TOTAL SYNTHESIS OF 8-(1,1-DIMETHYLALLYL)-APIGENIN

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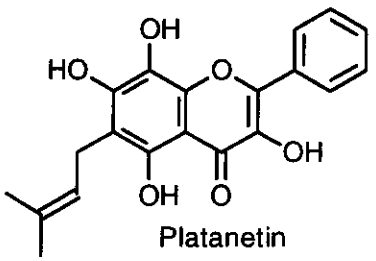
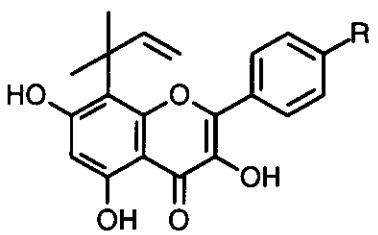
Abstract - 8-(1,1-Dimethylallyl)apigenin has been synthesized in 5 steps from 2', 4'-dibenzylphloroacetophenone and 4-*O*-methoxyethoxymethylbenzaldehyde. The strategy involved protection of the 4'-hydroxyl in apigenin by a methoxyethoxymethyl group, followed by specific *O*-prenylation at position 7. Claisen rearrangement of the 7-prenyl-4'-methoxyethoxymethylapigenin performed in one step both the 1,1-dimethylallylation at position 8, and removal of the 4'-methoxyethoxymethyl protecting group.

Isoprenoid flavonoids are reported in the plant kingdom with increasing frequency. [1] Within this class, those having a *C*-(1,1-dimethylallyl) chain are rare natural products which include chalcones, [2,3] flavanones [4] and flavonols. [5-7] The major source of latter compounds (Figure 1) is represented by *Platanus acerifolia* buds.



Platanetin



R = H: 8-(1,1-Dimethylallyl)galangin
R = OMe: 8-(1,1-Dimethylallyl)kaempferid
R = OH: 8-(1,1-Dimethylallyl)kaempferol

Figure 1: Structures of some isoprenoid flavonoids from *Platanus acerifolia* buds.

