One-Pot Synthesis of Benzo[*f*]indole-4,9-diones from 1,4-Naphthoquinones and Terminal Acetylenes

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In this paper, a concise one-pot method for the construction of benzo[*f*]indole-4,9-dione motifs is described. These transformations proceed *via* a sequential palladium- and copper-catalyzed coupling reaction of 1,4-naphthoquinones with terminal acetylenes, followed by a copper-catalyzed intramolecular cyclization reaction of the resulting coupling product.

Key words indolequinone; Sonogashira coupling; cascade reaction; copper; palladium

Indolequinones are interesting and valuable compounds because they are often found in antitumor agents such as mitomycin C **1**[1—3] and EO9 **2**[4,5] (Fig. 1). Despite their attractive biological activities, there are a limited number of efficient methods for synthesizing indolequinones.[6—15] Among those reported, the following three strategies exceptionally provide versatile entries to indolequinones: reactions of 1,4-naphthoquinones with enamines;[16—19] Mn(III)-initiated oxidative free radical reactions of 2-amino-1,4-naphthoquinones with β-dicarbonyl compounds[20—22]; and cyclization of 3-acetylamino-2-alkynyl-1,4-naphthoquinones, which are synthesized from 3-acetylamino-2-bromo-1,4-naphthoquinone and terminal acetylenes by the Sonogashira reaction.[23] However, these methods have some drawbacks such as a limited range of substituents on substrates and/or unsatisfactory yields because of structural changes in the substrates. In an earlier report, our group described the one-pot synthesis of indolequinones from 2-amino-3-bromo-1,4-naphthoquinone derivatives and terminal acetylenes by the Sonogashira coupling/cyclization cascade reaction.[24] Although this method provided concise access to benzo[*f*]indole-4,9-dione motifs, a stoichiometric amount of copper salt was required to obtain satisfactory yields. According to the reported methods typically used for indole syntheses, we tested the reactions using a catalytic amount of copper(I) salts with bidentate ligands such as bipyridine, 1,10-phenanthroline, and *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine.[25—27] However, no coupling reactions were observed, and degradation of the starting naphthoquinone to a dehalogenated compound gradually occurred during the reaction.[28] Thus, we attempted to develop more efficient reaction conditions for preparing indolequinones. In this paper, we describe the development of a cascade reaction for constructing benzo[*f*]indole-4,9-dione motifs involving the Sonogashira reaction and intramolecular cyclization with a catalytic amount of copper salts (Chart 1).

