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Synthesis of the Pentacyclic Intermediate for Dynemicin A and Unusual Formation of Spiro-oxindole Ring[1]

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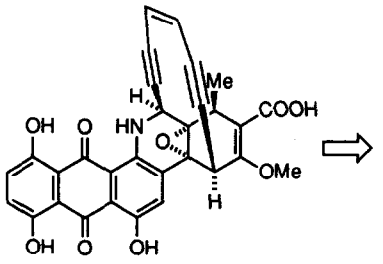
Abstract: *A pentacyclic compound was synthesized as an important intermediate of antitumor antibiotic dynemicins. The key step was the intramolecular Heck reaction using catalytic Pd reagent. During the course of the synthetic studies, an unusual spiro ring compound was found to be produced* via *intramolecular conjugate addition.*

Dynemicin A (**1**) was isolated from the fermentation broth of *Micromonospora chersina* and possesses potent cytotoxicity and in vivo antitumor activity.[2] This antibiotic is a hybrid of two typical chemotypes of antitumor agent, enediyne and anthraquinone. There are many synthetic[3,4] and biological studies[5] on the models including enediyne moiety. Mode of actions of enediyne unit is unveiling.[5] On the other hand, this pentacyclic framework possessing anthraquinone is novel. Reports on synthesis of the anthraquinone part are few,[6] including Schreiber's impressive work[4b] on methylated dynemicin A, and its role in the action of the drug is still unclear. In order to clarify the biological role of this pentacycles and also serve as an important intermediate for dynemicin synthesis we tried to investigate the synthesis of pentacyclic skeleton. Formation of carbon-carbon bonds at the C2 position on anthraquinone skeleton is indispensable for constructing a pentacyclic system and derivatization of a new family of anthraquinones. However very limited methods were known such as the Marschalk reaction,[7] the Claisen rearrangement[8] and the Stille coupling of triflate.[9] On the other hand, several groups have demonstrated that the intramolecular Heck reaction is a powerful methodology for constructing a five or six membered ring.[10] Here, we report a new carbon-carbon bond formation at C2 position of anthraquinone via the intramolecular Heck reaction, palladium catalyzed cyclization under mild conditions.

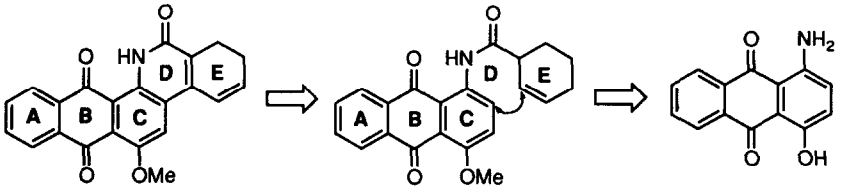
Scheme 1 illustrates retrosynthetic analysis of **1**, where pentacyclic intermediate **2** leading to enediyne bridge is indicated to be constructed by D-ring formation in **3**. Construction of the requisite pentacyclic framework **2** was envisioned to comprise two essential steps: thus, 1) cyclization of D-ring by bonding at the arrows in **3**, 2) amide formation as **3** from the aniline **4**. The aminophenol **4** (Celliton Fast Pink B) exhibited interesting reactivity in the acylation and alkylation between the two functional moieties, OH and NH_2. Selective O-methylation yielding **5**[11] was achieved with MeI and *t*-BuOK in DMSO solvent, whilst the N-acylation occurred under the conditions of acyl halide and *t*-BuOK in the presence of 18-crown-6 in THF (figure not shown).

Initially we prepared 1-amino-2-bromo-4-methoxy anthraquinone (**7**) from **4** (Scheme 2). Selective methylation of **4** with methyl iodide in the presence of *t*-BuOK gave the O-methylated compound **5**[11] in

Scheme 1.



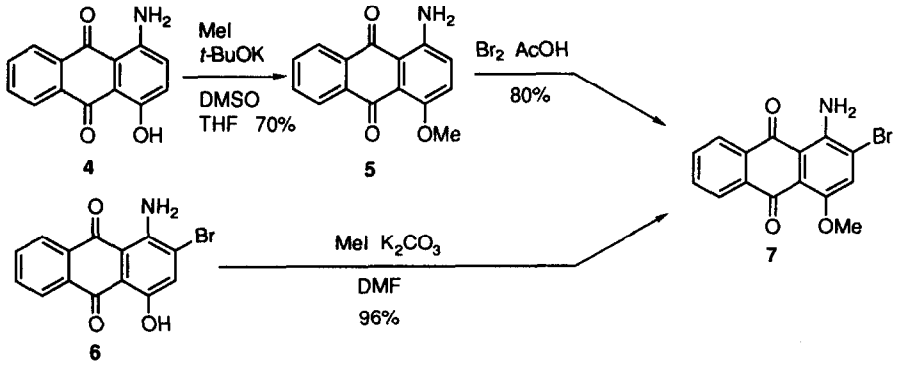
Dynemicin A (1)



2 **3** **4**

70% yield. Bromination of **5** in acetic acid afforded the bromide **7** in 80% yield. An alternative way to prepare **7** is also shown in Scheme 2. Utilizing low reactivity of the amino substituent of compound **6**, which is commercially available, the hydroxy group of **6** was selectively methylated to give **7** in 96% yield under the conventional conditions (MeI, K_2CO_3 and DMF).

