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REGIOSELECTIVE SYNTHESIS OF 1,5-DIAZAANTHRAQUINONES *VIA* DIELS-ALDER REACTION OF 4-HYDROXY-QUINOLINEQUINONE WITH 1-AZA-1,3-BUTADIENE

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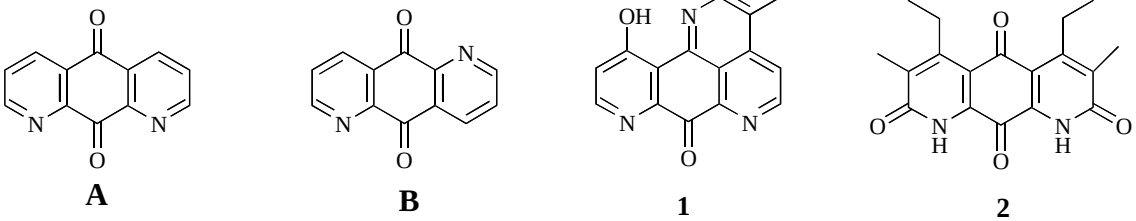
Abstract - Diels-Alder (D-A) reaction of 4-methoxy-2-phenylquinoline-5,8-dione (**3a**) and 4-hydroxy-2-phenylquinoline-5,8-dione (**3c**) with 3-methyl-1-dimethylamino-1-aza-1,3-butadiene proceeded in a regioselective manner to give 4-methoxy-7-methyl-2-phenylpyrido[3,2-*g*]quinoline-5,10-dione (1,8-diazaanthraquinone) (**7**) and 4-hydroxy-8-methyl-2-phenylpyrido[2,3-*g*]quinoline-5,10-dione (1,5-diazaanthraqinone) (**10**), respectively, after the C ring aromatization. The inverse regioselectivity observed in the case of **3c** is related to the presence of the hydrogen bonding between 4-OH and 5-CO group. This result demonstrated that D-A reaction of the azadienophiles with 1-azadiene provides a method for synthesizing 1,8-diaza- and 1,5-diazaanthraquinone, respectively.

Polycyclic nitrogen heterocycles with pyrido[3,2-*g*]quinoline-5,10-dione (1,8-diazaanthraquinone) (**A**) and pyrido[2,3-*g*]quinoline-5,10-dione (1,5-diazaanthraquinone) (**B**) ring units are known as biologically active alkaloids.[1] The construction of the 1,8-diazaanthraquinone

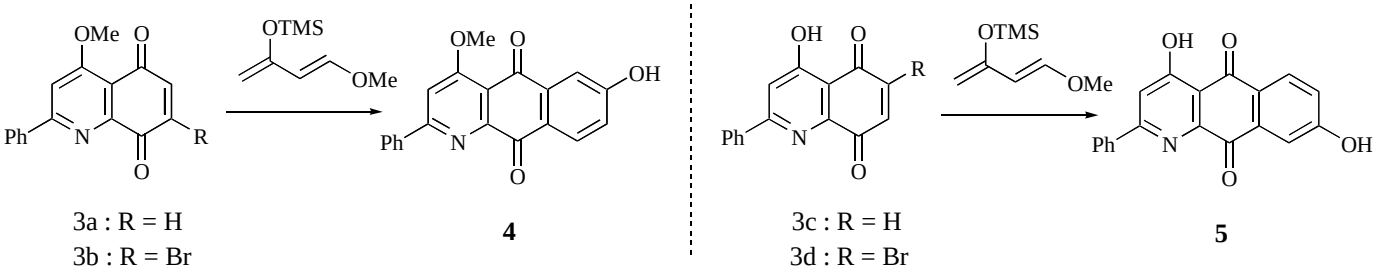


A **B** **1** **2**

Scheme 1

ring system was efficiently achieved by Diels-Alder (D-A) reactions of quinoline-5,8-diones (quinolinequinone) with 1-aza-1,3-butadines,[2] which were successfully applied to the total synthesis of meridine (**1**) [3] and diazaquinomicine A (**2**) .[4] On the other hand, construction of 1,5-diazaanthraquinone ring system by using D-A reaction seems to be difficult if a regio-directing group such as halogen is absent.

