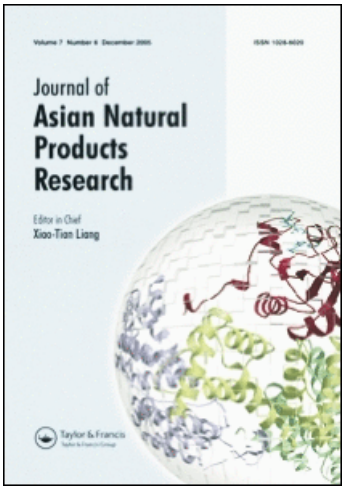

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Synthesis of 1,7-Bis(4-Hydroxyphenyl)-3-Hydroxy-1,3-Heptadiene-5-One, an Antiplatelet Diarylheptanoid from *Alpinia blepharocalyx* K. Schum

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SYNTHESIS OF 1,7-BIS(4-HYDROXYPHENYL)-3-HYDROXY-1,3-HEPTADIENE-5-ONE, AN ANTIPLATELET DIARYLHEPTANOID FROM *ALPINIA BLEPHAROCALYX* K. SCHUM

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A general and straight forward total synthesis of 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadiene-5-one (**5**) starting from 4-methoxycinnamic acid (**6**) via ethyl 5-(4-methoxyphenyl)-3-hydroxy-2,4-pentadienoate (**14**) was accomplished in 19% overall yield.

Keywords: Diarylhepatanoid; 1,7-Bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadiene-5-one; Dihydrocurcumin; *A. blepharocalyx*

INTRODUCTION

1,7-Diarylheptanoids are a small group of bioactive natural products, derived biosynthetically from phenylalanine (C_9 precursors) [1]. More than 70 linear diarylheptanoids have been isolated from nature [2]. Curcuminoids (**1–3**), metabolites of *Curcuma* species are important members of this group. Curcuminoids have been reported to possess antibacterial [3] antioxidant [4,5], antiinflammatory [6], antitumour [7,8] and anti-HIV [9] activities.

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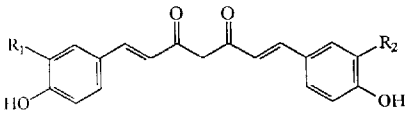
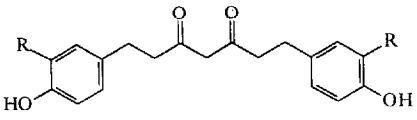


1 $R_1 = R_2 = OCH_3$

2 $R_1 = H$; $R_2 = OCH_3$

3 $R_1 = R_2 = H$



4 $R = OCH_3$

16 $R = H$

FIGURE 1

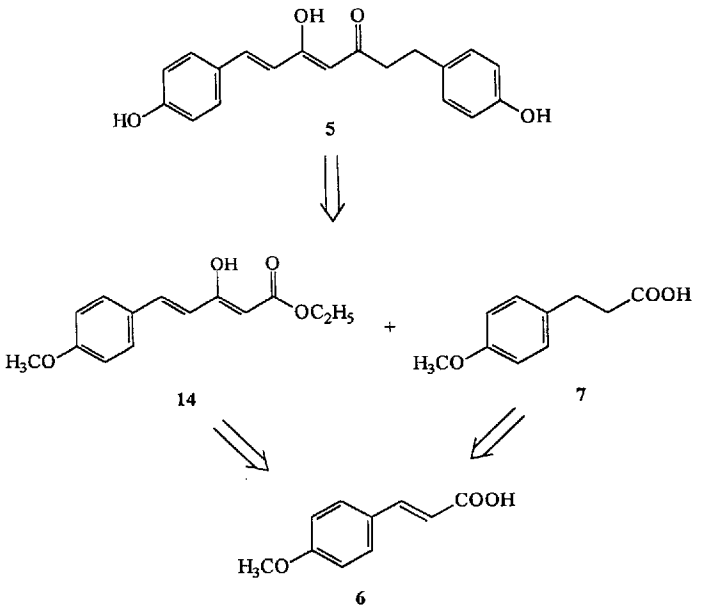
1,2,6,7-Tetrahydrocurcumin-1 (**4**) was found to be more potent antioxidant than **1** [10] (Fig. 1). Recently, 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadiene-5-one (**5**, dihydrocurcumin-3) has been isolated as an antiplatelet diarylheptanoid from a Chinese medicinal plant, *Alpina blepharocalyx* K. Schum (Zingeberaceae) [11]. In view of the interesting bioactivities exhibited by curcuminoids and lack of general synthetic strategies for dihydrocurcumins, we have undertaken the first total synthesis of **5** and the results are reported in this paper.

