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Rearrangement of 5-*O*-prenyl flavones: a regioselective access to 6-*C*-(1,1-dimethylallyl)- and 8-*C*-(3,3-dimethylallyl)-flavones

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Abstract—Regioselective control of the Claisen rearrangement of 7-MEM-5-prenyl chrysin was achieved by microwave irradiation. The nature of the products was influenced by the irradiation power and the type of solvent. Irradiation at 750 W in *N*,*N*-diethylaniline specifically yielded the 8-(3,3-dimethylallyl) *para*-rearranged product while refluxing in *N*,*N*-diethylbutylamine gave selective access to the 6-(1,1-dimethylallyl) *ortho*-rearranged compound.

Flavones have been recognized[1] as efficient in vitro effectors of P-glycoprotein (Pgp), one of the transporters involved in multidrug resistance (MDR).[2] Recently, *C*-isoprenylation has been shown to enhance the binding affinity of the flavone chrysin towards Pgp.[3] In addition, only isoprenoid derivatives were able to inhibit Pgp-mediated daunomycin efflux from leukemic K562/R7 cells. In fact, 8-prenyl chrysin displayed a stronger effect than cyclosporin A, one of the most potent modulators available.[3] Isoprenoid chrysins have been obtained in the past by direct *C*-alkylation in aqueous alkaline medium and in catalytic phase transfer conditions.[3] However, the yields of isoprenoid derivatives were in the 20–30% range and chromatographic separation of the isomers was necessary.[3] This prompted us to develop more efficient and more regioselective methods for the preparation of isoprenoid flavones, providing easier access to the amounts required for in vivo studies. Claisen rearrangements are usually the method of choice for the regioselective isoprenylation of phenolic natural products.[4] Recently,[5] the rearrangement of 7-acetyl-5-prenyl naringenin has been studied in the presence of catalytic amounts of $Eu(fod)_3$. However, this approach failed to produce the 6-(1,1-dimethylallyl) *ortho*-rearranged product selectively, and there has been no report of *para* rearrangement in the flavone series. Indeed, such a rearrangement will be difficult, because the 5-*O*-prenylated intermediate, the substrate of the rearrangement, is unstable in solution, and when chromatographed on silica gel, submitted to recrystallization, or heated. Therefore, under the conditions of a thermal Claisen rearrangement, elimination of the 5-*O*-prenyl chain with no rearrangement may largely prevail. Our strategy is based on two points: improved preparation of 5-*O*-prenyl chrysin, and microwave-assisted rearrangement ensuring excellent control of the nature of the products.

The syntheses of *C*-prenyl chrysins is a three-step process, which involves (Fig. 1): (i) protection of the 7-hydroxyl; (ii) *O*-alkylation of the 5-hydroxyl group, and (iii) *C*-alkylation at the 6- or 8-positions by Claisen rearrangement. Protection of the 7-hydroxyl by the methoxyethoxymethyl (MEM) group proceeded smoothly, leading to 7-MEM chrysin **2**[6] in very good yield (82%). Alkylation of flavone **2** was performed in the presence of tetrabutylammonium hydroxide as a base, yielding the 5-*O*-alkylated product **3**[7] in 89% yield. On the COLOC 2D NMR spectrum of **3**, a strong correlation was visible between C-5 at 160.05 ppm and H-1″ at 4.64 ppm, confirming the success of 5-*O*-prenylation. Subsequent rearrangements of **3** were carried out under microwave irradiation using either *N*,*N*-dimethylaniline or *N*,*N*-diethylaniline as solvents.[8] All compounds have been fully characterized on the basis of their elemental analyses, HRMS, ^1H and ^{13}C NMR spectroscopic properties. The nature of the product(s) of the microwave-induced rearrangement was highly influenced by two factors: the type of the solvent, and the irradiation power (Table 1). Decreasing microwave irradiation power was associated with longer reaction times (Table 1, entries 1 to 3). When the rearrangement was performed in diethylaniline and at

