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Total Synthesis of Graphislactones A, C, D, and H, of Ulocladol, and of the Originally Proposed and Revised Structures of Graphislactones E and F

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To the memory of Prof. Dr. Maximilian Steiner

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Graphislactones A–H and the structurally related ulocladol are highly oxygenated resorcylic lactones produced by lichens and fungi. We present total syntheses of graphislactones A, C–F, H and of ulocladol. Graphislactones E, F, and H were synthesized for the first time. The spectra of graphislactones E and F synthesized as the originally proposed structures were not in agreement with published data. Consequently, revised structures for these compounds are proposed, whose correctness is unambiguously proven by total synthesis and comparison of the spectroscopic data. Key steps in all syntheses are Suzuki couplings for the construction of the central biaryl bond and Dakin reactions to supply further hydroxy groups required in these highly oxygenated substrates. Graphislactones A, C, and H, acylated graphislactone D and ulocladol were prepared in 8–11 steps with 7–20 % yield starting with purchasable compounds, where the longest linear sequence consists of 5–9 steps. The syntheses are thus significantly shorter than the previously published syntheses of graphislactones A–D and of ulocladol. Graphislactones E and F were synthesized in 8 steps, where the longest linear sequences consist of 6 and 5 steps, respectively. They were isolated as the respective acetylated compounds with 25 and 10 % yield.

Introduction

Nature has long been identified as a cornucopia of biologically active compounds. While bacteria,[1] fungi,[2] marine organisms[3] and many other organisms have been thoroughly investigated in that context, lichens have been significantly less considered.[4] As a symbiosis of algae and fungi, the latter supply the lichens with secondary metabolites; the metabolism is consequently similar to that of fungi. Graphislactone A was identified as reduction product of botrallin in 1968,[5] but it was first isolated as a natural product from the lichen *Graphis scripta* var. *pulverulenta*[6] in the late 1990s together with graphislactones B, C, and D.[6a–6d] Graphislactones E and F have been isolated from *Graphis scripta* and *Graphis prunicola*[6d] and graphislactones G and H have been isolated from the endophytic fungus *Cephalosporium acemonium* IFB-E007.[7] The structurally related botrallin was isolated from *Botrytis allii*[5a,5b,6e] and ulocladol was isolated from the marine sponge-derived fungus *Ulocladium botrytis* (Figure 1).[6e,8a,8b] The biosynthesis of graphislactones is strongly related to that of *Alternaria* metabolites,[6d,9] in fact, 3-desmethylgraphislactone A was identified in the metabolism of *Alternaria* toxins.[10a,10b]

A number of biological activities have been reported for graphislactones and the related compounds. Graphislactone A is an antioxidant and a scavenger of free radicals,[11] graphislactones A, G, and H were found to be active against the SW1116 cell line (IC_{50} 8.5, 21, and 12 mg/mL, respectively),[7] graphislactone A and botrallin are moderate inhibitors of AChE,[6e] and ulocladol is a tyrosine kinase ($p56^{lck}$) inhibitor.[8b] Total syntheses of graphislactones A–D[12] and of ulocladol have been published previously,[13] though neither experimental details nor spectroscopic data have been provided for the syntheses of graphislactones A–D. These graphislactones have been prepared in 10–12 steps with 9–20% yield starting with 3,5-dimethoxyaniline and methyl 3-*O*-methylgallate, where the longest linear sequence consisted of 7–9 steps. Ulocladol has been prepared in 13 steps with 2–6% yield, where the longest linear sequence consisted of 10 steps. The synthetic strategy in the pub-

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[‡] X-ray crystallographic analyses.
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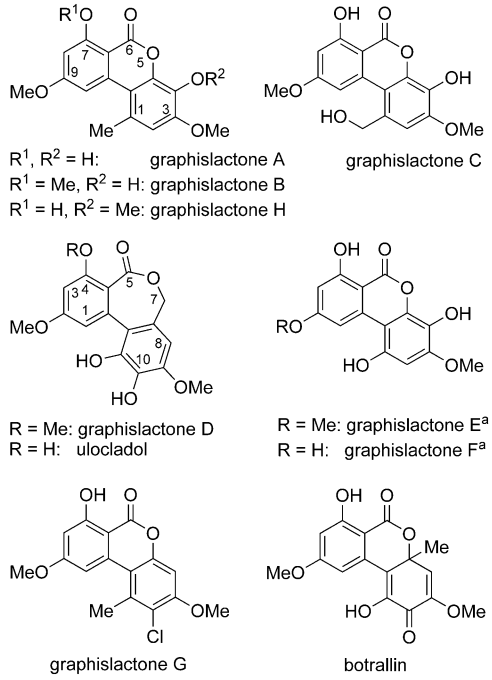


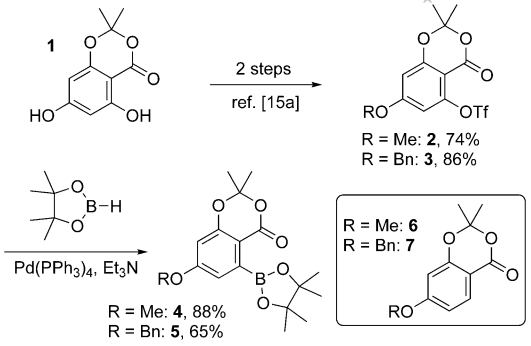
Figure 1. Structure of graphislactones and of related compounds. [a] Originally proposed structures; for corrected structures vide infra.

lished procedures commenced with the installation of the ester bond from suitable precursors with subsequent palladium-mediated couplings.

Results and Discussion

Retrosynthesis and Construction of the Boronates

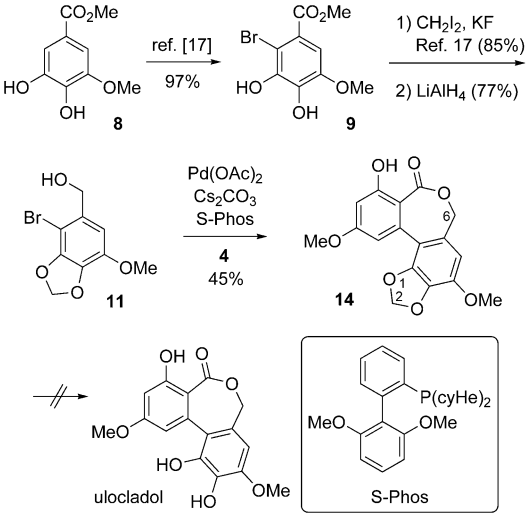
Retrosynthesis of the target compounds suggested Suzuki couplings[14] as key steps for the construction of the central biaryl bonds. Boronates suitable for these transformations could be prepared according to published procedures[15] and a subsequent palladium-catalyzed Miyaura cross coupling[16] starting with commercially available acetal-protected phloroglucinic acid **1** (Scheme 1). No boronate was isolated in the Miyaura reaction when bis(pinacolato)diborane was used as boron component and a poor 34% yield was observed with pinacolborane and $PdCl_2$(dppf) as a catalyst. The significant amount of reduced side products **6** and **7**, respectively, obtained in the initial experiments was suppressed with $Pd(PPh_3)_4$ as a catalyst and a reduced reaction time (2 h rather than 4 h). The boronates **4** and **5** were thus accessible from protected phloroglucinic acid **1** in three steps with 65 and 56% yield, respectively. Graphislactone F bearing a free hydroxy group in position C-9 was prepared starting with a boronate **5** protected as benzyl ether while the methyl ether as needed in the other natural products was introduced with boronate **4**.



Scheme 1. Synthesis of the boronates suitable for Suzuki coupling.

Total Synthesis of Ulocladol and Graphislactone D

Bromide **11**, which was assumed to be suitable for the synthesis of ulocladol was obtained starting with purchasable methyl 3,4-dihydroxy-5-methoxybenzoate (**8**) (Scheme 2). A published two-step sequence[17] with subsequent reduction using lithium aluminium hydride yielded benzyl alcohol **11**. The desired regioselectivity in the bromination was unambiguously clarified by X-ray crystallographic analysis of intermediate **9**.[18] An alternative approach to benzyl alcohol **11** starting with purchasable 3,4-dihydroxy-5-methoxybenzaldehyde (**12**) gave significantly lower yields.[19] Suzuki coupling was achieved with a protocol, which already proved to be suitable for the construction of the related resorcylic lactones altenuene and isoaltenuene.[20] The best results for the C–C coupling were obtained with palladium(II) acetate as a catalyst, caesium carbonate as a base and S-Phos[14b] as a ligand, which is especially suitable for sterically hindered couplings. With these conditions a concomitant formation of the lactone moiety was achieved, a pleasant side effect already observed in previous syntheses.[20] X-ray crystallographic analysis proved the correct constitution for ulocladol derivative **14** (Figure 2).[18] As expected, the structure is significantly dis-



Scheme 2. Attempted synthesis of ulocladol starting with substituted gallate **8** (cyHe: cyclohexyl).

torted from planarity, an effect similarly observed in NMR spectra, where the diastereotopic methylene groups (2-H_2 and 7-H_2) gave sets of two signals. Coalescence in the ^{1}H NMR spectra was observed at 65 °C (500 MHz). Nevertheless, ulocladol could not be liberated from precursor **14** with any tested method. Neither utilization of Lewis acids like PCl_5[21] or BCl_3,[22] nor oxidative cleavage with lead tetraacetate[23] led to a clean cleavage of the methylene acetal.

