Diastereoselective Conjugate Addition Reactions of 2′-Hydroxypropiophenone to 2′-Hydroxychalcones – Synthesis and Structural Characterization of the Diastereomers of (±)-3-Aryl-1,5-bis(2-hydroxyphenyl)-2,4-dimethyl-1,5-pentanediones

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The diastereoselective synthesis of 3-aryl-1,5-bis(2-hydroxyphenyl)-2,4-dimethyl-1,5-pentanediones has been carried out by conjugate addition reactions of 2′-hydroxypropiophenone to 2′-hydroxy-α-methylchalcone derivatives, or in single one-pot reactions of 2′-hydroxypropiophenone with appropriate benzaldehyde derivatives. The structures and stereochemistry of the obtained diastereomers have been determined using various NMR techniques, and the factors determining their formation are investigated and discussed.

Introduction

The nucleophilic addition of enolates to the carbon−carbon double bonds of α,β-unsaturated ketones is one of the most fundamental reactions in the synthesis of 1,5-dicarbonyl compounds.[1][2] When an α,β-unsaturated substrate has prochiral centres at the α- and/or β-positions, such conjugate additions allow the creation of new chiral centres. New chiral centres can also be introduced in the nucleophile moiety. The relative and/or absolute stereochemistry thus generated can often be efficiently controlled. In fact, great advances in asymmetric conjugate addition reactions have been made during the last decade.[1][2]

It has been known for many years that the stereochemistry generated in conjugate addition reactions of enolates with α,β-unsaturated systems is highly dependent on the experimental conditions used and on the structures of the reagents. Heathcock[3] has shown that the stereoselectivity of these reactions directly reflects the stereoselective formation of the alternative enolate (*E*) and (*Z*) stereoisomers. In general, (*Z*)-enolates give *anti* addition products, whereas (*E*)-enolates give *syn* products. The formation of the enolate stereoisomers is dependent on their substituents and on the solvent used.

This study was initiated by the challenging goal of developing an efficient synthesis of a new type of β-substituted 2′-hydroxydihydrochalcones. Over the past years we have been investigating new syntheses of several flavonoid-type compounds.[4] Now we are extending our research to the development of new syntheses of 2′-hydroxydihydrochalcones, which should thus be made available for further biological assessment. These molecules constitute a class of natural compounds that can be found in a number of higher plants, gymnosperms, and angiosperms, as well as in a few lower plants.[5] Biological functions of dihydrochalcones in plants include protection against diseases caused by microorganisms; some may also play a role as feeding deterrents to insects and other herbivorous animals. These natural compounds and their synthetic analogues appear to possess a variety of other biological activities.[5][6] However, the most interesting feature of dihydrochalcones is that they can exhibit taste properties, being bitter, sweet, or bitter-sweet. Some of them can be used as non-nutritive sweeteners in foods and beverages.[5][6] In view of these important potential applications of dihydrochalcones, it would be advantageous if they could be made available through simple, straightforward synthetic transformations.

Stereoselective conjugate addition reactions of organometallic reagents, nitroalkane anions, and enolates to chalcones in the presence of chiral auxiliaries have been extensively studied.[7] The conjugate addition of ketones to chalcones in the absence of any chiral auxiliary has also been studied, but in these cases only *erythro*/*threo* mixtures of products have been obtained.[8] We report herein the first study of the diastereoselective conjugate addition of 2′-hydroxypropiophenone to 2′-hydroxychalcones. The 2′-hydroxychalcones used have prochiral centres at the β-position and, in the case of 2′-hydroxy-4-methoxy-α-methylchalcone, also at the α-position; the nucleophile also bears a methyl substituent at the α-position. This leads to the creation of two or three chiral centres in the conjugate addition products, but only one diastereomer was obtained in each case. The conjugate addition of 2′-hydroxypropiophenone to 2′-hydroxy-4-methoxy-α-methylchalcone gave only one diastereomer of the corresponding 1,5-pentanedione. This product, as well as several other derivatives, have also been obtained in single one-pot reactions of 2′-hydroxypropiophenone with benzaldehyde derivatives. The structures and

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stereochemistry of the new diastereomers have been elucidated by means of various NMR techniques.