Recently, we have discovered that the D-A reaction of 4-methoxy-2-phenyl- (**3a**) and 4-hydroxy-2-phenylquinolinequinone (**3c**) with 1-methoxy-3-trimethylsilyloxy-1,3-butadine proceeded in a stereo- and regio-specific manner to give regioisomeric 4,6- (**4**) and 4,7-dioxygenated 1-azaanthraquinones (**5**) respectively.[5] The assigned regiochemistry was unambiguously established by the D-A reaction of quinolinequinones (**3b** and **3d**) with a regio-directing bromine atom at C-6 and C-7 positions.[6] The regiochemistry observed in the D-A reaction of 4-hydroxyquinolinequinone (**3c**) was opposite to that of **3a**. This is identical with the regiochemistry of non-substituted quinolinequinones.[2, 7] The results suggest that the D-A reaction of 4-hydroxyquinolinequinones with a 1-aza-1,3-butadiene will provide a method of regioselective synthesis of 1,5-diazaanthraquinones ring system.



Scheme 2

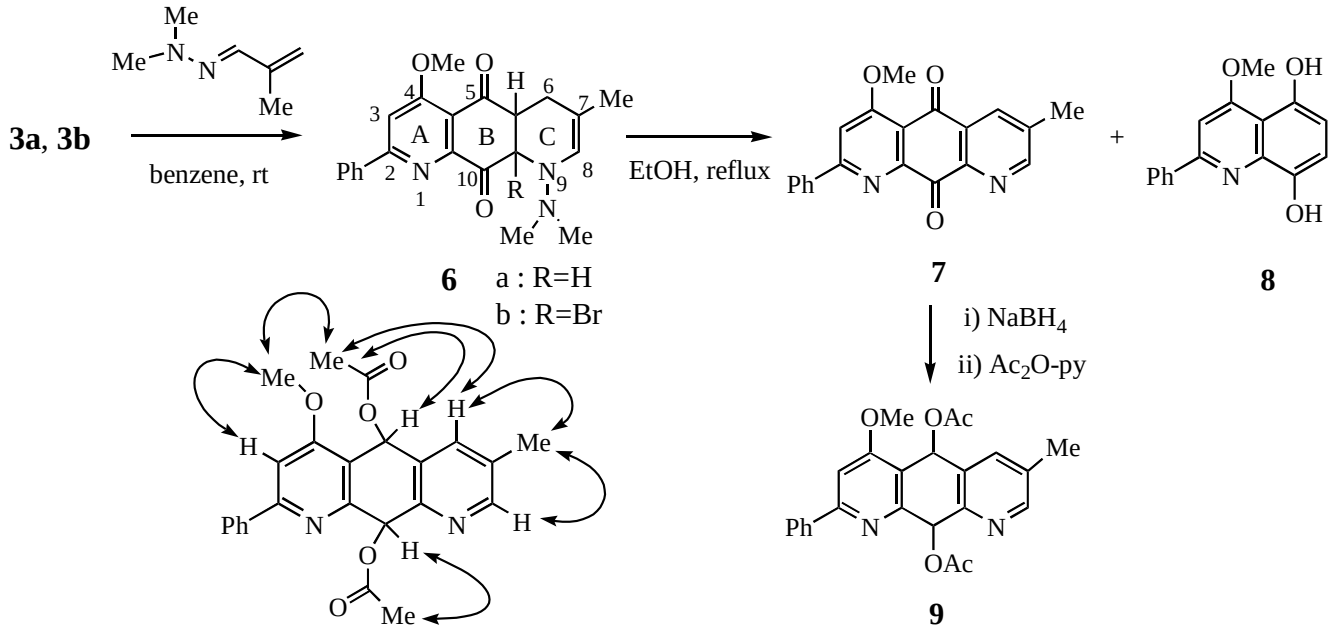
Synthesis of 1,8-diazaanthraquinone

A mixture of **3a**[5] and 3-methyl-1-dimethlyamino-1-aza-1,3-butadiene (1-azadiene)[8] in benzene was treated at room temperature for 3 h under argon atmosphere to give **6a** as a sole product in 65% yield. The product (**6a**), although it was fairly unstable, was well characterized by MS, IR, UV and ^{1}H-NMR spectra which indicated that **6a** was a [4+2] cycloadduct. Heating of the adduct (**6a**) in EtOH for a short time caused aromatization of the C ring to give pyrido[3,2-*g*]quinoline-5,10-dione (**7**) in 22% yield, and at the same time reverse D-A reaction was accompanied to give 4-methoxy-5,8-dihydroxyquinoline (**8**) in 29% yield.

The structural evidences of **7** were obtained as follows. Reduction of **7** with sodium borohydride in EtOH followed by acetylation with acetic anhydride in pyridine gave a

diacetate (**9**) in 11% yieled. The cross peaks observed in the 2D-NOESY of **9** revealed correlation between the 3-aromatic proton (δ 7.21) and the 7-Me (δ 2.58), through the signals 4-OMe (δ 4.14), 5-OAc (δ 2.56), and the 6-aromatic proton (δ 8.07), thus establishing the location of 7-Me. A further correlation was observed between the 7-Me and 8-aromatic proton (δ 8.93), thus indicating that the compound (**7**) possesses 1,8-diazaanthraquinone skeleton.

In order to obtain a decisive structural evidence of the adduct, we carried out the D-A reaction using quinolinequinones possessing a regio-directing bromine atom at C-7 position. A mixture of 7-bromo-4-methoxy-2-phenylquinolinequinone (**3b**)[6] and the 1-azadiene in benzene was similarly treated at room temperature to give an unstable adduct (**6b**). Chromatography of **6b** over SiO_2 caused C ring aromatization to give **7** in 67% yield. The compound was identical with the 1,8-diazaanthraquinone (**7**) prepared from **3a**.