RESULTS AND DISCUSSION

Retrosynthetic analysis (Scheme 1) of **5** revealed that 4-methoxycinnamic acid (**6**) is a suitable starting material for the synthesis of **5**.

The desired 4-methoxycinnamic acid (**6**) was prepared according to the literature procedure [12] and was converted into its acid chloride using thionyl chloride. The reaction of 4-methoxycinnamoyl chloride with ethyl acetoacetate in presence of NaH gave ethyl 5-(4-methoxyphenyl)-2-acetyl-3-oxo-4-pentenoate (**9**) in 79% yield. Decarboxylation of **9** using DMSO/NaCl [13] afforded 6-(4-methoxyphenyl)-4-hydroxy-3,5-hexadiene-2-one (**10**) [14] but, in 54% yield only (Scheme 2).

Hydrogenation of **6** using Pd/C as catalyst yielded **7** in 91% yield. The propionic acid **7** was also converted into corresponding acid chloride, **8** using thionyl chloride. The reaction of the 3-(4-methoxyphenyl)propionyl chloride (**8**) with **10** using NaH as a base resulted in the formation of 1,7-bis(4-methoxyphenyl)-3-hydroxy-4-acetyl-1,3-heptadiene-5-one (**11**) in 83% yield. Deacetylation of **11** using aqueous acetic acid gave the desired product (**12**) in low yield (21%), along with **10** (66%). Compound **10** was recycled to give further quantities of **12**. Demethylation of **12** using BBr_3 [15]



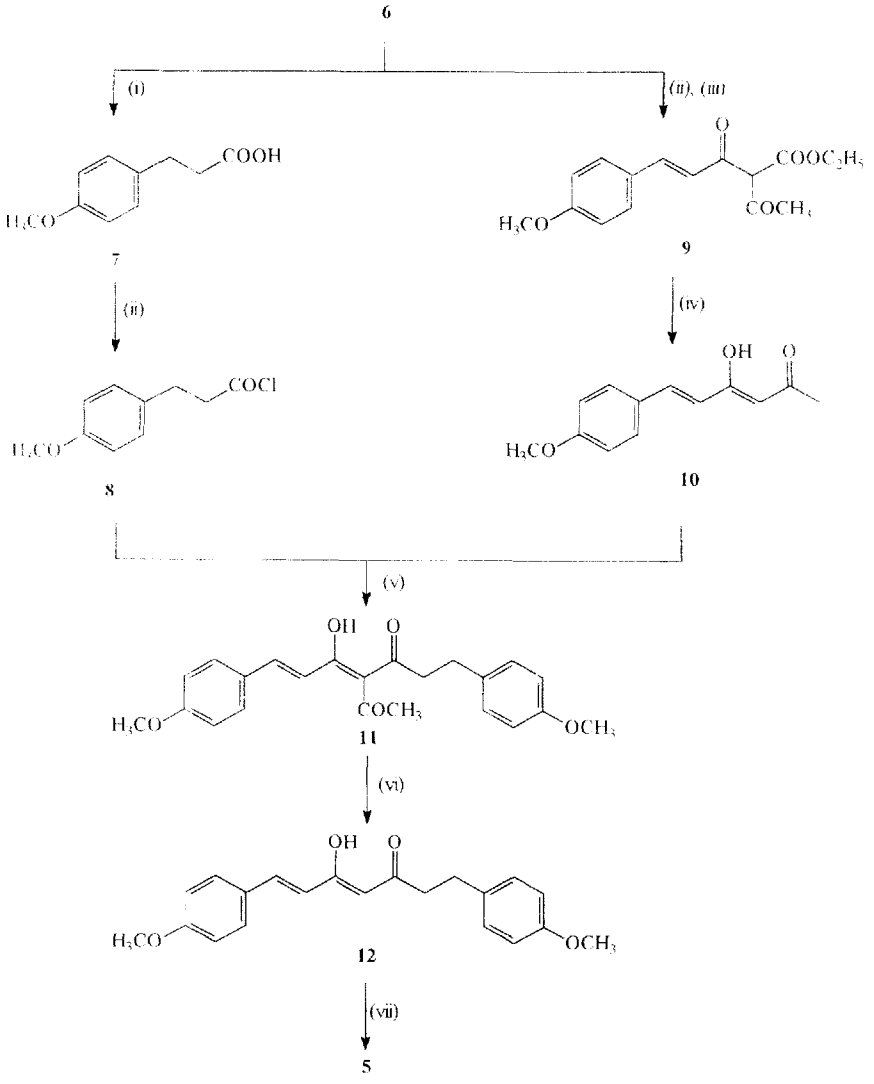
SCHEME 1 Retrosynthetic analysis of diarylheptanoid, **5**.

