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Three New Benzophenone–Xanthone Dimers from the Root of *Garcinia dulcis*

Munekazu IINUMA,*[,a] Hideki TOSA,[a] Tetsuro ITO,[a] Toshiyuki TANAKA,[a] and Soedarsono RISWAN[b]

Department of Pharmacognosy, Gifu Pharmaceutical University,[a] 6–1 Mitahora-higashi 5-chome, Gifu 502, Japan, and Herbarium Bogoriense, The Indonesian Institute of Science, Research and Development Center for Biology,[b] Jl. Ir. Juanda 18, Bogor 16122, Indonesia. Received April 11, 1996; accepted May 28, 1996

Investigation of the chemical constituents of the roots of *Garcinia dulcis* resulted in the isolation of three new benzophenone–xanthone dimers named garciduols A—C (1—3) in addition to a new xanthone, 1,3,6-trihydroxy-7-methoxyxanthone (4). Five known xanthones [2,5-dihydroxy-1-methoxy- (5), 1,4,5-trihydroxy- (6), 1,3,5-trihydroxy- (7), 1,3,6-trihydroxy-5-methoxy- (8) and 1,3,6-trihydroxy-8-isoprenyl-7-methoxyxanthone (9)] were also isolated from the roots. Their structures were determined by spectroscopic analysis including two dimensional NMR. The behaviors of chemical shifts caused by acetylation and the position of the methoxyl group in the dimers characterized by model synthetic benzophenones are also discussed.

Key words *Garcinia dulcis*; Guttiferae; benzophenone–xanthone dimer; xanthone; garciduol A, B, C

Garcinia dulcis KURZ (Guttiferae) is a sub-woody plant widely distributed in Southeast Asia. Its leaves and seeds have been used as traditional medicine against lymphatitis, struma, parotitis, and so on.[1] In continuation of our study of chemical constituents with bioactive potency in Guttifereous plants, the chemical constituents (xanthones, benzophenones, anthrones *etc.*) had been investigated in some plants of *Garcinia*,[2–4] *Calophyllum*,[5] *Harungana*,[6] and *Mammea*.[7] We also characterized some xanthone derivatives with potent anti-microbacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[8] In our preceding papers, the structure elucidation of five new xanthones (dulciols A—E) in *G. dulcis* was described,[9] and the structures of garcidulols A and B[10] have also been communicated. We report here in detail the structural characterization of new bezophenone–xanthone dimers, garciduols A—C in the roots of *G. dulcis*, in addition to some xanthones, including a new one.

Results and Discussion

Air-dried roots of *G. dulcis*, collected in Indonesia, were extracted successively with benzene, acetone and 70% MeOH. The acetone extract was repeatedly subjected to column chromatography on silica gel, Sephadex LH-20 and preparative TLC (PTLC) to isolate compounds **1**, **2** and **5**—**8**. The 70% MeOH extract also gave **3**, **4** and **9** after repeated chromatography in a manners similar to the acetone extract.

