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FIRST TOTAL SYNTHESIS OF PALMARUMYCIN C_6 BASED ON DOUBLE OXA-MICHAEL ADDITION OF 1,8-DIHYDROXYNAPHTHALENE TO 3-BROMO-1-INDENONE

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Dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday

Abstract – Synthetic studies on palmarumycin C_6 with a naphthyl acetal at the C-3 position in 4,7-dihydroxy-1-indanone as a lower homologue of spirobisnaphthalenes are described herein. We investigated three approaches: 1) Nazarov cyclization of benzoylketene acetal, 2) intramolecular Friedel-Crafts acylation of naphtho[1,8-*de*]-1,3-dioxin-2-aryl-2-acetic acid chloride, and 3) double oxa-Michael addition of 1,8-dihydroxynaphthalene to 3-bromo-1-indenone. The last approach successfully afforded the natural product after the removal of acetates that serve as protecting groups for phenolic hydroxyls under acidic conditions.

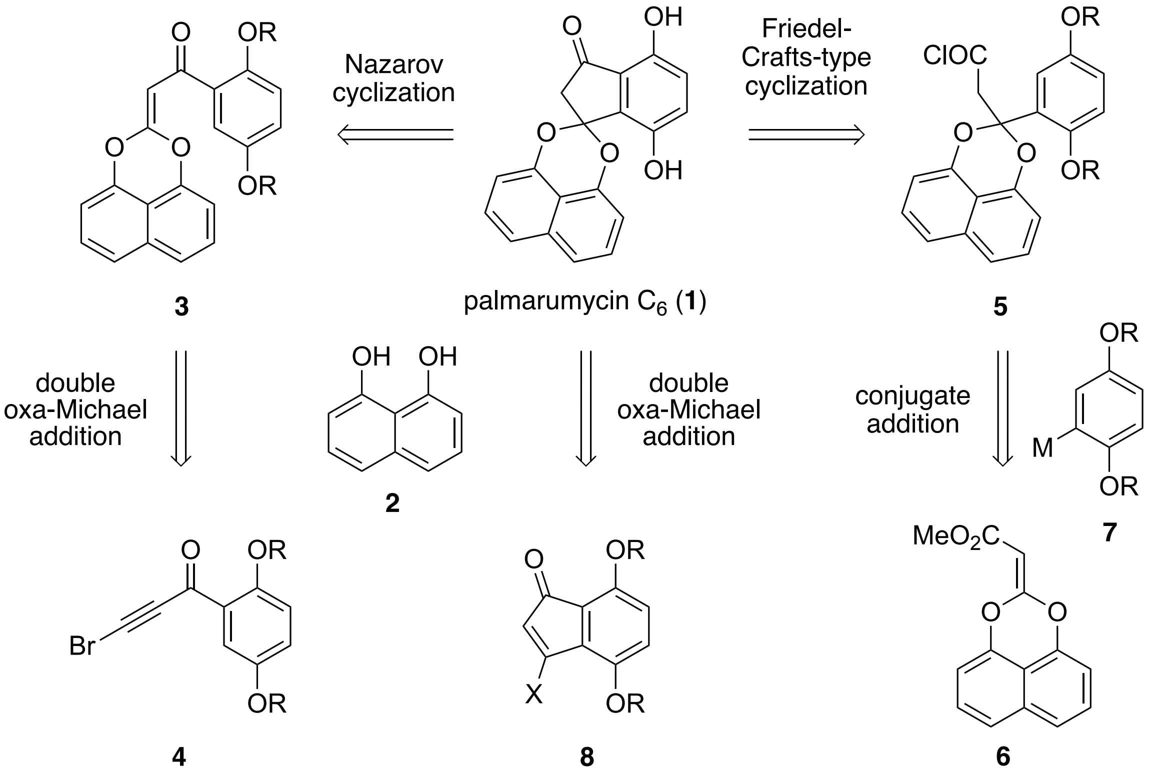
INTRODUCTION

Spirobisnaphthalenes are fungal secondary metabolites that have unique, highly oxidized structures and diverse biological activities.[1] Their structural complexity and important biological activities have prompted significant research into their synthesis. Most of this research has focused on C10-spirobisnaphthalenes with a naphthyl acetal on a six-membered ring. However, some members of the spirobisnaphthalene family have a 9-carbon skeleton bearing the naphthyl acetal on a five-membered ring.[2–5] The formation of an acetal from 1,8-dihydroxynaphthalene (DHN) is not trivial because the conventional method, which is performed under acidic conditions, also leads to competitive autopolymerization of 1,8-dihydroxynaphthalene and can only be applied to the synthesis of the former six-membered-ring acetal.[6] Thus, if we are to synthesize the latter five-membered-ring acetal spirobisnaphthalene analogs, the development of an efficient method for constructing the acetal under neutral or basic conditions is required.

Recently, we reported the synthesis of spiromamakone A benzo analogs based on a double oxa-Michael addition of 1,8-dihydroxynaphthalene to 2-(pseudohalo)alkylidene-1,3-cyclopentanedione under basic conditions.[7] In addition, we also reported an alternative method for constructing the acetal based on conjugate addition of carbon- or heteroatom-nucleophiles to β-oxoketene naphthyl acetals prepared from 3-bromo-2-propyn-1-ones.[8]

Herein, we describe three approaches to synthesize palmarumycin C_6 (**1**),[2] which was isolated from *Coniothyrium* sp. and has never been synthesized (Scheme 1). Although no biological activity for this compound itself has been reported, the structural motif upon which it is based can be seen in other natural products[3] as well as biologically active spiromamakone A benzo analogs.[7]

