JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis, Photochemical Properties, and Cytotoxicities of 2*H*-Naphtho[1,2-*b*]pyran and Its Photodimers

Motohiro Ota,[†] Takahiro Sasamori,[‡] Norihiro Tokitoh,[‡] Takefumi Onodera,[§,∥] Yoshiyuki Mizushina,[§,∥] Kouji Kuramochi,*[,†] and Kazunori Tsubaki[†]

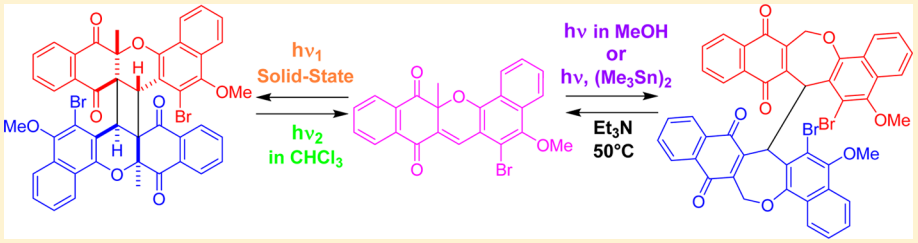
[†]Graduate School for Life and Environmental Sciences, Kyoto Prefectural University, 1-5 Shimogamo Hangi-cho, Sakyo-ku, Kyoto 606-8522, Japan

[‡]Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

[§]Laboratory of Food and Nutritional Sciences, Faculty of Nutrition, Kobe Gakuin University, Nishi-ku, Kobe, Hyogo 651-2180, Japan

[∥]Cooperative Research Center of Life Sciences, Kobe Gakuin University, Chuo-ku, Kobe, Hyogo 651-8586, Japan

Supporting Information



ABSTRACT: A 2*H*-naphtho[1,2-*b*]pyran, prepared by dimerization of 2-bromo-3-methyl-1,4-naphthoquinone and *O*-methylation, readily undergoes solid-state [2 + 2] photodimerization to give a photodimer in excellent yield and with excellent selectivity. Retro [2 + 2] cycloaddition can be achieved by irradiation of a solution of the photodimer in chloroform. Interestingly, the 2*H*-naphtho[1,2-*b*]pyran dimerizes with a skeletal rearrangement to afford 2,5-dihydro-1-benzoxepin dimers upon irradiation in methanol or via irradiation with hexamethylditin. Furthermore, treatment of the resulting dimers with triethylamine regenerates the 2*H*-naphtho[1,2-*b*]pyran monomer. Significant differences in the color, fluorescence, and cytotoxic properties of the monomer and dimers were observed.

INTRODUCTION

Photoreactive molecules change their structures or conformations upon photoirradiation.[1] That is, the properties of these molecules can be changed and controlled spatially and temporally simply by irradiation with light. They can therefore be used as light-responsive materials such as switching sensors,[2] caged molecules,[3] and cross-linking agents.[4] The photoinduced [2 + 2] cycloaddition of two alkenes to form cyclobutanes is one of the most attractive photoswitching reactions.[5] Reversible [2 + 2] cycloaddition reactions have been used for photoinduced cross-linking and cleavage.[6−9] Solid-state [2 + 2] cycloaddition reactions give excellent yields and are highly regio- and stereoselective.[10−12] For these reactions to occur, the double bonds must be aligned in parallel, with a center-to-center distance of 4.2 Å.[13] It is therefore necessary to control crystal packing in order to enable [2 + 2] photocycloaddition.[14,15] The use of intermolecular interactions such as $\pi-\pi$,[16,17] halogen-bonding,[16,18] electron donor−acceptor,[19−21] hydrogen-bonding,[22−24] and cation−π[25,26] interactions facilitates regio- and stereoselective [2 + 2] photocycloaddition in the solid state.

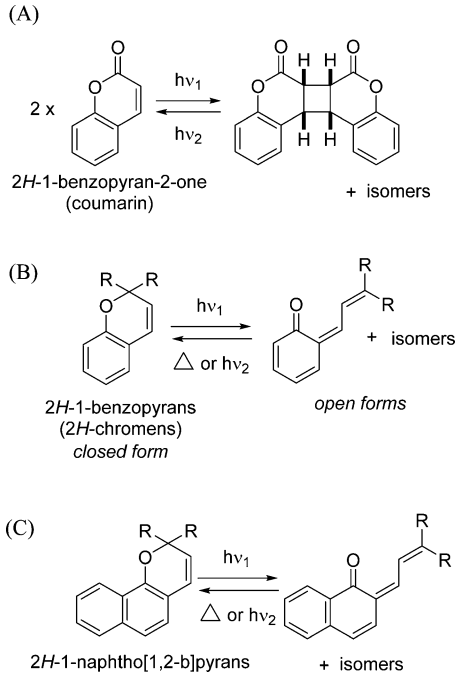
There have been several reports of the [2 + 2] photodimerization of 2*H*-1-benzopyran-2-ones (coumarins) in both solution and the solid state (Scheme 1A).[9,27,28] UV irradiation of the coumarin dimers with a different wavelength of light regenerates the coumarin monomers. The reversible photodimerization of coumarins can be used as a photochemical switch in such applications as photocontrolled storage and release systems.[9] On the other hand, the structurally related 2*H*-1-benzopyrans (2*H*-chromenes) isomerize to the open forms upon UV irradiation (Scheme 1B).[28] The open forms are generally unstable and return to the 2*H*-1-benzopyrans (closed forms) depending on the thermal or photochemical conditions. Because the ring-opening and -closing reactions are accompanied by color changes, applications of 2*H*-1-benzopyrans as photochromic molecules have been widely exploited. 2*H*-Naphtho[1,2-*b*]pyrans have the 2*H*-chromen moiety and show photochromic properties (Scheme 1C).[28,29]

Quinones are known to dimerize in various ways.[30] In a previous study, we developed three pathways for the dimerization of 2-bromo-3-methyl-1,4-naphthoquinone (Scheme 2).[31] Because this molecule has multiple reaction sites, other possible dimerizations can take place under different reaction conditions. In this paper, we report another novel dimerization, forming a 2*H*-naphtho[1,2-*b*]pyran. The rever-

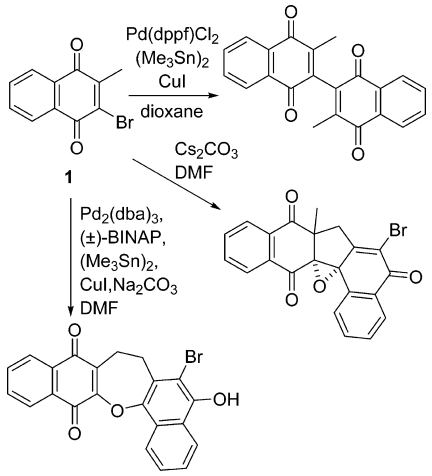
Received: March 22, 2015
Published: April 30, 2015

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695

Scheme 1. Photoreactions of 2*H*-Benzopyran-2-one (A), 2*H*-1-Benzopyrans (B), and 2*H*-Naphtho[1,2-*b*]pyrans (C)



Scheme 2. Our Previous Studies on Dimerization of 2-Bromo-3-methyl-1,4-naphthoquinone[31]

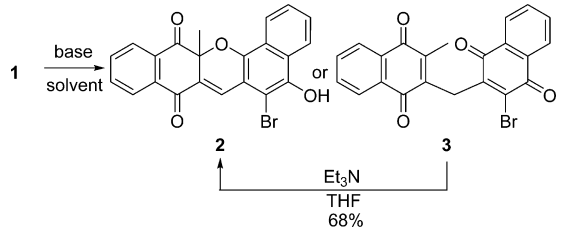


sible [2 + 2] photocycloaddition and photoinduced dimerization of its methyl ether are also described. Significant differences in the optical and cytotoxic properties of the monomer and dimers are reported.