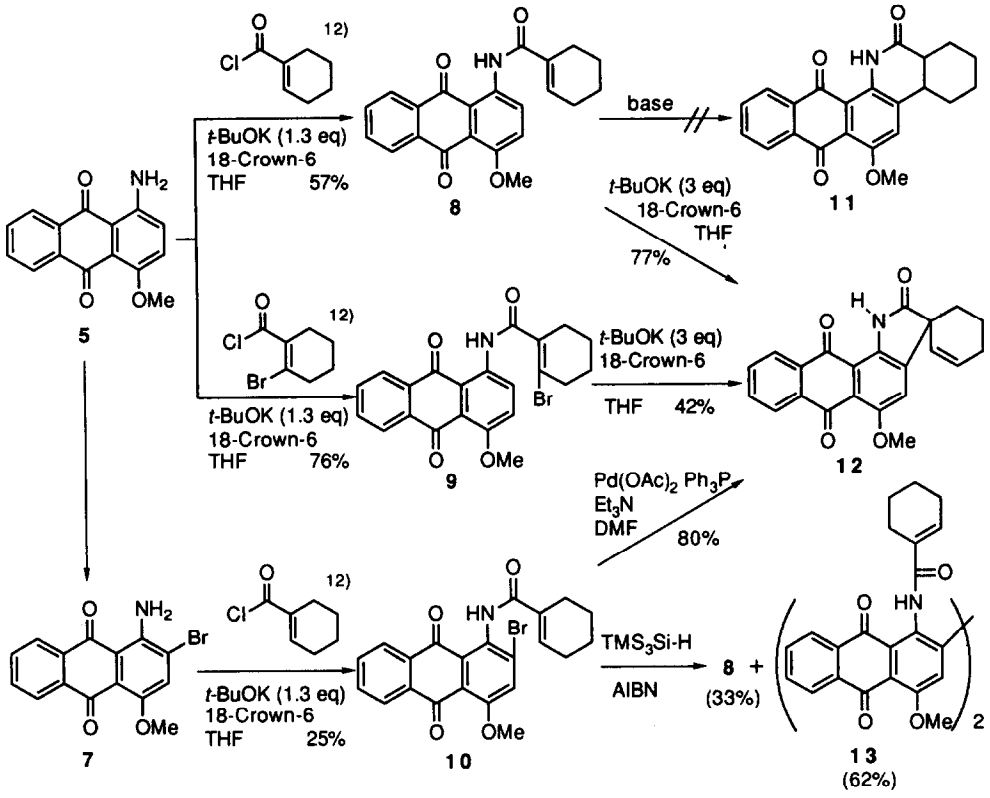
Scheme 2.



Scheme 3 illustrates formation of the amide **8** which was provided from **5** by treatment with *t*-BuOK (1.3 equiv.) and 1-cyclohexene-1-carbonyl chloride[12] in the presence of 18-crown-6 in THF solvent. Two other bromo acyl compounds **9**, **10** were obtained by a similar procedure.[12] Low yield of **10** was due to the steric hindrance of **7** decreasing reactivity of the adjacent amino group.

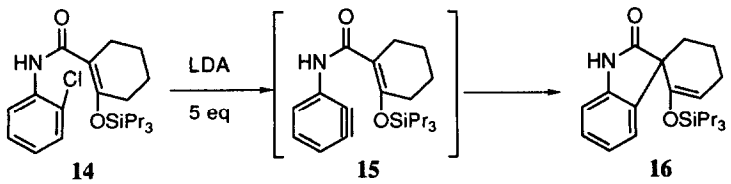
For the intramolecular cyclization, we initially attempted that **8** might cyclize into the pentacyclic compound **11** under basic (18-crown-6 and 3 equiv. of *t*-BuOK) or heating conditions. Contrary to our expectation the obtained product was **12** which had a partial structure of spiro-oxindole (Scheme 3). The

Scheme 3.



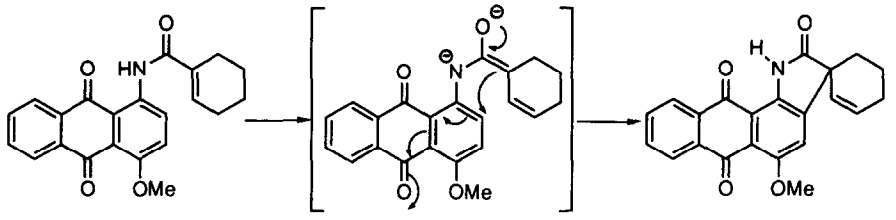
bromo acyl compound **9** was allowed to react under the same reaction conditions to afford the same spiro compound **12**. This spiro compound **12** was also obtained by the palladium-catalyzed cyclization of **10** in 80% yield. Interestingly, this kind of cyclization proceeded in low yield in the usual Heck reaction without a protection of amide functionality.[10c] Attempted radical cyclization of **10** did not give **11** but yielded the dimer **13** as a major product together with **8** when tris(trimethylsilyl)silane[13] and azobisisobutyronitrile (AIBN) were used. Treatment of **10**, on the other hand, with tri-*n*-butytinhydride (*n*-Bu_3SnH) and AIBN in benzene at reflux yielded only the reduced product **8** in 48% with recovery of **10** (28%).