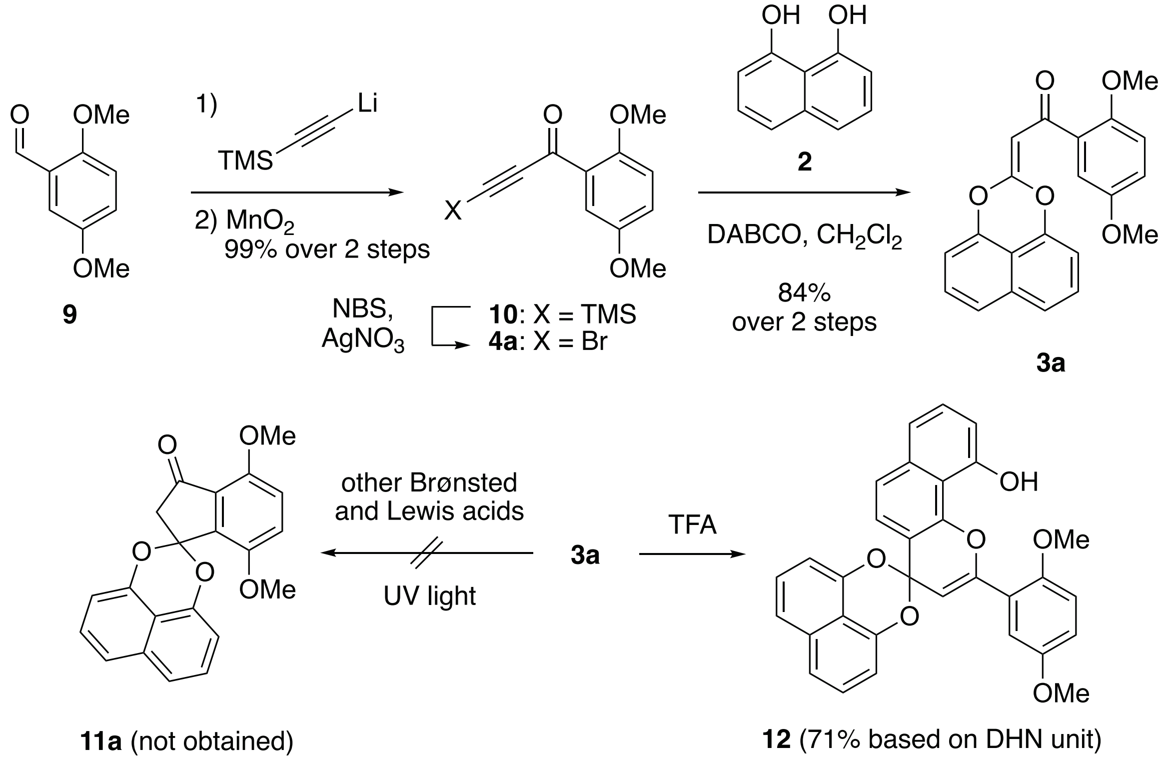
We investigated three synthetic approaches, as shown in Scheme 1: 1) Nazarov cyclization[9] of aryl vinyl ketone **3** derived from 1-aryl-3-bromo-2-propyn-1-one **4**, 2) intramolecular Friedel-Crafts acylation of **5** prepared by arylation of β-oxoketene naphthyl acetal **6** with **7** followed by transformation of the ester to an acid chloride; and 3) double oxa-Michael addition[10] of DHN (**2**) to 3-halo- or pseudohalo-1-indenone **8**.



Scheme 1. Retrosyntheses of palmarumycin C_6 (**1**)

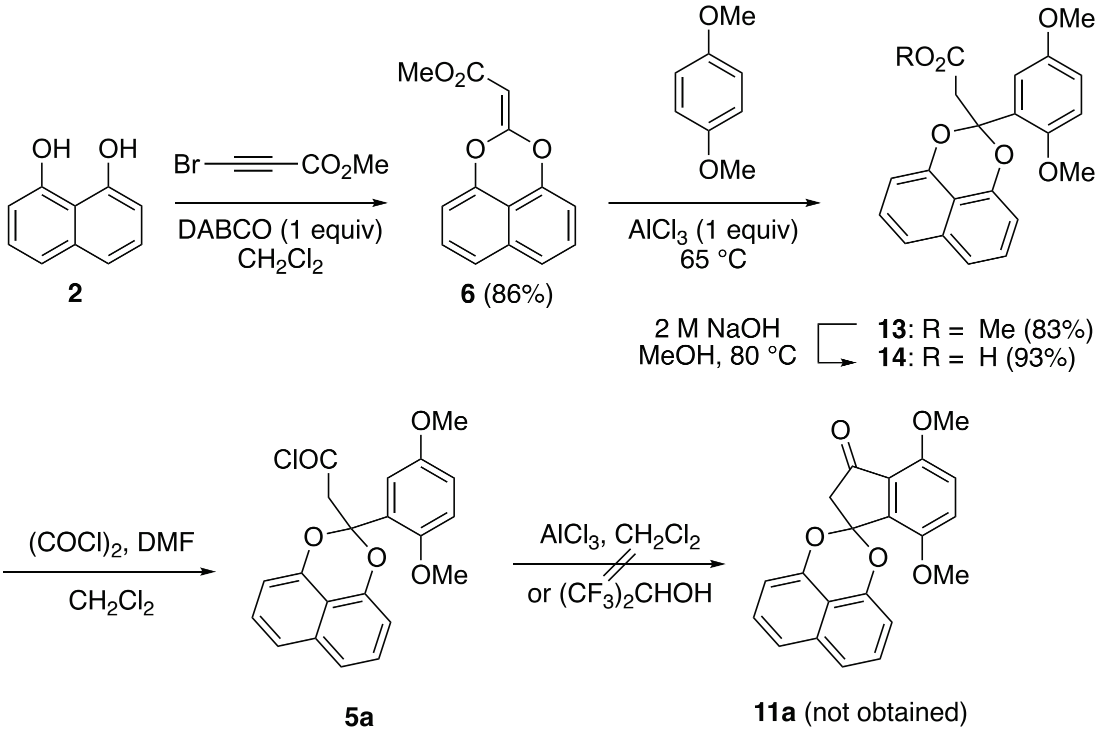
RESULTS AND DISCUSSION

First, aryl vinyl ketone **3a** for the Nazarov cyclization was readily prepared from commercially available 2,5-dimethoxybenzaldehyde (**9**) (Scheme 2). Addition of lithium (trimethylsilyl)acetylide to **9** and subsequent oxidation with MnO_2 afforded TMS-protected ethynyl ketone **10** in good yield. Substitution of the TMS group in **10** with bromide was achieved by treatment with NBS and a catalytic amount of silver nitrate,[11] which was followed by double oxa-Michael addition of DHN to give acylketene acetal **3a**. Although a variety of reaction conditions have been explored for the Nazarov cyclization of substituted aryl vinyl ketones, including Brønsted acids (PPA,[12] MsOH,[13] TfOH,[14] and TFA[15]), Lewis acids (BF_3·OEt_2,[16] $FeCl_3$,[17] TMSOTf,[18] and $AlCl_3$[19]), and UV irradiation,[20, 21] none of these conditions converted **3a** to naphthyl acetal **11a**. Steric and electronic factors in the naphthyl acetal moiety destabilize the *s-trans* conformer of **3a** and stabilize the pentadienyl cation, respectively, preventing cyclization.[22] It should be noted that heating **3a** in trifluoroacetic acid led to the formation of **12**, which results from the liberation of DHN from **3a** followed by 1,4-addition of DHN to another molecule of **3a** and dehydration.