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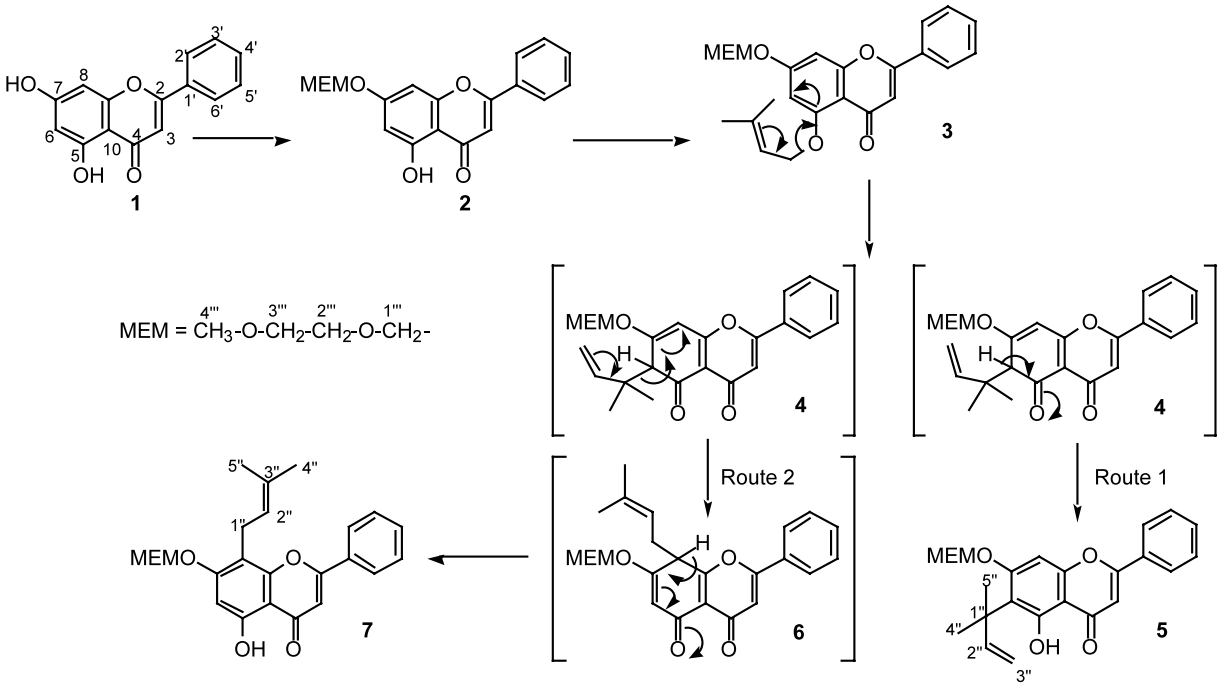

Figure 1. Strategy for the regioselective syntheses of 6-(1,1-dimethylallyl)- and 8-(3,3-dimethylallyl)-chrysins. **2**: MEM-Cl, iPr$_2$NEt, DMF, 82%; **3**: 1-bromo-3-methyl-2-butene, tetrabutylammonium hydroxide, toluene/CH_2Cl_2, 89%; **5** and **7**: see Table 1.

Table 1. Parameters influencing Claisen rearrangement of flavone **3**

Entry no.	1	2	3	4	5
Solvent	*N*,*N*-Diethylaniline	*N*,*N*-Diethylaniline	*N*,*N*-Diethylaniline	*N*,*N*-Dimethylaniline	*N*,*N*-Diethylbutylamine
Conditions	Microwave	Microwave	Microwave	Microwave	Oil bath 160°C, 72 h
Irradiation power (W)	750	620	570	570	–
Irradiation time (min)	2×15	4×15	6×15	10×15	–
Products formed (%)	**5** (1.4), **7** (82)	**5** (14), **7** (76)	**5** (30), **7** (60)	**5** (39), **7** (48)	**5** (81), **7** (5)
5/**7** Ratio	0.02	0.18	0.5	0.81	16.2
Total **5**+**7**	83%	90%	90%	87%	86%