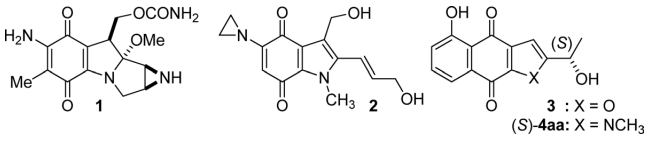

Fig. 1. Heterocycle-Fused Quinones

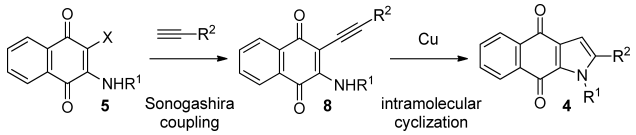

Chart 1. Construction of Benzo[*f*]indole-4,9-dione Motifs

Results and Discussion

We have previously reported that (*S*)-5-hydroxy-2-(1′-hydoxyethyl)naphtho[2,3-*b*]furan-4,9-dione (**3**), which is a secondary metabolite found in the inner bark of *Tabebuia avellanedae*, exhibits potent antiproliferative effects against several human tumor cell lines.[29,30] To develop a concise method to synthesize its related structural motifs such as 5-hydroxy-2-(1-hydroxyethyl)-1-methyl-1*H*-benzo[*f*]indole-4,9-dione (**4aa**), 3-bromo-5-hydroxy-2-(methylamino)naphthalene-1,4-dione (**5a**) and but-3-yn-2-ol (**6a**)[31] were selected as substrates. To identify the most active catalyst system, additive screening was conducted. According to the optimal reaction conditions reported by our group,[24] all experiments were performed with 2.0 eq of acetylene, 0.8 eq of an additive, 20 mol% of copper salt, and 200 eq of pyridine in *N*,*N*′-dimethylformamide (DMF) at 80 °C.[32] However, bidentate ligands such as *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine, 2,2′-bipyridine, L-proline, and 1,10-phenanthroline, which are typically used in copper-mediated coupling reactions,[25,26] were ineffective in promoting the reaction (Table 1, entries 3—6). In contrast, most inorganic bases proved applicable and furnished the cyclized product **4aa** in 13—63% yields with K_2CO_3 being suitable (Table 1, entries 7—10). Test reactions with 0.2 and 2.0 eq of K_2CO_3 (Table 1, entries 11, 12) resulted in lower yields of **4aa**, which suggests that the optimum amount of K_2CO_3 is 0.8 eq ($K_2CO_3 : Cu_2O = 4 : 1$). Without pyridine or Cu_2O, the desired product **4aa** was obtained in low yields (Table 1, entries 13, 14). Furthermore, the coupling reaction did not initiate without $Pd(OAc)_2$ (Table 1, entry 15). A blank experiment confirmed that in the absence of K_2CO_3, almost no **4aa** was formed (Table 1, entry 2). The base pyridine is essential for this reaction, and the yield of **4aa** significantly decreased

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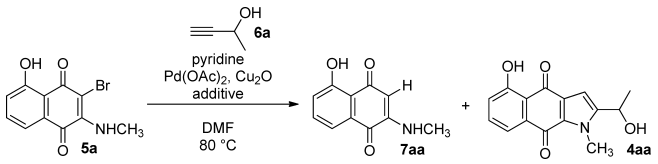
Table 1. Effect of Additives and Reagents on the Conversion of Naphthoquinone **5a** to the Cyclized Product **4aa**[a)]



Entry	Time (h)	Additives	Yield (%)[b,c)]	
			7aa	**4aa**
1[d)]	1	None	Trace	58
2	24	None	42	Trace
3	24	*trans*-*N*,*N*′-Dimethylcyclohexane-1,2-diamine	17 (8)[e)]	Trace
4	24	2,2′-Bipyridine	5 (21)[e)]	Trace
5	12	L-Proline	22	<6
6	24	1,10-Phenanthroline	17 (20)[e)]	Trace
7	12	K_3PO_4	16	34
8	1	Cs_2CO_3	51	13
9	4	Na_2CO_3	11	39
10	1	K_2CO_3	5	63
11[f)]	12	K_2CO_3	5	34
12[g)]	1	K_2CO_3	12	56
13[h)]	24	K_2CO_3	13	<4
14[i)]	12	K_2CO_3	46	<4
15[j)]	12	K_2CO_3	43 (13)[e)]	0
16[k)]	16	K_2CO_3	19 (27)[e)]	<7

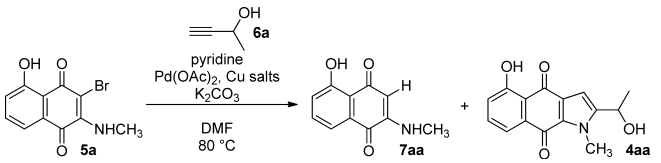
a) Substrate **5a** (0.5 mmol), $Pd(OAc)_2$ (3 mol%), copper salt (0.1 mmol), acetylene **6a** (1.0 mmol), pyridine (8.0 ml), and K_2CO_3 (0.4 mmol) were stirred in DMF at 80 °C. *b*) Isolated yield. *c*) Recovery of **5a** was less than 5%, unless otherwise noted. *d*) Cu_2O (0.05 mmol) was used. *e*) The numbers in parentheses are the yields of recovered **5a**. *f*) Additive (0.1 mmol) was used. *g*) Additive (1.0 mmol) was used. *h*) Without pyridine. *i*) Without Cu_2O. *j*) Without $Pd(OAc)_2$. *k*) Et_3N was used instead of pyridine.

when Et_3N was used instead of pyridine (Table 1, entry 16).

To determine the optimal copper salts, reactions with various copper(I) (CuI, CuBr, and CuOTf) and copper(II) salts (CuO, $CuBr_2$, and $CuCl_2$)[33)] were examined. The results are shown in Table 2. Both copper(I) and copper(II) salts afforded the cyclized product **4aa** in moderate yields (13—55%, Table 2, entries 1—6), but required a prolonged reaction time. Furthermore, decreasing the amount of Cu_2O led to a lower yield of **4aa** (Table 2, entry 7). Thus, it was determined that Cu_2O is the preferred catalyst and the optimal amount of Cu_2O is 0.2 eq (based on **4aa**).

