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Regioselective syntheses of 6-(1,1-dimethylallyl)- and 8-(3,3-dimethylallyl) chrysins

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Abstract—The first regioselective syntheses of 6-(1,1-dimethylallyl)- and 8-(3,3-dimethylallyl) chrysins have been designed. Claisen rearrangement of protected 5-*O*-(3,3-dimethylallyl) chrysin in *N*,*N*-diethylaniline at 200–217°C gave selective access to the 8-(3,3-dimethylallyl) isomer. Similar rearrangement in *N*,*N*-diethylbutylamine at 140–160°C, or in cycloheptane/Eu(fod)$_3$ at 100°C, led to the formation of the 6-(1,1-dimethylallyl) isomer. Four different protecting groups for position 7 of chrysin have been compared, and found to follow the order of interest Bz>MOM>TBDPS>MEM.

1. Introduction

Isoprenoid derivatives of chrysin have been recently recognized[1] as efficient inhibitors of P-glycoprotein (Pgp), one of the transporters involved in multidrug resistance.[2] While a number of common flavones and flavonols were able to bind to Pgp,[3] *C*-isoprenylation greatly enhanced the affinity of chrysin towards Pgp.[1] In addition, only isoprenoid derivatives were able to inhibit Pgp-mediated daunomycin efflux from leukemic K562/R7 cells.[1] The latter compounds have been obtained by direct C-alkylation in aqueous alkaline medium and in catalytic phase transfer conditions.[1] This method had the advantage of giving direct access to series of isomers, rapidly used for biological assays. However the yields in isoprenoid derivatives were in the 20–30% range and chromatographic separation of the different isomers was necessary.[1] On the other hand, Claisen rearrangements are usually the method of choice for the regioselective isoprenylation of phenolic natural products.[4] Such rearrangements have been applied to the syntheses of a number of isoprenoid chalcones[5] and flavanones like naringenin.[6] In fact Claisen rearrangement of 7-*O*-(1,1-dimethylallyl) chrysin in boiling *N*,*N*-diethylaniline yielded 8-*C*-(3,3-dimethylallyl) chrysin as sole product.[7] Similar rearrangements of 7-*O*-(3,3-dimethylallyl) flavones and flavonols in acetic anhydride/sodium acetate gave selective access to the 8-*C*-(1,1-dimethylallyl) isomers.[8] However it is only very recently that our group has published a selective synthesis of a 6-*C*-(1,1-dimethylallyl)-7-*O*-methoxyethoxymethyl derivative of chrysin by refluxing its 5-*O*-(3,3-dimethylallyl) precursor in *N*,*N*-diethylbutylamine.[9] In continuation to the development of more efficient and more regioselective methods for the preparation of isoprenoid chrysins, providing easier access to preparative amount of compounds for in vivo studies, we wish now to report on the first regioselective preparation of unprotected 6-(1,1-dimethylallyl) chrysin. In the present study, the behavior of four protecting groups has been compared in terms of optimization of the parameters of the rearrangement, stability under the conditions of rearrangement, and nature of the products arising from the deprotection step.

2. Results and discussion

The synthesis of *C*-prenyl chrysin (Fig. 1) is a four-step process, which involves: protection of the 7-hydroxyl (I), *O*-alkylation of the 5-hydroxyl (II), *C*-alkylation at positions 6 or 8 depending on the conditions of a Claisen rearrangement (III or IV), and finally removal of the protective group (V). First we tested the methoxyethoxymethyl (MEM) group. Protection of the 7-hydroxyl by MEM led to 7-MEM chrysin **2a**[9] in 82% yield. Alkylation of flavone **2** was performed in presence of tetrabutylammonium hydroxide as a base, to give the 5-*O*-alkylated product **3a**[9] in 89% yield. Specific synthesis of 8-(3,3-dimethylallyl)-7-MEM chrysin **4a**[9] was achieved by exposure of a solution of **3a** in *N*,*N*-diethylaniline, either to microwave irradiation[9] (82%), or with heating at 217°C in an oil bath (93%). In the latter case, a strict control of the temperature of the oil bath was crucial since extensive degradation of the final product **4a** was found to occur at 220°C, while on the contrary the use of lower temperature conditions resulted in incomplete consumption of the starting compound **3a**.When the 5-*O*-prenyl flavone **3a** was refluxed in *N*,*N*-diethylbutylamine for 72 h, 6-(1,1-dimethylallyl)-7-MEM

Keywords: Claisen rearrangement; chrysins; regioselective synthesis.

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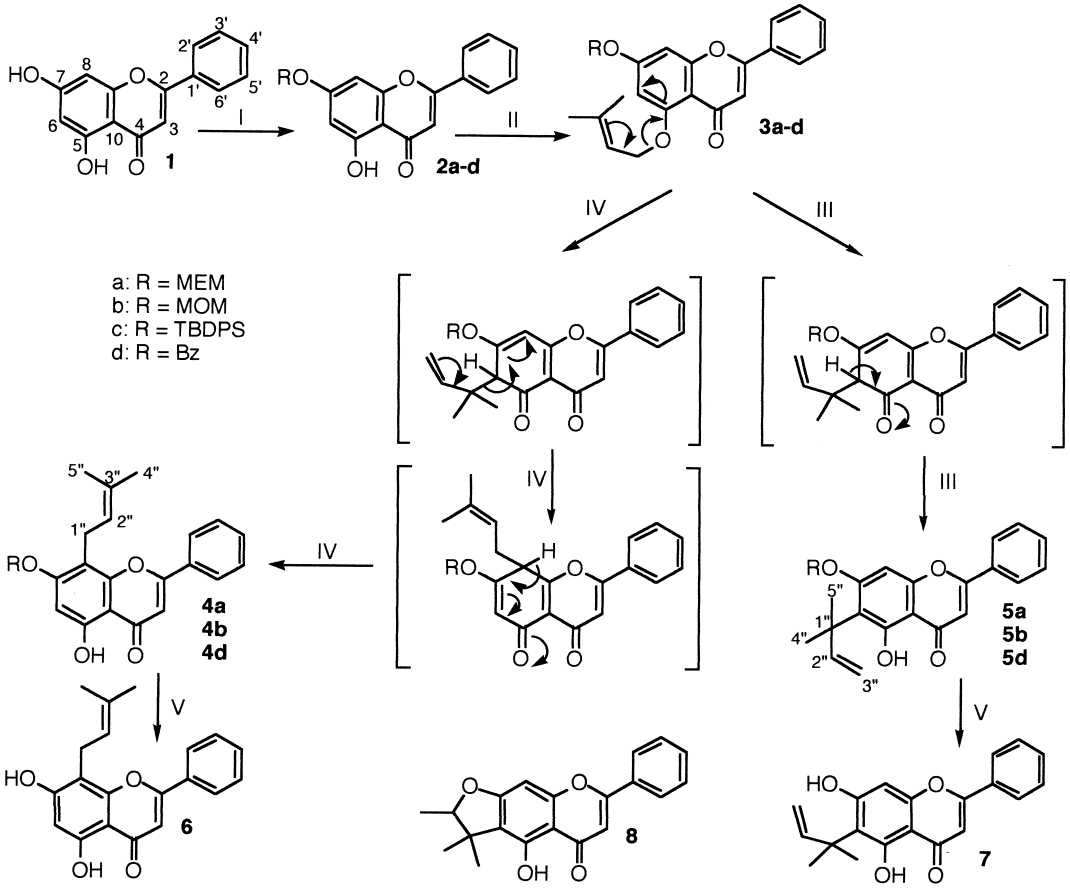