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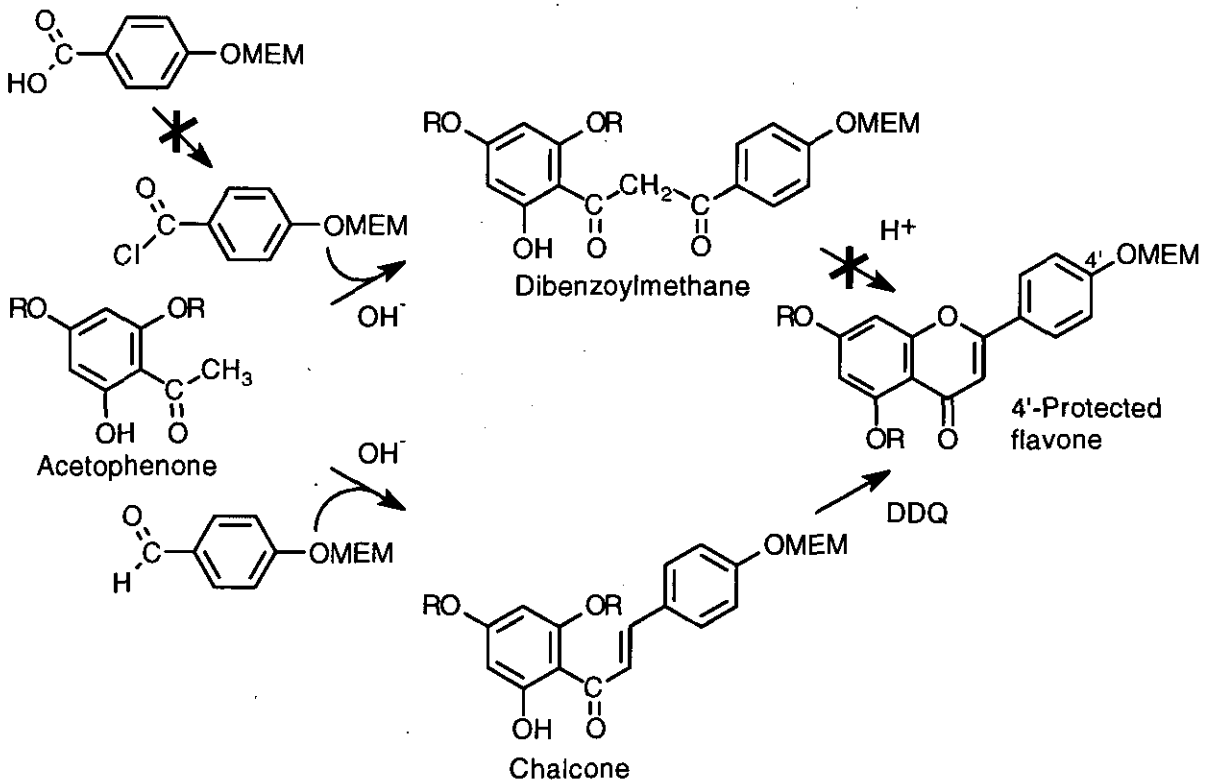
Some *Platanus* buds isoprenoid flavonoids have been demonstrated to have uncoupling properties, [8,9] and to inhibit the external NADH dehydrogenase of the inner plant mitochondrial membrane. [8,10]. The most active compound, platanetin (Figure 1), has the disadvantage of being highly unstable. In order to discover more stable active compounds, a number of synthetic analogues of *Platanus* isoprenoid flavonoids have been prepared in our laboratory. [11-13] The strategy of preparation of 8-*C*-(1,1-dimethylallyl)flavonoids is based on the sigmatropic (Claisen) rearrangement [14] of the corresponding 7-*O*-(3,3-dimethylallyl) compound. [12,13] The method has been successfully applied to a synthesis of flavones and flavonols having no free hydroxyl groups on ring B such as 8-(1,1-dimethylallyl)galangin or 8-(1,1-dimethylallyl)kaempferid (Figure 1). More difficulties are expected in the preparation of flavonoids having free 4'-hydroxyl group on ring B such as 8-(1,1-dimethylallyl)apigenin (**7**) (Scheme 2). In fact, when free hydroxyl groups are present on both positions 7 and 4' of the flavonoid ring, specific prenylation at position 7 is not possible. Thus direct *O*-prenylation of apigenin with one equivalent of prenyl bromide results in the formation of a mixture of 7-monoprenyl-, 4'-monoprenyl- and 7,4'-diprenylapigenin (while some apigenin remains unreacted). Therefore 7-monoprenylation requires protection of the 4'-hydroxyl group of the flavone.



R = Protecting group removable in different conditions than the MEM group.
MEM = Methoxyethoxymethyl.