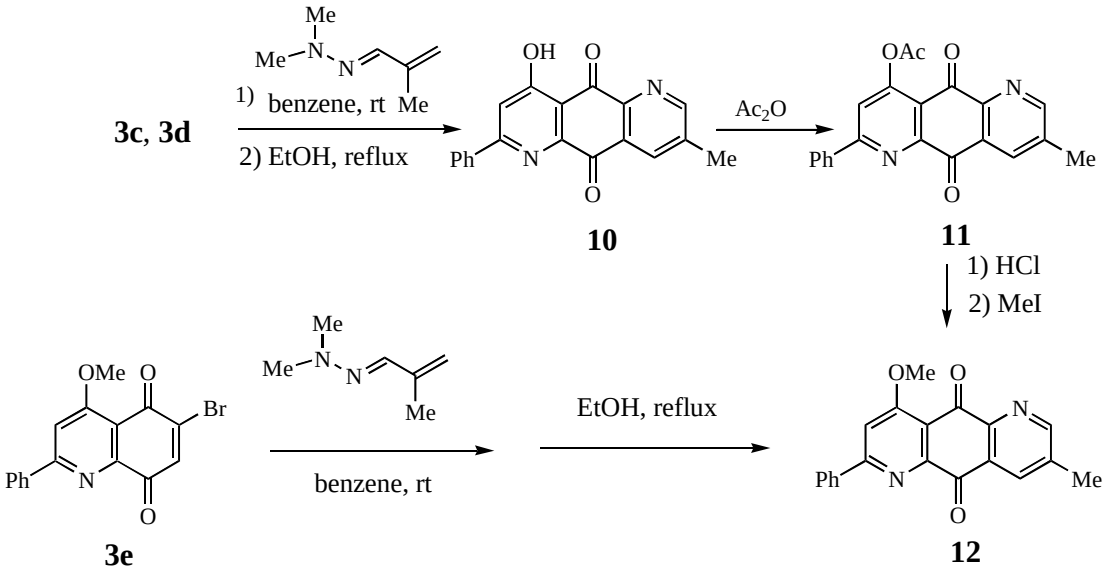


Scheme 3

Synthesis of 1,5-Diazaanthraquinone

The D-A reaction of 4-hydroxy-2-phenylquinolinequinone (**3c**)[5] with the 1-azadiene was carried out at room temperature for 3 h to give an unstable adduct (**10**) as sole product in 95% yield. The adduct (**10**) was acetylated with acetic anhydride-pyridine to give an acetate (**11**) in 65% yield. Hydrolysis of **11** with 10% HCl followed by methylation with methyl iodide gave a methoxy derivative (**12**) in 68% yield. The ^{1}H- and ^{13}C-NMR spectral data of **12** were clearly different from those of **7**, although they are very similar, indicating that the compound (**12**) is a 1,5-diazaanthraquinone, regio-isomer to **7**. This structural assignment was finally

confirmed by the synthesis of **11** and **12** *via* the regioselective D-A reaction of azadienophiles (**3d**[6] and **3e**[6]) carrying a bromine at C-6 position as shown in Scheme 4.



Scheme 4

Inversion of the regioselectivity due to the presence of 4-hydroxy group is attributable to hydrogen bonding between the 4-OH and 5-CO, which polarizes the C=O bond at the 5-position more than at 8-position. This electronic effect makes the carbon at C-7 more electrophilic than that at C-6, thus determining the regiochemistry of the D-A reaction of **3c**.

In conclusion the results demonstrate that the D-A reaction of non-halogenated 4-hydroxyquinolinequinone with 1-aza-1,3-butadiene provides a method for the regioselective synthesis of 1,5-diazaanthraquinone ring system.