To investigate the generality of this method, halonaphthoquinones **5b**—**d** were reacted with terminal acetylenes **6**. The results are summarized in Table 3. No coupling reactions occurred when naphthoquinone **5b** was used with an unsubstituted NH_2 group (Table 3, entry 1).[34)] The reaction of **5c**, which contains a more general naphthoquinone motif, with a stoichiometric amount of Cu_2O gave the cyclized product **4ca** in 56% yield at rt (Table 3, entry 2). A comparable result was attained when a catalytic amount of Cu_2O was used, demonstrating the utility of our catalytic cascade reaction (Table 3, entry 4). A TLC analysis during the reaction shown in Table 3 entry 4 revealed that the coupling reaction completed within 5 h at rt, although a small amount of a cyclized product was observed after 5 h.[35)] On the other hand, only a small amount of a coupling product was formed in the absence of K_2CO_3 (Table 3, entry 3).[36)] Thus, we assume that K_2CO_3 functions to regenerate the active copper acetylide/pyridine complexes and promote the coupling reaction although the exact role of K_2CO_3 is unclear. Contrary to our expectations, a lower yield was observed with catalytic amounts than stoichiometric quantities of Cu_2O when iodide

Table 2. Effect of Copper Salts on the Conversion of Naphthoquinone **5a** to the Cyclized Product **4aa**[a)]



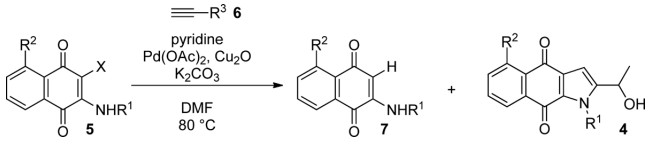
Entry	Time (h)	Cu salts	Yield (%)[b,c)]	
			7aa	**4aa**
1	12	CuI	10	38
2	12	CuBr	5	28
3	12	CuOTf	5	55
4	12	CuO	47	13
5	12	$CuBr_2$	9	48
6	16	$CuCl_2$	14	52
7[d)]	2	Cu_2O	6	30

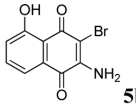
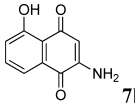
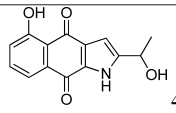
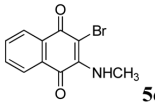
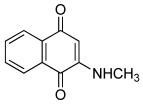
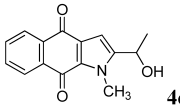
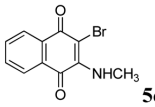
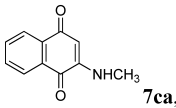
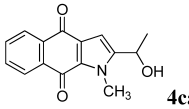
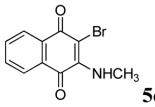
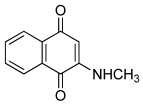
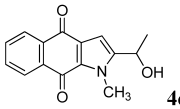
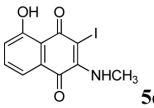
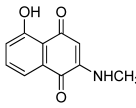
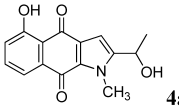
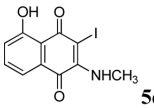
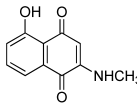
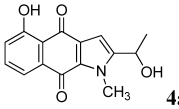
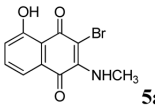
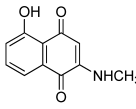
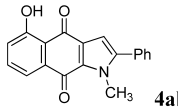
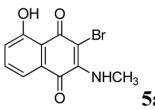
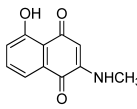
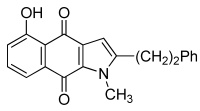
a) Substrate **5a** (0.5 mmol), $Pd(OAc)_2$ (3 mol%), Cu_2O (0.1 mmol), acetylene **6a** (1.0 mmol), pyridine (8.0 ml), and additives (0.4 mmol) were stirred in DMF at 80 °C. *b*) Isolated yield. *c*) Recovery of **5a** was less than 5%, unless otherwise noted. *d*) Cu_2O (0.5 mmol) was used.

