Concise Synthesis of Heterocycle-Fused Naphthoquinones by Employing Sonogashira Coupling and Tandem Addition-Elimination/Intramolecular Cyclization

Kazunori Ueda,[a] Mitsuaki Yamashita,[a] Koichi Sakaguchi,[a] Harukuni Tokuda,[b] and Akira Iida*[,a]

[a] *School of Agriculture, Kinki University; Nakamachi, Nara 631–8505, Japan: and* [b] *Department of Complementary and Alternative Medicine R&D, Graduate School of Medical Science, Kanazawa University; Takara-machi, Kanazawa 920–8640, Japan.*

Received February 2, 2013; accepted March 19, 2013

A concise method for the synthesis of heterocycle-fused naphthoquinones such as naphtho[2,3-*b*]-furan-4,9-dione, 1*H*-benz[*f*]indole-4,9-dione, and naphtho[2,3-*b*]thiophene-4,9-dione was developed. This method employed Sonogashira coupling and tandem addition-elimination/intramolecular cyclization, and it enabled the preparation of versatile heterocycle-fused naphthoquinones from one substrate.

Key words naphthoquinone; addition-elimination; intramolecular cyclization

Heterocycle-fused naphthoquinones such as naphtho[2,3-*b*]furan-4,9-dione,[1–7] 1*H*-benz[*f*]indole-4,9-dione,[8–17] and naphtho[2,3-*b*]thiophene-4,9-dione,[18–27] which display a variety of biological activities, are found in various natural and artificial compounds. Despite the importance of these compounds, a survey of the literature revealed that very few efficient general methods have been developed to prepare heterocycle-fused naphthoquinones although many procedures have been established to prepare specific compounds. We are interested in studying heterocycle-fused naphthoquinones isolated from *Tabebuia avellanedae* Lorentz *ex* Griseb[28] (Bignoniaceae) (syn. *T. impetiginosa*). Among these constituents, we previously reported that (−)-5-hydroxy-2-(1′-hydoxyethyl)naphtho[2,3-*b*]furan-4,9-dione (**1aa**) has a strong antiproliferative activity against various tumor cell lines[29–31] (Fig. 1). In addition, we reported the stereoselective synthesis of **1aa** using Noyori reduction as a key step although tedious manipulations necessary in the synthesis and an inadequate enantiomeric excess from the final asymmetric hydrogenation prevented its further application. Recently, indolequinones were synthesized *via* Sonogashira coupling effectively, followed by copper-catalyzed intramolecular cyclization.[32,33] In this synthesis, halogenated quinones reacted smoothly with terminal acetylenes to give the coupling product. Therefore, we decided to use this methodology to synthesize **1aa** and its related compounds. Here, we describe the development of a general and concise method for constructing heterocycle-fused naphthoquinone motifs involving Sonogashira coupling and tandem addition-elimination/intramolecular cyclization.

Results and Discussion

Chart 1 shows our strategies. The product **3** that is synthesized from the halogenated naphthoquinone **2** with the terminal acetylene **4** using Sonogashira coupling was a key intermediate in the synthesis of heterocycle-fused naphthoquinones **1** because the replacement of the dimethylamino group of **3** by another functional group (a hydroxyl, thiol, or amino group) followed by intramolecular cyclization would allow the construction of diverse heterocycle-fused naphthoquinone motifs.

First, we investigated the Sonogashira coupling of 3-bromo-2-(dimethylamino)-5-hydroxynaphthalene-1,4-dione (**2a**) with but-3-yn-2-ol (**4a**) because we[29] and another research group[34] independently reported that the presence of the phenolic hydroxy group at C-5 considerably increases the antiproliferative effect of naphthoquinones on human-tumor cell lines. We used our previously reported procedure with a few modifications[33,35] and examined the reaction of **2a** (1 eq) with racemic **4a** (2 eq) in the presence of Cu_2O (0.2 eq), pyridine (100 eq, *i.e.*, pyridine–copper = 50 : 1), and K_2CO_3 (0.4 eq) in *N*,*N*-dimethylformamide (DMF) at room temperature. The conversion of **2a** to **3aa** occurred using our reaction conditions, and **3aa** was obtained in 84% yield (Table 1, entry 1). Decreasing the amount of copper salt to 0.1 eq gave a lower yield of **3** (Table 1, entry 2). Next, using the reaction conditions shown in the entry 1 of Table 1, we tested the coupling reaction on a series of halogenated naphthoquinones **2** and terminal acetylenes **4**. Alkynes bearing an aryl or alkyl substituent reacted smoothly with the halogenated naphthoquinone **2a** to give the desired products **3ab** and **3ac** in good yields (Table 1, entries 3, 4). In addition, a satisfactory result was obtained using the halogenated naphthoquinone **2b** which does not have a hydroxyl group on the aromatic ring as a substrate (Table 1, entry 5). The yield of **3ca** decreased slightly when naphthoquinone **2c**, which has a hydroxyl group at C-8, was used as the substrate (Table 1, entry 6).