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 (ε). 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. Low-resolution MS spectra (LRMS) and high-resolution MS spectra (HRMS) were determined on a JEOL JMS-HX110A 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

(Mallinkroft type 150A or Wako-Gel C-200) was used. Thin layer chromatography (TLC) was performed on Merck precoated Silica-Gel 60 F254 plates. All organic extracts were washed with 5% HCl, 5% $NaHCO_3$, and water and dried over Na_2SO_4 before concentration *in vacuo*.

Diels-Alder Reaction of 3a with 3-Methyl-1-dimethylamino-1-aza-1,3-butadiene

A solution of **3a**[5] (100 mg, 0.45 mmol) and 3-methyl-1-dimethylamino-1-aza-1,3-butadiene (127 mg, 1.82 mmol) in benzene (3 mL) was stirred at rt for 3 h in a sealed tube under an Ar atmosphere. After removal of the solvent *in vacuo*, the product was crystallized from CH_2Cl_2-Et_2O to give 5a,6,9,9a-tetrahydro-4-methoxy-7-methyl-9-dimethylamino-2-phenylpyrido[3,2-*g*] quinoline-5,10-dione (**6a**) (91 mg, 65%) as yellow prisms, mp 165-168°C. IR: 1736, 1719, 1698, 1671. UV: 215 (20000), 255 (19500), 289 (20000). ^{1}H-NMR: 1.69 (3H, s, CH_3), 2.25 (6H, s, $N(CH_3)_2$), 2.56 (1H, m, 6-H), 2.72 (1H, m, 6-H), 3.53 (1H, m, 5a-H), 4.09 (3H, s, OCH_3), 4.21 (1H, d, *J*=3Hz, 9a-H), 5.87 (1H, s, 8-H), 7.46-7.53 (4H, m, 3-H and Ph), 8.01-8.18 (2H, m, Ph). LRMS (*m/z*): 377 (M^+). HRMS *m/z* (M^+): Calcd for $C_{22}H_{23}N_3O_3$: 377.1737. Found: 377.1737.

Aromatization of 6a

6a (200mg, 0.53 mmol) was refluxed in EtOH (50 mL) for 15 min. After removal of solvent *in vacuo*, the residue was purified by column chromatography with hexane-AcOEt (4:1) to give **7** (39 mg, 22%) and **8** (41 mg, 29%).