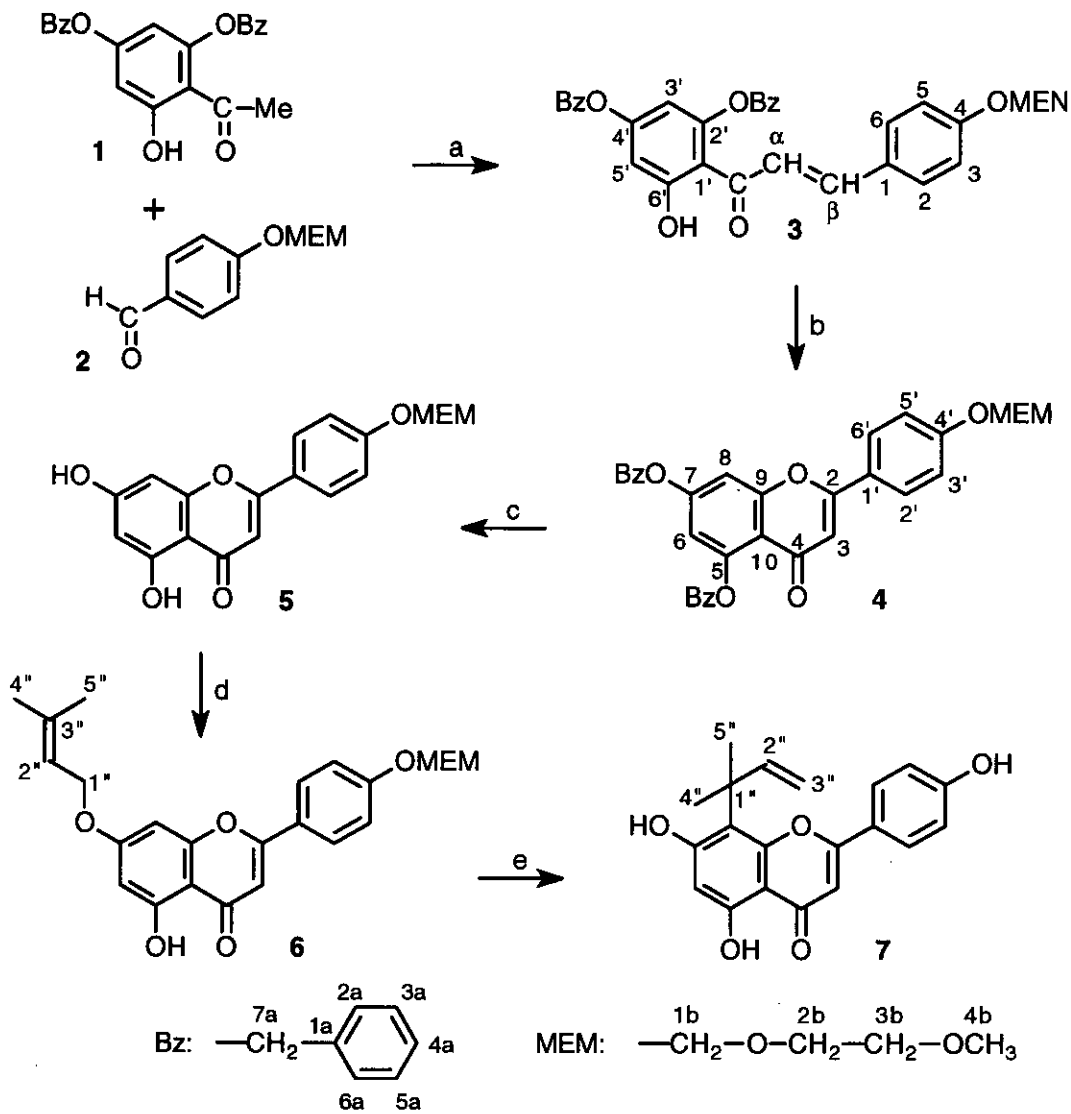
Scheme 1: The strategies for the synthesis of a 4'-protected apigenin.

Two main methods are available for the synthesis of flavones [15] and might be applied to the preparation of a 7-prenylapigenin (Scheme 1). Both methods make use of an acetophenone as precursor of ring A.

- In the first one (dibenzoylmethane route), the precursor of ring B is a benzoyl chloride. The reaction proceeds *via* a dibenzoylmethane intermediate, subsequently cyclized to a flavone in acidic conditions. [16]
- In the second one (chalcone route), the precursor of ring B is an aldehyde. The intermediate chalcone is transformed to a flavone by cyclodehydrogenation. [17]

In both cases, protection of the 4-hydroxyl of the acid chloride/aldehyde is followed by selective 7-prenylation of the resulted 4'-protected flavone. The 4'-protecting group must be removable in very mild conditions in order to avoid destruction/cyclization of the prenyl chain. Based on this assumption the dibenzoylmethane route was not considered since high probability of elimination of the 4'-protecting group existed both during the preparation of the acid chloride, and during the acidic cyclization process (Scheme 1). In the present paper, we wish to report on the total synthesis of 8-(1,1-dimethylallyl)apigenin from phloroacetophenone and a protected aldehyde *via* the chalcone route.

