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PAPER

Synthesis of the reported structure of crassiflorone, a naturally occurring quinone isolated from the African ebony *Diospyros crassiflora*, and regioisomeric pentacyclic furocoumarin naphthoquinones

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A synthesis of the structure reported for the natural product crassiflorone, a furocoumarin naphthoquinone, is described. The key steps are a Diels–Alder reaction to form 2-bromo-8-hydroxy-6-methylnaphthoquinone, followed by *O*-protection and copper(II) mediated coupling to 4-hydroxy-5-methylcoumarin to establish the pentacyclic framework whose structure was unambiguously confirmed by X-ray crystallography. Since the spectroscopic data of the synthetic material did not match those reported for the natural product, three further regioisomeric furocoumarin naphthoquinones were prepared by copper(II) mediated coupling of 4-hydroxy-5- or 8-methyl coumarins with 5-benzyloxy-2-bromo-7-methyl- or 8-benzyloxy-2-bromo-6-methyl-1,4-naphthoquinone. Again the spectroscopic data did not match those of the natural material and therefore the true structure of crassiflorone remains unknown.

Introduction

Quinones occur widely in Nature and constitute a large group of natural pigments,[1–4] although their contribution to natural colouring is relatively small. Many quinones have important functions in living systems where they participate in a range of important biological redox processes. Prominent amongst quinone natural products are the naphthoquinones, for example, phylloquinone (vitamin K_1) (Fig. 1) that occurs in green plants and participates in photosynthetic electron transport processes.[1,2] Recently, a new naphthoquinone with antibacterial properties was isolated from the stem bark of the African ebony (persimmon) tree *Diospyros crassiflora*.[5,6] The compound, named crassiflorone, was assigned the pentacyclic naphthoquinone structure **1** (Fig. 1) on the basis of NMR spectroscopic studies.[5] In addition to the naphthoquinone chromophore, crassiflorone also contains a furocoumarin ring system, in common with other natural products such as the phytoestrogens coumestan and coumestrol (Fig. 1).[7] We recently described the first synthesis of structure **1**,[8] which unfortunately appeared to cast some doubt on the original structural assignment of the natural product. We now report the details of this work, together with the synthesis of three regioisomeric pentacyclic furocoumarin naphthoquinones as possible candidate structures for the natural product.

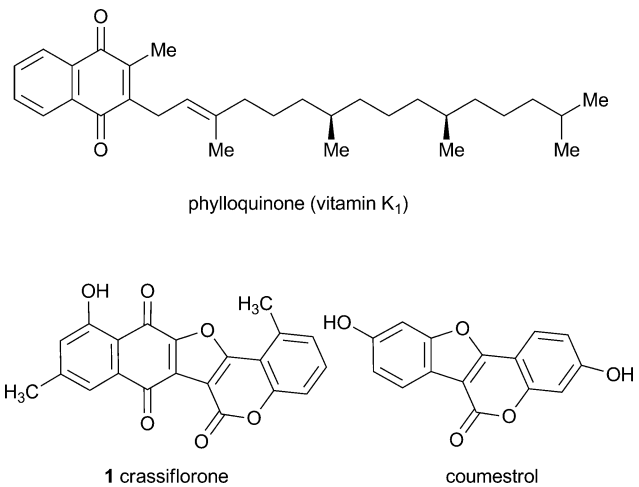

Fig. 1 Structures of phylloquinone, the reported structure of the naphthoquinone crassiflorone **1**, and the furocoumarin coumestrol.

Results and discussion

For the synthesis of the furocoumarin naphthoquinone **1** we planned to couple together a bromonaphthoquinone fragment **2** with 4-hydroxy-5-methylcoumarin **3**. To this end, Diels–Alder reaction of 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene, obtained by silylation of the LDA-generated enolate of methyl 3,3-dimethylacrylate,[9] with 2,6-dibromoquinone[10] in benzene at room temperature, followed by aromatization of the initial adduct by stirring over silica gel, delivered the known naphthoquinone **2**[11] in 50% yield (Scheme 1). Although the bromine in 2-bromobenzoquinones is known to direct the regiochemical

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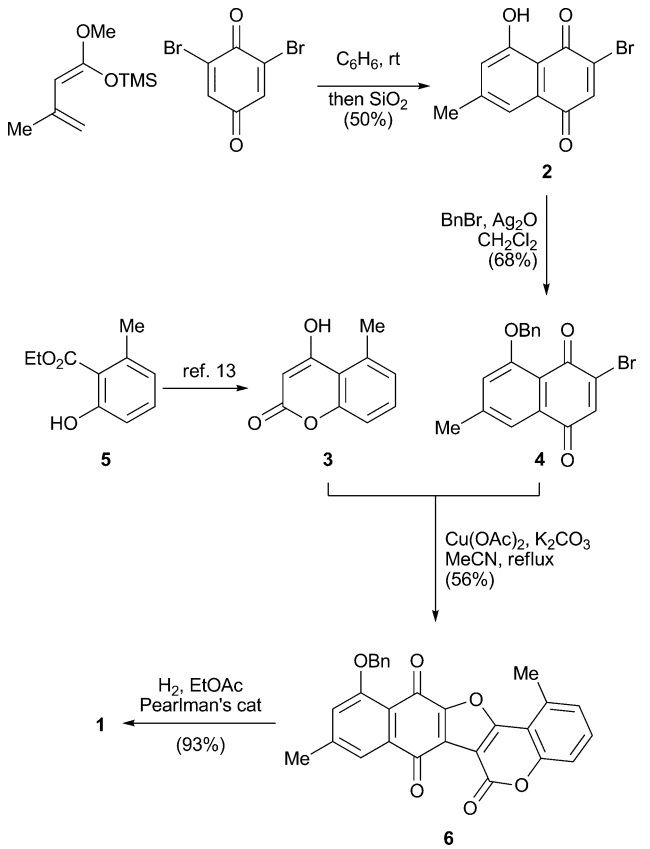


Scheme 1 Synthesis of the reported furocoumarin naphthoquinone structure **1** of crassiflorone.

outcome of Diels–Alder reactions,[12] the structure of 2-bromo-8-hydroxy-6-methyl-1,4-naphthoquinone **2** was confirmed by X-ray crystallography (Fig. 2). The H-bonded phenol **2** was subsequently protected as its benzyl ether **4** in order to avoid potential problems in ensuing coupling reactions.

4-Hydroxy-5-methylcoumarin **3** was also readily accessible, and was prepared from ethyl 6-methylsalicylate **5** by addition of the lithium enolate of *tert*-butyl acetate followed by acid mediated cyclization according to the literature procedure.[13] Hence we were ready for the pivotal union of quinone **4** and hydroxycoumarin **3** fragments. The bromine in bromo-benzo- and naphtho-quinones is known to be readily displaced under basic (K_2CO_3) conditions by various nucleophiles, including phenols,[14] and enamines. In the latter case, in the presence of copper(II) salts, the intermediate adducts can undergo oxidative cyclization onto the quinone ring.[15–17] Therefore 4-hydroxy-5-methylcoumarin **3** and the bromonaphthoquinone **4** were coupled in the presence of potassium carbonate and copper(II) acetate, and gave directly the pentacyclic framework **6** in 56% yield. Removal of the benzyl ether protecting group by hydrogenolysis over Pearlman's catalyst gave the desired furocoumarin naphthoquinone **1** (Scheme 1), the structure of which was unambiguously confirmed by X-ray crystallography (Fig. 3).

Although the structure of synthetic naphthoquinone **1** is not in doubt, we note that its ^{1}H NMR data are completely consistent with its structure. However, there are some significant differences between these data and those reported for the natural product (Table 1).[5] Likewise the ^{13}C NMR data (in $CDCl_3$) are at variance with those reported for the natural material (in DMSO-d_6),[5] although accurate comparison was hampered by the fact that the synthetic material was insufficiently soluble in DMSO to obtain good ^{13}C NMR spectroscopic data. Unfortunately it has proved impossible to obtain a sample of the natural material for direct comparison, and therefore our short synthesis of the furocoumarin naphthoquinone structure **1**, rather than confirming the structure of the unusual natural product crassiflorone, suggests that the original structural assignment is incorrect.