Scheme 2. Attempted synthesis of **11a** via Nazarov cyclization of **3a**

During screening of the reaction conditions for the Nazarov cyclization of **3a**, 1,4-addition of toluene (employed as the solvent) to acylketene acetal **3a** was observed under $AlCl_3$ catalysis.[23] The corresponding ester **6**[8] also underwent arylation with 1,4-dimethoxybenzene to give naphthyl acetal **13** (Scheme 3). Instead of arylmetal species, electron-rich arenes can be used as nucleophiles for the conjugate addition to acylketene acetal **6** under acidic conditions. Hydrolysis of the methyl ester in **13** and subsequent treatment with oxalyl chloride yielded acid chloride **5a**. Unfortunately, neither $AlCl_3$[24] nor 1,1,1,3,3,3-hexafluoroisopropanol as a solvent[25] promoted the intramolecular Friedel-Crafts acylation of **5a**.

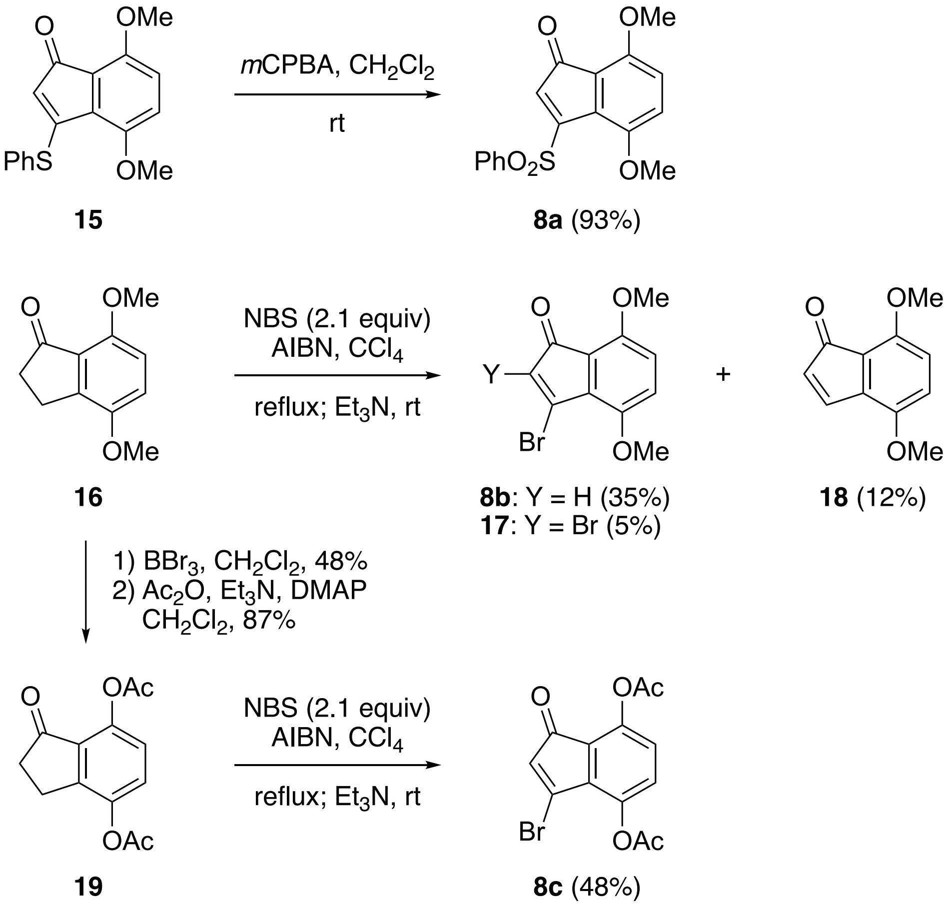


Scheme 3. Attempted synthesis of **11a** via intramolecular Friedel–Crafts acylation of **5a**

Finally, double oxa-Michael addition of DHN to 3-halo- and 3-pseudohalo-1-indenones was attempted (Table 1). The starting Michael acceptors **8a–c** and **17** were prepared as shown in Scheme 4. Sulfone **8a** with two methyl ethers was prepared by oxidation of literature-known sulfide **15**.[26] Preparation of 3-bromo-1-indenone **8b** from its parent indanone **16**[27] based on a one-pot sequence involving radical-mediated dibromination of the benzylic methylene carbon and base-promoted elimination of HBr also afforded dibromide **17** and 1-indenone **18**.[28] Conversely, Michael acceptor **8c**, in which two hydroxyl groups are protected by acetyl groups instead of methyl groups, was selectively synthesized from acetate **19**[29] by the above one-pot sequence. It is noteworthy that the efficiency of the one-pot sequence was strongly influenced by the electron density of the benzene ring.

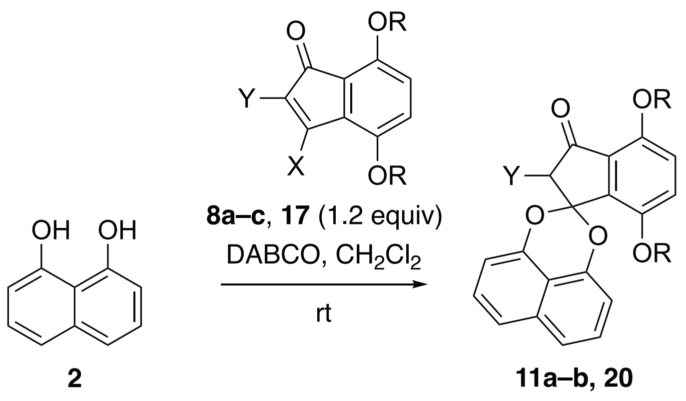
Unlike the vinylogous acyl sulfone activated by two carbonyl groups that we previously reported,[7] vinylogous acyl sulfone **8a** did not undergo an addition-elimination reaction with **2** in the presence of a stoichiometric amount of DABCO as base (Table 1, Entry 1). However, the corresponding bromide **8b** was converted to the naphthyl acetal **11a** under the same reaction conditions (Entry 2).

2,3-Dibromo-1-indenone **17**, which was obtained as a side product during the preparation of **8b**, also participated in the double oxa-Michael addition of **2** to give 2-bromo-1-indanone **20** in good yield (Entry 3). The α-bromo substituent in **20** was reduced using zinc powder in acetic acid to afford **11a** in 93% yield (Scheme 5). As well as methyl-protected indenone **8b**, acetyl-protected substrate **8c** was successfully transformed into naphthyl acetal **11b** without elimination of the acetyl groups (Table 1, Entry 4).



