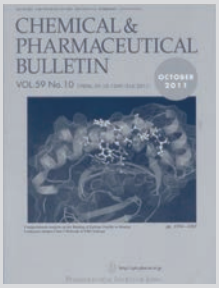


CHEMICAL&PHARMACEUTICAL BULLETIN

ケミカル・アンド・ファーマシューティカル・ブリティン Vol.59 No.10 (2011)

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

Akira Iida
School of Agriculture, Kinki University

Akira Iida[a,b], Kazunori Ueda[a], Koichi Sakaguchi[a], Mitsuaki Yamashita[c], Harukuni Tokuda[d],

[a] *School of Agriculture, Kinki University*
[b] *Research and Development Center for Medicinal Plants*
[c] *Faculty of Pharmacy, Takasaki University of Health and Welfare*
[d] *Department of Complementary and Alternative Medicine R&D, Graduate School of Medical Science, Kanazawa University*

abstract — 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.

Keywords: Indolequinones; 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

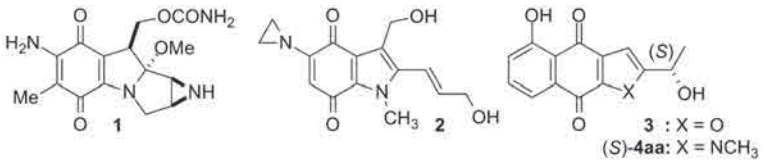
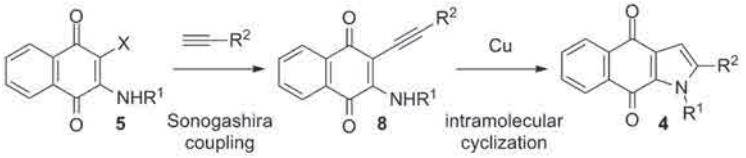


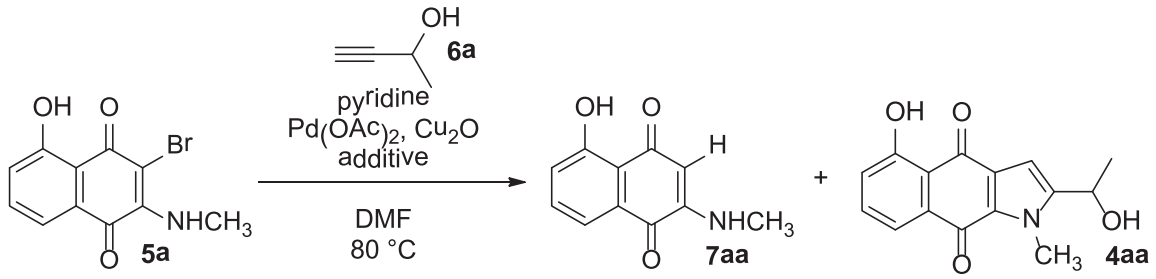
Chart 1. Construction of Benzo[*f*]indole-4,9-dione Motifs



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-1H-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'*-dimethylfomamide (DMF) at 80 ℃.[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 when Et_3N was used instead of pyridine (Table 1, entry 16).

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(22)[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%), Cu_2O (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 (0.5 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.

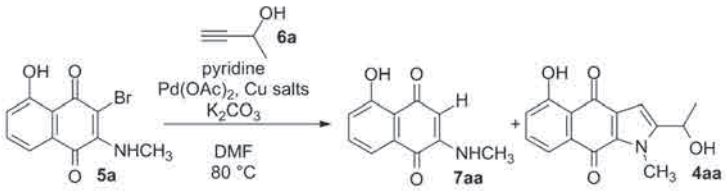
To determine the optimal copper salts, reactions with various copper(I) (CuI, CuBr, and CuOTf) and copper(II) salts (CuO, $CuBr_2$, and $CuCl_2$)[33] were examined. The results are shown in Table 2. Both copper(I) and copper(II) salts afforded the cyclized product **4aa** in moderate yields (13%–55%, 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 5h.[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 **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 and 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 determine 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.

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 (IC50 of (*S*)-**4aa**: 41.5 and 56.1 μM, respectively; IC_{50} of **3**: 0.92 and 0.48 μM, respectively).[29,30] Further SAR studies on **4aa** derivatives are underway in our laboratory and will be reported in due course.