Figure 1. The regioselective syntheses of 6-(1,1-dimethylallyl)- and 8-(3,3-dimethylallyl)- chrysins. **2a**, **3a** and **5a**: see Ref. 9; **2b**: MOM-Cl, *i*Pr_2Net, DMF, 81%; **2c**: TBDPS-Cl, imidazole, DMF, 79%; **2d**: Bz-Cl, *i*Pr_2Net, DMF, 100%; **3b**: Pr-Br, tetrabutylammonium hydroxide, toluene/CH_2Cl_2, 67%; **3c**: Pr-Br, NaH, tetrabutylammonium bromide, toluene/CH_2Cl_2, 43%; **3d**: Pr-Br, tetrabutylammonium hydroxide, toluene/CH_2Cl_2, 75%; **4a**: *N*,*N*-diethylaniline, 217°, 93%; **4b**: *N*,*N*-diethylaniline, 200°, 63%; **5b**: *N*,*N*-diethylbutylamine, 140°, 31%; **5d**: cyclooctane, Eu(fod)$_3$, 100°, 71%; **6–8**: see Section 3.

chrysin **5a**[9] was selectively obtained in 81% yield. Whereas removal of the MEM ether as present in **4a** was achieved in 45% yield with refluxing methanolic HCl, it failed to give compound **7** after similar treatment of **5a**. Therefore we replaced the MEM group by the slightly less stable methoxymethyl (MOM) protecting group. Protection of chrysin at position 7 followed by prenylation at position 5 furnished 7-MOM chrysin **2b** and 7-MOM-5-prenyl chrysin **3b** in 81 and 67% yields, respectively. 8-(3,3-Dimethylallyl)-7-MOM chrysin **4b** was prepared in 35% yield by rearrangement of **3b** in *N*,*N*-diethylaniline at 217°C. However, the yield in **4b** was raised to 63% when the same reaction was carried out at 200°. Rearrangement of **3b** in *N*,*N*-diethylbutylamine at 160°C for 36 h yielded the 1,1-dimethylallyl isomer **5b** in very poor yield, while the cyclic compound **8** was present as well. This demonstrated the instability of the MOM group at such temperature conditions. When the same rearrangement was carried out at 140°C for 48 h, no cyclized product was formed and the yield in **5b** reached 31%. However, most of the starting 7-MOM-5-prenyl chrysin **3b** remained unreacted. Deprotection of **4b** in methanolic HCl yielded 8-prenyl chrysin **6** in excellent yield (96%). Furthermore, deprotection of **5b**, in mild acidic conditions and at room temperature did result in the formation of 6-(1,1-dimethylallyl) chrysin **7** in 55% yield. Third we investigated the interest of *t*-butyldiphenylsilyl (TBDPS) as protective group. Protection of chrysin with *t*-butyldiphenylsilyl chloride resulted in the formation of **2c** in 79% yield. In the subsequent prenylation of the 5-hydroxyl, only strictly anhydrous conditions were compatible with the stability of the 7-TBDPS group. Therefore NaH was used as a base in replacement of tetrabutylammonium hydroxide 30 hydrate. The resulting 5-*O*-prenyl derivative **3c**, however, was found to extensively degrade during chromatographic purification. Thus, the three steps, prenylation, microwave rearrangement and deprotection, were performed on line without isolation of the intermediates. Quantitative HPLC analysis demonstrated that 6-(1,1-dimethylallyl) chrysin **7** and 8-(3,3-dimethylallyl) chrysin **6** were formed in 43 and 34% yields from **2c**, respectively. The last protective group that we have investigated was the benzoyl (Bz) group. 7-Benzoyl chrysin **2d** was synthesized in quantitative yield by esterification of chrysin **1** with benzoyl chloride in presence of *N*,*N*-diisopropylethylamine as a base. The good stability of the benzoyl group in cold alkaline conditions allowed 5-*O*-prenylation of **2d** by 3,3-dimethylallyl bromide in presence of tetrabutylammonium hydroxide. This resulted in the formation of 7-benzoyl-5-prenyl chrysin **3d** in 75% yield. When **3d** was refluxed in *N*,*N*-diethylbutylamine, *ortho* rearrangement of the 5-*O*-prenyl chain indeed took place but the cyclic compound **8** was formed instead of the desired 6-(1,1-dimethylallyl) product **5d**, probably due to extensive removal of the benzoyl group, followed by cyclization of the