afforded the title compound **5** in 69% yield. Thus, the overall yield of **5** from **6** is only 5%. The spectral data of synthetic **5** was found to be identical to those of natural metabolite, **5**.

We reasoned that low yield in Scheme 2 is mainly due to competitive deacylation occurring during decarboxylations of **9** and **11**. Therefore, we have modified the route as shown in Scheme 3.

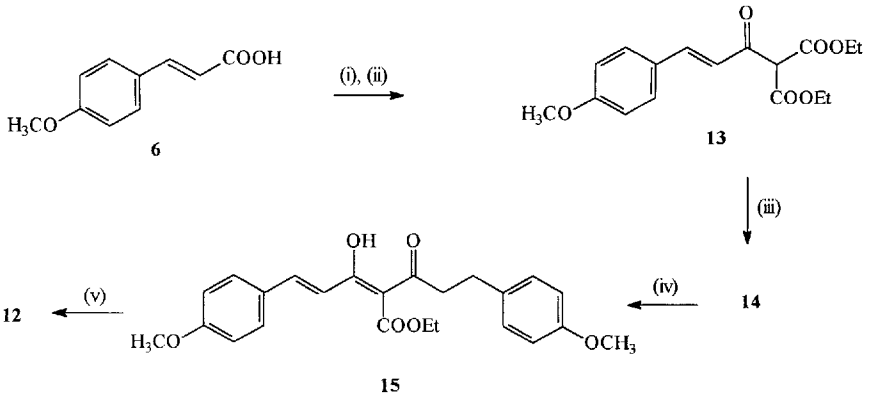
13 was obtained in 76% yield from **6** in two steps (Scheme 3). **13** underwent decarboxylation smoothly into **14** in 77% yield. Condensation of **14** with **8** in presence of NaH provided **15** in 60% yield. Decarboxylation of **15** afforded **12** in 79% yield. Compound **12** was identical to the product obtained in the first route. These modifications resulted in the improvement of overall yield from 5% for the first route (Scheme 2) to 19% for the second method (Scheme 3).

We have prepared 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (**3**) [16], a naturally occurring curcuminoid, and attempted to reduce one of the double bonds by H_2/Pd-C, but, we could isolate 1,7-bis(4-hydroxyphenyl) hepta-3,5-dione (**16**) as the sole product. Partial hydrogenation of **3** using Pd-C/$HCOONH_4$ (molar equivalents) was also not successful.



SCHEME 2 (i) H_2, 10% Pd-C, EtOAc, rt, 2 h, 91%; (ii) $SOCl_2$, Reflux, 2 h; (iii) NaH, $CH_3(COCH_3)COOEt$, THF, rt, 16 h, 79%; (iv) DMSO, NaCl, H_2O, 160–170°C, 4 h, 54%; (v) NaH, THF, rt, 16 h, 83%; (vi) AcOH, H_2O, Reflux, 1 h, 21%; (vii) BBr_3, CH_2Cl_2, rt, 3 h, 69%.