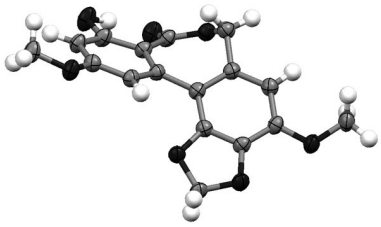
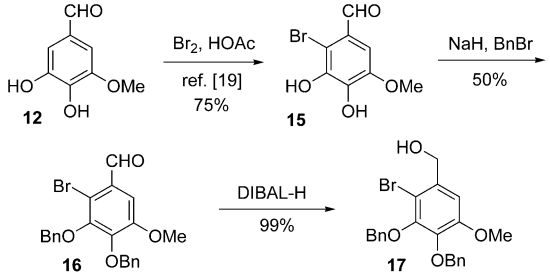


Figure 2. Structure of ulocladol derivative **14** in the crystal.[18]

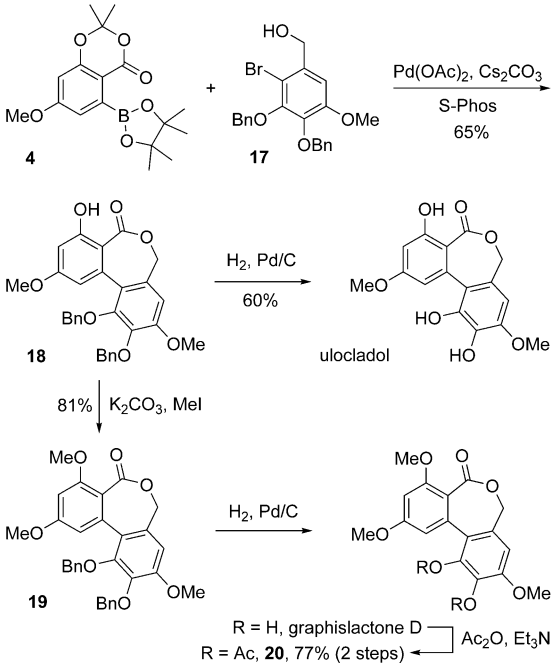
Consequently, we followed a different strategy starting with commercially available 3,4-dihydroxy-5-methoxybenzaldehyde (**12**). Bromide **15** was obtained by conventional bromination with bromine in acetic acid.[19] Dibenzylation only afforded a poor 50% yield due to significant amounts of monobenzylated product isolated and other non-specified side reactions. Subsequent reduction with diisobutylaluminium hydride (DIBAL-H) furnished a suitably protected bromide **17** (Scheme 3).



Scheme 3. Synthesis of the brominated benzyl alcohol **17**.

Suzuki coupling of boronate **4** and bromide **17** using the standard protocol yielded dibenzyl-protected ulocladol **18** with 65% yield, once again with immediate lactonization of the intermediate coupling product (Scheme 4). Hydrogenolytic cleavage of the benzyl groups furnished ulocladol with 60% yield. The total synthesis could thus be completed in 8 steps and 15% yield starting with 3,4-dihydroxy-5-methoxybenzaldehyde (**12**) and protected phloroglucinic acid **1**, where the longest linear sequence consisted of 5 steps. Our approach is thus significantly shorter and more effective than the previously published synthesis.[13]

Graphislactone D was similarly obtained by O^4-methylation of dibenzyl-protected ulocladol **18** and subsequent hydrogenolysis. NMR spectra showed that graphislactone D was essentially pure after deprotection. Nevertheless, it decomposed during chromatography on silica gel. Consequently we acetylated this compound for analytical purposes. The total synthesis of graphislactone D was thus achieved in 9 steps, where the longest linear sequence consisted of 6 steps. The respective acylated compound **20** was obtained with 7% overall yield.

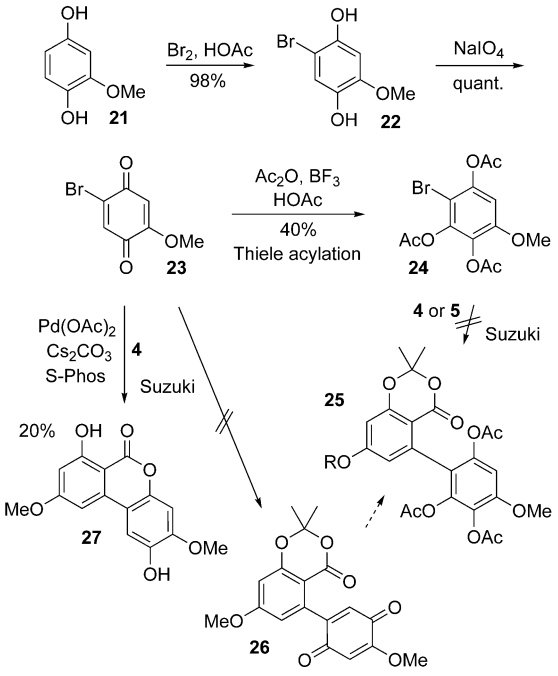


Scheme 4. Total synthesis of ulocladol and of graphislactone D.

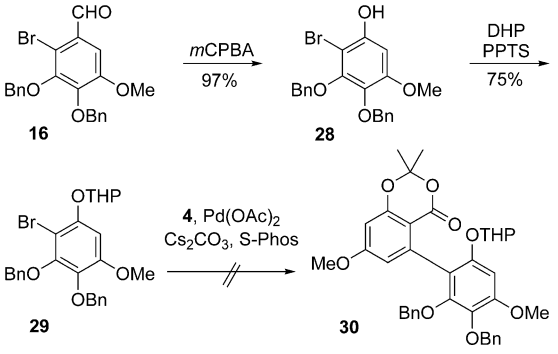
Total Synthesis of Graphislactones E and F

A first strategy for the total synthesis of graphislactones E and F started with purchasable 2-methoxyhydroquinone (**21**). Bromination and oxidation with sodium periodate yielded quinone **23**, which was subjected to a Thiele acylation (Scheme 5).[24] Nevertheless, the resulting highly oxygenated bromide **24** could not be reacted in a Suzuki coupling with any of the reaction conditions we applied. Consequently, we tested a different strategy using intermediate **23** in a Suzuki coupling with an intended subsequent Thiele acylation. But again, the targeted aryl-quinone **26** was not formed, but instead a reduced substrate **27**, which did not seem to be suitable for further transformations.

Aldehyde **16**, used for the synthesis of ulocladol, was assumed to be a suitable alternate starting material for the synthesis of graphislactones E and F. For the preparation of these compounds, a protected tetrahydroxylated bromobenzene was needed (Scheme 6). For this purpose the carbaldehyde function in brominated aldehyde **16** was oxidized with a Dakin reaction.[25] From the tested protocols, *meta*-chloroperbenzoic acid afforded the highest yields.[26] The crude phenol was formed with 97% yield, and was used without further purification. The hydroxy group was protected as tetrahydropyranyl (THP) ether, but Suzuki coupling of the resulting THP-protected substrate with boronate **4** failed even with a protocol optimized for sterically hindered substrates.[14b]



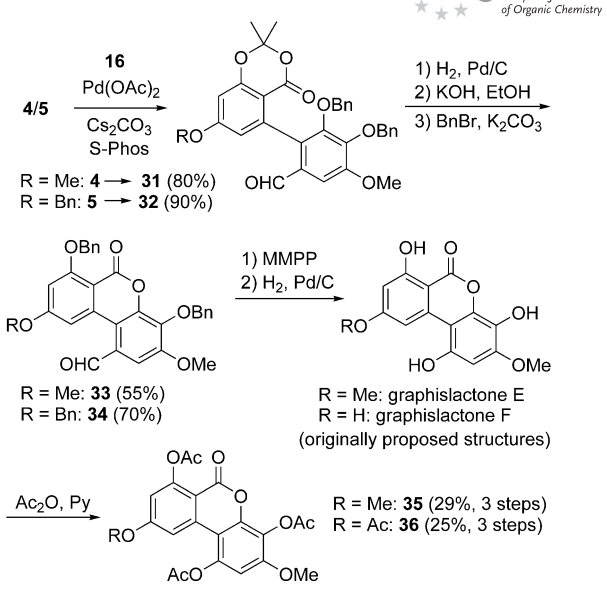
Scheme 5. Attempted synthesis of graphislactones E and F with Thiele acylation and Suzuki coupling as key steps.



Scheme 6. Attempted cross coupling of a highly hindered tetrahydroxyphenyl bromide. DHP: 3,4-dihydro-2*H*-pyrane, PPTS: pyridinium *p*-toluenesulfonate.

In a reversed strategy, boronates **4** and **5**, respectively, were coupled with aldehyde **16** yielding biaryls **31** and **32** with 80 and 90% (Scheme 7). Hydrogenolysis of the benzyl groups, saponification with concomitant translactonization and benzylation of the hydroxy groups yielded a tricyclic carbaldehyde suitable for a Dakin reaction. Oxidative degradation was here best achieved with magnesium monoperphthalate (MMPP).[27] Debenzylation with hydrogenolytic conditions yielded graphislactones E and F, respectively, which were immediately protected as acetates due to their low stability.

It turned out that NMR spectroscopic data of the synthesized acetylated graphislactones E (**35**) and F (**36**) are not identical with data published by Tanahashi et al. (Table 1 and Table 2).[6d] Significant deviations were detected especially in the ^{13}C NMR spectra for carbons C-1, C-2, C-4, and C-4a and in the ^{1}H NMR spectra for hydrogen 2-H. Because re-evaluation of the published data including data from NOE experiments suggested a misassignment of the substrates' constitutions, we now wish to correct the misassignment by giving revised structures in Figure 3, which are in full accordance with the NOE data given in the original paper.