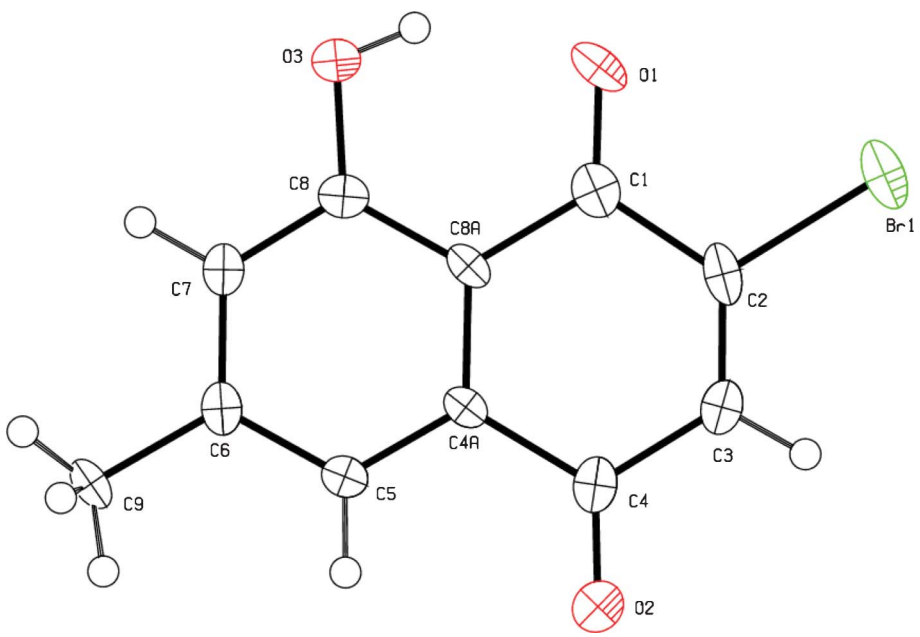


Fig. 2 X-Ray crystal structure of 2-bromo-8-hydroxy-6-methyl-1,4-naphthoquinone **2**.

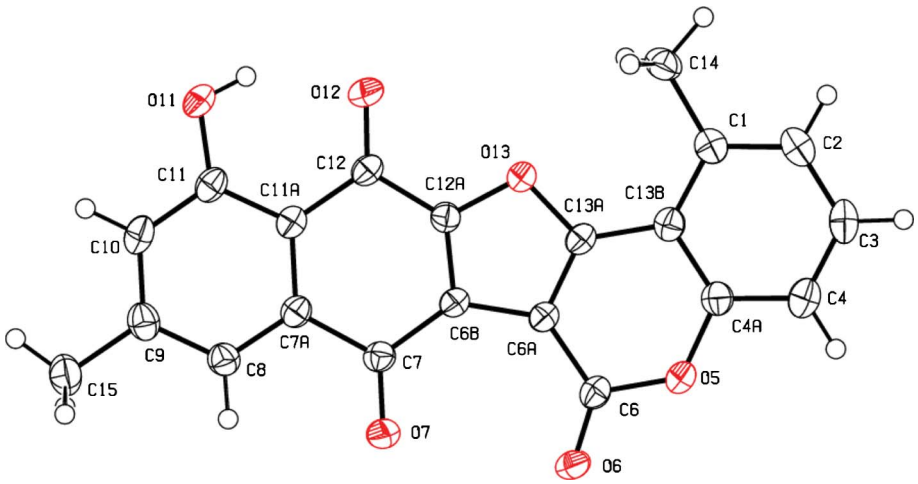
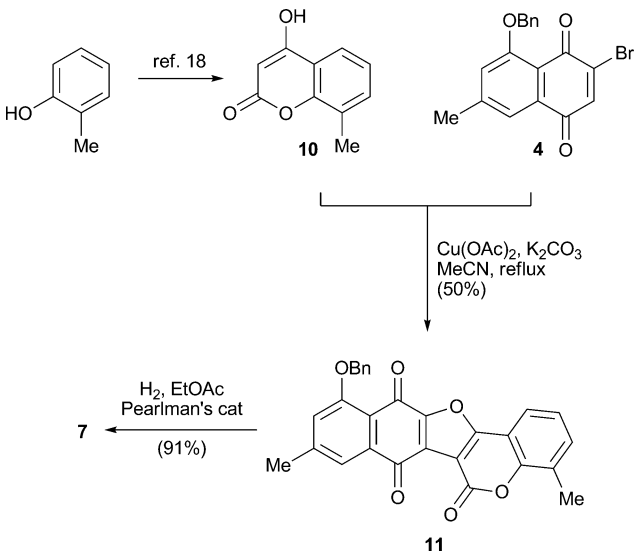


Fig. 3 X-Ray crystal structure of the synthetic furocoumarin naphthoquinone **1**.

In view of the above data, we considered other possible structures for the natural product crassiflorone based around the furocoumarin naphthoquinone framework (Fig. 4). Given the original data for the natural material and comparison with the synthetic sample, in particular the intramolecular H-bonded phenol, and the aromatic protons H-8 and H-10, it seemed fairly clear that the methyl substituted hydroxy naphthoquinone fragment was correct, and that the structural misassignment lay in the furocoumarin part of the molecule. Therefore we considered three structural variations of compound **1** as candidate structures for the natural material: the 4,9-dimethyl isomer **7**, and the corresponding two structures **8** and **9** with the furocoumarin inverted with respect to the naphthoquinone.

The synthesis of the 11-hydroxy-4,9-dimethyl isomer **7** required the coupling of 8-benzyloxy-2-bromo-6-methyl-1,4-naphthoquinone **4** with 4-hydroxy-8-methylcoumarin **10**. The coumarin was readily prepared by the reaction of *o*-cresol with Meldrum's acid followed by cyclization using Eaton's reagent (phosphorus pentoxide in methanesulfonic acid) following a literature protocol.[18] Thereafter the synthesis (Scheme 2) followed the methodology described for the isomeric furocoumarin naphthoquinone **1**, and delivered the desired isomer **7**, following deprotection of the intermediate benzyl ether **11**.

The synthesis of the 8-hydroxy-1,10- and 4,10-dimethyl furocoumarin naphthoquinones regioisomers **8** and **9** necessitated the use of 5-benzyloxy-2-bromo-7-methyl-1,4-naphthoquinone **13** in place of bromonaphthoquinone **4**. The quinone was readily prepared by an analogous Diels–Alder reaction of 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene with 2,5-dibromoquinone in benzene at room temperature to give the known naphthoquinone **12**[19] in 45% yield (Scheme 3), followed by benzylation to yield the bromoquinone coupling partner **13**, the structure of which was confirmed by X-ray crystallography (Fig. 5). Copper mediated coupling of bromoquinone **13** with the 4-hydroxycoumarins **3** and **10** delivered the required furocoumarin naphthoquinones **14** and **15** in good yield (Scheme 3), subsequently deprotected by hydrogenolysis over Pearlman's catalyst to provide the desired furocoumarin naphthoquinones **8** and **9** (Scheme 3). The structures of pentacycles **14** and **9** were confirmed by X-ray crystallography (Fig. 6 and 7) verifying that they were



Scheme 2 Synthesis of the 11-hydroxy-4,9-dimethyl furocoumarin naphthoquinone **7**.

indeed regioisomers of each other (albeit one benzyl protected), and also regioisomeric with the previously described furocoumarin naphthoquinones **1** and **7**.