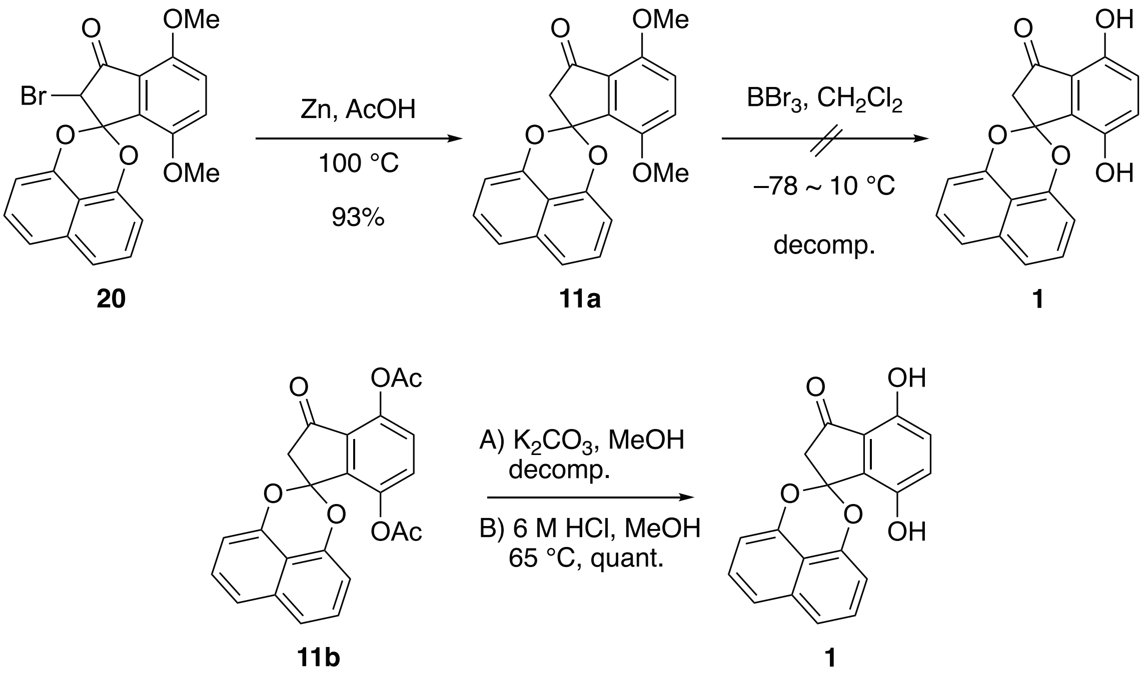
Scheme 4. Preparation of Michael acceptors **8a–c** and **17** for double oxa-Michael addition of **2**

Table 1. Double oxa-Michael addition of **2** to Michael acceptors **8a–c** and **17**



Entry	Michael acceptor	X	Y	R	Product	Yield
1	**8a**	SO_2Ph	H	Me	**11a**	0%
2	**8b**	Br	H	Me	**11a**	50%
3	**17**	Br	Br	Me	**20**	62%
4	**8c**	Br	H	Ac	**11b**	58%

Finally, deprotection of the two methyl ethers in **11a** was investigated (Scheme 5). Although BBr_3 has been employed for the removal of methyl groups from a substrate with a naphthyl acetal on tetralone,[30] treatment of **11a** with BBr_3 resulted in decomposition of the substrate. Interestingly, acid hydrolysis of the acetate **11b** proceeded well to produce palmarumycin C_6 (**1**) in quantitative yield, whereas basic hydrolysis of **11b** led to decomposition.[31] The spectroscopic data for **1** are in good agreement with those reported.[2]



Scheme 5. Total synthesis of palmarumycin C_6 (**1**)

In summary, we have achieved the first total synthesis of palmarumycin C_6 (**1**) through five steps from 4,7-dimethoxy-1-indanone (**16**) using double oxa-Michael addition of DHN to 3-bromo-1-indenone in the presence of DABCO. Although the naphthyl acetal is very sensitive to the deprotection conditions, acid hydrolysis of the phenolic acetates led to the successful formation of the natural product. Syntheses of other spirobisnaphthalene analogs based on the current methodology are underway.

EXPERIMENTAL

All commercially available reagents and anhydrous solvents including acetone, dichloromethane (CH_2Cl_2), and tetrahydrofuran (THF) were purchased and used without further purification otherwise noted. Anhydrous acetonitrile (MeCN), *N*, *N*-dimethylformamide (DMF), and nitromethane were obtained by distillation from calcium hydride. Anhydrous methanol (MeOH) was obtained by distillation from magnesium. All reactions were monitored by thin layer chromatography (TLC) performed on 0.25 mm silica gel glass plates (60 F_{254}) using UV light and ethanolic *p*-anisaldehyde-sulfuric acid, aqueous cerium sulfate-hexaammonium heptamolybdate-sulfuric acid, or aqueous potassium permanganate-potassium carbonate-sodium hydroxide solutions as visualizing agents. Yields refer to chromatographically and spectroscopically homogeneous materials. Melting points were measured on a melting point apparatus and were uncorrected. Only the strongest and/or structurally important absorptions of infrared (IR) spectra are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra (400 MHz and 600 MHz) and $^{13}C\{^1H\}$NMR spectra (100 MHz and 151 MHz) were recorded in the indicated solvent. Chemical shifts (δ) are reported in delta (δ) units, parts per million (ppm). Chemical shifts for ^1H NMR spectra are given relative to signals for internal tetramethylsilane (0 ppm) or residual nondeuterated solvents, i.e., chloroform (7.26 ppm), methanol (3.30 ppm) and dimethyl sulfoxide (DMSO, 2.49 ppm). Chemical shifts for ^{13}C NMR spectra are given relative to the signal for $CDCl_3$ (77.0 ppm), CD_3OD (49.0 ppm) and DMSO-d_6 (39.7 ppm). Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants (*J*) are represented in hertz (Hz). ^1H and ^{13}C NMR chemical shifts were assigned using a combination of COSY, NOESY, HMQC, and HMBC. EI mass spectra and EI high resolution mass spectra were measured on a JEOL JMS-DX303, JMS-700 and JMS-T100GC. ESI high resolution mass spectra were measured on a Thermo Scientific^{TM} Exactive^{TM} Plus Orbitrap mass spectrometer.

1-(2,5-Dimethoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-one (10): To a stirring solution of trimethylsilylacetylene (3.3 mL, 24 mmol) in anhydrous THF (20 mL) was added BuLi (8.2 mL, 22 mmol, 2.69 M in hexane) under an argon atmosphere at −78 °C. After being stirred at the same temperature for 30 min, the resulting solution was treated with a solution of 2,5-dimethoxybenzaldehyde (**9**) (3.32 g, 20.0 mmol) in anhydrous THF (20 mL). The mixture was warmed to room temperature and stirred for another 2.5 h before being treated with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield 1-(2,5-dimethoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol, which was used for the next reaction without further purification.