Compound **1**, garciduol A, obtained as a yellow amorphous powder, was positive to $FeCl_3$ and Gibbs tests. The $(M)^+$ at *m/z* 486.0959 in the high-resolution (HR) MS corresponds to the molecular formula $C_{27}H_{18}O_9$. The ^{1}H-NMR spectral data (Table 1) showed the presence of a 1,2,3-trisubstituted benzene ring [δ 7.34 (1H, t, J= 7.8 Hz), 7.39 (1H, dd, J=7.8, 2.0 Hz) and 7.74 (1H, dd, J=7.8, 2.0 Hz)], a monosubstituted benzene ring [δ 7.43, 7.70 (2H each, m), 7.50 (1H, m)] and two isolated aromatic protons [δ 6.27, 7.25 (1H each, s)], in addition to a methoxyl [δ 3.80 (3H, s)] and five phenolic hydroxyl groups [δ 8.82 (2H, br s), 9.85, 10.35 (1H each, br s) and 12.32 (1H, s, chelated)]. The number of hydroxyl groups in **1** was established by complete acetylation with acetic anhydride/pyridine to afford a pentaacetate (**1a**, HRMS: 696.1497 $(M)^+$). All protonated carbons were assigned by CH correlation spectroscopy (COSY). In the ^{13}C-NMR spectral data (Table 1), two carbonyl carbons (δ 183.3 and 200.0) were observed, along with 24 aromatic carbons, eight of which have an oxygen function. The heteronuclear multiple bond connectivity (HMBC) spectrum (Fig. 1) showed correlations between one of the protons (δ 7.74) on a 1,2,3-trisubstituted benzene ring and the carbonyl carbon (δ 183.3), which indicated that the proton was located at a *peri*-position to the carbonyl group. The same proton was further correlated to another aromatic carbon at δ 145.8. Another proton (δ 7.34) on the 1,2,3-trisubstituted benzene was correlated to an aromatic carbon (δ 147.1). The carbons at δ 145.8 and 147.1 were then assignable to the aromatic carbons of a cathecol type benzene ring. The aromatic protons at δ 7.39 (H-6) and 7.74 (H-8) in the ^{1}H-NMR spectrum were shifted to a lower field by 0.3 ppm by acetylation (**1a**) (Fig. 1), indicating the presence of hydroxyl group at an *ortho*- or

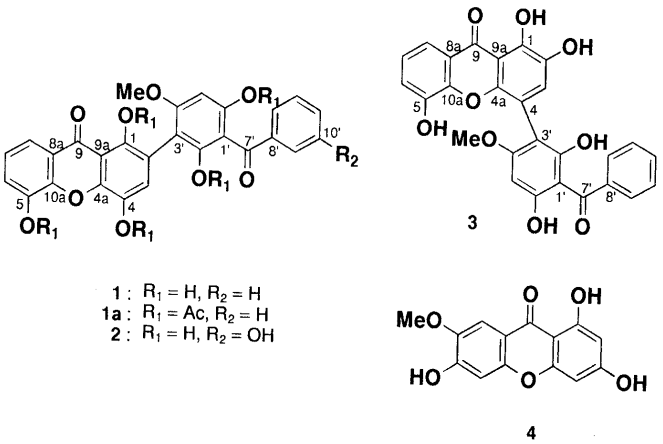

Chart 1

* To whom correspondence should be addressed.

Table 1. NMR Spectral Data of **1**—**3**

	1		**2**		**3**	
No.	δ_C	δ_H J (Hz)	δ_C	δ_H J (Hz)	δ_C	δ_H J (Hz)
1	153.2		153.1		152.9	
2	115.5		116.0		138.1	
3	128.2	7.25 (1H, s)	128.3	7.24 (1H, s)	128.1	7.23 (1H, s)
4	137.5		137.9		115.2	
5	147.1		147.8		148.3	
6	122.0	7.39 (1H, dd, 7.8, 2.0)	122.2	7.38 (1H, dd, 7.8, 2.0)	122.1	7.38 (1H, dd, 7.8, 2.0)
7	125.3	7.34 (1H, t, 7.8)	125.4	7.32 (1H, t, 7.8)	125.4	7.31 (1H, t, 7.8)
8	116.6	7.74 (1H, dd, 7.8, 2.0)	116.4	7.71 (1H, dd, 7.8, 2.0)	115.8	7.67 (1H, dd, 7.8, 2.0)
9	183.3		183.5		183.6	
4a	143.7		143.93[a]		144.0	
8a	122.1		122.1		122.0	
9a	109.4		109.6		109.5	
10a	145.8		146.1		146.3	
1′	106.0		106.3		106.1	
2′	160.3		160.1		160.1	
3′	105.7		105.9		105.9	
4′	164.7		164.6		164.8	
5′	92.4	6.27 (1H, s)	92.5	6.26 (1H, s)	92.4	6.27 (1H, s)
6′	163.1		163.0		163.2	
7′	200.0		199.9		200.1	
8′	142.5		143.87[a]		142.6	
9′	129.2	7.70 (1H, m)	116.2	7.19 (1H, m)	129.4	7.71 (1H, m)
10′	128.5	7.43 (1H, m)	157.9		128.6	7.42 (1H, m)
11′	131.9	7.50 (1H, m)	119.2	6.97 (1H, ddd, 7.9, 2.4, 1.2)	132.1	7.48 (1H, m)
12′	128.5	7.43 (1H, m)	129.8	7.25 (1H, t, 7.9)	128.6	7.42 (1H, m)
13′	129.2	7.70 (1H, m)	120.6	7.19 (1H, m)	129.4	7.71 (1H, m)
OMe	56.2	3.80 (3H, s)	56.3	3.79 (3H, s)	56.3	3.80 (3H, s)
OH-C-1		12.32 (1H, s)				
OHs		8.82 (2H, br s) 9.85, 10.35 (1H each, br s)		9.65, 12.36 (1H each, br s)		9.95, 12.18 (1H each, br s)

