A Novel Short-Step Synthesis of New Xanthenedione Derivatives from the Cyclization of 3-Cinnamoyl-2-styrylchromones

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Abstract: Novel (*E*)-3-aryl-4-benzylidene-8-hydroxy-3,4-dihydro-1*H*-xanthene-1,9(2*H*)-diones are prepared by the cyclization of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones efficiently catalyzed with boron tribromide. The (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones are obtained from the Baker–Venkataraman rearrangement of (*E*,*E*)-2-acetyl-1,3-phenylene bis(3-phenylacrylate), which is greatly improved under microwave irradiation.

Key words: xanthenediones, 3-cinnamoyl-5-hydroxy-2-styrylchromones, microwave irradiation, cyclization, boron tribromide

Xanthones are a class of secondary metabolites widely occurring in higher plant families such as *Guttiferae* and *Gentianaceae*.[1] The growing interest in this class of compounds is associated with the important pharmacological properties demonstrated by both natural and synthetic derivatives, such as anti-inflammatory,[2] antitumour,[3] and antioxidant activities.[4] To the best of our knowledge, xanthenedione derivatives are scarce in nature; so far four xanthene-2,9-dione derivatives have been found, garcinianones A (**1**) and B (**2**), isolated from *Garcinia multiflora*,[5] allanxanthone C (**3a**), isolated from *Allanblackia monticola* Staner L. C.,[6] and 1,2-dihydro-3,6,8-trihydroxy-1,1-diisoprenyl-5-(1,1-dimethylprop-2-enyl)xanthen-2,9-dione (**3b**), isolated from *Hypericum erectum* (Figure 1).[7] Allanxanthone C (**3a**) demonstrated moderate activity against two strains of *Plasmodium falciparum*.[6] References to synthetic xanthenediones are more frequent, however, the common type of substitution pattern is the 9-aryl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**4**, Figure 1).[8] Xanthene-1,9(2*H*)-diones have not been found in nature and synthetic derivatives also seem to be scarce, only 3,4-dihydro-1*H*-xanthene-1,9(2*H*)-dione (**5**, Figure 1) has been described.[9]

2-Styrylchromones are also a scarce group of naturally occurring compounds, only three derivatives have been isolated [hormothamnione (**6a**) and desmethoxyhormothamnione (**6b**), from the marine blue green alga *Chrysophaeum taylori*,[10] and (*E*)-5-hydroxy-2-styrylchromone (**6c**), from the rhizomes of *Imperata cylindrical* (Figure 1)].[11] Even so, 2-styrylchromone derivatives are associated with important biological properties, such as antinorovirus,[12] anti-inflammatory,[13] and antioxidant[14] activities.

Following our interest in the synthesis of biologically active compounds, especially polyhydroxy-2-styrylchromones, a program aimed at the synthesis of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **8** was initiated (Scheme 1).