Scheme 4.



Similar spiro-cyclization proceeding through a different mechanism was reported by Overman's group (Scheme 4).[14] They disclosed that treatment of compound **14** with excess base gave spiro-oxindole **16** *via* benzyne intermediate **15** as indicated in Scheme 4. Although the reaction conditions are similar to Overman's protocol, the reaction mechanism of the current reaction providing the spiro compound **12** must be quite different from that of furnishing spiro compound **16**. In compounds **8** and **9** no halide substituent leading to benzyne intermediate exists in the aromatic ring. Instead, the anthraquinone moiety of **8** plays an important role in this cyclization. Therefore we assume the reaction mechanism involves conjugate addition and elimination as illustrated in Scheme 5. The reaction mechanism forming **12** from **9** appeared to be identical with the process from **8** to **12** that involved an unknown reductive debromination.[15]

Scheme 5.



8 **8a** **12**

In recent publication Grigg[10b] and Overman[10c] have demonstrated that in the cyclization selectivity of the intramolecular Heck reaction *exo-trig* cyclization is preferred over *endo-trig* cyclization in forming 5- and 6-membered rings, and that 5-membered ring formation is kinetically favored over 6-membered ring formation. Accordingly, we expected that the palladium-catalyzed reaction with double bond isomer **18** would afford the target compound **19**.

The β,γ-unsaturated amide **18** was prepared from **7** as shown in Scheme 6. Acylation of sterically hindered amino group in **7** with an acid chloride was more difficult than we had anticipated. After various attempts,[16,17] **7** was converted to **18** by acylation with a pyridyl thioester **17**,[18] the modified Mukaiyama method.[19] Crucial cyclization of **18** using an intramolecular Heck reaction [$Pd(OAc)_2$, Ph_3P, Et_3N, BSA and DMF 100 °C] afforded initially a 1:1 mixture of **19** and its double bond regioisomer **20**. It should be noted that bis(trimethylsilyl)acetamide (BSA)[20] is indispensable reagent for this cyclization. The isomerization stems from readdition-elimination of Pd–H to the product.[10a] In order to minimize this double bond isomerization, we have searched for the reaction conditions. In the event a mixture of **18**, $Pd_2(dba)_3{\cdot}CHCl_3$, P(*o*-tol)$_3$, diisopropylethylamine (*i*-Pr_2NEt) and BSA was heated at 70 °C under nitrogen atmosphere to afford a mixture of 5:1 of **19** and **20** in 84% yield. Chromatographic purification followed by crystallization afforded **19** as orange needles in 67% yield. The isomer **20** was obtained from the mother liquor in 10% yield. The stereochemistry of the ring junction was *cis*, which was confirmed by the coupling constant (3 Hz)[21,22] and nOe study between the angular protons (Fig. 1). The stereochemistry of the cyclized products **19**, **20** is also predictable on the basis of a *syn* addition of the organopalladium group to the double bond of **18** (β face) followed by a *syn* elimination of palladium hydride group to give a normal *cis*-ring junction.[10a] In contrast to the conversion from **10** to the spiro-oxindole **12**, the current Heck type cyclization did not proceed without BSA, which was used for temporary protection of the amide group in

18. Preparation of the key intermediate **2** in Scheme 1 was accomplished in 2 steps from the pentacyclic compound **19**. Bromination of **19** with N-bromosuccinimide (NBS), followed by dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded **2** in 62% (2 steps) yield. Introduction of acetylene moieties to these compounds will be reported in the near future.[24]

Scheme 6.

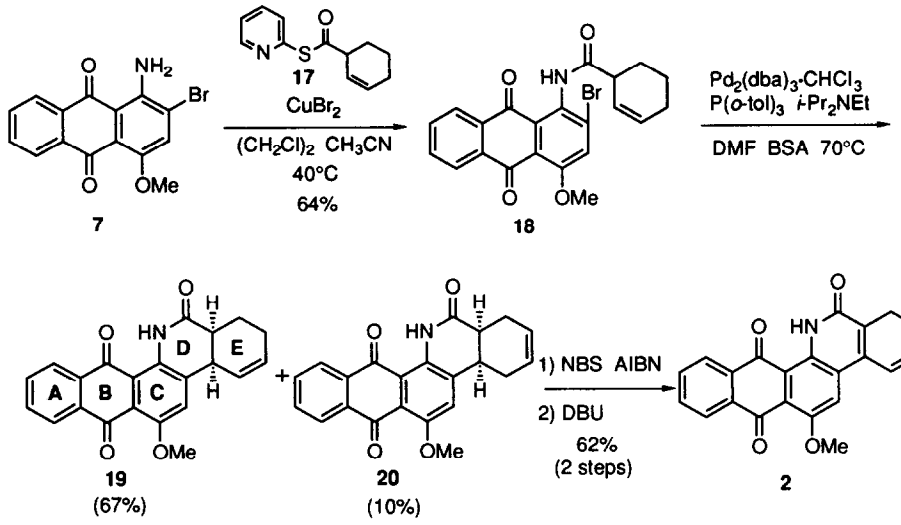
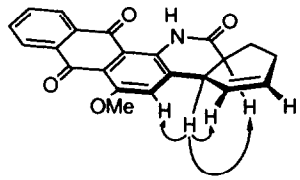