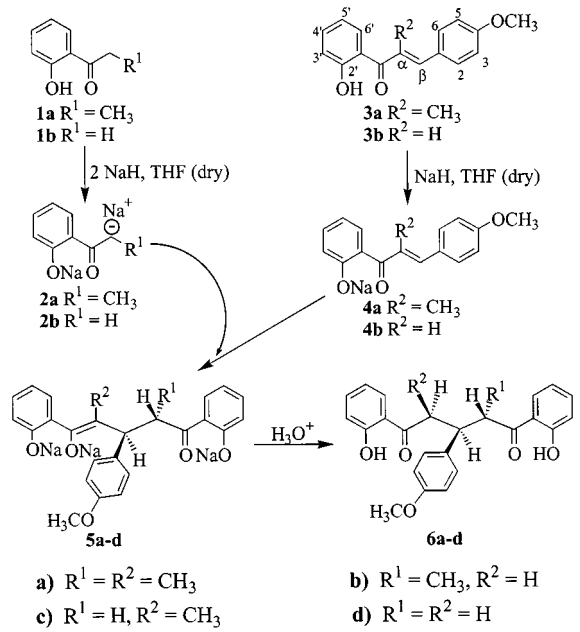
Results and Discussion

Conjugate Addition Reactions

Conjugate addition of the disodium salt of 2′-hydroxypropiophenone dianion **2a** to 4-methoxy-α-methylchalcone derivative **4a**, both obtained by treatment of the corresponding ketones **1a** and **3a** with sodium hydride in dry THF, gave, after protonation of the intermediate enolate sodium salt **5a**, only one diastereomer of the 1,5-pentanedione **6a**[9] (Scheme 1). In order to establish the role played by the α-methyl groups of both reagents in determining the diastereoselectivity of this reaction, addition reactions of the disodium salts of the 2′-hydroxypropiophenone and 2′-hydroxyacetophenone dianions **2a** and **2b** with the chalcone derivatives **4b** and **4a**, respectively, were carried out (Scheme 1). Conjugate addition of **2a** to **4b** again gave only one diastereomer **6b**,[9] whereas the reaction of **2b** with **4a** gave two diastereomers **6b** and **6c**,[9] which were separated by thin-layer chromatography. These results indicate that the nucleophilic addition of the disodium salt of 2′-hydroxypropiophenone dianion **2a** to α-substituted or α-unsubstituted chalconates **4a** and **4b** is stereoselective, leading to the formation of the *anti* species **5a** and **5b**. Protonation of **5a** gave only the diastereomer **6a**, probably as a result of 1,3-interaction between the two methyl groups. In enolate sodium salt **5b**, there is no such interaction as there is only one methyl group (R^2 = H) and hence the diastereomer **6b** was obtained. Nucleophilic addition of the disodium salt of 2′-hydroxyacetophenone dianion **2b** to α-substituted or α-unsubstituted chalconates **4a** and **4b** gave **5c** and **5d**.[9] In the case of the enolate sodium salt **5c**, there is no strong 1,3-interaction akin to that described above, hence protonation leads to the formation of a mixture of diastereomers **6b** and **6c**.[19] Protonation of **5d** leads to the formation of **6d**.

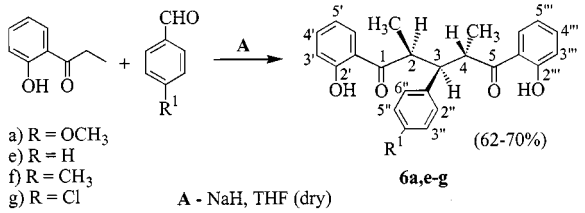
1,5-Pentanedione **6a** was also obtained by treating 2′-hydroxypropiophenone (HPP) with benzaldehyde in the presence of sodium hydride in a concentrated THF solution (4 mL HPP/20 mL THF), initially for 24 h at room temperature (Scheme 2). However, as an appreciable amount of propiophenone was still present after this period, more sodium hydride and benzaldehyde were added to the mixture and reaction was allowed to proceed for a further 24 h (see Experimental Section). The diastereomer **6a** was obtained in 62% yield. This synthesis was subsequently extended to the preparation of new 1,5-pentanedione derivatives **6e−g** (63−70%). When a more dilute 2′-hydroxypropiophenone solution (4 mL HPP/50 mL THF) or a larger excess of the benzaldehyde derivative was used, the corresponding 2′-hydroxy-α-methylchalcones were obtained in moderate yields (ca. 40%), contaminated with small amounts of the 1,5-pentanediones **6a**,**e−g** (3−7%).

This interesting result suggests that similar transformations might be carried out with 2′-hydroxyacetophenone



Scheme 1. Conjugate addition reactions of 2′-hydroxypropiophenone to 2′-hydroxychalcones

and benzaldehydes. However, in these cases only 2′-hydroxychalcones were obtained in good yields (60−70%).[10]



Scheme 2. One-pot synthesis of 1,5-pentanediones **6a**,**e−g**

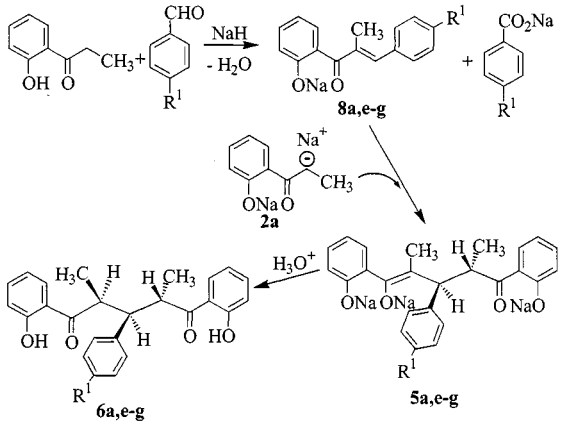
The results described above can be rationalized in terms of the formation of 1,5-pentanediones **6a**,**e−g** via the corresponding chalcone, followed by a conjugate addition of the disodium salt of 2′-hydroxypropiophenone dianion **2a** (Scheme 3). The strongly basic conditions employed ensure the formation of the latter and are also conducive to the oxidation of benzaldehyde derivatives by oxygen present in the solvent.

Aldol reaction of this disodium salt of dianion **2a** with the remaining benzaldehyde derivatives gave the corresponding chalconates **8a**,**e−g**, which underwent nucleophilic addition of the disodium salt of dianion **2a**, leading to the formation of enolates **5a**,**e−g**. Finally, protonation of the these anions **5a**,**e−g** by the addition of aqueous hydrochloric acid furnished the 1,5-pentanediones **6a**,**e−g**. Benzoic acid derivatives were also obtained as by-products.

The key step of the proposed mechanism is the oxidation of the benzaldehyde derivative. This oxidation was minimized when the reaction of 2′-hydroxypropiophenone with 4-methoxybenzaldehyde was carried out under the same experimental conditions as those used for the preparation of compounds **6a**,**e−g**, but with prior degassing of the solu-

tion with nitrogen and maintaining a carefully controlled nitrogen blanket at all times. In this case, 2′-hydroxy-4-methoxy-α-methylchalcone (**3a**) was obtained as the major product.

Owing to the highly reactive nature of the 2′-hydroxyacetophenone dianion, in the reactions of 2′-hydroxyacetophenone with benzaldehyde derivatives the aldol reaction with the benzaldehyde derivative is faster than the oxidation of the latter. Under these circumstances, only 2′-hydroxychalcones[10] are obtained.