5d was used as the substrate. This was owing to the increased formation of the dehalogenated product **7aa** (Table 3, entries 5, 6). Alkynes bearing phenyl or 2-phenylethyl substituent reacted smoothly with **5a** to give the desired product **4ab** and **4ac** in moderate yields, suggesting the hydroxyethyl moiety on the acetylene is not essential for the developed method (Table 3, entries 7, 8).

We have already reported that the cuprous acetylide/pyridine complex, which forms during the reaction, plays a crucial role in the intramolecular cyclization step.[24)] To deter-

Table 3. Effect of Varying Substrates and Acetylenes on the Conversion of Naphthoquinones **5** to the Cyclized Product **4**[a)]



Entry	Time (h)	Substrate	R^3	Product, Yield (%)[b,c)]	
				7	**4**
1	12	 **5b**	$CH(OH)CH_3$ (**6a**)	 **7ba**, 61	 **4ba**, 0
2[e,f,g,h)]	24	 **5c**	$CH(OH)CH_3$ (**6a**)	 **7ca**, trace	 **4ca**, 56
3[e,g,h)]	6	 **5c**	$CH(OH)CH_3$ (**6a**)	 **7ca**, trace (46)[d)]	 **4ca**, trace
4[e,h)]	24	 **5c**	$CH(OH)CH_3$ (**6a**)	 **7ca**, trace	 **4ca**, 53
5[e,f,g)]	0.5	 **5d**	$CH(OH)CH_3$ (**6a**)	 **7aa**, <3	 **4aa**, 88
6[e)]	0.5	 **5d**	$CH(OH)CH_3$ (**6a**)	 **7aa**, 15	 **4aa**, 63
7	1	 **5a**	Ph (**6b**)	 **7aa**, 6	 **4ab**, 69
8	1	 **5a**	CH_2CH_2Ph (**6c**)	 **7aa**, 10	 **4ac**, 64

a) Substrate **1** (0.5 mmol), $Pd(OAc)_2$ (3 mol%), Cu_2O (0.1 mmol), acetylene (1.0 mmol), pyridine (8.0 ml), and K_2CO_3 (0.4 mmol) were stirred in DMF at 80 °C. *b*) Isolated yield. *c*) Recovery of **5** was less than 5%, unless otherwise noted. *d*) The numbers in parentheses are the yields of recovered **5**. *e*) Pyridine (4.0 ml) was used. *f*) Cu_2O (0.5 mmol) was used. *g*) Without K_2CO_3. *h*) At rt.

mine the role of K_2CO_3 in the final cyclization step, the reaction of isolated **8ca** with K_2CO_3 in pyridine and DMF at rt was examined (Chart 2). After 24 h, the cyclized product **4ca** was obtained in 14% yield along with 46% recovery of unreacted **8ca**, suggesting that K_2CO_3 itself partially contributes to the cyclization process. Furthermore, the cuprous acetylide/pyridine complex functions as the primary catalyst for the intramolecular cyclization reaction.

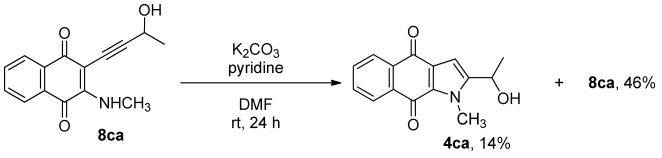


Chart 2. Conversion of the Coupling Product **8ca** to the Cyclized Product **4ca**

Finally, (*S*)-**4aa**, which was synthesized from **5a** and commercially available (*S*)-**6a** according to the developed method, was evaluated for its ability to suppress the growth of human tumor cell lines including A549 (lung) and MCF-7 (breast). Compared with **3**, compound (*S*)-**4aa** exhibited less potent antiproliferative effects against both cell lines (IC_{50} of (*S*)-**4aa**: 41.5 and 56.1 μM, respectively; IC_{50} of **3**: 0.92 and 0.48 μM, respectively).[29,30] Further structure–activity relationship (SAR) studies on **4aa** derivatives are underway in our laboratory and will be reported in due course.