With three new furocoumarin naphthoquinones available, we were able to compare their spectroscopic data with those reported for the natural product crassiflorone. Unfortunately none of the data were in agreement (Table 1), and therefore, based on the ^{1}H NMR spectroscopic data, we conclude that crassiflorone is not represented by structures **1**, **7**, **8**, or **9**. Again it was impossible to compare accurately the ^{13}C NMR data since the synthetic materials were insufficiently soluble in DMSO to obtain good ^{13}C NMR spectroscopic data. Differences in the IR spectra were also noted, in particular the lactone C=O stretching frequency reported as 1678 cm^{-1} (KBr) for the natural product, compared with the synthetic materials **1**, **7**, **8**, and **9** that have their coumarin carbonyl absorptions in KBr at 1760, 1754, 1772 and 1753 cm^{-1} respectively. These latter values compare favourably with data reported for furocoumarins of the coumestan and coumestrol family (1740–1717 cm^{-1}),[20,21] and hence the value reported for the

Table 1 Comparison of proton NMR data reported for the natural product crassiflorone (assigned as structure **1**), and four synthetic furocoumarin naphthoquinones **1**, **7**, **8** and **9**

Natural product crassiflorone	**1**	**7**	**8**	**9**
500 MHz; DMSO-d_6	400 MHz; DMSO-d_6	400 MHz; DMSO-d_6	400 MHz; DMSO-d_6	400 MHz; DMSO-d_6
11.91, 1H, s, 11-OH	11.60, 1H, s, 11-OH	11.65, 1 H, s, 11-OH	12.02, 1 H, s, 8-OH	12.06, 1 H, s, 8-OH
7.47, 1H, s, H-8	7.55, 1H, s, H-8	7.98, 1 H, d, *J* 7.2, H-1	7.66, 1 H, t, *J* 8.0, H-3	8.00, 1 H, d, *J* 7.2, H-1
7.45, 1H, t, *J* 8.0, H-3	7.66, 1H, t, *J* 7.6, H-3	7.69, 1 H, d, *J* 7.2, H-3	7.57, 1 H, s, H-11	7.73, 1 H, d, *J* 7.6, H-3
7.23, 1H, s, H-10	7.23, 1H, s, H-10	7.51, 1 H, s, H-8	7.43, 1 H, d, *J* 8.0, H-4	7.57, 1 H, s, H-11
7.11, 1H, br d, *J* 8.0, H-2	7.43, 1H, d, *J* 8.0, H-2	7.45, 1 H, t, *J* 7.6, H-2	7.37, 1 H, d, *J* 7.6, H-2	7.47, 1 H, t, *J* 7.6, H-2
7.09, 1H, br d, *J* 8.0, H-4	7.37, 1H, dd, *J* 7.6, 0.8, H-4	7.24, 1 H, s, H-10	7.24, 1 H, s, H-9	7.28, 1 H, s, H-9
2.61, 3H, s, 14-Me	2.88, 3H, s, 14-Me	2.51, 3 H, s, 14-Me	2.88, 3 H, s, 14-Me	2.51, 3 H, s, 14-Me
2.46, 3H, s, 15-Me	2.50, 3H, s, 15-Me	2.48, 3 H, s,15-Me	2.50, 3 H, s, 15-Me	2.48, 3 H, s 15-Me

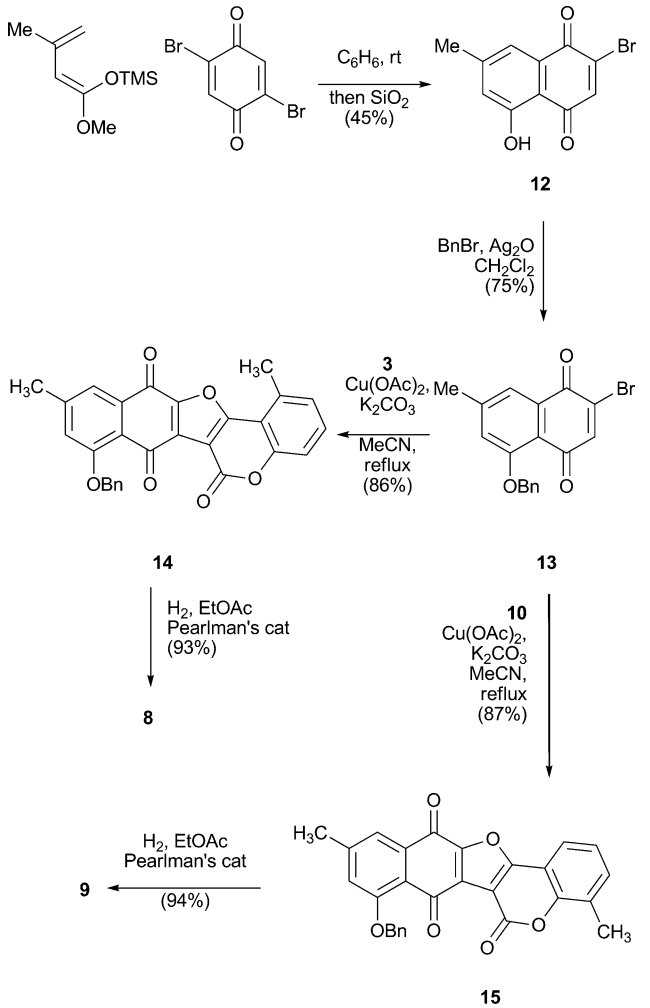
Fig. 4 Hydroxy-dimethyl-6*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,7,12-triones: structure reported for crassiflorone **1**, and three regioisomers **7–9** thereof, possible structures for the natural product.

natural product is unlikely to be compatible with any coumarin structure. In view of the combination of spectroscopic data on our four furocoumarin naphthoquinones, obtained by unambiguous chemical synthesis with additional confirmation by X-ray crystallography, we suggest that the structural misassignment of the natural product probably lies in the furocoumarin part of the molecule. Unfortunately, for the moment, the true structure of crassiflorone remains unknown.

Experimental section

General experimental information

Commercially available reagents were used throughout without further purification unless otherwise stated. Anhydrous tetrahydrofuran and dichloromethane were freshly distilled. Light petroleum refers to the fraction of petroleum boiling between 40 and 60 °C. All reactions were carried out under nitrogen or argon atmosphere. Thin layer chromatography was carried out



Scheme 3 Synthesis of the 8-hydroxy-1,10- and 4,10-dimethyl furocoumarin naphthoquinones **8** and **9**.

using aluminium backed plates coated with silica gel. The plates were visualized under UV light at 254 nm and/or by vanillin or permanganate stains. Flash column chromatography was carried out using silica gel with the eluent specified.

IR spectra were recorded using a Perkin ELMER 1600 FTIR spectrometer. Ultra-violet spectra were recorded in the range of 220–450 nm using either Perkin Elmer Lambda 5 spectrophotometer or ATI Unicam UV4. Mass spectra were carried out on Agilent 6890 series GC, micromass GCT, VG Autospec or Bruker microTOF (for ESI) spectrometers, using electron impact (EI) or electrospray ionization (ESI) techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker instruments (^{1}H frequencies 300, 400 and 500 MHz, corresponding ^{13}C frequencies are 75, 100, 125 MHz, respectively). Chemical shifts are quoted in parts per million (ppm). *J* values are recorded in Hz.