Scheme 3. Proposed mechanism for the one-pot synthesis of 1,5-pentanediones **6a**,**e**−**g**

Structural Characterization of the Diastereomers of (±)-3-Aryl-1,5-bis(2-hydroxyphenyl)-1,5-pentanediones 6a−g

The structures of the diastereomers **6a**−**g** were determined using several NMR techniques [^{1}H, ^{13}C, COSY (^{1}H/^{1}H), NOESY, HETCOR (^{1}H/^{13}C), one-dimensional selective INEPT], mass spectrometry, and elemental analysis.

In the ^{1}H-NMR spectra of compounds **6a**,**e**−**g**, signals were observed in the aromatic region corresponding to the proton resonances of two non-equivalent 2′-hydroxypropiophenone moieties and one benzaldehyde residue. The aliphatic region featured signals attributable to the proton resonances of two secondary methyl groups along with signals due to three other protons (2-H, 3-H, and 4-H). All of these signals, as well as those due to the two hydroxy groups (δ = 12.13−12.18 and δ = 12.26−12.30), which are involved in hydrogen bonds with carbonyl groups, are consistent with the proposed structures for compounds **6a**,**e**−**g**.

In the NOESY spectra of compounds **6a**,**e**−**g**, intense NOE cross-peaks were observed between the two methyl groups (δ = 1.02−1.03 and 1.29−1.30) and the multiplets corresponding to 2-H and 4-H. However, only the signal corresponding to the more shielded methyl group showed an NOE cross-peak with the 2′′-,6′′-H protons. Other significant and intense NOE cross-peaks were observed between 2′′-, 6′′-H and the 3-H and 4-H protons. These results are only compatible with the configurations of diastereoisomers **6a**,**e**−**g** shown in Schemes 1−3.

In the NOESY spectrum of compound **6c**, intense NOE cross-peaks were observed between the 2-methyl protons and the 2-H and 2′′-, 6′′-H protons and between 2′′-, 6′′-H and 3-H, while 2′′-, 6′′-H and 4-H were correlated more weakly. These results allowed us to establish the configuration of this compound as that depicted in Scheme 1. On the other hand, the NOESY spectrum of compound **6b** showed intense NOE cross-peaks between the 2-methyl protons and the 3-H and 4-H protons, as well as between 2′′-, 6′′-H and 4-H and the multiplet attributed to 2-, 3-H. These spatial proximities and the absence of an NOE between 2′′-, 6′′-H and 2-CH_3 are only compatible with the configuration of diastereomer **6b** shown in Scheme 1.

The NOESY spectra of compounds **6a**−**g** showed other notable NOE cross-peaks, such as between 2-CH_3 and 6′-H and between 4-CH_3 and 6′′′-H or between 4-H and 6′′′-H. These data, together with analysis of the COSY spectra of these compounds, allowed unequivocal assignments of their proton resonances.

The assignments of the resonances of the protonated carbon atoms in the ^{13}C-NMR spectra of compounds **6a**−**g** were made by means of HETCOR experiments. For the assignment of the quaternary carbon atoms it was necessary to use one-dimensional selective INEPT[11] measurements, which show the connectivity of a selected proton to the carbon atoms to which it is coupled by irradiation of the corresponding resonance. This technique can be optimized for different long-range *J* (C/H) couplings. The main results obtained from the selective INEPT measurements are shown in Table 1.

Table 1. ^{1}H-^{13}C long-range correlations of 1,5-pentanediones **6a**−**g** determined by 1D-selective INEPT

Compound	Irradiated proton resonance	Carbon atom(s) to which it is coupled
6a−**c**,**e**−**g**	2-CH_3	C-1, C-2, and C-3
6a,**e**−**g**	4-CH_3	C-3, C-4, and C-5
6a−**g**	6′-H	C-1, C-2′, and C-4′
6a−**g**	6′′′-H	C-2′′′, C-4′′′, and C-5
6a−**g**	2′-OH	C-1′, C-2′, and C-3′
6a−**g**	2′′′-OH	C-1′′′, C-2′′′, and C-3′′′
6a,**e**−**g**	3-H	C-1, C-1′′, and C-2′′,6′′
6f	4′′-CH_3	C-3′′,5′′, and C-4′′
6a−**d**	4′′-OCH_3	C-4′′

Experimental Section

General Remarks: Melting points (uncorrected): Reichert Thermovar apparatus fitted with a microscope. − NMR: Bruker AMX 300 spectrometer (300.13 and 75.47 MHz, for ^{1}H and ^{13}C, respectively); $CDCl_3$ as solvent, TMS as internal reference, chemical shifts (δ) in ppm, coupling constants (*J*) in Hz. Unequivocal ^{1}H assignments were made with the aid of 2D-COSY (^{1}H/^{1}H) and NOESY spectra (mixing time 800 ms), while ^{13}C assignments were made on the basis of 2D-HETCOR (^{1}H/^{13}C) experiments as well as one-dimensional selective INEPT[11] (long-range C/H coupling constants optimized to 7 Hz); 2D-COSY and HETCOR experiments: Bruker standard microprograms. − MS: Electron impact (EI, 70 eV) and fast-atom bombardment (using 3-nitrobenzyl alcohol as a matrix)

with VG Autospec Q and M mass spectrometers. − Elemental analysis: Microanalytical laboratory of the Department of Chemistry, University of Coimbra, and in-house with an LECO 932 CHN analyser. − Preparative thin-layer chromatography: Riedel silica gel 60 DGF_{254}. − Column chromatography: Merck silica gel 60, 70−230 mesh. − Dry sodium hydride (95%, w/w) was purchased from Aldrich (Madrid); all other chemicals and solvents were obtained from commercial sources and used as received or dried according to standard procedures.