The strategy for a total synthesis of 8-(1,1-dimethylallyl)apigenin is outlined in Scheme 2. For the protection of 4-hydroxybenzaldehyde we chosed the methoxyethoxymethyl (MEM) group. This protecting group already gave good results in our laboratory in the synthesis of prenyl chalcones. [18] In fact, MEM chloride reacts very well with phenolic hydroxyl groups and the protected derivative is obtained in good yield. On the other hand, the MEM can be removed by mild acid hydrolysis, preventing cyclization of the prenyl chain during deprotection. Since the preparation of the chalcone by aldol condensation requires strong alkaline conditions, the phloroacetophenone precursor must be protected as well. Obviously the protecting group for the acetophenone must be removable in different conditions than those required for the MEM elimination. For this purpose, we chosed the benzyl protecting group which can be removed by catalytic hydrogenation. Thus aldol condensation of 2',4'-dibenzylphloroacetophenone with 4-*O*-MEMbenzaldehyde yielded chalcone (**3**) in 70% yield. This yield is quite good as compared to the average 50% yields, usually obtained in the preparation of chalcones. Cyclodehydrogenation of chalcone (**3**) with DDQ in dioxane resulted in the formation of 5,7-dibenzyl-4'-MEMflavone (**4**) in 19% yield, only. Appreciable amounts of unreacted chalcone were detected in the medium. Similar low yields have been encountered in the cyclization of others 4-monosubstituted chalcones like 2'-hydroxy-4-methoxychalcone. [17b] Attemps to obtain complete reaction of the chalcone by increasing the reaction time resulted in lower yields in flavone (**4**) since obviously extensive degradation of **4** strarted to take place before complete reaction of the chalcone. Thus 3 h was considered as optimum reaction time. Flavone (**4**) was subsequently debenzylated by mild catalytic hydrogen transfert. [19] We used ammonium formate as hydrogen donnor. 4'-MEM apigenin (**5**) was obtained in good yield (79%). 4'-MEM apigenin (**5**) was prenylated at position 7 with prenyl bromide at room



a) KOH; b) DDQ; c) 5% Pd/C, $HCOONH_4$; d) Prenyl bromide; e) Claisen rearrangement.

Scheme 2: Total synthesis of 8-(1,1-dimethylallyl)apigenin.

temperature under phase transfert conditions. [20] The desired 7-prenyl-4'-MEM apigenin (**6**) was obtained in 50% yield, together with some 5,7-diprenyl-4'-MEM apigenin (**6'**) (12%). Sigmatropic rearrangement of **6** was performed in Ac_2O and in presence of anhydrous NaOAc. [12] Under these conditions, both the rearrangement and deprotection of the 4'-hydroxyl took place in one step. This directly gave rise to 8-(1,1-dimethylallyl)apigenin (**7**) in 53% yield.

The structures of the compounds were established on the basis of their Elms, ^1H nmr and ^{13}C nmr data. Attribution of H-7a (benzyl signals) on the ^1H nmr spectrum of **4**, as well as H-1",

H-2", H-4" and H-5" (3,3-dimethylallyl chains) on the ^{1}H nmr spectrum of **6'**, were made with the aid of a NOESY experiment. Attributions of the carbon signals on the ^{13}C nmr spectra of all compounds (except **7**) were confirmed by both direct and long distance proton-carbon correlations. [13]

To our knowledge, this compound is not known as a natural product yet. Undoubtedly, this synthetic strategy can be applied to the preparation of higher hydroxylated 8-(1,1-dimethylallyl)flavones.

EXPERIMENTAL

2',4'-Dibenzylphloroacetophenone was prepared by benzylation of phloroacetophenone (benzyl chloride-DMF/K_2CO_3) according to published procedure. [21] 4-*O*-MEM benzaldehyde was obtained by alkylation of 4-hydroxybenzaldehyde with MEM chloride in DMF and in presence of *N,N*-diisopropylethylamine. [18] 3,3-Dimethylallyl bromide (prenyl bromide) was from Fluka. DDQ and tetrabutylammonium iodide were from Janssen. Medium Pressure Liquid Chromatography (mplc) separations were carried out on a Buchi apparatus. A 70 x 460 mm column packed with 1 kg of silica gel 60 for column chromatography (Macherey-Nagel; 0.025-0.040 mm particle size) was used. Conventional column chromatography was performed on polyamide CC6 (Macherey-Nagel, particle size < 70 μm). Nmr spectra were measured on a Bruker AC 200 apparatus. 2D experiments were recorded using parameters as in reference. [13] EI mass spectra were obtained at 70 eV using a Trio 1000 apparatus (Fisons). The ionization current and the chamber temperature were 150 μA and 200°C, respectively. For high resolution EI-ms the ions were resolved at a resolution of 4000.