RESULTS AND DISCUSSION

First, the dimerization of 2-bromo-3-methyl-1,4-naphthoquinone (**1**) was examined under a variety of different conditions (Table 1). Treatment of **1** with 2.0 equiv of 1-ethylpiperidine in THF gave 2*H*-naphtho[1,2-*b*]pyran (**2**) in 48% yield (entry 1). The use of triethylamine instead of 1-ethylpiperidine gave **2** in 50% yield (entry 2). The reaction with 1.5 equiv of 1-ethylpiperidine in dichloromethane at 0 °C yielded bisquinone **3** in 13% yield, together with recovered **1** in 72% yield (entry 3). Treatment of **3** with 2.0 equiv of triethylamine in THF afforded **2** in 68% yield.

Table 1. Formation of 2*H*-Naphtho[1,2-*b*]pyran 2 or Bisquinone 3 by Dimerization of 2-Bromo-3-methyl-1,4-naphthoquinone (1)



					yield (%)[a]	
entry	base (equiv)	solvent	temp. (°C)	time (h)	2	3
1	1-ethylpiperidine (2.0)	THF	rt	11	48	0
2	triethylamine (2.0)	THF	rt	7	50	0
3[b]	1-ethylpiperidine (1.5)	CH_2Cl_2	0	0.5	0	13

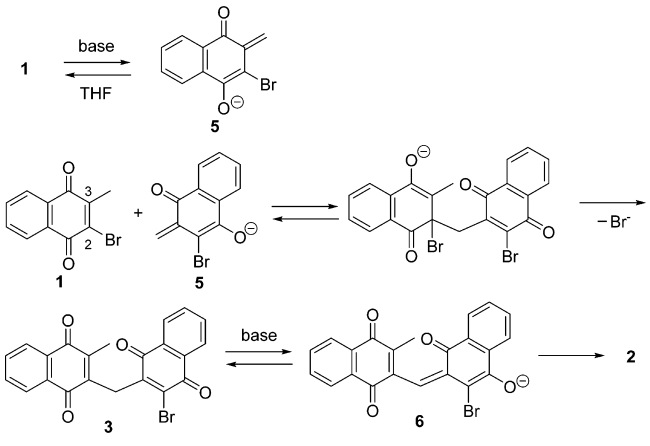
[a]Yields of the isolated product. [b]71% of **1** was recovered.

Based on these results, the following mechanism for the formation of pyran **2** is proposed (Scheme 3).[30b,32] The *o*-quinone methide **5** is generated by treatment of **1** with base. The methide attacks the enone moiety at the C-2 position in **1**. Elimination of a bromonium ion gives **3**. Formation of the *o*-quinone methide **6** by basic enolization of **3**, followed by 6π electrocyclization of **6** gives **2**.

Methylation of the hydroxyl group in **2** under Mitsunobu conditions (MeOH, diethyl azodicarboxylate (DEAD), PPh_3, and THF) readily gave **4** (Scheme 4). The solid-state [2 + 2] photodimerization of **4** proceeded efficiently in a regio- and stereoselective fashion (Scheme 5). Powdered **4** was irradiated for 45 min with a 500 W xenon lamp, using a glass slide to cut off wavelengths below 420 nm, giving **7** in 93% yield as the sole product. The structure of the photodimer **7** was determined by X-ray crystallography after recrystallization from $CHCl_3$ (Figure S1 in Supporting Information).

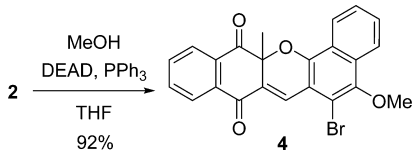
The stereoselectivity of the solid-state [2 + 2] photodimerization of **4** can be rationalized by the packing structure of **4** (Figure 1). The double bonds between C-7 and C-7a in the pyran ring in **4** are aligned in parallel, with a distance of 3.52 Å

Scheme 3. Plausible Mechanism for Formation of 2*H*-Naphtho[1,2-*b*]pyran 2 from 2-Bromo-3-methyl-1,4-naphthoquinone

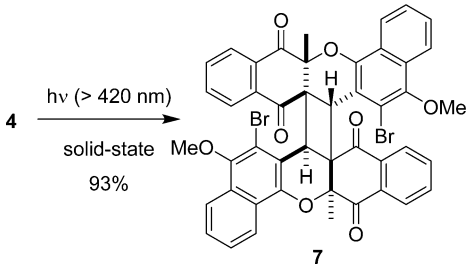


DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695

Scheme 4. Methylation of 2



Scheme 5. Solid-State Photodimerization of 4



(Figure 1A). Each of the methyl groups at C-13a in **4** is oriented in the opposite direction. Two molecules of **4** stack in opposite directions due to $\pi-\pi$ stacking interactions between the quinoid moieties and the naphthalene rings. The intermolecular distance between the methyl group at C-13a and the carbonyl oxygen at C-13 is 3.24 Å, which is shorter than the sum of their van der Waals radii (3.4 Å).[33] This result suggests the presence of an intermolecular CH···O interaction between the methyl group and the carbonyl oxygen (Figure 1B). The intermolecular distances between the carbon of the methoxy group and the carbon at C-5 (3.66 Å), and between the carbon of the methoxy group and the carbon at C-6 (3.65 Å), are also shorter than the sum of their van der Waals radii (3.70 Å),[33] suggesting the presence of CH$-\pi$ interactions.[34]

Thus, X-ray analysis of **4** clearly indicates that **4** is favorable for solid-phase [2 + 2] photodimerization.

The reverse reaction occurs upon irradiation of a solution of dimer **7** in chloroform at 303 nm for 48 h using a fluorometer equipped with a 150 W xenon lamp, giving monomer **4** in 41% yield and recovered **7** in 54% yield (Scheme 6). Prolonging the reaction time does not improve the yield of **4**, indicating that **4** absorbs light at 303 nm and interferes with the reverse photoreaction.

Next, the photodimerization of monomer **4** in solution was examined. No reaction occurred when **4** was irradiated in chloroform, dichloromethane, acetone, or benzene. However, irradiation of **4** in MeOH with a 150 W xenon lamp for 72 h afforded novel dimers **8a** and **8b** in 5% and 6% yield, respectively, with recovered **4** in 46% yield (Scheme 7). Compounds **8a** and **8b** are a pair of diastereomers with a molecular formula of $C_{46}H_{28}O_8Br_2$, as determined by high-resolution electron impact mass spectrometry (HREIMS) and NMR spectroscopic data. HMBC correlations from H-7 to C-7a, C-8, C-13a, and C-15 and HMBC correlations from H-14 to C-7a, C-13a, and C-15a in **8a** indicate the presence of a 2,5-dihydro-1-benzoxepin ring (Figure 2A). The proton signal of H-9 (δ_H 6.90) in **8b** was shifted upfield compared with the signal at H-9 (δ_H 7.95) in **8a**. The lowest energy conformation of **8a** and **8b** was determined by density functional theory (DFT) calculations at the B3LYP/6-31G(d,p) level (Figure 2B). These calculations indicate that the proton at H-9 in the lowest energy confirmation of **8a** is located close to the top of the carbon at C-13′ in the quinone ring (ring C′). On the other hand, the location of the proton at H-9 in the lowest energy confirmation of **8b** is estimated to be near the top of the carbon at C-1a′. Because the distance between H-9 and C-1a′ is estimated to be 4.68 Å, the proton at H-9 will be located in the