6-(1,1-dimethylallyl) chain with the 7-hydroxyl. Since no selective access to the 6-(1,1-dimethylallyl) isomer was expected by microwave irradiation, we decided to switch directly to totally different conditions, involving the use of a nitrogen-free solvent. Heating **3d** at 150°C in cyclooctane resulted in elimination of the 5-*O*-prenyl with no rearrangement and 7-benzoyl-chrysin **2d** was the sole product of the reaction. Similar treatment of **3d** in cycloheptane at 120°C induced the formation of traces of rearranged products but still, extensive formation of **2d** was taking place. On the contrary, catalysis of the same reaction by europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate) [Eu(fod)$_3$] allowed complete rearrangement with no formation of **2d**. However, a mixture of 8-(3,3-dimethylallyl)-7-benzoyl chrysin **4d** and of 6-(1,1-dimethylallyl)-7-benzoyl chrysin **5d** was produced. This was in accordance with a previous study[6] reporting the formation of a 1.2:1 mixture of 7-acetyl-8-(3,3-dimethylallyl)- and 7-acetyl-6-(1,1-dimethylallyl) naringenins by europium-catalyzed rearrangement of 7-acetyl-5-prenyl naringenin. Since compound **5d** is believed to represent a product of incomplete reaction during the synthesis of **4d**,[9] it was therefore expected that the use of milder rearrangement conditions would result in increased production of **5d**, as previously shown in the microwave-induced rearrangement of 7-MEM-5-prenyl chrysin **3a**.[9] In fact, rearrangement of **3d** in cyclooctane plus 10% of Eu(fod)$_3$ at 100°C, resulted in the regioselective preparation of 7-benzoyl-6-(1,1-dimethylallyl) chrysin **5d** in 71% yield. Finally, 6-(1,1-Dimethylallyl) chrysin **7** was easily prepared by saponification of **5d** in 5% methanolic KOH. Compounds have been fully characterized on the basis of their elemental analyses, HRMS, ^{1}H- and ^{13}C NMR spectroscopic properties. Detailed structural evidence for MEM derivatives **2a**–**5a** has been published in a previous paper.[9] Evidence for 5-*O*-prenylation was based on the chemical shifts of the atoms at position 1″ of the prenyl chain in compounds **3b** (H-1″: 4.67 ppm; C-1″: 68.04 ppm), **3c** (H-1″: 4.27 ppm; C-1″: 66.19 ppm) and **3d** (H-1″: 4.73 ppm; C-1″: 66.86 ppm). Furthermore, strong ^3J correlations were observed between H-1″ and C-5 in the HMBC spectra of compounds **3c** and **3d**. Again, evidence for 8-C-prenylation was based on the chemical shifts of the atoms at position 1″ of the prenyl chain and at position 8 of ring-A in compounds **4b** (H-1″: 3.60 ppm; C-1″: 23.58 ppm; C-8: 110.53) and **4d** (H-1″: 3.54 ppm; C-1″: 22.94 ppm; C-8: 113.26). In addition, in the HMBC spectrum of compound **4d**, H-1″ was strongly correlated with C-7, C-8 and C-9. This data is in accordance with that previously collected for the corresponding 5-*O*-prenyl-, and 8-*C*-prenyl MEM chrysins.[9] All 6-substituted derivatives displayed characteristic proton and carbon signals for a 1,1-dimethylallyl chain:[8b] compound **5b** (H-2″: 6.30, dd, J=17.6 and 10.6 Hz; H-3″: 4.84, d, J=10.6 Hz; H-3″: 4.88, d, J=17.6 Hz; H-4″/5″: 1.63, s; C-1″: 41.39; C-2″:150.54; C-3″: 106.91; C-4″/5″: 29.02); compound **5d** (H-2″: 6.23, dd, J=17.3 and 10.6 Hz; H-3″: 4.59, dd, J=10.6 and 1.1 Hz; H-3″: 4.81, dd, J=17.3 and 1.1 Hz; H-4″/5″: 1.62, s; C-1″: 41.30; C-2″:148.51; C-3″: 108.02; C-4″/5″: 27.76); compound **7** (H-2″: 6.37, dd, J=17.7 and 10.6 Hz; H-3″: 4.87, dd, J=10.6 and 1.1 Hz; H-3″: 4.96, dd, J=17.7 and 1.1 Hz; H-4″/5″: 1.63, s; C-1″: 42.76; C-2″:151.69; C-3″: 109.75; C-4″/5″: 30.17). No correlation was observed between the 1,1-dimethylallyl chain and the aromatic ring on the HMBC spectra of **5d** and **7**. Therefore this time evidence for 6-substitution was rather based on the presence of a proton at position 8 of ring-A. In fact, in the HMBC spectra of both compounds, this proton was correlated with C-7, C-9 and C-6, but not with C-5, in accordance with previous data[9] related to 6-(1,1-dimethylallyl)-7-MEM chrysin **5a**. In conclusion, the importance of the experimental conditions in the success of Claisen rearrangements of prenyl chrysins has been emphasized. Variation of the temperature of the rearrangement by only few degrees resulted in either incomplete reaction, or destruction of the products. A compromise had to be found between the conditions for stability of the protective groups, and those for appreciable rearrangement. Optimum conditions obviously vary in function of the nature of the protecting groups, but we also got evidence that they may equally depend on the nature of the flavonoid basic skeleton. In fact, best temperature and solvent conditions for the europium (III)-catalyzed rearrangement of 5-*O*-prenyl chrysins were appreciably different (cycloheptane, 100°C) from those previously reported for the rearrangement of 5-*O*-prenyl naringenin[6] ($CHCl_3$, 40 or 60°C). The best protective group was, by far, the benzoyl group which is compatible with the basic conditions used for 5-*O*-prenylation and could be subsequently easily eliminated. The other protecting groups are either too stable to deprotection (MEM), or too unstable in the conditions of the rearrangements (MOM, TBDPS). Finally, while the previous approach[6] of europium (III) rearrangement catalysis failed to specifically produce the 6-(1,1-dimethylallyl) compound, we have now reported the first preparations of 7-benzoyl-6-(1,1-dimethylallyl) chrysin, and its corresponding unprotected analogue with good regioselectivity.

3. Experimental

3.1. General

N,*N*-Dimethylaniline and *N*,*N*-diethylaniline were distilled from CaH_2 before use. Microwave irradiation was carried out in a domestic Bluewind 1797 oven. Quantitative HPLC analyses were performed at a flow rate of 1 ml/min on 250×4.6 analytical columns packed with Merck Lichrospher® 100DIOL 5 μm. Medium pressure liquid chromatographic (MPLC) and vacuum liquid chromatographic (VLC) separations were carried out either on Merck Silica gel Si 60 (40–63 μm), or on Lichroprep® Diol (40–63 μm) as supports. Attribution of signals in NMR spectroscopy was made after analysis of direct and long distance ^{13}C–^{1}H 2D correlation spectra. Furthermore attribution of the 4″- and 5″-Me signals of the prenyl chain was carried out with the aid of NOE difference experiments (irradiation of H-2″). Chemical ionization mass spectra were recorded in the positive mode, on a Finnigan MAT95XL apparatus, and using isobutane as gas reagent.