Scheme 7. Total synthesis of the originally proposed structures of graphislactones E and F.

Table 1. Comparison of significant NMR spectroscopic data for acetylated graphislactone E in the originally proposed structure **35** and in the revised structure **41**. Major deviations are given in boldface.[28]

Proposed structure **35**[a]		Synthetic **35**	Revised structure **41**	
Signal	δ [ppm]	δ [ppm][b]	Signal[c]	δ [ppm]
8-H	6.72	6.66	4-H	6.74
2-H	**6.85**	**6.74**	8-H	6.84
10-H	7.82	7.86	10-H	7.82
C-2	**99.1**	**104.3**	C-4	99.1
C-10b	105.1	105.3	C-10b	105.1
C-6a	106.6	106.5	C-6a	106.7
C-10	107.7	108.5	C-10	107.7
C-8	109.5	109.4	C-8	109.6
C-4	**129.8**	**125.2**	C-2	129.9
C-10a	136.8	136.8	C-10a	136.8
C-4a	**141.0**	**145.3**	C-1	141.1
C-1	**150.4**	**145.8**	C-4a	150.5
C-3	153.4	152.5	C-3	153.4
C-7	154.8	154.9	C-7	154.8
C-6	156.9	156.2	C-6	156.9
C-9	164.9	165.0	C-9	164.9

[a] Assignment as given in the original literature.[6d] [b] Signals given in increasing order. [c] Assignment was made according to C,H- and H,H-COSY, NOESY, and HMBC spectra.

Due to our modular synthetic strategy it was no significant additional effort to synthesize these revised structures. Graphislactones E and F were thus obtained starting with boronates **4** and **5** and with phenol **28**. Though Suzuki coupling was only achieved with poor 30 and 36% yield, the acetylated revised structures of graphislactones E (**41**)

Table 2. Comparison of significant NMR spectroscopic data for acetylated graphislactone F in the originally proposed structure **36** and in the revised structure **42**. Major deviations are given in boldface.[28]

Proposed structure **36**[a]		Synthetic **36**	Revised structure **42**	
Signal	δ [ppm]	δ [ppm][b]	Signal[c]	δ [ppm]
2-H	**6.86**	**6.70**	4-H	6.85
8-H	6.99	7.00	8-H	6.99
10-H	8.33	8.36	10-H	8.33
C-2	**100.0**	**104.5**	C-4	**99.0**
C-10b	104.9	105.1	C-10b	104.9
C-6a	110.8	110.7	C-6a	110.8
C-10	114.8	115.5	C-10	114.8
C-8	116.5	116.7	C-8	116.6
C-4	**130.1**	**125.1**	C-2	130.0
C-10a	136.6	136.6	C-10a	136.6
C-4a	**141.1**	**145.1**	C-1	141.1
C-1	**150.2**	**145.8**	C-4a	150.2
C-3	**153.71**	**152.8**	C-3	153.7
C-7	153.74	153.9	C-7	153.8
C-9	155.7	155.8	C-9	155.7
C-6	156.5	[d]	C-6	156.5

[a] Assignment as given in the original literature.[6d] [b] Signals given in increasing order. [c] Assignment was made according to C,H- and H,H-COSY, NOESY-, and HMBC-spectra. [d] One signal is covered.

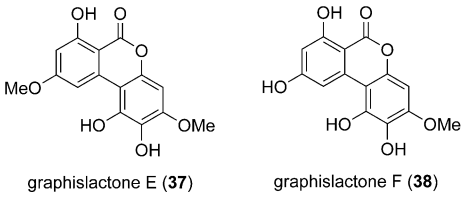
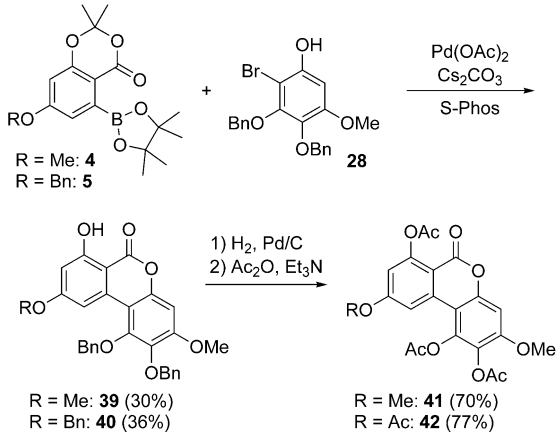


Figure 3. Revised structures of graphislactones E (**37**) and F (**38**).

and F (**42**) were obtained after protection group manipulations with 70 and 77% yield, respectively (Scheme 8). Precursor **39** can furthermore be prepared in superior 70% yield by Dakin degradation of carbaldehyde **31** with concomitant translactonization. Compounds corresponding to the revised structures of graphislactones E and F were synthesized in 8 steps, where the longest linear sequences consisted of 5 steps. The corresponding acylated compounds **41** and **42** were obtained with 8 and 10% yield. The alternative approach to acylated graphislactone E (**42**) via carbaldehyde **31** afforded an overall yield of 26%, though an additional step was necessary in this sequence.

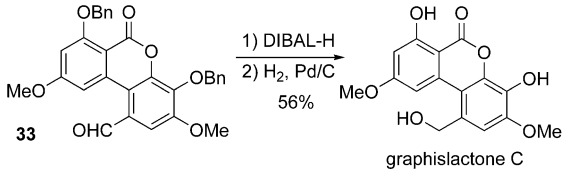


Scheme 8. Total synthesis of the revised structures of acetylated graphislactones E (**41**) and F (**42**).

Data for the revised structures are in full accordance with data given in the original publication (see Tables 1 and 2) giving unambiguous evidence for the revised structures as depicted in Figure 3.

Total Synthesis of Graphislactone C

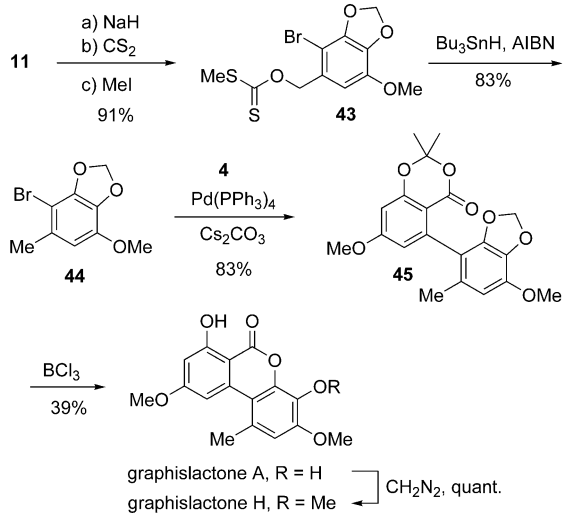
Graphislactone C was accessible in two steps starting with intermediate **33** by reduction of the carbaldehyde function and deprotection in 56% yield (Scheme 9). The total synthesis could thus be completed with 11 steps and 16% yield, where the longest linear sequence consisted of 9 steps.



Scheme 9. Total synthesis of graphislactone C.

Total Synthesis of Graphislactones A and H

The total synthesis of graphislactone A was achieved starting with bromide **11** used for the unsuccessful approach towards the synthesis of ulocladol (Scheme 10). The benzyl alcohol was degraded to a methyl group by a Barton–McCombie protocol with 76% yield. Suzuki coupling was achieved with 83% yield, where formation of a reduced side product **6** made it advantageous to use an excess of the boronate **4**. Subsequent cleavage of the dioxolane ring with boron trichloride furnished graphislactone A. With these conditions, a partial cleavage of the methoxy groups was observed causing a reduced yield of only 39%. Crystals suitable for X-ray crystallographic analysis were obtained, proving the identity of the proposed and synthesized structures (Figure 4).[18] The total synthesis of graphislactone A could thus be completed in 10 steps and with 16% yield, where the longest linear sequence consisted of 7 steps. The synthesis of graphislactone H was achieved for the first time by careful methylation of graphislactone A with diazomethane in quantitative yield. Over-methylation was avoided by portionwise addition of diazomethane with monitoring by thin layer chromatography. The identity of the proposed structure was unambiguously confirmed by comparison of published spectroscopic data,[6a] which are in full agreement with those of the synthesized compound. Here the total synthesis could be completed with 11 steps and 16% yield, where the longest linear sequence consisted of 8 steps.



Scheme 10. Total synthesis of graphislactones A and H.

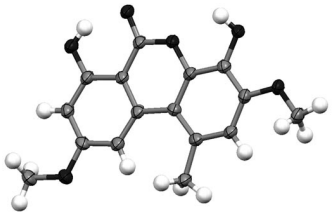


Figure 4. Structure of graphislactone A in the crystal.[18]

Experimental Section

General Remarks: Experimental procedures and spectroscopic data for the preparation of **1** starting with phloroglucinic acid, for **12** starting with vanillin, and an alternative synthesis of alcohol **11** starting with vanillin are given in the supplemental material. Abbreviations: 3,4-Dihydro-2*H*-pyran, (DHP), pyridinium *p*-toluenesulfonate (PPTS), tetrahydropyran (THP). Tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl radical, and CH_2Cl_2 was distilled from CaH_2. All moisture-sensitive reactions were carried out under oxygen-free nitrogen atmosphere using oven-dried glassware and a vacuum line. Flash column chromatography was carried out using Merck SiO_2 60 (230–400 mesh) and thin layer chromatography (tlc) was carried out using commercially available Merck F_{254} pre-coated sheets. Medium pressure liquid chromatography (MPLC): Detection by UV absorption (Latek UVIS 200). ^1H and ^{13}C NMR spectra were recorded with a Bruker Cryospek WM-250, an AM-400, a DRX 500, or with an Avance 600 instrument. Chemical shifts are given in ppm downfield of tetramethylsilane. ^{13}C NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT 135 and DEPT 90 experiments. Melting points were measured with a Büchi apparatus and were not corrected. IR spectra were recorded with a Bruker IFS-88 spectrometer. Elemental analyses were performed with a Heraeus CHN-O-rapid and with an Elementar vario MICRO instrument. EI, FAB and high resolution mass spectra were recorded with a Finnigan MAT-90 mass spectrometer. UV/Vis spectra were recorded on a Perkin–Elmer Lambda 2 spectrometer. The extinction coefficient ε is given for quantitative measurements.