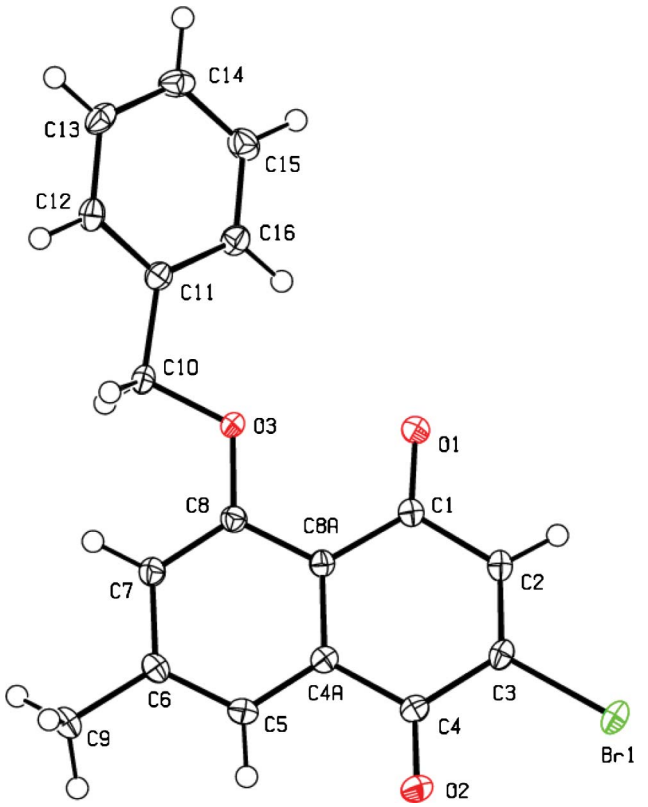
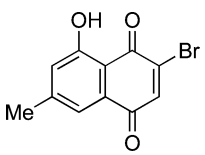


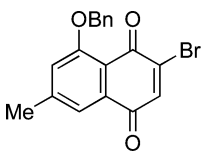
Fig. 5 X-Ray crystal structure of 2-bromo-5-benzyloxy-7-methyl-1,4-naphthoquinone **13**.

To a solution of 2,6-dibromobenzoquinone[10] (3.00 g, 11.3 mmol) in benzene (60 mL) was added dropwise 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene[22] (3.15 g, 16.9 mmol) with constant stirring at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for another 7 h. The reaction mixture was poured onto silica gel (100 g) in dichloromethane (400 mL). The suspension was stirred for 24 h at room temperature. After removing the solvent under reduced pressure the silica gel was eluted with dichloromethane and methanol (10 : 1). The eluant was concentrated *in vacuo* and the residue was subjected to silica gel flash column chromatography in 10% ethyl acetate and light petroleum to give the title compound (1.50 g, 50%); mp 188–189 °C (lit.,[11] mp 186–187 °C); (Found: M + Na$^+$, 288.9460. $C_{11}H_7{}^{79}BrO_3$ + Na$^+$ requires 288.9471); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1664, 1642, 1587, 1385, 1302, 1257, 1175, 1143, 866; δ_H (400 MHz; $CDCl_3$) 11.71 (1 H, s, OH), 7.48 (1 H, d, *J* 1.6, ArH), 7.47 (1 H, s, H-3), 7.12 (1 H, d, *J* 1.6, ArH), 2.47 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 182.3 (C), 181.9 (C), 162.3 (C), 149.3 (C), 140.9 (CH), 139.6 (C), 131.4 (C), 124.3 (CH), 121.3 (CH), 111.0 (C), 22.3 (Me); *m*/*z* (ESI) 288 (M + Na$^+$, 100%), 266 (38), 251 (35), 226 (76), 192 (24) 190 (47), 185 (51), 158 (45), 151 (43), 149 (73).

2-Bromo-8-hydroxy-6-methyl-1,4-naphthoquinone 2



8-Benzyloxy-2-bromo-6-methyl-1,4-naphthoquinone 4



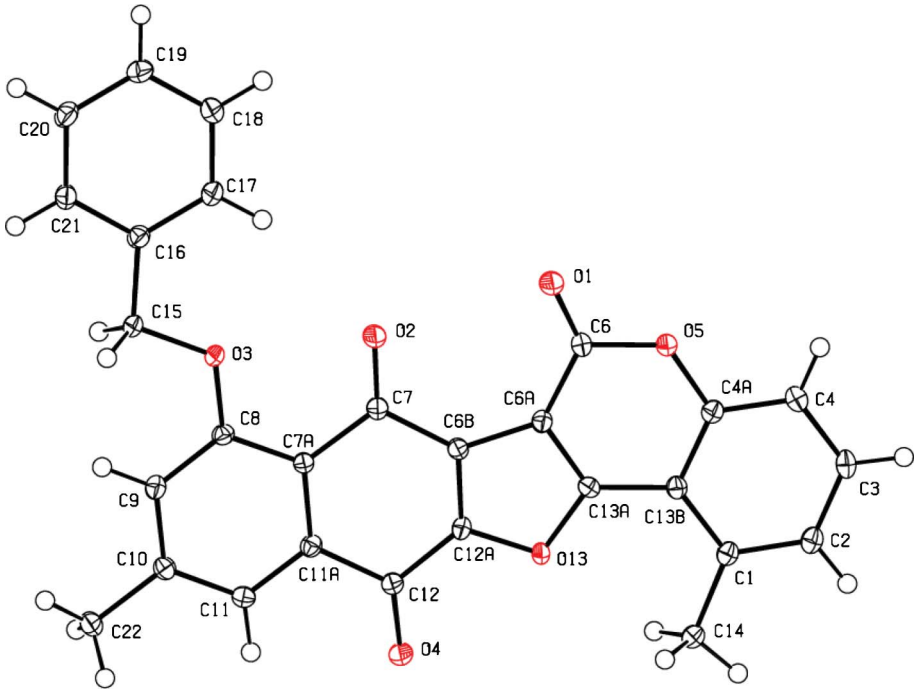


Fig. 6 X-Ray crystal structure of 8-benzyloxy-1,10-dimethyl furocoumarin naphthoquinone **14**.

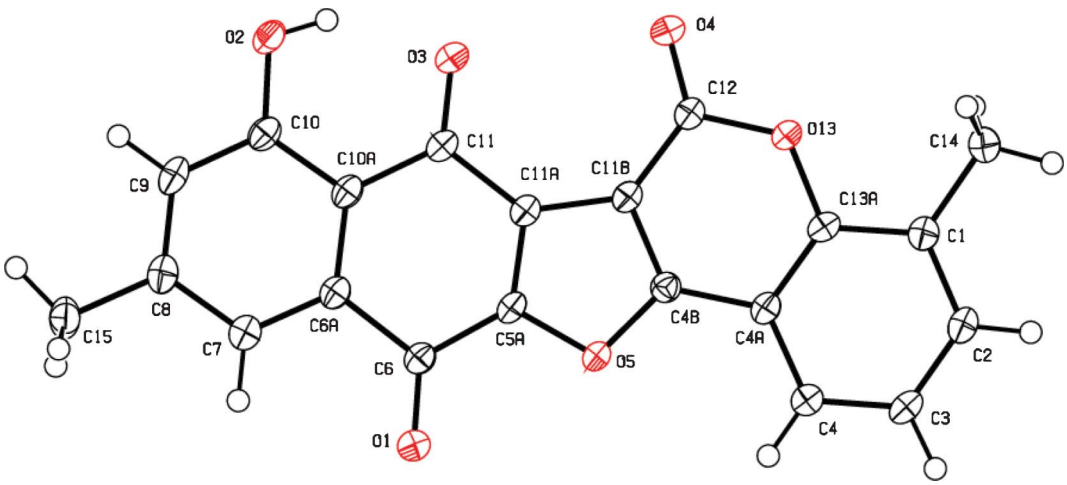
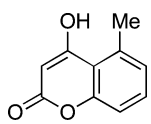


Fig. 7 X-Ray crystal structure of 8-hydroxy-4,10-dimethyl furocoumarin naphthoquinone **9**.