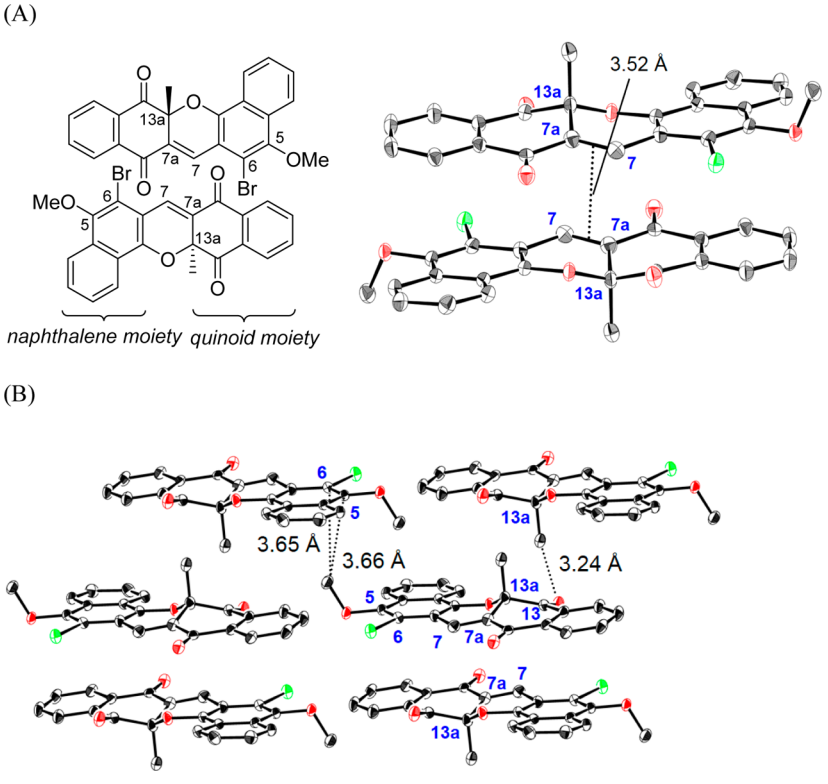
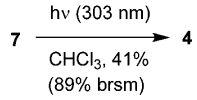


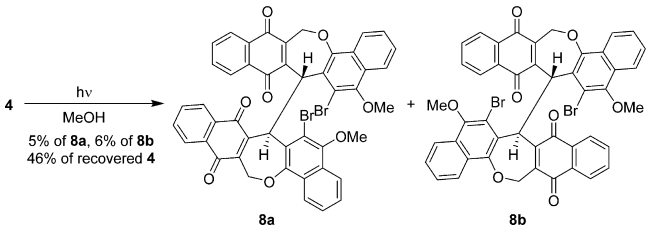
Figure 1. ORTEP diagrams of **4** with 50% ellipsoid probability.

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695

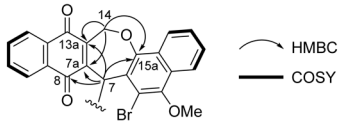
Scheme 6. Formation of Monomer 4 by Irradiation of Dimer 7 in $CHCl_3$ at 303 nm



Scheme 7. Irradiation of 4 in MeOH



(A)



(B)

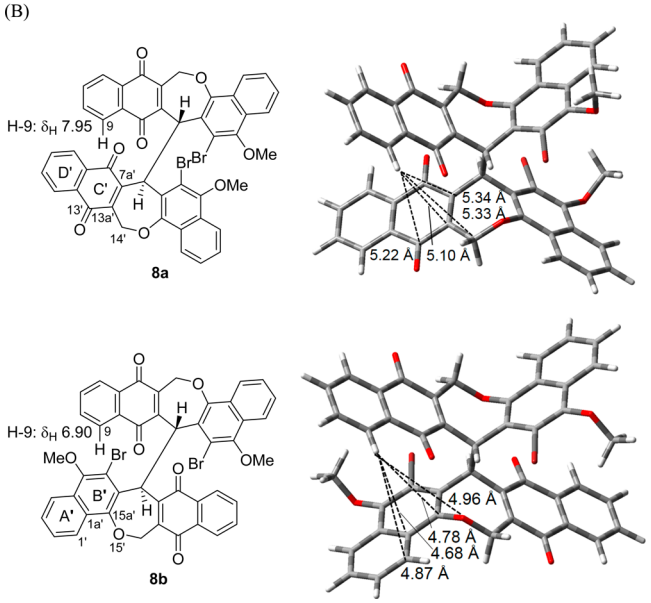
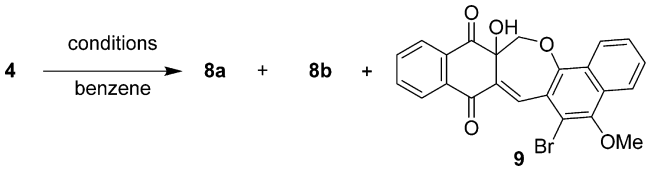


Figure 2. Determination of the structures of **8a** and **8b**. (A) Key HMBC and COSY correlations in **8a**. (B) The lowest energy conformation of **8a** and **8b** optimized by DFT calculations at the B3LYP/6-31G(d,p) level. Selected bond distances (Å) and angles (deg) estimated via DFT calculations: **8a**, H(9)−C(7a′), 5.33; H(9)−C(13′), 5.10; H(9)−C(13a′), 5.22; H(9)−C(14a′), 4.64; H(9)−C(13a′)−C(7a′), 92.9; H(9)−C(13a′)−C(13′), 86.2; H(9)−C-(13a′)−C(14′), 90.6. **8b**, H(9)−C(1′), 4.87; H(9)−C(1a′), 4.68; H(9)−C(15′), 4.96; H(9)−C(15a′), 4.78; H(9)−C(1a′)−C(1′), 89.3; H(9)−C(1a′)−C(4a′), 95.3; H(9)−C(1a′)−C(15a′), 85.4.

shielding region of space inside the aromatic dialkoxynaphthalene ring (rings A′ and B′).[35] Thus, the upfield shift of H-9 in **8b** can be explained by through-space shielding effects due to the aromatic dialkoxynaphthalene ring.[35]

The conditions for the formation of dimers **8a** and **8b** were then optimized (Table 2). Irradiation of **4** in the presence of hexamethylditin afforded **8a** and **8b** in 29 and 33% yields,

Table 2. Optimization of the Conditions for Formation of Dimers 8a and 8b



entry	conditions	time (h)	yield (%)[a] 8a	8b	9	recovered 4
1[b]	hν, $(Me_3Sn)_2$ (1.1 equiv)	60	29	33	–	–
2[c]	hν (>420 nm), $(Me_3Sn)_2$ (1.1 equiv)	60	24	23	1	2

[a]Yields of the isolated products. [b]Irradiation was performed using a 150 W xenon lamp. [c]Irradiation was performed using a 150 W Xe lamp with a filter to cut off wavelengths <420 nm.

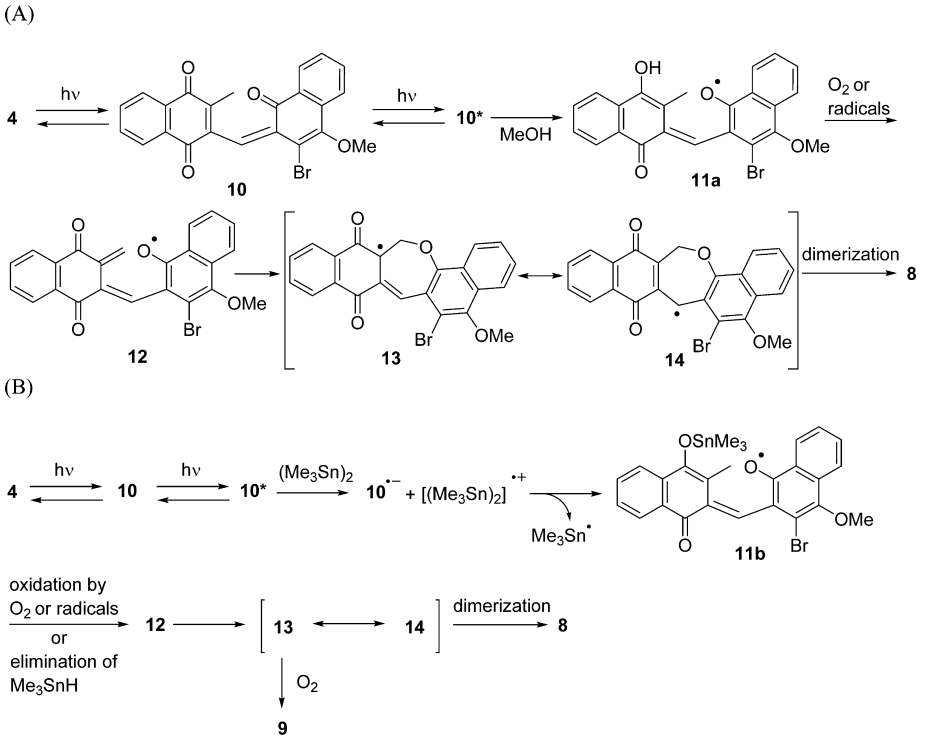
respectively (entry 1). The dimerization of **4** under irradiation above 420 nm in the presence of hexamethylditin gave **8a** and **8b** and **9** in 24%, 23%, and 1% yields, respectively (entry 2). Because hexamethylditin does not absorb light at wavelengths above 420 nm (Figure S2, Supporting Information), compound **4** must be excited by the radiation and then react with hexamethylditin to dimerize.