Fig. 1. NOE experiments of **19**[22]



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Experimental section

General: Melting points were recorded on a Yanaco MP-S3 apparatus and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX-270 (^{1}H, 270 MHz; ^{13}C, 67.9 MHz) and JEOL FX-200 (^{1}H, 200 MHz; ^{13}C, 50 MHz) spectrometers. Ultra-violet spectra were recorded on JASCO Ubest-50. Mass spectra were recorded on JEOL DX-705L and JEOL JMS-D 100 spectrometers. Elemental analyses were performed by Analytical Laboratory at School of Agriculture, Nagoya University. Unless otherwise noted, nonaqueous reactions were carried out under nitrogen atmosphere. THF was distilled from potassium metal in the color development by benzophenone ketyl. Chlorinated solvents, CH_2Cl_2 and $ClCH_2CH_2Cl$, were dried over active alumina. DMF, DMSO and acetonitrile were dried over MS 4A. Amines and HMPA were dried over CaH_2 and distilled before use. N-Bromosuccinimide (NBS) was recrystallized from water and dried.

Column chromatography was routinely performed on Fuji Devison (BW 820-MH) silica gel. Merck precoated silica gel (Art 5715) was used for analytical purpose. Silica gel (Merck Art 7747) preparative plates were used for separation.

1-Amino-2-bromo-4-methoxyanthraquinone (7) Method A: A mixture of 1-amino-2-bromo-4-hydroxyanthraquinone **(6)** (63.6 g, 0.30 mol), K_2CO_3 (63.6 g, 0.46 mol) and MeI (85.2 g, 0.60 mol) in DMF (1.0 l) was heated at 40 °C for 14 h with vigorous stirring. Volatile materials were evaporated under reduced pressure, then the concentrate was poured into ice water (*ca.* 4 l). The resulting precipitate was filtered off, washed well with water and dried. The dry solid was dissolved into 30% MeOH-CH_2Cl_2 and the solution was concentrated to afford 64.0 g (96%) of crystalline product **7**.

Method B: To a cold solution of 1-amino-4-hydroxyanthraquinone **(4)** (25.0 g, 0.11 mol) in THF (25 ml) and DMSO (225 ml) was added a solution of *t*-BuOK (11.8 g, 0.11 mol) in THF (20 ml) and DMSO (10 ml) maintaining the temperature between 12 °C and 15 °C. The mixture was stirred at the same temperature for 1 h and MeI (29.8 g, 0.21 mol) was added over 3 min. The reaction mixture was poured into ice water and the resulting precipitate was collected by filtration and crystallized from CH_2Cl_2 to give 1-amino-4-methoxyanthraquinone **(5)** as needles (16.6 g, 70%). To a cold solution of **5** (14.1 g, 55.5 mmol) in acetic acid (60 ml) and CH_2Cl_2 (120 ml) was added Br_2 (3.52 ml, 69 mmol) in CH_2Cl_2 (10 ml) over 20 min at 0 °C and the mixture was stirred for 1 h at rt. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed well with water, neutralized with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was crystallized from CH_2Cl_2-MeOH to give **7** (14.9 g, 80%): Mp 171-174 °C. UV (EtOH) λ_{max} (log ε) 279 (3.95), 507 (3.95) nm. IR (KBr) ν_{max} 3440, 1661, 1591, 1527 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 4.03 (3H, s, C*H*$_3$O), 7.32 (2H, brs, N*H*), 7.57 (1H, s, aromatic), 7.71 (2H, m, aromatic), 8.20 (2H, m, aromatic). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 57.6 (q) 113.8 (s), 119.1 (s), 120.6 (s), 120.7 (s), 126.3 (d), 126.4 (d), 126.7 (d), 133.2 (d), 133.4 (d), 134.3 (s), 143.3 (s), 151.6 (s), 182.5 (s), 185.1 (s). Anal. Calcd for $C_{15}H_{10}BrNO_3$: C, 54.24; H, 3.03; N, 4.22. Found: C, 53.98; H, 2.85; N, 3.97.