3.2. MEM Protective group

3.2.1. 7-MEM chrysin 2a.[9] Pale yellow crystals, mp 90–93°C. UV/Vis (MeOH): λ_{max} (nm)=305sh, 268. Preparation, ^{1}H NMR, ^{13}C NMR, MS, HRMS, Anal: see Ref. 9.

3.2.2. 7-MEM-5-prenyl chrysin 3a.[9] White crystals, mp 90°C. UV/Vis (MeOH): λ_{max} (nm)=297, 264. Preparation, ^{1}H NMR, ^{13}C NMR, MS, HRMS, Anal: see Ref. 9.

3.2.3. 8-(3,3-Dimethylallyl)-7-MEM chrysin 4a.[9] 1 g of compound **3a** (2.44 mmol) and 10 ml of freshly distilled *N*,*N*-diethylaniline were heated at 217°C (oil bath) for 4 h under stirring. The reaction medium was diluted with 20% aqueous HCl and extracted with ethyl acetate. Evaporation of the solvent yielded 0.93 g (2.27 mmol, 93%) of 8-(3,3-dimethylallyl)-7-MEM chrysin **4a**.[9] Yellow crystals, mp 120–122°C. UV/Vis (MeOH): λ_{max} (nm)=315sh, 274. ^{1}H NMR, ^{13}C NMR, MS, HRMS, Anal: Ref. 9.

3.2.4. 8-(3,3-Dimethylallyl) chrysin 6[1] **from 4a.** 40 mg (0.10 mmol) of compound **4a** were dissolved in 5 ml of methanol plus 1 ml of 1N HCl. The solution was refluxed for 1 h. After dilution with water the medium was extracted with ethyl acetate and the extract purified by MPLC on silica using a gradient of ethyl acetate in hexane as solvent. This yielded 14.5 mg (0.045 mmol, 45%) of 8-(3,3-dimethylallyl)-chrysin **7**.[1] Yellow crystals, mp 206–211°C. UV, ^{1}H NMR, ^{13}C NMR, MS, HRMS, Anal: Ref. 1.

3.2.5. 6-(1,1-Dimethylallyl)-7-MEM chrysin 5a.[9] 0.2 g of **3a** and 5 ml of *N*,*N*-diethylbutylamine were refluxed for 72 h under stirring. After dilution with water and acidification (1N HCl), the medium was extracted with ethyl acetate. Quantitative HPLC analysis (diol-bonded silica using 0.5% isopropanol in hexane as solvent) of the extract demonstrated the formation of 81% of 6-(1,1-dimethylallyl)-7-MEM chrysin **5a**.[9] Yellow crystals, mp 94–100°C. UV/Vis (MeOH): λ_{max} (nm)=312, 274, 247. ^{1}H NMR, ^{13}C NMR, MS, HRMS, Anal: see Ref. 9.

3.3. MOM Protective group

3.3.1. 7-MOM chrysin 2b. A solution of 4 g of chrysin (15.7 mmol) in 100 ml of dry DMF was cooled to 0°C (ice bath). To this 5.5 ml of *N*,*N*-diisopropylethylamine (31.6 mmol, 2 equiv.) and 2.4 ml of chloromethyl methyl ether (31.6 mmol, 2 equiv.) were successively added dropwise. After complete addition of the reagents reaction was allowed to take place at room temperature for 1 h. Water dilution of the medium gave rise to a precipitate which was crystallized in ethanol, to give 3.8 g (81%) of pure **2b**. Pale yellow crystals, mp 133°C. UV/Vis (MeOH): λ_{max} (nm)=307sh, 268. ^{1}H NMR (acetone-d_6, 300 MHz): δ 12.84 (s, 5-OH), 8.08 (m, H-2′/6′), 7.60 (m, H-3′/4′/5′), 6.83 (s, H-3), 6.79 (d, J=2.2 Hz, H-8), 6.43 (d, J=2.2 Hz, H-6), 5.34 (s, H-1‴), 3.49 (s, H-2‴). ^{13}C NMR (acetone-d_6, 75.5 MHz): δ 184.34 (C-4), 166.03 (C-2), 165.22 (C-7), 163.99 (C-5), 159.55 (C-9), 133.84 (C-4′), 133.14 (C-1′), 131.02 (C-3′/5′), 128.32 (C-2′/6′), 107.76 (C-10), 107.33 (C-3), 101.46 (C-6), 96.33 (C-8), 96.15 (C1‴), 57.58 (C-2‴). MS (CI) *m*/*z*: 299 (M+H$^+$). HRMS (CI): *m*/*z* calcd for $C_{17}H_{15}O_5$, 299.0919, found 299.0919. Anal. calcd for $C_{17}H_{14}O_5$+0.3 acetone: C, 68.10; H, 5.04. Found C, 67.80; H, 4.87.

3.3.2. 7-MOM-5-*O*-prenyl chrysin 3b. 1 g of **2b** (3.3 mmol) was dissolved in a mixture of 15 ml of methylene chloride and 10 ml of toluene. 5.3 g (6.7 mmol, 2 equiv.) of tetrabutylammonium hydroxide 30 hydrate were added under stirring, and after complete dissolution of the solid, 0.6 ml (5 mmol, 1.5 equiv.) of prenyl bromide were further added. After 45 min reaction under stirring at room temperature, the medium was diluted with water, acidified (1N HCl) and extracted with ethyl acetate. After evaporation of the extract the residue was taken in minimum acetone and hexane was added dropwise until the solution starts to get cloudy. Leaving the solution overnight at 4°C led to the crystallisation of 0.82 g (67%) of pure **3b**. White crystals, mp 124–126°C. UV/Vis (MeOH): λ_{max} (nm)=310sh, 264. ^{1}H NMR (acetone-d_6, 300 MHz): δ 8.02 (m, H-2′/6′), 7.57 (m, H-3′/4′/5′), 6.86 (d, J=2.3 Hz, H-8), 6.60 (s, H-3), 6.59 (d, J=2.3 Hz, H-6), 5.53 (brt, J=6.4 Hz, H-2″), 5.35 (s, H-1‴), 4.67 (d, J=6.4 Hz, H-1″), 3.49 (s, H-2‴), 1.78 (brs, H-4″/5″). ^{13}C NMR (acetone-d_6, 75.5 MHz): δ 177.27 (C-4), 163.37 (C-7), 162.02 (C-2), 161.87 (C-5), 161.34 (C-9), 138.67 (C-2″), 133.58 (C-1′), 132.98 (C-4′), 130.87 (C-3′/5′), 127.78 (C-2′/6′), 121.86 (C-2″), 111.89 (C-10), 110.41 (C-3), 100.53 (C-6), 97.59 (C-8), 96.18 (C-1‴), 68.04 (C-1″), 57.56 (C-2‴), 26.82 (C-4″), 19.33 (C-5″). MS (CI) *m*/*z*: 367 (M+H$^+$), 299 (M+H−$C_5H_8$$^+$). HRMS (CI): *m*/*z* calcd for $C_{22}H_{23}O_5$, 367.1545, found 367.1546. Anal. calcd for $C_{22}H_{22}O_5$+0.3 ethyl acetate: C, 70.93; H, 6.26. Found C, 70.91; H, 5.95.