Table 2. Effect of copper salts on the conversion of naphthoquinone **5a** to the cyclized product **4aa**[a]



Entry	Time (h)	Additives	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),acety(1.0mmol), pyridine(8.0 mL),and additives(0.4 mmol)were stirred in DMF at 80℃.
b)Isolated yield. c)Recovery of **5a** was less than 5%,unlessotherwise noted.
d)Cu_2O(0.5 mmol)was used.

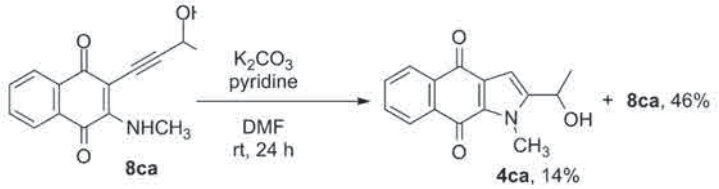
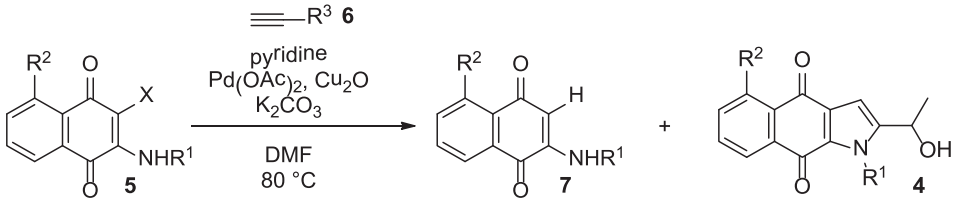


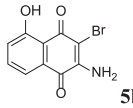
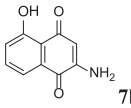
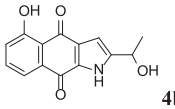
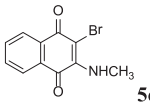
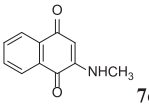
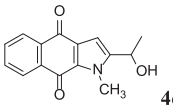
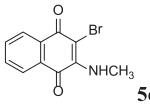
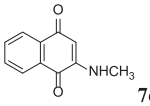
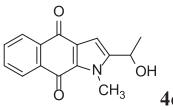
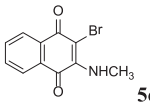
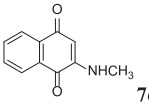
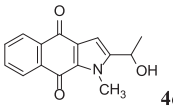
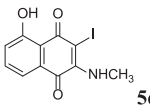
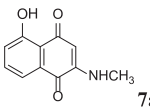
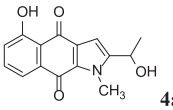
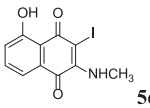
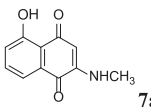
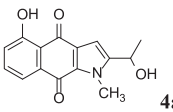
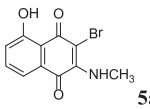
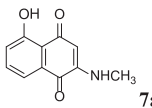
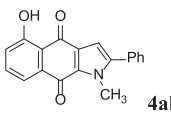
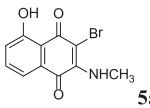
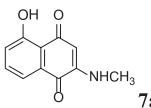
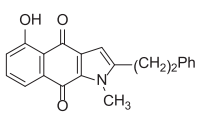
Chart 2. Conversion of the coupling product **8ca** to the cyclized product **4ca**

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.

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℃.
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.

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 ℃. **5b**: rf (hexane/EtOAc = 2/1) = 0.40. 1H-NMR δ: 5.37 (1H, brs), 6.21 (1H, brs), 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. HRMS (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 ℃ for 1 h. The mixture was quenched with H_2O at 0 ℃ 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-1H-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 ℃. **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. HRMS (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 ℃. $[\alpha]_D^{25}$ +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-1H-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 ℃. **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. HRMS (ESI) m/z: [M+H]$^+$ calcd for $[C_{15}H_{14}NO_3]^+$, 256.0974; Found, 256.0985.

5-Hydroxy-1-methyl-2-phenyl-1H-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 ℃. **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. HRMS (ESI) m/z: [M+H]$^+$ calcd for $[C_{19}H_{14}NO_3]^+$, 304.0974; Found, 304.0973.

5-Hydroxy-1-methyl-2-phenethyl-1H-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 ℃. **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. HRMS (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 4h. 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 ℃. rf (hexane/EtOAc = 1/1) = 0.1. ^{1}H-NMR δ: 1.56 (3H, d, J = 7.0 Hz), 1.67 (1H, brs), 3.52 (3H, d, J = 5.5 Hz), 4.83 (1H, q, J = 7.0 Hz), 6.45 (1H, brs), 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. HRMS (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 ℃, 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.