Conclusion

We have demonstrated a concise method for constructing substituted indolequinones using a Sonogashira coupling/cyclization cascade reaction with K_2CO_3 and a catalytic amount of Cu_2O. The experimental simplicity of the proposed catalytic system is expected to have a variety of applications in synthetic and medicinal chemistry.

Experimental

General All melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra (500 MHz for ^{1}H and 125 MHz for ^{13}C) were obtained in $CDC1_3$, unless otherwise noted. The chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. IR is expressed in cm^{-1}. Purification was performed using silica gel column chromatography. All reagents were purchased from chemical companies and used as received. All reactions were conducted under an argon atmosphere, unless otherwise stated. Product **7ba**[37] is a known compound.

Synthesis of Starting Materials Compounds **5a**,[24] **5c**,[38] and **5d**[24] were prepared by the reported methods.

2-Amino-3-bromo-5-hydroxynaphthalene-1,4-dione (5b) To a solution of 2-bromo-8-hydroxynaphthalene-1,4-dione[38] (253 mg, 1.0 mmol) in EtOH (8.0 ml), 28% aqueous NH_3 (0.7 ml, 10 mmol) was added, and then, the mixture was stirred for 24 h at rt. After evaporation to remove the solvent, the crude product was dissolved in DMF (2.0 ml). NBS (178 mg, 1.0 mmol) was added to the solution, and the mixture was stirred for 1 h at rt. The mixture was extracted with EtOAc. The organic extracts were washed with brine and dried over Na_2SO_4. The column chromatography (hexane/EtOAc=2/1) gave **5b** (130 mg, 49% yield) as orange needles with mp 222—223 °C. **5b**: rf (hexane/EtOAc=2/1)=0.40. ^{1}H-NMR δ: 5.37 (1H, br s), 6.21 (1H, br s), 7.28 (1H, d, J=9.0 Hz), 7.52 (1H, dd, J=7.5, 9.0 Hz), 7.64 (1H, d, J=7.5 Hz), 12.48 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 99.4, 114.4, 119.7, 125.7, 130.4, 135.1, 150.6, 160.6, 178.5, 181.8. IR (KBr): 3439, 3333, 1638, 1616, 1572, 1458, 1383, 1267, 1240, 1059, 766, 683. High resolution (HR)-MS (electrospray ionization (ESI)) m/z: $[M+Na]^+$ Calcd for $[C_{10}H_6BrNNaO_3]^+$, 289.9429; Found, 289.9420.

General Procedure for Synthesis of Benzo[*f*]indole-4,9-diones Under Ar atmosphere, a mixture of Cu_2O (14 mg, 0.10 mmol), acetylene **6** (1.0 mmol), K_2CO_3 (55 mg, 0.40 mmol), and pyridine (8.0 ml, 100 mmol) was stirred for 2 h at rt. A solution of compound **5** (0.50 mmol) and $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) in DMF (5.0 ml) was added to this suspension, and the reaction mixture was stirred at 80 °C for 1 h. The mixture was quenched with H_2O at 0 °C and extracted with $CHCl_3$. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated.

5-Hydroxy-2-(1-hydroxyethyl)-1-methyl-1*H*-benzo[*f*]indole-4,9-dione (4aa) Starting from **5a** and **6a**, this compound was prepared according to the general procedure. The column chromatography (hexane/EtOAc=2/1) gave **7aa**[39] (5 mg, 5% yield) and **4aa** (86 mg, 63% yield) as yellow needles with mp 219—220 °C. **4aa**: rf (hexane/EtOAc=1/1)=0.33. ^{1}H-NMR δ: 1.68 (3H, d, J=6.5 Hz), 1.98 (1H, d, J=7.5 Hz), 4.11 (3H, s), 4.93 (1H, dq, J=6.5, 7.5 Hz), 6.65 (1H, s), 7.17 (1H, dd, J=1.0, 8.5 Hz), 7.53 (1H, dd, J=7.5, 8.5 Hz), 7.63 (1H, dd, J=1.0, 7.5 Hz), 12.6 (1H, s). ^{13}C-NMR δ: 22.1, 33.4, 62.0, 105.1, 115.4, 119.2, 124.1, 126.8, 131.8, 134.3, 135.4, 145.4, 162.0, 175.7, 186.7. IR (KBr): 3530, 1630, 1458, 1374, 1352, 1219, 1080. HR-MS (ESI) m/z: $[M-H]^-$ Calcd for $[C_{15}H_{13}NO_4]^-$, 270.0766; Found, 270.0757.