Benzyl bromide (0.09 mL, 0.75 mmol), was added to a mixture of 2-bromo-8-hydroxy-6-methyl-1,4-naphthoquinone **2** (0.10 g, 0.37 mmol), and silver(I) oxide (0.17 g, 0.74 mmol) in dichloromethane (5 mL) and the resulting suspension was stirred for 48 h at room temperature. Then, additional silver(I) oxide (0.17 g, 0.74 mmol) and benzyl bromide (0.09 mL, 0.75 mmol) were added and stirring was continued for another 24 h. The mixture was filtered through a plug of Celite and rinsed with dichloromethane. After removal of the solvent under reduced pressure the crude product was subjected to silica gel flash column chromatography in 20% ethyl acetate and light petroleum to give the *title compound* (90 mg, 68%); mp 146–148 °C; (Found: C, 61.11; H, 3.75. $C_{18}H_{13}BrO_3$ requires C, 61.03, H, 3.70); (Found: M + H^+, 358.0025. $C_{18}H_{13}{}^{79}BrO_3$ + H^+ requires 358.0027); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1671, 1600, 1456, 1329, 1260, 1239, 1155, 1056, 851; δ_H (400 MHz; $CDCl_3$) 7.62 (2 H, m, ArH), 7.57 (1 H, s, H-3), 7.45 (3 H, m, ArH), 7.37 (1 H, m, ArH), 7.18 (1 H, s, ArH), 5.29 (2 H, s, CH_2), 2.47 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 182.9 (C), 175.6 (C), 159.5 (C), 147.1 (C), 142.9 (C), 138.2 (CH), 135.8 (C), 133.7 (C), 128.7 (CH), 128.0 (CH), 126.7 (CH), 120.7 (CH), 119.9 (CH), 116.7 (C), 70.9 (CH_2), 22.3 (Me); *m/z* (EI) 358/356 (M^+, 3%), 108 (14), 91 (100), 79 (11).

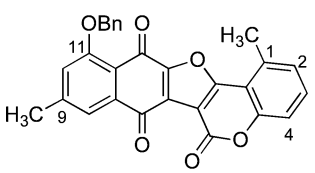
4-Hydroxy-5-methylcoumarin 3



(a) To a 100 mL 2 neck round bottomed flask equipped with magnetic stirrer, nitrogen inlet and thermometer; diisopropylamine (4.45 mL, 31.8 mmol), *N*-benzylbenzamide (5 mg) and dry THF (20 mL) were added. The solution was cooled to −78 °C and *n*-BuLi (2.5 M in hexanes; 17.17 mL, 42.92 mmol) was added slowly. The solution becomes dark blue immediately with addition of *n*-BuLi. After 1.5 h, a solution of *tert*-butyl acetate (2.26 g, 19.5 mmol) in THF (5 mL) was added over 5 min during which time the solution turned yellow. The solution was stirred at −78 °C for 1 h and a solution ethyl 2-hydroxy-6-methylbenzoate **5**[23] (1.0 g, 5.58 mmol) in THF (5 mL) was added over 5 min. The colour changes from yellow to orange; after warming to room temperature overnight, the reaction was quenched by addition of ice cooled saturated aqueous ammonium chloride (40 mL) and ethyl acetate (80 mL). The organic layer was washed with brine (100 mL) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% ethyl acetate in light petroleum) to give *tert*-butyl 3-(2-hydroxy-6-methylphenyl)-3-oxopropanoate as a pale yellow oil (0.95 g, 68%); (Found: M^+, 250.1205. $C_{14}H_{18}O_4$ requires 250.1205); ν_{max} ($CHCl_3$)/cm^{-1} 2983, 1730, 1627, 1443, 1370, 1254, 1145; δ_H (400 MHz; $CDCl_3$) 11.01 (1 H, s, OH), 7.29 (1 H, dd, *J* 8.1, 7.6, ArH), 6.85 (1 H, d, *J* 8.1, ArH), 6.75 (1 H, d, *J* 7.6, ArH), 3.93 (2 H, s, CH_2), 2.53 (3 H, s, CH_3), 1.47 (9 H, s, CMe_3); δ_C (100 MHz; $CDCl_3$) 200.6 (C), 166.7 (C), 161.2 (C), 138.6 (C), 134.4 (CH), 123.2 (CH), 122.3 (C), 116.2 (CH), 82.4 (C), 52.1 (CH_2), 27.9 (Me), 23.2 (Me); *m*/*z* (ESI) 194 (M^+, 41%), 176 (76), 135 (97), 134 (100).

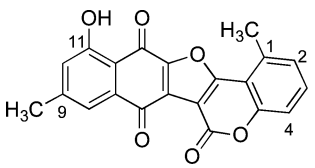
(b) A small reaction vial was charged with *tert*-butyl 3-(2-hydroxy-6-methylphenyl)-3-oxopropanoate (1.7 g, 6.8 mmol) and trifluoroacetic acid (0.9 mL). The reaction mixture was stirred vigorously for 15 min and allowed to settle at room temperature for 4 h. A pale yellow solid was formed which was collected on a sintered glass funnel and washed with a mixture of light petroleum and ether (3 : 1) to give 4-hydroxy-5-methylcoumarin. The filtrate was concentrated and cooled to give a second crop (total 1.1 g, 92%), mp 232–234 °C (lit.,[13] mp 229–230 °C); (Found: M + H^+, 177.0547. $C_{10}H_8O_3$ + H^+ requires 177.0546); ν_{max} (solid)/cm^{-1} 1599, 1324, 1204, 1256, 828; δ_H (400 MHz; $CDCl_3$) 12.36 (1 H, s, br, OH), 7.46 (1 H, t, *J* 8.0, ArH), 7.18 (1 H, d, *J*, 7.6, ArH), 7.10 (1 H, d, *J*, 7.6, ArH), 5.56 (1 H, s, ArH), 2.67 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 169.1 (C), 161.9 (C), 155.4 (C), 137.6 (C), 132.2 (CH), 127.6 (CH), 115.2 (CH), 114.7 (C), 91.6 (CH), 23.1 (Me).

11-Benzyloxy-1,9-dimethyl-6*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,7,12-trione 6



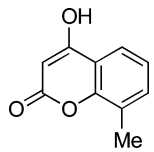
A mixture of 8-benzyloxy-2-bromo-6-methyl-1,4-naphthoquinone **4** (0.20 g, 0.56 mmol), copper(II) acetate (0.33 g, 1.7 mmol), 4-hydroxy-5-methyl coumarin **3** (0.12 g, 1.7 mmol) and potassium carbonate (0.23 g, 1.7 mmol) in acetonitrile (10 mL) was heated to reflux for 8 h with constant stirring. After 8 h the mixture was diluted with dichloromethane (100 mL) and filtered through Celite while exhaustively washing with dichloromethane–methanol (9 : 1) (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography to give the *title compound* (0.14 g, 56%), mp 236–238 °C; (Found: M + Na^+, 473.0985. $C_{28}H_{18}O_6$ + Na^+ requires 473.0996); ν_{max} ($CHCl_3$)/cm^{-1} 2985, 1731, 1446, 1374, 1249, 1045; δ_H (400 MHz; $CDCl_3$) 7.71 (1 H, s, H-10), 7.62 (2 H, d, *J* 7.4, ArH), 7.52 (1 H, dd, *J* 7.3, 7.7, H-3), 7.42 (2 H, dd, 7.3, 7.7, ArH), 7.33 (2 H, d, *J* 7.6, ArH), 7.22 (1 H, d, *J* 7.5, H-4), 7.18 (1 H, s, H-8), 5.28 (2 H, s, CH_2), 2.94 (3 H, s, Me), 2.50 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 177.9 (C), 172.2 (C), 162.0 (C), 159.8 (C), 155.2 (C), 154.9 (C), 154.3 (C), 147.4 (C), 136.0 (C), 135.9 (C), 136.6 (C), 132.5 (CH), 128.7 (CH), 127.9 (CH), 127.1 (CH), 126.7 (CH), 124.2 (C), 121.9 (C), 120.1 (CH), 117.2 (C), 115.2 (CH), 110.7 (C), 107.3 (C), 70.8 (CH_2), 22.5 (Me), 21.5 (Me).