3.3.3. Rearrangements of 3b in diethylaniline. 0.72 g (1.97 mmol) of **3b** in 45 ml of freshly distilled *N*,*N*-diethylaniline were heated under argon in an oil bath at 217°C for 3 h under stirring. The medium was diluted with water, acidified (1N HCl) and extracted with ethyl acetate. Purification of the extract by MPLC on diol-bonded silica using a gradient of ethyl acetate in hexane as solvent resulted in the isolation of 0.25 g (0.68 mmol, 35%) of 8-(3,3-dimethylallyl)-7-MOM-chrysin **4b**. Similar reaction of 0.4 g of **3b** (1.09 mmol) in 25 ml of freshly distilled *N*,*N*-diethylaniline for 4.5 h at 200°C, yielded after same work up of the reaction as above, 253 mg (63%) of **4b**.

3.3.4. Rearrangements of 3b in diethylbutylamine. 162 mg (0.44 mmol) of **3b** in 3.5 ml of *N*,*N*-diethylbutylamine were immersed in an oil bath at 160°C and stirred for 36 h under argon. The medium was diluted with water, acidified (1N HCl), extracted with ethyl acetate and the extract purified by MPLC on diol using hexane as solvent. This led to the isolation of 5.5 mg of **5b** (0.015 mmol, 3.4%) and 6.8 mg of **8** (0.021 mmol, 4.8%). In a subsequent experiment 500 mg (1.3 mmol) of **3b** in 9 ml of *N*,*N*-diethylbutylamine were immersed in an oil bath at 140°C and stirred for 48 h under argon. Similar treatment of the medium and purification of the extract by MPLC on diol using a gradient of ethyl acetate in hexane as solvent furnished 131 mg of **5b** (0.4 mmol, 31%) and 302 mg of unreacted **3b** (0.8 mmol, 62%).

3.3.5. 8-(3,3-Dimethylallyl)-7-MOM chrysin 4b. Pale yellow crystals, mp 150.6–152°C. UV/Vis (MeOH): λ_{max} (nm)=274. ^{1}H NMR (acetone-d_6, 300 MHz): δ 12.85 (s, 5-OH), 8.09 (m, H-2′/6′), 7.62 (m, H-3′/4′/5′), 6.81 (s, H-6), 6.58 (s, H-3), 5.38 (s, H-1‴), 5.27 (brt, J=7.0 Hz H-2″), 3.60 (d, J=7.0 Hz, H-1″), 3.49 (s, H-2‴), 1.83 (s, H-5″), 1.66 (s, H-4″). ^{13}C NMR (Acetone-d_6, 75 MHz) δ 184.71

(C-4), 165.97 (C-2), 162.47 (C-7), 162.17 (C-5), 156.37 (C-9), 133.81 (C-4′), 133.53 (C-3″), 133.35 (C-1′), 131.07 (C-3′/5′), 128.32 (C-2′/6′), 124.25 (C-2″), 110.53 (C-8), 107.37 (C-10), 107.05 (C-3), 99.53 (C-6), 96.19 (C-1‴), 57.58 (C-2‴), 26.82 (C-4″), 23.58 (C-1″), 19.09 (C-5″). MS (CI) *m/z*: 367 ($M+H^+$). HRMS (CI): *m/z* calcd for $C_{22}H_{23}O_5$, 367.1545, found 367.1549. Anal. calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found C, 71.76; H, 5.98.

3.3.6. 6-(1,1-Dimethylallyl)-7-MOM chrysin 5b. Yellow crystals, mp 102–104°C. UV/Vis (MeOH): λ_{max} (nm)=314, 275, 249. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.60 (s, 5-OH), 7.90 (m, H-2′/6′), 7.53 (m, H-3′/4′/5′), 6.76 (s, H-8), 6.67 (s, H-3), 6.30 (dd, *J*=17.6 and 10.6 Hz, H-2″), 5.21 (s, H-1‴), 4.88 (d, *J*=17.6 Hz, H-3″), 4.84 (d, *J*=10.6 Hz, H-3″), 3.51 (s, H-2‴), 1.63 (s, H-4″/5″). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 183.01 (C-4), 163.43 (C-2), 162.32 (C-7), 160.89 (C-5), 156.02 (C-9), 150.54 (C-2″), 131.76 (C-4′), 131.21 (C-1′), 129.05 (C-3′/5′), 126.25 (C-2′/6′), 118.48 (C-6), 106.91 (C-3″), 106.31 (C-10), 105.82 (C-3), 94.14 (C-8), 93.21 (C-1‴), 56.60 (C-2‴), 41.39 (C-1″), 29.02 (C-4″/5″). MS (CI) *m/z*: 367 ($M+H^+$). HRMS (CI): *m/z* calcd for $C_{22}H_{23}O_5$, 367.1545, found 367.1543. Anal. calcd for $C_{22}H_{22}O_5$+0.1 hexane: C, 72.38; H, 6.29. Found C, 72.43; H, 6.39.

3.3.7. Deprotection of 8-(3,3-dimethylallyl)-7-MOM chrysin 4b. 0.1 g of **4b** were dissolved in 40 ml of methanol and 8 ml of 1N HCl and the solution refluxed for 90 min. HPLC quantification (diol-bonded silica, gradient from 1 to 10% of isopropanol in hexane in 20 min) of the medium demonstrated that 8-(3,3-dimethylallyl)-chrysin **6**[1] was produced in 96% yield.

3.3.8. Deprotection of 6-(1,1-dimethylallyl)-7-MOM chrysin 5b. 82 mg (0.22 mmol) of compound **5b** in 5 ml of 3% ethanolic HCl were stirred at room temperature for 7 days. The medium was diluted with water, extracted with ethyl acetate and the extract purified by VLC on diol-bonded silica using 10% $CHCl_3$ in hexane as solvent. This yielded 40 mg (0.12 mmol, 55%) of 6-(1,1-dimethylallyl) chrysin **7**.

