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Total Synthesis of Unsymmetrical Benzils, Scandione and Calophione A

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The synthesis of the title unsymmetrical benzils, scandione and calophione A, is described. The key processes involve intramolecular cyclization reaction of the carbanion at the benzylic position of the arylbenzyl ether to the adjacent ester group followed by oxidation. The palladium(II)-catalyzed oxidative cyclization was also used to establish the benzofuran unit of calophione A.

Introduction

2-Hydroxybenzil **1** is the core structure of a small family of natural products isolated from the Leguminosae family of plants.[1] Their structures typically consist of a 1,2-diarylethane-1,2-dione framework, which often occurs concurrently with other flavanoids as common constituents in this plant family (Figure 1). Licoagrodione (**2**), isolated from the Chinese herb *Glycyrrhiza glabra* (licorice), was found to exhibit antimicrobial activity.[2] Scandione (**3**) was isolated from the stem of a Thai medicinal plant, *Derris scandens*.[3] Calophione A (**4**), isolated from the roots of *Tephrosia calophylla*, was tested with mouse macrophage cells (RAW) and colon cancer cells HT-29 and showed significant cytotoxicity, with IC_{50} of 5.00 (RAW) and 2.9 μM (HT-29).[4] Recently, tenuifodione (**5**) was isolated from the whole plant of *Iris tenuifolia* Pall (Iridaceae).[5] (Dimethylethylamino)ethanediones, saxoguattine (**6**)[6] and cryptopleurospermine (**7**),[7] are widely distributed in the Annonaceae, Lauraceae, and Papaveraceae families, and have been classified as a group of oxoprotopine alkaloids that also show antibacterial activity.

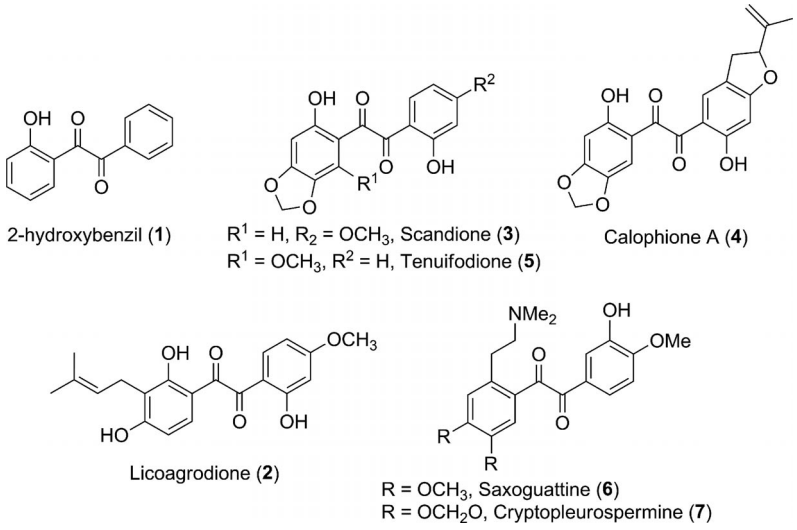

Figure 1. Selected unsymmetrical bioactive benzils.

In our ongoing research on organolithiation,[8,9] we previously reported the synthesis of unsymmetrical 2-hydroxybenzils by using intramolecular cyclization of the carbanion of benzylic ether to the adjacent *ortho*-substituted ester group followed by oxidation with dioxirane.[10]

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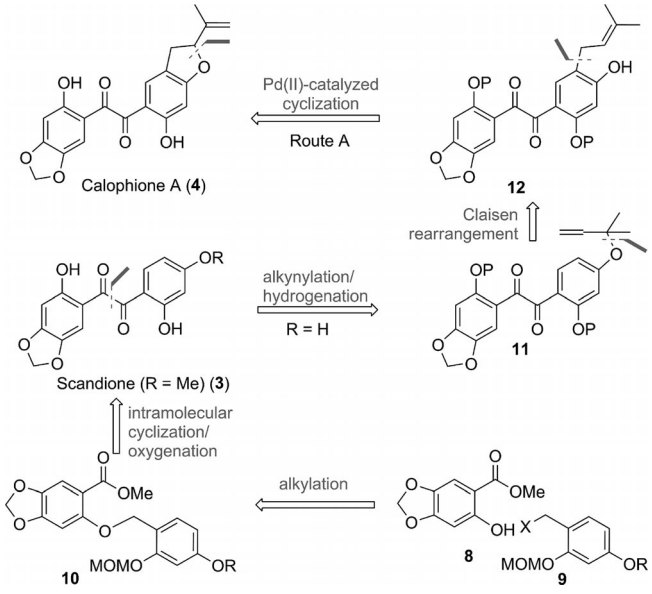
Licoagrodione (**2**) was then synthesized by using the Claisen rearrangement of the isoprene unit under neutral conditions and microwave irradiation.[10] Herein, by using our developed method and palladium(II)-catalyzed oxidative cyclization, we report a convenient convergent synthetic route to scandione (**3**) and calophione A (**4**).[11] The antibacterial activity, antioxidant activity, and the results of cytotoxicity testing of the unsymmetrical benzils are also reported.

Results and Discussion

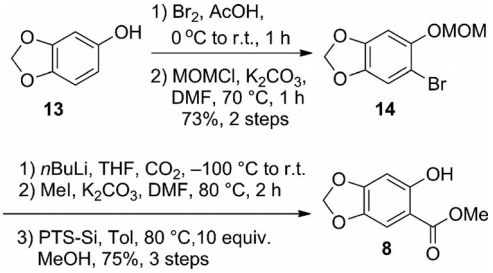
Our synthetic plan to construct natural unsymmetrical benzils **3** and **4** involved intramolecular cyclization of the carbanion at the benzylic position of the arylbenzyl ether to the adjacent ester group, followed by oxidation to afford the target compound **3** as shown in Scheme 1. Benzylation of methyl salicylate derivative **8** with benzyl halides **9** could afford the key intermediates, aryl benzyl ethers **10**. The "C-5" isoprene unit could be introduced into the core structure through alkynylation followed by hydrogenation to afford the alkenyl ether **11**. Claisen rearrangement of **11** would then give the prenylated 2-hydroxybenzil **12**, which could undergo further cyclization by using palladium(II)-catalyzed dihydrofuran formation to afford calophione A (**4**).



Scheme 1. Retrosynthetic plan for the synthesis of scandione (**3**) and calophione A (**4**).

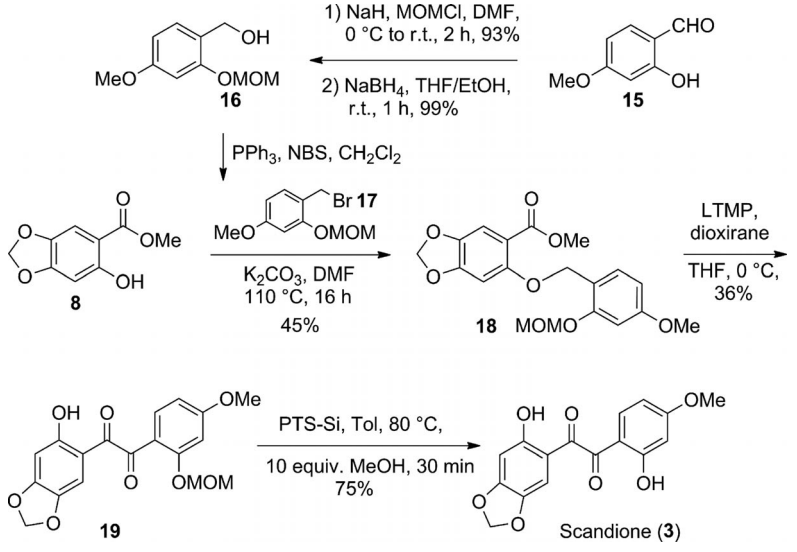
Synthesis of Scandione (3)

To synthesize scandione (**3**) and calophione A (**4**), the corresponding methyl salicylate **8** was prepared in five steps from sesamol **13**. Bromination and MOM protection gave the corresponding bromo compound **14** in 73% yield (two steps). The key step was lithium–bromine exchange followed by carboxylation of **14** to furnish the carboxylic acid moiety, which underwent further methylation with methyl iodide and MOM deprotection with *p*TsOH immobilized on silica (PTS-Si) in toluene and a small amount of methanol at 80 °C.[12] Methyl salicylate derivative **8** was obtained in 75% yield (three steps) as shown in Scheme 2.



Scheme 2. Preparation of methyl salicylate (**8**).

Benzylation of methyl salicylate **8** with benzyl bromide **17**, which was prepared in three steps from 2-hydroxy-4-methoxybenzaldehyde (**15**), afforded *O*-benzyl ether **18** in



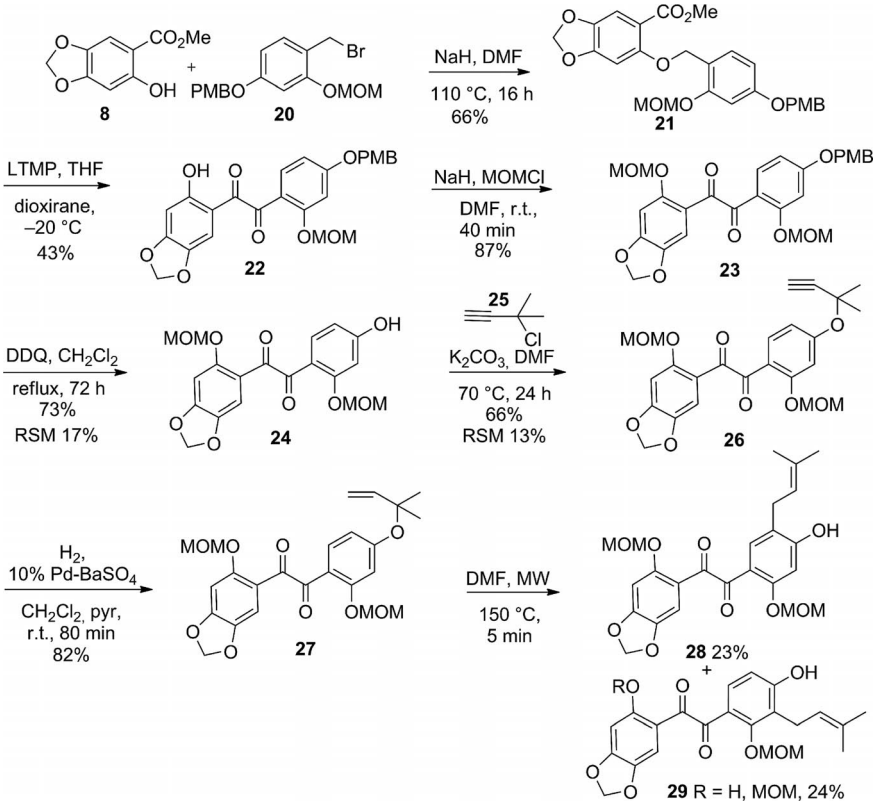
Scheme 3. Synthesis of scandione (**3**).