Combining the results in Scheme 7 and Table 2, Scheme 8 is proposed as the mechanism for the formation of **8**. The proposed mechanism for the formation of **8** by irradiation of **4** in methanol is depicted in Scheme 8A. 2*H*-Naphtho[1,2-*b*]pyran **4** isomerizes to an open form **10** upon UV irradiation.[28,29] Subsequently, the naphthoquinone moiety in **10** is excited by UV irradiation to afford the excited triplet state (**10***), which can abstract hydrogen from methanol to give **11a**.[36] Oxidation of **11a** by oxidants such as oxygen or radicals derived from methanol or **10*** gives the *o*-quinone methide **12**. An intramolecular ring-closing reaction of **12** affords benzoxepin radical **13**, which leads to **14** by radical resonance. Dimerization of **14** affords the dimers **8**. The proposed mechanism for the formation of **8** and **9** upon irradiation of **4** in the presence of hexamethylditin is shown in Scheme 8B. After generation of the excited triplet state **10*** from **4**, single electron transfer from hexamethylditin to **10*** gives a radical cation of hexamethylditin and a radical anion of **10**.[37] Formation of the phenoxy radical **11b**, followed by oxidation by oxidants or elimination of trimethyltin hydride[31] gives **12**. The dimers **8** are formed from **12** as shown in Scheme 8A. Reaction of **13** with oxygen and decomposition of the resultant hydroperoxide or dialkyl peroxide affords the alcohol **9**.[38]

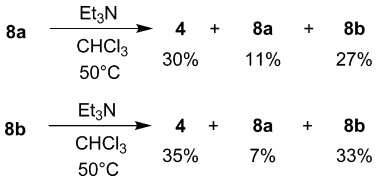
Interestingly, treatment of **8a** with Et_3N (4.8 equiv) in $CHCl_3$ at 50 °C gave **4** and **8b** in 30% and 27% yields, respectively, along with recovered **8a** in 11% yield (Scheme 9). Similarly, treatment of **8b** with Et_3N (4.8 equiv) in $CHCl_3$ at 50 °C gave **4** and **8a** in 35% and 7% yields, with a 33% yield of recovered **8b**. The mechanism for the formation of **4** from **8** is proposed in Scheme 10. Treatment of **8** with Et_3N gives the *o*-quinone methide **15**, which rearranges to form *o*-quinone methide **16** and benzoxepin **17**. Because these reactions are reversible, the reaction between **16** and **17** affords dimers **8a** and **8b**. A ring-opening reaction of **16** affords the *o*-quinone methide **18**, which can isomerize to **10**. Finally, 6π electrocyclization of **10** gives **4**. The benzoxepin **17** was not isolated from the reaction of **8** with Et_3N, suggesting that **17** might be

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695

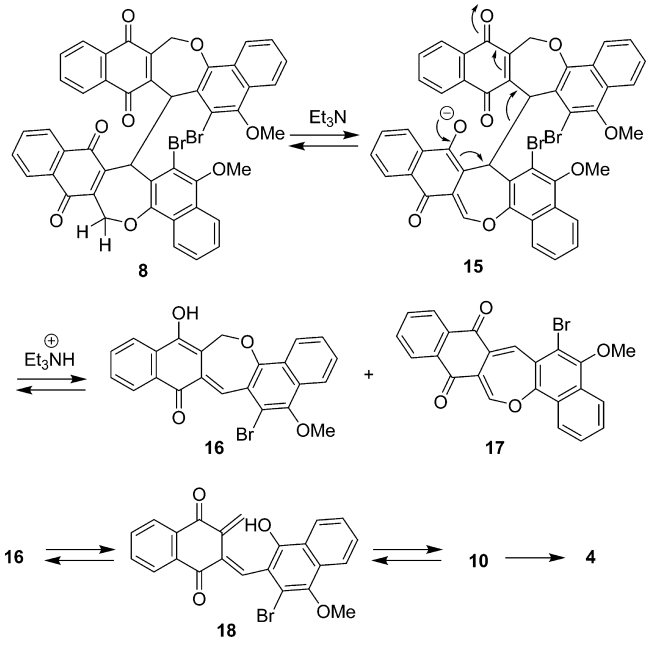
Scheme 8. Proposed Mechanism for Formation of 8 and 9: (A) Formation of 8 by Irradiation of 4 in MeOH and (B) Formation of 8 and 9 by Irradiation of 4 in the Presence of Hexamethylditin



Scheme 9. Formation of Monomer 4 by Treatment of Dimer 8a or 8b with Et_3N



Scheme 10. Possible Mechanism for Formation of Monomer 4 by Treatment of Dimer 8 with Et_3N



unstable and decompose under the reaction conditions. Decomposition of **17** may shift the equilibrium toward formation of **16** from **8** and induce the substituent reactions, affording **4**.

The optical and fluorescent properties of monomer **4** are different from dimers **7**, **8a**, and **8b** (Figure 3). Monomer **4** has an absorption maximum at 452 nm, but dimers **7**, **8a** and **8b** show no absorption in the visible region (Figure 3A). Compound **4** fluoresces yellow with an excitation maximum at 460 nm and an emission maximum (λ_{em}) at 562 nm (Figure 3B). Its fluorescence quantum yield (Φ) was determined to be 0.03, using fluorescein in 0.1 M aqueous NaOH solution (Φ = 0.95)[39] as a reference standard. On the other hand, dimers **7**, **8a**, and **8b** do not fluoresce.

The biological activity of monomer **4** is also different from that of dimers **7**, **8a**, and **8** (Figure 4). Monomer **4** shows cytotoxicity to HCT116 human colon cancer cells and HeLa cervical cancer cells, with IC_{50} values of 15.2 and 78.8 μM, respectively (Figure 4A, B). In contrast, dimers **7**, **8a**, and **8b** have no discernible effect on these cells at concentrations of 200 μM or less. These results suggest that the enone moiety of the pyran ring is important for the cytotoxicity observed.

CONCLUSION

In conclusion, 2*H*-naphtho[1,2-*b*]pyran **2** was prepared by base-induced dimerization of 2-bromo-3-methyl-1,4-naphthoquinone. The crystal structure of its methyl ether **4**, which is stabilized by weak intermolecular noncovalent interactions including $\pi-\pi$, CH···O, and CH$-\pi$ interactions, shows a favorable orientation for [2 + 2] photodimerization. The solid-state photodimerization of **4** was accomplished, giving dimer **7**