General Procedure 1 for Suzuki Cross Couplings: Degassed solvent (dioxane/H_2O, 6:1, 7 mL/mmol) was added under an argon atmosphere to a mixture of aryl bromide (1 equiv.), boronate (**4** or **5**, 1.3 equiv.), Cs_2CO_3 (3 equiv.), $Pd(OAc)_2$ (0.03 equiv.) and S-Phos (0.06 equiv.). The solution was heated to 80 °C for 2–6 h (monitoring with tlc). After cooling to room temperature, saturated aqueous NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by chromatography (silica gel).

General Procedure 2 for Dakin Reactions:[26] *m*-CPBA (70%, 1.6 equiv.) in CH_2Cl_2 (0.1 M) was added to the respective aromatic aldehyde (1 equiv.) and heated for 18 h to 60 °C. The organic layer was extracted with saturated aqueous $NaHCO_3$ solution and with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in 10% aqueous KOH solution; the solution was stirred for 2 h at room temperature, acidified to pH 2 with 6 N HCl and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and concentrated to yield the respective phenol.

General Procedure 3 for the Hydrogenolytical Cleavage of Benzyl Groups: Pd/C (10–15 mol-%) and MeOH (2 mL) was added to the protected substrate (0.10 mmol). The mixture was stirred under a H_2 atmosphere for 2–24 h at room temperature (monitoring with tlc) and filtered. The filtrate was concentrated to yield the crude product.

Synthesis of Boronates

5-Hydroxy-7-methoxy-2,2-dimethylbenzo[1,3]dioxin-4-one:[15a] Acetonide **1** (2.50 g, 11.9 mmol) was methylated following a published procedure yielding the title compound (2.09 g, 9.32 mmol, 78%).

7-Methoxy-2,2-dimethyl-5-(trifluoromethylsulfonyloxy)benzo[1,3]-dioxin-4-one (2):[15a] Following a published procedure, the phenol synthesized as given above (2.96 g, 13.2 mmol) was converted into triflate **2** (4.44 g, 12.5 mmol, 95%).

7-Methoxy-2,2-dimethyl-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)benzo[1,3]dioxin-4-one (4) and 7-Methoxy-2,2-dimethylbenzo-[1,3]dioxin-4-one (6): Freshly distilled Et_3N (1.18 mL, 8.41 mmol) and $Pd(PPh_3)_4$ (162 mg, 5 mol-%) were added to a solution of triflate **2** (1.00 g, 2.80 mmol) in anhydrous dioxane (50 mL). Oxygen was expelled by ultrasonication under argon for 10 min, and pinacolborane (1.07 mg, 8.41 mmol) was added dropwise within 5 min. The solution was stirred for 2 h at 80 °C, and the solvent was removed in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 10:1) yielding boronate **4** (709 mg, 2.12 mmol, 75%) and the reduced compound **6** (69 mg, 0.33 mmol, 12%).

7-Benzyloxy-5-hydroxy-2,2-dimethylbenzo[1,3]dioxin-4-one:[15b] Following a published procedure, phenol **1** (2.57 g, 12.2 mmol) was converted into the title compound (3.28 g, 10.9 mmol, 90%).

7-Benzyloxy-2,2-dimethyl-5-(trifluoromethylsulfonyloxy)benzo[1,3]-dioxin-4-one (3):[15a] Following a published procedure, the phenol synthesized as given above (2.71 g, 9.04 mmol) was converted into triflate **3** (3.74 g, 8.63 mmol, 95%).

7-Benzyloxy-2,2-dimethyl-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)benzo[1,3]dioxin-4-one (5) and 7-Benzyloxy-2,2-dimethylbenzo-[1,3]dioxin-4-one (7): Freshly distilled Et_3N (5.00 mL, 8.65 mmol) and $Pd(PPh_3)_4$ (490 mg, 5 mol-%) were added to a solution of triflate **3** (3.74 g, 8.65 mmol) in anhydrous dioxane (100 mL). Oxygen

was expelled by ultrasonication under argon for 10 min and pinacolborane (2.51 mL, 17.3 mmol) was added dropwise within 5 min. The solution was stirred for 2 h at 80 °C and the solvent was removed in vacuo. The residue was purified by chromatography (hexanes/EtOAc, 10:1) yielding boronate **5** (2.30 g, 5.61 mmol, 65%) and the reduced compound **7** (849 mg, 2.98 mmol, 34%).

Synthesis of Ulocladol

Methyl 2-Bromo-3,4-dihydroxy-5-methoxybenzoate (9):[17] *N*,*N*′-Dibromo-5,5-dimethylhydantoin (DBDMH, 20.7 g, 67.7 mmol) was added portionwise to a solution of methyl ester **8** (26.2 g, 133 mmol) in $CHCl_3$ (700 mL). Every addition led to a red-brown colour, and the next portion was added after a significant decolouration. The mixture was stirred overnight, washed with 10% aqueous $Na_2S_2O_4$ solution (3 × 300 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield a brownish residue of **9** (35.7 g, 129 mmol, 97%).

Methyl 4-Bromo-7-methoxybenzo[1,3]dioxole-5-carboxylate (10):[17] A mixture of **9** (10.0 g, 36.1 mmol), KF (10.5 g, 181 mmol), CH_2I_2 (4.31 mL, 54.1 mmol), and anhydrous DMF (350 mL) was stirred for 2 h at 110 °C and extracted with Et_2O (3 × 200 mL) after cooling. The combined organic layers were washed with brine (3 × 150 mL), dried (Na_2SO_4), concentrated and the residue was purified by chromatography (hexanes/EtOAc, 4:1) yielding **10** as a colourless solid (7.50 g, 25.9 mmol, 72%).

(4-Bromo-7-methoxybenzo[1,3]dioxol-5-yl)methanol (11) and (7-Methoxybenzo[1,3]dioxol-5-yl)methanol: A solution of **10** (1.00 g, 3.46 mmol) in anhydrous Et_2O (50 mL) was added within 10 min at 0 °C under an argon atmosphere to a suspension of $LiAlH_4$ (147 mg, 3.76 mmol) in anhydrous Et_2O (20 mL), and the mixture was stirred for 15 min. H_2O (0.15 mL), 5 N NaOH (0.15 mL), and H_2O (0.45 mL) were added very carefully, and the mixture was stirred for 30 min and filtered through celite. Extraction with Et_2O (4 × 30 mL), combination of the organic layers, concentration and purification of the residue with chromatography (hexanes/EtOAc, 2:1) yielded **11** as a colourless solid (696 mg, 2.67 mmol, 77%). Debrominated substrate was obtained as a side product.

6,8-Dihydro-9-hydroxy-4,11-dimethoxybenz[1,3]dioxolo[4,5-*e*]benzo-[*c*]oxepin-8-one (14): Bromide **11** (130 mg, 0.5 mmol) and boronate **4** (217 mg, 0.65 mmol) were reacted according to general procedure 1 for 3 h. Purification by MPLC (CH_2Cl_2) yielded **14** (101 mg, 0.31 mmol, 61%) as a colourless solid.

3,4-Bis(benzyloxy)-2-bromo-5-methoxybenzaldehyde (16): A suspension of NaH (60% in paraffin, 910 mg, 26.2 mmol) was placed with exclusion of air and moisture in anhydrous DMF (15 mL). At –78 °C, bromide **15** (3.00 g, 12.2 mmol) in anhydrous DMF (15 mL) and BnBr (5.19 g, 30.3 mmol) were added successively. After stirring for an additional 15 min at –78 °C, the mixture was warmed to room temperature. H_2O (200 mL) was added, and the mixture was extracted with EtOAc (4 × 20 mL). The organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by chromatography (hexanes/EtOAc, 10:1) to yield **16** as a colourless solid (2.55 g, 5.97 mmol, 50%).

[3,4-Bis(benzyloxy)-2-bromo-5-methoxyphenyl]methanol (17): DIBAL-H (1 M in toluene, 3.28 mL, 3.28 mmol) was added at –78 °C within 5 min to a solution of aldehyde **16** (700 mg, 1.64 mmol) in anhydrous THF (10 mL). After stirring for 2 h at –78 °C, HCl (1 M, 3 mL) and H_2O (10 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were dried (Na_2SO_4) and concentrated, yielding crude alcohol **17** (695 mg, 1.62 mmol, 99%) as a colourless solid, which was used without further purification.