Acknowledgements The authors are grateful to Taheebo Japan Co., Ltd. and Sanshin Metal Working Co., Ltd. for the generous financial support for this project.

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, pp. 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) Otero, J. M., Barcia, J. C., 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**,in press.
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 ℃ 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 ℃, probably owing to fast cyclization process or degradations to unknown compounds. Recovery of **5** is shown in Table 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).

ケミカル・アンド・ファーマシューティカル・ブリティン
第59巻 No.10 (2011)

1,4ーナフトキノン類と末端アセチレンを用いたベンゾ[f]インドールー4,9ージオンのワンポット合成

飯田　彰
近畿大学 農学部

飯田　彰・上田和典・阪口晃一（近畿大学 農学部）、山下光明（高崎健康福祉大学）

【要旨】本論文では、ベンゾ[f]インドールー4,9ージオン骨格を形成するための簡便なワンポット合成法が述べられている。これらの変換は、1,4ーナフトキノンと末端アセチレンとの連続したパラジウムおよび銅により触媒されるカップリング反応とそれにより生じたカップリング生成物の銅により触媒される分子内環化反応を経由して進行した。

【キーワード】インドールキノン、 薗頭カップリング、 カスケード反応、 銅、 パラジウム

インドールキノンはマイトマイシンC（1）、EO9（2）といった抗腫瘍剤にしばしば見うけられることから、興味と価値あるものである（Figure1）。それらの興味を引かれる生物活性にも関わらず、インドールキノンの効果的な合成には限りがある。それら報告された手法のなかで、以下の3つの戦略は非常に多様なインドールキノンを与える。3つの戦略として1,4ーナフトキノンとエンアミンとの反応、Mn（III）により誘導される1,4ーナフトキノンとβージカルボニル化合物との酸化フリーラジカル反応、3ーアセチルアミノー2ーブロモー1,4ーナフトキノンと末端アセチレンとの薗頭反応により合成できる3ーアセチルアミノー2ーアルキニルー1,4ーナフトキノンの環化反応がある。しかしながら、これらの手法は基質上の置換基に制限があることや基質の構造変化により引き起こされる収率の低下といったいくつかの欠点がある。最近の報告で、我々のグループは薗頭反応／環化反応カスケード反応による2ーアミノー3ーブロモー1,4ーナフトキノンと末端アセチレンのインドールキノンワンポット合成を発表した。この合成法は、簡便なベンゾ[f]インドールー4,9ージオン骨格へのアプローチを可能にしたが、満足いく収率を得るために化学量論量の銅塩が必要とされた。一方、我々はインドール合成において一般的に用いられる合成法に従い、触媒量の銅（I）塩とジピリジン、1,10ーフェナントロリン、*N,N'*ージメチルシクロヘキサンー1,2ージアミンといった二座配位子を用いる反応を試みた。しかしながら、環化反応は進行せず、脱ハロゲン化化合物への出発物質の分解が徐々におこった。それゆえに、我々はインドールキノンを合成するためのより効果的な反応条件の開発を試みた。

ここに我々は、ベンゾ[f]インドールー4,9ージオン骨格を形成するための触媒量の銅塩による薗頭反応と分子内環化を含むカスケード反応について説明する（Chart 1）。

Fig. 1. Heterocycle-fused Quinones

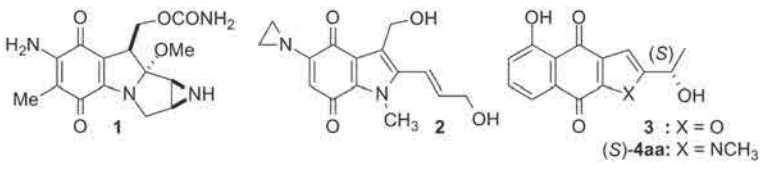
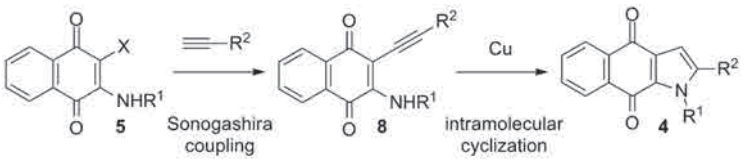