Next, we tested a range of reaction conditions for the cyclization step, whose results are summarized in Table 2. Unfortunately, the hydrolysis and cyclization of **3aa** under acidic or basic conditions failed, and only the degradation of the starting material **3aa** was observed.[36] We assumed that degradation occurred under these reaction conditions because of the lability of the compound **3** as hydrolysis occurred smoothly under acidic conditions in the absence of an alkynyl group at C-3.[37] However, we found that the desired product could be obtained when the reaction mixture was

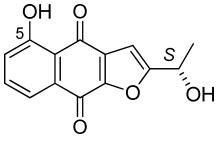


Fig. 1. Structure of **1aa**

The authors declare no conflict of interest.

* To whom correspondence should be addressed. e-mail: iida@nara.kindai.ac.jp

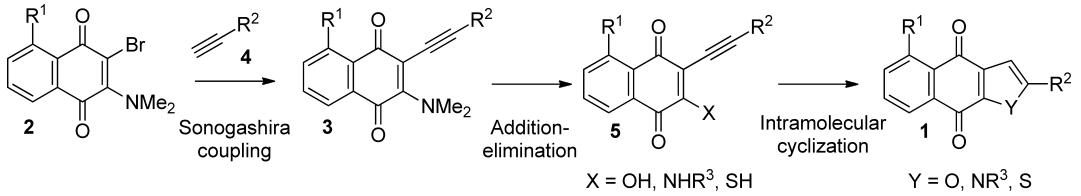
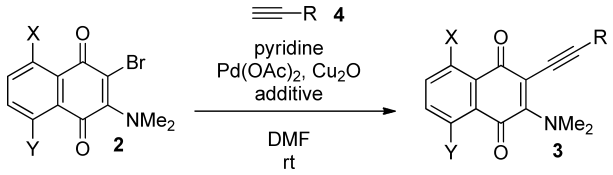


Chart 1. Synthesis of **1** from **2**

Table 1. Reaction of 3-Bromo-2-(dimethylamino)-naphthalene-1,4-dione (**2**) with Acetylene (**4**)[a)]



Entry	Substrate **2** X, Y	Acetylene **4** R	Time (h)	Product	Yield (%)[b)]
1	OH, H (**2a**)	$CH(OH)CH_3$ (**4a**)	17	**3aa**	84
2[c)]	OH, H (**2a**)	$CH(OH)CH_3$ (**4a**)	22	**3aa**	59 (24)[d)]
3	OH, H (**2a**)	Ph (**4b**)	17	**3ab**	93
4[e)]	OH, H (**2a**)	CH_2CH_2Ph (**4c**)	5	**3ac**	92
5	H, H (**2b**)	$CH(OH)CH_3$ (**4a**)	17	**3ba**	91
6	H, OH (**2c**)	$CH(OH)CH_3$ (**4a**)	21	**3ca**	62

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 (0.2 mmol) were stirred in DMF at rt. *b*) Isolated yield. *c*) Cu_2O (0.05 mmol) was used. *d*) The numbers in parentheses are the yields of **2a** recovered. *e*) At 50°C.

refluxed in wet methanol (Table 2, entry 1). We screened a range of solvents and solvent-volume ratios to identify the most-effective reaction system and found that polar aprotic solvents such as MeCN, tetrahydrofuran (THF), acetone, and dioxane were ineffective in promoting the reaction (Table 2, entries 4–8). In contrast, polar protic solvents such as alcohols afforded the cyclized product **1aa** in 55–61% yields (Table 2, entries 2, 3). The reaction of **3aa** in MeOH (without H_2O) was examined, but only a trace of the desired product was found indicating that a certain amount of H_2O is essential for this reaction (Table 2, entry 9). Therefore, we tested the effect of reaction concentration and the volume ratio of H_2O to MeOH. Irrespective of reaction concentration, the reactions were completed within approximately 4 h, and cyclized products were obtained in similar yields (Table 2, entries 10, 11). Using one equivalent or 0.5 eq of H_2O to 1 eq of MeOH did not increase the yield (the total volume was 30 mL in each case) (Table 2, entries 12, 13), suggesting that the optimum solvent mixture contains 2 eq of H_2O to 1 eq of MeOH (with a total volume of 30 mL). Finally, we found that using DMF as a co-solvent increased the yield (Table 2, entry 14), and we speculate that the increased solubility of the substrate **3aa** contributed to better yields. Moreover, we tested large-scale reactions at higher and lower concentrations (Table 2, entries 15, 16, respectively) and found results comparable to those shown in the entry 14 of the Table 2.