Measured in acetone-d_6. *a*) Interchangeable.

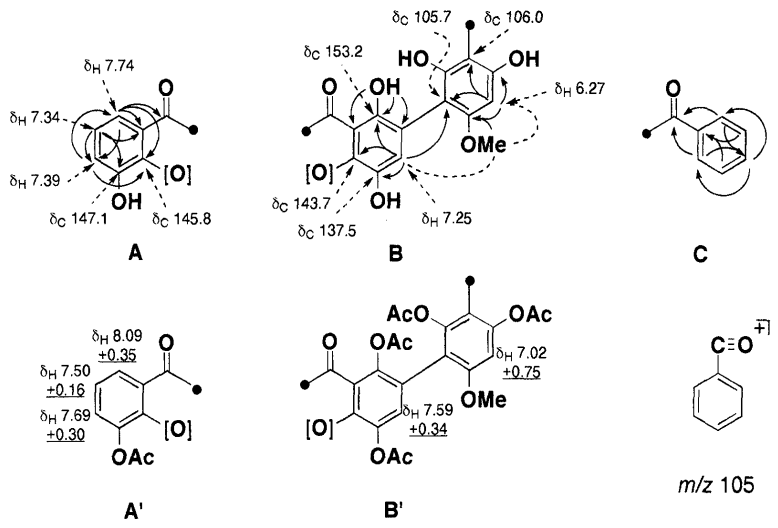

Fig. 1. Possible Partial Structures (**A**, **B** and **C**) of **1** and Acetylated Derivatives (**A′** and **B′**)

The downfield shift values caused by acetylation are shown by underline in **A′** and **B′**. Arrows denote long-range correlations in HMBC (J=10 Hz), and dotted lines do NOEs.

a *para*-position of these protons (δ 7.39 and 7.74). Therefore, the plausible partial structure of **1** was considered to be **A** in Fig. 1. On the other hand, spectral evidence, fragment ion peaks at m/z 105 and 77 in the electron impact (EI)MS, and the correlation of the protons (δ 7.70) on a monosubstituted benzene ring (H-9′ and H-13′) to another carbonyl carbon (δ 200.0) in the HMBC spectrum (Fig. 1), suggested that **1** has a benzoyl moiety (**C**) as the other partial structure shown in Fig. 1. The HMBC spectrum (Fig. 1) exhibited correlations between the chelated hydroxyl proton (δ 12.32) and three quaternary carbons (δ 153.2, 115.5, 109.4) assignable to C-1, C-2 and C-9a. The former carbon was further correlated to an aromatic proton (δ 7.25), which also cor-

