gave **5a** (30 mg, 60%).

Typical Procedure for DA Reaction of 1a with 2d a) A solution of **1a** (100 mg, 0.49 mmol) and **2d** (0.30 ml, 2.45 mmol) in DME (3 ml) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was then concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography. The first fraction that was eluted using acetone–hexane (1 : 2) was evaporated to give **8a** (50 mg, 36%). The second fraction that was eluted using acetone–hexane (1 : 2) gave **1a** (59 mg, 59%).

8a: Yellow powder ($CHCl_3$), mp 170 °C. IR (KBr) cm^{-1}: 1645, 1610, 771, 719. ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s, CMe), 2.42 (3H, s, CMe), 3.79 (3H, s, NMe), 7.18 (1H, s, H-7), 7.53 (1H, dd, J=7.9, 7.9 Hz, H-3), 7.72 (1H, ddd, J=1.0, 7.9, 8.1 Hz, H-2), 8.0 (1H, s, H-10), 8.23 (1H, d, J=8.1 Hz, H-1), 8.53 (1H, dd, J=1.0, 8.1 Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ: 19.45, 20.47, 29.94, 116.01, 117.05, 121.34, 123.86, 125.32, 127.34, 128.89, 130.94, 132.23, 133.63, 136.25, 138.78, 161.69. MS *m*/*z*: 237 (M^+). HR-MS *m*/*z*: Calcd for $C_{16}H_{15}NO$, 237.1154. Found: 237.1170.

Typical Procedures for DA Reaction of 1a, b with 2e a) A solution of **1a** (100 mg, 0.49 mmol) and **2e** (0.32 ml, 2.45 mmol) in *o*-xylene (3 ml) was heated at 180 °C for 3 d in a sealed tube. The reaction mixture was then concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography. The first fraction that was eluted using ethyl acetate–hexane (1 : 1) was evaporated to give **8c** (38 mg, 28%). b) A solution of **1b** (100 mg, 0.526 mmol) and **2e** (0.32 ml, 2.45 mmol) in DME (3 ml) was heated at 180 °C for 5 d in a sealed tube. The reaction mixture was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel. The solvent of fraction eluted with ethyl acetate was evaporated, and the residure diluted with chloroform (20 ml). The chloroform was washed with saturated aqueous NaCl (10 ml) and was evaporated. The residue was rechromatographed on a column of silica gel. The first fraction that was eluted using ethyl acetate–hexane (1 : 2) was evaporated to give **1b** (40 mg, 40%). The second fraction that was eluted using ethyl acetate–hexane (1 : 2) was evaporated to give **8d** (25 mg, 21%). c) Reaction of **1a** or **1b** (0.49 mmol) with **2e** (2.45 mmol) was carried out under conditions as listed in Table 1. The products were purified as described above to give **8c** or **8d**, with yields as summarized in Table 1.

8c: Pale yellow powder ($CHCl_3$), mp 140 °C. IR (KBr) cm^{-1}: 1648, 1611, 771, 719. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s, NMe), 4.04 (6H, s, OMe×2), 6.88 (1H, s, H-7), 7.53 (1H, dd, J=7.1, 7.8 Hz, H-3), 7.68 (1H, s, H-10), 7.73 (1H, ddd, J=1.0, 7.1, 8.2 Hz, H-2), 8.13 (1H, d, J=8.2 Hz, H-1), 8.54 (1H, dd, J=1.0, 7.8 Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ: 30.20, 30.91, 56.14, 98.61, 105.41, 111.96, 121.15, 124.69, 126.89, 129.05, 132.26, 133.10, 133.50, 145.18, 150.85, 161.66. MS *m*/*z*: 269 (M^+). HR-MS *m*/*z*: Calcd for $C_{16}H_{15}NO_3$, 269.1052. Found: 269.1067.