11-Hydroxy-1,9-dimethyl-6*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,7,12-trione ("crassiflorone") 1



The benzyl ether **6** (0.10 g) was dissolved in ethyl acetate (10 mL) and Pearlman's catalyst (20 mg) was added. The reaction mixture was flushed with nitrogen followed by hydrogen. The reaction mixture was stirred for 16 h under a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad while exhaustively washing with 5% methanol in dichloromethane (100 mL). The filtrate was concentrated under reduced pressure and the residue was subjected to silica gel flash column chromatography to give the *title compound* (0.09 g, 93%), mp 230 °C (decomp) (lit.,[5] mp 230–232 °C); (Found: M + H^+, 361.0700. $C_{21}H_{12}O_6$ + H^+ requires 361.0707; M + Na^+, 383.0537. $C_{21}H_{12}O_6$ + Na^+ requires 383.0526); ν_{max} ($CHCl_3$)/cm^{-1} 3689, 3604, 3043, 1755, 1644, 1603, 1239; ν_{max} (KBr)/cm^{-1} 1760, 1640, 1606, 1541, 1460, 1384, 1235, 1193, 1064; λ_{max} (MeOH) 305 (log ε 4.056) and 440 nm (log ε 3.54); δ_H (400 MHz; $CDCl_3$) (400 MHz; $CDCl_3$) 11.84 (1 H, s, 11-OH), 7.66 (1 H, s, H-8), 7.58 (1 H, dd, *J* 8.2, 7.6, H-3), 7.38 (1 H, d, *J* 8.2, H-4), 7.28 (1 H, d, *J* 7.6, H-2), 7.13 (1 H, s, H-10), 2.96 (3 H, s, 14-Me), 2.50 (3 H, s, 15-Me); δ_H (400 MHz; DMSO-d_6) 11.60 (1 H, s, 11-OH), 7.66 (1 H, t, *J* 7.6, H-3), 7.55 (1 H, s, H-8), 7.43 (1 H, d, *J* 8.0, H-2), 7.37 (1 H, dd, *J* 7.6, 0.8, H-4), 7.23 (1 H, s, H-10), 2.88 (3 H, s, 14-Me), 2.50 (3 H, s, 15-Me); δ_C (100 MHz; $CDCl_3$) 177.6 (C), 177.3 (C), 162.84(C), 162.8 (C), 155.1 (C), 154.7 (C), 152. 9 (C), 149.4 (C), 136.0 (C), 133.2 (CH), 133.1 (CH), 127.3 (CH), 127.2 (C), 124.7 (CH), 122.5 (C), 115.4 (CH), 112.4 (C), 110.5 (C), 107.9 (C), 22.4 (Me), 21.4 (Me).

4-Hydroxy-8-methylcoumarin 10

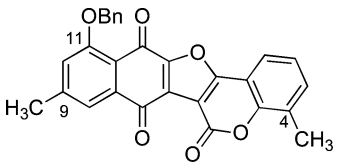


A mixture of *o*-cresol (0.50 g, 4.6 mmol) and Meldrum's acid (0.66 g, 4.6 mmol) was heated at 110 °C for 3 h. After cooling to room temperature, the acetone formed was removed under vacuum

to give 3-oxo-3-phenoxypropanoic acid (0.89 g, 100%) as viscous oil that was used directly for the next step.

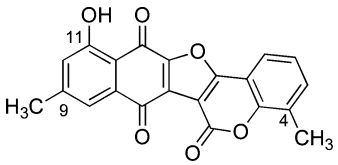
To the above product 3-oxo-3-phenoxypropanoic acid (0.89 g, 4.9 mmol), Eaton's reagent (7.7 wt% phosphorus pentoxide solution in methanesulfonic acid (5 mL)) was added and the reaction mixture was heated at 70 °C with constant stirring for 5 h. After cooling to room temperature the reaction mixture was poured into ice-cooled water (50 mL) with vigorous stirring. The aqueous solution was stirred for 30 min at 0 °C and then filtered. The solid was washed with cold water, dried under high vacuum, and purified by recrystallization from 20% acetone in *n*-pentane gave pure 4-hydroxy-8-methyl-coumarin (0.85 g, 98%); mp 238–239 °C (lit.,[18] mp 231.1–233.4 °C); (Found: C, 68.01, H, 4.57. $C_{10}H_8O_3$ requires C, 68.18, H, 4.58); (Found: M + H^+, 177.0554. $C_{10}H_8O_3$ + H^+ requires 177.0546; M + Na^+, 199.0378. $C_{10}H_8O_3$ + Na^+ requires 199.0366); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3906, 1720, 1602, 1265, 1239; δ_H (400 MHz; DMSO-d_6) 12.39 (1 H, s, OH), 7.63 (1 H, dd, *J* 0.8, 7.6, ArH), 7.46 (1 H, dd, *J* 0.8, 7.6, ArH), 7.19 (1 H, t, *J* 7.6, ArH), 5.59 (1 H, s, H-3), 2.33 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 166.3 (C), 162.3 (C), 152.2 (C), 133.7 (CH), 125.6 (C), 123.9 (CH), 121.4 (CH), 115.9 (C), 91.2 (CH), 15.7 (Me).

11-Benzyloxy-4,9-dimethyl-6*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,7,12-trione 11



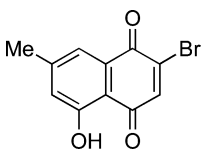
A mixture of 8-benzyloxy-2-bromo-6-methyl-1,4-naphthoquinone **4** (0.10 g, 0.28 mmol), copper(II) acetate monohydrate (0.17 g, 0.84 mmol), 4-hydroxy-8-methyl coumarin **10** (0.06 g, 0.34 mmol) and potassium carbonate (0.12 g, 0.84 mmol) in acetonitrile (10 mL) was heated under reflux for 8 h with constant stirring. The reaction mixture was diluted with dichloromethane (100 mL) and filtered through Celite with exhaustive washing by dichloromethane: methanol (9 : 1) (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography to give the *title compound* (0.06 g, 50%); mp 236–238 °C; (Found: M + Na^+, 473.0998. $C_{28}H_{18}O_6$ + Na^+ requires 473.0996; M + H^+, 451.1187. $C_{28}H_{18}O_6$ + H^+ requires 451.1176); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3008, 1751, 1664, 1600, 1529, 1295, 1021; λ_{max} (MeOH) 298 (log ε 4.07) and 404 nm (log ε 4.53); δ_H (400 MHz; $CDCl_3$) 7.98 (1 H, d, *J* 7.2, ArH), 7.78 (1 H, s, ArH), 7.68 (2 H, d, *J* 7.2, ArH), 7.53 (1 H, d, 7.2, ArH), 7.45 (2 H, t, *J* 7.2, ArH), 7.35 (2 H, t, *J* 7.6, ArH), 7.24 (1 H, s, ArH), 5.34 (2 H, s, CH_2), 2.56 (3 H, s, Me), 2.53 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 178.1 (C), 172.7 (C), 161.6 (C), 159.9 (C), 155.0 (C), 154.4 (C), 152.6 (C), 147.5 (C), 135.9 (C), 135.6 (C), 134.6 (CH), 128.7 (CH), 127.9 (CH), 127.3 (C), 126.6 (CH), 124.9 (C), 124.6 (CH), 122.0 (CH), 120.2 (CH), 119.9 (CH), 117.2 (C), 112.5 (C), 111.0 (C), 70.9 (CH_2), 22.5 (Me), 16.1 (Me).