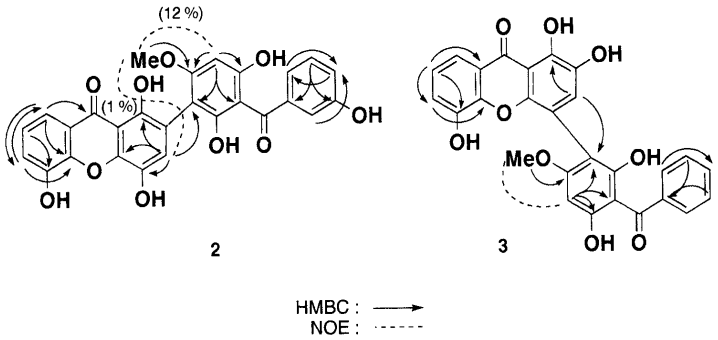

Fig. 2. HMBC Spectrum ($J=10$ Hz) and NOE Experiments of **2** and **3**

related to the aromatic carbons (δ 137.5 and 143.7). Considering the chemical shifts of these aromatic carbons with an oxygen function, this aromatic ring was regarded as a 1,3,4-trioxygenated benzene. As the singlet signal at δ 7.25 in **1** shifted to 7.59 in **1a** (Fig. 1), the presence of a hydroxyl group at the *ortho*-position was clarified. A nuclear Overhauser effect (NOE) (13%) was observed at a singlet proton signal (δ 6.27) when the methoxyl signal (δ 3.80) was irradiated. The signal at δ 6.27 in **1** moved to 7.02 (+0.75 ppm) in **1a** (Fig. 1), indicating that the *ortho*- and *para*-positions of the proton were substituted by hydroxyl groups. Furthermore, in the ^{13}C-NMR spectrum, three other aromatic carbons with an oxygen function were observed at δ 160.3, 163.1 and 164.7, suggesting the presence of a phloroglucinol type benzene ring. In the HMBC spectrum, the aromatic proton (δ 6.27) was correlated to the aromatic carbon (δ 105.7), which was further correlated to another aromatic proton (δ 7.25), showing that the partial structure of **1** was characterized as **B** in Fig. 1. Other correlations observed in the HMBC spectrum supported the partial structure **B**. The UV spectral features were very similar to those of 1,4,5-trihydroxyxanthone (subelliptenone G),[3] and the chemical shift of the carbonyl carbon at δ 183.3 was characteristic of 1-hydroxyxanthone.[11] Therefore, **1** was concluded to be a benzophenone–xanthone dimer. Comparing the ^{1}H- and ^{13}C-NMR spectral data with those of an authentic sample, subelliptenone G,[3] the spectral data based on the xanthone moiety were superimposed. As the aromatic proton (δ 7.25) was assignable to H-3, the C-2 in the xanthone was connected to the C-3′ in the benzophenone. To substantiate the structure of the benzophenone moiety, phloroglucinol monomethyl ether was benzoylated to give 2,6-dihydroxy-4-methoxybenzophenone (**10**) and 2,4-dihydroxy-6-methoxybenzophenone (**11**). In their ^{1}H-NMR spectra, the chemical shift due to a methoxyl group in **1** (δ 3.80) corresponded with that of **10** (δ 3.82), but the shift of **11** (δ 3.49) agreed with that of a 2-methoxyl group in 6,4′-dihydroxy-2,4,3′-trimethoxybenzophenone.[12] Thus, the methoxyl group was concluded to attach at C-4 in the benzophenone moiety, which was further established by the observation of an NOE (1%) between the methoxyl group and the aromatic proton at δ 7.25 (H-3). Thus, the total structure of garciduol A was characterized as **1**.

Compound **2**, garciduol B, obtained as a yellow amorphous powder, was positive to $FeCl_3$ and Gibbs tests. The HRMS showed (M^+) at m/z 502.0916, which corresponds to the molecular formula $C_{27}H_{18}O_{10}$. The ^{1}H- and ^{13}C-NMR spectral data of **2** (Table 1) were similar to those of **1** except for the presence of a 1,3-disubstituted benzene ring [δ 6.97 (1H, ddd, $J=7.9$, 2.4, 1.2 Hz), 7.19 (2H, m), 7.25 (1H, t, $J=7.9$ Hz)] instead of a monosubstituted benzene ring composed of a benzophenone moiety. Thus, garciduol B was a derivative of garciduol A with another hydroxyl group at C-10′. The structure was well supported by an NOE experiment and by the correlations observed in the HMBC spectrum (Fig. 2).