(*S*)-**4aa**: Pale yellow needles with mp 234—235 °C. $[\alpha]_D^{25}$ +12.1 (c=0.11, CH_3OH) for >99% ee (HPLC, Daicel Chiralpak AD-H, hexane/*i*-PrOH=7/3, 1.0 ml/min, 254 nm, minor: 5.44 min and major: 8.59 min).

2-(1-Hydroxyethyl)-1-methyl-1*H*-benzo[*f*]indole-4,9-dione (4ca) Starting from **5c** and **6a**, this compound was prepared according to the general procedure. Pyridine (4.0 ml) was used. The reaction was performed at rt for 24 h. The column chromatography (hexane/EtOAc=2/1) gave **7ca**[37] (trace) and **4ca** (67 mg, 53% yield) as pale yellow needles with mp 200—201 °C. **4ca**: rf (hexane/EtOAc=1/1)=0.2. ^{1}H-NMR δ: 1.69 (3H, d, J=6.5 Hz), 2.00 (1H, d, J=7.0 Hz), 4.12 (3H, s), 4.94 (1H, dq, J=6.5, 7.0 Hz), 6.69 (1H, s), 7.65—7.69 (2H, m), 8.11—8.14 (2H, m). ^{13}C-NMR δ: 22.1, 33.7, 60.1, 104.6, 125.8, 126.0, 126.7, 130.2, 132.8, 133.2, 133.4, 133.7, 147.6, 175.1, 179.9. IR (KBr): 3433, 1647, 1586, 1474, 1443, 1358, 1246, 963, 714. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{15}H_{14}NO_3]^+$, 256.0974; Found, 256.0985.

5-Hydroxy-1-methyl-2-phenyl-1*H*-benzo[*f*]indole-4,9-dione (4ab) Starting from **5a** and **6b**, this compound was prepared according to the general procedure. The column chromatography (hexane/EtOAc=5/1) gave **7aa** (6 mg, 6% yield) and **4ab** (104 mg, 69% yield) as orange needles with mp 208—209 °C. **4ab**: rf (hexane/EtOAc=2/1)=0.60. ^{1}H-NMR δ: 4.05 (3H, s), 6.79 (1H, s), 7.20 (1H, dd, J=1.5, 8.5 Hz), 7.44—7.58 (6H, m), 7.71 (1H, dd, J=1.5, 7.5 Hz), 12.65 (1H, s). ^{13}C-NMR δ: 34.7, 108.0, 115.6, 119.1, 124.0, 127.6, 128.9, 129.2, 129.3, 130.1, 131.6, 134.5, 135.4, 144.1, 162.1, 175.5, 187.0. IR (KBr): 3109, 1630, 1458, 1439, 1323, 1265, 1234, 826, 758, 698. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{19}H_{14}NO_3]^+$, 304.0974; Found, 304.0973.

5-Hydroxy-1-methyl-2-phenethyl-1*H*-benzo[*f*]indole-4,9-dione (4ac) Starting from **5a** and **6c**, this compound was prepared according to the general procedure. The column chromatography (hexane/EtOAc=5/1) gave **7aa** (10 mg, 10% yield) and **4ac** (106 mg, 64% yield) as pale yellow prisms with mp 163—164 °C. **4ac**: rf (hexane/EtOAc=2/1)=0.60. ^{1}H-NMR δ: 2.93 (2H, t, J=7.5 Hz), 3.02 (2H, t, J=7.5 Hz), 3.88 (3H, s), 6.56 (1H, s), 7.15—7.33 (6H, m), 7.52 (1H, dd, J=7.0, 7.0 Hz), 7.65 (1H, d, J=7.0 Hz), 12.64 (1H, s). ^{13}C-NMR δ: 28.1, 32.6, 34.4, 106.2, 115.5, 119.0, 123.9, 126.7, 127.5, 128.3, 128.7, 130.8, 134.6, 135.3, 140.1, 143.7, 162.0, 175.1, 187.0. IR (KBr): 3109, 1626, 1465, 1450, 1438, 1362, 1346, 1263, 1217, 1150, 1017, 826, 785, 746, 702. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{21}H_{18}NO_3]^+$, 332.1287; Found, 332.1291.