To a stirring solution of the crude propargylic alcohol in CH_2Cl_2 (80 mL) was added MnO_2 (20 g). After being stirred at room temperature for 3 h, the reaction mixture was filtered through a Celite pad, which was thoroughly rinsed with CH_2Cl_2. The filtrate was concentrated *in vacuo* to yield the title compound (5.17 g, 19.7 mmol, 99%) as a yellow oil, which was pure enough for analysis. R_f 0.19 (33% EtOAc/hexane). IR ν (neat, cm^{-1}): 2959, 2836, 2151, 1650, 1496, 1464, 1415, 1281, 1228, 1176, 1039, 849, 762. ^1H-NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 3.2 Hz, 1H), 7.09 (dd, *J* = 9.2, 3.2 Hz, 1H), 6.94 (d, *J* = 9.2 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 0.29 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.5, 155.1, 153.7, 127.2, 122.5, 116.3, 114.7, 103.7, 99.4, 57.0, 56.4, 0.00. HRMS (ESI, $[M+H]^+$): calcd for $C_{14}H_{19}O_3Si$, 263.1098; found, 263.1094.

1-(2,5-Dimethoxyphenyl)-2-(naphtho[1,8-*de*][1,3]dioxin-2-ylidene)ethan-1-one (3a): To a stirring solution of TMS-protected ethynyl ketone **10** (528 mg, 2.01 mmol) in anhydrous acetone (7 mL) were added $AgNO_3$ (70.4 mg, 0.414 mmol) and *N*-bromosuccinimide (428 mg, 2.40 mmol) under an argon atmosphere. After being stirred at room temperature for 3 h, the mixture was treated with another portion of *N*-bromosuccinimide (72.9 mg, 0.410 mmol) and stirred for 1 h. Again, another portion of *N*-bromosuccinimide (37.7 mg, 0.212 mmol) was added to the mixture. The mixture was stirred at the same temperature for another 2 h before being filtered through a Celite pad, which was thoroughly rinsed with Et_2O. The filtrate was washed with 20% aqueous $Na_2S_2O_3•5H_2O$ and H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to yield 3-bromo-1-(2,5-dimethoxyphenyl)prop-2-yn-1-one, which was used for the next reaction without further purification.

To a stirring solution of the crude 3-bromo-1-(2,5-dimethoxyphenyl)prop-2-yn-1-one and 1,8-dihydroxynaphthalene (**2**) (313 mg, 1.95 mmol) in anhydrous CH_2Cl_2 (10 mL) was added 1,4-diazabicyclo[2.2.2]octane (DABCO) (222 mg, 1.98 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 4 h, the reaction mixture was diluted with Et_2O. The organic layer was washed with 1 M aqueous HCl, 1 M aqueous NaOH, H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10–33% EtOAc/hexane to yield the title compound (572 mg, 1.64 mmol, 84%) as a dark green oil. R_f 0.19 (33% EtOAc/hexane). IR ν (neat, cm^{-1}): 3003, 2942, 2834, 1668, 1557, 1494, 1415, 1380, 1273, 1221, 1037, 926, 844, 812, 752. ^1H-NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.45 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.44 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.23 (d, *J* = 3.2 Hz, 1H), 7.00–6.96 (m, 3H), 6.91 (d, *J* = 9.0 Hz, 1H), 6.06 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 189.3, 158.2, 153.5, 151.7, 144.3, 143.9, 133.4, 131.6, 127.9, 127.7, 121.8, 121.6, 118.0, 113.9, 113.0, 110.6, 108.3, 107.6, 89.0, 56.4, 55.7. HRMS (ESI, $[M+H]^+$): calcd for $C_{21}H_{17}O_5$, 349.1071; found, 349.1064.

2-(2,5-Dimethoxyphenyl)spiro[benzo[*h*]chromene-4,2'-naphtho[1,8-*de*][1,3]dioxin]-10-ol (12): To a test tube containing 1-(2,5-dimethoxyphenyl)-2-(naphtho[1,8-*de*][1,3]dioxin-2-ylidene)ethan-1-one (**3a**) (20.0 mg, 0.0574 mmol) was added TFA (300 μL) under an argon atmosphere. The resulting mixture was sealed with a screw cap, stirred at 72 °C for 5 h, cooled to room temperature, and then treated with H_2O and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC eluting with 50% EtOAc/hexane to yield the title compound (10.0 mg, 0.0204 mmol, 71% based on dihydroxynaphthalene unit) as a green oil. R_f 0.45 (50% EtOAc/hexane). IR ν (neat, cm^{-1}): 3449, 3056, 3008, 2935, 2835, 1605, 1583, 1497, 1412, 1383, 1270, 1234, 1087, 1058, 912, 822, 755. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 9.10 (s, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.49 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.45 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.89 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 5.87 (s, 1H), 3.85 (s, 3H), 3.69 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 154.3, 153.5, 151.3, 151.0, 147.91, 147.86, 136.9, 134.3, 129.0, 127.6, 125.0, 123.4, 122.3, 120.6, 119.3, 116.6, 115.6, 113.5, 113.0, 112.8, 112.6, 112.5, 109.6, 98.5, 94.4, 56.1, 55.9. LRMS (EI) *m/z* (relative intensity): 491 $[M+1]^+$ (33), 490 $[M]^+$ (100), 348 (30), 162 (26). HRMS (EI, $[M]^+$): calcd for $C_{31}H_{22}O_6$, 490.1416; found, 490.1425.

Methyl 2-(naphtho[1,8-*de*][1,3]dioxin-2-ylidene)acetate (6): To a stirring solution of 1,8-dihydroxynaphthalene (**2**) (1.74 g, 10.9 mmol) and methyl 3-bromopropiolate[32] (2.65 g, 16.3 mmol) in anhydrous CH_2Cl_2 (40 mL) was added DABCO (2.66 g, 21.8 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 3 h, the reaction mixture was treated with 1 M aqueous HCl. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 25% EtOAc/hexane to yield the title compound (2.17 g, 8.96 mmol, 82%) as a white solid. R_f 0.34 (20% EtOAc/hexane). Mp 115–118 °C. IR ν (neat, cm^{-1}): 1721, 1654, 1602, 1419, 1381, 1281, 1248, 1131, 1089, 815, 799, 753. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.45 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.42 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.97 (s, 1H), 3.75 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.2, 158.6, 144.4, 144.1, 133.6, 128.0, 127.8, 121.9, 121.7, 110.6, 108.4, 107.6, 78.2, 50.9. HRMS (ESI, $[M+H]^+$): calcd for $C_{14}H_{11}O_4$, 243.0652; found, 243.0653.