11-Hydroxy-4,9-dimethyl-6*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,7,12-trione 7



The benzyl ether **11** (0.14 g, 0.31 mmol) was dissolved in the ethyl acetate (10 mL) and dichloromethane (5 mL) and then Pearlman's catalyst (30 mg) was added. The reaction mixture was flushed carefully with nitrogen followed by hydrogen. The reaction mixture was stirred for 16 h under a hydrogen atmosphere. The reaction mixture was filtered through a Celite while exhaustively washing with 5% methanol in dichloromethane (100 mL). The filtrate was concentrated under reduced pressure and the residue was subjected to silica gel flash column chromatography to give the *title compound* (0.10 g, 91%); mp 304–306 °C (decomp); (Found: M + Na^+, 383.0546. $C_{21}H_{12}O_6$ + Na^+ requires 383.0526); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1757, 1644, 1621, 1552, 1386, 1239, 1260, 1188, 1056, 1018; ν_{max} (KBr)/cm^{-1} 3442, 1754, 1643, 1550, 1459, 1384, 1292, 1184, 1054, 1015; λ_{max} (MeOH) 295 (log ε 4.25) and 300 nm (log ε 4.25); δ_H (500 MHz; $CDCl_3$) 11.81 (1 H, s, 11-OH), 7.96 (1 H, d, *J* 8.0, H-1), 7.64 (1 H, s, H-8), 7.55 (1 H, d, *J* 7.5, H-3), 7.36 (1 H, t, *J* 7.5, H-2), 7.13 (1 H, s, H-10), 2.56 (3 H, s, 14-Me), 2.49 (3 H, s, 15-Me); δ_H (400 MHz; DMSO-d_6) 11.65 (1 H, s, 11-OH), 7.98 (1 H, d, *J* 7.2, H-1), 7.69 (1 H, d, *J* 7.2, H-3), 7.51 (1 H, s, H-8), 7.45 (1 H, t, *J* 7.6, H-2), 7.24 (1 H, s, H-10), 2.51 (3 H, s, 14-Me), 2.48 (3 H, s, 15-Me); δ_C (125 MHz; $CDCl_3$) 177.8 (C), 177.4 (C), 162.9 (C), 162.3 (C), 154.6 (C), 153.0 (C), 152.8 (C), 149.4 (C), 135.0 (CH), 133.0 (C), 127.7 (C), 127.5 (C), 124.8 (2 × CH), 122.6 (CH), 119.9 (CH), 112.4 (C), 110.8 (C), 107.6 (C), 22.4 (Me), 16.1 (Me).

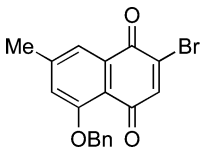
2-Bromo-5-hydroxy-7-methyl-1,4-naphthoquinone 12



To a solution of 2,5-dibromobenzoquinone[24] (0.20 g, 0.75 mmol) in toluene (10 mL) was added dropwise 1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (0.21 g, 1.13 mmol) with constant stirring at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for another 7 h, and then poured onto silica gel (50 g) in dichloromethane (100 mL). The suspension was stirred for 24 h at room temperature. After removing the solvent under reduced pressure the silica gel was eluted with dichloromethane and methanol (10 : 1). The organic layer was concentrated *in vacuo*. The residue was subjected to silica gel flash column chromatography in 10% ethyl acetate and light petroleum to give 2-bromo-5-hydroxy-7-methyl-1,4-naphthoquinone (0.09 g, 45%); mp 114–116 °C (lit.,[19] mp 132–133.5 °C); (Found: M – H^+, 264.9493. $C_{11}H_7{}^{79}BrO_3$ – H^+ requires 264.9506); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 1678, 1639, 1584, 1373, 1312, 1257; δ_H (400 MHz; $CDCl_3$) 11.73 (1 H, s, ArOH), 7.56 (1 H, d, *J* 1.6, ArH), 7.48 (1 H, s, H-3), 7.12 (1 H, d, *J* 1.6,

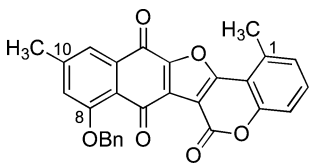
ArH), 2.47 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 186.9 (C), 177.5 (C), 161.9 (C), 148.5 (C), 140.5 (C), 140.4 (CH), 130.4 (C), 124.8 (CH), 122.4 (CH), 112.7 (C), 22.2 (Me).

5-Benzyloxy-2-bromo-7-methyl-1,4-naphthoquinone 13



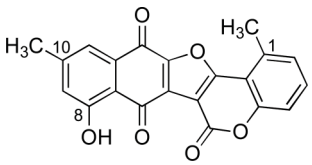
Benzyl bromide (0.08 mL, 0.7 mmol), was added to a mixture of 2-bromo-5-hydroxy-7-methyl-1,4-naphthoquinone (0.090 g, 0.34 mmol), and silver(I) oxide (0.23 g, 1.0 mmol) in dichloromethane (5 mL) and the resulting suspension was stirred for 48 h at room temperature. Then, additional silver(I) oxide (0.076 g, 0.34 mmol) and benzyl bromide (0.04 mL, 0.34 mmol), were added and stirring was continued for another 24 h. The mixture was filtered through a plug of Celite and rinsed with dichloromethane. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash column chromatography in 20% ethyl acetate and light petroleum to give *5-benzyloxy-2-bromo-6-methyl-1,4-naphthoquinone* (90 mg, 75%); mp 131–133 °C; (Found: C, 61.12; H, 3.79. $C_{18}H_{13}BrO_3$ requires C, 61.03, H, 3.70); (Found: M + H^+, 356.0037. $C_{18}H_{13}{}^{79}BrO_3$ + H^+ requires 356.0048); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1678, 1654, 1603, 1252, 1063, 899; λ_{max} (MeOH) 212 (log ε 4.53) and 250 nm (log ε 4.016); δ_H (400 MHz; $CDCl_3$) 7.65 (1 H, s, ArH), 7.60 (2 H, d, *J* 7.2, ArH), 7.44 (2 H, dd, *J* 7.2, 7.7, ArH), 7.38 (1 H, s, ArH), 7.36 (1 H, d, *J* 7.2, ArH), 7.18 (1 H, s, ArH), 5.29 (2 H, s, C*H*$_2$), 2.47 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 181.0 (C), 178.5 (C), 159.0 (C), 146.5 (C), 142.4 (CH), 136.6 (C), 135.9 (C), 132.8 (C), 128.7 (CH), 128.0 (CH), 126.6 (CH), 121.8 (CH), 120.5 (CH), 117.6 (C), 70.9 (CH_2), 22.3 (Me).

8-Benzyloxy-1,10-dimethyl-12*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,11,12-trione 14



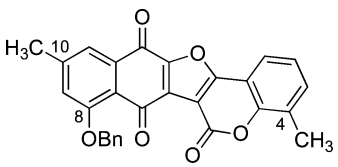
A mixture of 5-benzyloxy-2-bromo-7-methyl-1,4-naphthoquinone **13** (0.20 g, 0.56 mmol), copper(II) acetate (0.33 g, 1.7 mmol), 4-hydroxy-5-methylcoumarin **3** (0.12 g, 1.7 mmol) and potassium carbonate (0.23 g, 1.7 mmol) acetonitrile was stirred at room temperature for 2 h. After 2 h the mixture was diluted with dichloromethane (100 mL) and filtered through Celite while exhaustively washing with dichloromethane–methanol (9 : 1) (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography to give the *title compound* (0.21 g, 86%); mp 266–268 °C; (Found: C, 74.74, H, 4.15. $C_{28}H_{18}O_6$ requires C, 74.66, H, 4.03); (Found: M + Na^+, 473.0996. $C_{28}H_{18}O_6$ + Na^+ requires 473.0996); ν_{max} ($CHCl_3$)/cm^{-1} 3051, 1758, 1678, 1600, 1454, 1362, 1296, 1265, 1063; λ_{max} (MeOH) 201 (log ε 4.17) and 305 nm (log ε 3.90); δ_H (400 MHz; $CDCl_3$) 7.74 (1 H, s, ArH), 7.63 (2 H, d, *J* 7.6, ArH), 7.56 (1 H, dd, *J* 8.2, 7.7, ArH), 7.45 (2 H, dd, 7.2, 7.7, ArH), 7.37 (2 H, m, ArH), 7.25 (1 H, d, *J* 7.6, ArH), 7.21 (1 H, s, ArH), 5.36 (2 H, s, C*H*$_2$), 2.96 (3 H, s, Me), 2.48 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 176.8 (C), 173.5 (C), 162.7 (C), 159.9 (C), 155.1 (C), 154.7 (C), 151.8 (C), 146.3 (C), 136.1 (C), 136.0 (C), 133.9 (C), 132.8 (CH), 128.8 (CH), 128.3 (C), 128.0 (CH), 127.1 (CH), 126.9 (CH), 121.4 (CH), 120.7 (CH), 119.0 (C), 115.2 (CH), 110.7 (C), 108.1 (C), 71.0 (CH_2), 22.2 (Me), 21.5 (Me).