2-(3-Hydroxybut-1-yn-1-yl)-3-(methylamino)naphthalene-1,4-dione (8ca) Starting from **5c** and **6a** with a stoichiometric amount of Cu_2O, this compound was prepared according to the general procedure. The reaction was quenched after 4 h. The column chromatography (hexane/EtOAc=2/1) gave **4ca** (47 mg, 37% yield) and **8ca** (39 mg, 31% yield). **8ca**: red needles with mp 154—156 °C. rf (hexane/EtOAc=1/1)=0.1. ^{1}H-NMR δ: 1.56 (3H, d, J=7.0 Hz), 1.67 (1H, br s), 3.52 (3H, d, J=5.5 Hz), 4.83 (1H, q, J=7.0 Hz), 6.45 (1H, br s), 7.61 (1H, dd, J=1.0, 7.5 Hz), 7.73 (1H, dd, J=1.0, 7.5 Hz), 8.02 (1H, dd, J=1.0, 7.5 Hz), 8.12 (1H, dd, J=1.0, 7.5 Hz). ^{13}C-NMR δ: 23.7, 31.7, 59.0, 77.2, 97.0, 101.3, 126.5, 126.6, 130.0, 132.3, 133.4, 135.0, 148.4, 181.0, 181.5. IR (KBr): 3318, 1674, 1597, 1566, 1516, 1331, 1292, 721. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{15}H_{14}NO_3]^+$, 256.0974; Found, 256.0987.

Antiproliferative Effect Assay The antiproliferative effects of indolequinone (*S*)-**4aa** was examined in cancer cell lines. These cells were maintained in usual 10% fetal serum Dulbecco's minimum essential medium (DMEM) through experiments and exposed to four dose concentrations of (*S*)-**4aa** in a humidified atmosphere (37 °C, 5% CO_2) for 72 h. After the reaction, cells were further incubated with 0.25% trypan blue dye for 20 min and counted for viable cells under light microscopic apparatus. IC_{50} values were calculated from separate experiments performed in triplicate.

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References and Notes

1) Carter S. K., Crooke S. T., "Mitomycin C: Current Status and New Developments," Academic Press, New York, 1979.
2) Remers W. A., Dorr R. T., "Alkaloids: Chemical and Biological Perspectives," ed. by Pelletier, S. W., Wiley, New York, 1988, p. 1.
3) Franck R. W., Tomasz M., "Chemistry of Antitumor Agents," ed. by Wilman, D. E. V., Blackie & Son, Ltd., Glasgow, 1990, pp. 379—393.
4) Oostveen E. A., Speckamp W. N., *Tetrahedron*, **43**, 255—262 (1987).
5) Jain A., Phillips R. M., Scally A. J., Lenaz G., Beer M., Puri R., *Urology*, **73**, 1083—1086 (2009).
6) Newsome J. J., Swann E., Hassani M., Bray K. C., Slawin A. M. Z., Beall H. D., Moody C. J., *Org. Biomol. Chem.*, **5**, 1629—1640 (2007).
7) Barcia J. C., Otero J. M., Estevez J. C., Estevez R. J., *Synlett*, **9**,