2′-Hydroxy-4-methoxy-α-methylchalcone (3a):[12] To a dried solution of 2′-hydroxypropiophenone (4.0 mL, 29 mmol) in THF (50 mL) under nitrogen, dry sodium hydride (1.60 g, 66.7 mmol) was slowly added. After stirring for 15 min, 4-methoxybenzaldehyde (3.5 mL, 40.4 mmol) was slowly added and the reaction mixture was stirred for 24 h. After this period, further dry sodium hydride (0.70 g, 29 mmol) and 4-methoxybenzaldehyde (1.25 mL, 14.4 mmol) were added and the reaction mixture was stirred for a further 24 h. It was then poured into water (150 mL), ice (150 g), and commercial hydrochloric acid (pH of resulting mixture ca. 2). This mixture was extracted with chloroform (3 × 100 mL), the combined organic layers were dried with anhydrous sodium sulfate, and the solvent was evaporated. The residue was redissolved in chloroform (10 mL) and purified by column chromatography using dichloromethane as eluent. 2′-Hydroxy-4-methoxy-α-methylchalcone (**3a**) was obtained in 41% yield as a yellow oil. − ^{1}H NMR: δ = 2.27 (d, *J* = 1.2 Hz, 3 H, α-CH_3), 3.82 (s, 3 H, 4-OCH_3), 6.86 (ddd, *J* = 7.8, 7.6, and 1.1 Hz, 1 H, 5′-H), 6.93 (d, *J* = 8.7 Hz, 2 H, 3-,5-H), 6.96 (br s, 1 H, β-H), 7.02 (dd, *J* = 8.1 and 1.1 Hz, 1 H, 3′-H), 7.39 (d, *J* = 8.7 Hz, 2 H, 2-,6-H), 7.45 (ddd, *J* = 8.1, 7.6, and 1.7 Hz, 1 H, 4′-H), 7.73 (dd, *J* = 7.8 and 1.7 Hz, 1 H, 6′-H), 11.85 (s, 1 H, 2′-OH). − ^{13}C NMR: δ = 15.2 (α-CH_3), 55.2 (OCH_3), 113.9 (C-3,5), 118.2 (C-3′), 118.3 (C-5′), 119.1 (C-1′), 127.9 (C-1), 131.3 (C-2,6), 132.7 (C-6′), 133.4 (C-α), 135.6 (C-4′), 139.2 (C-β), 159.8 (C-4), 162.7 (C-2′), 203.7 (C=O). − MS (EI); *m/z* (%): 268 [$M^{+\bullet}$] (21), 267 (15), 254 (15), 253 (43), 237 (10), 170 (28), 161 (56), 148 (67), 147 (29), 146 (29), 145 (57), 134 (49), 133 (49), 122 (24), 121 (100), 115 (29), 108 (50), 105 (50), 103 (55), 93 (50), 91 (60).

2′-Hydroxy-4-methoxychalcone (3b) was obtained as reported previously.[10]

Conjugate Addition Reactions of 2′-Hydroxychalcones 3a and 3b with 2′-Hydroxypropiophenone (2a) and 2′-Hydroxyacetophenone (2b): To a dried solution of 2′-hydroxypropiophenone (**2a**) or 2′-hydroxyacetophenone (**2b**) (7.25 mmol) in THF (5 mL), dry sodium hydride (401 mg, 16.7 mmol) was slowly added and the reaction mixture was stirred for 15 min under nitrogen. Meanwhile, a solution of 2′-hydroxychalcone **3a** or **3b** (7.25 mmol) in THF (5 mL) was similarly treated with dry sodium hydride (174 mg, 7.25 mmol) and stirred for 15 min. After this period, the first solution was added and the resulting reaction mixture was stirred for 24 h. It was then poured into water (150 mL), ice (150 g), and commercial hydrochloric acid (pH of resulting mixture ca. 2). This mixture was extracted with chloroform (3 × 100 mL), the combined organic layers were dried with anhydrous sodium sulfate, and the solvent was evaporated. The residue was redissolved in chloroform (10 mL) and purified by column chromatography with dichloromethane as eluent. With 2′-hydroxy-4-methoxy-α-methylchalcone (**3a**) and 2′-hydroxypropiophenone (**2a**) as starting materials, 1,5-pentanedione **6a** (65%) was obtained. However, starting with 2′-hydroxy-4-methoxy-α-methylchalcone (**3a**) and 2′-hydroxyacetophenone (**2b**), a mixture of two diastereomers of 1,5-pentanedione, **6b** (36%) and **6c** (31%), was obtained. These two compounds were separated by thin-layer chromatography of a very dilute chloroform solution (50 mL), eluting several times with a 95:5 mixture of light petroleum ether/ethyl acetate. With 2′-hydroxy-4-methoxychalcone (**3b**) and 2′-hydroxypropiophenone (**2a**) or 2′-hydroxyacetophenone (**2b**) as starting materials, 1,5-pentanediones **6b** (81%) and **6d** (71%), respectively, were obtained.