4-Methoxy-7-methyl-2-phenylpyrido[3,2-*g*]quinoline-5,10-dione (**7**), yellow prisms crystallized from CH_2Cl_2-Et_2O, mp 274-282°C. IR: 1702, 1670, 1590, 1582. UV: 238 (17100), 283 (31500). ^{1}H-NMR: 2.57 (3H, s, 7-CH_3), 4.21 (3H, s, 4-OCH_3), 7.48-7.52 (3H, m, Ph), 7.57 (1H, s, 3-H), 8.1-8.2 (2H, m, Ph), 8.34 (1H, d, *J*=2 Hz, 6-H), 8.94 (1H, d, *J*=2 Hz, 8-H). ^{13}C-NMR: 19.1 (CH_3), 56.9 (OCH_3), 107.2 (C3), 118.1 (C4a), 127.8 (C3' and C5'), 129.0 (C2' and C6'), 130.7 (C5a), 130.9 (C4'), 134.9 (C6), 137.6 (C7), 139.3 (C1'), 145.8 (C9a), 151.1 (C4), 155.7 (C8), 163.3 (C2), 167.1 (C10a), 180.2 (C5), 181.4 (C10). LRMS (*m/z*): 330 (M^+). HRMS m/z (M^+): Calcd for $C_{20}H_{14}N_2O_3$; 330.1002. Found: 330.0999. Anal Calcd for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.71; H, 4.37; N, 7.98.

5,8-Dihydroxy-4-methoxy-2-phenylquinoline (**8**), yellow needles crystallized from MeOH-Et_2O, mp 145-147°C. IR: 1638, 1607. UV: 276 (43100), 353 (6200). ^{1}H-NMR: 4.35 (3H, s, OCH_3), 6.74 (1H, d, *J*=9 Hz, 7-H), 7.02 (1H, d, *J*=9 Hz, 8-H), 7.5-8.4 (6H, m, 3-H and Ph). LRMS (*m/z*): 267 (M^+). HRMS *m/z* (M^+): Calcd for $C_{16}H_{13}NO_3$; 267.0893. Found: 267.0893

Reduction and Acetylation of 7

$NaBH_4$ (13 mg, 0.34 mmol) was added to a solution of **7** (50 mg, 0.15 mmol) in EtOH (5 mL) at 0°C and the mixture was stirred at 0°C for 30 min and at rt for 30 min. Water was added to the reaction mixture and extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was

purified by short column chromatography ($CHCl_3$) and the product was treated with acetic anhydride-pyridine (1:2, 3 mL) at rt for 17 h. The reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography ($CHCl_3$) to give 5,10-dihydro-5,10-diacetoxy-4-methoxy-7-methyl-2-phenylpyrido[3,2-*g*]quinoline (**9**) (11 mg, 11%) as yellow powder . IR: 1702, 1671, 1657. UV: 235 (3500), 279 (6100). ^{1}H-NMR: 2.56 (3H, s, 5-OCOCH_3), 2.58 (3H, s, CH_3), 2.72 (3H, s, 10-OCOCH_3), 4.14 (3H, s, OCH_3), 7.12 (1H, s, 3-H), 7.5-7.6 (4H, m, Ph and 5-H, 10-H), 8.07 (1H, d, *J*=2 Hz, 6-H), 8.1-8.2 (3H, m, Ph), 8.93 (1H, d, *J*=2 Hz, 8-H). LRMS (*m/z*): 418 (M^+)

Diels-Alder Reaction of 3b with 3-Methyl-1-dimethylamino-1-aza-1,3-butadiene

A solution of **3b**[6] (100 mg, 0.29 mmol) and 3-methyl-1-dimethylamino-1-aza-1,3-butadiene (97 mg, 0.87 mmol) in benzene (3 mL) was stirred at rt for 15 min in a sealed tube under an Ar atmosphere. After removal of the solvent *in vacuo*, the product was purified by column chromatography with hexane-AcOEt (1:10) and crystallized from $CHCl_3$-Et_2O to give **7** (64 mg, 67%) as yellow prisms.