maximum irradiation power, the isoprenoid chrysin **7**[9] was the major product, formed after only 30 min irradiation (Table 1, entry 1). The occurrence of a *C*-(3,3-dimethylallyl) chain in **7** was demonstrated by the presence of the usual signals for *C*-prenyl chrysin derivatives,[3,10] both on its ^{1}H- (H-2″: 5.19, brt, J=6.8 Hz; H-4″: 1.66, s; H-5″: 1.79, s) and ^{13}C NMR (C-1″: 21.99; C-2″: 122.22; C-3″: 131.90; C-4″: 25.66; C-5″: 17.91) spectra. In addition, the chemical shift of the benzylic methylene carbon of the prenyl group (C-1″) confirmed the presence of oxygen substituents in the two positions *ortho* to the *C*-prenyl group.[11] This located the 3,3-dimethylallyl chain at either the 6- or 8-positions, but not at the 3-position.[11] Final assignment of the position of prenylation was derived from the analysis of the 2D COLOC experiment. The methine carbon at 97.97 ppm was found to correlate with the 5-phenolic hydroxyl at 12.66 ppm, while its associated proton at 6.62 ppm displayed a cross peak with the C-5 signal at 160.20 ppm. This clearly demonstrated that the 6-position of chrysin was free of substitution. On the other hand, the signals at 160.46 (C-7), 154.47 (C-9) and 108.72 ppm (C-8) correlated with the H-1″ signal at 3.53 ppm. Therefore, compound **7** was identified as 7-MEM-8-prenyl-chrysin. When lower irradiation power was used, compound **5**[12] was detected in addition to **7**. NMR data for **5** showed the presence of a *C*-(1,1-dimethylallyl) residue (H-2″: 6.30, dd, J= 17.4 and 10.6 Hz; H-3″: 4.83, dd, J=10.6 and 1.3 Hz; H-3″: 4.87, dd, J=17.4 and 1.3 Hz; H-4″/5″: 1.62, s; C-1″: 41.50; C-2″:150.56; C-3″: 106.91; C-4″/5″: 29.05), in accordance with published values.[10] The 5-phenolic hydroxyl of **5** appeared at higher chemical shift (12.96 ppm) than that of **7** (12.66 ppm). Taking into account previous observations in the flavone[3] and flavanone series,[13] this suggested that compound **5** was *C*-alkylated at the 6-position. This was confirmed by the results of a 2D HMBC NMR experiment. In fact, the singlet at 6.82 ppm (H-8) was correlated with the quaternary carbons at 162.70 (C-7), 156.05 (C-9) and 118.80 (C-6), but not with that at 160.91 ppm (C-5). Finally the double doublet at 6.30 ppm (H-2″) crosslinked with C-6 at 118.80 ppm. Therefore, the structure 6-(1,1-dimethylallyl)-7-MEM-chrysin was

assigned to compound **5**. The amount of **5** increased with decreasing power (Table 1, entries 1 to 3) and solvent boiling point (entries 3 and 4). It is noteworthy that, modification of the parameters only affected the **5**/**7** ratio, but not the total amount of *C*-isoprenoid flavones **5**+**7** which was found to stay in the 83–90% range (Table 1). Selected preparation of the 6-(1,1-dimethylallyl) isomer **5** was not achieved by microwave irradiation. The latter compound, however, was synthesized in 81% yield by refluxing compound **3** in *N*,*N*-diethylbutylamine (Table 1, entry 5). It is likely that both compounds **5** and **7** are formed from a common intermediate **4**[14] (Fig. 1). In relatively mild rearrangement conditions (route 1), aromatisation of **4** would preferably give rise to **5**. Under more drastic conditions (route 2), intermediate **4** would undergo a second rearrangement, leading to **7**, possibly though a second intermediate **6**. The use of intermediate conditions (lower irradiation power or lower solvent boiling point) would furnish a mixture of both compounds. By proper adjustment of the conditions of the rearrangement, the formation of one of the two compounds can be favored. In this respect, microwave irradiation represents a fast and simple method for the regioselective *C*-isoprenylation of flavonoids. In addition, appropriate conditions for the selective preparation of 6-(1,1-dimethylallyl)-flavonoids are reported here for the first time.

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6. **7-MEM-Chrysin 2**. To a solution of 5 g of chrysin **1** (19.6 mmol, 1 equiv.) in 110 ml of dry DMF were added *N*,*N*-diisopropylethylamine (7 ml, 39.5 mmol, 2 equiv.). The mixture was cooled (ice bath) and 4.4 ml of MEM chloride (39.3 mmol, 2 equiv.) were added dropwise under stirring. After complete addition of the reagent, the mixture was stirred for 15 min at room temperature. The medium was diluted with water and left overnight at 4°C. The resulting precipitate of crude flavone **2** was isolated by filtration and recrystallized in EtOH, yielding 5.5 g (16 mmol, 82%) of pure **2**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.62 (s, 5-OH), 7.83 (m, H-2′/6′), 7.48 (m, H-3′/4′/5′), 6.66 (d, $J=2.2$ Hz, H-8), 6.61 (s, H-3), 6.44 (d, $J=2.2$ Hz, H-6), 5.30 (s, H-1‴), 3.81 (m, H-2‴), 3.54 (m, H-3‴), 3.35 (s, H-4‴). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 182.41 (C-4), 163.93 (C-2), 162.98 (C-7), 161.94 (C-5), 157.52 (C-9), 131.75 (C-4′), 131.11 (C-1′), 128.96 (C-3′/5′), 126.17 (C-2′/6′), 106.27 (C-10), 105.72 (C-3), 100.09 (C-6), 94.28 (C-8), 93.19 (C-1‴), 71.42 (C-3‴), 68.15 (C-2‴), 58.94 (C-4‴). MS (EI) m/z: 342 (M^+), 283 (M^+–$MeOCH_2CH_2$), 267 (M^+–$MeOCH_2CH_2O$), 254 (M^+–$MeOCH_2CH_2$-OCH_2+H). HRMS (EI): m/z calcd for $C_{19}H_{18}O_6$, 342.1103, found 342.1104. Anal. calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found C, 66.71; H, 5.34.
7. **7-MEM-5-Prenyl chrysin 3**. To a solution of 1 g of flavone **2** (2.9 mmol, 1 equiv.) in 15 ml CH_2Cl_2 and 10 ml toluene at 0°C (ice bath), were directly added (stirring) solid tetrabutylammonium hydroxide 30 hydrate (4.6 g, 5.8 mmol, 2 equiv.). After complete dissolution of the base, 0.5 ml of 3,3-dimethylallyl bromide (4.4 mmol, 1.5 equiv.) were added dropwise under stirring at 0°C. Reaction was allowed to proceed at room temperature for 2 h (stirring). After dilution with water and acidification (1N HCl) the products of the reaction were extracted with EtOAc. HPLC dosage (silica, 10% isopropanol in hexane) of the extract revealed that flavone **3** has been prepared in 89% yield. After evaporation of the solvent, the residue was taken up in minimum acetone, and hexane was added dropwise until the solution started to become cloudy. Leaving the solution overnight at 4°C lead to crystallization of pure flavone **3** (0.8 g, 69%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.82 (m, H-2′/6′), 7.44 (m, H-3′/4′/5′), 6.76 (d, $J=2.2$ Hz, H-8), 6.59 (s, H-3), 6.43 (d, $J=2.2$ Hz, H-6), 5.54 (brt, $J=6.4$ Hz, H-2″), 5.31 (s, H-1‴), 4.64 (d, $J=6.3$ Hz, H-1″), 3.82 (m, H-2‴), 3.54 (m, H-3‴), 3.34 (s, H-4‴), 1.75 (brs, H-4″), 1.72 (brs, H-5″). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 177.23 (C-4), 161.26 (C-7), 160.43 (C-2), 160.05 (C-5), 159.45 (C-9), 137.35 (C-3″), 131.46 (C-1′), 130.97 (C-4′), 128.75 (C-3′/5′), 125.82 (C-2′/6′), 119.36 (C-2″), 110.19 (C-10), 108.84 (C-3), 98.40 (C-6), 95.60 (C-8), 93.24 (C-1‴), 71.41 (C-3‴), 68.07 (C-2‴), 66.50 (C-1″), 58.90 (C-4‴), 25.66 (C-4″), 18.27 (C-5″). MS (FAB) m/z: 411 (M+H$^+$), 343 (M+H–$C_5H_8^+$). HRMS (FAB): m/z calcd for $C_{24}H_{27}O_6$, 411.1808, found 411.1795. Anal calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found C, 70.35; H, 6.21.
8. Example of typical procedure for microwave-induced rearrangement: Preparation of **7** (Table 1, entry 1). Flavone **3** (0.2 g, 0.49 mmol) was dissolved in 4 ml of freshly distilled *N*,*N*-diethylaniline. The solution was