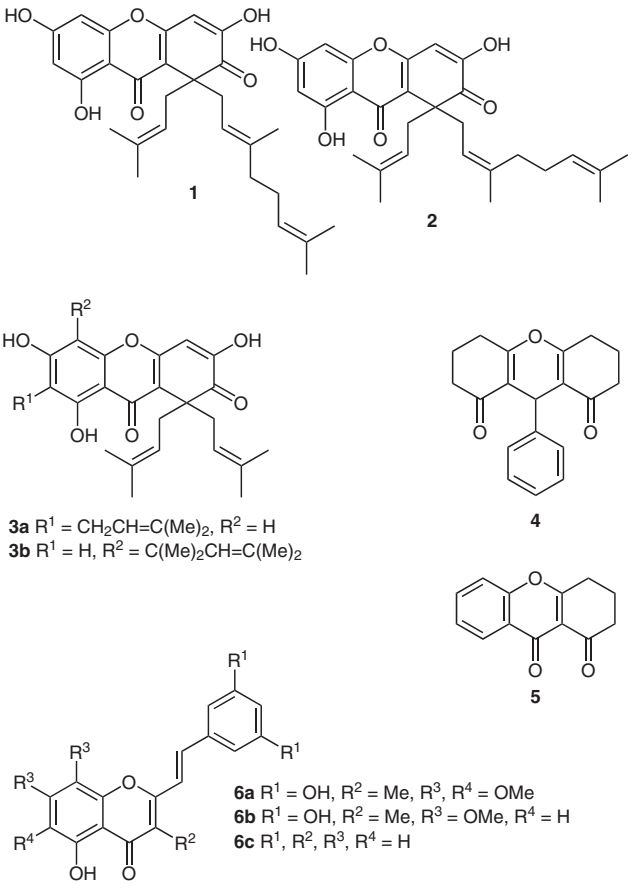

Figure 1 Naturally occurring xanthenediones and (*E*)-2-styrylchromones

Knowing the importance of the catechol moiety to improve the antioxidant activity of 2-styrylchromones,[15] it was decided to synthesize (*E*,*E*)-3-(3,4-dihydroxycinnamoyl)-5-hydroxy-2-(3,4-dihydroxystyryl)chromone. In order to achieve this we firstly obtained the corresponding methoxy derivative **8g**. Its synthesis could be accomplished in a two-step approach as previously reported[16] or

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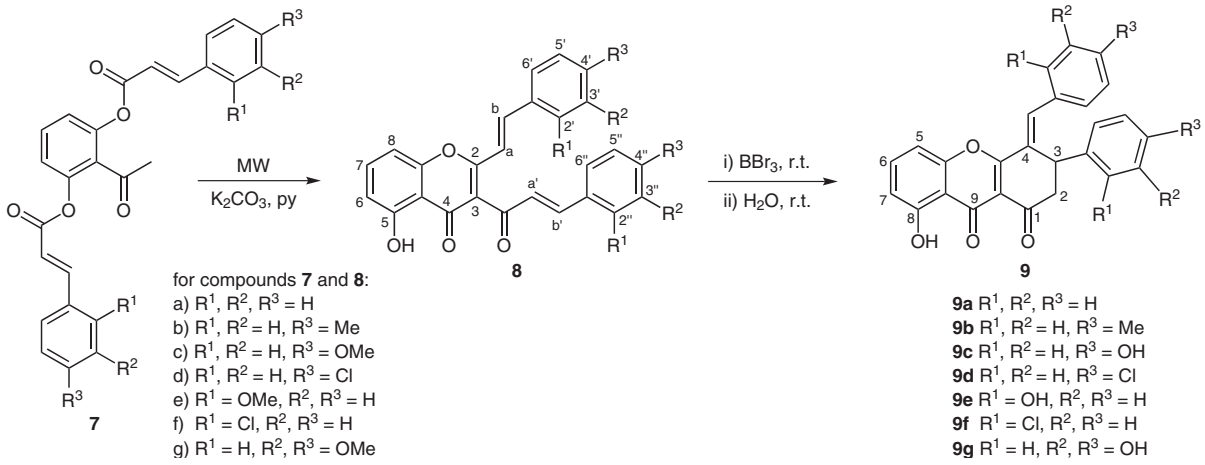