10,11-Bis(benzyloxy)-4-hydroxy-2,9-dimethoxy-7*H*-dibenzo[*c*,*e*]oxepin-5-one (18) and 7,7′-Dimethoxy-2,2,2′,2′-tetramethyl[5,5′]bi-[benzo[1,3]dioxinyl]-4,4′-dione: According to general procedure 1, bromide **17** (430 mg, 1 mmol) and boronate **4** (434 mg, 1.3 mmol) were reacted for 2 h. Purification by chromatography (hexanes/EtOAc, 10:1 to 6:1) yielded **18** (325 mg, 0.65 mmol, 65%) as a colourless solid. Homocoupling resulted in a biphenyl derivative (84 mg, 0.22 mmol, 20%) as a side product.

4,10,11-Trihydroxy-2,9-dimethoxy-7*H*-dibenzo[*c*,*e*]oxepin-5-one (Ulocladol): According to general procedure 3, protected ulocladol **18** (96.0 mg, 0.192 mmol) was reacted for 2 h and purified by chromatography (CH_2Cl_2/MeOH, 20:1) to yield ulocladol as a colourless solid (36.0 mg, 0.11 mmol, 60%). NMR spectroscopic data were assigned according to H,H-COSY, C,H-COSY, and HMBC spectra; m.p. 180–182 °C. R_f (CH_2Cl_2/MeOH, 10:1) = 0.55. IR (DRIFT): $\tilde{\nu}$ = 3429 (s), 2949 (m), 1652 (s, C=O), 1616 (s), 1569 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, 9-OMe), 3.93 (s, 3 H, 2-OMe), 4.79 (d, ^2J = 12.0 Hz, 1 H, CH_aH$_b$), 5.11 (d, ^2J = 12.0 Hz, 1 H, CH$_a$$H_b$), 5.98 (br. s, 2 H, 10-OH, 11-OH), 6.57 (d, ^4J = 2.6 Hz, 1 H, 3-H), 6.59 (s, 1 H, 8-H), 6.94 (d, ^4J = 2.6 Hz, 1 H, 1-H), 10.30 (s, 1 H, 4-OH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.5 (q, 2-OMe), 56.3 (q, 9-OMe), 70.3 (t, C-7), 100.7 (d, C-3), 103.4 (d, C-9), 106.5 (s, C-4a), 110.2 (d, C-1), 118.7 (s, C-11a), 126.9 (s, C-7a), 133.9 (s, C-10), 135.9 (s, C-11), 142.2 (s, C-1a), 146.4 (s, C-8), 162.9 (s, C-4), 163.2 (s, C-2), 172.5 (s, C-5) ppm. UV/Vis: λ^{EtOH} (ε) = 204 (>100,000), 235 (29,000), 286 (3,800) nm. MS (EI, 130 °C): *m*/*z* (%) = 318 (100) [M$^+$], 301 (12) [[M – OH]$^+$], 300 (63), 274 (12), 273 (17), 259 (14), 254 (16), 84 (33), 66 (36), 43 (27). HRMS ($^{12}C_{16}{}^1H_{14}{}^{16}O_7$, FAB): calcd. 318.0740; found 318.0737. Analytical data are in full accordance with published data.[8a]

Synthesis of Graphislactone D

10,11-Bis(benzyloxy)-2,4,9-trimethoxy-7*H*-dibenzo[*c*,*e*]oxepin-5-one (19): K_2CO_3 (113 mg, 0.820 mmol) and MeI (116 mg, 0.82 mmol) were added to a solution of phenol **18** (203 mg, 0.41 mmol) in anhydrous acetone. The mixture was heated to reflux for 12 h, concentrated and purified by chromatography (CH_2Cl_2) to yield methyl ether **19** (169 mg, 0.33 mmol, 81%) as a colourless solid.

10,11-Dihydroxy-2,4,9-trimethoxy-7*H*-dibenzo[*c*,*e*]oxepin-5-one (Graphislactone D): Bisbenzyl ether **19** (16 mg, 0.031 mmol) was treated with Pd/C (10 mol-%) for 2 h according to general procedure 3. The crude graphislactone D contained only small amounts of impurities. Chromatographic purification led to decomposition. R_f (CH_2Cl_2/MeOH, 10:1) = 0.23. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.50–2.00 (br. s, 2 H, OH), 3.87 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 4.72 (d, ^2J = 11.9 Hz, 1 H, 7-CH$_2$), 4.97 (d, ^2J = 11.9 Hz, 1 H, 7-CH$_2$), 6.53 (d, ^4J = 2.3 Hz, 1 H, Ar-H), 6.58 (s, 1 H, 8-H), 6.95 (d, ^4J = 2.3 Hz, 1 H, Ar-H) ppm. Analytical data are in full accordance with published data.[6a]

10,11-Diacetoxy-2,4,9-trimethoxy-7*H*-dibenzo[*c*,*e*]oxepin-5-one (Acetylated Graphislactone D, 20): Bisbenzyl ether **19** (183 mg, 0.031 mmol) was treated with Pd/C (10 mol-%) for 2 h according to general procedure 3. Ac_2O (100 μL, 1.06 mmol) and anhydrous pyridine (86 μL, 1.06 mmol) were added to the crude graphislactone D dissolved in CH_2Cl_2 (5 mL). The mixture was stirred for 12 h at room temperature under argon, then it was washed with HCl (0.1 M, 3 mL) and saturated aqueous $NaHCO_3$ solution (3 mL). The organic layers were dried (Na_2SO_4), concentrated and purified by precipitation from H_2O/MeCN. Lyophilisation yielded acetylated graphislactone D (**20**) (50 mg, 0.120 mmol, 34%) as a colourless solid. NMR spectroscopic data were assigned according to H,H-COSY, C,H-COSY, and HMBC spectra; m.p. 223–225 °C.

R_f (CH_2Cl_2/MeOH, 10:1) = 0.30. IR (DRIFT): $\tilde{\nu}$ = 2935 (m), 2849 (m), 1784 (s, C=O), 1725 (C=O), 1599 (s), 1504 (s), 1457 (s), 1415 (s), 1373 (s), 1328 (s), 1294 (m), 1265 (m), 1243 (m), 1209 (s), 1187 (s), 1159 (s), 1083 (s) cm^{-1}. ^1H NMR (400 MHz. $CDCl_3$): δ = 2.18 (s, 3 H, OAc), 2.31 (s, 3 H, OAc), 3.82 (s, 3 H, 2-OMe), 3.89 (s, 6 H, 4-OMe, 9-OMe), 4.81 (d, ^2J = 12.1 Hz, 1 H, CH_aH_b), 4.96 (d, ^2J = 12.1 Hz, 1 H, CH_aH_b), 6.55 (d, ^4J = 2.3 Hz, 1 H, 3-H), 6.59 (d, ^4J = 2.3 Hz, 1 H, 1-H), 6.96 (s, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz. $CDCl_3$): δ = 20.3 (q, OAc), 20.4 (q, OAc), 55.5 (q, OMe-2), 56.2 (q, OMe), 56.4 (q, OMe), 68.5 (t, C-7), 99.1 (d, C-3), 104.8 (d, C-1), 110.0 (d, C-8), 113.5 (s), 124.7 (s), 133.6 (s), 134.6 (s), 134.8 (s), 141.5 (s), 152.1 (s, C-9), 159.8 (s, C-4), 161.7 (s, C-2), 165.6 (s), 167.3 (s), 167.5 (s) ppm. UV/Vis: λ^{EtOH} = 202, 251 nm. MS (FAB): *m*/*z* (%) = 417 (83) [[M + H]$^+$], 136 (58). HRMS ($^{12}C_{21}{}^1H_{21}{}^{16}O_9$, FAB): calcd. 417.1185; found 417.1183. Analytical data are in full accordance with published data.[6d]

Synthesis of Graphislactones E and F

2-Methoxybenzene-1,4-diol (2-Methoxyhydroquinone, 21):[29] Vanillin (5.00 g, 32.9 mmol) was reacted according to a published procedure to yield hydroquinone **21** (3.22 g, 22.9 mmol, 70%) as a yellowish solid.

2-Bromo-5-methoxybenzene-1,4-diol (22):[30] Bromination of hydroquinone **21** (3.00 g, 21.4 mol) was achieved according to a published procedure yielding **22** as brown crystals (2.96 g, 13.5 mmol, 63%)after recrystallization from benzene.

2-Bromo-5-methoxy[1,4]benzoquinone (23):[30] Bromide **22** (1.56 g, 7.12 mmol) was oxidized according to a published procedure yielding quinone **23** (1.46 g, 6.73 mmol, 95%).

1,3,4-Triacetoxy-2-bromo-5-methoxybenzene (24):[31] Thiele acylation of quinone **23** (4.03 g, 18.6 mmol) was achieved following a published procedure. Purification by chromatography (hexanes/EtOAc, 4:1) triacetate yielded **24** (2.70 g, 7.48 mmol, 40%) as a colourless solid and starting material (1.20 g, 5.53 mmol, 30%).

2,7-Dihydroxy-3,9-dimethoxybenzo[*c*]chromen-6-one (27): Bromoquinone **23** (109 mg, 0.50 mmol) and boronate **4** (334 mg, 1 mmol) were reacted according to general procedure 1 for 5 h. Purification by chromatography (hexanes/EtOAc, 8:1) yielded lactone **27** (28 mg, 0.10 mmol, 20%) as a colourless solid.

3,4-Bis(benzyloxy)-2-bromo-5-methoxyphenol (28): According to general procedure 2 aldehyde **16** (1.62 g, 3.79 mmol) was oxidized, yielding phenol **28** (1.52 g, 3.67 mmol, 97%) as reddish brown oil, which could not be further purified because it decomposed during chromatography. It was thus used as crude material.