8d: Yellow powder (AcOEt), mp 240 °C. IR (KBr) cm^{-1}: 1648, 1613, 787, 760. ^{1}H-NMR ($CDCl_3$) δ: 4.01 (6H, s, OMe×2), 6.92 (1H, s, H-7), 7.48—7.55 (2H, m, H-10, 2 or 3), 7.76 (1H, dd, J=7.7, 8.0 Hz, H-2 or 3), 8.12 (1H, d, J=8.0 Hz, H-1), 8.52 (1H, d, J=7.7 Hz, H-4), 11.54—11.61 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 56.15, 56.34, 99.39, 104.43, 111.09, 121.43, 124.57, 126.57, 128.24, 131.06, 132.64, 134.95, 145.73, 151.22, 163.06. MS *m*/*z*: 255 (M^+). HR-MS *m*/*z*: Calcd for $C_{15}H_{13}NO_3$, 255.0895. Found: 255.0894.

Calculation of Activation Energy Structures of the initial and the transition states (TS) were optimized using Gaussian 03 at HF/6-31G(d) level.[15] The solvent effect was not considered. We assumed that the diene and the dienophile were far apart in the initial state. We calculated the activation energy as the difference in energy between the TS and the initial state. After optimizing the TS structure, vibrational calculation was performed to confirm that the TS had only one imaginary vibrational frequency. Iintrinsic reaction coordinate calculation was also carried out to ensure that the TS connected the initial and the intended final state.

References and Notes

1) Tomisawa H., Fujita R., *Chem. Pharm. Bull.*, **21**, 2585—2589 (1973).
2) Horning D. E., Lacassf G., Muchowski J. M., *Can. J. Chem.*, **49**, 2785—2796 (1971), and references cited therein.
3) Dyke S. F., Sainsbury M., Brown D. W., Clipperton R. D. J., *Tetrahedron*, **26**, 5969—5980 (1970).
4) For biological properties of phenanthridine alkaloids, see: Rigby J. H., Holsworth D. D., James K., *J. Org. Chem.*, **54**, 4019—4020 (1989).
5) For biological properties of phenanthridine alkaloids, see: Narasimhan N. S., Chandrachood P. S., *Tetrahedron*, **37**, 825—827 (1981).
6) For biological properties of phenanthridine alkaloids, see: Okamoto T., Torri Y., Isogai Y., *Chem. Pharm. Bull.*, **16**, 1860—1864 (1968).
7) For biological properties of phenanthridine alkaloids, see: Mondon A., Krohn K., *Chem. Ber.*, **108**, 445—468 (1975).
8) Weltin D., Picard V., Aupeix K., Varn M., Oth D., Marchal J., Dufour P., Bischoff P., *Int. J. Immunopharmc.*, **17**, 265—271 (1995).
9) Snders G. M., van Dijk M., den Hertog H. J., *Recueil J. Royal Netherlands Chemical Society*, **93**, 298—300 (1974).
10) Harayama T., Akiyama T., Nakano Y., Nishioka H., Abe H., Takeuchi Y., *Chem. Pharm. Bull.*, **50**, 519—522 (2002).
11) Rigby J. H., Laurent S., *J. Org. Chem.*, **63**, 6742—6744 (1998).
12) Kraatz U., Korte F., *Chem. Ber.*, **106**, 62—68 (1973).
13) Naito T., Ninomiya I., *Heterocycles*, **22**, 1705—1708 (1984).
14) Laltha S., Rajeswari S., Pai B. R., Suguna H., *Indian J. Chem.*, **15**, 180—182 (1977).
15) Gaussian 03, Revision B.05, Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Montgomery J. A., Jr., Vreven T., Kudin K. N., Burant J. C., Millam J. M., Iyengar S. S., Tomasi J., Barone V., Mennucci B., Cossi M., Scalmani G., Rega N., Petersson G. A., Nakatsuji H., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Klene M., Li X., Knox J. E., Hratchian H. P., Cross J. B., Adamo C., Jaramillo J., Gomperts R., Stratmann R. E., Yazyev O., Austin A. J., Cammi R., Pomelli C., Ochterski J. W., Ayala P. Y., Morokuma K., Voth G. A., Salvador P., Dannenberg J. J., Zakrzewski V. G., Dapprich S., Daniels A. D., Strain M. C., Farkas O., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Ortiz J. V., Cui Q., Baboul A. G., Clifford S., Cioslowski J., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., 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., Gonzalez C., Pople J. A., Gaussian, Inc., Pittsburgh PA, 2003.