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695

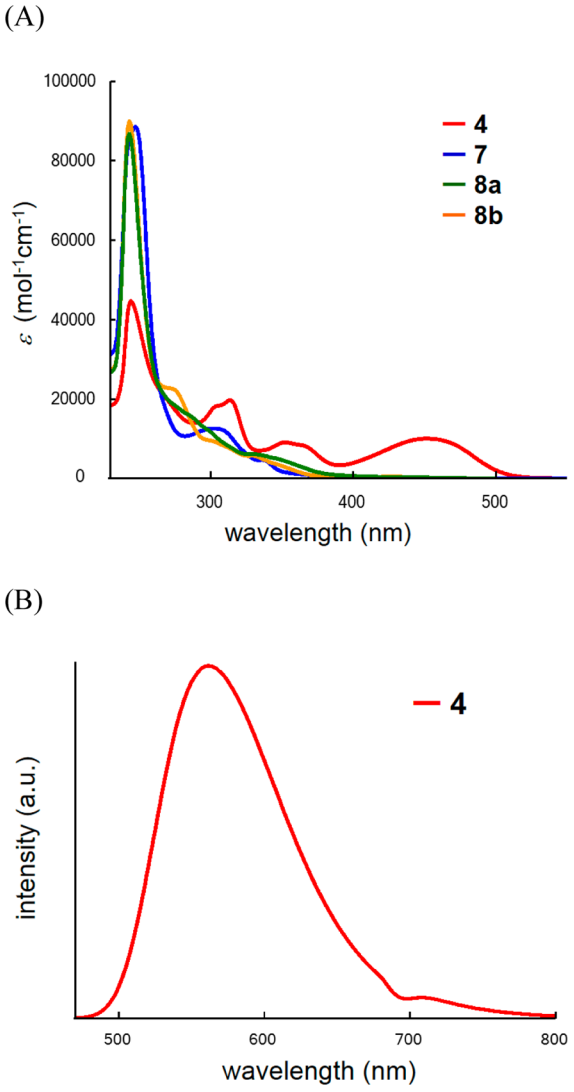


Figure 3. (A) UV−vis spectra of **4**, 7, **8a**, and **8b** and (B) fluorescence spectrum of **4** in $CHCl_3$. (A) Conditions: 25 °C, **4**: 5.0×10^{-5} M, 7, **8a** and **8b**: 5.0×10^{-6} M, light path length = 10 mm. (B) Conditions: 25 °C, 5.0×10^{-5} M, excited at 460 nm, light path length = 10 mm.

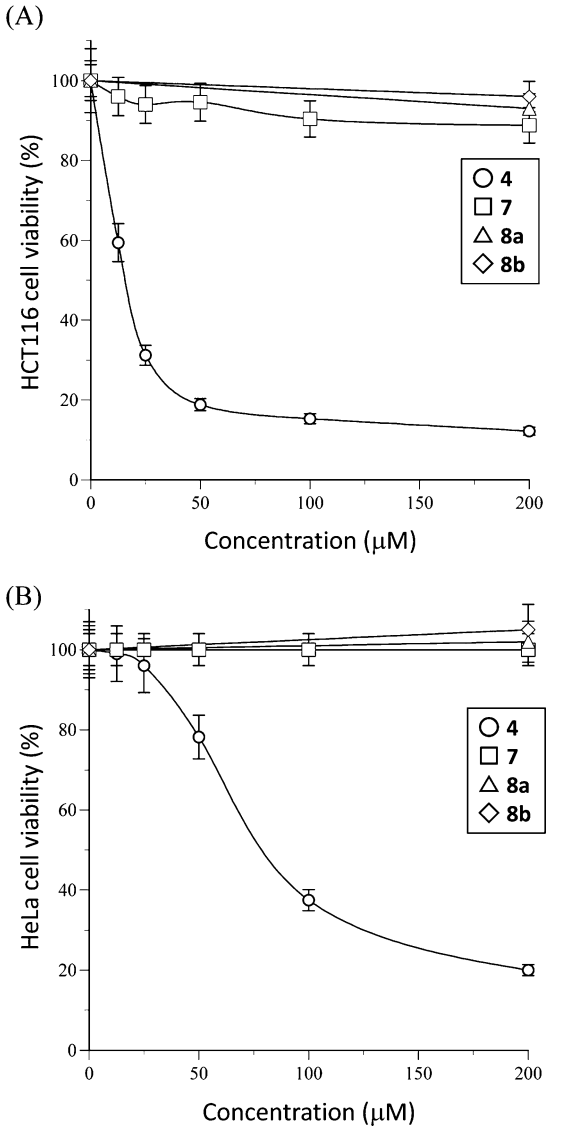


Figure 4. Cytotoxicities of **4**, 7, **8a**, and **8b** to HCT116 (A) and HeLa cells (B). The cell viability was measured by the MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) colorimetric assay.[40] These data represent mean values ± standard deviation (n = 3).

in good yield in a regio- and stereoselective manner. The reverse photoreaction was observed upon irradiation of 7 at 303 nm in $CHCl_3$ solution. Interestingly, irradiation of **4** in methanol or with hexamethylditin gives 2,5-dihydro-1-benzooxepin dimers **8a** and **8b**. Furthermore, treatment of dimers **8a** and **8b** with Et_3N reproduces monomer **4**. Significant differences in the optical, fluorescent, and cytotoxic properties of monomer **4** and dimers 7, **8a**, and **8b** were observed, and thus they are candidates for molecular photoreactive or cage molecules. That is, nontoxic dimers 7, **8a**, and **8b** can be converted into the toxic monomer **4** by UV irradiation or basic treatment. In particular, one molecule of nontoxic dimer 7 could produce two molecules of toxic monomer **4** upon UV irradiation at a specific time and location. Thus, this compound has attractive properties for drug delivery and phototherapy.

EXPERIMENTAL SECTION

General Information. All nonaqueous reactions were carried out by using distilled solvents under N_2 atmosphere in dried glassware unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with silica gel. Flash chromatography was carried out on silica gel (230−400 mesh). NMR spectra were recorded on a 400 M Hz spectrometer. Chemical shifts are expressed in δ (ppm) relative to Me_4Si or the residual solvent resonance, and coupling constants (J) are expressed in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet. Infrared spectra (IR) were recorded on a FT-IR spectrometer, using KBr pellets or NaCl plates, and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were obtained on a magnetic sector mass spectrometer using either electron impact ionization (EI) or fast atom bombardment (FAB) or an ion trap mass spectrometer using electrospray ionization (ESI) techniques. Melting points, determined on a micro melting point apparatus, are uncorrected. UV−vis and fluorescence spectra were measured on a UV−vis spectrophotometer and a spectrofluorometer, respectively.

General Procedure for Formation of 2 and 3 (Table 1). A base (2.0 or 1.5 equiv) was added to a solution of **1** in THF or CH_2Cl_2 at the indicated temperature (rt or 0 °C). The mixture was stirred under a N_2 atmosphere. After the indicated time in Table 1, the reaction was quenched by the addition of 1 M HCl aqueous solution, and the

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695

mixture diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc (× 2). The combined organic layer was washed with water (×2) and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (EtOAc/hexane).

*6-Bromo-5-hydroxy-13a-methyl-8H-dibenzo[b,h]xanthene-8,13-(13aH)-dione (**2**).* Following the general procedure, the reaction of **1** (200 mg, 0.79 mmol) with triethylamine (0.22 mL, 1.58 mmol) in THF (30 mL) for 7 h gave **2** (83.1 mg, 50%) as a red solid after purification by silica gel column chromatography (EtOAc/hexane =1/5). Mp = 180 °C (decomposition). IR (KBr) ν_{max} = 3415, 3093, 3062, 1705, 1655, 1591, 1545, 1498, 1441, 1419, 1363, 1302, 1273, 1200, 1171, 1144, 1093, 1057, 974, 881, 824, 795, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.47 (m, 1H), 8.33 (m, 1H), 8.25 (m, 1H), 8.21 (m, 1H), 8.13 (s, 1H), 7.87 (m, 2H), 7.64 (m, 2H), 5.85 (s, 1H), 1.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.1, 181.2, 145.0, 143.7, 135.1, 135.0, 134.6, 132.4, 131.9, 129.1, 129.0, 127.9, 127.6, 127.4, 126.4, 124.7, 123.5, 122.6, 113.6, 102.8, 80.4, 24.5. HRMS (FAB+) calcd for $C_{22}H_{13}{}^{79}BrO_4$ ([M]$^+$), 419.9997; found, 420.0001.