3.4. TBDPS Protective group

3.4.1. 7-TBDPS chrysin 2c. To a solution of 4 g chrysin (15.7 mmol) in 70 ml of dry DMF were added 4.7 g of imidazole (69.2 mmol, 4.4 equiv.) and 9 ml of *t*-butyl chlorodiphenylsilane (34.6 mmol, 2;2 equiv.). After 2 h reaction at 50°C, the medium was diluted with water, acidified (1N HCl) and extracted with ethyl acetate. Purification of the extract by MPLC on diol bonded silica using a gradient of methylene chloride in hexane as solvent, yielded 6.1 g (12.4 mmol, 79%) of pure **2c**. Pale yellow crystals, mp 118–119°C. UV/Vis (MeOH): λ_{max} (nm)=306, 269. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.60 (s, 5-OH), 7.80 (dd, *J*=7.5 and 1.5 Hz, H-2′/6′), 7.73 (dd, *J*=8.3 and 1.9 Hz, H-2‴/6‴), 7.49 (m, H-3′/4′/5′), 7.42 (m, H-3‴/4‴/5‴), 6.62 (s, H-3), 6.37 (d, *J*=2.0 Hz, H-8), 6.26 (d, *J*=2.0 Hz, H-6), 1.12 (s, 3×Me-Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 182.53 (C-4), 163.95 (C-2), 162.03 (C-7), 161.85 (C-5), 157.40 (C-9), 135.37 (C-2‴/6‴), 131.75 (C-4′+C-1‴), 131.31 (C-1′), 130.32 (C-4‴), 129.01 (C-3′/5′), 128.02 (C-3‴/5‴), 126.29 (C-2′/6′), 106.17 (C-10), 105.82 (C-3), 103.99 (C-6), 98.67 (C-8), 26.35 (3×Me-Si), 19.47 (C–Si). MS (CI) *m/z*: 493 ($M+H^+$). HRMS (CI): *m/z* calcd for $C_{31}H_{29}O_4Si$, 493.1835, found 493.1841. Anal. calcd for $C_{31}H_{28}O_4Si$+0.1 CH_2Cl_2: C, 74.54; H, 5.61. Found C, 74.60; H, 5.67.

3.4.2. 7-TBDPS-5-*O*-prenyl chrysin 3c. The reaction was carried out at 0°C (ice bath) until complete addition of all the reagents. To a solution of 100 mg of **2c** (0.2 mmol) in 15 ml of CH_2Cl_2 plus 10 ml of toluene were added 65 mg of tetrabutylammonium bromide (0.2 mmol, 1 equiv.), 8 mg of NaH (60% dispersion in mineral oil, 0.3 mmol, 1 equiv.) and 24 μl of prenyl bromide (0.2 mmol, 1 equiv.), successively, under stirring. The reaction was allowed to proceed at room temperature for 90 min under stirring. The medium was diluted with water, extracted with ethyl acetate, and the extract submitted to a MPLC on diol-bonded silica using a gradient of CH_2Cl_2 in hexane as solvent. This afforded 48 mg (0.086 mmol, 43%) of compound **3c**. Orange oil. UV/Vis (MeOH): λ_{max} (nm)=310sh, 265. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (m, H-2′/6′), 7.74 (m, H-2‴/6‴), 7.47 (m, H-3′/4′/5′), 7.41 (m, H-3‴/4‴/5‴), 6.59 (s, H-3), 6.54 (d, *J*=2.0 Hz, H-8), 6.14 (d, *J*=2.0 Hz, H-6), 5.35 (brt, *J*=6.4 Hz, H-2″), 4.27 (d, *J*=6.4 Hz, H-1″), 1.69 (brs, H-4″), 1.58 (brs, H-5″), 1.15 (s, 3×Me-Si). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 177.54 (C-4), 160.49 (C-7*), 160.25 (C-2*), 159.84 (C-5), 159.33 (C-9), 137.17 (C-3″), 135.39 (C-2‴/6‴), 131.98 (C-1‴), 131.63 (C-1′), 131.01 (C-4′), 130.32 (C-4‴), 128.82 (C-3′/5′), 128.02 (C-3‴/5‴), 125.93 (C-2′/6′), 119.30 (C-2″), 109.85 (C-10), 108.82 (C-3), 101.73 (C-6), 100.33 (C-8), 66.19 (C-1″), 26.40 (3×Me-Si), 25.66 (C-4″), 19.50 (C–Si), 18.22 (C-5″). MS (CI) *m/z*: 561 ($M+H^+$), 493 ($M+H-C_5H_8^+$). HRMS (CI): *m/z* calcd for $C_{36}H_{37}O_4Si$, 561.2461, found 561.2467. Anal. calcd for $C_{36}H_{36}O_4Si$+0.9 hexane+0.1 $CHCl_3$: C, 76.65; H, 7.55. Found C, 76.85; H, 7.27.

3.4.3. Microwave rearrangement of 3c. 100 mg of 7-TBDPS-chrysin **2c** were prenylated as described above. The ethyl acetate extract, however, was not purified. The dry residue was directly dissolved in 4 ml of *N*,*N*-dimethylaniline and introduced in a well-stoppered 10 ml teflon bottle. The bottle was submitted to successive 15 min microwave irradiations at 570 W (15 min pause between two irradiations). Total irradiation time was 4.5 h (or until complete consumption of **2c**). The medium, after water dilution and acidification (1N HCl) was extracted with ethyl acetate. After evaporation of the solvent, the residue was dissolved in 10 ml of THF, 56 mg of tetrabutylammonium fluoride were added and reaction was allowed to take place under stirring for 0.5 h. The reaction medium was diluted with water, acidified (1N HCl) and extracted with ethyl acetate. Quantification of the reaction products by HPLC on diol-bonded silica using a gradient of isopropanol in hexane (from 1 to 15% in 30 min), demonstrated the formation of 8-(3,3-dimethylallyl) chrysin **6** and 6-(1,1-dimethylallyl) chrysin **7** in 34 and 43% yields, respectively.