(±)-1,5-Bis(2-hydroxyphenyl)-2,4-dimethyl-3-phenyl-1,5-pentanedione (6a): M.p. 110−112°C (recrystallization from ethanol). − ^{1}H NMR: δ = 1.02 (d, *J* = 6.6 Hz, 3 H, 2-CH_3), 1.29 (d, *J* = 6.9 Hz, 3 H, 4-CH_3), 3.84 (t, *J* = 8.1 Hz, 1 H, 3-H), 3.99−4.11 (m, 2 H, 2-,4-H), 6.79 (ddd, *J* = 7.9, 7.7, and 1.1 Hz, 1 H, 5′′′-H), 6.89 (dd, *J* = 8.2 and 1.1 Hz, 1 H, 3′′′-H), 6.95 (ddd, *J* = 7.9, 7.7, and 1.1 Hz, 1 H, 5′-H), 7.03 (dd, *J* = 8.1 and 1.1 Hz, 1 H, 3′-H), 7.10−7.25 (m, 5 H, 2′′-,3′′-,4′′-,5′′-,6′′-H), 7.39 (ddd, *J* = 8.2, 7.7, and 1.5 Hz, 1 H, 4′′′-H), 7.51 (ddd, *J* = 8.1, 7.7, and 1.5 Hz, 1 H, 4′-H), 7.69 (dd, *J* = 7.9 and 1.5 Hz, 1 H, 6′′′-H), 7.85 (dd, *J* = 7.9 and 1.5 Hz, 1 H, 6′-H), 12.15 (s, 1 H, 2′′′-OH), 12.30 (s, 1 H, 2′-OH). − ^{13}C NMR: δ = 15.7 (2-CH_3), 16.6 (4-CH_3), 41.8 (C-2), 43.5 (C-4), 49.5 (C-3), 118.5 (C-1′), 118.7 (C-1′′′), 118.8 (C-3′′′,5′′′), 119.0 (C-3′), 119.2 (C-5′), 127.1 (C-4′′), 128.3 (C-3′′,5′′), 128.9 (C-2′′,6′′), 129.3 (C-6′), 129.4 (C-6′′′), 136.3 (C-4′′′), 136.5 (C-4′), 139.6 (C-1′′), 162.9 (C-2′′′), 163.2 (C-2′), 208.75 (C-5), 208.78 (C-1). − MS (FAB$^+$); *m/z* (%): 389 (8) [M + H]$^+$, 239 (23), 150 (7), 122 (7), 121 (100), 105 (7), 93 (7), 91 (11). − $C_{25}H_{24}O_4$ (388.5): calcd. C 77.30, H 6.23; found C 77.46, H 6.05.

(±)-1,5-Bis(2-hydroxyphenyl)-2-methyl-3-(4-methoxyphenyl)-1,5-pentanedione (6b): M.p. 115−117°C (recrystallization from ethanol). − ^{1}H NMR: δ = 1.32 (d, *J* = 6.9 Hz, 3 H, 2-CH_3), 3.44−3.51 (m, 2 H, 4-H), 3.72 (s, 3 H, 4′′-O*C*H_3), 3.86−3.92 (m, 1 H, 3-H), 3.95 (quint, *J* = 6.9 Hz, 1 H, 2-H), 6.75 (d, *J* = 8.7 Hz, 2 H, 3′′-,5′′-H), 6.88 (ddd, *J* = 7.8, 7.3, and 1.1 Hz, 1 H, 5′′′-H), 6.88 (ddd, *J* = 8.5, 7.2 and 0.9 Hz, 1 H, 5′-H), 6.93 (dd, *J* = 8.6 and 1.1 Hz, 1 H, 3′′′-H), 6.94 (dd, *J* = 8.4 and 0.9 Hz, 1 H, 3′-H), 7.15 (d, *J* = 8.7 Hz, 2 H, 2′′-,6′′-H), 7.44 (ddd, *J* = 8.6, 7.3, and 1.7 Hz, 1 H, 4′′′-H), 7.45 (ddd, *J* = 8.4, 7.2, and 1.8 Hz, 1 H, 4′-H), 7.75 (dd, *J* = 7.8 and 1.7 Hz, 1 H, 6′′′-H), 7.78 (dd, *J* = 8.5 and 1.7 Hz, 1 H, 6′-H), 12.08 (s, 1 H, 2′′′-OH), 12.35 (s, 1 H, 2′-OH). − ^{13}C NMR: δ = 14.7 (2-CH_3), 39.9 (C-4), 42.2 (C-3), 45.3 (C-2), 55.1 (4′′-O*C*H_3), 113.9 (C-3′′,5′′), 118.6 (C-3′,3′′′), 118.80 (C-1′), 118.86 (C-5′′′), 118.9 (C-5′), 119.4 (C-1′′′), 128.7 (C-2′′,6′′), 129.6 (C-6′′′), 129.7 (C-6′), 134.1 (C-1′′), 136.4 (C-4′′′), 136.5 (C-4′), 158.3 (C-4′′), 162.4 (C-2′′′), 163.2 (C-2′), 204.5 (C-5), 209.2 (C-1). − MS (EI); *m/z* (%): 404 (15) [$M^{+\bullet}$], 269 (11), 268 (8), 256 (16), 255 (40), 253 (10), 148 (7), 134 (9), 122 (19), 121 (100), 93 (16). − $C_{25}H_{24}O_5$ (404.5): calcd. C 74.24, H 5.98; found C 73.83, H 6.36.