We tested a range of reaction conditions to evaluate the potential of the general synthetic methods for heterocycle-fused naphthoquinones. The reaction of the substrate **3aa** with Na_2S in H_2O and MeOH (H_2O–MeOH=1 : 10) proceeded smoothly to give thiophene-fused naphthoquinone **1bb** in 88% yield (Table 3, entry 1). However, the replacement of the dimethylamino group of **3aa** by an amino group, without a second cyclization, occurred when aqueous NH_3 solution was used. Adding an excess of K_2CO_3 to the reaction mixture resulted in conversion to the cyclized product **1cc** in 57% yield (Table 3, entry 2). Moreover, these reaction conditions were suitable for the reaction with methylamine although sodium hydroxide was used as the base, giving *N*-methylated pyrrole-fused naphthoquinones **1dd** in 72% yield. We conducted further investigations using various substrates and reacted the coupling products **3ba**, **3ab**, **3ac**, and **3ca** under conditions A–D (detailed in Table 3). The reaction of **3ba**, which contains a more general naphthoquinone motif, using reaction conditions A–C gave the cyclized products **1ee**, **1ff**, and **1gg**, respectively, with rather lower chemical yields than those obtained for **1bb** or **1dd**. (Table 3, entries 4–6). The substrate **3ab**, which has a phenyl substituent, gave the desired product **1hh** in moderate yield, whereas a lower yield was surprisingly found when the substrate **3ac**, which has a 2-phenylethyl substituent, was used (Table 3, entries 7, 8). Unsatisfactory yields were obtained when the naphthoquinone **3ca**, which has a hydroxyl group at C-8, was used as the substrate (Table 3, entry 9). TLC analysis during the reaction shown in the entry 9 of the Table 3 revealed that the consumption of the substrate was slower in this reaction than that while using the substrate shown in the entry 14 of the Table 2, under the same reaction conditions. Thus, we speculated that the lower reactivity of the substrate **3ca** in the first addition-elimination step causes degradation to unknown compounds during the reaction, and the intramolecular hydrogen bond between carbonyl oxygen at C-4 and hydroxyl group at C-5 plays a crucial role in the addition-elimination step.

Finally, the ability of (*S*)-**1bb**, which was synthesized from **3aa** and commercially available (*S*)-**4a** using the developed method, to suppress the growth of human tumor cell lines, including A549 (lung) and MCF-7 (breast), was tested. The compound (*S*)-**1bb** exhibited comparable antiproliferative effects to that of β-lapachone against both cell lines, with the IC_{50} of (*S*)-**1bb** and β-lapachone against A549 being 5.57 and 4.21 μM, respectively, and the IC_{50} of (*S*)-**1bb** and β-lapachone against MCF-7 being 5.57 and 9.96 μM, respectively. β-Lapachone is known as a potent anticancer compound contained in *Tabebuia avellanedae* similarly to **1aa** and β-lapachone-based anticancer drug is recently developing in U.S.A.[38] Therefore, heterocycle-fused naphthoquinone analogues are promising anticancer compounds.

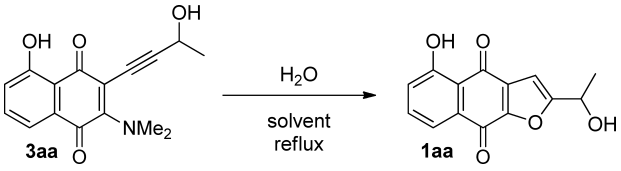
Conclusion

In conclusion, we developed a general method to construct heterocycle-fused naphthoquinones utilizing Sonogashira coupling and tandem addition-elimination/intramolecular cyclization. The future applications of this strategy and the biological activities of the various naphthoquinones synthesized are currently being investigated and will be reported in due course.

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

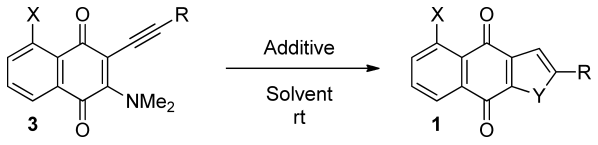
Table 2. Conversion of the Coupling Product **3aa** to the Cyclized Product **1aa**[a]

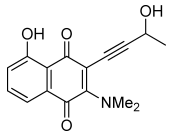
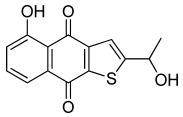
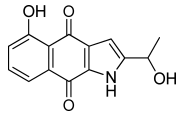
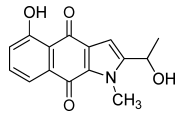
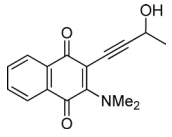
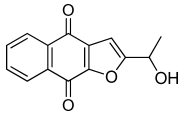
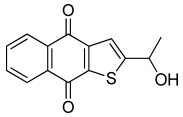
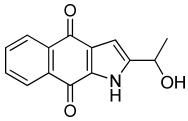
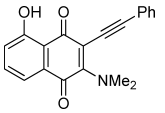
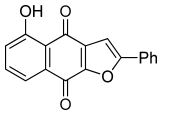
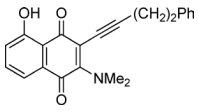
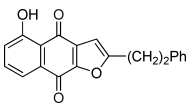
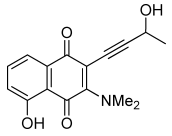
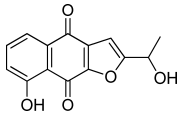