Methyl 2-(2-(2,5-dimethoxyphenyl)naphtho[1,8-*de*][1,3]dioxin-2-yl)acetate (13): To a stirring solution of aluminum chloride (66.1 mg, 0.124 mmol) in 1,4-dimethoxybenzene (0.3 mL) was added acylketene acetal **6** (30.0 mg, 0.0500 mmol) at 65 °C under an argon atmosphere. After being stirred at the same temperature for 2 h, the reaction mixture was cooled to room temperature, diluted with Et_2O, and then treated with 1 M aqueous Rochelle salt. The aqueous layer was extracted with Et_2O twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC eluting with 6% EtOAc/toluene to yield the title compound (21.4 mg, 0.0563 mmol, 56%) as a yellow solid. R_f 0.42 (6% EtOAc/toluene). Mp 136–139 °C. IR ν (neat, cm^{-1}): 2952, 2835, 1742, 1607, 1497, 1414, 1381, 1277, 1227, 1188, 1038, 818, 758. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38–7.32 (m, 4H), 7.05 (d, J = 3.4 Hz, 1H), 7.01–6.96 (m, 2H), 6.75 (d, J = 9.3 Hz, 1H), 6.66 (dd, J = 3.4, 9.3 Hz, 1H), 3.86 (s, 3H), 3.65 (s, 3H), 3.55 (s, 3H), 3.51 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.6, 152.7, 151.5, 147.9, 134.1, 127.2, 127.0, 120.3, 115.25, 115.20, 114.1, 113.5, 108.9, 100.8, 56.5, 55.5, 51.8, 44.0. LRMS (EI) *m/z* (relative intensity): 380 $[M]^+$ (78), 307 (30), 221 (100), 206 (27), 189 (25), 161 (25), 160 (47). HRMS (EI, $[M]^+$): calcd for $C_{16}H_{14}O_4$, 380.1260; found, 380.1253.

2-(2-(2,5-Dimethoxyphenyl)naphtho[1,8-*de*][1,3]dioxin-2-yl)acetic acid (14): To a stirring solution of ester **13** (41.3 mg, 0.109 mmol) in MeOH (0.3 mL) was added 2 M aqueous NaOH (0.6 mL) under an argon atmosphere. After being stirred at 80 °C for 2 h, the mixture was cooled to room temperature and acidified with 1 M aqueous HCl. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield the title compound (37.3 mg, 0.102 mmol, 93%) as a white solid, which was pure enough for analysis. R_f 0.33 (50% EtOAc/hexane). Mp 173–176 °C. IR ν (neat, cm^{-1}): 1710, 1601, 1495, 1411, 1376, 1270, 1220, 1187, 1171, 1036, 815, 768. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.47 (br-s, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.36 (dd, J = 8.3, 7.8 Hz, 2H), 7.03 (d, J = 2.9 Hz, 1H), 7.01 (d, J = 7.8 Hz, 2H), 6.75 (d, J = 9.0 Hz, 1H), 6.67 (dd, J = 9.0, 2.9 Hz, 1H), 3.86 (s, 3H), 3.55 (s, 3H), 3.54 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 152.5, 151.4, 147.7, 133.9, 127.1, 126.8, 120.2, 115.1, 114.0, 113.4, 108.8, 100.7, 56.3, 55.3, 43.9 (One signal is missing due to overlap). HRMS (ESI, $[M+Na]^+$): calcd for $C_{21}H_{18}O_6Na$, 389.0996; found, 389.0995.

4,7-Dimethoxy-3-(phenylsulfonyl)-1*H*-inden-1-one (8a): To a stirring solution of 4,7-dimethoxy-3-(phenylthio)-1*H*-inden-1-one[26] (**15**) (15.8 mg, 0.0530 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *m*CPBA (13.1 mg, 0.0531 mmol, containing *ca*. 30% H_2O) at 0 °C under an argon atmosphere. After being stirred at the same temperature for 1 h, the mixture was treated with another portion of *m*CPBA (13.1 mg, 0.0531 mmol) and stirred for 30 min. Again, another portion of *m*CPBA (13.0 mg, 0.0530 mmol) was added to the mixture. The mixture was stirred at room temperature for another 30 min before being treated with 1 M aqueous $Na_2S_2O_3$. The aqueous layer was extracted with

CH_2Cl_2 twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield the title compound (37.3 mg, 0.102 mmol, 93%) as a bright red solid, which was pure enough for analysis. R_f 0.28 (50% EtOAc/hexane). Mp 225–228 °C. IR ν (neat, cm^{-1}): 1697, 1489, 1279, 1146, 1057, 801, 728, 603. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 7.1 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.58 (dd, J = 7.5, 7.1 Hz, 2H), 7.01 (d, J = 9.3 Hz, 1H), 6.92 (d, J = 9.3 Hz, 1H), 6.14 (s, 1H), 3.92 (s, 3H), 3.75 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 191.4, 158.3, 152.7, 147.5, 138.8, 133.9, 130.2, 129.0, 128.3, 126.2, 123.2, 118.0, 116.8, 56.6, 56.4. LRMS (EI) *m/z* (relative intensity): 331 $[M+1]^+$ (20), 330 $[M]^+$ (100), 189 (36), 175 (15), 161 (27), 159 (23), 131 (15), 125 (21). HRMS (EI, $[M]^+$): calcd for $C_{17}H_{14}O_5S$, 330.0562; found, 330.0528.

Bromination of 4,7-dimethoxy-2,3-dihydro-1*H*-inden-1-one (16): To a stirring solution of 4,7-dimethoxy-2,3-dihydro-1*H*-inden-1-one (**16**) (22.7 mg, 0.118 mmol) in CCl_4 (3 mL) were added *N*-bromosuccinimide (44.1 mg, 0.248 mmol) and 2,2'-azobis(isobutyronitrile) (1.9 mg, 0.012 mmol) under an argon atmosphere. The resulting solution was refluxed for 5 h and then cooled to room temperature. Triethylamine (50 μL, 0.361 mmol) was added to the solution and the resulting mixture was stirred at room temperature. After being stirred for another 11 h, the mixture was treated with 1 M aqueous $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC eluting with 40% EtOAc/hexane to yield 3-bromo-4,7-dimethoxy-1*H*-inden-1-one (**8b**) (11.0 mg, 0.0409 mmol, 35%), 2,3-dibromo-4,7-dimethoxy-1*H*-inden-1-one (**17**) (2.1 mg, 0.0060 mmol, 5%) and 4,7-dimethoxy-1*H*-inden-1-one (**18**) (2.6 mg, 0.014 mmol, 12%).