*2-Bromo-3-{(1,4-dihydro-3-methyl-1,4-dioxo-2-naphthalenyl)-methyl}-1,4-naphthalenedione (**3**).* Following the general procedure, the reaction of **1** (50.0 mg, 0.20 mmol) with 1-ethylpiperidine (41 μL, 0.30 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C gave **3** (5.4 mg, 13%) as a greenish yellow solid and the recovered **1** (35.9 mg, 72%) after purification by silica gel column chromatography (EtOAc/hexane =1/15 to 1/5). Mp = 186 °C (decomposition). IR (KBr) ν_{max} = 2924, 2852, 1668, 1591, 1514, 1456, 1414, 1371, 1331, 1281, 1254, 1186, 1149, 1101, 1065, 964, 918, 800, 773, 731 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16 (m, 2H), 8.10 (dd, J = 7.2 Hz, 2.0 Hz, 1H), 8.00 (dd, J = 7.2 Hz, 2.0 Hz, 1 H), 7.77 (m, 2H), 7.69 (m, 2H), 4.18 (s, 2H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.6, 183.9, 181.4, 177.4, 149.9, 144.8, 143.8, 138.1, 134.3, 134.0, 133.7, 133.6, 132.0, 131.7, 131.5, 131.1, 127.6, 127.5, 126.6, 126.5, 30.5, 13.5. HRMS (FAB+) calcd for $C_{22}H_{14}{}^{79}BrO_4$ ([M + H]$^+$), 421.0075; found, 421.0073.

*Formation of **2** by Treatment of **3** with Triethylamine (Table 1).* Triethylamine (7.0 μL, 50 μmol) was added to a solution of **3** (10.6 mg, 25.2 μmol) and in THF (6.0 mL) at rt. The mixture was stirred for 12 h under N_2 atmosphere. The reaction was quenched by the addition of 1 M HCl aqueous solution, and the mixture was diluted with EtOAc. After the layers were separated, the aqueous layer was extracted with EtOAc (× 2). The combined organic layer was washed with water (× 2) and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (EtOAc/hexane =1/5) to give **2** (7.1 mg, 68%).

*6-Bromo-5-methoxy-13a-methyl-8H-dibenzo[b,h]xanthene-8,13-(13aH)-dione (**4**).* Diethyl azodicarboxylate (674 mg of 40% solution in toluene, 1.55 mmol) was added to a solution of **2** (327 mg, 0.78 mmol), methanol (189 μL, 4.66 mmol), and triphenylphosphine (407 mg, 1.55 mmol) in THF (20 mL) at rt. After the mixture was stirred for 10 min under N_2 atmosphere, the reaction mixture was concentrated. The residue was purified by column chromatography ($CHCl_3$) to give **4** (312 mg, 92%) as a yellow solid. Mp = 189−190 °C. IR (KBr) ν_{max} = 3068, 2976, 2949, 2929, 2845, 1713, 1662, 1595, 1545, 1491, 1450, 1356, 1331, 1269, 1227, 1200, 1163, 1092, 1057, 1032, 974, 895, 820, 795, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.51 (m, 1H), 8.34 (m, 1H), 8.26 (s, 1H), 8.25 (m, 1H), 8.08 (m, 1H), 7.87 (m, 2H), 7.64 (m, 2H), 4.00 (s, 3H), 1.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.0, 181.1, 148.3, 147.5, 135.0, 135.0 134.6, 132.3, 132.2, 130.6, 129.4, 128.9, 127.9, 127.6, 127.0, 125.0, 124.0, 122.3, 114.6, 112.8, 80.5, 61.4, 24.8. HRMS (EI+) calcd for $C_{23}H_{15}{}^{79}BrO_4$ ([M]$^+$), 434.0154; found, 434.0148.

*Preparation of Dimer **7** by [2 + 2] Photodimerization of Monomer **4**.* The powdered solid of **4** (17.3 mg, 39.7 μmol) was irradiated for 45 min with a 500 W xenon lamp using a glass slide to cut off wavelengths below 420 nm. The reaction mixture was purified by column chromatography ($CHCl_3$) to give **7** (16.1 mg, 93%) as a white solid. Mp = 241 °C. IR (KBr) ν_{max} = 3074, 2985, 2954, 2929, 2845, 1720, 1701, 1597, 1572, 1452, 1408, 1362, 1317, 1261, 1244, 1167, 1117, 1088, 993, 968 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.58 (dd, J = 7.6 Hz, 0.8 Hz, 2H), 8.28 (dd, J = 7.6 Hz, 0.8 Hz, 2H), 7.90 (dd, J = 7.6 Hz, 0.8 Hz, 2H), 7.69 (td, J = 7.5 Hz, 1.2 Hz, 2H), 7.64 (m, 2H), 7.58 (m, 2H), 7.37 (td, J = 7.5 Hz, 1.2 Hz, 2H), 6.93 (dd, J = 7.6 Hz, 0.8 Hz, 2H), 5.69 (s, 2H), 3.52 (s, 6H), 0.97 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.3 (2C), 190.7 (2C), 148.6 (2C), 146.9 (2C), 135.1 (2C), 134.0 (2C), 134.0 (2C), 133.8 (2C), 128.3 (2C), 127.9 (2C), 127.8 (2C), 127.0 (2C), 126.6 (2C), 125.7 (2C), 123.0 (2C), 121.7 (2C), 119.6 (2C), 114.7 (2C), 82.1 (2C), 65.1 (2C), 61.5 (2C), 38.6 (2C), 21.5 (2C). HRMS (ESI+): calcd for $C_{46}H_{30}Br^{79}Br^{81}O_8Na$ ([M + Na]$^+$), 893.0185; found, 893.0192.

*Formation of Monomer **4** by Irradiation of Dimer **7**.* A solution of **7** (4.1 mg, 4.71 μmol) in $CHCl_3$ (2.5 mL) was irradiated at 303 nm for 48 h using a fluorometer equipped with a 150 W xenon lamp. The reaction mixture was concentrated. The residue was purified by column chromatography ($CHCl_3$) to give **4** (1.7 mg, 41%) and the recovered **7** (2.2 mg, 54%).

*Formation of Dimers **8a** and **8b** by Irradiation of Monomer **4** in MeOH (Scheme 7).* A solution of **4** (22.2 mg, 51 μmol) in MeOH (250 mL) was irradiated with a 150 W xenon lamp for 72 h. The mixture was concentrated. The residue was purified by column chromatography ($CHCl_3$) and further purified by column chromatography (hexane/EtOAc = 5:1) to give **8a** (1.0 mg, 5%), **8b** (1.3 mg, 6%) as yellow solids, respectively, and the recovered **4** (10.2 mg, 46%). **8a**: Mp = 236 °C (decomposition). IR (KBr) ν_{max} = 3070, 2954, 2929, 2846, 1660, 1627, 1591, 1495, 1452, 1412, 1358, 1329, 1282, 1213, 1174, 1124, 1084, 1053, 1034, 972, 887, 866, 822, 796, 771, 733 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, J = 8.4 Hz, 2H), 7.95 (ddd, J = 8.8 Hz, 5.6 Hz, 3.2 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.88 (ddd, J = 8.8 Hz, 5.6 Hz, 3.2 Hz, 2H), 7.61 (m, 2H), 7.57 (ddd, J =8.8 Hz, 5.6 Hz, 3.2 Hz, 2H), 7.56 (ddd, J =8.8 Hz, 5.6 Hz, 3.2 Hz, 2H), 7.51 (m, 2H), 6.92 (s, 2H), 6.03 (d, J = 18.8 Hz, 2H), 5.07 (d, J = 18.8 Hz, 2H), 3.45 (s, 6H).^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.7 (2C), 184.6 (2C), 150.8 (2C), 150.0 (2C), 145.9 (2C), 143.4 (2C), 133.8 (2C), 133.5 (2C), 131.6 (2C), 131.5 (2C), 130.8 (2C), 128.3 (2C), 127.7 (2C), 127.4 (2C), 127.0 (2C), 126.8 (2C), 125.6 (2C), 122.5 (2C), 122.1 (2C), 115.7 (2C), 69.0 (2C), 61.0 (2C), 43.2 (2C). HRMS (FAB+) calcd for $C_{46}H_{29}{}^{79}Br_2O_8$ ([M + H]$^+$), 867.0229; found, 867.0227. **8b**: Mp = 237 °C (decomposition). IR (KBr) ν_{max} = 3072, 2960, 2929, 2848, 1662, 1630, 1591, 1454, 1416, 1360, 1286, 1246, 1211, 1178, 1128, 1082, 1055, 1034, 974, 889, 866, 818, 798, 768, 729, 708 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.49 (d, J = 8.0 Hz, 2H), 7.87 (dd, J = 7.6, 1.2 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.69 (m, 2H), 7.57 (m, 2H), 7.51 (td, J = 7.6 Hz, 1.2 Hz, 2H), 7.30 (td, J = 7.6 Hz, 1.2 Hz, 2H), 6.93 (s, 2H), 6.90 (dd, J = 7.6, 1.2 Hz, 2H), 6.02 (d, J = 18.4 Hz, 2H), 5.04 (d, J = 18.4 Hz, 2H), 3.32 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.6 (2C), 182.9 (2C), 151.5 (2C), 150.2 (2C), 144.1 (2C), 143.4 (2C), 133.5 (2C), 133.1 (2C), 131.8 (2C), 131.2 (2C), 128.3 (2C), 128.3 (2C), 127.6 (2C), 127.6 (2C), 127.3 (2C), 125.8 (2C), 125.4 (2C), 122.7 (2C), 122.0 (2C), 116.0 (2C), 68.7 (2C), 60.6 (2C), 43.0 (2C). HRMS (ESI+) calcd for $C_{46}H_{28}{}^{79}Br^{81}BrO_8Na$ ([M + Na]$^+$), 891.0028; found, 891.0047.