1399—1402 (2007).
8) Marie A., Colucci M. A., Reigan P., Siegel D., Chilloux A., Ross D., Moody C. J., *J. Med. Chem.*, **50**, 5780—5789 (2007).
9) Bernardo P. H., Chai C. L. L., *J. Org. Chem.*, **68**, 8906—8909 (2003).
10) Knölker H.-J., Reddy K. R., *Heterocycles*, **60**, 1049—1052 (2003).
11) Nicolaou K. C., Sugita K., Baran P. S., Zhong Y.-L., *J. Am. Chem. Soc.*, **124**, 2221—2232 (2002).
12) Naylor M. A., Swann E., Everett S. A., Jaffar M., Nolan J., Robertson N., Lockyer S. D., Patel K. B., Dennis M. F., Stratford M. R. L., Wardman P., Adams G. E., Moody C. J., Stratford I. J., *J. Med. Chem.*, **41**, 2720—2731 (1998).
13) Kinugawa M., Masuda Y., Arai H., Nishikawa H., Ogasa T., Tomioka S., Kasai M., *Synthesis*, **5**, 633—636 (1996).
14) Cotterill A. S., Moody C. J., Roffey R. A., *Tetrahedron*, **51**, 7223—7230 (1995).
15) Sakai M., Abe M., Takagaki H., Ogawa S., Yamazaki K., Ikegawa T., JP Patent 04211650 (1992).
16) Inman M., Moody C. J., *J. Org. Chem.*, **75**, 6023—6026 (2010).
17) Comer E., Murphy W. S., *ARKIVOC*, **7**, 286—296 (2003).
18) Murphy W. S., O'Sullivan P. J., *Tetrahedron Lett.*, **33**, 531—534 (1992).
19) Tanaka K., Takanohashi A., Morikawa O., Konishi H., Kobayashi K., *Heterocycles*, **55**, 1561—1567 (2001).
20) Tsai A.-I., Chuang C.-P., *Tetrahedron*, **64**, 5098—5102 (2008).
21) Chuang C.-P., Tsai A.-I., *Tetrahedron*, **63**, 11911—11919 (2007).
22) Tseng C.-M., Wu Y. L., Chuang C.-P., *Tetrahedron*, **60**, 12249—12260 (2004).
23) Shvartsberg M. S., Kolodina E. A., Lebedeva N. I., Fedenok L. G., *Tetrahedron Lett.*, **50**, 6769—6771 (2009).
24) Yamashita M., Ueda K., Sakaguchi K., Iida A., *Tetrahedron Lett.*, **52**, 4665—4670 (2011).
25) Wu M., Mao J., Guo J., Ji S., *Eur. J. Org. Chem.*, **23**, 4050—4054 (2008).
26) Liu F., Ma D., *J. Org. Chem.*, **72**, 4844—4850 (2007).
27) Recently, synthesis of indoles by the CuI-catalyzed Sonogashira coupling/cyclization reactions of 2-haloaniline derivatives with terminal alkynes in the presence of palladium and a base was reported. See Wang R., Mo S., Lu Y., Shen Z., *Adv. Synth. Catal.*, **353**, 713—718 (2011).
28) The following conversion of **5c** to **4ca** was observed in DMF at 80 °C for 24 h using Cu_2O (10 mol%), acetylene (2 eq), and K_2CO_3 (2 eq), 30 mol% of bidentate ligand: using bipyridine, no desired product and 50% yield of dehalogenated product **7ca** were obtained; using 1,10-phenanthroline, no desired product and 50% yield of dehalogenated product **7ca** were obtained; using *trans-N*,*N*′-dimethylcyclohexane-1,2-diamine, no desired product and 62% yield of dehalogenated product **7ca** were obtained.
29) Yamashita M., Kaneko M., Tokuda H., Nishimura K., Kumeda Y., Iida A., *Bioorg. Med. Chem.*, **17**, 6286—6291 (2009).
30) Yamashita M., Kaneko M., Iida A., Tokuda H., Nishimura K., *Bioorg. Med. Chem. Lett.*, **17**, 6417—6420 (2007).
31) Racemate **6a** was used for the following reactions, unless otherwise noted.
32) The coupling product **8**, which initially forms during the reaction between **5** and **6**, was not observed during the reactions at 80 °C, probably owing to fast cyclization process or degradations to unknown compounds. Recovery of **5** is shown in Tables 1—3.
33) Monnier F., Taillefer M., *Angew. Chem. Int. Ed.*, **48**, 6954—6971 (2009).
34) Trace amount of starting material **5b** was recovered.
35) Coupling product **8ca** and cyclized product **4ca** were obtained in 60% and 8% yields, respectively when the reaction was quenched after 5 h.
36) Starting material **5c** was recovered in 46% yield and the coupling product **8ca** was obtained in 15% yield.
37) Parker K. A., Sworin M. E., *J. Org. Chem.*, **46**, 3218—3223 (1981).
38) Ohta S., Hinata Y., Yamashita M., Kawasaki I., Jinda Y., Horie S., *Chem. Pharm. Bull.*, **42**, 1730—1735 (1994).
39) Lin T.-S., Zhu L.-Y., Xu S.-P., Divo A. A., Sartorelli A. C., *J. Med. Chem.*, **34**, 1634—1639 (1991).