Entry	Solvent	Volume ratio H_2O : Solvent	Time (h)	(±)-**1aa** Yield (%)[b]
1	MeOH	2 : 1	1.5	56
2	EtOH	2 : 1	5	55
3	BuOH	2 : 1	12	61
4	MeCN	2 : 1	12	41
5	THF	2 : 1	12	No reaction
6	Acetone	2 : 1	12	37
7	Dioxane	2 : 1	12	0
8	DMF	2 : 1	4	39
9	MeOH	MeOH only	36	Trace
10[c]	MeOH	2 : 1	2	52
11[d]	MeOH	2 : 1	4	52
12	MeOH	1 : 1	4	39
13	MeOH	1 : 2	20	44
14[e]	MeOH	2 : 1	5	74
15[f–h]	MeOH	2 : 1	5	66
16[f,h,i]	MeOH	2 : 1	5	77

a) A solution of the substrate **3** (0.11 mmol) in H_2O and solvent (total volume: 30 mL) were refluxed. *b*) Isolated yield. *c*) Total volume was 9 mL. *d*) Total volume was 90 mL. *e*) DMF (500 μL) was used. *f*) Substrate **3** (0.50 mmol) was used. *g*) Total volume was 45 mL. *h*) DMF (2.5 mL) was used. *i*) Total volume was 144 mL.

Table 3. Conversion of the Coupling Product **3** to the Cyclized Product **1**



Entry	Substrate	Time (h)	Conditions	Product	Yield (%)[a]
1	 **3aa**	15	Na_2S, H_2O–MeOH (1 : 10), rt (condition B)	 **1bb**	88
2	**3aa**	3	28% NH_3 aq, K_2CO_3, DMF, at 80°C (condition C)	 **1cc**	57
3	**3aa**	3	$CH_3NH_2 \cdot HCl$, Et_3N, NaOH, NMP–H_2O (10 : 1), at 80°C (Condition D)	 **1dd**	72
4	 **3ba**	20	H_2O–MeOH (2 : 1), reflux (condition A)	 **1ee**	47
5	**3ba**	24	Condition B	 **1ff**	56
6	**3ba**	3	Condition C	 **1gg**	38
7	 **3ab**	24	Condition A	 **1hh**	70
8	 **3ac**	24	Condition A	 **1ii**	40
9	 **3ca**	24	Condition A	 **1jj**	30

a) Isolated yield. Condition A: Substrate **3** (0.5 mmol) were refluxed in H_2O–MeOH (2 : 1) (total volume: 144 mL). Condition B: Substrate **3** (0.5 mmol) and Na_2S (1.0 mmol) were stirred in H_2O–MeOH (1 : 10) (total volume: 11 mL) at rt. Condition C: Substrate **3** (0.5 mmol), 28% NH_3 aq. (5.0 mmol) and K_2CO_3 (2.5 mmol) were stirred in the solvent (30 mL) at 80–100°C. Condition D: Substrate **3** (0.5 mmol), $CH_3NH_2 \cdot HCl$ (1.5 mmol), Et_3N (1.5 mmol) and NaOH (5.0 mmol) were stirred in the solvent (33 mL) at 80°C.

chromatography. All reagents were purchased from chemical companies and used as received. All reactions were conducted under an argon atmosphere, unless otherwise stated.

3-Bromo-2-(dimethylamino)-5-hydroxynaphthalene-1,4-dione (**2a**)[39]: To a solution of 2-(dimethylamino)-5-hydroxynaphthalene-1,4-dione (500 mg, 2.30 mmol) in DMF (15 mL) was added a solution of *N*-bromosuccinimide (NBS) (491 mg, 2.76 mmol) in DMF (6 mL), and the mixture was stirred for 0.5 h at rt. The mixture was quenched with H_2O at 0°C and extracted with EtOAc. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The column chromatography (hexane–EtOAc=12 : 1) gave **2a**

(656 mg, 96% yield) as red solid with mp 90–91°C. ^{1}H-NMR δ: 3.29 (6H, s), 7.18–7.20 (1H, m), 7.46–7.50 (2H, m), 12.45 (1H, s). ^{13}C-NMR δ: 45.0, 109.7, 113.7, 119.5, 124.4, 131.3, 134.6, 154.3, 160.5, 181.2, 183.1.

2-Bromo-3-(dimethylamino)naphthalene-1,4-dione (**2b**)[35]: To the solution of 2-bromonaphthalene-1,4-dione (2.00 g, 8.44 mmol) in toluene (100 mL) was added dimethylamine (12.6 mL, 2.0 M solution in THF, 25.3 mmol) at 0°C. After the mixture was stirred for 12 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc=4 : 1) to give 2-(dimethylamino)-naphthalene-1,4-dione (2.13 g, 90% yield) as red solid. To a solution of 2-(dimethylamino)naphthalene-1,4-dione (1.50 g, 7.50 mmol) in DMF (30 mL) was added a solution of NBS (1.60 g, 9.00 mmol) in DMF (15 mL), and the mixture was stirred for 0.5 h at rt. The mixture was quenched with H_2O at 0°C and extracted with EtOAc. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The column chromatography (hexane–EtOAc=12 : 1) gave **2b** (1.60 g, 76% yield) as red solid with mp 110–112°C. ^{1}H-NMR δ: 3.25 (6H, s), 7.61–7.69 (2H, m), 7.96–7.98 (1H, m), 8.07–8.09 (1H, m). ^{13}C-NMR δ: 44.7, 112.9, 126.6, 126.7, 131.2, 131.3, 132.7, 133.9, 153.5, 177.8, 181.8.