1-(1'-Cyclohexenecarboxamido)-4-methoxyanthraquinone (8) A suspension of 1-amino-2-bromo-4-methoxyanthraquinone **(7)** (500 mg, 2.0 mmol), *t*-BuOK (300 mg, 2.7 mmol) and 18-crown-6 (53 mg, 0.2 mmol) in THF (7.5 ml) was stirred at rt for 30 min and 1-cyclohexene-1-carbonyl chloride[12] (385 mg, 2.7 mmol) was added at 0 °C. The mixture was stirred for 1 h at the same temperature. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified chromatographically (CH_2Cl_2 as eluant) to afford **8** (390 mg, 57%): mp 219-221 °C (from CH_2Cl_2-MeOH). UV (EtOH) λ_{max} (log ε) 252 (4.62), 307 (3.97), 448 (3.89), 462 (3.91) nm. IR (KBr) ν_{max} 3392, 2926, 1654, 1592, 1516 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.6-1.9 (4H, m, C*H*$_2$), 2.32 (2H, m, C*H*$_2$-C=C), 2.48 (2H, m, C*H*$_2$-C=C), 4.01 (3H, s, C*H*$_3$O), 7.00 (1H, m, C*H*=C), 7.42 (1H, d, J = 10 Hz, aromatic), 7.62 (1H, s, aromatic), 7.68-7.80 (2H, m, aromatic), 8.2-8.3 (2H, m, aromatic), 9.17 (1H, d, J = 10 Hz, aromatic), 12.6 (1H, brs, N*H*). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.5 (t), 22.2 (t), 24.1 (t), 25.9 (t), 56.8 (q), 119.0 (s), 120.7 (s), 121.1 (d), 126.6 (d), 126.8 (d), 128.5 (d), 128.7 (s), 133.0 (s), 133.2 (d), 133.9 (s), 134.3 (s), 136.3 (d), 156.0 (s), 167.7 (s), 182.5 (s), 187.7 (s), 187.7 (s). Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.02; H, 5.35; N, 3.90.

1-(2'-Bromo-1'-cyclohexenecarboxamido)-4-methoxyanthraquinone (9) By a procedure similar to that described for the synthesis of **8** except the acid chloride,[12] **9** was obtained as a crystalline solid from

MeOH in 76% yield. Mp 231-233 °C. UV (EtOH) λ_{max} (log ε) 250 (4.23), 444 (3.81), 462 (3.79) nm. IR (KBr) ν_{max} 1664, 1499, 1226 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.7-1.9 (4H, m, CH_2), 2.3-2.7 (4H, m, CH_2-C=C), 4.05 (3H, s, CH_3O), 7.45 (1H, d, J = 10 Hz, aromatic), 7.70-7.80 (2H, m, aromatic), 8.2-8.3 (2H, m, aromatic), 9.18 (1H, d, J = 10 Hz, aromatic), 12.38 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.5 (t), 24.1 (t), 29.3 (t), 36.3 (t), 56.9 (q), 119.6 (s), 120.9 (d), 121.0 (s), 122.2 (s), 126.7 (d), 126.9 (d), 128.5 (d), 133.0 (s), 133.3 (d), 134.4 (s), 134.5 (d), 135.2 (s), 135.5 (s), 156.5 (s), 168.6 (s), 182.5 (s), 187.6 (s), 187.7 (s). Anal. Calcd for $C_{22}H_{18}BrNO_4$: C, 60.02; H, 4.12; N, 3.18. Found: C, 60.05; H, 3.88; N, 3.06.

2-Bromo-1-(1'-cyclohexenecarboxamido)-4-methoxyanthraquinone (10) By a procedure similar to that described for the synthesis of **8**, **10** was obtained as a crystalline solid from MeOH in 25% yield. Mp 205-208 °C. UV (EtOH) λ_{max} (log ε) 226 (4.39), 258 (4.45), 447 (3.79), 462 (3.80) nm. IR (KBr) ν_{max} 2926, 1665, 1591, 1516 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.6-1.9 (4H, m, CH_2), 2.28 (2H, m, CH-C=C), 2.46 (2H, m, CH-C=C), 4.04 (3H, s, CH_3O), 7.03 (1H, m, CH=C), 7.61 (1H, s, aromatic), 7.70-7.80 (2H, m, aromatic), 8.1-8.2 (2H, m, aromatic), 12.53 (1H, s, NH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.5 (t), 22.1 (t), 24.1 (t), 25.7 (t), 56.7 (q), 120.8 (s), 123.2 (d), 123.5 (s), 126.6 (d), 126.8 (d), 130.5 (s), 133.0 (s), 133.3 (s), 133.5 (d), 134.0 (s), 134.1 (s), 134.5 (d), 136.6 (d), 157.6 (s), 166.9 (s), 181.8 (s), 186.1 (s). Anal. Calcd for $C_{22}H_{18}BrNO_4$: C, 60.02; H, 4.12; N, 3.18. Found: C, 60.10; H, 3.80; N, 3.06.