45% yield. The corresponding benzil **19** was obtained in moderate yield (36%) by using our developed method.[10] The key reaction involved intramolecular cyclization of the carbanion at the benzylic position of the arylbenzyl ether to the adjacent methyl ester of methyl *O*-benzyl salicylate **18** followed by oxygenation with dioxirane. The carbanion was generated upon addition of 4.5 equiv. of lithium tetramethylpiperidine (LTMP) in tetrahydrofuran (THF). Deprotection with PTS-Si in toluene[12] and a small amount of methanol at 80 °C for 30 min gave scandione (**3**) in 75% yield, as shown in Scheme 3. The overall yield of the synthesis of compound **3** was 5%, which was obtained in eight steps from two readily available precursors.

Synthesis of Calophione A (4); Route A

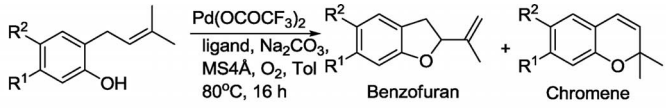
Having successfully established the synthesis of scandione (**3**), we sought to develop the synthesis of calophione A (**4**) via the same benzil skeleton and further introduction of a "C-5" dimethylallyl group equivalent. The palladium(II)-catalyzed oxidative cyclization could then establish the benzofuran moiety of compound **4**.[11]

Benzylation of methyl salicylate **8** with benzyl bromide **20**[13] afforded *O*-benzyl ether **21** in moderate yield (66%) as shown in Scheme 4. The unsymmetrical benzil **22** was obtained in 43% yield by using the intramolecular cyclization of the carbanion at the benzylic ether position of methyl *O*-benzyl salicylate **21** with 4.5 equiv. LTMP in THF followed by oxygenation with dioxirane.[10] The protection of a hydroxyl group with chloromethyl methyl ether (MOMCl) gave **23** in good yield. Subsequent deprotection of the *p*-methoxybenzyl (PMB) group by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) released the strategic phenolic group, whereas the other two phenolic groups were protected as shown in **24** in good yield. The free phenolic group so obtained could then be used as a handle for further modification. The "C-5" dimethylallyl group equivalent was introduced onto the molecule as the corresponding alkynyl ether of the phenolic group by reacting **24** with 3-chloro-3-methyl-1-butyne **25** in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF) to afford the corresponding alkyne **26** in 66% yield.[14] Lindlar's reduction of alkyne **26** gave alkene **27** in good yield.[15] The Claisen rearrangement was then performed to prepare the corresponding C-5 isoprene diketone **28**. However, a mixture of isomeric products **28** and **29** was obtained in a 1:1 ratio. The mixture was easily purified by PTLC to obtain compound **28** for further study. Dihydrobenzofuran formation of the corresponding isoprene **28** was then studied by using 5 mol-% $Pd(TFA)_2$ and 20 mol-% pyridine as ligand in the presence of Na_2CO_3 and molecular sieves (MS, 4 Å) in toluene at 80 °C.[11d] ^{1}H NMR spectroscopic analysis of the mixture showed key peaks of two isomers, dihydrobenzofuran **30** and chromene **31**. The former compound was obtained in poor yield (16%) after chromatography, and its deprotection with PTS-Si in toluene and a small amount of methanol at 80 °C for 1 h gave calophione A (**4**) in 44% yield.



Scheme 4. Synthesis of calophione A (**4**); Route A.

Table 1. Screening of the Pd^{II}-catalyzed oxidative cyclization.



Entry	Condition	Benzofuran, yield [%][a]	Chromene, yield [%][a]
1	A	**30**: 7[c]	**31**: trace
2	B	**30**: 16	**31**: trace
3	B	**32**: 47	**33**: trace
4	B	**34**: 23	**35**: 3
5	B	**36**: 49	**37**: 11

[a] Isolated yields of pure product after PTLC on silica. [b] Conditions A: $Pd(TFA)_2$ (5 mol-%), sparteine sulfate (40 mol-%); Conditions B: $Pd(TFA)_2$ (5–20 mol-%), pyridine (20–40 mol-%). [c] Recovered starting materials 6%.

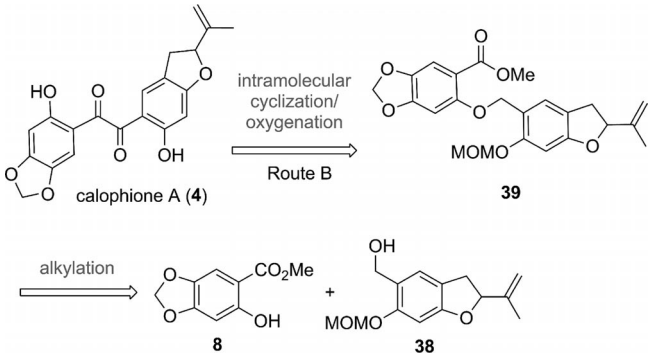
The overall yield of the synthesis of **4** was 0.1% in fourteen steps from commercially available **13**.

Due to the low yield of the synthesis of **30**, we then re-examined the palladium(II)-catalyzed oxidative cyclization to construct the dihydrobenzofuran as shown in Table 1. 2′-Hydroxyarylbutenes were studied to form the dihydrobenzofuran system based on the conditions previously reported by Stoltz et al.[11d] A mixture of products resulting from competitive cyclizations, dihydrobenzofuran and chromene, was obtained in moderate yields. The use of 10 mol-% $Pd(TFA)_2$ and 40 mol-% pyridine as ligand in the presence of 2 equiv. Na_2CO_3 and 500 mg/mmol MS (4 Å) in toluene at 80 °C under an oxygen atmosphere gave the dihydrobenzofuran as a major cyclization product. As shown in Table 1, dihydrobenzofuran **36** was successfully prepared by using the palladium(II)-catalyzed oxidative cyclization. These findings prompted us to investigate an alternative route for the synthesis of the target calophione A (**4**).

Synthesis of Calophione A (4); Route B

The retrosynthetic analysis of calophione A (**4**) through Route B is shown in Scheme 5. Compound **4** could be assembled by two segments, methyl salicyalte derivative **8** and dihydrofuran **38**, to give the key intermediate, alkylation product **39**. The intramolecular cyclization followed by oxygenation could then give the target **4**.

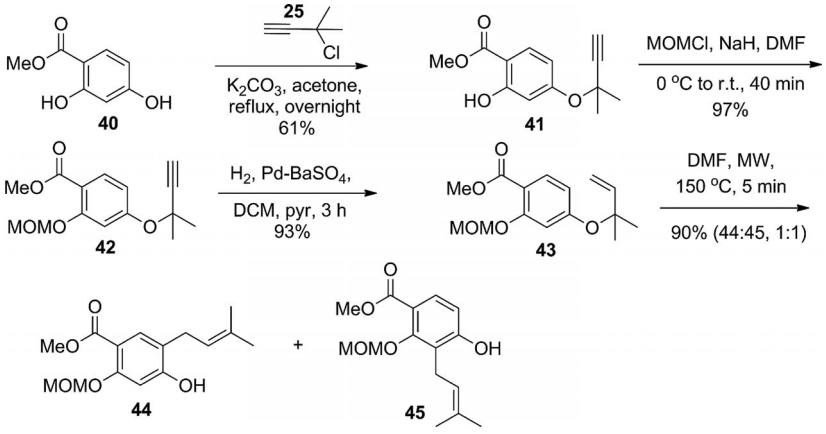
The synthesis of dihydrofuran **36** was achieved in five steps from methyl 2,4-dihydroxy benzoate (**40**). The selective alkynylation at the hydroxyl group *para* to the ester group of **40** with 3-chloro-3-methyl-1-butyne (**25**) in the presence of K_2CO_3 in acetone gave alkyne **41** in 61% yield. Protection of the *ortho*-hydroxyl group with MOMCl in the presence of NaH in DMF gave alkyne **42** in 97% yield.



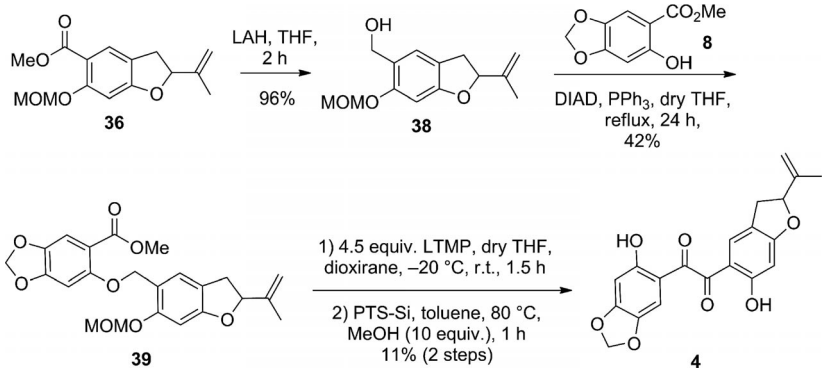
Scheme 5. Retrosynthetic plan for the synthesis of calophione A (**4**).

Lindlar's reduction of alkyne **42** gave alkene **43** in 93% yield. Claisen rearrangement of alkene **43** in DMF with microwave irradiation gave a mixture of alkenes **44** and **45** in very good yield in a 1:1 ratio, as shown in Scheme 6. Compound **44** was then cyclized to give dihydrobenzofuran **36** by using 10 mol-% $Pd(TFA)_2$ and 40 mol-% pyridine as ligand in the presence of Na_2CO_3 and MS4 Å in toluene at 80 °C under an oxygen atmosphere overnight, giving **36** in 49% yield (Table 1, entry 5).

To synthesize the target compound **4**, dihydrobenzofuran **36** was then reduced with LAH in THF to give benzyl alcohol **38** in excellent yield (Scheme 7). Mitsunobu reaction of **8** and **38** gave the corresponding methyl *O*-benzyl salicylate **39** in moderate yield. Calophione A (**4**) was obtained through intramolecular cyclization of the anion of the benzylic ether of **39** as described previously, followed by oxygenation with dioxirane[10] and deprotection with PTS-Si in toluene and a small amount of methanol at 80 °C for 1 h to give **4** in low yield. This low yield could be due to competing deprotonation at the undesirable allylic position,



Scheme 6. Synthesis of compound **44**.