*Irradiation of **4** in the Presence of Hexamethylditin (Table 2, entries 1 and 2).* Hexamethylditin (26.6 μL, 129 μmol) was added to a solution of **4** (51.0 mg, 117 μmol) in benzene (8.8 mL) at rt. The mixture was irradiated for 60 h using a 150 W xenon lamp without or with a UV cutoff filter (λ > 420 nm). The reaction mixture was concentrated. The residue was purified by column chromatography ($CHCl_3$/Toluene = 1/10) to give **8a** and **8b**.The irradiation without the glass slide gave **8a** (14.6 mg, 29%) and **8b** (17.0 mg, 33%). The irradiation with the glass slide gave **8a** (12.2 mg, 24%), **8b** (11.9 mg, 23%), **9** (0.7 mg, 1%), and recovered **4** (1.2 mg, 2%).

*6-Bromo-13a-hydroxy-5-methoxy-13a,14-dihydrodinaphtho-[1,2-b:2′,3′-e]oxepine-8,13-dione (**9**).* A yellow oil. IR (neat) ν_{max} = 3417, 3072, 3014, 2933, 2850, 1703, 1670, 1591, 1551, 1493, 1452, 1392, 1360, 1321, 1261, 1161, 1092, 1045, 1028, 972, 939, 874, 800, 723 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.45 (s, 1H), 8.38 (dd, J = 7.6, 1.2 Hz, 1H), 8.29 (ddd, J = 6.8, 2.4, 0.4 Hz, 1H), 8.09 (dd, J = 7.6, 1.2 Hz, 1H), 8.03 (ddd, J = 6.8, 2.4, 0.4 Hz, 1H), 7.81 (ddd, J = 6.8, 6.8, 2.4 Hz, 1H), 7.79 (ddd, J = 6.8, 6.8, 2.4 1H), 7.68 (td, J = 7.6, 1.2 Hz, 1H), 7.63 (td, J = 7.6, 1.2 Hz, 1H), 5.20 (d, J = 12.4 Hz, 1H), 4.46 (d, J = 12.4 Hz, 1H), 3.99 (s, 3H), 3.09 (s, 1H).^{13}C NMR ($CDCl_3$,

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695

100 MHz) δ 192.9, 185.6, 156.8, 150.0, 137.5, 136.1, 134.7, 134.3, 133.7, 129.8, 129.7, 127.7, 127.4, 127.2, 126.6, 124.2, 122.3, 118.9, 116.9, 77.3, 76.1, 61.3. HRMS (ESI+) calcd for $C_{23}H_{15}{}^{79}BrO_5Na$ ([M + Na]$^+$), 472.9995; found, 473.0000.

Formation of 2H-Naphtho[1,2-b]pyran **4** *by Treatment of* **8a** *or* **8b** *with* Et_3N *(Scheme 9).* Triethylamine (5.6 μL, 40.2 μmol) was added to a solution of **8** (7.3 mg, 8.4 μmol) in $CHCl_3$ (15 mL) at rt, and the mixture was stirred at 50 °C for 120 h. The mixture was concentrated. The residue was purified by column chromatography (toluene/$CHCl_3$ = 10/1) and further purified by column chromatography (hexane/EtOAc = 5:1) to give **4**, **8a**, and **8b**. Compounds **4** (1.1 mg, 30%), **8a** (0.8 mg, 11%), and **8b** (2.0 mg, 27%) were obtained from **8a**. Compounds **4** (1.3 mg, 35%), **8a** (0.5 mg, 7%), and **8b** (2.4 mg, 33%) were obtained from **8b**.

Determination of the Fluorescent Quantum Yield. A 5.0 × 10^{-5} M solution of **4** in $CHCl_3$ was prepared. The fluorescence quantum yield of **4** was measured using fluorescein in 0.1 M aqueous NaOH solution (f = 0.95)[39] as a reference standard.

X-ray Crystal Data and Measurement Conditions. The single crystal of **4** and **7** was grown by slow recrystallization from $CHCl_3$. The intensity data was collected on a CCD diffractometer equipped with a X-ray optics system using graphite monochromated Mo Kα radiation (λ = 0.71075 or 0.71000 Å). The structure was solved by direct method[41] and refined by full-matrix least-squares procedures on F2 for all reflections.[42] All hydrogen atoms were placed in calculated positions and refined using a riding model, while all the other atoms were refined anisotropically.

Computational Details. Conformational analyses of **8a** and **8b** were performed using the conformational search algorithm.[43] The lower energy conformers of each compound, which differed from the most stable confer by <10 kcal/mol, were optimized using DFT calculations at the B3LYP/6-31G(d,p) level, that were implemented in the Gaussian 09 program package.[44] The lowest energy conformations of **8a** and **8b** were determined by comparing the sum of the electronic and zero-point energies of each conformer.

Cell Culture and Measurement of Cancer Cell Viability. Human colon (HCT116) and cervix (Hela) cancer cells were cultured in RPMI 1640 medium and Dulbecco's modified Eagle's medium (DMEM), respectively, supplemented with 10% fetal bovine serum, penicillin (100 units/mL), streptomycin (100 μg/mL), and 1.6 mg/mL $NaHCO_3$ at 37 °C in a humid atmosphere of 5% CO_2/95% air. For the cell viability assay, cells were seeded at 1 × 10^3 cells/well in a 96-well microplate with various concentrations of the test compounds and incubated for 48 h. MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) solution[40] was added to a final concentration 0.6 mg/mL in purified water for 2 h, after which time the medium was discarded and the cells lysed in DMSO. A_{540} was then measured in a microplate reader.

■ ASSOCIATED CONTENT

Supporting Information

CIF files, ORTEP drawings and X-ray crystallographic data of **4** and **7**·2$CHCl_3$, results of DFT calculations of **8a** and **8b**, UV–vis spectrum of hexamethylditin, and ^{1}H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00645.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kuramoch@kpu.ac.jp. Phone and fax: +81-75-703-5603.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by Grant-in-Aid for Young Scientists (B) (25850083). This study was carried out using the mass spectrometers in the Joint Usage/Research Center (JURC) at the Institute for Chemical Research, Kyoto University. We are grateful to Prof. Masaharu Nakamura, Prof. Hikaru Takaya, and Prof. Katsuhiro Isozaki of Kyoto University for assistance with HRMS measurements.