Diels-Alder Reaction of 3c with 3-Methyl-1-dimethylamino-1-aza-1,3-butadiene

A solution of **3c**[5] (100 mg, 0.40 mmol) and 3-methyl-1-dimethylamino-1-aza-1,3-butadiene (134 mg, 1.2 mmol) in benzene (3 mL) was stirred at rt for 3 h in a sealed tube under an Ar atmosphere. After removal of the solvent *in vacuo*, the crude product was washed with Et_2O to give 4-hydroxy-8-methyl-2-phenylpyrido[2,3-*g*]quinoline-5,10-dione (**10**) (87 mg, 95%) as yellow prisms, mp 165-168°C. IR: 1685, 1648. ^{1}H-NMR: 2.64 (3H, s, CH_3), 7.5-7.7 (4H, m, 3-H and Ph), 8.16-8.17 (2H, m, Ph), 8.55 (1H, d, *J*=1 Hz, 9-H), 8.95 (1H, d, *J*=1 Hz, 7-H). LRMS (*m/z*): 316 (M^+). HRMS *m/z* (M^+): Calcd for $C_{19}H_{12}N_2O_3$: 316.0848. Found: 316.0883.

Acetylation of 10

The crude product (**10**) which was obtained from D-A reaction of **3c** (100 mg, 0.40 mmol) with 1-azadiene, described above was treated with acetic anhydride-pyridine (2:1, 2 mL) at rt for 15 h. The reaction mixture was extracted with $CHCl_3$. The residue was purified by column chromatography with $CHCl_3$ and crystallized from $CHCl_3$ to give 4-acetoxy-8-methyl-2-phenylpyrido[2,3-*g*]quinoline-5,10-dione (**11**) (92 mg, 65%) as yellow needles, mp 251-253°C. IR: 1775, 1688, 1595. UV: 242 (19000), 271 (23700). ^{1}H-NMR: 2.57 (3H, s, CH_3), 2.59 (3H, s, OCOCH_3), 7.5-7.6 (3H, m, Ph), 7.81 (1H, s, 3-H), 8.2-8.3 (2H, m, Ph), 8.47 (1H, dd, *J*=2, 1 Hz, 9-H), 8.94 (1H, dd, *J*=2, 1 Hz, 7-H). ^{13}C-NMR: 19.1 (CH_3), 21.4 (OCO<u>C</u>H_3), 120.0 (C3), 122.1 (C4a), 128.1 (C2' and C6'), 129.6 (C3' and C5'), 129.9 (C9a), 131.7 (C4'), 135.4 (C9), 137.1 (C8), 139.9 (C1'), 146.8 (C5a), 150.8 (C4), 156.7 (C7), 159.4 (C2), 163.8 (C10a), 168.9 (O<u>C</u>OCH_3), 180.1 (C5), 181.4 (C10). LRMS (*m/z*): 358 (M^+). HRMS *m/z* (M^+): Calcd for $C_{21}H_{14}N_2O_4$:

358.0951. Found: 358.0948.

Conversion of 11 to 12

11 (20 mg, 0.056 mmol) in 10%-HCl solution of dioxane-H_2O (3:1, 4 mL) was refluxed for 30 min. The reaction mixture was extracted with $CHCl_3$. The residue in DMF (30 mL) was treated with MeI (excess), K_2CO_3 (106 mg, 0.17 mmol) at rt for 12 h under Ar atmosphere. After removal of insoluble precipitate by filtration the filtrate was extracted with $CHCl_3$. The residue was purified by column chromatography with hexane-AcOEt (4:1) and crystallized from $CHCl_3$-Et_2O to give 4-methoxy-8-methyl-2-phenylpyrido[2,3-*g*]quinoline-5,10-dione (**12**) (11 mg, 68%) as yellow prisms, mp 283-289°C. IR: 1688, 1673. UV: 240 (20900), 278 (28300). ^{1}H-NMR: 2.56 (3H, s, CH_3), 4.20 (3H, s, OCH_3) 7.5-7.6 (4H, m, 3-H and Ph), 8.1-8.2 (2H, m, Ph), 8.40 (1H, d, *J*=2 Hz, 9-H), 8.93 (1H, d, *J*=2 Hz, 7-H). ^{13}C-NMR: 18.8 (CH_3), 56.9 (OCH_3), 107.5 (C3), 119.1 (C4a), 127.8 (C3' and C5'), 128.8 (C9a), 129.0 (C2' and C6'), 130.9 (C4'), 135.0 (C9), 137.7 (C8), 138.6 (C1'), 147.0 (C5a), 150.7 (C4), 156.3 (C7), 163.3 (C2), 167.5 (C10a), 180.0 (C5), 182.0 (C10). LRMS: (*m/z*) 330 (M^+). HRMS *m/z* (M^+): Calcd for $C_{20}H_{14}N_2O_3$; 330.1002. Found: 330.0965.