3.5. Benzoyl protective group

3.5.1. 7-Benzoyl chrysin 2d. To a solution of 1 g chrysin (3.9 mmol) in 20 ml of dry DMF were added 2 ml of

N,*N*-diisopropylethylamine (11.7 mmol, 3 equiv.) dropwise at 0°C. After 15 min, 0.6 ml of benzoyl chloride (5.2 mmol, 1.3 equiv.) were added dropwise, still at 0°C. Reaction was allowed to take place at room temperature for 1 h. Dilution of the medium with water resulted in the formation of a bulky precipitate which was isolated by filtration and washed with cold ethanol. Yield: 1.4 g (3.9 mmol, 100%). White solid, mp 191.5–192°C. UV/Vis (MeOH): λ_{max} (nm)=300sh, 269, 228. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.78 (s, 5-OH), 8.22 (m, H-2‴/6‴), 7.91 (m, H-2′/6′), 7.69 (brt, J=7.5 Hz, H-4‴), 7.56 (m, H-3′/4′/5′ and H-3‴/5‴), 7.01 (d, J=1.9 Hz, H-8), 6.77 (s, H-3), 6.72 (d, J=1.9 Hz, H-6). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 182.89 (C-4), 164.71 (C-2), 164.18 (C-7‴), 161.97 (C-5), 156.80 (C-9), 156.29 (C-7), 134.07 (C-4‴), 132.15 (C-4′), 130.96 (C-1′), 130.32 (C-2‴/6‴), 129.17 (C-3′/5′), 128.80 (C-1‴), 128.72 (C-3‴/5‴), 126.40 (C-2′/6′), 108.98 (C-10), 106.14 (C-3), 105.68 (C-6), 101.19 (C-8). MS (CI) *m*/*z*: 359 ($M+H^+$). HRMS (CI): *m*/*z* calcd for $C_{22}H_{15}O_5$, 359.0919, found 359.0911. Anal. calcd for $C_{22}H_{14}O_5$: C, 73.74; H, 3.94. Found C, 73.66; H, 3.95.

3.5.2. 7-Benzoyl-5-*O*-prenyl chrysin 3d. 1 g (2.8 mmol) of 7-benzoyl-chrysin **2d** was dissolved in a mixture of 45 ml of CH_2Cl_2 and 30 ml of toluene. The solution was cooled to 0°C (ice bath) and 4.5 g (5.6 mmol, 2 equiv.) of tetrabutylammonium hydroxide 30 hydrate, followed by 0.7 ml (6 mmol, 2 equiv.) of prenyl bromide were added under stirring. After addition of all the reagents, the reaction was allowed to take place at room temperature for 2 h under stirring. The organic layer was washed with water and evaporated. The residue was taken in a minimum amount of acetone and diluted with hexane until the solution turned slightly cloudy. Overnight crystallization at 4°C led to the isolation of 0.88 g (2.1 mmol, 75%) of **3d**. Cream crystals, mp 133–140°C. UV/Vis (MeOH): λ_{max} (nm)=319, 295sh, 264. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.23 (m, H-2‴/6‴), 7.88 (m, H-2′/6′), 7.69 (brt, J=7.5 Hz, H-4‴), 7.54 (m, H-3′/4′/5′ and H-3‴/5‴), 7.11 (d, J=2.3 Hz, H-8), 6.73 (d, J=2.3 Hz, H-6), 6.72 (s, H-3), 5.61 (brt, J=6.4 Hz, H-2″), 4.73 (d, J=6.4 Hz, H-1″), 1.80 (brs, H-4″), 1.76 (brs, H-5″). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 177.37 (C-4), 164.26 (C-7‴), 161.04 (C-2), 160.10 (C-5), 158.69 (C-9), 154.73 (C-7), 138.12 (C-3″), 134.07 (C-4‴), 131.32 (C-1′ and C-4′), 130.28 (C-2‴/6‴), 128.94 (C-3′/5′), 128.85 (C-1‴), 128.73 (C-3‴/5‴), 126.02 (C-2′/6′), 118.98 (C-2″), 113.00 (C-10), 109.18 (C-3), 103.24 (C-8), 102.69 (C-6), 66.86 (C-1″), 25.80 (C-4″), 18.41 (C-5″). MS (CI) *m*/*z*: 427 ($M+H^+$), 359 ($M+H-C_5H_8^+$). HRMS (CI): *m*/*z* calcd for $C_{27}H_{23}O_5$, 427.1545, found 427.1548. Anal. calcd for $C_{27}H_{22}O_5$: C, 76.04; H, 5.20. Found C, 75.84; H, 5.28.

3.5.3. Rearrangement of 3d in *N*,*N*-diethylbutylamine. 200 mg of **3d** (0.47 mmol) were refluxed in 5 ml of *N*,*N*-diethylbutylamine (oil bath at 160°C) for 3 days. The medium was diluted with water, acidified (1N HCl) and extracted with ethyl acetate. Purification of the extract by VLC on diol-bonded silica, using 5% $CHCl_3$ in hexane as solvent, afforded 74 mg of compound **8** (0.23 mmol, 49%).

3.5.4. Eu(fod)$_3$ catalyzed rearrangement of 3d. 204 mg (0.48 mmol) of compound **3d** plus 50 mg (0.048 mmol) of $Eu(fod)_3$ were suspended in 10 ml of cycloheptane and the mixture heated at 100°C for 4 h. Purification of the medium by MPLC on diol-bonded silica using a gradient of $CHCl_3$ in hexane as solvent led to the isolation of 31 mg (0.07 mmol, 15%) of 8-(3,3-dimethylallyl)-7-benzoyl chrysin **4d**, and of 145 mg (0.34 mmol, 71%) of 6-(1,1-dimethylallyl)-7-benzoyl chrysin **5d**.

3.5.5. 7-Benzoyl-8-(3,3-dimethylallyl) chrysin 4d. Pale yellow crystals, mp 184.8–185°C. UV/Vis (MeOH): λ_{max} (nm)=335, 272. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.67 (s, 5-OH), 8.22 (m, H-2‴/6‴), 7.90 (m, H-2′/6′), 7.68 (brt, J=7.5 Hz, H-4‴), 7.54 (m, H-3′/4′/5′ and H-3‴/5‴), 6.77 (s, H-3), 6.69 (s, H-6), 5.20 (brt, J=6.0 Hz, H-2″), 3.54 (d, J=6.0 Hz, H-1″), 1.61 (brs, H-4″), 1.59 (brs, H-5″). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 183.33 (C-4), 164.53 (C-7‴), 164.27 (C-2), 159.51 (C-5), 154.81 (C-9), 154.61 (C-7), 133.97 (C-4‴), 132.68 (C-3″), 132.06 (C-4′), 131.36 (C-1′), 130.33 (C-2‴/6‴), 129.18 (C-3′/5′), 128.80 (C-1‴), 128.68 (C-3‴/5‴), 126.42 (C-2′/6′), 121.40 (C-2″), 113.26 (C-8), 109.43 (C-10), 106.49 (C-6), 106.10 (C-3), 25.58 (C-4″), 22.94 (C-1″), 17.98 (C-5″). MS (CI) *m*/*z*: 426 (M^+). HRMS (CI): *m*/*z* calcd for $C_{27}H_{22}O_5$, 426.1467, found 426.1464. Anal. calcd for $C_{27}H_{22}O_5$+0.1 hexane: C, 76.19; H, 5.42. Found C, 76.33; H, 5.66.