2-[3,4-Bis(benzyloxy)-2-bromo-5-methoxyphenoxy]tetrahydro-2*H*-pyran (29): Phenol **28** (831 mg, 1.96 mmol), DHP (495 mg, 5.87 mmol) and PPTS (25 mg, 0.10 mmol) were dissolved in CH_2Cl_2 (10 mL) and stirred for 12 h at room temperature. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried (Na_2SO_4), concentrated and purified by chromatography (hexanes/EtOAc, 10:1), yielding THP-protected product **29** (724 mg, 1.45 mmol, 75%) as a colourless oil.

The unsucessful reaction of **29** towards coupling product **30** is given in the Supporting Information.

3,4-Bis(benzyloxy)-5-methoxy-2-(7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[1,3]dioxin-5-yl)-benzaldehyde (31): Bromide **16** (100 mg, 0.23 mmol) and boronate **4** (99 mg, 0.30 mmol) were reacted according to general procedure 1 for 1.5 h. Purification by MPLC (hexanes/EtOAc, 8:1) yielded **31** (103 mg, 0.18 mmol, 80%) as a colourless solid.

3,4-Bis(benzyloxy)-2-(7-benzyloxy-2,2-dimethyl-4-oxo-4*H*-benzo[1,3]-dioxin-5-yl)-5-methoxybenzaldehyde (32): Bromide **16** (106 mg, 0.25 mmol) and boronate **5** (135 mg, 0.33 mmol) were reacted according to general procedure 1 for 1.5 h. Purification by MPLC (hexanes/EtOAc, 8:1) yielded **32** (144 mg, 0.23 mmol, 90%) as a colourless solid.

3,4-Dihydroxy-5-methoxy-2-(7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[1,3]dioxin-5-yl)benzaldehyde: Aldehyde **31** (56.0 mg, 0.10 mmol), Pd/C (5%, 21 mg, 10 mol-%), and EtOAc (3 mL) were stirred under a hydrogen atmosphere for 2 h at room temperature. The mixture was filtered, and the filtrate was concentrated to yield the title compound (31.0 mg, 0.098 mmol, 98%) as a colourless solid, which was used without further purification.

4,7-Bis(benzyloxy)-3,9-dimethoxy-6-oxo-6*H*-benzo[*c*]chromene-1-carbaldehyde (33): The catechol synthesized as given above (100 mg, 0.27 mmol) was dissolved in KOH solution (1 M in EtOH, 15 mL) and stirred for 1 h at 60 °C. The mixture was cooled to room temperature, acidified with aqueous 1 M HCl (pH 2), and extracted with EtOAc (3 × 15 mL). The organic layers were dried (Na_2SO_4) and concentrated to yield lactone **30** (56 mg, 0.17 mmol, 66%). To this residue was added under argon K_2CO_3 (71.0 mg, 0.51 mmol), anhydrous DMF (5 mL), and BnBr (87.0 mg, 0.51 mmol), and the solution was stirred at room temperature overnight. The mixture was diluted with H_2O (35 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were dried (Na_2SO_4), concentrated, and purified by chromatography (hexanes/EtOAc, 8:1 to 2:1) yielding **33** (74.0 mg, 0.15 mmol, 82%, 55% over 3 steps) as a colourless solid.

1,2,9-Tris(benzyloxy)-3-methoxy-6-oxo-6*H*-benzo[*c*]chromene-1-carbaldehyde (34): Aldehyde **32** (200 mg, 0.38 mmol) was deprotected in EtOAc overnight according to general procedure 3, and the crude product was treated with KOH (1 M in EtOH, 15 mL) and stirred for 1 h at 60 °C. The mixture was cooled to room temperature, acidified with aqueous 1 M HCl to pH 2, and extracted with EtOAc (3 × 15 mL). The organic layers were dried (Na_2SO_4) and concentrated to yield the debenzylated substrate as a crude product (84 mg, 0.28 mmol, 88%), which was treated under argon with K_2CO_3 (192 mg, 1.39 mmol), anhydrous DMF (5 mL), and BnBr (238 mg, 1.39 mmol) and stirred at room temperature overnight. The mixture was diluted with H_2O (35 mL), extracted with EtOAc (3 × 15 mL) and the organic layers were dried (Na_2SO_4), concentrated and purified by chromatography (hexanes/EtOAc, 8:1 to 2:1) to yield **34** (124 mg, 0.22 mmol, 78%, 70% over 3 steps) as a colourless solid.

4,7-Bis(benzyloxy)-1-hydroxy-3,9-dimethoxybenzo[*c*]chromen-6-one: MMPP (152 mg, 0.30 mmol) and MeOH (3 mL) were added to aldehyde **33** (51 mg, 0.10 mmol), and the mixture was stirred for 18 h at room temperature. The organic layer was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), and concentrated. Aqueous KOH solution (10%, 5 mL) was added, and the mixture was stirred for 2 h at room temperature, brought to pH 2 with 6 N HCl, and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated to yield the title compound (20 mg, 0.040 mmol, 40%) as a colourless solid.

1,4,7-Triacetoxy-3,9-dimethoxy-6*H*-benzo[*c*]chromen-6-one (Acetylated Graphislactone E, Originally Proposed Structure, 35): The pre-

cursor synthesized as given above (22 mg, 0.042 mmol) was treated with Pd/C (15 mol-%) according to general procedure 3. The crude product was reacted after workup with Ac_2O (32 μL, 0.33 mmol) and anhydrous pyridine (27 μL, 0.33 mmol) and dissolved in anhydrous CH_2Cl_2 (5 mL). The mixture was stirred for 12 h at room temperature under argon, concentrated, and purified by chromatography (hexanes/EtOAc, 2:1) and by subsequent precipitation from H_2O/MeCN. Lyophilisation yielded acetylated graphislactone E (**35**, 13 mg, 0.030 mmol, 73%) as a colourless solid; m.p. 168–170 °C. R_f (hexanes/EtOAc, 1:1) = 0.11. IR (DRIFT): $\tilde{\nu}$ = 2962 (s), 2852 (m), 1775 (s, C=O), 1737 (s, C=O), 112 (s), 1566 (m), 1451 (m), 1369 (m), 1343 (m), 1260 (s), 1244 (s), 1179 (s), 1021 (s) cm^{-1}. Assignment of NMR spectroscopic data was made according to H,H-COSY, C,H-COSY, NOESY, and HMBC spectra. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, 4-OAc), 2.41 (s, 3 H, 7-OAc), 2.47 (s, 3 H, 1-OAc), 3.88 (s, 3 H, 3-OMe), 3.93 (s, 3 H, 9-OMe), 6.66 (s, 1 H, 2-H), 6.74 (d, ^4J = 2.4 Hz, 1 H, 8-H), 7.86 (d, ^4J = 2.4 Hz, 1 H, 10-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.4 (q, OAc-4), 21.2 (q, OAc-7), 21.6 (q, OAc-1), 55.9 (q, OMe-9), 56.5 (q, OMe-3), 104.3 (d, C-2), 105.3 (s, C-10b), 106.5 (s, C-6a), 108.5 (d, C-10), 109.4 (d, C-8), 125.2 (s, C-4), 136.8 (s, C-10a), 145.3 (s, C-4a), 145.8 (s, C-1), 152.5 (s, C-3), 154. 9 (s, C-7), 156.2 (s, C-6); 165.0 (s, C-9), 168.2 (s, 2 C, OAc-2 and OAc-4), 169.5 (s, OAc-7) ppm. UV/Vis: λ^{EtOH} = 193, 234, 258, 284, 325 nm. MS (FAB): *m/z* (%) = 431 (12) [[M + H]$^+$], 389 (36), 136 (48), 133 (100). HRMS ($^{12}C_{21}{}^1H_{19}{}^{16}O_{10}$, FAB): calcd. 431.0978; found 431.0974.

4,7,9-Tris(benzyloxy)-1-hydroxy-3-methoxybenzo[*c*]chromen-6-one: MMPP (237 mg, 0.48 mmol) and MeOH (3 mL) were added to aldehyde **34** (90 mg, 0.16 mmol), and the mixture was stirred for 18 h at room temperature. The organic layer was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), and concentrated. Aqueous KOH solution (10%, 5 mL) was added, and the mixture was stirred for 2 h at room temperature, brought to pH 2 with 6 N HCl, and extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated to yield the title compound (32 mg, 0.057 mmol, 35%) as a colourless solid.