(±)-1,5-Bis(2-hydroxyphenyl)-2-methyl-3-(4-methoxyphenyl)-1,5-pentanedione (6c): Yellow oil. − ^{1}H NMR: δ = 1.04 (d, *J* = 6.0 Hz, 3 H, 2-CH_3), 3.23 (dd, *J* = 15.6 and 9.0 Hz, 1 H, 4-H), 3.32 (dd, *J* = 15.6 and 4.2 Hz, 1 H, 4-H), 3.73 (s, 3 H, 4′′-OCH_3), 3.78−3.92 (m, 2 H, 2-,3-H), 6.81 (d, *J* = 8.6 Hz, 2 H, 3′′-,5′′-H), 6.84 (dd, *J* = 8.2 and 7.7 Hz, 1 H, 5′′′-H), 6.89 (d, *J* = 8.5 Hz, 1 H, 3′′′-H), 6.93 (dd, *J* = 7.8 and 7.6 Hz, 1 H, 5′-H), 7.02 (d, *J* = 8.1 Hz, 1 H, 3′-H), 7.12 (d, *J* = 8.6 Hz, 2 H, 2′′-,6′′-H), 7.39 (dd, *J* = 8.5 and 7.7 Hz, 1 H, 4′′′-H), 7.49 (dd, *J* = 8.1 and 7.6 Hz, 1 H, 4′-H), 7.65 (d, *J* = 8.2 Hz, 1 H, 6′′′-H), 7.92 (d, *J* = 7.8 Hz, 1 H, 6′-H), 12.13 (s, 1 H, 2′′′-OH), 12.53 (s, 1 H, 2′-OH). − ^{13}C NMR: δ = 16.9 (2-CH_3), 43.2 (C-4), 43.3 (C-3), 45.2 (C-2), 55.0 (4′′-OCH_3), 113.8 (C-3′′,5′′), 118.2 (C-3′′′), 118.8 (C-5′,5′′′), 119.0 (C-3′), 119.1 (C-1′,1′′′), 129.0 (C-2′′,6′′), 129.8 (C-6′), 129.9 (C-6′′′), 132.4 (C-1′′), 136.2 (C-4′′′), 136.7 (C-4′), 158.3 (C-4′′), 162.3 (C-2′′′), 163.0 (C-2′), 204.4 (C-5), 209.8 (C-1). − MS (EI); *m/z* (%): 404 (10) [$M^{+\bullet}$], 269 (12), 268 (8), 256 (12), 255 (40), 253 (8), 148 (9), 134 (9), 122 (13), 121 (100), 93 (11).

(±)-1,5-Bis(2-hydroxyphenyl)-3-(4-methoxyphenyl)-1,5-pentanedione (6d): Yellow oil. − ^{1}H NMR: δ = 3.47 (dd, *J* = 6.8 and 16.7 Hz, 2 H, 2-,4-H), 3.75 (s, 3 H, 4′′-OCH$_3$), 4.03 (quint, *J* = 6.8 Hz, 1 H, 3-H), 6.82 (d, *J* = 6.6 Hz, 2 H, 3′′-,5′′-H), 6.88 (ddd, *J* = 7.9, 7.7, and 0.9 Hz, 2 H, 5′-,5′′′-H), 6.95 (dd, *J* = 8.2 and 0.9 Hz, 2 H, 3′-,3′′′-H), 7.19 (d, *J* = 6.6 Hz, 2 H, 2′′-,6′′-H), 7.44 (ddd, *J* = 8.2, 7.7, and 1.6 Hz, 2 H, 4′-,4′′′-H), 7.80 (dd, *J* = 7.9 and 1.6 Hz, 2 H, 6′-,6′′′-H), 12.17 (s, 2 H, 2′-,2′′′-OH). − ^{13}C NMR: δ = 36.1 (C-3), 44.6 (C-2,4), 55.1 (4′′-O*C*H$_3$), 114.0 (C-3′′,5′′), 118.5 (C-3′,3′′′), 118.9 (C-5′,5′′′), 119.3 (C-1′,1′′′), 128.2 (C-2′′,6′′), 129.9 (C-6′,6′′′), 134.9 (C-1′′), 136.4 (C-4′,4′′′), 158.3 (C-4′′), 162.4 (C-2′,2′′′), 204.5 (C-1,5). − MS (EI); *m/z* (%): 390 (28) [M$^{+\bullet}$], 372 (5), 256 (32), 255 (85), 254 (23), 253 (20), 237 (13), 161 (6), 134 (26), 122 (20), 121 (100), 119 (9), 93 (23).

Synthesis of (±)-3-Aryl-1,5-bis(2-hydroxyphenyl)-2,4-dimethyl-1,5-pentanediones 6a, e−g: To a dried solution of 2′-hydroxypropiophenone (4.0 mL, 29 mmol) in THF (20 mL) under nitrogen, dry sodium hydride (1.60 g, 66.7 mmol) was slowly added. After stirring for 15 min, the appropriate benzaldehyde derivative (40.6 mmol) was slowly added and the reaction mixture was stirred for 24 h. After this period, further dry sodium hydride (0.70 g, 29 mmol) and benzaldehyde derivative (14.5 mmol) were added, and the reaction mixture was stirred for an additional 24 h. The mixture was subsequently poured into water (150 mL), ice (150 g), and commercial hydrochloric acid (pH of resulting mixture ca. 2). The solid formed was filtered off, redissolved in chloroform (20 mL), and purified by column chromatography using dichloromethane as eluent. Finally, the product was crystallized from ethanol. With benzaldehyde as starting material, 1,5-pentanedione **6e** was obtained (62%); 4-methylbenzaldehyde gave 1,5-pentanedione **6f** (70%), 4-methoxybenzaldehyde gave 1,5-pentanedione **6a** (68%), and 4-chlorobenzaldehyde gave 1,5-pentanedione **6g** (63%).

(±)-1,5-Bis(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2,4-dimethyl-1,5-pentanedione (6a): This product was found to give spectroscopic and analytical data identical to those described above.