3.5.6. 7-Benzoyl-6-(1,1-dimethylallyl) chrysin 5d. Pale yellow crystals, mp 138–139°C. UV/Vis (MeOH): λ_{max} (nm)=340, 307sh, 274, 231. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.85 (s, 5-OH), 8.15 (m, H-2‴/6‴), 7.88 (m, H-2′/6′), 7.66 (brt, J=7.5 Hz, H-4‴), 7.53 (m, H-3′/4′/5′ and H-3‴/5‴), 6.75 (H-8), 6.74 (H-3), 6.23 (dd, J=17.3 and 10.6 Hz, H-2″), 4.81 (dd, J=17.3 and 1.1 Hz, H-3″), 4.59 (dd, J=10.6 and 1.1 Hz, H-3″), 1.62 (s, H-4″/5″). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 183.50 (C-4), 164.90 (C-7‴), 164.24 (C-2), 161.96 (C-5), 154.89 (C-9), 154.56 (C-7), 148.51 (C-2″), 133.75 (C-4‴), 132.07 (C-4′), 130.96 (C-1′), 130.39 (C-2‴/6‴), 129.34 (C-1‴), 129.13 (C-3′/5′), 128.60 (C-3‴/5‴), 126.35 (C-2′/6′, 123.28 (C-6), 108.97 (C-10), 108.02 (C-3″), 105.85 (C-3), 102.69 (C-8), 41.30 (C-1″), 27.76 (C-4″/5″). MS (CI) *m*/*z*: 426 (M^+). HRMS (CI): *m*/*z* calcd for $C_{27}H_{22}O_5$, 426.1467, found 426.1467. Anal. calcd for $C_{27}H_{22}O_5$: C, 76.04; H, 5.20. Found C, 76.08; H, 5.57.

3.6. Unprotected final products

3.6.1. 6-(1,1-Dimethylallyl) chrysin 7. 102 mg (0.24 mmol) of compound **3d** plus 25 mg (0.024 mmol) of $Eu(fod)_3$ were suspended in 10 ml of cycloheptane and the mixture heated at 100°C for 4 h. The solution was evaporated to dryness, the residue redissolved in methanolic KOH (5%) and submitted to sonication for 5 min. After dilution of the medium with water, acidification (1N HCl) and extraction with ethyl acetate, 45 mg (0.14 mmol, 58%) of **7** were isolated by VLC on diol-bonded silica using a gradient of $CHCl_3$ in hexane as solvent. Yellow crystals, mp 193.6–208°C. UV/Vis (MeOH): λ_{max} (nm)=320, 274, 250sh. ^{1}H NMR (acetone-d_6, 300 MHz): δ 13.97 (s, 5-OH), 8.04 (m, H-2′/6′), 7.59 (m, H-3′/4′/5′), 6.77 (s, H-3), 6.58 (s, H-8), 6.37 (dd, J=17.7 and 10.6 Hz, H-2″), 4.96 (dd, J=17.7 and 1.1 Hz, H-3″), 4.87 (dd, J=10.6 and 1.1 Hz, H-3″), 1.63 (s,

H-4″/5″). ^{13}C NMR (acetone-d_6, 75 MHz): δ 184.57 (C-4), 165.13 (C-2*), 165.05 (C-7*), 163.49 (C-5), 157.75 (C-9), 151.69 (C-2″), 133.67 (C-4′), 133.23 (C-1′), 131.00 (C-3′/5′), 128.20 (C-2′/6′), 117.93 (C-6), 109.75 (C-3″), 107.09 (C-3), 106.58 (C-10), 96.38 (C-8), 42.76 (C-1″), 30.17 (C-4″/5″). MS (CI) *m/z*: 322 (M^+). HRMS (CI): *m/z* calcd for $C_{20}H_{18}O_4$, 322.1205, found 322.1206. Anal. calcd for $C_{20}H_{18}O_4$+0.3 hexane: C, 75.20; H, 6.43. Found C, 75.09; H, 6.61.

3.6.2. 4-Hydroxy-2,3,3-trimethyl-7-phenyl-2,3 dihydrofurano[3,2-*g*]4*H*-chromen-5-one 8. Pale yellow crystals, mp 143–151°C. UV/Vis (MeOH): λ_{max} (nm)=319, 271, 255sh. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.93 (s, 5-OH), 7.87 (m, H-2′/6′), 7.52 (m, H-3′/4′/5′), 6.64 (s, H-3), 6.40 (s, H-8), 4.51 (q, *J*=6.6 Hz, H-2″), 1.50 (s, H-4″ or H-5″), 1.40 (d, *J*=6.6 Hz, H-3″), 1.26 (s, H-4″ or H-5″).^{13}C NMR ($CDCl_3$, 75 MHz): δ 182.86 (C-4), 164.95 (C-7), 163.53 (C-2), 157.89 (C-9), 157.40 (C-5), 131.65 (C-4′), 131.40 (C-1′), 129.04 (C-3′/5′), 126.23 (C-2′/6′), 118.03 (C-6), 106.20 (C-10), 105.68 (C-3), 90.92 (C-2″), 89.39 (C-8), 43.34 (C-1″), 25.05 (C-4″ or C-5″), 20.57 (C-4″ or C-5″), 14.31 (C-3″). MS (CI) *m/z*: 323 ($M+H^+$). HRMS (CI): *m/z* calcd for $C_{20}H_{19}O_4$, 323.1283, found 323.1284. Anal. calcd for $C_{20}H_{18}O_4$+0.5 hexane+0.1 CH_2Cl_2: C, 74.20; H, 6.79. Found C, 74.36; H, 6.64.

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