Scheme 7. Synthesis of calophione A (**4**).

which could lead to the unidentified products. The overall yield of the synthesis of calophione A (**4**) was 0.54% in nine steps from commercially available compound **40**.

The ^{1}H and ^{13}C NMR spectroscopic data of the synthetic scandione (**3**) and calophione A (**4**) were identical with those of the natural products (see the Supporting Information).[3,4]

Antibacterial Activity

A panel of four bacterial strains was used to evaluate antimicrobial activity of unsymmetrical benzils **1**–**4** by using a disc diffusion susceptibility test in accordance with NCCLS Performance Standards (Table 2).[16] The test organisms were *Escherichia coli* (TISTR 887, ATCC 25922), *Staphylococcus aureus* (TISTR517, ATCC 25923), *Pseudomonas aeruginosa* (TISTR 1467, ATCC 27853), and *Salmonella typhimurium* (TISTR 292, ATCC 13311). Pure cultures were selected and transferred from an agar plate culture into a tube containing saline broth (3–5 mL). The broth cultures were adjusted to match the turbidity of the 0.5 McFarland standard. Adjusted inocolumn suspensions were swabbed uniformly onto the dried surface of a Mueller–Hinton agar (MHA) plate.

Table 2. Antibacterial activities of synthetic benzils **1**–**4** based on NCCLS performance standards for antimicrobial disk susceptibility tests.[a]

Entry	Compounds	Zone of inhibition [mm][b]			
		E. coli	*S. aureus*	*P. aeruginosa*	*S. typhimurium*
1	**1**	–	8	–	–
2	**2**	–	11	–	–
3	**3**	–	–	–	–
4	**4**	–	–	–	–
5	gentamicin	24	23	20	28
6	chloramphenicol	26	23	–[c]	32

[a] A concentration of 40 μg/disc was used for **1**–**4**, 10 μg/disc for gentamicin, and 30 μg/disc for chloramphenicol; DMSO was used as negative control. [b] Results reported are mean values from two replicate experiments. [c] *P. aeruginosa* has resistance against chloramphenicol.

Compounds **1**–**4**, dissolved in dimethyl sulfoxide (DMSO), were prepared as 2 μg/mL samples (40 mg/disc) and loaded on 6 mm sterile discs. The loaded disc was placed onto the surface of the inoculated agar plate and the diameters of zones of complete inhibition were measured (mm), after incubation at 35 °C for 18 h. Gentamycin (OXOID®) and chloramphenicol (OXOID®) were used as the positive control drugs.

The antimicrobial result showed that compounds **1** and **2** have positive action against gram-positive bacteria, *S. aureus*, at 40 μg/disc concentration (Table 2).

Cancer Chemoprevention Activity[17]

The radical scavenging, antioxidant, and aromatase inhibitory activities of unsymmetrical benzils **1**–**4** were also evaluated as shown in Table 3. Licoagrodione (**2**) showed cytotoxicity against HL-60 with an IC_{50} value of 41.3 μM.[18] Compound **2** inhibited aromatase activity with an IC_{50} value of 16.5 μM.[19] Compounds **2**–**4** exhibited potent antioxidant activities in the oxygen radical absorbance capacity (ORAC) assay, with 25.2, 46.1, and 20.3 ORAC units, respectively, whereas their core structure **1** showed very weak activity.[20]

Table 3. Radical scavenging, antioxidant, and aromatase inhibitory activities of unsymmetrical benzils **1**–**4**.[a]

Benzil	IC_{50} [μM]				ORAC[b]
	DPPH	HL-60[18]	XXO	AIA	
1	–	–	–	–	0.6
2	–	41.3	–	16.5	25.2
3	–	–	–	–	46.1
4	–	–	–	–	20.3

[a] Inactive compounds are indicated as a dash. Positive controls for each assay were as follows: DPPH: ascorbic acid (IC_{50} = 21.2 μM); XXO: superoxide dismutase (scavenging 100% of the radical); IXO: allopurinol (IC_{50} = 3.0 μM); aromatase inhibition: ketoconazole (IC_{50} = 2.4 μM). [b] The results are expressed as ORAC units: 1 ORAC unit equals the net protection of β-phycoerythrin produced by 1 μM of Trolox.

Cytotoxic Activity

Calophione A (**4**) was previously reported to exhibit cytotoxicity against mouse macrophage cells (RAW) and colon cancer cells HT-29.[4] Unsymmetrical benzils **1**–**4** were thus evaluated for cytotoxicity against a panel of four human tumor cell lines; cholangiocarcinoma HUCCA-1, lung carcinoma A549, hepatoblastoma HepG2, and T-lymphoblast (acute lymphoblastic leukemia) MOLT-3, by using MTT and XTT assays depending on the cell-line types, as shown in Table 4.[21] The results showed that Licoagrodione (**2**) demonstrated the most potent IC_{50} values for all cancer cell lines tested. Compound **2** was active against T-lymphoblast (acute lymphoblastic leukemia) MOLT-3 in the micromolar range (IC_{50} = 39.3 μM).

Table 4. Cytotoxic activities of synthetic benzils **1**–**4** in MTT and XTT assays.[a]

Entry	Compounds	IC_{50} [μM]			
		HuCCA-1[b,f]	A549[c,f]	HepG2[d,f]	MOLT-3[e,g]
1	**1**	inactive	inactive	inactive	136.9
2	**2**	120.8	101.1	63.3	39.3
3	**3**	inactive	inactive	inactive	82.9
4	**4**	123.6	123.3	107.3	68.3
5	etoposide	ND	ND	29.8	0.047
6	doxorubicin	0.83	0.63	0.57	ND

[a] Prepared as DMSO solution (10 mg/mL); the inhibitory concentration of a compound in μM necessary to achieve 50% growth inhibition (IC_{50}). Results obtained are mean values from three replicate experiments; n.d.: not determined. [b] HuCCA-1: cholangiocarcinoma. [c] A549: Lung Carcinoma. [d] HepG2: hepatoblastoma. [e] MOLT-3: T-lymphoblast (acute lymphoblastic leukemia). [f] MTT assay. [g] XTT assay.

Conclusions

We have reported the total synthesis of two natural unsymmetrical benzils, scandione (**3**) and calophione A (**4**). The key reaction involved intramolecular cyclization of the carbanion of the benzylic ether of methyl *O*-benzyl salicylate to the adjacent ester group followed by oxygenation with dioxirane. The Pd^{II}-catalyzed oxidative cyclization of dihydrobenzofuran was also investigated. Scandione (**3**) was synthesized in 5% overall yield in eight steps, whereas calophione A (**4**) was prepared in 0.1% overall yield in fourteen steps through Route A and 0.54% overall yield in nine steps through Route B. Benzils **1** and **2** showed potent antimicrobial activity. Compound **2** also showed cytotoxicity against HL-60 and antioxidant activity.

Experimental Section

General Methods: Melting points were measured with a Thermo Fisher Scientific IA920 digital melting point apparatus and reported without correction. ^1H NMR spectra were recorded with Varion Germini 2000, Bruker AV-300, and Bruker AV-400 NMR instruments operating at 200, 300, and 400 MHz, respectively, using $CDCl_3$ as solvents with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded with Varion Gemini 2000, Bruker AV-300, and Bruker AV-400 NMR instruments operating at 50, 75, and 100 MHz, respectively, using $CDCl_3$ with tetramethylsilane as an internal standard and [D_6]DMSO for some compounds. FTIR spectra were obtained with a Spectrum One FTIR spectrometer Perkin–Elmer System with the universal ATR (UATR) accessory. Mass spectra were recorded with an AEI-MS-902. High-resolution mass spectra were recorded with a Micro-TOF-LC, Bruker Daltonics.

Column chromatography was carried out using Fluka aluminum oxide (type 507 C neutral; 100–125 mesh) and Merck silica gel (70–230 mesh ASTM). Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were carried out on silica gel (E. Merck PF 254). All reagents were purified and dried according to standard procedures. Solvents were removed by using an Eyela Aspirator CA-1111 and Büchi Rotavapor R200.

5-Bromo-6-(methoxymethoxy)benzo[*d*][1,3]dioxole (14): To a solution of bromine (0.87 mL, 23.9 mmol) in glacial acetic acid (25 mL) was added dropwise over 10 min a stirred solution of sesamol **13** (3.00 g, 21.7 mmol) in glacial acetic acid (25 mL) at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3× 30 mL), and the combined organic layers were washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to give a pale-yellow solid. The residue was dissolved with DMF (38 mL) then treated with K_2CO_3 (4.50 g, 32.6 mmol), MOMCl (2.48 mL, 32.6 mmol) and heated at 70 °C for 1 h. The reaction was quenched with water and extracted with ethyl acetate (3× 25 mL), washed with water, brine, dried with anhydrous Na_2SO_4, and concentrated to furnish a brown oil. The crude product was then purified by

column chromatography (ethyl acetate/hexane, 5–10%) to afford **14** (4.15 g, 73%) as a colorless oil. R_f = 0.49 (EtOAc/hexane, 3:7). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.98 (s, 1 H, ArH), 6.78 (s, 1 H, ArH), 5.95 (s, 2 H, OCH_2O), 5.13 (s, 2 H, OCH_2), 3.53 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.6, 147.6, 143.1, 112.2, 103.1, 101.8, 100.0, 96.1, 56.3 ppm. IR (UATR): $\tilde{\nu}$ = 2953, 2901, 1501, 1473, 1383 cm^{-1}. MS (EI): *m*/*z* (%) = 262 (93) $[C_9H_9{}^{81}BrO_4]^+$, 260 (97) $[C_9H_9{}^{79}BrO_4]^+$, 181 (100). HRMS (microTOF): calcd. for $C_9H_{10}{}^{81}BrO_4$ $[M + H]^+$ 262.9737; found 262.9731; calcd. for $C_9H_{10}{}^{79}BrO_4$ $[M + H]^+$ 260.9757; found 260.9750.