2',4'-Dibenzyloxy-6'-hydroxy-4-methoxyethoxymethoxychalcone (3):
2 g (5.75 mmol) of 2',4'-dibenzylphloroacetophenone (**1**) and 1.3 g (5.75 mmol) of 4-*O*-MEM benzaldehyde (**2**) were dissolved in 10 ml of MeOH and 10 ml of 50% aqueous KOH. The mixture was refluxed for 30 min, diluted with water (ice bath), acidified (3N HCl) and extracted with EtOAc. After evaporation of the solvent under reduced pressure the oily residue was dissolved in EtOH. Pure **3** crystallized from the EtOH solution as yellow needles, mp 76°C. More **3** was isolated after purification of the filtrate by gel filtration on Sephadex LH-20 using MeOH as solvent. Yield: 2.17 g of **3** (70%).
^{1}H Nmr ($CDCl_3$; δ ppm/TMS): 12.68 (1 H, s, 6'-OH), 7.79 (1 H, d, J = 15.6 Hz, H-α), 7.66 (1 H, d, J = 15.6 Hz, H-β), 7.30-7.50 (10 H, m, aromatic benzyl signals), 6.99 (2 H, d, J = 8.8 Hz, H-2/6), 6.85 (2 H, d, J = 8.8 Hz, H-3/5), 6.20 (1 H, d, J = 2.2 Hz, H-5'), 6.14 (1 H, d, J = 2.2 Hz, H-3'), 5.26 (2 H, s, H-1b 4-MEM), 5.06 (2H, s, H-7a 4'-benzyl), 5.02 (2 H, s, H-7a 2'-benzyl), 3.81 (2 H, m, H-2b 4-MEM), 3.55 (2 H, m, H-3b 4-MEM) and 3.37 (3 H, s, H-4b 4-MEM). ^{13}C Nmr ($CDCl_3$; δ ppm/TMS): 192.6 (C=0), 168.8 (C-6'), 165.1 (C-4'), 161.7 (C-2'), 158.7 (C-4), 142.6 (C-β), 135.9 (C-1a 4'-benzyl), 135.5 (C-1a 2'-benzyl), 130.0 (C-2/6), 128.9, 128.8, 128.7,

128.6, 128.3 (C-2a to C-6a benzyls), 127.6 (C-α), 125.6 (C-1), 116.2 (C-3/5), 106.3 (C-1'), 95.1 (C-5'), 93.2 (C-1b 4-MEM), 92.5 (C-3'), 71.6 (C-3b 4-MEM), 71.4 (C-7a 2'-benzyl), 70.3 (C-7a 4'-benzyl), 67.8 (C-2b 4-MEM) and 59.0 (C-4b 4-MEM). EI-ms, *m/z* (rel. int.): 541 $[M+1]^+$ (3), 540 $[M]^+$ (6), 449 (4), 373 (6), 271 (12), 243 (7), 235 (6), 181 (4), 147 (4), 91 (100), 89 (75), 86 (23), 84 (34), 59 (67), 51 (13), 49 (35). HR-Elms: Calcd for $C_{33}H_{32}O_7$: 540.2148. Found: 540.2148. Anal. Calcd for $C_{33}H_{32}O_7$: C, 73.30; H, 5.97. Found: C, 73.06; H, 5.91.

5,7-Dibenzyl-4'-methoxyethoxymethylapigenin (4):

1.2 g (2.23 mmol) of chalcone (**3**) in solution in 25 ml of dried dioxane and 2.03 g (8.94 mmol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) were stirred at 130 °C for 5 h. The reaction medium, after dilution with 5% aqueous KOH was extracted with Et_2O. The Et_2O extract was purified by mplc on silica gel using toluene-Me_2CO as elution solvent. 0.23 g (19%) of pure **4** were obtained as an oil.