(±)-1,5-Bis(2-hydroxyphenyl)-2,4-dimethyl-3-phenyl-1,5-pentanedione (6e): M.p. 110−112°C (recrystallization from ethanol). − ^{1}H NMR: δ = 1.02 (d, *J* = 6.6 Hz, 3 H, 2-CH$_3$), 1.29 (d, *J* = 6.9 Hz, 3 H, 4-CH$_3$), 3.84 (t, *J* = 8.1 Hz, 1 H, 3-H), 3.99−4.11 (m, 2 H, 2-,4-H), 6.79 (ddd, *J* = 7.9, 7.7, and 1.1 Hz, 1 H, 5′′′-H), 6.89 (dd, *J* = 8.2 and 1.1 Hz, 1 H, 3′′′-H), 6.95 (ddd, *J* = 7.9, 7.7, and 1.1 Hz, 1 H, 5′-H), 7.03 (dd, *J* = 8.1 and 1.1 Hz, 1 H, 3′-H), 7.10−7.25 (m, 5 H, 2′′-,3′′-,4′′-,5′′-,6′′-H), 7.39 (ddd, *J* = 8.2, 7.7, and 1.5 Hz, 1 H, 4′′′-H), 7.51 (ddd, *J* = 8.1, 7.7, and 1.5 Hz, 1 H, 4′-H), 7.69 (dd, *J* = 7.9 and 1.5 Hz, 1 H, 6′′′-H), 7.85 (dd, *J* = 7.9 and 1.5 Hz, 1 H, 6′-H), 12.15 (s, 1 H, 2′′′-OH), 12.30 (s, 1 H, 2′-OH). − ^{13}C NMR: δ = 15.7 (2-CH$_3$), 16.6 (4-CH$_3$), 41.8 (C-2), 43.5 (C-4), 49.5 (C-3), 118.5 (C-1′), 118.7 (C-1′′′), 118.8 (C-3′′′,5′′′), 119.0 (C-3′), 119.2 (C-5′), 127.1 (C-4′′), 128.3 (C-3′′,5′′), 128.9 (C-2′′,6′′), 129.3 (C-6′), 129.4 (C-6′′′), 136.3 (C-4′′′), 136.5 (C-4′), 139.6 (C-1′′), 162.9 (C-2′′′), 163.2 (C-2′), 208.75 (C-5), 208.78 (C-1). − MS (FAB$^+$); *m/z* (%): 389 (8) [M + H]$^+$, 239 (23), 150 (7), 122 (7), 121 (100), 105 (7), 93 (7), 91 (11). − $C_{25}H_{24}O_4$ (388.5): calcd. C 77.30, H 6.23; found C 77.46, H 6.05.

(±)-1,5-Bis(2-hydroxyphenyl)-2,4-dimethyl-3-(4-methylphenyl)-1,5-pentanedione (6f): M.p. 171−173°C (recrystallization from ethanol). − ^{1}H NMR: δ = 1.03 (d, *J* = 6.9 Hz, 3 H, 2-CH$_3$), 1.30 (d, *J* = 7.2 Hz, 3 H, 4-CH$_3$), 2.26 (s, 3 H, 4′′-CH$_3$), 3.80 (t, *J* = 8.1 Hz, 1 H, 3-H), 3.97−4.09 (m, 2 H, 2-,4-H), 6.79 (ddd, *J* = 7.9, 7.7, and 1.1 Hz, 1 H, 5′′′-H), 6.90 (dd, *J* = 8.1 and 1.1 Hz, 1 H, 3′′′-H), 6.95 (ddd, *J* = 7.9, 7.7, and 1.0 Hz, 1 H, 5′-H), 6.98 (d, *J* = 8.3 Hz, 2 H, 2′′-,6′′-H), 7.03 (d, *J* = 8.3 Hz, 2 H, 3′′-,5′′-H), 7.03 (dd, *J* = 7.9 and 1.0 Hz, 1 H, 3′-H), 7.40 (ddd, *J* = 8.1, 7.7, and 1.5 Hz, 1 H, 4′′′-H), 7.51 (ddd, *J* = 7.9, 7.7, and 1.5 Hz, 1 H, 4′-H), 7.70 (dd, *J* = 7.9 and 1.5 Hz, 1 H, 6′′′-H), 7.84 (dd, *J* = 7.9 and 1.5 Hz, 1 H, 6′-H), 12.17 (s, 1 H, 2′′′-OH), 12.30 (s, 1 H, 2′-OH). − ^{13}C NMR: δ = 15.4 (2-CH$_3$), 16.6 (4-CH$_3$), 21.0 (4′′-CH$_3$), 41.7 (C-2), 43.3 (C-4), 49.1 (C-3), 118.5 (C-1′), 118.7 (C-3′′′), 118.80 (C-1′′′), 118.83 (C-5′′′), 119.0 (C-3′), 119.1 (C-5′), 128.7 (C-2′′,6′′), 129.0 (C-3′′,5′′), 129.3 (C-6′), 129.4 (C-6′′′), 136.3 (C-1′′), 136.4 (C-4′′′), 136.5 (C-4′), 136.6 (C-4′′), 162.9 (C-2′′′), 163.1 (C-2′), 208.8 (C-5), 208.9 (C-1). − MS (FAB$^+$); *m/z* (%): 403 (16) [M + H]$^+$, 253 (29), 154 (7), 150 (7), 136 (7), 122 (7), 121 (100), 105 (7), 93 (5), 91 (7). − $C_{26}H_{26}O_4$ (402.5): calcd. C 77.59, H 6.51; found C 77.91, H 6.40.