5'-Methoxy-2-cyclohexenespiro-3'-anthra[1,2-b]pyrrol-2'(1'H),6',11'-trione (12) Preparation from **8**: To a mixture of **8** (200 mg, 0.55 mmol) and *t*-BuOK (198 mg, 1.8 mmol) in THF (1.5 ml) was added 18-crown-6 (35 mg, 0.13 mmol) in THF (0.5 ml) at 0 °C and the mixture was stirred for 1 h at rt. The reaction mixture was worked up and purified by preparative TLC (benzene/acetone = 10:1 as developing solvent) to give **12** (153 mg, 77%).

Preparation from **9**: By a similar procedure described above except reaction time (2 h), **12** (50 mg) was obtained from **9** (17 mg) in 42% yield.

Preparation from **10**: A solution of **10** (15 mg, 0.034 mmol), $Pd(OAc)_2$ (1.6 mg, 0.0070 mmol), $P(C_6H_5)_3$ (3.7 mg, 0.014 mmol) and Et_3N (0.01 ml, 0.070 mmol) in DMF (1 ml) was heated for 15 h at 60 °C. After the usual work-up, the concentrate was purified by preparative TLC (benzene/acetone = 10:1) to afford **12** (10.0 mg, 80%): mp 152-155°C (AcOEt). UV (EtOH) λ_{max} (log ε) 248 (4.50), 446 (3.58) nm. IR (KBr) ν_{max} 3220, 2930, 1733, 1654 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.8-2.4 (6H, m, CH_2), 4.03 (3H, s, CH_3O), 5.37 (1H, dd, J = 10, 1.5 Hz, CH=CH-CH_2), 6.28 (1H, dt, J = 10, 3.5 Hz, CH=CH-CH_2), 7.27 (1H, s, aromatic), 7.77 (2H, m, aromatic), 8.25 (2H, m, aromatic), 9.94 (1H, brs, NH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.9 (t), 24.0 (t), 32.1 (t), 48.8 (s), 57.0 (q), 114.8 (s), 115.4 (d), 118.5 (s), 122.8 (d), 126.1 (d), 127.1 (d), 132.1 (s), 133.0 (d), 133.6 (d), 134.5 (d), 135.0 (s), 136.3 (s), 145.1 (s), 157.0 (s), 180.3 (s), 181.5 (s), 184.8 (s). Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.30; H, 4.65; N, 3.87.

2,2'-Bis-1,1'-(1,1'-cyclohexenecarboxamido)-4,4'-methoxyanthraquinone (13)[25] A solution of **10** (50 mg, 0.11 mmol), tris(trimethylsilyl)silane (0.15 ml, 0.49 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (2 ml) was heated at reflux overnight. The reaction mixture was partitioned with diluted HCl and AcOEt. The organic layer was washed with water and brine, dried and concentrated *in vacuo*. The residue was purified on a preparative TLC (CH_2Cl_2/acetone = 10:1 as developing solvent) to give dimer **13** (25.5 mg, 62%): mp >200 °C (MeOH). UV (EtOH) λ_{max} (log ε) 249 (4.46), 462 (3.92) nm. IR (KBr) ν_{max} 3210, 1663 1590cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.6-1.8 (8H, m, CH_2), 2.35 (4H, m, CH_2-C=C), 2.75 (4H,

m, CH_2-C=C), 4.10 (6H, s, CH_3O), 7.19 (2H, m, C*H*=C), 7.44 (2H, s, aromatic), 7.70 (4H, m, aromatic), 8.25 (4H, m, aromatic). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.6 (t), 21.9 (t), 24.8 (t), 26.2 (t), 57.1 (q), 99.9 (d), 119.3 (s), 126.1 (s), 125.8 (s), 126.5 (d), 127.1 (d), 133.0 (s), 133.3 (d), 133.4 (s), 134.1 (d), 134.8 (s), 138.0 (d), 155.5 (s), 159.2 (s), 167.6 (s), 182.7 (s), 183.3 (s). Anal. Calcd for $C_{44}H_{36}N_2O_8$: C, 73.32 ; H, 4.99; N, 3.89. Found: C, 73.51; H, 4.69; N, 3.87.