3-Bromo-4,7-dimethoxy-1*H*-inden-1-one (8b): Bright orange solid. R_f 0.59 (50% EtOAc/hexane). IR ν (neat, cm^{-1}): 2918, 1712, 1587, 1496, 1440, 1275, 1028, 772. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.03 (d, J = 9.3 Hz, 1H), 6.90 (d, J = 9.3 Hz, 1H), 6.05 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.3, 150.4, 148.2, 142.7, 127.8, 127.7, 122.2, 117.7, 116.8, 56.6, 56.2. HRMS (ESI, $[M+Na]^+$): calcd for $C_{11}H_{10}O_3Br$, 268.9808; found, 268.9807.

2,3-Dibromo-4,7-dimethoxy-1*H*-inden-1-one (17): Bright red solid. R_f 0.35 (50% EtOAc/hexane). Mp 162–167 °C. IR ν (neat, cm^{-1}): 2940, 2839, 1712, 1544, 1493, 1275, 1175, 1053, 967, 926, 796. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.03 (d, J = 9.4 Hz, 1H), 6.86 (d, J = 9.4 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 184.4, 151.2, 147.5, 140.3, 127.4, 123.1, 122.3, 117.4, 115.2, 56.7, 56.4. LRMS (EI) *m/z* (relative intensity): 350 $[M+4]^+$ (51), 348 $[M+2]^+$ (100), 346 $[M]^+$ (50), 319 (34), 269 (82), 267 (86), 241 (50), 239 (86), 237 (35), 209 (38), 149 (44), 102 (23). HRMS (EI, $[M]^+$): calcd for $C_{11}H_8O_3Br_2$, 345.8840; found, 345.8830.

4,7-Dimethoxy-1*H*-inden-1-one (18): Yellow solid. R_f 0.47 (50% EtOAc/hexane). Mp 72–76 °C. IR ν (neat, cm^{-1}): 2941, 2838, 1699, 1592, 1491, 1462, 1439, 1265, 1175, 1089, 1049, 1020, 948, 825. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 5.9 Hz, 1H), 6.94 (d, *J* = 9.3 Hz, 1H), 6.80 (d, *J* = 9.3 Hz, 1H), 5.74 (d, *J* = 5.9 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 196.8, 151.2, 147.0, 144.5, 132.4, 125.8, 120.8, 116.2, 115.9, 56.4, 56.2. LRMS (EI) *m/z* (relative intensity): 190 [M]$^+$ (100), 161 (49), 147 (27), 131 (24), 119 (29), 91 (21). HRMS (EI, [M]$^+$): calcd for $C_{11}H_{10}O_3$, 190.0630; found, 190.0634.

1-Oxo-2,3-dihydro-1*H*-indene-4,7-diyl diacetate (19): To a stirring solution of **16** (165 mg, 0.858 mmol) in anhydrous CH_2Cl_2 (2 mL) was added boron tribromide (2.6 mL, 2.6 mmol, 1 M solution in CH_2Cl_2) at −78 °C under an argon atmosphere. The resulting mixture was allowed to warm to room temperature. After being stirred for 8 h, the reaction mixture was treated with MeOH. The resulting mixture was stirred for another 1 h at room temperature and then concentrated *in vacuo* to yield 4,7-dihydroxy-2,3-dihydro-1*H*-inden-1-one as a pale brown solid, which was used for the next reaction without further purification. R_f 0.25 (2% MeOH/$CHCl_3$). Mp 168–172 °C. IR ν (neat, cm^{-1}): 3203, 1653, 1600, 1476, 1277, 937, 823, 772, 747, 669. ^{1}H-NMR (400 MHz, CD_3OD): δ 6.81 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 2.87 (t, *J* = 5.7 Hz, 2H), 2.54 (t, *J* = 5.7 Hz, 2H). ^{13}C-NMR (100 MHz, CD_3OD): δ 211.0, 151.2, 148.3, 141.9, 124.6, 124.3, 115.1, 37.0, 23.5. LRMS (EI) *m/z* (relative intensity): 165 [M+1]$^+$ (11), 164 [M]$^+$ (100), 136 (17). HRMS (EI, [M]$^+$): calcd for $C_9H_8O_3$, 164.0473; found, 164.0466.
To a stirring solution of the above dihydroxyindenone in anhydrous CH_2Cl_2 (3 mL) were added acetic anhydride (487 μL, 5.15 mmol), triethylamine (1.07 mL, 7.72 mmol) and DMAP (5.2 mg, 0.043 mmol) under an argon atmosphere. After being stirred at room temperature for 11 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 25% EtOAc/hexane to yield the title compound (189 mg, 0.761 mmol, 89% for 2 steps) as a white solid. R_f 0.25 (2% MeOH/$CHCl_3$). Mp 106–110 °C. IR ν (neat, cm^{-1}): 1767, 1715, 1614, 1485, 1369, 1183, 1014, 894, 772. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 2.98 (t, *J* = 6.1 Hz, 2H), 2.67 (t, *J* = 6.1 Hz, 2H), 2.38 (s, 3H), 2.35 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 202.7, 169.1, 168.4, 148.1, 145.7, 145.0, 129.9, 128.5, 121.8, 36.3, 22.5, 20.70, 20.66. HRMS (ESI, [M+H]$^+$): calcd for $C_{13}H_{13}O_5$, 249.0757; found, 249.0759.

3-Bromo-1-oxo-1*H*-indene-4,7-diyl diacetate (8c): To a stirring solution of **19** (18.9 mg, 0.0761 mmol) in CCl_4 (2 mL) were added *N*-bromosuccinimide (28.5 mg, 0.160 mmol) and 2,2'-azobis(isobutyronitrile) (1.3 mg, 0.0079 mmol) under an argon atmosphere. The resulting solution was refluxed for 5 h and then cooled to room temperature. Triethylamine (30 μL, 0.22 mmol) was added to the mixture and the resulting mixture was stirred at room temperature. After being stirred for another 5 h, the mixture was treated with 1 M aqueous $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC eluting with 50% EtOAc/hexane to yield the title compound (11.5 mg, 0.0354 mmol, 47%) as a yellow solid. R_f 0.60 (50% EtOAc/hexane). Mp 133–135 °C. IR ν (neat, cm^{-1}): 1770, 1709, 1539, 1473, 1369, 1180, 1090, 1016, 901, 846. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 9.3 Hz, 1H), 7.01 (d, J = 9.3 Hz, 1H), 6.21 (s, 1H), 2.38 (s, 3H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 190.0, 169.2, 168.3, 143.4, 142.8, 141.8, 132.4, 131.3, 129.6, 127.1, 122.0, 21.1, 20.7. LRMS (EI) *m/z* (relative intensity): 326 $[M+2]^+$ (2), 324 $[M]^+$ (2), 284 (19), 282 (19), 242 (99), 240 (100), 162 (38), 161 (74). HRMS (EI, $[M]^+$): calcd for $C_{13}H_9O_5Br$, 323.9633; found, 323.9633.