Scheme 1

in one-pot sequence as recently described.[17] Our choice, due to the less expensive reagents and shorter reaction time, was the two-step approach (bisesterification of the appropriate 2′-hydroxyacetophenone with cinnamoyl chloride derivatives followed by the Baker–Venkataraman rearrangement of the formed diester),[16] in combination with a great improvement achieved by using microwave irradiation.[18] This methodology was successfully employed for the rearrangement of (*E*,*E*)-2-acetyl-1,3-phenylene bis(3-phenylacrylate) (**7g**) leading to (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromone (**8g**) in good yield (86%, Scheme 1).[19,20] Next, cleavage of the methoxy group with boron tribromide was attempted, but mixtures of compounds bearing methoxy and hydroxy groups were obtained. Therefore, we decided to extend the reaction time and after 22 hours, cleavage of the methoxy group was complete and a pure yellow solid was obtained. NMR analysis indicated that the expected demethylation occurred but the compound obtained was (*E*)-4-(3,4-dihydroxy-benzylidene)-8-hydroxy-3-(3,4-dihydroxyphenyl)-3,4-dihydro-1*H*-xanthene-1,9(2*H*)-dione (**9g**, 81%). This result means that there was the expected deprotection together with an unprecedented cyclization of (*E*,*E*)-3-(3,4-dimethoxycinnamoyl)-5-hydroxy-2-(3,4-dimethoxystyryl)chromone (**8g**, Scheme 1).[21] This surprising result and the reported important biological applications for similar derivatives prompted us to study this synthetic methodology. We herein report an efficient and concise synthetic route for (*E*)-3-aryl-4-benzylidene-8-hydroxy-3,4-dihydro-1*H*-xanthene-1,9(2*H*)-diones **9a**–**g** (Scheme 1).[22,23]

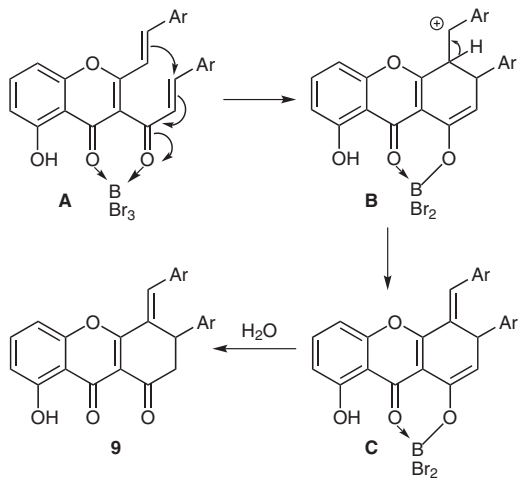
The use of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **8a**–**g** as starting materials is very attractive due to the fact that their reactivity has never been reported and we could also study the scope of the Baker–Venkataraman rearrangement of (*E*,*E*)-2-acetyl-1,3-phenylene bis(3-phenylacrylates) **7a**–**g** under microwave irradiation.[19] This strategy proved to be excellent since almost all compounds were obtained in very good yields (over 80%) and in less than 20 minutes reaction time. Furthermore, purification procedures were needed only for derivatives **8d** and **8f**, which were obtained in good yields (over 60%). These results, together with the fact that all attempts to obtain nitro derivatives failed, indicate that withdrawing groups do not favor the Baker–Venkataraman rearrangement.[24]

The next step in our strategy was the cyclization of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **8** with boron tribromide as Lewis acid catalyst. After three hours at room temperature the starting material **8a** was completely consumed, and (*E*)-4-benzylidene-8-hydroxy-3-phenyl-3,4-dihydro-1*H*-xanthene-1,9(2*H*)-dione (**9a**) was obtained in good yield (66%). The scope of this reaction was investigated and it was demonstrated that, in the case of **8d** and **8f**, eight hours were needed to complete the reaction and in the case of **8c** and **8e** one-pot cyclization and demethylation occurred furnishing hydroxy derivatives **9c** and **9e** in moderate yields (over 40%).[21]

The described cyclization reaction presumably proceeds by the activation of (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **8a**–**g** through a chelation with BBr_3 (intermediate **A**), which promotes the subsequent cyclization and deprotonation reactions (intermediate **B** and **C**). Finally, the treatment with water performs the cleavage of the oxygen–boron bond to give the desired compounds (Scheme 2).[25]

The stereochemical assignment of compounds **9a**–**g** was based on the analysis of ^1H–^1H coupling constants and of the NOESY spectra (Figure 2). Taking into account that there are no NOE between the benzylidene proton with those of the 3-phenyl ring or with H-3, but there is a small NOE between H-5 and the benzylidene proton and between H-3 and the aromatic protons of the benzylidene group, we conclude that the benzylidene double bond of compounds **9a**–**g** has the *E*-configuration.

In summary, we have established a successful methodology to perform the Baker–Venkataraman rearrangement of (*E*,*E*)-2-acetyl-1,3-phenylene bis(3-phenylacrylates) into the corresponding (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones. The beneficial effect of using micro-



Scheme 2

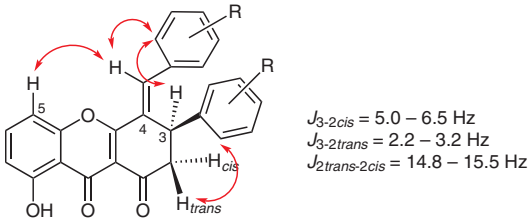


Figure 2 Main NOE and *J* values of **9**

wave irradiation was the shortening of the reaction time from 1 hour to 17 minutes. We have also developed a novel efficient synthesis of (*E*)-3-aryl-4-benzylidene-8-hydroxy-3,4-dihydro-1*H*-xanthene-1,9(2*H*)-diones. Good yields of the novel products and experimental simplicity are the main advantages of this method.

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References and Notes

(1) (a) Roberts, J. C. *Chem. Rev.* **1961**, *38*, 591. (b) Gales, L.; Damas, A. M. *Curr. Med. Chem.* **2005**, *12*, 2499.
(2) Park, H. H.; Park, Y.-D.; Han, J.-M.; Im, K.-R.; Lee, B. W.; Jeong, I. Y.; Jeong, T.-S.; Lee, W. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5580.
(3) (a) Shadid, K. A.; Shaari, K.; Abas, F.; Israf, D. A.; Hamzah, A. S.; Syakroni, N.; Saha, K.; Lajis, N. Hj. *Phytochemistry* **2007**, *68*, 2537. (b) Ee, G. C. L.; Daud, S.; Izzaddin, S. A.; Rahmani, M. *J. Asian Nat. Prod. Res.* **2008**, *10*, 475.
(4) Suvarnakuta, P.; Chaweerungrat, C.; Devahastin, S. *Food Chem.* **2011**, *125*, 240.
(5) Chiang, Y.-M.; Kuo, Y.-H.; Oota, S.; Fukuyama, Y. *J. Nat. Prod.* **2003**, *66*, 1070.
(6) Azebaze, A. G. B.; Meyer, M.; Valentin, A.; Nguemfo, E. L.; Fomum, Z. T.; Nkengfack, A. E. *Chem. Pharm. Bull.* **2006**, *54*, 111.
(7) An, T. Y.; Hu, L. H.; Chen, Z. L. *Chin. Chem. Lett.* **2002**, *13*, 623.
(8) (a) Brito-Arias, M.; Tapia-Albarrán, M.; Padilla-Martínez, I.; Martínez-Martínez, F.; Espinosa, G.; Molins, E.; Espinosa, E. *J. Chem. Crystallogr.* **1999**, *29*, 759. (b) Karthikeyan, G.; Pandurangan, A. *J. Mol. Catal. A: Chem.* **2009**, *311*, 36. (c) Pore, D. M.; Shaikh, T. S.; Patil, N. G.; Dongare, S. B.; Desai, U. V. *Synth. Commun.* **2010**, *40*, 2215.
(9) Gabbutt, C. D.; Hepworth, J. D.; Urquhart, M. W. J.; Miguel, L. M. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1819.
(10) (a) Gerwick, W. H.; Lopez, A.; Van Duyne, G. D.; Clardy, J.; Ortiz, W.; Baez, A. *Tetrahedron Lett.* **1986**, *27*, 1979. (b) Gerwick, W. H. *J. Nat. Prod.* **1989**, *52*, 252.
(11) Yoon, J. S.; Lee, M. K.; Sung, S. H.; Kim, Y. C. *J. Nat. Prod.* **2006**, *69*, 290.
(12) Rocha-Pereira, J.; Cunha, R.; Pinto, D. C. G. A.; Silva, A. M. S.; Nascimento, M. S. J. *Bioorg. Med. Chem.* **2010**, *18*, 4195.
(13) Gomes, A.; Fernandes, E.; Silva, A. M. S.; Pinto, D. C. G. A.; Santos, C. M. M.; Cavaleiro, J. A. S.; Lima, J. L. F. C. *Biochem. Pharmacol.* **2009**, *78*, 171.
(14) Gomes, A.; Neuwirth, O.; Freitas, M.; Couto, D.; Ribeiro, D.; Figueiredo, A. G. P. R.; Silva, A. M. S.; Seixas, R. S. G. R.; Pinto, D. C. G. A.; Tomé, A. C.; Cavaleiro, J. A. S.; Fernandes, E.; Lima, J. L. F. C. *Bioorg. Med. Chem.* **2009**, *17*, 7218.
(15) Gomes, A.; Fernandes, E.; Garcia, M. B. Q.; Silva, A. M. S.; Pinto, D. C. G. A.; Santos, C. M. M.; Cavaleiro, J. A. S.; Lima, J. L. F. C. *Bioorg. Med. Chem.* **2008**, *16*, 7939.
(16) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *New J. Chem.* **2000**, *24*, 85.
(17) Königs, P.; Neumann, O.; Kataeva, O.; Schnakenburg, G.; Waldvogel, S. *Eur. J. Org. Chem.* **2010**, 6417.
(18) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Synlett* **2007**, 1897.
(19) **Optimized Experimental Procedure**
A two-necked flask equipped with a magnetic stirring bar, fibre-optic temperature control, and reflux condenser was charged with a mixture of the appropriate (*E*,*E*)-2-acetyl-1,3-phenylene bis(3-phenylacrylate) **7a–g** (1 mmol) and anhyd K_2CO_3 (28 mg, 2 mmol) in anhyd pyridine (10 mL) and was then irradiated in an Ethos SYNTH microwave (Milestone Inc.) at constant power of 400 W for 17 min. After this period the reaction mixture was poured onto a mixture of ice (10 g) and H_2O (20 mL), and the pH was adjusted to 2 with dilute HCl. The so-formed solids (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromones **8a–g** were filtered off. In the case of compounds **8d** and **8f** a column chromatography purification, using CH_2Cl_2 as eluent, was necessary; **8a**, 378 mg, 96%; **8b**, 409 mg, 97%; **8c**, 445 mg, 98%; **8d**, 301 mg, 65%; **8e**, 422 mg, 93%; **8f**, 287 mg, 62%; **8g**, 443 mg, 86%.
(20) **Physical Data of 5-Hydroxy-3′,4′-dimethoxy-3-(3,4-dimethoxycinnamoyl)-2-styrylchromone (8g)**
Mp 208–211 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.93 (s, 4 × 3 H, 3′,4′,3″,4″-OCH_3), 6.84 (dd, 1 H, *J* = 0.7, 8.2 Hz, H-6), 6.88 (d, 1 H, *J* = 8.3 Hz, H-5″), 6.89 (d, 1 H, *J* = 8.3 Hz, H-5′), 6.90 (d, 1 H, *J* = 15.8 Hz, H-α), 7.02 (dd, 1 H, *J* = 0.7, 8.2 Hz, H-8), 7.07 (d, 1 H, *J* = 1.8 Hz, H-2′), 7.10 (d, 1 H, *J* = 15.8 Hz, H-α′), 7.13 (d, 1 H, *J* = 1.8 Hz, H-2″), 7.20 (dd, 2 H, *J* = 1.8, 8.3 Hz, H-6′,6″), 7.59 (t, 1 H, *J* = 8.2 Hz, H-7), 7.62 (d, 1 H, *J* = 15.8 Hz, H-β′), 7.75 (d, 1 H, *J* = 15.8 Hz, H-β), 12.50 (s, 1 H, 5-OH) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 56.0 (3′,4′,3″,4″-OCH_3), 106.7 (C-8), 109.9 and 110.1 (C-2′ and/or C-2″), 110.5 (C-10), 111.0 and 111.1 (C-5′ and/or C-5″), 111.8 (C-6), 115.1 (C-α), 120.3 (C-3), 123.1 (C-6′), 123.8 (C-6″), 125.4 (C-α′),

127.3 (C-1″), 127.8 (C-1′), 135.8 (C-7), 140.7 (C-β), 145.3 (C-β′), 149.2 and 149.3 (C-3′ and/or C-3″), 151.5 and 151.7 (C-4′ and/or C-4″), 155.4 (C-9), 161.0 (C-5), 162.6 (C-2), 181.6 (C-4), 190.9 (C=O) ppm. MS (ESI$^+$): *m/z* (%) = 515 (60) [M + H]$^+$, 537 (100) [M + Na]$^+$, 553 (45) [M + K]$^+$. HRMS (EI): *m/z* calcd for $[C_{30}H_{26}O_8]^+$: 514.1628; found: 514.1639.

(21) **Optimized Experimental Procedure**
A CH_2Cl_2 solution of BBr_3 (2 mmol) was slowly added to a solution of the appropriate (*E*,*E*)-3-cinnamoyl-5-hydroxy-2-styrylchromone **8a**–**g** (0.4 mmol) in anhyd CH_2Cl_2 (20 mL) at low temperature (–78 °C). After the addition, the cooling system was removed, and the reaction mixture was stirred at r.t. for 3 h (8 h for **8d** and **8f** and 22 h for **8g**). Then, H_2O (80 mL) was added, and the resulting reaction mixture was stirred at r.t. for 3–4 h. The mixture was extracted with $CHCl_3$ (3 × 80 mL) and the combined extracts evaporated and purified by TLC, using CH_2Cl_2 as eluent (except in the case of compound **9g** which was filtered off): **9a**, 99 mg, 63%; **9b**, 150 mg, 89%; **9c**, 118 mg, 69%; **9d**, 95 mg, 51%; **9e**, 70 mg, 41%; **9f**, 69 mg, 37%; **9g**, 148 mg, 81%.

(22) **Physical Data of (*E*)-8-Hydroxy-4-(4-hydroxybenzylidene)-3-(4-hydroxyphenyl)-3,4-dihydro-1*H*-xanthene-1,9 (2*H*)-dione (9c)**
Mp 319–320 °C. ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 2.69 (dd, 1 H, *J* = 2.2, 14.8 Hz, H-2$_{trans}$), 3.23 (dd, 1 H, *J* = 5.9, 14.8 Hz, H-2$_{cis}$), 4.66 (dd, 1 H, *J* = 2.2, 5.9 Hz, H-3), 6.72 (br d, 2 H, *J* = 8.6 Hz, H-3′,5′), 6.83 (d, 2 H, *J* = 8.7 Hz, H-3″,5″), 6.84 (dd, 1 H, *J* = 0.9, 8.3 Hz, H-7), 7.12 (br d, 2 H, *J* = 8.6 Hz, H-2′,6′), 7.29 (dd, 1 H, *J* = 0.9, 8.3 Hz, H-5), 7.37 (d, 2 H, *J* = 8.7 Hz, H-2″,6″), 7.72 (t, 1 H, *J* = 8.3 Hz, H-6), 8.18 (s, 1 H, H-7″), 9.57 (s, 1 H, 4′-OH), 10.50 (s, 1 H, 4″-OH), 12.71 (s, 1 H, 8-OH) ppm. ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 39.2 (C-3), 46.4 (C-2), 107.7 (C-5), 110.4 (C-8a), 111. 9 (C-7), 112.5 (C-9a), 116.0 (C-3″,5″), 115.9 (C-3′,5′), 125.2 (C-1″), 125.7 (C-4), 128.1 (C-2′,6′), 130.8 (C-1′), 132.7 (C-2″,6″), 136.4 (C-6), 139.4 (C-7″), 154.6 (C-4b), 156.5 (C-4′), 160.0 (C-4″), 160.6 (C-8), 169.9 (C-4a), 179.8 (C-9), 191.8 (C-1) ppm. MS (ESI$^+$): *m/z* (%) = 427 (15) [M + H]$^+$, 449 (100) [M + Na]$^+$, 465 (10) [M + K]$^+$. HRMS (EI): *m/z* calcd for $[C_{26}H_{18}O_6]^+$: 426.1103; found: 426.1116.