Compound **3**, garciduol C, obtained as a yellow amorphous powder, was also positive to $FeCl_3$ and Gibbs tests. The HRMS [486.0941 (M^+)] indicated a molecular formula of $C_{27}H_{18}O_9$. The similarities between **1** and **3** in the spectral data, including the ^{1}H- and ^{13}C-NMR spectrum (Table 1), indicated that **3** was an isomer of **1**. Their differences were oxygenation patterns in a xanthone moiety, that is, either 1,2,5- or 1,4,5-trioxygenation.[3,13] These patterns were explained from the viewpoint of a recent biosynthetic study showing that xanthones are formed through a series of benzophenones.[2] Thus, the total structure of garciduol C was characterized as **3**. The structure was further substantiated by an NOE experiment and by correlations in the HMBC spectrum (Fig. 2).

Compound **4**, obtained as a yellow amorphous powder, was positive to $FeCl_3$ and Gibbs tests. The $(M)^+$ at m/z 336.0986 in the HRMS indicated the molecular formula $C_{14}H_{10}O_6$. The UV absorptions closely resembled those of 1,3,7-trihydroxy-6-methoxyxanthone.[14] In the ^{1}H-NMR spectrum, signals assignable to H-2 and H-4 at δ 6.24 and 6.40 (1H each, d, $J=2.2$ Hz), H-5 and H-8 at δ 6.94 and 7.55 (1H each, s), in addition to a chelated hydroxyl [δ 13.16 (1H, s)] and a methoxyl group [δ 3.99 (3H, s)] were observed. An NOE (10%) was observed between the methoxyl group (δ 3.99) and the aromatic proton at δ 7.55. Therefore, the methoxyl group was attached to the C-7 position. Finally, **4** was characterized as 1,3,6-trihydroxy-7-methoxyxanthone. Although **4** has already been synthesized,[14] this is the first instance of such from a natural source.

Compounds **5**—**9** were characterized as 2,5-dihydroxy-1-methoxy- (**5**),[13] 1,4,5-trihydroxy- (**6**),[13] 1,3,5-trihydroxy- (**7**),[16] 1,3,6-trihydroxy-5-methoxy- (**8**),[17] 1,3,6-trihydroxy-8-isoprenyl-7-methoxyxanthone (**9**), respectively, by spectroscopic analysis, including the two dimensional (2D) NMR technique.

Garciduols A—C have a new skeleton of benzophenone–xanthone dimer, which is the first reported instance

of this in naturally occurring compounds.

Experimental

IR spectra were recorded on a JASCO IR-AI spectrophotometer. UV spectra were recorded on a Shimadzu UV-2200 spectrophotometer. MS were recorded on a JEOL JMS-D300 (70 eV). NMR spectra were measured at 400 MHz for ^{1}H and 100 MHz for ^{13}C, on a JEOL JMN EX-400 instrument. Samples were dissolved in acetone-d_6 and referenced indirectly to tetramethylsilane (TMS) as an internal standard. The following adsorbents were used for purification: analytical TLC, Merck Kieselgel 60 F_{254}; column chromatography, Merck Kieselgel 60, Fuji Davison Silica gel BW-300, and Pharmacia Fine Chemicals AB Sephadex LH-20.

Plant Material and Extraction The roots of *G. dulcis* were collected at Pasoeroean (Java Timur) in Indonesia, in September 1995. Voucher specimens are deposited in the Herbarium of Gifu Pharmaceutical University. The air-dried and ground roots (950 g) were extracted with benzene (2 l × 12 h × 3 times), acetone (2 l × 12 h × 3) and 70% MeOH (2 l × 12 h × 3) under reflux, successively, to yield 27, 68 and 70 g of the respective extracts.

Isolation The acetone extract (50 g) was fractionated on a silica gel column and eluted with a mixture of benzene–acetone of increasing polarity to give 11 fractions (frs. 1—11). Fraction 6 (benzene : acetone = 5 : 1) was subjected to vacuum liquid chromatography (VLC) on silica gel and eluted with a benzene–acetone system which resulted in eight fractions (frs. 6-1—6-8). Fraction 6-6 was further subjected to Sephadex LH-20 (acetone) to give four fractions. The third fraction was purified with PTLC ($CHCl_3$: MeOH = 20 : 1) to give **5** (5 mg) and **8** (5 mg). The fourth fraction was purified by recrystallization (MeOH) after being subjected to PTLC (benzene : EtOAc = 5 : 1) to give **1** (10 mg). Fraction 6-2 was purified by Sephadex LH-20 (acetone) and PTLC (*n*-hexane : EtOAc : MeOH = 8 : 2 : 1) to give **7** (5 mg). From fr. 6-4, **6** (8 mg) was obtained. Fraction 7 (benzene : acetone = 2 : 1) was chromatographed on silica gel eluted with a $CHCl_3$–MeOH system. One of the eluents (10 : 1) was further purified by Sephadex LH-20 (MeOH) to give **2** (8 mg).

The 70% MeOH extract (50 g) was suspended in H_2O and partitioned with EtOAc. The EtOAc soluble extract (20 g) was subjected to silica gel column chromatography eluted with a benzene–acetone system to give eight fractions (frs. A—H). Fraction B (benzene : acetone = 7 : 1) was subjected to Sephadex LH-20 and eluted with MeOH to give four fractions. The third fraction was purified with PTLC ($CHCl_3$: MeOH = 10 : 1) to give **9** (2 mg). Fraction E (benzene : acetone = 7 : 1) was repeatedly subjected to Sephadex LH-20 (MeOH) and PTLC ($CHCl_3$: MeOH = 20 : 1) to give **3** (8 mg) and **4** (3 mg).

Garciduol A (1) A yellow amorphous solid. HRMS: Calcd for $C_{27}H_{18}O_9$: 486.0951 (M^+). Found: 486.0959. MS *m/z* (rel. int.): 486 (M^+, 75), 468 (36), 439 (5), 391 (6), 366 (6), 314 (7), 312 (7), 281 (5), 234 (54), 232 (34), 204 (27), 154 (100), 105 (27), 77 (75). UV λ (MeOH): 212, 230 sh, 250, 265 sh, 311, 400 nm; +$AlCl_3$: 213, 231, 250, 266, 327; +$AlCl_3$/HCl: 204, 212, 250, 265 sh, 320; +NaOAc: 222, 262, 312, 315, 415; +NaOAc/H_3BO_3: 223, 303; +NaOMe: 215, 255, 320. IR (KBr): 3365, 3184, 1624, 1587 cm^{-1}. ^{1}H- and ^{13}C-NMR spectral data are shown in Table 1.

Preparation of 1a To Garciduol A (4 mg) dissolved in pyridine (1 ml), Ac_2O (100 mg) was added and the solution was kept at room temperature for 12 h. The reaction mixture was poured into H_2O and extracted with EtOAc. After washing with H_2O, the organic solvent was evaporated. The residue was purified by PTLC (benzene : acetone = 20 : 1) to yield **1a** (3 mg) as a non-crystalline solid. **1a**: HRMS: Calcd. for $C_{37}H_{28}O_{14}$: 696.1479 (M^+). Found: 696.1497. MS *m/z* (rel. int.): 696 (M^+, 2), 654 (42), 612 (58), 570 (65), 552 (10), 528 (100), 487 (16), 467 (41), 439 (4), 340 (5), 311 (2), 129 (2), 105 (27). UV λ (MeOH): 212, 248, 270 sh, 342 nm. ^{1}H-NMR δ: 2.02, 2.04, 2.21, 2.47, 2.47 (3H each, s, Ac × 5), 7.02 (1H, s, H-3′), 7.50 (1H, t, J = 7.8 Hz, H-7), 7.53 (2H, br d, J = 7.2 Hz, H-10′, 12′), 7.59 (1H, s, H-3), 7.65 (1H, br t, J = 7.2 Hz, H-11′), 7.69 (1H, dd, J = 7.8, 1.6 Hz, H-6), 7.76 (2H, br d, J = 7.2 Hz, H-9′, 13′), 8.09 (1H, dd, J = 7.8, 1.6 Hz, H-8).

Garciduol B (2) A yellow amorphous solid. HRMS: Calcd for $C_{27}H_{18}O_{10}$: 502.0900 (M^+). Found: 502.0916. MS *m/z* (rel. int.): 502 (M^+, 6), 486 (10), 464 (8), 421 (8), 396 (10), 379 (12), 363 (7), 339 (15), 328 (45), 311 (88), 295 (100), 285 (40), 273 (50), 260 (45), 244 (86), 218 (10), 187 (7), 149 (20), 135 (20), 121 (16). UV λ (MeOH): 207, 250, 268 sh, 314, 400 sh nm; +$AlCl_3$: 205, 250, 267, 285 sh, 325, 395; +$AlCl_3$/HCl: 205, 250, 263 sh, 322, 395; +NaOAc: 212, 261, 315; +NaOAc/H_3BO_3: 213, 249, 260 sh, 310; +NaOMe: 214, 245. IR (KBr): 3400, 2927, 2855, 1704, 1617, 1596 cm^{-1}.

Garciduol C (3) A yellow amorphous solid. HRMS: Calcd for $C_{27}H_{18}O_9$: 486.0951 (M^+). Found: 486.0941. MS *m/z* (rel. int.): 486 (M^+, 100), 468 (56), 444 (8), 391 (9), 243 (8), 218 (29), 164 (27), 157 (26), 135 (47), 105 (22). UV λ (MeOH): 212, 228 sh, 250, 275 sh, 312, 401 nm. IR (KBr); 3360, 3200, 1625, 1587 cm^{-1}.

1,3,6-Trihydroxy-7-methoxyxanthone (4) A yellow amorphous solid. HRMS: Calcd for $C_{14}H_{10}O_6$: 274.0494 (M^+). Found: 274.0471. MS *m/z* (rel. int.): 274 (M^+, 100), 259 (37), 245 (16), 231 (30), 203 (13), 167 (15), 149 (20), 123 (13). UV λ (MeOH): 212, 248, 270 sh, 343 nm. ^{1}H-NMR δ: 3.99 (3H, s, OMe-C-7), 6.24 (1H, d, J = 2.2 Hz, H-2), 6.40 (1H, d, J = 2.2 Hz, H-4), 6.94 (1H, s, H-5), 7.55 (1H, s, H-8), 13.16 (1H, s, OH-C-1).

Synthesis of Benzophenones (10 and 11) Powdered $AlCl_3$ (1 g) was added to a sodium-dry ether solution (200 ml) of phloroglucinol monomethyl ether (500 mg, 3.57 mmol) and benzoyl chloride (400 mg, 2.85 mmol). After being stirred at room temperature for 12 h, the reaction mixture was acidified by dil. HCl and extracted with ether. The organic solvent was removed and the residue was subjected to silica gel column chromatography eluted with benzene–acetone (50 : 1) to give 2,6-dihydroxy-4-methoxybenzophenone (**10**) (120 mg) and 2,4-dihydroxy-6-methoxybenzophenone (**11**) (270 mg). **10**: A pale yellow amorphous solid. MS *m/z* (rel. int.): 244 (M^+, 56), 243 (100), 167 (41), 105 (8), 77 (11). ^{1}H-NMR δ: 3.82 (3H, s, OMe-C-4), 6.04 (2H, s, H-3, 5), 7.41 (2H, m, H-10, 12), 7.50 (1H, m, H-11), 7.62 (2H, m, H-9, 13), 10.45 (2H, br s, OH-C-2, 6). **11**: A pale yellow amorphous solid. MS *m/z* (rel. int.): 244 (M^+, 66), 243 (100), 167 (64), 149 (8), 105 (13), 77 (16). ^{1}H-NMR δ: 3.49 (3H, s, OMe-C-6), 6.04 (1H, d, J = 2.3 Hz, H-5), 6.08 (1H, d, J = 2.3 Hz, H-3), 7.45 (2H, m, H-10, 12), 7.51 (1H, m, H-11), 7.55 (2H, m, H-9, 13), 9.33 (1H, br s, OH-C-4), 11.74 (1H, br s, OH-C-2).

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