4,7-Dimethoxyspiro[indene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-3(2*H*)-one (11a) (Table 1, Entry 2): To a stirring solution of 1,8-dihydroxynaphthalene (**2**) (7.5 mg, 0.047 mmol) and 3-bromo-4,7-dimethoxy-*1H*-inden-1-one (**8b**) (15.2 mg, 0.0565 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added DABCO (11.5 mg, 0.0941 mmol) at 0 °C under an argon atmosphere. After being stirred at room temperature for 1.5 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC eluting with 20% EtOAc/hexane to yield the title compound (8.2 mg, 0.024 mmol, 50%) as a yellow solid. R_f 0.44 (10% EtOAc/toluene). Mp 230–240 °C (decomp). IR ν (neat, cm^{-1}): 3015, 1723, 1608, 1500, 1411, 1379, 1296, 1271, 1216, 1060, 1028, 757. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.3 Hz, 2H), 7.44 (dd, J = 8.3, 7.3 Hz, 2H), 7.27 (d, J = 8.9 Hz, 1H), 7.07 (d, J = 8.9 Hz, 1H), 6.97 (d, J = 7.3 Hz, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 2.91 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 196.9, 151.1, 151.0, 148.5, 144.8, 134.5, 127.3, 121.0, 120.5, 114.8, 114.2, 109.8, 103.7, 56.8, 56.3, 49.6 (One signal is missing due to overlap). HRMS (ESI, $[M+H]^+$): calcd for $C_{21}H_{17}O_5$, 349.1071; found, 349.1069.

2-Bromo-4,7-dimethoxyspiro[indene-1,2'-naphtho[1,8-*de*][1,3]dioxin]-3(2*H*)-one (20) (Table 1, Entry 3): By following the procedure described above for **11a**, the title compound (10.5 mg, 0.0247 mmol, 62%, yellow solid) was obtained from 1,8-dihydroxynaphthalene (**2**) (6.4 mg, 0.040 mmol), 2,3-dibromo-4,7-dimethoxy-1*H*-inden-1-one (**17**) (16.8 mg, 0.0483 mmol) and DABCO (9.8 mg, 0.080 mmol) through preparative TLC eluting with 20% EtOAc/hexane. R_f 0.30 (10% EtOAc/toluene). Mp 215–225 °C (decomp). IR ν (neat, cm^{-1}): 3016, 1726, 1608, 1501, 1412, 1378, 1282, 1221, 1060, 819, 770. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 8.5, 7.5

Hz, 1H), 7.42 (dd, J = 8.5, 7.5 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 4.54 (s, 1H), 3.99 (s, 3H), 3.89 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 191.4, 152.2, 151.3, 147.5, 147.3, 134.4, 134.1, 127.6, 127.1, 123.3, 121.6, 121.5, 121.0, 115.4, 113.6, 110.6, 109.6, 101.6, 56.8, 56.4, 52.7. HRMS (ESI, [M+Na]$^+$): calcd for $C_{21}H_{15}O_5BrNa$, 448.9995; found, 448.9991.

3-Oxo-2,3-dihydrospiro[indene-1,2'-naphtho[1,8-*de*][1,3]dioxine]-4,7-diyl diacetate (11b): By following the procedure described above for **11a**, the title compound (4.2 mg, 0.010 mmol, 58%, yellow oil) was obtained from 1,8-dihydroxynaphthalene (**2**) (2.9 mg, 0.018 mmol), 3-bromo-1-oxo-1*H*-indene-4,7-diyl diacetate (**8c**) (7.0 mg, 0.022 mmol) and DABCO (4.0 mg, 0.036 mmol) through preparative TLC eluting with 13% EtOAc/hexane. R_f 0.37 (10% EtOAc/toluene). IR ν (neat, cm^{-1}): 3024, 1773, 1732, 1609, 1490, 1411, 1377, 1274, 1180, 1012, 923, 820, 757. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.46 (dd, J = 7.8, 7.3 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 7.3 Hz, 2H), 2.91 (s, 2H), 2.40 (s, 3H), 2.14 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 195.1, 169.2, 168.7, 147.9, 145.7, 144.3, 140.7, 134.5, 132.0, 130.1, 127.4, 126.4, 121.4, 113.9, 109.9, 102.8, 49.2, 20.7 (One signal is missing due to overlap). LRMS (EI) *m/z* (relative intensity): 404 [M]$^+$ (29), 362 (14), 321 (24), 320 (100), 303 (31), 149 (17), 85 (10), 71 (13), 57 (13). HRMS (EI, [M]$^+$): calcd for $C_{23}H_{16}O_7$, 404.0896; found, 404.0881.

Debromination of 20: To a stirring solution of **20** (10.8 mg, 0.0253 mmol) in acetic acid (0.5 mL) was added activated zinc powder (15.0 mg, 0.229 mmol) under an argon atmosphere. The resulting suspension was stirred at 100 °C for 9 h, cooled to room temperature, and then diluted with EtOAc. The resulting mixture was filtered through a Celite pad. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield **11a** (8.2 mg, 0.024 mmol, 93%) as a yellow oil, which was pure enough for analysis. Spectral data of the compound **11a** were in good agreement with that obtained by the double oxa-Michael addition of 1,8-dihdroxynaphthalene to 3-bromo-4,7-dimethoxy-1*H*-inden-1-one (**8b**), which was indicated above.

Palmarumycin C_6 (1): To a stirring solution of **11b** (4.0 mg, 0.0099 mmol) in MeOH (300 μL) was added 6 M aqueous HCl (60 μL) under an argon atmosphere. After being refluxed for 3 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC eluting with 25% EtOAc/toluene to yield the title compound (3.4 mg, 0.011 mmol, quant.) as a yellow oil. R_f 0.41 (25% EtOAc/toluene). IR ν (neat, cm^{-1}): 3236, 2925, 1667, 1602, 1509, 1477, 1413, 1381, 1336, 1303, 1195, 1108, 1028, 993, 895, 822, 797, 752, 688. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.83 (br-s, 1H), 9.56 (br-s,

1H), 7.61 (d, J = 8.3 Hz, 2H), 7.50 (dd, J = 8.3, 7.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 8.6 Hz, 1H), 2.76 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 196.8, 148.2, 147.4, 134.0, 131.7, 127.5, 125.7, 123.0, 120.6, 120.4, 113.5, 109.5, 103.4, 49.0 (One signal is missing due to overlap). HRMS (ESI, $[M+H]^+$): calcd for $C_{19}H_{13}O_5$, 321.0757; found, 321.0751.
Spectral data of synthesized **1** were in good agreement with that reported by Krohn *et al*.[2]

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