Methyl 6-Hydroxybenzo[*d*][1,3]dioxole-5-carboxylate (8): *n*BuLi (2.86 M, 2.87 mL, 8.22 mmol) was added to a stirred solution of **14** (1.95 g, 7.47 mmol) in anhydrous THF (76 mL) at –100 °C under an argon atmosphere. After stirring at –100 °C for 15 min, an excess of carbon dioxide gas was passed through the reaction mixture and the mixture was stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature for 30 min and concentrated to dryness. The residue was dissolved in DMF (33 mL) and K_2CO_3 (2.06 g, 14.9 mmol) was added followed by methyl iodide (1.40 mL, 22.4 mmol), and the reaction mixture was heated at 80 °C for 2 h. The reaction was quenched with water, extracted with ethyl acetate (3 × 25 mL), washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to furnish a yellow oil. The crude yellow oil was dissolved in toluene (98 mL) and treated with PTS-Si (5.53 g, 4.48 mmol), MeOH (3.48 mL, 74.7 mmol), then heated at 80 °C for 1 h. The reaction mixture was filtered and concentrated to provide a yellow solid, which was purified by column chromatography (ethyl acetate/hexane, 5%) to give **8** (1.10 g, 75%) as a white solid. R_f = 0.45 (EtOAc/hexane, 2:8), m.p. 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.05 (s, 1 H, O*H*), 7.17 (s, 1 H, ArH), 6.45 (s, 1 H, ArH), 5.96 (s, 2 H, OCH_2O), 3.90 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 160.1, 153.8, 140.6, 106.7, 103.9, 101.7, 98.3, 52.0 ppm. IR (UATR): $\tilde{\nu}$ = 3065, 1664, 1636, 1480, 1439 cm^{-1}. MS (EI): *m*/*z* (%) = 196 (100) $[M]^+$, 164 (36). HRMS (microTOF): calcd. for $C_9H_9O_5$ $[M + H]^+$ 197.0445; found 197.0441.

Methyl 6-[4-Methoxy-2-(methoxymethoxy)benzyloxy]benzo[*d*][1,3]-dioxole-5-carboxylate (18): A suspension of **8** (517 mg, 2.64 mmol) and K_2CO_3 (547 mg, 3.96 mmol) in DMF (15 mL) was treated with a solution of 1-(bromomethyl)-4-methoxy-2-(methoxymethoxy)-benzene **17**[13] (1.72 g, 6.60 mmol) in DMF (2 mL) at room temperature and the mixture was heated at 110 °C for 16 h. The reaction was quenched with water, extracted with ethyl acetate (3 × 25 mL), washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to furnish a brown oil, which was purified by column chromatography (ethyl acetate/hexane, 25–30%) to give **18** (445 mg, 45%) as a pale-yellow solid. R_f = 0.29 (EtOAc/hexane, 3:7), m.p. 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.5 Hz, 1 H, ArH), 7.32 (s, 1 H, ArH), 6.71 (d, *J* = 2.4 Hz, 1 H, ArH), 6.65 (s, 1 H, ArH), 6.59 (dd, *J* = 8.5, 2.4 Hz, 1 H, ArH), 5.97 (s, 2 H, OCH_2O), 5.21 (s, 2 H, OCH_2), 5.10 (s, 2 H, OCH_2-OCH$_3$), 3.85 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 160.4, 156.1, 155.4, 151.8, 141.2, 129.6, 118.0, 112.6, 110.4, 106.4, 101.9, 101.1, 97.5, 94.6, 67.0, 56.1, 55.4, 51.8 ppm. IR (UATR): $\tilde{\nu}$ = 1723, 1616, 1507 cm^{-1}. MS (EI): *m*/*z* (%) = 361 (5), 181 (100), 151 (72), 121 (17). HRMS (microTOF): calcd. for $C_{19}H_{21}O_8$ $[M + H]^+$ 377.1231; found 377.1246.

1-(6-Hydroxybenzo[*d*][1,3]dioxol-5-yl)-2-[4-methoxy-2-(methoxymethoxy)phenyl]ethane-1,2-dione (19): A solution of LTMP was prepared by dropwise addition of *n*BuLi (2.03 M in hexane, 1.11 mL, 2.25 mmol) to tetramethylpiperidine (0.78 mL, 4.50 mmol) in anhydrous THF (6 mL) under an argon atmosphere at –78 °C. The mixture was warmed to 0 °C and stirred at this temperature for 1 h. A solution of **18** (188 mg, 0.50 mmol) in anhydrous THF (3 mL) was added and the mixture was stirred at this temperature for 40 min. The pale-yellow solution became brown, and dimethyldioxirane (5 mL) was added dropwise at –78 °C. The mixture was stirred at this temperature for 30 min, then warmed to room temperature for 1.5 h and quenched with saturated NH_4Cl, extracted with ethyl acetate (3 × 10 mL), washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to furnish a brown oil. The crude product was purified by PTLC (ethyl acetate/hexane, 20%) to afford **19** (64.5 mg, 36%) as a pale-yellow oil, which was recrystallized with CH_2Cl_2 and hexane to give a pale-yellow solid. R_f = 0.24 (EtOAc/hexane, 3:7), m.p. 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.05 (s, 1 H, O*H*), 8.03 (d, *J* = 8.8 Hz, 1 H, ArH), 6.76 (s, 1 H, ArH), 6.70 (dd, *J* = 8.8, 2.2 Hz, 1 H, ArH), 6.61 (d, *J* = 2.2 Hz, 1 H, ArH), 6.52 (s, 1 H, ArH), 5.97 (s, 2 H, OCH_2O), 4.97 (s, 2 H, OCH_2OCH$_3$), 3.88 (s, 3 H, OCH_3), 3.23 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.8, 189.9, 166.8, 162.7, 160.0, 154.9, 140.8, 132.7, 116.8, 109.0, 108.5, 107.9, 102.1, 100.0, 98.8, 94.3, 56.5, 55.8 ppm. IR (UATR): $\tilde{\nu}$ = 1716, 1628, 1592, 1501, 1479 cm^{-1}. MS (EI): *m*/*z* (%) = 360 (22) $[M]^+$, 343 (3), 299 (9), 298 (8), 195 (100), 165 (95). HRMS (microTOF): calcd. for $C_{18}H_{17}O_8$ $[M + H]^+$ 361.0918; found 361.0916.

Scandione (3): A solution of compound **19** (54.0 mg, 0.150 mmol) in toluene (2 mL) was treated with PTS-Si (185 mg, 0.150 mmol) and MeOH (0.07 mL, 1.50 mmol) and heated at 80 °C for 30 min. The reaction mixture was filtered and concentrated to provide a yellow solid. The crude product was recrystallized from CH_2Cl_2 and hexane to furnish scandione **3** (35.5 mg, 75%) as a yellow solid. R_f = 0.35 (EtOAc/hexane, 3:7), m.p. 147–148 °C (ref.[3] 132–133 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.22 (s, 1 H, O*H*), 11.82 (s, 1 H, O*H*), 7.40 (d, *J* = 9.0 Hz, 1 H, ArH), 6.80 (s, 1 H, ArH), 6.53 (s, 1 H, ArH), 6.50 (d, *J* = 2.4 Hz, 1 H, ArH), 6.45 (dd, *J* = 9.0, 2.4 Hz, 1 H, ArH), 6.00 (s, 2 H, OCH_2O), 3.88 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.2, 193.7, 167.8, 166.9, 164.3, 156.4, 141.3, 134.0, 110.8, 109.4, 109.0, 107.8, 102.4, 101.2, 99.0, 55.8 ppm. IR (UATR): $\tilde{\nu}$ = 1625, 1603, 1594, 1476 cm^{-1}. MS (EI): *m*/*z* (%) = 316 (20) $[M]^+$, 298 (10), 165 (57), 151 (100). HRMS (microTOF): calcd. for $C_{16}H_{13}O_7$ $[M + H]^+$ 317.0656; found 317.0660.

Methyl 6-[4-(4-Methoxybenzyloxy)-2-(methoxymethoxy)benzyloxy]benzo[*d*][1,3]dioxole-5-carboxylate (21): A suspension of **8** (584 mg, 2.98 mmol) and NaH (260 mg, 5.96 mmol) in DMF (20 mL) was treated with a solution of 1-(bromomethyl)-4-(4-methoxybenzyloxy)-2-(methoxymethoxy) benzene (**20**)[13] (2.80 g, 7.63 mmol) in DMF (2 mL) at 0 °C and the mixture was heated at 110 °C for 16 h. The reaction was quenched with water and extracted with ethyl acetate (3 × 25 mL), washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to furnish a brown solid. The crude mixture was purified by column chromatography (ethyl acetate/hexane, 30%) to give **21** (954 mg, 66%) as a white solid. R_f = 0.27 (EtOAc/hexane, 3:7), m.p. 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.5 Hz, 1 H, ArH), 7.36 (d, *J* = 8.7 Hz, 2 H, ArH), 7.33 (s, 1 H, ArH), 6.92 (d, *J* = 8.7 Hz, 2 H, ArH), 6.79 (d, *J* = 2.4 Hz, 1 H, ArH), 6.66 (dd, *J* = 8.5, 2.4 Hz, 1 H, ArH), 6.65 (s, 1 H, ArH), 5.97 (s, 2 H, OCH_2O), 5.20 (s, 2 H, OCH_2), 5.10 (s, 2 H, OCH_2), 4.97 (s, 2 H, OCH_2OCH$_3$), 3.85 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 159.6, 159.4, 156.2, 155.3, 151.8, 141.2, 129.5, 129.3 (2 C), 128.8, 118.2, 114.0 (2 C), 112.6, 110.4, 107.3, 102.0, 101.9, 97.4, 94.6, 69.9, 67.0, 56.1, 55.3, 51.8 ppm. IR (UATR): $\tilde{\nu}$ = 1716, 1611, 1587, 1505 cm^{-1}. MS (EI):

m/*z* (%) = 482 (0.4) $[M]^+$, 287 (13), 255 (9), 121 (100). HRMS (microTOF): calcd. for $C_{26}H_{27}O_9$ $[M + H]^+$ 483.1650; found 483.1663.