^1H Nmr ($CDCl_3$; δ ppm/TMS): 7.76 (2 H, d, J = 8.8 Hz, H-2'/6'), 7.59 (2 H, d, J = 6.9 Hz, H-2a/6a 5-benzyl), 7.32-7.41 (8 H, m, aromatic benzyl signals), 7.12 (2 H, d, J = 8.7 Hz, H-3'/5'), 6.60 (1 H, d, J = 2.2 Hz, H-8), 6.55 (1 H, s, H-3), 6.45 (1 H, d, J = 2.2 Hz, H-6), 5.30 (2 H, s, H-1b 4'-MEM), 5.18 (2 H, s, H-7a 5-benzyl), 5.07 (2 H, s, H-7a 7-benzyl), 3.81 (2 H, m, H-2b 4'-MEM), 3.54 (2 H, m, H-3b 4'-MEM) and 3.36 (3 H, s, H-4b 4'-MEM). ^{13}C Nmr ($CDCl_3$; δ ppm/TMS): 177.2 (C-4), 162.7 (C-7), 160.4 (C-2), 159.5 (C-5 + C-9 + C-4'), 136.3 (C-1a 5-benzyl), 135.6 (C-1a 7-benzyl), 128.6, 128.4, 128.3 (C-3a + C-4a + C-5a benzyls), 127.4 (C-2'/6' + C-2a/6a 7-benzyl), 126.5 (C-2a/6a 5-benzyl), 124.8 (C-1'), 116.3 (C-3'/5'), 109.7 (C-10), 107.8 (C-3), 98.3 (C-6), 94.2 (C-8), 93.1 (C-1b 4'-MEM), 71.4 (C-3b 4'-MEM), 70.6 (C-7a 5-benzyl), 70.3 (C-7a 7-benzyl), 67.8 (C-2b 4'-MEM) and 58.9 (C-4b 4'-MEM). EI-ms, *m/z* (rel. int.): 539 $[M+1]^+$ (6), 538 $[M]^+$ (17), 448 (6), 91 (100), 89 (49), 59 (59). HR-Elms: Calcd for $C_{33}H_{30}O_7$: 538.1991. Found: 538.1987.

4'-Methoxyethoxymethylapigenin (5):

To a solution of 223 mg of **4** (0.43 mmol) in 5 ml of dry DMF are successively added 178 mg of 5% Pd on activated carbon and 415 mg of ammonium formate. The mixture was left at room temperature for 4 h (no agitation). After dilution of the medium with MeOH the precipitate was eliminated by filtration (filter paper). The filtrate was diluted with water, acidified (ice bath) with 3N HCl and extracted with EtOAc. 120 mg (79%) of **5** were obtained as a light yellow powder (crystallized from MeOH), mp 136°C.

^1H Nmr (Acetone-d_6; δ ppm/TMS): 12.94 (1 H, s, 5-OH), 9.68 (1 H, br s, 7-OH), 7.96 (2 H, d, J = 8.9 Hz, H-2'/6'), 7.19 (2 H, d, J = 8.9 Hz, H-3'/5'), 6.65 (1 H, s, H-3), 6.53 (1 H, d, J = 2.1 Hz, H-8), 6.25 (1 H, d, J = 2.1 Hz, H-6), 5.36 (2 H, s, H-1b 4'-MEM), 3.80 (2 H, m, H-2b 4'-MEM), 3.51 (2 H, m, H-3b 4'-MEM) and 3.27 (3 H, s, H-4b 4'-MEM). ^{13}C Nmr (Acetone-d_6; δ ppm/TMS): 183.0 (C-4), 164.9 (C-7), 164.6 (C-2), 163.3 (C-5), 161.3 (C-4'), 158.8 (C-9), 128.9 (C-2'/6'), 125.3 (C-1'), 117.4 (C-3'/5'), 105.4 (C-10), 104.8 (C-3), 99.8 (C-6), 94.8 (C-8), 94.0 (C-1b 4'-MEM), 72.3 (C-3b 4'-MEM), 68.8 (C-2b 4'-MEM) and 58.8 (C-4b 4'-MEM). EI-ms, *m/z*

(rel. int.): 359 $[M+1]^+$ (4), 358 $[M]^+$ (17), 282 (5), 270 (5), 241 (5), 153 (4), 89 (81), 59 (100). HR-Elms: Calcd for $C_{19}H_{18}O_7$: 358.1052. Found: 358.1048. Anal. Calcd for $C_{19}H_{18}O_7$: C, 63.66; H, 5.16. Found: C, 63.32; H, 5.34.