1,4,7,9-Tetraacetoxy-3-methoxy-6*H*-benzo[*c*]chromen-6-one (Acetylated Graphislactone F, Originally Proposed Structure, 36): The precursor synthesized as given above (17 mg, 0.028 mmol) was treated with Pd/C (15 mol-%) according to general procedure 3. The crude product was reacted after workup with Ac_2O (32 μL, 0.34 mmol) and anhydrous pyridine (27 μL, 0.34 mmol), and dissolved in anhydrous CH_2Cl_2 (5 mL). The mixture was stirred for 12 h at room temperature under argon, concentrated, and purified by chromatography (hexanes/EtOAc, 2:1) to yield acetylated graphislactone F (**36**, 9.2 mg, 0.020 mmol, 71%) as a colourless solid; m.p. 200–203 °C. R_f (hexanes/EtOAc, 1:1) = 0.09. IR (DRIFT): $\tilde{\nu}$ = 2940 (m), 1772 (s, C=O), 1626 (s, C=O), 1608 (s, C=O), 1519 (m), 1438 (s), 1390 (m), 1367 (s), 1346 (m), 1239 (m), 1187, (s), 1139 (s) cm^{-1}. Assignment of NMR spectroscopic data was made according to H,H-COSY, C,H-COSY, NOESY, and HMBC spectra. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, 9-OAc), 2.41 (s, 3 H, 4-OAc), 2.42 (s, 3 H, 7-OAc), 2.47 (s, 3 H, 1-OAc), 3.90 (s, 3 H, 3-OMe), 6.70 (s, 1 H, 2-H), 7.00 (d, ^4J = 2.2 Hz, 1 H, 8-H), 8.36 (d, ^4J = 2.2 Hz, 1 H, 10-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.4 (q, OAc-4), 21.1 (q, 2 C, OAc-1 and 9), 21.4 (q, OAc-7), 56.5 (q, OMe-3), 104.5 (s, C-2), 105.1 (s, C-10b), 110.7 (s, C-6a), 115.5 (d, C-10), 116.7 (d, C-8), 125.1 (s, C-4), 136.6 (s, C-10a), 145.1 (s, C-4a), 145.8 (s, C-1), 152.8 (s, C-3), 153.9 (s, C-7), 155.8 (s, C-6), 167.8 (s, OAc-9), 168.1 (s, OAc-4), 168.3 (s, OAc-1), 169.3 (s, OAc-7) ppm; the signal for C-9 is covered. UV/Vis: λ^{EtOH} = 195, 229, 251, 323 nm. MS (FAB): *m/z* (%) = 459 (23) [[M + H]$^+$], 417 (38) [M – $C_2H_2O^+$], 375 (21), 155 (25), 136 (77). HRMS ($^{12}C_{22}{}^1H_{19}{}^{16}O_{11}$, FAB): calcd. 459.0927; found 459.0930.

1,2-Bis(benzyloxy)-7-hydroxy-3,9-dimethoxy-6*H*-benzo[*c*]chromen-6-one (39). Method 1: Bromide **28** (118 mg, 0.280 mmol) and boronate **4** (123 mg, 0.360 mmol) were reacted according to general procedure 1 for 2.5 h. Purification by chromatography (hexanes/EtOAc, 10:1) yielded product **39** (42 mg, 0.090 mmol, 30%) as a colourless solid.

Method 2: Aldehyde **31** (49 mg, 0.09 mmol) was reacted according to general procedure 2 for 18 h at 45 °C. The resulting crude product was purified by chromatography (hexanes/EtOAc, 10:1) yielding product **39** (30 mg, 0.06 mmol, 70%) as a colourless solid.

1,2,7-Triacetoxy-3,9-dimethoxy-6*H*-benzo[*c*]chromen-6-one (Acetylated Graphislactone E, Revised Structure, 41): Bisbenzyl ether **39** (80 mg, 0.14 mmol) was treated with Pd/C (15 mol-%) according to general procedure 3. The crude product was reacted after workup with Ac_2O (105 μL, 1.11 mmol) and anhydrous pyridine (90 μL, 1.11 mmol), and dissolved in anhydrous CH_2Cl_2 (5 mL). The mixture was stirred for 12 h at room temperature under argon, concentrated, and purified by chromatography (hexanes/EtOAc, 2:1) to yield acetate **41** (25 mg, 0.057 mmol, 70%) as a colourless solid; m.p. 183–185 °C. R_f (hexanes/EtOAc, 1:1) = 0.12. IR (DRIFT): $\tilde{\nu}$ = 2943 (m), 1789 (s, C=O), 1734 (s, C=O), 1607 (s, C=O), 1560 (m), 1505 (m), 1419 (s), 1373 (s), 1350 (s), 1301 (m), 1240 (s), 1194 (s), 1153 (s), 1118 (m) cm^{-1}. Assignment of NMR spectroscopic data was made according to H,H-COSY, C,H-COSY, NOESY, and HMBC spectra. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, 2-OAc), 2.43 (s, 3 H, 7-OAc), 2.45 (s, 3 H, 1-OAc), 3.90 (s, 3 H, 9-OMe), 3.92 (s, 3 H, 3-OMe), 6.84 (s, 1 H, 4-H), 6.74 (d, ^4J = 2.4 Hz, 1 H, 8-H), 7.82 (d, ^4J = 2.4 Hz, 1 H, 10-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.2 (q, OAc-2), 20.8 (q, OAc-1), 21.2 (q, OAc-7), 55.8 (q, OMe-3), 56.5 (q, OMe-9), 99.1 (d, C-4), 105.1 (s, C-10b), 106.7 (s, C-6a), 107.7 (d, C-10), 109.6 (d, C-8), 129.9 (s, C-2), 136.8 (s, C-10a), 141.1 (s, C-1), 150.5 (s, C-4a), 153.4 (s, C-3), 154.8 (s, C-7), 156.9 (s, C-6), 164.9 (s, C-9), 167.0 (s, OAc-1), 167.6 (s, OAc-2), 169.6 (s, OAc-7) ppm. UV/Vis: λ^{EtOH} = 194, 225, 256, 300, 323 nm. MS (FAB): *m/z* (%) = 431 (29) [[M + H]$^+$], 389 (75) [M – $C_2H_2O^+$], 347 (35), 304 (39), 136 (100). HRMS ($^{12}C_{19}{}^1H_{17}{}^{16}O_{10}$, FAB): calcd. 389.0872; found 389.0869. Analytical data are in full accordance with published data.[6d]

1,2,9-Tris(benzyloxy)-7-hydroxy-3-methoxy-6*H*-benzo[*c*]chromen-6-one (40): Bromide **28** (204 mg, 0.490 mmol) and boronate **5** (263 mg, 0.640 mmol) were reacted for 2.5 h according to general procedure 1. Chromatography (hexanes/EtOAc, 10:1) yielded product **40** (98 mg, 0.18 mmol, 36%) as a colourless solid.

1,2,7,9-Tetraacetoxy-3-methoxy-6*H*-benzo[*c*]chromen-6-one (Acetylated Graphislactone F, Revised Structure, 42): Bisbenzyl ether **40** (35 mg, 0.061 mmol) was treated with Pd/C (15 mol-%) according to general procedure 3. The crude product was reacted after workup with Ac_2O (73 μL, 0.74 mmol) and anhydrous pyridine (60 μL, 0.74 mmol), and dissolved in anhydrous CH_2Cl_2 (5 mL). The mixture was stirred for 12 h at room temperature under argon, concentrated, and purified by chromatography (hexanes/EtOAc, 2:1) to yield acetate **42** (21 mg, 0.047 mmol, 77%) as a colourless solid; m.p. 208–210 °C. R_f (hexanes/EtOAc, 2:1) = 0.11. IR (DRIFT): $\tilde{\nu}$ = 1781 (s, C=O), 1764 (s, C=O), 1625 (s), 1609 (s), 1427 (m), 1370 (s), 1350 (s), 1300 (m), 1200 (s), 1142 (s) cm^{-1}. Assignment of NMR spectroscopic data was made according to H,H-COSY, C,H-COSY, and HMBC spectra. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, 2-OAc), 2.35 (s, 3 H, 9-OAc), 2.43 (s, 3 H, 7-OAc), 2.46 (s, 3 H, 1-OAc), 3.91 (s, 3 H, 3 OMe), 6.85 (s, 1 H, 4-H), 6.99 (d, ^4J = 2.2 Hz, 1 H, 8-H), 8.33 (d, ^4J = 2.2 Hz, 1 H,

10-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.2 (q, OAc-7), 20.6 (q, OAc-9), 21.0 (q, OAc-2), 21.4 (q, OAc-1), 56.5 (q, OMe-3), 99.0 (d, C-4), 104.9 (s, C-10b), 110.8 (s, C-6a), 114.8 (d, C-10), 116.6 (d, C-8), 130.0 (s, C-2), 136.6 (s, C-10a), 141.1 (s, C-1), 150.2 (s, C-4a), 153.7 (s, C-3), 153.8 (s, C-7), 156.5 (s, C-6), 167.1 (s, OAc-2), 167.5 (s, OAc-1), 167.7 (s, OAc-9), 169.2 (s, OAc-7) ppm. UV/Vis: λ^{MeOH} = 221, 243, 278, 299, 328 nm. MS (FAB): *m*/*z* (%) = 459 (40) [[M + H]$^+$], 417 (100). HRMS ($^{12}C_{22}{}^1H_{19}{}^{16}O_{11}$, FAB): calcd. 459.0927; found 459.0932. Analytical data are in full accordance with published data.[6d]

Synthesis of Graphislactone C

4,7-Bis(benzyloxy)-1-hydroxymethyl-3,9-dimethoxybenzo[*c*]chromen-6-one: DIBAL-H (1 M in toluene, 0.20 mL, 0.20 mmol) was added dropwise at –78 °C with exclusion of air and moisture to a solution of aldehyde **33** (50 mg, 0.10 mmol) in anhydrous THF (6 mL). The reaction was quenched after stirring for 2 h at –78 °C by addition of aqueous HCl (1 M, 2 mL) and H_2O (3 mL). The mixture was extracted with EtOAc (3 × 3 mL), and the organic layers were dried (Na_2SO_4), concentrated and purified by chromatography (CH_2Cl_2/MeOH, 50:1) to yield the title compound as a colourless solid (35 mg, 0.07 mmol, 70%).