2-Bromo-1-(2-cyclohexenecarboxamido)-4-methoxyanthraquinone (18) To a solution of $CuBr_2$ (25.0 g, 0.11 mol) in acetonitrile (900 ml) was added active ester **17**[18] (50.0 g, 0.23 mol), which was freshly prepared from cyclohex-2-ene-1-carbonyl chloride[23] and 2-mercaptopyridine, in $ClCH_2CH_2Cl$ (50 ml) at 0 °C. After stirring for 10 min, the mixture was warmed to 10 °C and **7** (25.0 g, 0.075 mol) in $ClCH_2CH_2Cl$ (250 ml) was added to the solution at the same temperature. The mixture was stirred overnight at 35 °C. AcOEt (200 ml) was added to the suspension and it was allowed to stand for 1 day at rt. The precipitate was filtered off and dried. The solid was treated with 20% MeOH-CH_2Cl_2, filtered and washed well with the same solvent. The filtrate was concentrated *in vacuo* and crystallized from AcOEt to give **18** (17.0 g, 51%). Mother liquors containing the product were collected and purified by column chromatography (CH_2Cl_2/n-hexane = 4:1 as eluant) to give 4.2 g (13%) of the second crop. The total yield was 21.2 g (64%). Mp 225-228 °C. UV (EtOH) λ_{max} (log ε) 226 (4.36), 258 (4.42), 382 (3.68) nm. IR (KBr) ν_{max} 3440, 1662, 1641, 1581, 1529 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.6-2.3 (6H, m, CH_2), 3.22 (1H, m, COC*H*), 4.03 (3H, s, CH_3O), 6.03 (1H, ddd, *J* = 10, 3, 2 Hz, CH-C*H*=CH), 6.16 (1H, dtd, *J* = 10, 2.5, 2 Hz, CH-CH=C*H*), 7.62 (1H, s, aromatic), 7.68-7.80 (2H, m, aromatic), 8.07-8.2 (2H, m, aromatic), 9.49 (1H, brs, N*H*). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 20.5 (t), 25.0 (t), 26.2 (t), 43.7 (d), 57.0 (q), 121.1 (s), 123.1 (d), 124.0 (d), 126.5 (d), 126.8 (d), 129.3 (s), 130.4 (s), 130.5 (s), 132.2 (d), 133.1 (s), 133.5 (d), 134.1 (s), 134.3 (d), 157.9 (s), 173.4 (s), 181.9 (s), 185.6 (s). Anal. Calcd for $C_{22}H_{18}BrNO_4$:C, 60.02; H, 4.12; N, 3.18. Found: C, 59.98; H, 3.93; N, 3.08.

***cis*-1,2,4a,14a-tetrahydro-6-methoxyanthra[1,2-c]isoquinolin-7,12,14(13H)-trione (19)** A mixture of **18** (2.20 g, 5.0 mmol), $Pd_2(dba)_3$·$CHCl_3$ (515.9 mg, 0.50 mmol), P(*o*-tol)$_3$ (605 mg, 2.0 mmol), BSA (32.9 ml, 0.13 mol) and *i*-Pr_2NEt (1.10 ml, 8.1 mmol) in DMF (32.9 ml) was heated at 70 °C for 1 h. The cooled mixture was poured into ice water containing 1.1 ml of formic acid. The resulting precipitate was filtered off, washed with water and dried. The crude product was purified chromatographically on a column of silica gel (CH_2Cl_2 as eluant) and crystallized from CH_2Cl_2-AcOEt to give 1.2 g (67%) of **19**: mp 193-197 °C. UV (EtOH) λ_{max} (log ε) 249 (4.45), 446 (3.77), 464 (3.74) nm. IR (KBr) ν_{max} 3261, 1663, 1592, 1474, 1442 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.7-1.85 (2H, m, CH_2), 2.0-2.5 (2H, m, CH_2), 2.96 (1H, td, *J* = 6, 3 Hz, C*H*-CO), 3.79 (1H, ddd, *J* = 3, 2.5, 1 Hz, C*H*-CH=CH), 4.03 (3H, s, CH_3O), 5.61 (1H, ddd, *J* = 10, 2.5, 2 Hz, CH-C*H*=CH), 5.95 (1H, dtd, *J* = 10, 3, 1 Hz, CH-CH=C*H*), 7.30 (1H, s, aromatic), 7.75 (2H, m, aromatic), 8.20 (2H, m, aromatic), 11.76 (1H, brs, N*H*). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.1 (t), 22.2 (t), 37.6 (d), 38.5 (d), 57.0 (q), 116.2 (s), 119.6 (s), 120.2 (d), 124.5 (d), 126.7 (d), 126.8 (d), 131.0 (d), 133.4 (s), 133.6 (d), 133.7 (s), 134.3 (d), 136.8 (s), 138.5 (s), 156.1 (s), 171.7 (s), 182.2 (s), 186.8 (s). Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.49; H, 4.63; N, 3.87.

Careful concentration of the mother liquor of the above recrystallization followed by standing at rt, yielded 179 mg (10%) of isomer **20**: mp 205-208 °C. UV (EtOH) λ_{max} (log ε) 249 (4.59), 444 (3.90), 461 (3.92) nm. IR (KBr) ν_{max} 3255, 1682, 1659, 1593 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.0-2.5 (3H, m,

CH_2), 2.91 (1H, m, CH_2), 2.96 (1H, t, J = 5.5 Hz, C*H*-CO), 3.33 (1H, td, J = 8, 5.5 Hz, C*H*-C=C), 4.03 (3H, s, CH_3O), 5.70 (1H, ddd, J = 10.5, 2, 0.5 Hz, C*H*=C), 5.80 (1H, ddd, J = 10.5, 4, 2 Hz, C*H*=C), 7.28 (1H, s, aromatic), 7.75 (2H, m, aromatic), 8.18 (2H, m, aromatic), 11.65 (1H, brs, N*H*). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 22.7 (t), 27.4 (t), 36.5 (d), 37.2 (d), 56.9 (q) 116.6 (s), 118.8 (d), 119.6 (s), 124.0 (d), 125.8 (d), 126.6 (d), 126.7 (d), 132.8 (s), 133.3 (d), 133.6 (s), 134.3 (d), 134.4 (s), 138.4 (s), 156.0 (s), 171.5 (s), 182.1 (s), 186.8 (s). Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.49; H, 4.61; N, 3.83.