1-(6-Hydroxybenzo[*d*][1,3]dioxol-5-yl)-2-[4-(4-methoxybenzyloxy)-2-(methoxymethoxy)phenyl]ethane-1,2-dione (22): A solution of LTMP was prepared by dropwise addition of *n*BuLi (2.86 M in hexane, 0.94 mL, 2.70 mmol) to tetramethylpiperidine (0.94 mL, 5.40 mmol) in anhydrous THF (10 mL) under an argon atmosphere at –78 °C. The reaction was then warmed to 0 °C and, after 1 h, placed at –20 °C and a solution of **21** (289 mg, 0.60 mmol) in anhydrous THF (5 mL) was added. The mixture was stirred at this temperature for 30 min. The pale-yellow solution turned brown and dimethyldioxirane (5 mL) was added dropwise at –78 °C. The reaction was stirred at this temperature for 30 min. The reaction mixture was warmed to room temperature for 1.5 h and quenched with saturated NH_4Cl, extracted with ethyl acetate (3 × 15 mL), washed with water, brine, dried with anhydrous Na_2SO_4, and concentrated to furnish a brown oil. The crude product was purified by PLC (ethyl acetate/hexane, 30%) to afford **22** (121 mg, 43%) as a yellow oil, which was recrystallized with CH_2Cl_2 and hexane to give a yellow solid. R_f = 0.43 (EtOAc/hexane, 3:7, developed twice), m.p. 137–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.04 (br. s, 1 H, O*H*), 8.02 (d, *J* = 8.8 Hz, 1 H, ArH), 7.35 (d, *J* = 8.6 Hz, 2 H, ArH), 6.93 (d, *J* = 8.6 Hz, 2 H, ArH), 6.76 (s, 1 H, ArH), 6.75 (dd, *J* = 8.8, 2.0 Hz, 1 H, ArH), 6.69 (d, *J* = 2.0 Hz, 1 H, ArH), 6.52 (s, 1 H, ArH), 5.96 (s, 2 H, OCH_2O), 5.05 (s, 2 H, OCH_2), 4.94 (s, 2 H, OCH_2OCH$_3$), 3.82 (s, 3 H, OCH_3), 3.22 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6 (2 C), 165.8, 162.6, 159.7, 159.6, 154.7, 140.7, 132.5, 129.2 (2 C), 127.4, 116.6, 113.9 (2 C), 109.0, 108.9, 107.6, 101.9, 100.8, 98.6, 94.1, 70.2, 56.3, 55.1 ppm. IR (UATR): $\tilde{\nu}$ = 2910, 1628, 1593, 1515, 1479 cm^{-1}. MS (EI): *m*/*z* (%) = 466 (6) $[M]^+$, 301 (30), 121 (100). HRMS (microTOF): calcd. for $C_{25}H_{23}O_9$ $[M + H]^+$ 467.1337; found 467.1358.

1-[4-(4-Methoxybenzyloxy)-2-(methoxymethoxy)phenyl]-2-[6-(methoxymethoxy)benzo[*d*][1,3]dioxol-5-yl]ethane-1,2-dione (23): To a suspension of **22** (121 mg, 0.26 mmol) and NaH (23.0 mg, 0.52 mmol) in anhydrous DMF (2.5 mL) was added dropwise MOMCl (0.03 mL, 0.39 mmol) at 0 °C under an argon atmosphere. The ice-bath was removed and the mixture was stirred at room temperature for 40 min. The reaction was quenched with water, extracted with ethyl acetate (3 × 5 mL), washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to furnish a pale-yellow oil. The crude product was recrystallized with CH_2Cl_2 and hexane to afford **23** (115 mg, 87%) as a white solid. R_f = 0.30 (EtOAc/hexane, 3:7, developed twice), m.p. 141–143 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1 H, ArH), 7.51 (s, 1 H, ArH), 7.35 (d, *J* = 8.4 Hz, 2 H, ArH), 6.92 (d, *J* = 8.4 Hz, 2 H, ArH), 6.80–6.68 (m, 3 H, ArH), 6.03 (s, 2 H, OCH_2O), 5.04 (s, 2 H, OCH_2), 4.90 (s, 2 H, OCH_2OCH$_3$), 4.80 (s, 2 H, OCH_2OCH$_3$), 3.82 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 3.17 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 191.4, 191.2, 164.8, 159.6, 159.4, 155.7, 153.7, 143.1, 131.9, 129.3 (2 C), 127.8, 117.2, 117.0, 114.0 (2 C), 108.6, 107.6, 102.2, 101.0, 97.1, 95.1, 94.2, 70.1, 56.3, 56.2, 55.3 ppm. IR (UATR): $\tilde{\nu}$ = 2907, 2836, 1655, 1596, 1477 cm^{-1}. MS (EI): *m*/*z* (%) = 510 (5) $[M]^+$, 301 (54), 209 (16), 121 (100). HRMS (microTOF): calcd. for $C_{27}H_{27}O_{10}$ $[M + H]^+$ 511.1599; found 511.1610.

1-[4-Hydroxy-2-(methoxymethoxy)phenyl]-2-[6-(methoxymethoxy)-benzo[*d*][1,3]dioxol-5-yl]ethane-1,2-dione (24): A solution of **23** (114 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was treated with DDQ (66.0 mg, 0.29 mmol) and heated to reflux for 72 h. The reaction was quenched with water and extracted with CH_2Cl_2 (3 × 5 mL), washed with water, brine, dried with anhydrous Na_2SO_4, and concentrated to give a brown oil. The crude product was purified by PTLC (ethyl acetate/hexane, 40%) to furnished **24** (63.5 mg, 73%) as a white solid and recovered **23** (19.0 mg, 17%). Compound **24**: R_f = 0.26 (EtOAc/hexane, 4:6, developed twice), m.p. 183–184 °C. ^{1}H NMR [200 MHz, $CDCl_3$ + CD_3OD (2 drops)]: δ = 7.96 (d, *J* = 8.4 Hz, 1 H, ArH), 7.49 (s, 1 H, ArH), 6.71 (s, 1 H, ArH), 6.60 (dd, *J* = 8.4, 2.2 Hz, 1 H, ArH), 6.53 (d, *J* = 2.2 Hz, 1 H, ArH), 6.06 (s, 2 H, OCH_2O), 4.91 (s, 2 H, OCH_2OCH$_3$), 4.82 (s, 2 H, OCH_2OCH$_3$), 3.82 (br. s, 1 H, O*H*), 3.21 (s, 3 H, OCH_3), 3.19 (s, 3 H, OCH_3) ppm. ^{13}C NMR [50 MHz, $CDCl_3$ + CD_3OD (2 drops)]: δ = 191.8, 191.6, 164.4, 159.7, 155.8, 153.8, 143.0, 131.9, 116.7, 115.3, 109.9, 107.3, 102.2, 100.8, 96.8, 94.9, 93.8, 56.1 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 3318, 2908, 1647, 1582, 1477 cm^{-1}. MS (EI): *m*/*z* (%) = 390 (9) $[M]^+$, 209 (100), 181 (44), 149 (36). HRMS (microTOF): calcd. for $C_{19}H_{19}O_9$ $[M + H]^+$ 391.1024; found 391.1023.

1-[2-(Methoxymethoxy)-4-(2-methylbut-3-yn-2-yloxy)phenyl]-2-[6-(methoxymethoxy)benzo[*d*][1,3]dioxol-5-yl]ethane-1,2-dione (26): To a suspension of **24** (68.4 mg, 0.18 mmol) and K_2CO_3 (48.3 mg, 0.35 mmol) in DMF (1.7 mL) was added 3-chloro-3-methyl-1-butyne **25** (0.07 mL, 0.61 mmol) and the mixture was heated at 70 °C for 24 h. The resulting reaction was quenched with water and extracted with ethyl acetate (3 × 5 mL), brine, dried with anhydrous Na_2SO_4 and concentrated to give a yellow oil. The crude product was purified by PTLC (ethyl acetate/hexane, 30%) to afford **26** (52.5 mg, 66%) as a pale-yellow oil and recovered compound **24** (8.6 mg, 13%). Compound **26**: R_f = 0.42 (EtOAc/hexane, 3:7, developed twice). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.7 Hz, 1 H, ArH), 7.52 (s, 1 H, ArH), 7.03 (dd, *J* = 8.7, 2.1 Hz, 1 H, ArH), 6.97 (d, *J* = 2.1 Hz, 1 H, ArH), 6.70 (s, 1 H, ArH), 6.04 (s, 2 H, OCH_2O), 4.91 (s, 2 H, OCH_2OCH$_3$), 4.81 (s, 2 H, OCH_2OCH$_3$), 3.22 (s, 3 H, OCH_3), 3.17 (s, 3 H, OCH_3), 2.65 (s, 1 H, C*H*≡C), 1.70 [s, 6 H, (CH_3)$_2$C] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.5, 191.4, 162.1, 158.9, 155.8, 153.7, 143.2, 131.2, 117.7, 117.3, 113.0, 107.7, 105.4, 102.2, 97.1, 95.2, 94.3, 85.0, 74.9, 72.6, 56.24, 56.2, 29.5 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 3281, 2908, 1655, 1595, 1477 cm^{-1}. MS (EI): *m*/*z* (%) = 456 (1) $[M]^+$, 247 (34), 209 (45), 181 (100), 151 (24). HRMS (microTOF): calcd. for $C_{24}H_{25}O_9$ $[M + H]^+$ 457.1493; found 457.1490.

1-[2-(Methoxymethoxy)-4-(2-methylbut-3-en-2-yloxy)phenyl]-2-[6-(methoxymethoxy)-benzo[*d*][1,3]dioxol-5-yl]ethane-1,2-dione (27): To a solution of **26** (114 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added 10% Pd-$BaSO_4$ (27.0 mg, 0.03 mmol) and pyridine (0.17 mL, 2.11 mmol). The alkyne was hydrogenated at room temperature and atmospheric pressure (1 atm of H_2) over 80 min. The catalyst was filtered through Celite and eluted with CH_2Cl_2, the solvent was concentrated to provide a yellow oil. The residue was purified by short pad column chromatography (ethyl acetate/hexane, 40%) to afford **27** (94.0 mg, 82%) as a pale-yellow oil. R_f = 0.47 (EtOAc/hexane, 3:7, developed twice). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.7 Hz, 1 H, ArH), 7.51 (s, 1 H, ArH), 6.75 (dd, *J* = 8.7, 1.8 Hz, 1 H, ArH), 6.73 (s, 1 H, ArH), 6.69 (s, 1 H, ArH), 6.12 (dd, *J* = 17.8, 10.4 Hz, 1 H, C*H*=CH$_2$), 6.03 (s, 2 H, OCH_2O), 5.28–5.16 (m, 2 H, CH_2=CH), 4.87 (s, 2 H, OCH_2OCH$_3$), 4.80 (s, 2 H, OCH_2OCH$_3$), 3.20 (s, 3 H, OCH_3), 3.16 (s, 3 H, OCH_3), 1.52 [s, 6 H, (CH_3)$_2$C] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 191.5, 191.4, 163.1, 158.9, 155.7, 153.7, 143.6, 143.1, 131.1, 117.3, 117.0, 114.0, 113.2, 107.7, 105.3, 102.2, 97.1, 95.1, 94.3, 80.7, 56.2, 56.1, 27.2 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 2924, 1656, 1617, 1595, 1477 cm^{-1}. MS (EI): *m*/*z* (%) = 458 (2) $[M]^+$, 293 (9), 249 (69), 217 (43), 209 (100), 181 (29), 149 (53). HRMS (microTOF): calcd. for $C_{24}H_{27}O_9$ $[M + H]^+$ 459.1650; found 459.1665.