Diels-Alder Reaction of 3d with 3-Methyl-1-dimethylamino-1-aza-1,3-butadiene

A solution of **3d**[6] (50 mg, 0.145 mmol) and 3-methyl-1-dimethylamino-1-aza-1,3-butadiene (50 mg, 0.435 mmol) in benzene (5 mL) was stirred at rt for 5 min in a sealed tube under an Ar atmosphere. After removal of the solvent the reaction mixture in EtOH (30 mL) was refluxed for 1 h. After removal of the solvent *in vacuo*, the residue was treated with acetic anhydride-pyridine(1:2, 3 mL) at rt for 14 h. The reaction mixture was extracted with $CHCl_3$. The product was crystallized from $CHCl_3$-Et_2O to give **11** (17 mg, 32%) as yellow prisms.

Diels-Alder Reaction of 3e with 3-Methyl-1-dimethylamino-1-aza-1,3-butadiene

A solution of **3e**[6] (100 mg, 0.29 mmol) and 3-methyl-1-dimethylamino-1-aza-1,3-butadiene (100 mg, 0.87 mmol) in benzene (5 mL) was stirred at rt for 30 min in a sealed tube under an Ar atmosphere. After removal of the solvent the reaction mixture in EtOH (30 mL) was refluxed for 1 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography with AcOEt-hexane (10:1) and crystallized from $CHCl_3$-Et_2O to give **12** (48 mg, 50%) as yellow prisms.

REFERENCES

1. T. Ozturk, "The Alkaloids", Vol. 49, ed. by G. A. Cordell, Academic Press Inc., San Diego, 1997, pp. 79-219.
2. K. T. Potts, E. B. Walsh, and D. Bhattacharjee, *J. Org. Chem.*, 1987, **52**, 2285; C. Gesto , E. de la Cuesta, and C. Avendano, *Tetrahedron*, 1989, **45**, 4477: C. Gesto, E. de la Cuesta, C. Avendano, and F. Emling, *J. Pham. Sci.*, 1992, **81**, 815; B. Ocana, M. Espada, and C.

Avendano, *Tetrahedron*, 1994, **50**, 10047; R. A. Tapia, C. Quintanar, and A. Valderrama, *Heterocycles*, 1996, **43**, 447; J. M. Pérez, P. L. Alvarado, M. Á. Alonso, C. Avendano, and J. C. Ménendez, *Tetrahedron Lett.*, 1996, **37**, 6955.

3. Y. Kitahara, F. Tamura, and A. Kubo, *Chem. Pharm. Bull.*, 1994, **42**, 1363; Y. Kitahara, F. Tamura, M. Nishimura, and A. Kubo, *Tetrahedron*, 1998, **54**, 8421.
4. J. M. Pérez, P. L. Alvarado, C. Avendano, and J. C. Ménendez, *Tetrahedron Lett.*, 1998, **39**, 673 .
5. Y. Horiguchi, A. Toeda, K. Tomoda, H. Suzuki, and T. Sano, *Chem. Pharm. Bull.*, 1998, **46**, 1356.
6. Y. Horiguchi, K. Tomoda, and T. Sano, *Heterocycles*, 1999, **51**, 1669.
7. A. J. Birch, D. N. Butler, and J. B. Siddal, *J. Chem. Soc.*, **1964**, 2941; K. T. Potts, D. Bhattacharjee, and E. B. Walsh, *J. Org. Chem.,* 1986, **51**, 2011.
8. A. Waldner, *Helv. Chim. Acta*, 1988, **71**, 486.