7-(3,3-Dimethylallyl)-4'-methoxyethoxymethylapigenin (6):

0.15 g (1.08 mmol) of anhydrous K_2CO_3 and 15 mg (0.04 mmol) of tetrabutylammonium iodide were agitated with a solution of 120 mg (0.34 mmol) of **5** in 5 ml of dry DMF. Then 0.08 ml of prenyl bromide (6.7 mmol) were added under agitation. After 1.5 h agitation at room temperature the reaction medium was diluted with H_2O, acidified (ice bath, 3N HCl) and extracted with EtOAc. The EtOAc extract contained a mixture of 7-prenyl-4'-MEM apigenin (**6**) and 5,7-diprenyl-4'-MEM apigenin (**6'**) which was separated by mplc on silica gel using hexane/EtOAc 8:2 as elution solvent. This yielded 72 mg (50%) of **6** and 20 mg (12%) of **6'** as oils.

^1H Nmr of compound (**6**) ($CDCl_3$; δ ppm/TMS): 12.72 (1 H, s, 5-OH), 7.78 (2 H, d, J = 9 Hz, H-2'/6'), 7.13 (2 H, d, J = 9 Hz, H-3'/5'), 6.52 (1 H, s, H-3), 6.44 (1 H, d, J = 2.2 Hz, H-8), 6.32 (1 H, d, J = 2.2 Hz, H-6), 5.46 (1 H, br t, J = 6.7 Hz, H-2"), 5.31 (2 H, s, H-1b 4'-MEM), 4.55 (2 H, d, J = 6.7 Hz, H-1"), 3.81 (2 H, m, H-2b 4'-MEM), 3.54 (2 H, m, H-3b 4'-MEM), 3.35 (3 H, s, H-4b 4'-MEM), 1.79 (3 H, s, H-4") and 1.74 (3 H, s, H-5"). ^{13}C Nmr of compound (**6**) ($CDCl_3$; δ ppm/TMS): 182.3 (C-4), 164.7 (C-7), 163.7 (C-2), 162.0 (C-5), 160.1 (C-4'), 157.6 (C-9), 139.1 (C-3"), 127.9 (C-2'/6'), 124.6 (C-1'), 118.6 (C-2"), 116.5 (C-3'/5'), 105.4 (C-10), 104.5 (C-3), 98.6 (C-6), 93.2 (C-8 + C-1b 4'-MEM), 71.5 (C-3b 4'-MEM), 67.9 (C-2b 4'-MEM), 65.4 (C-1"), 59.0 (C-4b 4'-MEM), 25.7 (C-4") and 18.2 (C-5"). Anal. Calcd for $C_{24}H_{26}O_7$: C, 67.58; H, 6.15. Found: C, 67.34; H, 6.16.