1-[2-(Methoxymethoxy)-4-(2-methylbut-3-en-2-yloxy)phenyl]-2-[6-(methoxymethoxy)benzo[*d*][1,3]dioxol-5-yl]ethane-1,2-dione (28): In a 10 mL microwave vessel, **27** (108 mg, 0.24 mmol) was dissolved in DMF (1 mL). The solution was heated in microwave reactor (200 W, 50 psi) at 150 °C for 5 min, then the solution was diluted with ethyl acetate (15 mL) and washed with water (3× 10 mL), brine (10 mL), dried with anhydrous Na_2SO_4, filtered and evaporated to give a yellow oil. The crude product was purified by PTLC (ethyl acetate/hexane, 25%) to afford **28** (28.9 mg, 23%) as a pale-yellow solid and a mixture of **29** (28.5 mg, 24%) as a pale-yellow oil. Compound **28**: R_f = 0.16 (EtOAc/hexane, 3:7, developed twice), m.p. 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1 H, ArH), 7.50 (s, 1 H, ArH), 6.70 (s, 1 H, ArH), 6.55 (s, 1 H, ArH), 6.03 (s, 2 H, OCH_2O), 5.34–5.25 (m, 1 H, C=CHCH$_2$), 4.83 (s, 2 H, OCH_2OCH$_3$), 4.81 (s, 2 H, OCH_2OCH$_3$), 3.33 (d, J = 7.2 Hz, 2 H, C=CHCH_2), 3.20 (s, 3 H, OCH_3), 3.19 (s, 3 H, OCH_3), 1.77 [s, 6 H, (CH_3)$_2$C] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.7, 191.6, 161.2, 158.2, 155.9, 153.8, 143.2, 135.4, 131.8, 121.4, 121.3, 117.2, 116.4, 107.7, 102.3, 101.8, 97.2, 95.2, 94.2, 56.22, 56.20, 29.0, 25.8, 17.9 ppm. IR (UATR): $\tilde{\nu}$ = 3299, 2910, 1648, 1587, 1504, 1477 cm^{-1}. MS (EI): *m*/*z* (%) = 458 (1) [M]$^+$, 249 (100), 209 (66). HRMS (microTOF): calcd. for $C_{24}H_{27}O_9$ [M + H]$^+$ 459.1650; found 459.1654.

General Procedure for Palladium(II)-Catalyzed Oxidative Cyclization

Method A: A mixture of phenol (1.00 mmol), $Pd(TFA)_2$ (5 mol-%), sparteine sulfate (40 mol-%), Na_2CO_3 (2 equiv.), and MS (4 Å, 125 mg/mmol SM) in anhydrous toluene (0.1 M) under O_2 was heated at 80 °C for 16 h. The resulting mixture was filtered through silica gel and eluted with ethyl acetate, and concentrated to give the crude product, which was purified by preparative thin-layer chromatography (PTLC).

Method B: A mixture of phenol (1.00 mmol), $Pd(TFA)_2$ (5–20 mol-%), pyridine (20–40 mol-%), Na_2CO_3 (2 equiv.), and MS (4 Å, 125–500 mg/mmol SM) in anhydrous toluene (0.1 M) under O_2 was heated at 80 °C for 16 h. The resulting mixture was filtered through silica gel and eluted with ethyl acetate, and concentrated to give crude product, which was purified by preparative thin-layer chromatography (PTLC).

1-[6-(Methoxymethoxy)-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-yl]-2-[6-(methoxymethoxy)benzo[*d*][1,3]dioxol-5-yl]ethane-1,2-dione (30): By following Method A, with **28** (123 mg, 0.27 mmol), 5 mol-% $Pd(TFA)_2$ (4.5 mg, 0.01 mmol), 40 mol-% sparteine sulfate (45 mg, 0.11 mmol), Na_2CO_3 (57 mg, 0.54 mmol), and MS (4 Å, 34 mg, 125 mg/mmol SM) in anhydrous toluene (0.1 M, 2.7 mL) and purification by PTLC (ethyl acetate/hexane, 40%), compound **30** (8.5 mg, 7%) was obtained as a yellow solid. By following Method B, with **28** (36 mg, 0.08 mmol), 20 mol-% $Pd(TFA)_2$ (5.2 mg, 0.02 mmol), 20 mol-% pyridine (1.2 μL, 0.004 mmol), Na_2CO_3 (17 mg, 0.16 mmol) and MS (4 Å, 9.8 mg, 125 mg/mmol SM) in anhydrous toluene (0.1 M, 0.8 mL) and purification by PTLC (ethyl acetate/hexane, 40%), compound **30** (5.6 mg, 16%) was obtained as a pale-yellow oil. R_f = 0.38 (EtOAc/hexane, 4:6). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (s, 1 H, ArH), 7.51 (s, 1 H, ArH), 6.71 (s, 1 H, ArH), 6.57 (s, 1 H, ArH), 6.03 (s, 2 H, OCH_2O), 5.28 (dd, J = 9.3, 8.1 Hz, 1 H, CHCH$_2$), 5.08 (s, 1 H, CHH=C), 4.94 (s, 1 H, CHH=C), 4.88 (s, 2 H, OCH_2OCH$_3$), 4.83 (s, 2 H, OCH_2OCH$_3$), 3.35 (dd, J = 15.3, 9.3 Hz, 1 H, CHH-CH), 3.21 (s, 6 H, 2× OCH_3), 3.02 (dd, J = 15.3, 8.1 Hz, 1 H, CHH-CH), 1.76 (s, 3 H, CH_3C=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4 (2 C), 166.3, 160.0, 155.7, 153.7, 143.2, 143.1, 126.3, 121.1, 117.3, 116.8, 112.6, 107.8, 102.2, 97.2, 95.9, 95.2, 94.4, 87.8, 56.3, 56.2, 33.3, 17.1 ppm. IR (UATR): $\tilde{\nu}$ = 2917, 2851, 1651, 1611, 1476 cm^{-1}. MS (EI): *m*/*z* (%) = 456 (4) [M]$^+$, 247 (100), 217 (13), 209 (15). HRMS (microTOF): calcd. for $C_{24}H_{24}O_9Na$ [M + Na]$^+$ 479.1313; found 479.1309.

2-(Prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-carbaldehyde (32): By following Method B, with 4-hydroxy-3-(3-methylbut-2-enyl)benzaldehyde (72.0 mg, 0.38 mmol), 5 mol-% $Pd(TFA)_2$ (6.5 mg, 0.02 mmol), 20 mol-% pyridine (6 μL, 0.08 mmol), Na_2CO_3 (80 mg, 0.76 mmol) and MS (4 Å, 47.4 mg) (125 mg/mmol SM) in anhydrous toluene (0.1 M, 3.8 mL) and purification by PTLC (ethyl acetate/hexane, 10%), compound **32** (33.4 mg, 47%) was obtained as a pale-yellow oil. R_f = 0.24 (EtOAc/hexane, 1:9). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.82 (s, 1 H, CHO), 7.71 (s, 1 H, ArH), 7.68 (d, J = 8.3 Hz, 1 H, ArH), 6.89 (d, J = 8.3 Hz, 1 H, ArH), 5.29 (t, J = 8.7 Hz, 1 H, CH$_2$CH), 5.10 (s, 1 H, CHH=C), 4.95 (s, 1 H, CHH=C), 3.40 (dd, J = 15.9, 9.6 Hz, 1 H, CHH-CH), 3.08 (dd, J = 15.9, 8.0 Hz, 1 H, CHH-CH), 1.77 (s, 3 H, =CCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.5, 165.1, 143.0, 133.0, 130.4, 128.1, 125.7, 112.7, 109.4, 87.1, 33.6, 17.0 ppm. IR (UATR): $\tilde{\nu}$ = 2920, 2820, 2733, 1683, 1604 cm^{-1}. EI-MS: *m*/*z* (%) = 188 (98) [M]$^+$, 173 (100), 159 (45), 144 (38), 141 (32), 131 (24), 115 (31), 91 (27), 77 (13). HRMS (microTOF): calcd. for $C_{12}H_{12}O_2Na$ [M + Na]$^+$ 211.0730; found 211.0735.

Methyl 2-(Prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-carboxylate (34): By following Method B, with methyl 4-hydroxy-3-(3-methylbut-2-enyl)benzoate (100 mg, 0.46 mmol), 5 mol-% $Pd(TFA)_2$ (7.6 mg, 0.02 mmol), 20 mol-% pyridine (9 μL, 0.09 mmol), Na_2CO_3 (96 mg, 0.91 mmol), and MS (4 Å, 57 mg, 125 mg/mmol SM) in anhydrous toluene (0.1 M, 4.6 mL) and purification by PTLC (ethyl acetate/hexane,10%), benzofuran **34** (23.1 mg, 23%) was obtained as a pale-yellow oil, together with chromene **35** (2.8 mg, 3%) as a pale-yellow oil and recovered methyl 4-hydroxy-3-(3-methylbut-2-enyl)benzoate (7.0 mg, 7%).

Compound 34: R_f = 0.47 (EtOAc/hexane, 1:9, developed twice). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (d, J = 9.0 Hz, 1 H, ArH), 7.85 (s, 1 H, ArH), 6.80 (d, J = 9.0 Hz, 1 H, ArH), 5.25 (t, J = 8.3 Hz, 1 H, CH$_2$CH), 5.09 (s, 1 H, CHH=C), 4.93 (s, 1 H, CHH=C), 3.87 (s, 3 H, OCH_3), 3.37 (dd, J = 15.8, 9.8 Hz, 1 H, CHH-CH), 3.05 (dd, J = 15.8, 8.3 Hz, 1 H, CHH-CH), 1.76 (s, 3 H, =CCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 163.8, 143.4, 131.1, 127.0, 126.6, 122.7, 112.5, 108.9, 86.8, 51.8, 34.0, 17.1 ppm. IR (UATR): $\tilde{\nu}$ = 2951, 1712, 1611, 1489 cm^{-1}. MS (EI): *m*/*z* (%) = 219 (14), 218 (100) [M]$^+$, 203 (90), 187 (36), 171 (30), 159 (82), 144 (58). HRMS (microTOF): calcd. for $C_{13}H_{14}O_3Na$ [M + Na]$^+$ 241.0835; found 241.0832.