8-Hydroxy-1,10-dimethyl-12*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,11,12-trione 8



The benzyl ether **14** (0.19 g, 0.42 mmol) was dissolved in the ethyl acetate (20 mL) and methanol (5 mL) and then Pearlman's catalyst (20 mg) was added. The reaction mixture was flushed with nitrogen followed by hydrogen. The reaction mixture was stirred for 16 h under a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad while exhaustively washing with 5% methanol in dichloromethane (100 mL). The filtrate was concentrated under reduced pressure, and the residue was subjected to the silica gel flash column chromatography to give the *title compound* (0.14 g, 93%); mp 300 °C (decomp); (Found: M + H^+, 361.0724. $C_{21}H_{12}O_6$ + H^+ requires 361.0707; M + Na^+, 383.0523. $C_{21}H_{12}O_6$ + Na^+ requires 383.0526); ν_{max} ($CHCl_3$)/cm^{-1} 3689, 3608, 3006, 1754, 1677, 1602, 1543, 1386, 1267, 1074; ν_{max} (KBr)/cm^{-1} 3440, 1772, 1675, 1638, 1604, 1541, 1384, 1267, 1079; λ_{max} 202 (log ε 4.27) and 305 nm (log ε 4.092), δ_H (400 MHz; $CDCl_3$) 12.29 (1 H, s, 8-OH), 7.67 (1 H, s, H-11), 7.59 (1 H, dd, *J* 8.2, 7.8, H-3), 7.40 (1 H, d, *J* 8.2, H-4), 7.28 (1 H, d, *J* 7.8, H-2), 7.18 (1 H, s, H-9), 2.97 (3 H, s, 14-Me), 2.51 (3 H, s, 15-Me); δ_H (400 MHz; DMSO-d_6) 12.02 (1 H, s, 8-OH), 7.66 (1 H, t, *J* 8.0, H-3), 7.57 (1 H, s, H-11), 7.43 (1 H, d, *J* 8.0, H-4), 7.37 (1 H, d, *J* 7.6, H-2), 7.24 (1 H, s, H-9), 2.88 (3 H, s, 14-Me), 2.50 (3 H, s, 15-Me); δ_C (125 MHz; $CDCl_3$) 183.7 (C), 172.8 (C), 163.1 (C), 162.8 (C), 155.1 (C), 154.8 (C), 153.3 (C), 148.6 (C), 136.1 (C), 133.1 (CH), 131.7 (CH), 127.3 (CH), 126.6 (C), 125.8 (CH), 121.6 (C), 115.3 (CH), 113.3 (C), 110.5 (C), 107.6 (C), 22.1 (Me), 21.5 (Me

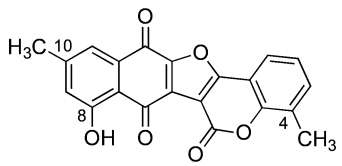
8-Benzyloxy-4,10-dimethyl-12*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,11,12-trione 15



A mixture of 5-benzyloxy-2-bromo-7-methyl-1,4-naphthoquinone **13** (0.10 g, 0.28 mmol), copper(II) acetate monohydrate (0.17 g, 0.84 mmol), 4-hydroxy-8-methyl coumarin **10** (0.06 g, 0.34 mmol) and potassium carbonate (0.12 g, 0.84 mmol) in acetonitrile (10 mL) was stirred at room temperature under nitrogen atmosphere. After 2 h the mixture was diluted with dichloromethane (100 mL) and filtered through Celite while exhaustively washing with dichloromethane: methanol (9 : 1) (100 mL). The filtrate

was concentrated under reduced pressure and the residue was purified by flash column chromatography (30% ethyl acetate in light petroleum) to give the *title compound* (0.11 g, 87%); mp 260–262 °C; (Found: C, 74.30; H, 3.89. $C_{28}H_{18}O_6$ requires C, 74.66, H, 4.03); (Found: M + Na^+, 473.0999. $C_{28}H_{18}O_6$ + Na^+ requires 473.0996); ν_{max} ($CHCl_3$)/cm^{-1} 1764, 1677, 1621, 1599, 1558, 1296, 1250, 1023; λ_{max} (MeOH) 300 (log ε 4.20) and 390 nm (log ε 3.76); δ_H (400 MHz; $CDCl_3$) 7.96 (1 H, d, *J* 7.6, ArH), 7.74 (1 H, s, ArH), 7.62 (2 H, d, *J* 7.2, ArH), 7.53 (1 H, d, 7.2, ArH), 7.44 (2 H, dd, *J* 7.6, 7.2, ArH), 7.37–7.32 (2 H, m, ArH), 7.20 (1 H, s, ArH), 5.36 (2 H, s, C*H*$_2$), 2.57 (3 H, s, Me), 2.47 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 176.8 (C), 173.7 (C), 162.1 (C), 159.1 (C), 154.5 (C), 152.8 (C), 151.8 (C), 146.3 (C), 136.1 (C), 134.8 (CH), 133.8 (C), 128.8 (C), 128.7 (CH), 128.0 (CH), 127.3 (C), 126.9 (CH), 124.6 (CH), 121.5 (CH), 120.8 (CH), 119.9 (CH), 118.9 (C), 111.0 (C), 107.8 (C), 71.0 (CH_2), 22.2 (Me), 16.1 (Me).

8-Hydroxy-4,10-dimethyl-12*H*-naphtho[2′,3′:4,5]furo[3,2-*c*]chromene-6,11,12-trione 9



The benzyl ether **15** (0.20 g, 0.44 mmol) was dissolved in the ethyl acetate (15 mL) and dichloromethane (5 mL) and then Pearlman's catalyst (40 mg) was added. The reaction mixture was flushed with nitrogen followed by hydrogen. The reaction mixture was stirred for 16 h under hydrogen atmosphere. The reaction mixture was filtered through Celite while exhaustively washing with 5% methanol in dichloromethane (100 mL). The filtrate was concentrated under reduced pressure and the residue was subjected to silica gel flash column chromatography to give the *title compound* (0.15 g, 94%) mp 310 °C (decomp); (Found: M + H^+, 361.0688. $C_{21}H_{12}O_6$ + H^+ requires 361.0707; M + Na^+, 383.0515. $C_{21}H_{12}O_6$ + Na^+ requires 383.0526); ν_{max} ($CHCl_3$)/cm^{-1} 3692, 3044, 2337, 1752, 1676, 1642, 1553, 1260, 1071; ν_{max} (KBr)/cm^{-1} 3441, 1753, 1675, 1638, 1551, 1501, 1384, 1258, 1183, 1071; λ_{max} (MeOH) 295 (log ε 4.25) and 302 nm (log ε 4.27); δ_H (500 MHz; $CDCl_3$) 12.25 (1 H, s, 8-OH), 7.97 (1 H, d, *J* 8.0, H-1), 7.65 (1 H, s, H-11), 7.55 (1 H, d, *J* 7.0, H-3), 7.36 (1 H, t, *J* 7.5, H-2), 7.16 (1 H, s, H-9), 2.57 (3 H, s, 14-Me), 2.48 (3 H, s, 15-Me); δ_H (400 MHz; DMSO-d_6) 12.06 (1 H, s, 8-OH), 8.00 (1 H, d, *J* 7.2, H-1), 7.73 (1 H, d, *J* 7.6, H-3), 7.57 (1 H, s, H-11), 7.47 (1 H, t, *J* 7.6, H-2), 7.28 (1 H, s, H-9), 2.51 (3 H, s, 14-Me), 2.48 (3 H, s, 15-Me); δ_C (125 MHz; $CDCl_3$) 183.7 (C), 173.1 (C), 163.1 (C), 162.3 (C), 154.7 (C), 153.3 (C), 152.8 (C), 148.6 (C), 135.1 (CH), 131.6 (C), 127.5 (C), 127.2 (C), 125.9 (CH), 124.8 (C), 121.6 (CH), 119.9 (CH), 113.2 (C), 110.8 (C), 107.3 (C), 22.1 (Me), 16.1 (Me).

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