2-Bromo-3-(dimethylamino)-5-hydroxynaphthalene-1,4-dione (**2c**)[39]: To a solution of 2-(dimethylamino)-8-hydroxynaphthalene-1,4-dione (1.0 g, 4.61 mmol) in DMF (30 mL) was added a solution of NBS (980 mg, 5.53 mmol) in DMF (12 mL), and the mixture was stirred for 0.5 h at rt. The mixture was quenched with H_2O at 0°C and extracted with EtOAc. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The column chromatography (hexane–EtOAc=12 : 1) gave **2c** (980 mg, 72% yield) as red solid with mp 109–111°C. ^{1}H-NMR δ: 3.25 (6H, s), 7.17 (1H, dd, J= 1.1, 8.3 Hz), 7.54–7.58 (1H, m), 7.65 (1H, dd, J=1.1, 7.5 Hz), 11.81 (1H, s). ^{13}C-NMR δ: 44.9, 114.3, 114.8, 119.5, 123.3, 131.5, 136.6, 153.0, 161.8, 177.4, 186.9.

General Procedure for Sonogashira Reaction of Naphthoqionone 2 with Acetylene 4 Under Ar atmosphere, a mixture of Cu_2O (14 mg, 0.10 mmol), acetylene **4** (1.00 mmol), K_2CO_3 (28 mg, 0.20 mmol), and pyridine (8.0 mL, 100 mmol) was stirred for 2 h at rt. A solution of compound **2** (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 rt. 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.

2-(Dimethylamino)-5-hydroxy-3-(3-hydroxybut-1-yn-1-yl)-naphthalene-1,4-dione (**3aa**): Starting from **2a** and **4a**, this compound was prepared according to the general procedure. The column chromatography (hexane–EtOAc=3 : 1) gave **3aa** (120 mg, 84% yield) as purple solid with mp 126–128°C. ^{1}H-NMR δ: 1.57 (3H, d, J=6.6 Hz), 3.42 (6H, s), 4.86 (1H, q, J=6.6 Hz), 7.18–7.20 (1H, m), 7.45–7.47 (2H, m), 12.68 (1H, s). ^{13}C-NMR δ: 24.0, 45.3, 59.1, 78.3, 103.0, 104.2, 114.5, 119.0, 124.6, 132.2, 134.5, 155.5, 160.4, 182.6, 187.7. IR (KBr): 3464, 1624, 1547, 1473, 1068, 935, 895, 779. High resolution (HR)-MS (electrospray ionization (ESI)) m/z: $[M+H]^+$ Calcd for $[C_{16}H_{16}NO_4]^+$, 286.1079; Found, 286.1077.

2-(Dimethylamino)-5-hydroxy-3-(phenylethynyl)-naphthalene-1,4-dione (**3ab**): Starting from **2a** and **4b**, this compound was prepared according to the general procedure. The column chromatography (hexane–EtOAc=12 : 1) gave **3ab** (147 mg, 93% yield) as purple solid with mp 128–129°C. ^{1}H-NMR δ: 3.47 (6H, s), 7.17–7.19 (1H, m), 7.31–7.35 (3H, m), 7.43–7.48 (2H, m), 7.50–7.53 (2H, m), 12.78 (1H, s). ^{13}C-NMR δ: 45.1, 84.2, 102.4, 104.1, 114.5, 118.8, 123.4, 124.4, 128.3, 128.4, 130.9, 132.2, 134.4, 154.9, 160.4, 182.4, 187.4. IR (KBr): 1680, 1618, 1338, 1161, 1067, 922, 880, 754. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $[C_{20}H_{15}NO_3Na]^+$, 340.0950; Found, 340.0939.

2-(Dimethylamino)-5-hydroxy-3-(4-phenylbut-1-yn-1-yl)-naphthalene-1,4-dione (**3ac**): Starting from **2a** and **4c**, this compound was prepared according to the general procedure at 50°C. The column chromatography (hexane–EtOAc=12 : 1) gave **3ac** (159 mg, 92% yield) as purple solid with mp 88–90°C. ^{1}H-NMR δ: 2.85–2.89 (2H, dd), 2.93–2.97 (2H, dd), 3.17 (6H, s), 7.15–7.32 (6H, m), 7.43–7.44 (2H, m), 12.80 (1H, s). ^{13}C-NMR δ: 22.1, 34.7, 44.7, 75.5, 103.0, 104.7, 114.4, 118.7, 124.3, 126.3, 128.4, 128.5, 132.1, 134.3, 140.5, 155.2, 160.3, 182.6, 187.9. IR (KBr): 2920, 1666, 1616, 1475, 1383, 1066, 947, 845, 783, 762. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $[C_{22}H_{19}NO_3Na]^+$, 368.1263; Found, 368.1255.

2-(Dimethylamino)-3-(3-hydroxybut-1-yn-1-yl)-naphthalene-1,4-dione (**3ba**): Starting from **2b** and **4a**, this compound was prepared according to the general procedure. The column chromatography (hexane–EtOAc=2 : 1) gave **3ba** (122 mg, 91% yield) as purple solid with mp 117–118°C. ^{1}H-NMR δ: 1.55 (3H, d, J=6.6 Hz), 3.35 (6H, s), 4.86 (1H, q, J=6.6 Hz), 7.56 (1H, ddd, J=1.4, 7.5, 7.5 Hz), 7.63 (1H, ddd, J=1.4, 7.5, 7.5 Hz), 7.88 (1H, dd, J=1.4, 7.5 Hz), 8.00 (1H, dd, J=1.4, 7.5 Hz). ^{13}C-NMR δ: 23.8, 44.9, 58.8, 78.9, 104.5, 104.6, 125.8, 126.3, 132.0, 132.3, 132.4, 133.9, 154.6, 182.2, 183.0. IR (KBr): 3423, 1670, 1547, 1340, 1279, 1016, 978, 723. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{16}H_{16}NO_3]^+$, 270.1130; Found, 270.1136.

3-(Dimethylamino)-5-hydroxy-2-(3-hydroxybut-1-yn-1-yl)-naphthalene-1,4-dione (**3ca**): Starting from **2c** and **4a**, this compound was prepared according to the general procedure. The column chromatography (hexane–EtOAc=3 : 1) gave **3ca** (88 mg, 62% yield) as purple solid with mp >135°C (dec). ^{1}H-NMR δ: 1.57 (3H, d, J=6.6 Hz), 3.42 (6H, s), 4.87 (1H, q, J=6.6 Hz), 7.13 (1H, dd, J=1.5, 7.9 Hz), 7.55 (1H, dd, J=7.5, 7.9 Hz), 7.59 (1H, dd, J=1.5, 7.5 Hz), 11.87 (1H, s). ^{13}C-NMR δ: 23.9, 45.3, 59.0, 78.8, 105.5, 106.5, 114.9, 118.6, 123.0, 132.4, 136.9, 153.9, 161.7, 181.6, 187.8. IR (KBr): 1680, 1618, 1550, 1477, 1386, 1296, 1066, 922, 754. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{16}H_{16}NO_4]^+$, 286.1079; Found, 286.1077.

General Procedure for Tandem Addition-Elimination/Intramolecular Cyclization Reaction Condition A: A solution of compound **3** (0.50 mmol) in DMF (2.5 mL) was added to the solution of H_2O (96 mL) and MeOH (48 mL) and was stirred at reflux. The mixture was extracted with EtOAc and the organic extracts were washed with brine, dried over Na_2SO_4, and then concentrated.

Condition B: To a suspension of Na_2S (78 mg, 1.00 mmol) in MeOH (10 mL) and H_2O (1 mL) was added compound **3** (0.50 mmol), then stirred at rt. The mixture was quenched with H_2O at 0°C and extracted with EtOAc. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated.

Condition C: To a solution of compound (0.50 mmol) in DMF (30 mL) was added 28% aqueous NH_3 (0.40 mL,

5.00 mmol), and then, the mixture was stirred at 80°C. TLC of the mixture (hexane–EtOAc=1 : 1) showed absence of starting material. After adding K_2CO_3 (345 mg, 2.50 mmol), the reaction mixture was stirred at 80°C. The mixture was extracted with $CHCl_3$. The organic extracts were washed with H_2O and brine and dried over Na_2SO_4 and then concentrated.

Condition D: A mixture of compound **3** (0.50 mmol), $MeNH_2 \cdot$ HCl (101 mg, 1.50 mmol) and Et_3N (0.21 mL, 1.50 mmol) in NMP (30 mL) was stirred for 0.5 h at 80°C. A solution of NaOH (200 mg, 5.00 mmol) in H_2O (3 mL) was added to this mixture and was stirred at 80°C. The mixture was extracted with $CHCl_3$. The organic extracts were washed with H_2O and brine and dried over Na_2SO_4 and then concentrated.

5-Hydroxy-2-(1-hydroxyethyl)naphtho[2,3-*b*]furan-4,9-dione (**1aa**)[2]: Starting from **3aa**, this compound was prepared according to the general procedure (Condition A). The column chromatography (hexane–EtOAc=4 : 1) gave **1aa** (100 mg, 77% yield) as yellow solid with mp 164–165°C. ^{1}H-NMR δ ($CDCl_3$): 1.66 (d, 3H, J=6.6 Hz), 2.23 (d, 1H, J=5.3 Hz), 5.05 (m, 1H), 6.85 (d, 1H, J=0.7 Hz), 7.28 (dd, 1H, J=1.2, 8.5 Hz), 7.62 (dd, 1H, J=7.6, 8.5 Hz), 7.76 (dd, 1H, J=1.2, 7.6 Hz), 12.18 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 21.5, 63.8, 103.4, 115.2, 120.0, 125.3, 131.0, 132.7, 136.3, 152.1, 162.3, 165.4, 172.7, 186.5.

5-Hydroxy-2-(1-hydroxyethyl)naphtho[2,3-*b*]thiophene-4,9-dione (**1bb**): Starting from **3aa**, this compound was prepared according to the general procedure (Condition B). The column chromatography (hexane–EtOAc=4 : 1) gave **1bb** (121 mg, 88% yield) as yellow solid with mp 179–181°C. ^{1}H-NMR ($CDCl_3$–MeOD) δ: 1.62 (3H, d, J=6.5 Hz), 5.14 (1H, q, J=6.5 Hz), 7.26 (1H, dd, J=1.0, 8.3 Hz), 7.47 (1H, s), 7.62 (1H, dd, J=7.5, 8.3 Hz), 7.74 (1H, dd, J=1.0, 7.5 Hz), 12.33 (1H, s). ^{13}C-NMR ($CDCl_3$–MeOD) δ: 25.1, 65.9, 115.7, 120.0, 121.1, 124.8, 133.9, 136.3, 142.6, 144.0, 162.4, 162.6, 177.7, 185.3. IR (KBr): 3290, 1634, 1454, 1296, 1223, 1093, 752, 702. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $[C_{14}H_{10}SO_4Na]^+$, 297.0198; Found, 297.0207.

(*S*)-**1bb**: Pale yellow needles with mp 209–211°C. $[\alpha]_D^{25}$ −10.8 (c=0.12, $CHCl_3$) for >99% ee (HPLC, Daicel Chiralpak AD-H, hexane–*i*-PrOH=9 : 1, 1.0 mL/min, 254 nm, minor: 24.9 min and major: 30.4 min).

5-Hydroxy-2-(1-hydroxyethyl)-1*H*-benzo[*f*]indole-4,9-dione (**1cc**): Starting from **3aa**, this compound was prepared according to the general procedure (Condition C). The column chromatography (hexane–EtOAc=4 : 1) gave **1cc** (73 mg, 57% yield) as yellow solid with mp >215°C (dec). ^{1}H-NMR (dimethyl sulfoxide (DMSO)) δ: 1.49 (3H, d, J=6.5 Hz), 4.83 (1H, dq, J=5.3, 6.5 Hz), 5.50 (1H, d, J=5.3 Hz), 6.63 (1H, s), 7.29 (1H, dd, J=1.2, 8.3 Hz), 7.63 (1H, dd, J=1.2, 7.4 Hz), 7.71 (1H, dd, J=7.4, 8.3 Hz), 12.69 (1H, s), 12.93 (1H, s). ^{13}C-NMR (DMSO) δ: 23.9, 62.6, 104.5, 115.7, 119.1, 124.4, 126.8, 132.4, 134.1, 136.4, 148.8, 161.8, 174.1, 187.5. IR (KBr): 3290, 1628, 1253, 1207, 1097, 827, 764, 704. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $[C_{14}H_{11}NO_4Na]^+$, 280.0586; Found, 280.0575.

5-Hydroxy-2-(1-hydroxyethyl)-1-methyl-1*H*-benzo[*f*]-indole-4,9-dione (**1dd**)[33]: Starting from **3aa**, this compound was prepared according to the general procedure (Condition D). The column chromatography (hexane–EtOAc=3 : 1) gave **1ee** (98 mg, 72% yield) as yellow solid with mp 219°C. ^{1}H-NMR δ: 1.69 (3H, d, J=6.5 Hz), 4.13 (3H, s), 4.95 (1H, q, J=6.5 Hz), 6.68 (1H, s), 7.18 (1H, dd, J=1.1, 8.4 Hz), 7.54 (1H, dd, J=7.3, 8.4 Hz), 7.65 (1H, dd, J=1.1, 7.3 Hz), 12.58 (1H, s). ^{13}C-NMR δ: 22.2, 33.4, 62.1, 105.1, 115.5, 119.2, 124.1, 126.8, 131.8, 134.4, 135.4, 145.4, 162.0, 175.7, 186.8.

2-(1-Hydroxyethyl)naphtho[2,3-*b*]furan-4,9-dione (**1ee**): Starting from **3ba**, this compound was prepared according to the general procedure (Condition A). The column chromatography (hexane–EtOAc=2 : 1) gave **1ee** (57 mg, 47% yield) as yellow solid with mp 153–155°C. ^{1}H-NMR δ: 1.59 (d, 3H, J=6.7 Hz), 4.98 (1H, q, J=6.7 Hz), 6.79 (1H, s), 7.66–7.71 (2H, m), 8.10–8.16 (2H, m). ^{13}C-NMR δ: 21.5, 63.9, 103.8, 126.9, 127.0, 131.3, 132.4, 133.1, 133.8, 134.0, 152.0, 165.1, 173.5, 180.7. IR (KBr): 3350, 1680, 1591, 1537, 1365, 1219, 1196, 1103, 955, 713. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{14}H_{11}O_4]^+$, 243.0657; Found, 243.0670.

2-(1-Hydroxyethyl)naphtho[2,3-*b*]thiophene-4,9-dione (**1ff**): Starting from **3ba**, this compound was prepared according to the general procedure (Condition B). The column chromatography (hexane–EtOAc=2 : 1) gave **1ff** (72 mg, 56% yield) as yellow solid with mp 175–176°C. ^{1}H-NMR δ: 1.67 (3H, d, J=6.3 Hz), 5.21 (1H, q, J=6.3 Hz), 7.74–7.76 (2H, m), 8.15–8.31 (2H, m). ^{13}C-NMR δ: 25.3, 66.5, 121.9, 126.9, 127.2, 133.3, 133.6, 133.7, 133.8, 142.9, 144.0, 160.4, 178.1, 179.6. IR (KBr): 3280, 1668, 1593, 1460, 1325, 1301, 1265, 1096, 710. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $[C_{14}H_{10}SO_3Na]^+$, 281.0248; Found, 281.0242.