Compound 35: R_f = 0.51 (EtOAc/hexane, 1:9, developed twice). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.4 Hz, 1 H, ArH), 7.68 (s, 1 H, ArH), 6.77 (d, J = 8.4 Hz, 1 H, ArH), 6.34 (d, J = 9.9 Hz, 1 H, CH=CHAr), 5.64 (d, J = 9.9 Hz, 1 H, CH=CHAr), 3.87 (s, 3 H, OCH_3), 1.45 [s, 6 H, (CH_3)$_2$C] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 157.1, 131.1, 131.0, 128.1, 122.5, 121.7, 120.6, 116.1, 77.4, 51.8, 28.3 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 2976, 2927, 1714, 1641, 1609, 1576 cm^{-1}. EI-MS: *m*/*z* (%) = 218 (9) [M]$^+$, 203 (100), 144 (12), 115 (8). HRMS (microTOF): calcd. for $C_{13}H_{14}O_3Na$ [M + Na]$^+$ 241.0835; found 241.0832.

Methyl 6-(Methoxymethoxy)-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-carboxylate (36): By following Method B, with **44** (87.0 mg, 0.31 mmol), 10 mol-% $Pd(TFA)_2$ (10.0 mg, 0.03 mmol), 40 mol-% pyridine (11 μL, 0.12 mmol), Na_2CO_3 (66.0 mg, 0.62 mmol) and MS (4 Å, 155 mg, 500 mg/mmol SM) in anhydrous toluene (0.1 M, 3.1 mL) and purification by PTLC (ethyl acetate/hexane, 10%), compound **36** (42.8 mg, 49%) was obtained as a colorless oil to-

gether with [6-(methoxycarbonyl)-7-(methoxymethoxy)-2-methyl-2*H*-chromen-2-yl]methylium **37** (9.1 mg, 11%) as a colorless oil.

Compound 36: R_f = 0.35 (EtOAc/hexane, 1.5:8.5, developed twice). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (s, 1 H, ArH), 6.66 (s, 1 H, ArH), 5.24 (t, J = 8.7 Hz, 1 H, CH_2CH), 5.22 (s, 2 H, OCH_2OCH_3), 5.08 (s, 1 H, C*H*H=C), 4.92 (s, 1 H, CH*H*=C), 3.85 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 3.30 (dd, J = 15.5, 9.5 Hz, 1 H, C*H*H-CH), 2.98 (dd, J = 15.5, 8.0 Hz, 1 H, CH*H*-CH), 1.75 (s, 3 H, =CCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 164.3, 159.0, 143.3, 127.8, 120.0, 112.8, 112.4, 98.3, 95.4, 87.4, 56.3, 51.6, 33.5, 17.0 ppm. IR (UATR): $\tilde{\nu}$ = 2950, 1723, 1622, 1592, 1487, 1439 cm^{-1}. MS (EI): *m*/*z* (%) = 279 (12), 278 (66) $[M]^+$, 263 (75), 233 (95), 202 (68), 187 (100). HRMS (microTOF): calcd. for $C_{15}H_{19}O_5$ $[M + H]^+$ 279.1227; found 279.1222.

Compound 37: R_f = 0.43 (EtOAc/hexane, 1.5:8.5, developed twice). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 1 H, ArH), 6.62 (s, 1 H, ArH), 6.28 (d, J = 9.9 Hz, 1 H, CH=C*H*), 5.54 (d, J = 9.9 Hz, 1 H, C*H*=CH), 5.22 (s, 2 H, OCH_2OCH_3), 3.85 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 1.43 [s, 6 H, $(CH_3)_2C$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 158.6, 157.6, 129.8, 128.9, 121.0, 114.8, 112.8, 104.2, 95.0, 77.4, 56.3, 51.6, 28.3 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 2975, 2947, 1724, 1615, 1565, 1493 cm^{-1}. MS (EI): *m*/*z* (%) = 279 (5), 278 (28) $[M]^+$, 263 (96), 247 (15), 233 (100), 187 (93), 160 (25), 77 (16). HRMS (microTOF): calcd. for $C_{15}H_{19}O_5$ $[M + H]^+$ 279.1227; found 279.1225.

[6-(Methoxymethoxy)-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-yl-]methanol (38): A solution of **36** (229 mg, 0.82 mmol) in anhydrous THF (2 mL) was added into a suspension of LAH (78.0 mg, 2.06 mmol) in anhydrous THF (3 mL) at 0 °C and the mixture was warmed to room temperature. After 2 h, the mixture was cooled to 0 °C and the reaction was quenched with a mixture of water/ethyl acetate (1:1, 10 mL) and filtered. The residue was extracted with ethyl acetate (3× 10 mL), washed with water, brine, dried with anhydrous Na_2SO_4, and evaporated to give **38** (197 mg, 96%) as a colorless oil. R_f = 0.29 (EtOAc/hexane, 3:7, developed twice). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (s, 1 H, ArH), 6.54 (s, 1 H, ArH), 5.09 (s, 2 H, OCH_2OCH_3), 5.09 (app. t, J = 8.9 Hz, 1 H, C*H*CH_2), 4.98 (s, 1 H, C*H*H=C), 4.81 (s, 1 H, CH*H*=C), 4.51 (s, 2 H, CH_2OH), 3.39 (s, 3 H, OCH_3), 3.18 (dd, J = 15.3, 9.6 Hz, 1 H, C*H*H-CH), 2.88 (dd, J = 15.3, 8.1 Hz, 1 H, CH*H*-CH), 2.37 (br. s, 1 H, O*H*), 1.67 (s, 3 H, CH_3C=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 155.6, 143.8, 125.2, 122.0, 119.4, 112.0, 97.1, 95.0, 86.6, 61.6, 56.2, 34.0, 17.1 ppm. IR (UATR): $\tilde{\nu}$ = 3390, 2919, 1621, 1604, 1487 cm^{-1}. MS (EI): *m*/*z* (%) = 250 (29) $[M]^+$, 218 (17), 188 (100), 173 (53), 145 (38). HRMS (microTOF): calcd. for $C_{14}H_{18}O_4Na$ $[M + Na]^+$ 273.1097; found 273.1091.

Methyl 6-{[6-(Methoxymethoxy)-2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran-5-yl]methoxy}benzo[*d*][1,3]dioxole-5-carboxylate (39): To a solution of **8** (180 mg, 0.92 mmol), alcohol **38** (153 mg, 0.61 mmol), and PPh_3 (241 mg, 0.92 mmol) in anhydrous THF (6 mL) was added diisopropyl azodicarboxylate (0.17 mL, 0.92 mmol) dropwise at 0 °C under an argon atmosphere. The solution was then heated to reflux for 24 h and concentrated in vacuo to give a yellow oil. The crude product was purified by PTLC (ethyl acetate/hexane, 20%) to furnish **39** (110 mg, 42%) as a pale-yellow solid. R_f = 0.26 (EtOAc/hexane, 2:8), m.p. 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 1 H, ArH), 7.32 (s, 1 H, ArH), 6.67 (s, 1 H, ArH), 6.65 (s, 1 H, ArH), 5.97 (s, 2 H, OCH_2O), 5.177 (s, 2 H, OCH_2OCH_3), 5.176 (app. t, J = 8.7 Hz, 1 H, C*H*-CH_2), 5.08 (s, 3 H, OCH_2, C*H*H=C), 4.90 (s, 1 H, CH*H*=C), 3.85 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3), 3.29 (dd, J = 15.0, 9.6 Hz, 1 H, C*H*H-CH), 2.99 (dd, J = 15.0, 8.3 Hz, 1 H, CH*H*-CH), 1.76 (s, 3 H, CH_3C=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 160.5, 156.2, 154.8, 151.8, 143.9, 141.2, 124.8, 119.5, 117.4, 112.5, 111.9, 110.3, 101.8, 97.6, 96.5, 94.8, 86.6, 67.4, 56.0, 51.7, 34.2, 17.2 ppm. IR (UATR): $\tilde{\nu}$ = 2949, 2907, 1723, 1697, 1622, 1484 cm^{-1}. MS (EI): *m*/*z* (%) = 428 (0.2) $[M]^+$, 234 (16), 233 (100), 203 (18), 201 (21), 149 (34). HRMS (microTOF): calcd. for $C_{23}H_{25}O_8$ $[M + H]^+$ 429.1544; found 429.1533.

Methyl 2-Hydroxy-4-(2-methylbut-3-yn-2-yloxy)benzoate (41): To a suspension of **40** (500 mg, 2.98 mmol) and K_2CO_3 (617 mg, 4.47 mmol) in acetone (20 mL) under an argon atmosphere was added 3-chloro-3-methyl-1-butyne **25** (1.23 mL, 10.4 mmol) and the mixture was heated to reflux for 16 h. The reaction was quenched with water, extracted with ethyl acetate (3× 20 mL), brine, dried with anhydrous Na_2SO_4 and concentrated to give a yellow-brown oil. The crude product was purified by column chromatography (ethyl acetate/hexane, 5–10%) to afford **41** (427 mg, 61%) as a pale-yellow solid. R_f = 0.49 (EtOAc/hexane, 2:8), m.p. 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.91 (s, 1 H, O*H*), 7.74 (d, J = 9.0 Hz, 1 H, ArH), 6.92 (d, J = 2.4 Hz, 1 H, ArH), 6.68 (dd, J = 9.0, 2.4 Hz, 1 H, ArH), 3.93 (s, 3 H, OCH_3), 2.67 (s, 1 H, C*H*≡C), 1.72 [s, 6 H, $(CH_3)_2C$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 162.8, 161.9, 130.6, 111.3, 106.3, 106.1, 84.8, 74.8, 72.1, 51.8, 29.4 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 3291, 2992, 2955, 1669, 1620, 1578, 1497, 1439, 1347 cm^{-1}. MS (EI): *m*/*z* (%) = 234 (5) $[M]^+$, 219 (13), 175 (26), 168 (76), 136 (100). HRMS (microTOF): calcd. for $C_{13}H_{15}O_4$ $[M + H]^+$ 235.0965; found 235.0969.