In conclusion, we have accomplished the first total synthesis of 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadiene-5-one (**5**) and developed a general method for the synthesis of unsymmetrically substituted diarylheptanoids.



SCHEME 3 (i) $SOCl_2$, Reflux, 2 h; (ii) Mg, $CH_2(COOEt)_2$, THF, 5 h, 76%; (iii) DMSO, NaCl, H_2O, 110–120°C, 5 h, 77%; (iv) **8**, NaH, THF, rt, 4 h, 60%; (v) DMSO, NaCl, H_2O, 130–140°C, 2 h, 79%.

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were recorded in open capillaries and are not corrected. UV spectra were recorded on a Shimadzu UV-190 spectrophotometer, IR spectra were recorded on a Perkin-Elmer BX1 FT-IR spectrophotometer, ^{1}H NMR (90 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on Jeol JNM EX 90 FT NMR spectrometer. Mass spectra were recorded on VG micromass 70-70H spectrometer and elemental analysis were carried out on a Perkin-Elmer 240 C Instrument. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively.

3-(4-Methoxyphenyl)propionic acid (**7**) To a solution of **6** (2 g, 11.24 mmol) in ethyl acetate (80 mL) was added Pd-C (10%, 100 mg) and the reaction mixture was stirred under hydrogen atmosphere for 2 h. The catalyst was filtered off and the solvent was evaporated, the residue was recrystallised from chloroform–hexane, to give **7** (1.83 g, 91%), m.p. 100–102°C.

Ethyl 5-(4-methoxyphenyl)-2-acetyl-3-oxo-4-pentenoate (**9**) To an ice cold stirred solution of sodium hydride (50% dispersion in oil, 165 mg, 3.36 mmol), in dry THF (5 mL) was added dropwise ethyl acetoacetate (360 mg, 2.80 mmol) and the mixture was stirred at room temperature for 30 min. A solution of 4-methoxycinnamoyl chloride [prepared from **6**

(500 mg) and thionyl chloride] in THF (5 mL) was added dropwise to the reaction mixture at 5°C and the mixture was stirred at room temperature for 16 h. The reaction was quenched by careful addition of water (10 mL) and diluted with diethyl ether (10 mL). The ether layer was separated and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined ether extract was washed with brine (1 × 10 mL), dried over sodium sulfate and filtered. Solvent was evaporated and the residue was chromatographed over silica gel column using hexane–ethyl acetate (96 : 4) as eluent to furnish the ester, **9** (647 mg, 79%) as light yellow oil. UV (MeOH) λ_{max} (log ϵ) 352 (4.64), 226 (4.37); IR (Neat) ν_{max} 2975, 1692, 1625, 1601, 1572, 1511, 1422, 1254, 1084, 1026, 972, 951, 827 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 2.40 (3H, s, $COCH_3$), 3.84 (3H, s, Ar–OCH_3), 4.35 (2H, q, J = 7.1 Hz, $O\underline{CH_2}CH_3$), 6.91 (2H, d, J = 8.8 Hz, H-2′,6′), 7.19 (1H, d, J = 15.6 Hz, H-2), 7.52 (2H, d, J = 9 Hz, H-3′,5′), 7.79 (1H, d, J = 15.6 Hz, H-1).

6-(4-Methoxyphenyl)-4-hydroxy-3,5-hexadiene-2-one (**10**) A mixture of **9** (2 g, 6.9 mmol), sodium chloride (524 mg, 9.0 mmol), water (0.5 mL, 27.6 mmol) and DMSO (10 mL) was heated at 160–170°C for 4 h. The reaction mixture was quenched with water (100 mL) and extracted with chloroform (4 × 20 mL). The chloroform layer was washed with brine and dried. The solution was filtered and evaporated. The residue was chromatographed over silica gel column eluting with hexane ethyl acetate (96 : 4) afforded **10** (800 mg, 54%), m.p. 94–96°C (Ref. [14]: 92–93°C); UV (MeOH) λ_{max} (log ϵ) 354 (4.65), 227 (4.12); IR (Neat) ν_{max} 2972, 1631, 1588, 1569, 1417, 1025, 975, 826, 786 cm $^{-1}$; ^1H NMR ($CDCl_3$) δ 2.14 (3H, s, $COCH_3$), 3.82 (3H, s, Ar–OCH_3), 5.61 (1H, s, H-4), 6.32 (1H, d, J = 15.6 Hz, H-2), 6.89 (2H, d, J = 8.8 Hz, H-2′,6′), 7.46 (2H, d, J = 8.8 Hz, H-3′,5′), 7.56 (1H, d, J = 15.6 Hz). Further elution of the column with the same solvent system gave 4-(4-methoxyphenyl)-3-buten-2-one (140 mg, 11%), m.p. 70–72°C.

1,7-Bis(4-methoxyphenyl)-3-hydroxy-4-acetyl-1,3-heptadiene-5-one (**11**) To a solution of sodium hydride (87 mg, 1.81 mmol, 50% dispersion in oil) in dry tetrahydrofuran (5 mL) at 5°C was added **10** (330 mg, 1.51 mmol) and the mixture was stirred at room temperature for 20 min. A solution of 3-(4-methoxyphenyl)propionyl chloride (**8**) in THF (5 mL) was added to the reaction mixture at 0°C and the mixture was stirred at room temperature for 16 h. The reaction was quenched by careful addition of water and diluted with ether (10 mL). The ethereal layer was separated and aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined ether extract was washed with brine (1 × 10 mL), dried and the solvent was removed, to give **11** (480 mg, 83%), which was used in the next step without further purification.

1,7-Bis(4-methoxyphenyl)-3-hydroxy-1,3-heptadiene-5-one (**12**) A mixture of **11** (480 mg, 1.26 mmol), acetic acid (6 mL) and water (3.6 mL) was refluxed for 1 h. The reaction mixture was diluted with cold water (100 mL) and extracted with chloroform (2 × 25 mL) and the combined chloroform layer was washed with brine (1 × 10 mL), dried and the solvent was evaporated. Chromatography of the residue obtained over silica gel column using hexane–chloroform (4 : 1) as eluent furnished, **10** (180 mg, 66%). Further elution of the column gave **12** (90 mg, 21%) as light yellow solid, which was recrystallised from chloroform–hexane, m.p. 110–111°C; UV (MeOH) λ_{max} (log ϵ) 358 (4.59), 227 (4.39); IR (Neat) ν_{max} 2920, 1638, 1601, 1512, 1439, 1322, 1258, 1175, 1029, 970, 821 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (2H, t, $J = 7.0$ Hz, H-6), 2.93 (2H, t, $J = 7.0$ Hz, H-7), 3.78 (3H, s, Ar–OCH_3), 3.83 (3H, s, Ar–OCH_3), 5.58 (1H, s, H-4), 6.32 (1H, d, $J = 15.7$ Hz, H-2), 6.83 (2H, d, $J = 8.4$ Hz, H-2″,6″), 6.91 (2H, d, $J = 8.6$ Hz, H-2′,6′), 7.13 (2H, d, $J = 8.4$ Hz, H-3″,5″), 7.47 (2H, d, $J = 8.6$ Hz, H-3′,5′), 7.56 (1H, d, $J = 15.7$ Hz, H-1), anal. C 74.65%, H 6.58%, calcd. for $C_{21}H_{22}O_4$, C 74.56%, H 6.51%.

1,7-Bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadiene-5-one (**5**) To a cold stirred solution of methyl ether **12** (200 mg, 0.59 mmol) in CH_2Cl_2 at −10°C was added boron tribromide (3.5 mL, 3.54 mmol, 1 M solution). The reaction mixture was slowly brought to room temperature and stirred for 3 h. The solvent was evaporated and dil. HCl (2 N, 10 mL) was added. The solution was extracted with ethyl acetate (2 × 10 mL), dried over sodium sulfate. Evaporation of the solvent, followed by chromatography of the residue over silica gel column using chloroform–methanol (99 : 1) as eluent furnished 1,7-bis(4-hydroxyphenyl)-3-hydroxy-1,3-heptadiene-5-one (**5**) (126 mg, 69%), light yellow crystals, m.p. 140–142°C (Ref. [11]: 148–149°C); UV (MeOH) λ_{max} (log ϵ) 361 (4.62), 223 (4.48); IR (Neat) ν_{max} 3305, 1637, 1594, 1514, 1435, 1248, 1020, 967, 829 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 2.61 (2H, t, $J = 7.0$ Hz, H-6), 2.75 (2H, t, $J = 7.0$ Hz, H-7), 5.66 (1H, s, H-4), 6.34 (1H, d, $J = 15.9$ Hz, H-2), 6.70 (2H, d, $J = 8.4$ Hz, H-2″,6″), 6.79 (2H, d, $J = 8.6$ Hz, H-2′,6′), 7.00 (2H, d, $J = 8.4$ Hz, H-3″,5″), 7.40 (2H, d, $J = 8.6$ Hz, H-3′,5′), 7.48 (1H, d, $J = 15.9$ Hz, H-1), 8.84 and 9.65 (each 1H, br s, 4″-OH and 4′-OH); ^{13}C NMR (DMSO) δ 198.9 (C-5), 177.9 (C-3), 159.7 (C-4′), 155.6 (C-4″), 139.9 (C-1), 130.9 (C-1″), 130.1 (C-2′,6′), 129.1 (C-3″,5″), 125.9 (C-1′), 119.5 (C-2), 116.0 (C-3′,5′), 115.2 (C-2″,6″), 100.1 (C-4), 41.2 (C-6), 29.9 (C-7); EIMS m/z $[M]^+$ 310(4), 189(8), 161(8), 147(38), 120(23), 107(100), 77(43); anal. C 73.71%, H 5.88%, calcd. for $C_{19}H_{18}O_4$, C 73.55%, H 5.81%.

Ethyl 5-(4-methoxyphenyl)-2-(ethoxycarbonyl)-3-oxo-4-pentenoate (**13**) A mixture of absolute ethanol (0.2 mL) and carbon tetrachloride (0.1 mL) was added to the magnesium turnings (132 mg, 5.5 mmol) and the mixture was stirred for 5 min at room temperature. After this period THF (5 mL) was added and warmed to about 60°C. To this warm reaction mixture was added a solution of diethyl malonate (860 mg, 5.4 mmol) in THF (2 mL). The mixture was refluxed for 3 h and then a solution of 4-methoxycinnamoyl chloride [prepared from 4-methoxycinnamic acid, **6** (1 g) and thionyl chloride] in THF (5 mL) was added and refluxing was continued for 2 h. The reaction mixture was cooled, acidified with dil. sulfuric acid (4 N) and extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with water (2 × 10 mL), brine (1 × 10 mL), dried over sodium sulfate and filtered. Evaporation of the solvent followed by chromatography over silica gel column using hexane ethyl acetate (96 : 4) as eluent, furnished the diester **13** (1.36 g, 76%) as light yellow solid, m.p. 86–88°C; UV (MeOH) λ_{max} (log ϵ) 345 (4.50), 237 (4.0); IR (Neat) ν_{max} 2970, 1705, 1633, 1580, 1511, 1408, 1248, 1173, 1044, 799 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J = 7.0 Hz), 1.35 (3H, t, J = 7.0 Hz), 3.82 (3H, s, Ar–OCH_3), 4.29 (2H, q, J = 7.0 Hz), 4.32 (2H, q, J = 7.0 Hz), 6.88 (2H, d, J = 8.8 Hz), 6.92 (1H, d, J = 15.2 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.60 (1H, d, J = 15.2 Hz), 13.33 (1H, s, enolic OH).

Ethyl 5-(4-methoxyphenyl)-3-hydroxy-2,4-pentadienoate (**14**) A mixture of **13** (2 g, 8.06 mmol), sodium chloride (530 mg, 9.01 mmol), water (0.5 mL, 27.6 mmol) and DMSO (10 mL) was heated at 110–120°C, for 5 h. The reaction mixture was quenched with water (100 mL) and extracted with diethyl ether (4 × 20 mL). The ether layer was washed with brine, dried and filtered. The residue was chromatographed over silica gel column eluting with hexane ethyl acetate (96 : 4) afforded the ester **14** (1.2 g, 77%) as an oil. UV (MeOH) λ_{max} (log ϵ) 321 (4.57), 231 (4.13); IR (Neat) ν_{max} 2981, 1738, 1646, 1599, 1573, 1511, 1417, 1253, 1173, 1032, 826 cm^{-1}.

1,7-Bis(4-methoxyphenyl)-3-hydroxy-4-(ethoxycarbonyl)-1,3-heptadiene-5-one (**15**) To a solution of sodium hydride (70 mg, 1.45 mmol, 50% dispersion in oil) in dry THF (5 mL) at 5°C, was added **14** (300 mg, 1.2 mmol) and the mixture was stirred at room temperature for 20 min. A solution of 3-(4-methoxyphenyl)propionyl chloride (**8**) in THF (5 mL) was added to the reaction mixture at 0°C and the mixture was stirred at room temperature for 4 h. Work-up as described for **11** followed by chromatography of the residue over a silica gel column using hexane ethyl acetate (96 : 4) as eluent furnished the ester, **15** (300 mg, 60%) as light yellow solid, m.p. 72–74°C; UV (MeOH) λ_{max} (log ϵ) 327 (4.54), 224 (4.33); IR (Neat) ν_{max} 2975, 1704, 1626, 1600, 1574, 1512, 1251, 1173, 1033, 826 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36

(3H, t, $J = 7.1$ Hz), 2.96 (4H, br s), 3.77 (3H, s, Ar–OCH_3), 3.82 (3H, s, Ar–OCH_3), 4.32 (2H, q, $J = 7.1$ Hz), 6.81 (2H, d, $J = 8.8$ Hz), 6.90 (2H, d, $J = 8.5$ Hz), 6.93 (1H, d, $J = 15.6$ Hz), 7.13 (2H, d, $J = 8.5$ Hz), 7.49 (2H, d, $J = 8.8$ Hz), 7.77 (1H, d, $J = 15.6$ Hz), anal. C 70.45%, H 6.40%, calcd. for $C_{24}H_{26}O_6$, C 70.24%, H 6.34%.

1,7-Bis(4-methoxyphenyl)-3-hydroxy-1,3-heptadiene-5-one (**12**) A mixture of **15** (100 mg, 0.243 mmol), sodium chloride (40 mg, 0.68 mmol), water (50 mg, 2.77 mmol) and DMSO (1 mL) was heated at 130–140°C for 2 h. Work-up as described for **10** followed by chromatography of the residue over silica gel column using hexane–ethyl acetate (98 : 2) as eluent furnished **12** (65 mg, 79%), light yellow solid, m.p. 108–110°C.

1,7-Bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione (**3**) This was prepared according to the literature procedure, m.p. 219–222°C (Ref. [16], m.p. 220–224°C).

Hydrogenation of **3** A solution of **3** (0.5 g, 1.62 mmol) in EtOAc (25 mL) was added Pd/C (10%, 100 mg) and the reaction mixture was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration and the solvent was evaporated. The residue obtained was recrystallised from chloroform–hexane to give 1,7-bis(4-hydroxyphenyl)-heptan-3,5-dione (**16**) (0.45 g, 89%) as colourless crystals, m.p. 104–105°C; IR (Neat) ν_{max} 3153, 1602, 1517, 1447, 1248, 1099, 826 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (4H, t, $J =$ 7.5 Hz), 2.84 (4H, t, $J = 7.5$ Hz), 5.36 (1H, s), 6.73 (4H, d, $J = 8.3$ Hz), 7.01 (4H, d, $J = 8.3$ Hz).

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