(±)-3-(4-Chlorophenyl)-1,5-bis(2-hydroxyphenyl)-2,4-dimethyl-1,5-pentanedione (6g): M.p. 148−150°C (recrystallization from ethanol). − ^{1}H NMR: δ = 1.02 (d, *J* = 6.9 Hz, 3 H, 2-CH$_3$), 1.29 (d, *J* = 6.9 Hz, 3 H, 4-CH$_3$), 3.81 (t, *J* = 8.1 Hz, 1 H, 3-H), 3.96−4.08 (m, 2 H, 2-,4-H), 6.78 (ddd, *J* = 7.9, 7.7, and 1.0 Hz, 1 H, 5′′′-H), 6.89 (dd, *J* = 8.1 and 1.0 Hz, 1 H, 3′′′-H), 6.94 (ddd, *J* = 7.9, 7.7, and 1.1 Hz, 1 H, 5′-H), 7.02 (dd, *J* = 8.1 and 1.1 Hz, 1 H, 3′-H), 7.06 (d, *J* = 8.5 Hz, 2 H, 2′′-,6′′-H), 7.20 (d, *J* = 8.5 Hz, 2 H, 3′′-,5′′-H), 7.39 (ddd, *J* = 8.1, 7.7, and 1.4 Hz, 1 H, 4′′′-H), 7.50 (ddd, *J* = 8.1, 7.7, and 1.4 Hz, 1 H, 4′-H), 7.65 (dd, *J* = 7.9 and 1.4 Hz, 1 H, 6′′′-H), 7.81 (dd, *J* = 7.9 and 1.4 Hz, 1 H, 6′-H), 12.13 (s, 1 H, 2′′′-OH), 12.26 (s, 1 H, 2′-OH). − ^{13}C NMR: δ = 15.5 (2-CH$_3$), 17.0 (4-CH$_3$), 41.7 (C-2), 43.1 (C-4), 48.9 (C-3), 118.3 (C-1′), 118.6 (C-1′′′), 118.8 (C-5′′′), 118.9 (C-3′′′), 119.1 (C-5′), 119.2 (C-3′), 128.5 (C-3′′,5′′), 130.3 (C-2′′,6′′), 129.2 (C-6′,6′′′), 132.6 (C-4′′), 136.6 (C-4′′′), 136.7 (C-4′), 138.0 (C-1′′), 163.0 (C-2′′′), 163.2 (C-2′), 208.5 (C-1,5). − MS (FAB$^+$); *m/z* (%): 425 (2) [M + H]$^+$ ^{37}Cl, 423 (6) [M + H]$^+$ ^{35}Cl, 275 (5), 273 (15), 150 (10), 133 (5), 122 (8), 121 (100), 93 (5). − $C_{25}H_{23}ClO_4 \cdot 0.25$ H_2O (427.4): calcd. C 70.25, H 5.50; found C 70.44, H 5.33.

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[1] J. Leonard, *Contemp. Org. Synth.* **1994**, 387−415.
[2] J. Leonard, E. Díez-Barra, S. Merino, *Eur. J. Org. Chem.* **1998**, 2051−2061.
[3] C. H. Heathcock, M. A. Henderson, D. A. Oare, M. A. Sanner, *J. Org. Chem.* **1985**, *50*, 3019−3021. C. H. Heathcock, D. A. Oare, *J. Org. Chem.* **1985**, *50*, 3022−3024. D. A. Oare, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 157−172.
[4] D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, *J. Heterocycl. Chem.* **1996**, *33*, 1887−1893. A. M. S. Silva, J. A. S. Cavaleiro, J. Elguero, *Liebigs Ann.* **1997**, 2065−2068. D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, A. Lévai, T. Patonay, *J. Heterocycl. Chem.* **1998**, *35*, 217−224. A. M. S. Silva, D. C. G. A. Pinto, H. R. Tavares, J. A. S. Cavaleiro, M. L. Jimeno, J. Elguero, *Eur. J. Org. Chem.* **1998**, 2031−2038.
[5] R. J. Grayer in *Methods in Plant Biochemistry* (Eds.: P. M. Dey, J. B. Harborne), Academic Press, London, **1989**, chapter 8. B. A. Bohm in *The Flavonoids − Advances in Research Since 1986* (Ed.: J. B. Harborne), Chapman and Hall, London, **1994**, chapter 9.
[6] G. E. Dubois, G. A. Crosby, R. A. Stephenson, R. E. Wingard, Jr., *J. Agric. Food Chem.* **1977**, *25*, 763−772. G. E. Dubois, G. A. Crosby, R. A. Stephenson, *J. Med. Chem.* **1981**, *24*, 408−412. A. Krutosíková, M. Uher, *Natural and Synthetic Sweet Substances*, Ellis Horwood, New York, **1992**, p. 101−108.

S. Esaki, K. Nishiyama, N. Sugiyama, R. Nakajima, Y. Takao, S. Kamiya, *Biosci. Biotech. Biochem.* **1994**, *58*, 1479−1485. A. D. Kinghorn, E. J. Kennelly, *J. Chem. Educ.* **1995**, *72*, 676−680. A. von Gadow, E. Joubert, C. F. Hansmann, *J. Agric. Food Chem.* **1997**, *45*, 632−638.

[7] K. Maruoka, I. Shimada, H. Imoto, H. Yamamoto, *Synlett* **1994**, 519−520. A. H. M. de Vries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* **1994**, *50*, 4479−4491. M. Shimizu, Y. Onogawa, T. Fujisawa, *Synlett* **1996**, 827−828. P. Bakó, A. Szöllõsy, P. Bombicz, L. Tõke, *Synlett* **1997**, 291−292. E. Díez-Barra, A. Hoz, S. Merino, P. Sánchez-Verdú, *Tetrahedron Lett.* **1997**, *38*, 2359−2362. A. Hoz, A. H. M. Vries, R. Imbos, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 1467−1473. A. Hoz, E. Díez-Barra, F. Langa, S. Merino, A. Rodríguez, P. Sánchez-Verdú, *Tetrahedron* **1997**, *53*, 11693−11710.

[8] D. N. Dhar, *The Chemistry of Chalcones and Related Compounds*, John Wiley & Sons, New York, **1981**, chapter 6.

[9] Although all the described 3-aryl-1,5-bis(2-hydroxyphenyl)-1,5-pentanediones **6a−g** are racemates, owing to a better understanding of the stereochemistry, only one enantiomer is illustrated.

[10] The 2′-hydroxychalcones were found to exhibit spectroscopic and analytical properties identical to those previously reported in: A. M. S. Silva, H. R. Tavares, A. I. N. R. A. Barros, J. A. S. Cavaleiro, *Spectrosc. Lett.* **1997**, *30*, 1655−1667.

[11] A. Bax, *J. Magn. Reson.* **1984**, *57*, 314−318.

[12] Compound **3a** was obtained as the (*E*) isomer. In the NOESY spectrum of the product, intense NOE cross-peaks were observed between the α-methyl group and 6′-H and 2-, 6-H, which are only compatible with the configuration of the (*E*) stereoisomer.

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