4,7-Dihydroxy-1-hydroxymethyl-3,9-dimethoxybenzo[*c*]chromen-6-one (Graphislactone C): Protected graphislactone C as synthesized above (16 mg, 0.03 mmol) in EtOAc (3 mL) was deprotected according to general procedure 3 at room temperature overnight, yielding graphislactone C as a colourless solid (8.00 mg, 0.025 mmol, 79%); m.p. 213–215 °C. R_f (CH_2Cl_2/MeOH, 20:1) = 0.54. IR (DRIFT): $\tilde{\nu}$ = 3326 (s, OH), 3142 (s, OH), 1663 (s, C=O), 1609 (s), 1585 (m), 1471 (m), 1413 (s), 1325 (s), 1249 (s), 1123 (s) cm^{-1}. Assignment of NMR spectroscopic data was made according to H,H-COSY, C,H-COSY, and HMBC spectra. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 6 H, 2 OMe), 4.78 (d, ^3J = 4.9 Hz, 2 H, C*H*$_2$OH), 5.65 (t, ^3J = 4.9 Hz, 1 H, CH$_2$O*H*), 6.66 (d, ^4J = 2.1 Hz, 1 H, Ar*H*), 7.18 (s, 1 H, 2-H), 7.62 (d, ^4J = 2.1 Hz, 1 H, Ar*H*), 9.48 (s, 1 H, 4-OH), 11.76 (s, 1 H, 7-OH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 56.3 (q), 56.6 (q), 63.6 (t), 99.2 (s), 100.5 (d), 105.2 (d), 111.8 (s), 112 (d), 129.8 (s), 133.9 (s), 137.5 (s), 140.9 (s), 148.6 (s), 164.3 (s), 164.9 (s), 166.9 (s) ppm. UV/Vis: λ^{MeOH} = 193, 235, 259, 288, 299, 340 nm. MS (FAB): *m*/*z* (%) = 319 (20) [[M + H]$^+$], 217 (45), 136 (68). HRMS ($^{12}C_{16}{}^1H_{15}{}^{16}O_7$, FAB): calcd. 319.0818; found 319.0815. Analytical data are in full accordance with published data.[6a]

Synthesis of Graphislactones A and H

***O*-[(4-Bromo-7-methoxybenzo[1,3]dioxol-5-yl)methyl] *S*-Methyl Dithiocarbonate (43):** NaH (60%, 97 mg, 2.25 mmol) was added at room temperature to a solution of **11** (307 mg, 1.18 mmol) in anhydrous THF (9 mL), and the mixture was stirred for 30 min. CS_2 (15 mL, 2.4 mmol) was added, and the yellow-turning mixture was stirred for 1 h. MeI (0.45 mL, 7.23 mmol) was added, and the mixture was stirred for 45 min, diluted with CH_2Cl_2 (15 mL), carefully (!) extracted with H_2O (30 mL), dried (Na_2SO_4) and concentrated. The resulting yellow solid was purified by chromatography (hexanes/EtOAc, 4:1) to yield xanthogenate **43** (374 mg, 1.06 mmol, 91%) as a white solid.

4-Bromo-7-methoxy-5-methylbenzo[1,3]dioxole (44): A solution of Bu_3SnH (3.22 mL, 11.6 mmol) and AIBN (161 mg, 0.74 mmol) in toluene (50 mL) was added at 85 °C to a degassed solution of **43** (2.57 g, 7.31 mmol) in toluene (50 mL), and the solution was stirred for 40 min at this temperature. After cooling to room temperature, the mixture was concentrated and purified by chromatography (hexanes/EtOAc, 4:1) to yield **44** as a white solid (1.49 g, 6.08 mmol, 83%).

7-Methoxy-5-(7-methoxy-5-methylbenzo[1,3]dioxol-4-yl)-2,2-dimethyl-4*H*-benzo[1,3]dioxin-4-one (45): A solution of bromide **44** (39 mg, 0.16 mmol), boronate **4** (107 mg, 0.320 mmol), Cs_2CO_3 (158 mg, 0.485 mmol) and $Pd(PPh_3)_4$ (9.2 mg, 8.0 μmol) in anhydrous dioxane (5 mL) was stirred for 4 h under an argon atmosphere at 95 °C. The mixture was concentrated and purified by chromatography (hexanes/EtOAc, 10:1) to yield **45** (49 mg, 0.13 mmol, 83%) as a white solid and reduced side product **6** (24 mg, 0.12 mmol).

4,7-Dihydroxy-3,9-dimethoxy-1-methyl-6*H*-benzo[*c*]chromen-6-one (Graphislactone A): BCl_3 (1 M in CH_2Cl_2, 3.5 mL, 3.5 mmol) was added dropwise at room temperature under argon to a solution of **45** (110 mg, 0.295 mmol) in anhydrous CH_2Cl_2 (10 mL). The yellow-turning solution was stirred for 24 h, MeOH (5 mL) was added, and the mixture was stirred for an additional 2 h and concentrated. The brownish residue was purified by chromatography (CH_2Cl_2/MeOH, 10:1) and by MPLC (CH_2Cl_2) to yield graphislactone A (35 mg, 0.12 mmol, 39%); m.p. 221–223 °C (ref.[6a] 236–237 °C; ref.[6e] 220–225 °C). R_f (CH_2Cl_2/MeOH, 40:1) = 0.16. IR (KBr): $\tilde{\nu}$ = 3092 (m), 2987 (m), 2949 (m), 2853 (m), 1742 (m), 1657 (m), 1638 (m), 1575 (m), 1462 (m), 1446 (m), 1376 (m), 1345 (m), 1303 (m), 1236 (m), 1184 (m), 1148 (m), 1046 (m), 989 (m), 966 (m), 838 (m), 794 (m), 707 (m), 669 (m), 611 (m) cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 2.70 (s, 3 H, Ar*Me*), 3.88 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 6.60 (d, ^4J = 2.2 Hz, 1 H, Ar*H*), 6.92 (s, 1 H, Ar*H*), 7.20 (d, ^4J = 2.2 Hz, 1 H, Ar*H*), 9.24 (s, 1 H, OH), 11.87 (s, 1 H, OH) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 24.6 (q), 55.7 (q), 55.9 (q), 98.4 (s), 99.4 (d), 103.8 (d), 110.5 (s), 112.9 (d), 126.1 (s), 132.3 (s), 137.9 (s), 140.6 (s), 148.1 (s), 164.0 (s), 164.4 (s), 166.0 (s) ppm. UV/Vis: λ^{MeOH} = 200, 235, 259, 285, 297, 338 nm. MS (EI, 70 eV): *m*/*z* (%) = 302 (2) [M$^+$], 276 (8), 274 (8) [[M – CO]$^+$], 245 (20), 243 (21), 58 (38), 43 (100). HRMS ($^{12}C_{16}{}^1H_{14}{}^{16}O_6$, EI, 70 eV): calcd. 302.0790; found 302.0794. Analytical data are in full accordance with published data.[6a]

7-Hydroxy-3,4,9-trimethoxy-1-methyl-6*H*-benzo[*c*]chromen-6-one (Graphislactone H): Graphislactone A (3.6 mg, 12 mmol) was dissolved in CH_2Cl_2/MeOH (1:2, 3 mL). A solution of CH_2N_2 (***Caution!***) in Et_2O (0.4 M) was added in portions of 50–100 μL, each addition followed by stirring for 3 min. After addition of 475 μL, the reaction was complete (monitoring with tlc), and the solvents were removed in vacuo, yielding graphislactone H (3.7 mg, 12 mmol, quant.) as a pale yellow solid; m.p. 179–181 °C (ref.[7] 165–166 °C). R_f (CH_2Cl_2/MeOH, 40:1) = 0.57. IR (KBr): $\tilde{\nu}$ = 2965 (m), 2941 (m), 2845 (m), 1734 (s), 1664 (m), 1626 (s), 1603 (s), 1581 (s), 1519 (m), 1459 (m), 1441 (m), 1402 (m), 1350 (m), 1315 (m), 1297 (m), 1275 (m), 1248 (s), 1212 (s), 1164 (m), 1140 (s), 1115 (m), 1070 (m), 1024 (m), 1000 (m), 987 (m), 970 (m), 896 (m), 831 (m), 800 (m), 781 (m), 702 (m), 675 (m), 651 (m), 586 (m), 542 (m), 504 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.80 (s, 3 H, Ar*Me*), 3.91 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 6.55 (d, ^4J = 2.1 Hz, 1 H, Ar*H*), 6.73 (s, 1 H, Ar*H*), 7.24 (d, ^4J = 1.9 Hz, 1 H, Ar*H*), 11.95 (s, 1 H, OH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.8 (q), 55.7 (q), 56.1 (q), 61.5 (s), 99.1 (d), 99.2 (s), 104.8 (d), 111.7 (s), 112.9 (d), 131.7 (s), 135.2 (s), 137.9 (s), 146.0 (s), 152.6 (s), 164.9 (s), 165.2 (s), 166.3 (s) ppm. UV/Vis: λ^{MeOH} = 200, 224, 258, 287, 397, 339 nm; λ^{CHCl3} = 231, 260, 288, 298, 332, 342 nm. MS (FAB): *m*/*z* = 317 [[M + H]$^+$]. HRMS ($^{12}C_{17}{}^1H_{16}{}^{16}O_6$, EI, 70 eV): calcd. 316.0947; found 316.0949. Analytical data are in full accordance with published data.[7]

Supporting Information (see also the footnote on the first page of this article): Detailed NMR spectroscopic data of originally proposed and revised structures of graphislactones E and F. X-ray

crystallographic data of compounds **9** and **14** and of graphislactone A. Experimental details and spectroscopic data of all synthesized compounds.

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