^1H Nmr of compound (**6'**) ($CDCl_3$; δ ppm/TMS):7.76 (2 H, d, J = 8.9 Hz, H-2'/6'), 7.11 (2 H, d, J = 8.9 Hz, H-3'/5'), 6.52 (1 H, s, H-3), 6.50 (1 H, d, J = 2.2 Hz, H-8), 6.34 (1 H, d, J = 2.2 Hz, H-6), 5.54 (1 H, br t, J = 6.4 Hz, H-2" 5-prenyl), 5.48 (1 H, br t, J = 6.7 Hz, H-2" 7-prenyl), 5.29 (2 H, s, H-1b 4'-MEM), 4.62 (2 H, d, J = 6.4 Hz, H-1" 5-prenyl), 4.56 (2 H, d, J = 6.7 Hz, H-1" 7-prenyl), 3.80 (2 H, m, H-2b 4'-MEM), 3.53 (2 H, m, H-3b 4'-MEM), 3.34 (3 H, s, H-4b 4'-MEM), 1.79 (3 H, s, H-4" 7-prenyl), 1.75 (6 H, bs, H-5" 7-prenyl + H-4" 5-prenyl) and 1.70 (3 H, s, H-5" 5-prenyl). ^{13}C Nmr of compound (**6'**) ($CDCl_3$; δ ppm/TMS): 177.5 (C-4), 163.0 (C-7), 160.4 (C-2), 160.0 (C-5), 159.7 (C-9), 159.6 (C-4'), 139.2 (C-3" 7-prenyl), 137.2 (C-3" 5-prenyl), 127.9 (C-1'), 127.5 (C-2'/6'), 119.5 (C-2" 5-prenyl), 118.6 (C-2" 7-prenyl), 116.4 (C-3'/5'), 109.4 (C-10), 107.8 (C-3), 97.9 (C-6), 93.5 (C-8), 93.2 (C-1b 4'-MEM), 71.5 (C-3b 4'-MEM), 67.9 (C-2b 4'-MEM), 66.5 (C-1" 5-prenyl), 65.2 (C-1" 7-prenyl), 59.0 (C-4b 4'-MEM), 25.8 (C-4" 5-prenyl), 25.7 (C-4" 7-prenyl), 18.3 (C-5" 5-prenyl) and 18.2 (C-5" 7-prenyl). EI-ms, *m/z* (rel. int.): 495 $[M+1]^+$ (13), 494 $[M]^+$ (29), 480 (11), 479 (36), 427 (12), 426 (30), 425 (14), 411 (27), 358 (10), 323 (9), 89 (100), 69 (29), 59 (88). HR-Elms compound (**6'**): Calcd for $C_{29}H_{34}O_7$: 494.2304. Found: 494.2296.

8-(1,1-Dimethylallyl)apigenin (7):

72 mg (0.17 mmol) of **6** and 50 mg (0.61 mmol) of anhydrous NaOAc in 5 ml (53.2 mmol) of Ac_2O were refluxed under stirring for 48 h. Excess Ac_2O was destroyed by addition of ice. After 1 h the medium was extracted in $CHCl_3$. The $CHCl_3$ extract was concentrated under reduced pressure and the residue was dissolved in 5% methanolic KOH. After 15 min the medium was diluted with H_2O, acidified (ice bath, 3N HCl) and extracted with EtOAc. The EtOAc extract was purified by column chromatography on polyamide using toluene/MeOH 9:1 as elution solvent. This yielded 30 mg (53%) of pure **7** as a yellow powder.

^1H Nmr (Acetone-d_6; δ ppm/TMS): 13.40 (1 H, s, 5-OH), 9.34 (br s, 7-OH + 4'-OH), 7.94 (2 H, d, J = 8.9 Hz, H-2'/6'), 7.02 (2 H, d, J = 8.9 Hz, H-3'/5'), 6.59 (1 H, s, H-3), 6.37 (1 H, dd, J = 17.5 and 10.6 Hz, H-2"), 6.32 (1 H, s, H-6), 4.93 (1 H, dd, J = 17.4 and 1.1 Hz, H-3"), 4.88 (1 H, dd, J = 10.6 and 1.1 Hz, H-3"), and 1.68 (6 H, s, H-4" + H-5"). ^{13}C Nmr (Acetone-d_6; δ ppm/TMS): 183.6 (C-4), 166.0 (C-2), 163.6 (C-7), 161.7 (C-4'), 161.2 (C-5), 157.3 (C-9), 151.2 (C-2"), 130.0 (C-2'/6'), 123.7 (C-1'), 117.1 (C-8), 116.7 (C-3'/5'), 109.4 (C-3"), 1O6.2 (C-10), 104.5 (C-3), 100.9 (C-6) and 42.0 (C-1"). C-4" and C-5" are overlapped by the solvent signal. EI-ms, *m/z* (rel. int.): 339 $[M+1]^+$ (4), 338 $[M]^+$ (17), 271 (19), 270 (100), 69 (79). HR-Elms: Calcd for $C_{20}H_{18}O_5$: 338.1154. Found: 338.1151. Anal. