New Synthesis of 2,3-Diarylxanthones

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Received 23 September 2005

Abstract: A new synthesis for 2,3-diarylxanthones is described. This was accomplished by aldol condensation of 3-bromo-2-methylchromone with benzaldehydes leading to the formation of 3-bromo-2-styrylchromones, followed by Heck reaction with styrenes.

Key words: diarylxanthones, 2-styrylchromones, Heck reaction, 3-bromo-2-methylchromone, electrocyclisation

Xanthones (dibenzo-γ-pyrones) are a group of heterocyclic compounds, which are widely distributed in *Guttiferae* and *Gentianaceae* families. However, as aglycone derivatives, they also occur in six other families and xanthone-*C*-glycosides are widespread among angiosperms.[1]

Due to their potential biological properties, compounds with a xanthone core are of great interest for chemists, biologists and pharmacologists. Natural and synthetic derivatives have shown important anti-microbial, anti-tumour, anti-inflammatory as well as antioxidant activities.[1,2]

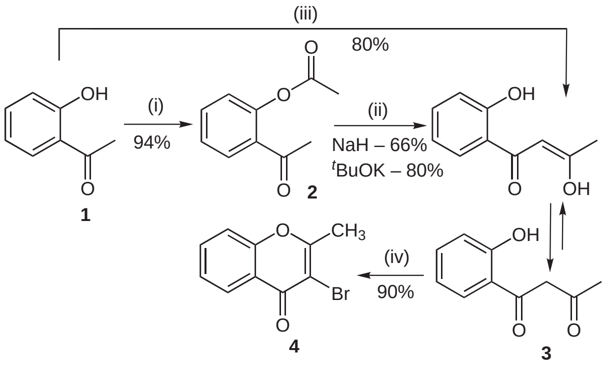
The biogenesis of xanthones largely dictates the nature and position of substituents. The development of new synthetic routes extends the possibilities of having other types of substituted xanthones for biological assessment and for the rationalisation of structure–activity relationships. In the present communication we report a new synthetic route to novel 2,3-diarylxanthones. To the best of our knowledge, xanthones bearing aryl substituents are scarce and no natural or synthetic xanthones have been reported with a 2,3-diaryl substitution pattern. A European Patent[3] describes the use of 2-phenylxanthone as solvent in the synthesis of aromatic polyketones whereas Kelkar et al.[4] reported the synthesis of 3-phenylxanthone derivatives from the Diels–Alder reactions of 2-styrylchromones with substituted enamines.

Several methods have been extensively described in literature for the synthesis of xanthones. The traditional synthetic route involves the bonding of two benzene rings through a pyran unit. The carbonyl group can be introduced by a Friedel–Crafts acylation or a Fries rearrangement, among others. However, these procedures usually present low yields and a range of secondary reactions.[5]

We report here a new synthesis of several novel 2,3-diarylxanthones, starting from 2′-hydroxyacetophenone (Schemes 1– 3).

SYNLETT 2005, No. 20, pp 3095–3098
Advanced online publication: 28.11.2005
DOI: 10.1055/s-2005-921928; Art ID: D29105ST

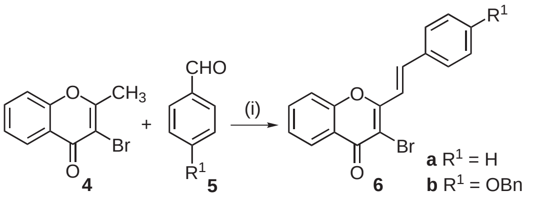
3-Bromo-2-methylchromone (**4**) was prepared in good overall yield according to the sequences shown in Scheme 1. In the three-step sequence, known as the Baker–Venkataraman[6] method, we performed the acetylation of 2′-hydroxyacetophenone (**1**) followed by treatment with sodium hydride or potassium *tert*-butoxide, in refluxing dry THF, leading to 1,3-diketone **3** (via intramolecular Claisen condensation). A modified Baker–Venkataraman process proposed by Ares et al.,[7] involving a one-pot synthesis, was also applied to the formation of the 1,3-diketone **3** (80%). Bromination and cyclisation of this 1,3-diketone **3** into the desired 3-bromo-2-methylchromone (**4**) was achieved in an one-pot synthesis, using 1.5 mol of bromine in ethanol followed by acidification.[8]



Scheme 1 *Reagents and conditions*: (i) CH_3COCl, pyridine, r.t., 15 h; (ii) NaH or *t*-BuOK, THF, reflux, 2 h; (iii) 1. CH_3COCl, *t*-BuOK, THF, r.t., 2 h; 2. *t*-BuOK, reflux, 2 h; (iv) 1. Br_2, EtOH, r.t., 2 h; 2. HCl, reflux, 2 h

Several methods have been applied to the synthesis of 2-styrylchromones; one of which involves the condensation of 2-methylchromones with benzaldehydes.[9] Extension of this methodology to the reaction of 3-bromo-2-methylchromone (**4**) with benzaldehydes **5a**,**b** allows access to 3-bromo-2-styrylchromones **6a**,**b** (Scheme 2).[10,11] We have found that it is necessary to use an excess (4 molar equiv) of base and extended reaction times to obtain the best yields (Table 1). The low yield of 3-bromo-2-styrylchomone **6b** when compared with that of compound **6a**, can be explained by considering the lower reactivity of the 4-benzyloxybenzaldehyde (**5b**), due to the presence of an electron-donating group in the 4-position.[12]

Over the last three decades, palladium-catalysed coupling of olefins with aryl- or vinyl halides (the Heck reaction) has become one of the most versatile methods for C–C



Scheme 2 *Reagents and conditions*: (i) NaOMe, MeOH, r.t., 48 h

Table 1 Condensation of 3-Bromo-2-methylchromone (**4**) with Benzaldehydes **5a**,**b**

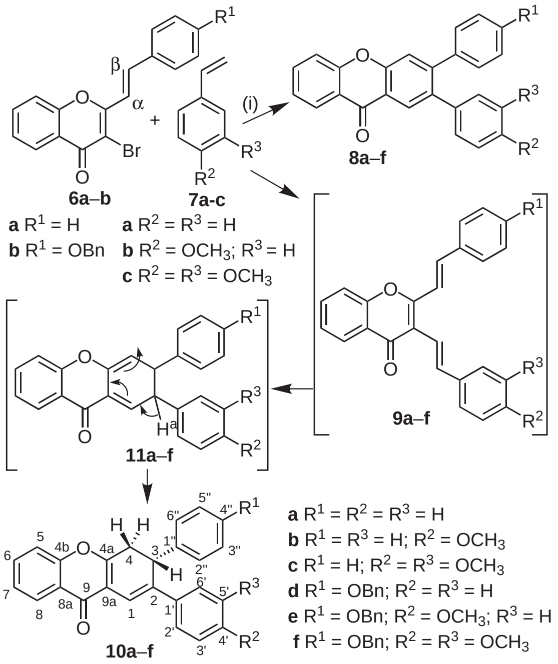
Base (equiv)	Time (h)	**6a** (%)	**6b** (%)
4	2	55	52
4	12	56	52
4	24	61	53
4	48	87	68
4	72	49	49

bond formation in organic synthesis.[13] In our work, the olefins are the styrenes **7a**–**c** and the bromine derivatives are the 3-bromo-2-styrylchromones **6a**,**b** (Scheme 3).[14]

In the first instance, we applied the Heck conditions to the reaction of 3-bromo-2-styrylchromone **6a** with styrene **7a** (Scheme 3). TLC analysis of the reaction mixture revealed the presence of a major and a minor product. The NMR spectrum of the main product indicates that we had the 2,3-diphenylxanthone **8a**,[15] and not the expected 2,3-distyrylchromone **9a**. The analysis of the NMR spectrum of the minor compound revealed the presence of 2,3-diphenyl-3,4-dihydroxanthone **10a**,[16] a semi-oxidized intermediate of the final xanthone. This fact indicates that the Heck reaction leads to the formation of the 2,3-distyrylchromone **9a**, and probably the high reaction temperature promotes the electrocyclisation followed by oxidation, to give the 2,3-diphenylxanthone **8a**. The same type of thermal electrocyclisation has been already reported[17] while the further oxidation is promoted by the aromaticity of the final compound.

When we applied the same Heck conditions to the reaction of **6a**,**b** with other styrenes similar results were obtained in each case: a major product corresponding to 2,3-diarylxanthones **8b**–**f** and the minor product, corresponding to the semi-oxidized products **10b**–**f**, were obtained.

The formation of compounds **10a**–**f** can be explained by the mechanism depicted in Scheme 3. The Heck reaction of **6a**,**b** with styrenes **7a**–**c** leads to the formation of the 2,3-distyrylchromones **9a**–**f** which undergo in situ electrocyclisation to give 2,3-diaryl-2,3-dihydroxanthones **11a**–**f** and these compounds are converted into 2,3-diphenyl-3,4-dihydroxanthones **10a**–**f** by a [1,5] sigmatropic hydrogen migration. This [1,5] sigmatropic hydrogen shift is facilitated by the resonance stabilisation of the chromone nucleus and by the acidity of H^a of compounds **11a**–**f** due to the resonance with carbonyl group.



Scheme 3 *Reagents*: (i) Et_3N, $Pd(PPh_3)_4$, PPh_3, NMP

After this study, an extensive investigation into the coupling reaction conditions of 3-bromo-2-styrylchromones **6a**,**b** with styrenes **7a**–**c** was performed.[18] This involved varying the amount and type of base, phosphine and catalyst and also several solvents, temperature and reaction time; the best obtained yields being accomplished with the conditions described in Table 2.

Table 2 Heck Reaction of 3-Bromo-2-styrylchromones **6a**,**b** with Styrenes **7a**–**c**

Comp	Et_3N (equiv)	Catalyst (equiv)[a]	**7a**–**c**	Conditions[b]	Yield (%)
8a	4	0.05	5	160 °C, 6 h	56
8b	4	0.05	5	Reflux, 3 h	49
8c	1	0.05	2	160 °C, 12 h	45
8d	1	0.05	5	Reflux, 6 h	51
8e	4	0.05	5	Reflux, 6 h	66
8f	1	0.05	5	Reflux, 3 h	20

[a] Catalyst: $Pd(PPh_3)_4$.
[b] In all cases 0.1 molar equiv of PPh_3 were used.

All the synthesized compounds have been characterized by NMR, MS and elemental analysis. The most important feature in the ^1H NMR spectra of 3-bromo-2-styrylchromones **6a**,**b** are the resonances assigned to vinylic protons H-β (d, J = 15.8–16.0 Hz; δ = 7.73, 7.62 ppm) that appear at higher frequency values than those of H-α (d, J = 15.8–16.0 Hz; δ = 7.51, 7.30 ppm) due to the mesomeric deshielding effect of the carbonyl group. The coupling constants $^3J_{H\alpha\text{-}H\beta}$ = ca. 16 Hz indicates a *trans*-configuration for such vinylic systems. The main characteristics in the ^{1}H NMR spectra of 2,3-diarylxanthones[15,19] **8a**–**f** are the resonances of H-1 and H-4, which appear as two singlets, at δ = 8.32–8.38 ppm and δ = 7.52–7.57 ppm, respectively. The identification of the structures of the intermediate 2,3-diaryl-3,4-dihydroxanthones **10a**–**f** was possible by the analyses of their HMBC and NOESY spectra (Figure 1). In the HMBC spectra of 3,4-dihydroxanthones **10a**–**f** it was possible to observe the connectivity between protons H-1 (singlet) and H-8 (double doublet) with carbon C-9. In the NOESY spectrum of compound **10f**[20] it was possible to observe the close proximity of H-1 with H-2′ and H-6′ and of H-3 with H-2′, H-6′, H-2″6″and H-4*cis* and H-4*trans* with H-2″6 ″.[21]

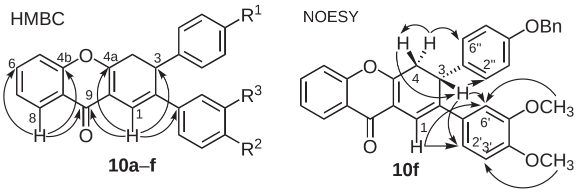


Figure 1 Main results obtained in the HMBC (connectivities) and NOESY (close proximity) spectra of compounds **10**

In conclusion, we have established a new route for the synthesis of novel 2,3-diarylxanthones **8a**–**f**. The condensation reaction of 3-bromo-2-methylchromone (**4**) with benzaldehydes **5a**,**b** led to the formation of new derivatives of 2-styrylchromone **6a**,**b**. The Heck type reaction of these derivatives with styrenes **7a**–**c** provides the novel 2,3-diarylxanthones **8a**–**f** and 2,3-diaryl-3,4-dihydroxanthones **10a**–**f**.

Acknowledgment

Thanks are due to the University of Aveiro, ‘Fundação para a Ciência e a Tecnologia’ and FEDER for funding the Organic Chemistry Research Unit and the project POCTI/QUI/38394/2001. One of us (C. M. M. Santos) is also grateful to PRODEP 5.3 for financial support.

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(10) **Typical Experimental Procedure.**
Sodium (0.4 g, 16.7 mmol) was gradually added to 20 mL of dry MeOH and the mixture was stirred until the solution reached r.t. 3-Bromo-2-methylchromone **4** (1 g, 4.2 mmol) and the appropriate benzaldehyde **5a**,**b** (5.0 mmol) were added and the reaction mixture allowed to stand at r.t. for 48 h. After this period, the solution was poured into ice and H_2O and the pH adjusted to 4 with HCl. The yellow solid was removed by filtration, taken up in CH_2Cl_2 and purified by silica gel column chromatography using CH_2Cl_2 as eluent. The solvent was evaporated to dryness and the residue was recrystallised from EtOH to give the 3-bromo-2-styrylchromones **6a**,**b** in good yields (Table 1).

(11) **Physical Data of 4′-Benzyloxy-3-bromo-2-styrylchromone (6b).**
Mp 176–178 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 5.09 (s, 2 H, 4′-OC$H_2$$C_6H_5$), 6.99 (d, 2 H, *J* = 8.8 Hz, H-3′,5′), 7.30 (d, 1 H, *J* = 15.8 Hz, H-α), 7.34–7.45 (m, 6 H, H-6 and 4′-OCH_2C_6*H*$_5$), 7.50 (d, 1 H, *J* = 7.8 Hz, H-8), 7.56 (d, 2 H, *J* = 8.8 Hz, H-2′,6′), 7.62 (d, 1 H, *J* = 15.8 Hz, H-β), 7.67 (dt, 1 H, *J* = 7.8, 1.6 Hz, H-7), 8.19 (dd, 1 H, *J* = 7.9, 1.6 Hz, H-5). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 70.0 (4′-O*C*$H_2C_6H_5$), 108.9 (C-3), 115.3 (C-3′,5′), 116.7 (C-α), 117.4 (C-8), 122.0 (C-10), 125.2 (C-6), 126.2 (C-5), 127.4 (C-2,6 of 4′-OCH_2*C*$_6H_5$), 127.8 (C-1′), 128.1 (C-4 of 4′-OCH_2*C*$_6H_5$), 128.6 (C-3,5 of 4′-OCH_2*C*$_6H_5$), 129.7 (C-2′,6′), 133.8 (C-7), 136.3 (C-1 of 4′-OCH_2*C*$_6H_5$), 139.2 (C-β), 154.7 (C-9), 158.7 (C-2), 160.6 (C-4′), 172.6 (C-4). MS (EI): *m/z* (rel. int.) = 434 (14) [$M^{+\bullet}$, ^{81}Br], 432 (14) [$M^{+\bullet}$, ^{79}Br], 388 (8), 234 (7), 205 (8), 92 (15), 91 (100), 65 (9). Anal. Calcd for $C_{24}H_{17}BrO_3$: C, 66.53; H, 3.95. Found: C, 66.48; H, 4.27.

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(14) **Typical Experimental Procedure.**
A mixture of the appropriate 3-bromo-2-styrylchromone **6a**,**b** (0.6 mmol), PPh_3 (15.7 mg, 0.06 mmol), tetrakis(triphenylphosphine)palladium(0) (34.7 mg, 0.03 mmol) and Et_3N (83.6 μL or 334.5 μL, 0.6 or 2.4 mmol) in *N*-methyl-2-pyrrolidinone (10 mL) was added to styrenes **7a**–**c** (3 mmol). Each reaction was stirred under different conditions of time and temperature according to the substitution of the compounds (Table 2). Then, the mixture was poured into H_2O and ice and extracted several times with Et_2O and dried over anhyd Na_2SO_4. The solvent was evaporated and the residue taken up in CH_2Cl_2 and purified by thin layer

chromatography (a 7:3 mixture of CH_2Cl_2–light PE as eluent). The product was crystallised from EtOH giving, in each case, the 2,3-diarylxanthones **9a–f** (yields described in Table 2).