1,2-Dihydro-6-methoxyanthra[1,2-c]isoquinolin-7,12,14(13H)-trione (2) A mixture of **19** (1.0 g, 2.80 mmol), NBS (500 mg, 2.81 mmol) and azobisisobutyronitrile (AIBN) (100 mg, 0.609 mmol) in $ClCH_2CH_2Cl$ (30 ml) was heated at 70 °C for 30 min. To a cold solution was added DBU (0.633 ml, 4.23 mmol) and the mixture was stirred for 1 h at rt. The reaction mixture was poured into ice water and extracted with 10% MeOH-CH_2Cl_2. The organic layer was washed well, dried over Na_2SO_4 and concentrated under diminished pressure. The residue was purified chromatographically (CH_2Cl_2/acetone = 10:1 as eluant) to afford **2** (619 mg, 62%): mp >250 °C (MeOH-CH_2Cl_2). UV (EtOH) λ_{max} (log ε) 228 (4.25), 264 (4.33), 476 (3.89) nm. IR (KBr) ν_{max} 3408, 1664, 1583 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.43 (2H, tdd, J = 10, 4.5, 2 Hz, CH_2CH=CH), 2.89 (2H, t, J = 10 Hz, CH_2CH_2), 4.10 (3H, s, CH_3O), 6.58 (1H, dt, J = 4.5 Hz, CH_2C*H*=CH), 6.88 (1H, dt, J = 10, 2 Hz, CH_2CH=C*H*), 7.69 (1H, s, aromatic), 7.78 (2H, m, aromatic), 8.25 (2H, m, aromatic), 9.49 (1H, brs, N*H*). ^{13}C NMR ($CDCl_3$, 67.9 MHz). δ 19.8 (t), 21.8 (t), 57.1 (q), 114.2 (d), 120.1 (d), 124.3 (s), 126.8 (d), 126.9 (d), 126.9 (s), 128.9 (s), 132.9 (s), 133.3 (s), 133.7 (d), 133.7 (s), 134.2 (s), 134.5 (d), 136.6 (d), 136.7 (s), 154.6 (s), 182.5 (s), 185.5 (s), 186.9 (s). Anal. Calcd for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23; N, 3.92. Found: C, 73.68; H, 3.99; N, 3.64. HRMS calcd for $C_{22}H_{15}NO_4$ 357.0972, found 357.0989.

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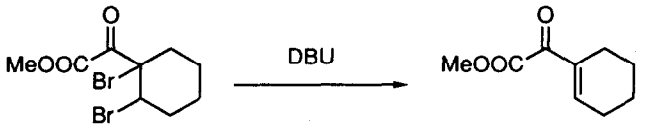
(15) The reaction mechanism is unclear. Based on the result of our experiment from **21** to **22**, we assume reductive debromination might occur prior to cyclization as illustrated in Scheme 5.



21 **22**

The dibromide **21** was prepared from **22** by bromination (Br_2, AcOH, 0°C, 1 h). Data for **21**: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.43 (8H, m, CH_2), 2.89 (1H, t, J = 10 Hz, CHBr), 4.10 (3H, s, CH_3O). MS (EI) m/z 221 (M-Br). α,β-Unsaturated ester **22** was confirmed by comparison with the authentic sample. A similar reduction was discussed in the literature; Caubère, P.; Coudert, G. *J. Chem. Soc., Chem. Commun.* **1972**, 1289.
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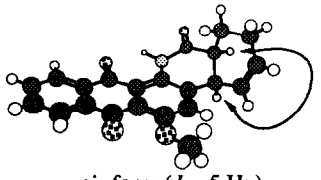
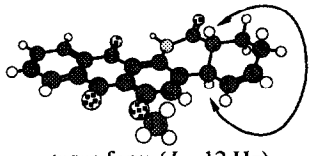
(22) A coupling constant of the ring-junction protons of **19** was observed as 3 Hz. Calculated coupling constants by BioGraf and Macro Model were J = 5 Hz for *cis* form and J = 12 Hz for *trans* form, which supported the *cis*-product.



cis form (J = 5 Hz)



trans form (J = 12 Hz)

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(25) Although the mass spectrum of **13** did not support directly the structure (m/z=360; cacld, m/z=720), we assumed **13** as a dimeric product based on the nmr spectra. Other data of **10** and **13** were almost the same, but the chemical shift of **10** at the C3 position of the anthraquinone skeleton in cmr greatly changed from 123.2 ppm to 99.9 ppm (**13**), due to the steric and electronic effect of the hetero atoms by dimerization.

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