2-(1-Hydroxyethyl)-1*H*-benzo[*f*]indole-4,9-dione (**1gg**): Starting from **3ba** (0.19 mmol), this compound was prepared according to the general procedure (Condition C). The column chromatography (hexane–EtOAc=4 : 1) gave **1gg** (17 mg, 38% yield) as yellow solid with mp >188°C (dec). ^{1}H-NMR ($CDCl_3$–MeOD) δ: 1.58 (3H, d, J=6.6 Hz), 4.94 (1H, q, J=6.6 Hz), 6.60 (1H, s), 7.67–7.70 (2H, m), 8.10–8.15 (2H, m). ^{13}C-NMR ($CDCl_3$–MeOD) δ: 22.9, 63.3, 104.7, 126.4, 126.9, 128.2, 132.2, 133.3, 133.4, 133.7, 134.2, 146.2, 175.8, 181.9. IR (KBr): 3340, 1630, 1513, 1371, 1200, 920, 723. HR-MS (ESI) m/z: $[M+H]^+$ Calcd for $[C_{14}H_{12}NO_3]^+$, 242.0817; Found, 242.0805.

5-Hydroxy-2-phenylnaphtho[2,3-*b*]furan-4,9-dione (**1hh**): Starting from **3ab**, this compound was prepared according to the general procedure (Condition A). The column chromatography (hexane–EtOAc=6 : 1) gave **1hh** (101 mg, 70% yield) as red solid with mp >237°C (dec). ^{1}H-NMR (pyridine) δ: 7.36 (1H, dd, J=1.2, 8.5 Hz), 7.42–7.48 (3H, m), 7.57 (1H, s), 7.60–7.62 (1H, m), 7.88 (1H, dd, J=1.2, 7.5 Hz), 7.91–7.94 (2H, m), 12.55 (1H, s). ^{13}C-NMR (pyridine) δ: 103.3, 115.6, 119.5, 122.7, 124.8, 125.6, 128.4, 129.3, 130.3, 133.4, 136.5, 150.0, 160.2, 162.2, 172.1, 193.0. IR (KBr): 3120, 1635, 1535, 1483, 1452, 1221, 823, 762. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $[C_{18}H_{10}O_4Na]^+$, 313.0477; Found, 313.0485.

5-Hydroxy-2-phenethylnaphtho[2,3-*b*]furan-4,9-dione (**1ii**): Starting from **3ac**, this compound was prepared according to the general procedure (Condition A). The column chromatography (hexane–EtOAc=6 : 1) gave **1ii** (64 mg, 40% yield) as yellow solid with mp 167–168°C. ^{1}H-NMR δ: 3.06–3.16 (4H, m), 6.54 (1H, s), 7.19–7.32 (6H, m), 7.60 (1H, dd, J=7.4, 8.3 Hz), 7.74 (1H, dd, J=1.1, 7.4 Hz), 12.17 (1H, s). ^{13}C-NMR δ: 30.1, 33.5, 104.4, 115.2, 119.8, 125.0, 126.6, 128.2, 128.6, 131.4, 132.8, 136.1, 139.7, 151.8, 162.2, 163.7, 172.4, 186.7. IR (KBr): 1678, 1635, 1472, 1379, 1043, 845, 762. HR-MS (ESI) m/z: $[M+Na]^+$ Calcd for $[C_{20}H_{14}O_4Na]^+$, 341.0790; Found, 341.0789.

8-Hydroxy-2-(1-hydroxyethyl)naphtho[2,3-*b*]furan-4,9-dione

(**1jj**)[2]: Starting from **3ca**, this compound was prepared according to the general procedure (Condition A). The column chromatography (hexane–EtOAc=4 : 1) gave **1jj** (39 mg, 30% yield) as yellow solid with mp 173–175°C. ^{1}H-NMR δ: 1.66 (3H, d, J=6.6 Hz), 5.05 (1H, q, J=6.6 Hz), 6.86 (1H, s), 7.26 (1H, dd, J=1.0, 8.4 Hz), 7.60 (1H, m), 7.71 (1H, dd, J=1.0, 7.4 Hz), 12.02 (1H, s). ^{13}C-NMR δ: 21.5, 63.8, 104.2, 114.7, 120.1, 125.2, 131.9, 133.2, 136.3, 151.2, 162.6, 165.8, 178.5, 179.7.

Antiproliferative Effect Assay The antiproliferative effects of (*S*)-**1bb** 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*)-**1bb** 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.

Acknowledgments This study was supported in part by Grants-in-Aid for Young Scientists (B) (KAKENHI: 24790116) to MY. The authors are grateful to Taheebo Japan Co., Ltd. and SANSHIN METAL WORKING Co., Ltd. for their generous financial support to this project.

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