placed in a well-stoppered 10 ml teflon bottle and submitted to successive 15 min microwave irradiations at 750 W (with 10 min intervals between treatments) using a domestic Bluewind 1797 oven. Evolution of the reaction was monitored by the disappearance of the blue fluorescent starting compound **3**. For selective preparation of **7**, two successive irradiations were necessary. After complete cooling, the reaction medium was diluted with H_2O, acidified (1N HCl), extracted with EtOAc and the products of the reaction quantified by HPLC on diol-bonded silica using 0.5% isopropanol in hexane as solvent.

9. **7-MEM-8-Prenyl chrysin 7**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.66 (s, 5-OH), 7.86 (m, H-2′/6′), 7.49 (m, H-3′/4′/5′), 6.62 (s, H-6), 6.61 (s, H-3), 5.33 (s, H-1‴), 5.19 (brt, $J=6.8$ Hz, H-2″), 3.80 (m, H-2‴), 3.53 (m, H-3‴+H-1″), 3.36 (s, H-4‴), 1.79 (s, H-5″), 1.66 (s, H-4″).). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 182.89 (C-4), 163.86 (C-2), 160.46 (C-7), 160.20 (C-5), 154.47 (C-9), 131.90 (C-3″), 131.69 (C-1′+C-4′), 129.03 (C-3′/5′), 126.23 (C-2′/6′), 122.22 (C-2″), 108.72 (C-8), 105.91 (C-10), 105.44 (C-3), 97.97 (C-6), 93.34 (C-1‴), 71.46 (C-3‴), 68.17 (C-2‴), 59.01 (C-4‴), 25.66 (C-4″), 21.99 (C-1″), 17.91 (C-5″). MS (EI) m/z: 410 (M^+), 322 (M^+–$MeOCH_2CH_2OCH_2$+H), 321 (M^+–$MeOCH_2CH_2OCH_2$). HRMS (EI): m/z calcd for $C_{24}H_{26}O_6$, 410.1729, found 410.1735. Anal. calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found C, 69.93; H, 6.39.
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12. **6-(1,1-Dimethylallyl-7-MEM chrysin 5**. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.96 (s, 5-OH), 7.90 (m, H-2′/6′), 7.53 (m, H-3′/4′/5′), 6.82 (s, H-8), 6.67 (s, H-3), 6.30 (dd, $J=17.4$ and 10.6 Hz, H-2″), 5.31 (s, H-1‴), 4.87 (dd, $J=17.4$ and 1.3 Hz, H-3″a), 4.83 (dd, $J=10.6$ and 1.3 Hz, H-3″b), 3.84 (m, H-2‴), 3.60 (m, H-3‴), 3.41 (s, H-4‴), 1.62 (s, H-4″+H-5″). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 183.03 (C-4), 163.80 (C-2), 162.70 (C-7), 160.91 (C-5), 156.05 (C-9), 150.56 (C-2″), 131.74 (C-4′), 131.24 (C-1′), 129.05 (C-3′/5′), 126.27 (C-2′/6′), 118.80 (C-6), 106.91 (C-10+C-3″), 105.82 (C-3), 93.36 (C-8), 93.26 (C-1‴), 71.48 (C-3‴), 68.28 (C-2‴), 59.03 (C-4‴), 41.50 (C-1″), 29.05 (C-4″+C-5″). MS (EI) m/z: 410 (M^+), 335 (M^+–$MeOCH_2CH_2O$), 322 (M^+–$MeOCH_2CH_2OCH_2$+H), 321 (M^+–$MeOCH_2$-CH_2OCH_2). HRMS (EI): m/z calcd for $C_{24}H_{26}O_6$, 410.1729, found 410.1731. Anal. calcd for $C_{24}H_{26}O_6$+0.1 hexane: C, 70.50; H, 6.59. Found C, 70.63; H, 6.40.
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