Methyl 2-(Methoxymethoxy)-4-(2-methylbut-3-yn-2-yloxy)benzoate (42): To a suspension of **41** (639 mg, 2.73 mmol) and NaH (238 mg, 5.46 mmol) in anhydrous DMF (6 mL) at 0 °C was added dropwise MOMCl (0.37 mL, 4.10 mmol) under an argon atmosphere. The ice-bath was removed and the reaction mixture was stirred at room temperature for 40 min. The reaction was quenched with water, extracted with ethyl acetate (3× 15 mL), washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to afford a yellow oil. The crude product was purified by column chromatography (ethyl acetate/hexane, 20%) to furnish **42** (740 mg, 97%) as a colorless oil. R_f = 0.26 (EtOAc/hexane, 2:8). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.7 Hz, 1 H, ArH), 7.07 (d, J = 1.7 Hz, 1 H, ArH), 6.94 (dd, J = 8.7, 1.7 Hz, 1 H, ArH), 5.25 (s, 2 H, OCH_2-OCH_3), 3.87 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 2.65 (s, 1 H, C*H*≡C), 1.70 [s, 6 H, $(CH_3)_2C$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 160.1, 158.2, 132.5, 114.4, 112.4, 107.9, 95.1, 85.1, 74.6, 72.3, 56.3, 51.7, 29.5 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 3284, 2991, 2951, 1723, 1603, 1575 cm^{-1}. MS (EI): *m*/*z* (%) = 278 (29) $[M]^+$, 247 (28), 233 (42), 219 (83), 212 (91), 197 (43), 181 (81), 165 (73), 151 (100), 136 (81). HRMS (microTOF): calcd. for $C_{15}H_{19}O_5$ $[M + H]^+$ 279.1227; found 279.1223.

Methyl 2-(Methoxymethoxy)-4-(2-methylbut-3-en-2-yloxy)benzoate (43): To a solution of **42** (761 mg, 2.74 mmol) in CH_2Cl_2 (50 mL) was added 10% Pd-$BaSO_4$ (290 mg, 0.274 mmol) and pyridine (1.85 mL, 23.0 mmol). The alkyne **42** was hydrogenated at room temperature and atmospheric pressure (1 atm of H_2) over 3 h. The catalyst was filtered through Celite and eluted with CH_2Cl_2, and the solvent was evaporated to provide a yellow oil. The residue was purified by column chromatography (ethyl acetate/hexane, 20–30%) to afford **43** (710 mg, 93%) as a colorless oil. R_f = 0.31 (EtOAc/hexane, 2:8). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.8 Hz, 1 H, ArH), 6.83 (d, J = 2.2 Hz, 1 H, ArH), 6.65 (dd, J = 8.8, 2.2 Hz, 1 H, ArH), 6.12 (dd, J = 17.7, 11.1 Hz, 1 H, C*H*=CH_2), 5.26–5.15 (m, 4 H, OCH_2OCH_3, CH=CH_2), 3.85 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 1.51 [s, 6 H, $(CH_3)_2C$] ppm. ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 166.0, 161.1, 158.2, 143.8, 132.4, 113.8, 113.6, 112.6, 107.9, 95.1, 80.3, 56.2, 51.6, 27.1 (2 C) ppm. IR (UATR): $\tilde{\nu}$ = 2983, 1725, 1603, 1572 cm^{-1}. MS (EI): *m*/*z* (%) = 280 (10) $[M]^+$, 212 (100), 197 (17), 181 (31), 165 (28), 151 (37), 136 (29), 69 (43). HRMS (microTOF): calcd. for $C_{15}H_{21}O_5$ $[M + H]^+$ 281.1384; found 281.1389.

Methyl 4-Hydroxy-2-(methoxymethoxy)-5-(3-methylbut-2-enyl)-benzoate (44): In a 10 mL microwave vessel, **43** (140 mg, 0.500 mmol) was dissolved in DMF (1 mL). The solution was heated in a microwave reactor (200 W, 50 psi) at 150 °C for 5 min, then the solution was diluted with ethyl acetate (15 mL) and washed with water (3× 10 mL), brine (10 mL), dried with anhydrous Na_2SO_4, filtered and evaporated to give a pale-yellow oil. The crude product was purified by PTLC (ethyl acetate/hexane, 20%) to afford **44** (63.2 mg, 45%) as a white solid and another isomer **45** (62.8 mg, 45%) as a white solid.

Compound 44: R_f = 0.29 (EtOAc/hexane, 3:7, developed twice), m.p. 106–107 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 1 H, ArH), 6.71 (s, 1 H, ArH), 6.61 (br. s, 1 H, O*H*), 5.35–5.25 (m, 1 H, =C*H*CH_2), 5.17 (s, 2 H, OCH_2OCH_3), 3.86 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 3.30 (d, *J* = 7.2 Hz, 2 H, =CHCH_2), 1.76 [s, 6 H, (CH_3)$_2$C] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 159.6, 157.5, 133.8, 133.2, 121.8, 121.0, 111.5, 103.6, 94.9, 56.1, 51.8, 28.2, 25.7, 17.8 ppm. IR (UATR): $\tilde{\nu}$ = 3267, 2925, 1678, 1607 cm^{-1}. MS (EI): *m*/*z* (%) = 280 (13) $[M]^+$, 279 (31), 256 (33), 178 (100), 167 (36), 149 (77). HRMS (microTOF): calcd. for $C_{15}H_{21}O_5$ $[M + H]^+$ 281.1384; found 281.1392.

Compound 45: R_f = 0.47 (EtOAc/hexane, 3:7, developed twice), m.p. 109–110 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.4 Hz, 1 H, ArH), 6.64 (d, *J* = 8.4 Hz, 1 H, ArH), 6.52 (s, 1 H, O*H*), 5.27–5.19 (m, 1 H, =C*H*CH_2), 5.06 (s, 2 H, OCH_2OCH_3), 3.86 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 3.51 (d, *J* = 6.9 Hz, 2 H, =CHCH_2), 1.81 (s, 3 H, =CCH_3), 1.73 (s, 3 H, =CCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 159.7, 157.3, 134.6, 130.8, 122.1, 121.6, 116.0, 111.8, 101.4, 57.6, 51.9, 25.7, 23.3, 17.9 ppm. IR (UATR): $\tilde{\nu}$ = 3382, 2935, 2827, 1698, 1596, 1578, 1435 cm^{-1}. MS (EI): *m*/*z* (%) = 280 (0.2) $[M]^+$, 248 (59), 203 (100), 161 (47), 149 (56). HRMS (microTOF): calcd. for $C_{15}H_{21}O_5$ $[M + H]^+$ 281.1384; found 281.1381.

Calophione A (4): A solution of LTMP was prepared by dropwise addition of *n*BuLi (1.67 M in hexane, 0.50 mL, 0.837 mmol) into tetramethylpiperidine (0.30 mL, 1.67 mmol) in anhydrous THF (5 mL) under an argon atmosphere at –78 °C. The solution was warmed to 0 °C and stirred at this temperature for 1 h, then placed at –20 °C and a solution of **39** (79.4 mg, 0.19 mmol) in anhydrous THF (2 mL) was added and the mixture was stirred at this temperature for 1 h. The pale-yellow solution turned brown and dimethyldioxirane (5 mL) was added dropwise at –78 °C. The mixture was stirred at this temperature for 30 min, then warmed to room temperature for 1.5 h and quenched with saturated NH_4Cl, extracted with ethyl acetate (3× 5 mL), washed with water, brine, dried with anhydrous Na_2SO_4 and concentrated to furnish a yellow-brown oil. The residue was dissolved with toluene (2.4 mL) and treated with PTS-Si (230 mg, 0.186 mmol), MeOH (0.09 mL, 1.86 mmol) under heated at 80 °C for 1 h. The reaction mixture was filtered and concentrated to provide a yellow solid. The crude product was purified by PTLC (ethyl acetate/hexane, 20%) to furnish calophione A (**4**; 7.8 mg, 11%) as a pale-yellow solid. R_f = 0.34 (EtOAc/hexane, 2:8), m.p. 153–154 °C (ref.[4] 120–122 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 12.25 (s, 1 H, O*H*), 12.06 (s, 1 H, O*H*), 7.23 (s, 1 H, ArH), 6.83 (s, 1 H, ArH), 6.54 (s, 1 H, ArH), 6.45 (s, 1 H, ArH), 6.00 (s, 2 H, OCH_2O), 5.28 (dd, *J* = 9.2, 7.5 Hz, 1 H, C*H*CH_2), 5.07 (s, 1 H, C*H*H=C), 4.95 (s, 1 H, CH*H*=C), 3.24 (dd, *J* = 15.6, 9.2 Hz, 1 H, C*H*H-CH), 2.91 (dd, *J* = 15.6, 7.5 Hz, 1 H, CH*H*-CH), 1.73 (s, 3 H, CH_3C=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.0, 193.5, 168.5, 167.6, 164.3, 156.4, 142.7, 141.3, 128.0, 120.4, 113.2, 110.6, 109.5, 108.0, 102.4, 99.0, 98.5, 88.3, 32.6, 16.9 ppm. IR (UATR): $\tilde{\nu}$ = 2916, 1623, 1591, 1475, 1387 cm^{-1}. MS (EI): *m*/*z* (%) = 368 (7) $[M]^+$, 203 (100), 165 (32). HRMS (microTOF): calcd. for $C_{20}H_{17}O_7$ $[M + H]^+$ 369.0969; found 369.0966.

Cytotoxicity Test: Benzil derivatives **1**–**4** were solubilized in DMSO and tested for their cytotoxic activities against HuCCA-1, A-549, HepG2, and MOLT-3 cancer cell lines. The cells, suspended in the corresponding culture medium, were inoculated in 96-well microtiter plates (Corning Inc., NY, USA) at a density of 10000–20000 cells per well, and incubated at 37 °C in a humidified atmosphere with 95% air and 5% CO_2. After 24 h, an equal volume of additional medium containing either serial dilutions of the test compounds, positive control (etoposide), or negative control (DMSO) was added to the desired final concentrations, and the microtiter plates were further incubated for an additional 48 h. The number of surviving cells in each well was determined by using either an MTT assay (for adherent cells) or an XTT assay (for suspended cells) to determine the IC_{50}, which is defined as the concentration that inhibits cell growth by 50% (relative to negative control) after 48 h of continuous exposure to each test compound. Within each experiment, determinations were performed in triplicate, and each compound was tested in at least two separate experiments. Any experiments with a variation greater than 10% were excluded from the analysis. The results are expressed as the mean IC_{50} value; standard deviations are omitted for visual clarity.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for compounds **3**, **4**, **8**, **14**, **18**, **19**, **21**–**24**, **26**–**28**, **30**, **32**, **34**–**39**, and **41**–**45**.

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