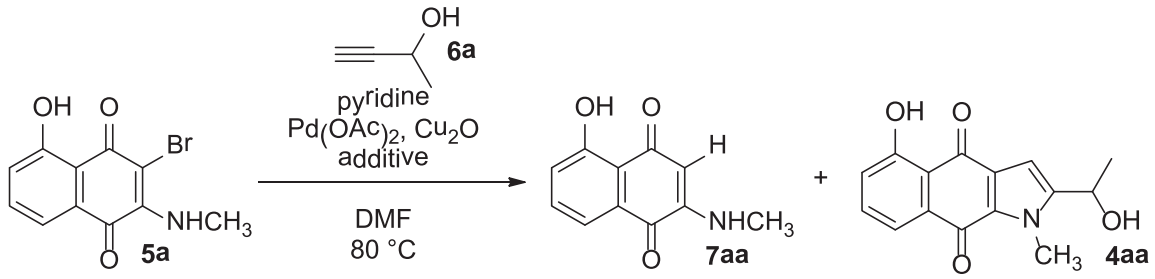
Chart 1. Construction of Benzo[f]indole-4,9-dione Motifs



結果と考察

我々は、すでにタベブイアアベラネダエの内皮に含まれる二次代謝産物である（*S*）−5−ヒドロキシ−2−（1'−ヒドロキシエチル）ナフト [2,3−*b*] フラン−4,9−ジオン（3）が、いくつかのヒト腫瘍細胞に対してがん予防効果を示すことを報告している。4aa のような関連した骨格を簡便に合成できる手法を開発するため、基質に 3−ブロモ−5−ヒドロキシ−2−（メチルアミノ）ナフタレン−1,4−ジオン（5a）とブット−3−イン−2−オール（6a）を用いた。最も活性な触媒系を見出すために、添加剤のスクリーニングを試みた。我々のグループが報告した最適条件に従って、すべての実験を DMF 溶液中、反応温度 80℃で 2 当量のアセチレン、0.8 当量の添加剤、20mol% の銅塩、200 当量のピリジンを用いて行った。しかしながら、*trans*−*N,N'*−ジメチルシクロヘキサン−1,2−ジアミン、2,2'−ジピリジン、L−プロリン、1,10−フェナントロリンといった二座配位子は、反応の促進に効果を示さなかった（Table1, entry3-6）。その一方、大部分の無機塩基を適用できることが明らかとなり、13% - 63% 収率で環化生成物 4aa を得た。また、その中でも炭酸カリウムが適していることも明らかとなった（Table1, entries7 - 10）。炭酸カリウム 0.2 当量および 2 当量用いた反応では、4aa の収率が低下する結果となった（Table1, entries11,12）。これは、炭酸カリウムの最適な量が 0.8 当量（炭酸カリウム：酸化銅（I）＝4：1）であることを示している。ピリジンあるいは酸化銅（I）を使用しない場合、目的生成物 4aa は低い収率で得られた（Table1, entries13,14）。そのうえ、カップリング反応は酢酸パラジウム（II）なしでは進行しなかった（Table1, entry15）。炭酸カリウム非存在下でのブランク実験では、ほとんど 4aa が形成されないことが確認された（Table1, entry2）。塩基であるピリジンはこの反応に不可欠であり、ピリジンの代わりにトリエチルアミンを用いた際には 4aa の収率が著しく低下した（Table1, entry16）。

Table 1. Effect of additives and reagents on the conversion of naphthoquinone 5a to the cyclized product 4aa[a)]



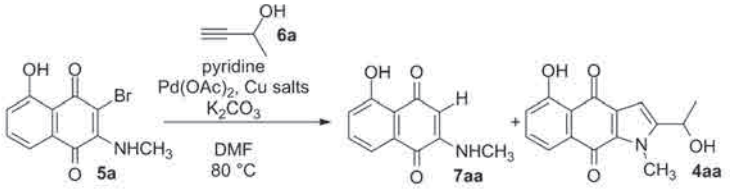
Entry	Time (h)	Additives	Yield (%)[b,c)]	
			7aa	**4aa**
1[d)]	1	none	trace	58
2	24	none	42	trace
3	24	***trans*-*N,N'*-dimethylcyclohexane-1,2-diamine**	17(8)[e)]	trace
4	24	2,2'-bipyridine	5(21)[e)]	trace
5	12	L-proline	22	<6
6	24	1,10-phenanthroline	17(22)[e)]	trace
7	12	K_3PO_4	16	34
8	1	Cs_2CO_3	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%), 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 ℃.
b) Isolated yield. c) Recovery of 5a was less than 5%, unless otherwise noted. d) Cu_2O (0.5 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.

最適な銅塩を決定するため、様々な銅（I）塩（ヨウ化銅、臭化銅、銅トリフラート）および銅（II）塩（酸化銅（II）、臭化銅（II）、塩化銅（II））との反応を行った。その結果をTable2に示した。銅（I）塩および銅（II）塩では、環化生成物**4aa**が中程度の収率（13%ー55%, Table2, entries 1ー6）で得られた。しかし、それらの反応には長い時間を必要とした。さらに、酸化銅（I）の使用量を減らした際には、**4aa**の収率が低下した（Table2,entry7）。それゆえに、酸化銅（I）が触媒として機能しており、その最適な使用量は0.2当量（**4aa**に対して）であることが明らかとなった。

この手法の一般性を検討するため、ブロモナフトキノン**5b**、**5c**、**5d**と末端アセチレン**6**との反応を行った。その結果をTable3にまとめている。無置換のNH_2基を含むナフトキノン**5b**を使用した際、カップリング反応は進行しなかった（Table3,entry1）。より一般的なナフトキノン骨格である**5c**と化学量論量の酸化銅（I）との反応では、室温で環化生成物**4ca**が56%収率で得られた（Table3,entry2）。触媒量の酸化銅（I）を用いた際でも同程度の結果が得られ、我々の触媒カスケード反応の有用性を示した（Table3,entry4）。

Table 2. Effect of copper salts on the conversion of naphthoquinone **5a** to the cyclized product **4aa**[a)]



Entry	Time (h)	Additives	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** (1.0mmol),pyridine(8.0 mL),and additives(0.4 mmol)were stirred in DMF at 80℃.
b)Isolated yield. c)Recovery of **5a** was less than 5%,unlessotherwise noted.
d)Cu_2O(0.5 mmol)was used.

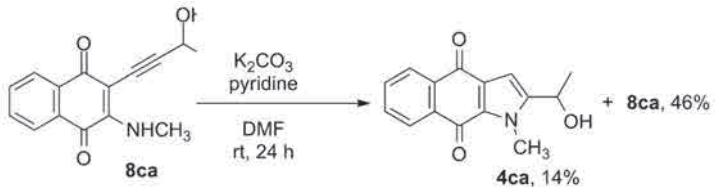


Chart 2. Conversion of the coupling product **8ca** to the cyclized product **4ca**

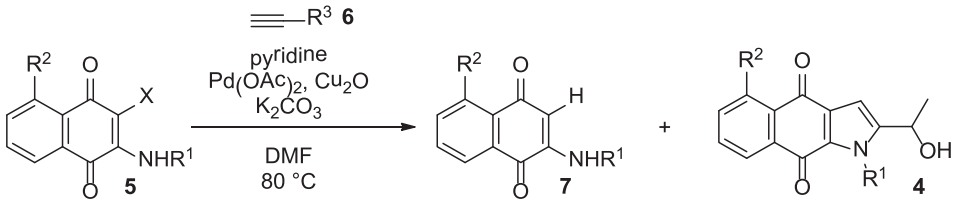
Table3,entry4の反応中、TLCにより5時間以内にカップリング反応が完了したことを明らかにしたが、5時間後にわずかな環化生成物が見られた。一方、炭酸カリウム非存在下では、微量のカップリング生成物のみが形成された（Table3,entry3）。それゆえに、我々は炭酸カリウムが活性化銅アセチリド/ピリジン錯体を再生する役割を果たしており、炭酸カリウムの正確な役割が不明確であるにも関わらずカップリング反応を促進していると推測している。我々の予想に反して、基質にヨウ素体**5d**を用いた際に化学量論量の酸化銅（II）に比べ触媒量でより低い収率が見られた。これは脱ハロゲン化化合物**7aa**形成の増加が原因であった（Table3,entries5,6）。フェニルや**2**ーフェニルエチル基を含むアセチレンは**5a**とゆっくり反応し、中程度の収率で目的生成物**4ab**、**4ac**を与えた。これはアセチレンのヒドロキシエチル部位がこの開発した手法にとって必須ではないことを示している（Table3, entries7,8）。我々はすでに反応中に形成する銅アセチリド／ピリジン錯体が分子内環化のステップで重要な役割を果たすことを報告している。最後の環化ステップでの炭酸カリウムの役割を明らかにするため、ピリジン、DMF溶液中、室温で単離した**8ca**と炭酸カリウムとの反応を行った（Chart2）。24時間後、環化生成物**4ca**が14%収率で得られ、原料**8ca**を46%回収した。これは、炭酸カリウム自体が環化過程である程度寄与することを示している。さらに、銅アセチリド／ピリジン錯体が分子内環化反応にとって主要な触媒として機能している。

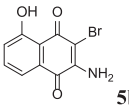
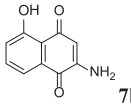
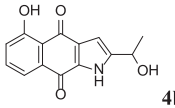
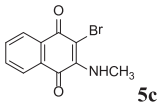
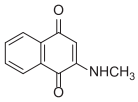
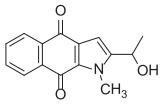
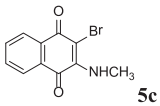
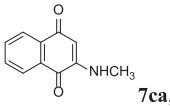
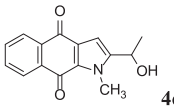
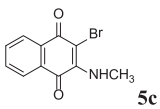
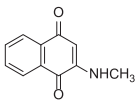
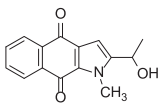
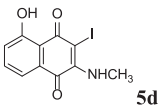
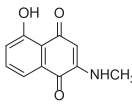
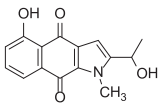
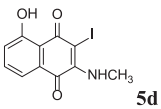
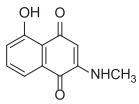
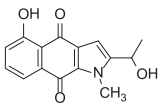
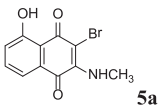
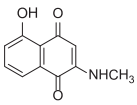
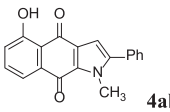
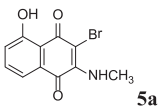
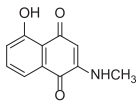
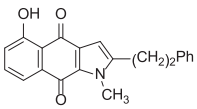
最後に、今回開発された方法に従って、**5a**と市販品(*S*) - **6a**から合成された(*S*)-**4aa**のA549（肺がん）、MCF-7（乳がん）を含むヒト腫瘍細胞株に対する成長抑制活性を評価した。**3**に比べて、(*S*)-**4aa**は両方の細胞株に対してより弱いがん予防効果を示した（(*S*)-**4aa**のIC_{50}：41.5μl、56.1μl；**3**のIC_{50}：0.92μl、0.48μl）。さらに、**4aa**誘導体のSAR研究は我々の研究室で進行しており、近々報告する予定である。

結論

我々は置換基を含むインドールキノンの構築にとって重要な手法である炭酸カリウムと触媒量の酸化銅（I）による薗頭カップリング／環化カスケード反応を開発した。その実験的容易さから、その触媒系が合成化学、医薬品化学において幅広く応用されることを期待する。

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 (0.1mmol), acetylene (1.0 mmol), pyridine (8.0 mL), and K_2CO_3 (0.4 mmol) were stirred in DMF at 80℃.

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.

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 ℃. **5b**: rf (hexane/EtOAc = 2/1) = 0.40. 1H-NMR δ: 5.37 (1H, brs), 6.21 (1H, brs), 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. HRMS (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 ℃ for 1 h. The mixture was quenched with H_2O at 0 ℃ 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-1H-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 ℃. **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. HRMS (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 ℃. $[\alpha]_D^{25}$ +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-1H-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 ℃. **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. HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{15}H_{14}NO_3]^+$, 256.0974; Found, 256.0985.

5-Hydroxy-1-methyl-2-phenyl-1H-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 ℃. **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. HRMS (ESI) m/z: $[M+H]^+$ calcd for $[C_{19}H_{14}NO_3]^+$, 304.0974; Found, 304.0973.

5-Hydroxy-1-methyl-2-phenethyl-1H-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 ℃. **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. HRMS (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 4h. 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 ℃. rf (hexane/EtOAc = 1/1) = 0.1. ^{1}H-NMR δ: 1.56 (3H, d, J = 7.0 Hz), 1.67 (1H, brs), 3.52 (3H, d, J = 5.5 Hz), 4.83 (1H, q, J = 7.0 Hz), 6.45 (1H, brs), 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. HRMS (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 ℃, 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.

Acknowledgements The authors are grateful to Taheebo Japan Co., Ltd. and Sanshin Metal Working Co., Ltd. for the generous financial support for this project.

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, pp. 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) Otero, J. M., Barcia, J. C., 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**,in press.
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 ℃ 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 ℃, probably owing to fast cyclization process or degradations to unknown compounds. Recovery of **5** is shown in Table 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).