(23) **Physical Data of (*E*)-4-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-8-hydroxy-3,4-dihydro-1*H*-xanthene-1,9 (2*H*)-dione (9d)**
Mp 110–113 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.05 (dd, 1 H, *J* = 2.5, 15.5 Hz, H-2$_{trans}$), 3.15 (dd, 1 H, *J* = 5.6, 15.5 Hz, H-2$_{cis}$), 4.68 (dd, 1 H, *J* = 2.5, 5.6 Hz, H-3), 6.84 (dd, 1 H, *J* = 0.6, 8.4 Hz, H-7), 7.02 (dd, 1 H, *J* = 0.6, 8.4 Hz, H-5), 7.19 (br d, 2 H, *J* = 8.4 Hz, H-2′,6′), 7.26 (d, 2 H, *J* = 8.6 Hz, H-2″,6″), 7.30 (br d, 2 H, *J* = 8.4 Hz, H-3′,5′), 7.37 (d, 2 H, *J* = 8.6 Hz, H-3″,5″), 7.59 (t, 1 H, *J* = 8.4 Hz, H-6), 8.06 (s, 1 H, H-7″), 12.54 (s, 1 H, 8-OH) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 39.8 (C-3), 45.5 (C-2), 106.8 (C-5), 111.0 (C-8a), 112. 9 (C-7), 113.6 (C-9a), 128.3 (C-2′,6′), 129.3 (C-3″,5″), 129.6 (C-3′,5′), 129.7 (C-4), 130.7 (C-2″,6″), 132.4 (C-1″), 133.7 (C-4′), 136.2 (C-6 and C-4″), 137.9 (C-7″), 138.3 (C-1′), 154.7 (C-4b), 161.7 (C-8), 168.7 (C-4a), 180.0 (C-9), 190.7 (C-1) ppm. MS (ESI$^+$): *m/z* (%) = 463 (70) [(M + H)$^+$, ^{35}Cl], 465 (40) [(M + H)$^+$, ^{35}Cl^{37}Cl], 467 (7) [(M + H)$^+$, ^{37}Cl], 485 (75) [(M + Na)$^+$, ^{35}Cl], 487 (45) [(M + Na)$^+$, ^{35}Cl^{37}Cl], 489 (8) [(M + Na)$^+$, ^{37}Cl], 501 (15) [(M + K)$^+$, ^{35}Cl], 503 (10) [(M + K)$^+$, ^{35}Cl^{37}Cl], 505 (2) [(M + K)$^+$, ^{37}Cl]. Anal. Calcd (%) for $C_{26}H_{16}Cl_2O_4 \cdot 0.5H_2O$ (456.32): C, 66.12; H, 3.63. Found: C, 66.05; H, 3.58. HRMS (EI): *m/z* calcd for $[C_{26}H_{16}{}^{35}Cl_2O_4]^+$: 462.0426; found: 462.0406; *m/z* calcd for $[C_{26}H_{16}{}^{35}Cl^{37}ClO_4]^+$: 464.0396; found: 464.0374; *m/z* calcd for $[C_{26}H_{16}{}^{37}Cl_2O_4]^+$: 466.0367; found: 466.0384.

(24) (a) Baker, W. *J. Chem. Soc.* **1933**, 1381. (b) Gualati, K. C.; Venkataraman, K. *J. Chem. Soc*. **1933**, 942.

(25) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 3819.