■ REFERENCES

(1) Szymański, W.; Beierle, J. M.; Kistemaker, H. A.; Velema, W. A.; Feringa, B. L. *Chem. Rev.* **2013**, *113*, 6114.
(2) *Molecular Switches*, 2nd ed.; Feringa, B. L., Browne, W. R., Eds.; Wiley-VCH: Weinheim, 2011.
(3) Ellis-Davies, G. C. R. *Nat. Methods* **2007**, *4*, 619.
(4) Tanaka, Y.; Bond, M. R.; Kohler, J. J. *Mol. BioSyst.* **2008**, *4*, 473.
(5) Alfimov, M. V.; Fedorova, O. A.; Gromov, S. P. *J. Photochem. Photobiol., A* **2003**, *158*, 183.
(6) Lendlein, A.; Jiang, H.; Jünger, O.; Langer, R. *Nature* **2005**, *434*, 879.
(7) Shi, D.; Matsusaki, M.; Kaneko, T.; Akashi, M. *Macromolecules* **2008**, *41*, 8167.
(8) Li, X.; Cui, J.; Zhang, W.; Huang, J.; Li, W.; Lin, C.; Jiang, Y.; Zhang, Y.; Li, G. *J. Mater. Chem.* **2011**, *21*, 17953.
(9) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059.
(10) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433.
(11) Hasegawa, M. *Pure Appl. Chem.* **1986**, *58*, 1179.
(12) Sonoda, Y. *Molecules* **2011**, *16*, 119.
(13) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647.
(14) Chung, J. W.; You, Y.; Huh, H. S.; An, B. K.; Yoon, S. J.; Kim, S. H.; Lee, S. W.; Park, S. Y. *J. Am. Chem. Soc.* **2009**, *131*, 8163.
(15) Coates, G. W.; Dunn, A. R.; Henling, L. M.; Ziller, J. W.; Lobkovsky, E. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 3641.
(16) Caronna, T.; Liantonio, R.; Logothetis, T. A.; Metrangolo, P.; Pilati, T.; Resnati, G. *J. Am. Chem. Soc.* **2004**, *126*, 4500.
(17) Ghosn, M. W.; Wolf, C. *J. Org. Chem.* **2010**, *75*, 6653.
(18) Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6114.
(19) Sharma, C. V. K.; Panneerselvam, K.; Shimoni, L.; Katz, H.; Carrell, H. L.; Desiraju, G. R. *Chem. Mater.* **1994**, *6*, 1282.
(20) Devic, T.; Batail, P.; Avarvari, N. *Chem. Commun.* **2004**, 1538.
(21) Pan, Z.; Hariharan, M.; Arkin, J. D.; Jalilov, A. S.; McCullagh, M.; Schatz, G. C.; Lewis, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 20793.
(22) Bhattacharya, S.; Stojaković, J.; Saha, B. K.; MacGillivray, L. R. *Org. Lett.* **2013**, *15*, 744.
(23) Feldman, K. S.; Campbell, R. F. *J. Org. Chem.* **1995**, *60*, 1924.
(24) Varshney, D. B.; Gao, X.; Friščić, T.; MacGillivray, L. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 646.
(25) Yamada, S.; Tokugawa, Y. *J. Am. Chem. Soc.* **2009**, *131*, 2098.
(26) Yamada, S.; Uematsu, N.; Yamashita, K. *J. Am. Chem. Soc.* **2007**, *129*, 12100.
(27) Tanaka, K. *Molecules* **2012**, *17*, 1408.
(28) Gemert, B. V. Benzo and Naphthopyrans (Chromenes). In *Organic Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R. J., Eds.; Plenum Press: New York, 1999; Vol. *1*, Chapter 3.
(29) For selected photochromism of 2*H*-naphtho[1,2-b]pyrans, see: (a) Kolc, J.; Becker, R. S. *Photochem. Photobiol.* **1970**, *12*, 383. (b) Favaro, G.; Romani, A.; Becker, R. S. *Photochem. Photobiol.* **2000**, *72*, 632. (c) Favaro, G.; Romani, A.; Becker, R. S. *Photochem. Photobiol.* **2001**, *74*, 378. (d) Brun, P.; Guglielmetti, R.; Anguille, S. *Appl. Organomet. Chem.* **2002**, *16*, 271. (e) Jockusch, S.; Turro, N. J.; Blackburn, F. R. *J. Phys. Chem. A* **2002**, *106*, 9236. (f) Gabbutt, C. D.; Heron, B. M.; Kolla, S. B.; Kilner, C.; Coles, S. J.; Horton, P. N.; Hursthouse, M. B. *Org. Biomol. Chem.* **2008**, *6*, 3096. (g) Alberti, A.; Campredon, M.; Demadrille, R. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 552. (h) Sousa, C. M.; Berthet, J.; Delbaere, S.; Coelho, P. J. *J. Org. Chem.*

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687–5695

2012, *77*, 3959. (i) Aiken, S.; Booth, K.; Gabbutt, C. D.; Heron, M.; Rice, C. R.; Charaf-Eddin, A.; Jacquemin, D. *Chem. Commun.* **2014**, *50*, 7900.
(30) For selected preparation of dimeric quinones, see: (a) Shand, A. J.; Thomson, R. H. *Tetrahedron* **1963**, *19*, 1919. (b) Dean, F. M.; Houghton, L. E. *Tetrahedron Lett.* **1969**, *40*, 3579. (c) Dean, F. M.; Houghton, L. E. *J. Chem. Soc. C* **1971**, 1902. (d) Chandrasenan, K.; Thomson, R. H. *Tetrahedron* **1971**, *27*, 2529. (e) Baxter, I.; Cameron, D. W.; Titman, R. B. *J. Chem. Soc. C* **1971**, 1253. (f) Ansell, M. F.; Bignold, A. J. *J. Chem. Soc. D* **1971**, 1562. (g) Laatsch, H. *Tetrahedron Lett.* **1978**, *41*, 3889. (h) Dean, F. M.; Houghton, L. E.; Mitchell, G. H.; Nayyir-Mashir, R.; Thebtaranonth, C. *Tetrahedron* **1986**, *42*, 3663.
(31) Azuma, S.; Nishio, K.; Kubo, K.; Sasamori, T.; Tokitoh, N.; Kuramochi, K.; Tsubaki, K. *J. Org. Chem.* **2012**, *77*, 4812.
(32) Thomson, R. H.; Worthington, R. D. *J. Chem. Soc., Perkin Trans 1* **1980**, 282.
(33) Pauling, L. *The Nature of the Chemical Bond and the Structure of Molecules and Crystals*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960.
(34) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/π Interaction. Evidence, Nature, and Consequences*; Wiley-VCH: New York, 1998.
(35) Kleinpeter, E.; Koch, A. *ARKIVOC* **2012**, *v*, 94.
(36) (a) Schulte-Frohlinde, D.; Werner, V. *Chem. Ber.* **1961**, *94*, 2726. (b) Bruce, J. M. *Q. Rev. Chem. Soc.* **1967**, *21*, 405. (c) Land, E. J.; Swallow, A. J. *J. Biol. Chem.* **1970**, *245*, 1890. (d) Bensasson, R. V.; Land, E. J.; Truscott, T. G. *Flash Photolysis and Pulse Radiolysis: Contribution to the Chemistry of Biology and Medicine*; Oxford University Press: New York, 1983; pp 8.
(37) (a) Kozima, S.; Fujita, H.; Hitomi, T.; Kobayashi, K.; Kobayashi, K.; Kawanishi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2953. (b) Kochi, J. K.; Chen, K. S.; Wan, J. K. S. *Chem. Phys. Lett.* **1980**, *73*, 557. (c) Chen, K. S.; Wan, J. K. S.; Kochi, J. K. *J. Phys. Chem.* **1981**, *85*, 1726.
(38) Denisov, E. T.; Denisova, T. G.; Pokidova, T. S. Dialkyl Peroxides and Hydroperoxides. In *Handbook of Free Radical Initiators*; John Wiley & Sons: Hoboken, NJ, 2003, Chapter 4.
(39) Brannon, J. H.; Magde, D. *J. Phys. Chem.* **1978**, *82*, 705.
(40) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55.
(41) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
(42) Sheldrick, G. M. *SHELXS97. Program for Crystal Structure Solution*; University of Göttingen: Göttingen, Germany, 1997.
(43) (a) Gotō, H.; Ōsawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950. (b) Gotō, H.; Ōsawa, E. *Tetrahedron Lett.* **1992**, *33*, 1343. (c) Gotō, H.; Ōsawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187.
(44) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision D.01;Gaussian, Inc.: Wallingford, CT, 2009.

DOI: 10.1021/acs.joc.5b00645
J. Org. Chem. 2015, 80, 5687−5695