(15) **Physical Data of 2,3-Diphenylxanthone (8a).**
Mp 152–153 °C. ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 7.18$–7.29 (m, 10 H, 2,3-C_6H_5), 7.41 (dt, 1 H, $J = 7.5$, 1.0 Hz, H-7), 7.53 (dd, 1 H, $J = 8.4$, 0.8 Hz, H-5), 7.57 (s, 1 H, H-4), 7.75 (dt, 1 H, $J = 7.8$, 1.6 Hz, H-6), 8.38 (dd, 1 H, $J = 7.9$, 1.6 Hz, H-8), 8.38 (s, 1 H, H-1). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 118.0$ (C-5), 119.5 (C-4), 120.7 (C-9a), 121.9 (C-8a), 124.0 (C-7), 126.8 (C-8), 126.9 (C-4′), 127.6 (C-4″), 128.0 (C-2′,6′), 128.1 (C-3″,5″), 128.4 (C-1), 129.6 (C-2″,6″), 129.9 (C-3′,5′), 134.8 (C-6), 137.0 (C-1′), 139.8 (C-2), 139.9 (C-1″), 147.6 (C-3), 155.2 (C-4a), 156.3 (C-4b), 177.0 (C-9). MS (EI): *m/z* (rel. int.) = 348 (100) $[M^{+\bullet}]$, 347 (45), 333 (14), 318 (8), 305 (4), 289 (15), 276 (4), 228 (8), 226 (8), 213 (5), 174 (9), 145 (4), 77 (3). HRMS (EI): *m/z* calcd for $C_{25}H_{16}O_2$: 348.1150; found: 348.1158.

(16) **Physical Data of 2,3-Diphenyl-3,4-dihydroxanthone (10a).**
^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.01$ (dd, 1 H, $J = 17.4$, 1.5 Hz, H-4_{trans}), 3.67 (dd, 1 H, $J = 17.4$, 9.0 Hz, H-4_{cis}), 4.31 (dd, 1 H, $J = 9.0$, 1.5 Hz, H-3), 7.19–7.30 (m, 8 H, H-2′,3′,4′,5′,6′,3″,4″,5″), 7.32–7.41 (m, 2 H, H-5,7), 7.46–7.50 (m, 2 H, H-2″,6″), 7.56 (s, 1 H, H-1), 7.60 (dt, 1 H, $J = 7.8$, 1.6 Hz, H-6), 8.29 (dd, 1 H, $J = 7.9$, 1.6 Hz, H-8). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 36.7$ (C-4), 41.7 (C-3), 116.8 (C-1), 116.9 (C-9a), 118.0 (C-5), 123.9 (C-8a), 125.1 (C-7), 125.7 (C-2″,6″), 126.2 (C-8), 127.2 (C-4′), 127.4 (C-2′,6′), 127.6 (C-4″), 128.5 (C-3″,5″), 129.0 (C-3′,5′), 133.0 (C-6), 135.3 (C-1″), 139.1 (C-1′), 140.7 (C-2), 155.9 (C-4b), 162.5 (C-4a), 174.2 (C-9). MS (FAB^+): *m/z* (rel. int.) = 351 (37) $[M + H]^+$, 212 (8), 77 (19). HRMS (EI): *m/z* calcd for $C_{25}H_{18}O_2$: 350.1307; found: 350.1315.

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(19) **Physical Data of 3-Phenyl-2-(4-methoxyphenyl)xanthone (8b).**
Mp 123–125 °C. ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.79$ (s, 3 H, 4′-OCH_3), 6.77 (d, 2 H, $J = 8.8$ Hz, H-3′,5′), 7.09 (d, 2 H, $J = 8.8$ Hz, H-2′,6′), 7.20–7.24 (m, 2 H, H-2″,6″), 7.26–7.30 (m, 3 H, H-3″,4″,5″), 7.39 (dt, 1 H, $J = 7.8$, 0.9 Hz, H-7), 7.51 (d, 1 H, $J = 8.0$ Hz, H-5), 7.53 (s, 1 H, H-4), 7.73 (dt, 1 H, $J = 8.0$, 1.6 Hz, H-6), 8.34 (s, 1 H, H-1), 8.37 (dd, 1 H, $J = 7.8$, 1.6 Hz, H-8). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta =$ 55.2 (4′-OCH_3), 113.4 (C-3′,5′), 118.0 (C-5), 119.5 (C-4), 120.7 (C-9a), 121.9 (C-8a), 123.9 (C-7), 126.7 (C-8), 127.5 (C-4″), 128.1 (C-1), 128.2 (C-3″,5″), 129.6 (C-2″,6″), 131.0 (C-2′,6′), 132.1 (C-1′), 134.7 (C-6), 136.7 (C-2), 140.0 (C-1″), 147.5 (C-3), 155.0 (C-4a), 156.3 (C-4b), 158.6 (C-4′), 177.0 (C-9). MS (EI): *m/z* (rel. int.) = 378 (100) $[M^{+\bullet}]$, 363 (12), 347 (9), 334 (7), 318 (3), 305 (9), 292 (2), 276 (4), 263 (2), 213 (3), 189 (5), 173 (3), 167 (5), 138 (3), 92 (2), 77 (2). Anal. Calcd for $C_{26}H_{18}O_3$: C, 82.52; H, 4.79. Found: C, 82.23; H, 4.94.

(20) **Physical Data of 3-(4-Benzyloxyphenyl)-2-(3,4-dimethoxyphenyl)-3,4-dihydroxanthone (10f).**
^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 2.95$ (dd, 1 H, $J = 17.3$, 1.5 Hz, H-4_{trans}), 3.61 (dd, 1 H, $J = 17.3$, 8.4 Hz, H-4_{cis}), 3.83 and 3.84 (2 s, 6 H, 3′,4′-OCH_3), 4.23 (d, 1 H, $J = 8.3$ Hz, H-3), 4.94 (s, 2 H, 4″-$OCH_2C_6H_5$), 6.74 (d, 1 H, $J = 8.5$ Hz, H-5′), 6.84 (d, 2 H, $J = 8.7$ Hz, H-3″,5″), 6.97 (dd, 1 H, $J = 8.5$, 2.1 Hz, H-6′), 7.09 (d, 1 H, $J = 2.1$ Hz, H-2′), 7.21 (d, 2 H, $J = 8.7$ Hz, H-2″,6″), 7.28–7.39 (m, 7 H, H-5,7 and H-2,3,4,5,6 of 4″-$OCH_2C_6H_5$), 7.44 (s, 1 H, H-1), 7.57 (dt, 1 H, $J = 7.8$, 1.6 Hz, H-6), 8.28 (dd, 1 H, $J = 7.9$, 1.6 Hz, H-8). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 36.7$ (C-4), 41.1 (C-3), 55.8 (3′,4′-OCH_3), 69.9 (4″-$OCH_2C_6H_5$), 108.7 (C-2′), 110.8 (C-5′), 114.8 (C-1), 115.2 (C-3″,5″), 116.9 (C-9a), 118.0 (C-5), 118.3 (C-6′), 123.8 (C-8a), 125.0 (C-7), 126.1 (C-8), 125.7 (C-2,6 of 4″-$OCH_2C_6H_5$), 127.9 (C-4 of 4″- $OCH_2C_6H_5$), 128.3 (C-2″,6″), 128.5 (C-3,5 of 4″-$OCH_2C_6H_5$), 132.0 (C-1′), 133.0 (C-6), 133.1 (C-1″), 135.5 (C-2), 136.9 (C-1 of 4″-$OCH_2C_6H_5$), 148.7 and 148.8 (C-3′,4′), 155.8 (C-4b), 157.9 (C-4″), 162.3 (C-4a), 174.2 (C-9). HRMS (EI): *m/z* calcd for $C_{32}H_{24}O_3$: 456.1725; found: 456.1735.

(21) The relative stereochemistry of protons H-3 and H-4 is referred as *cis* and *trans*.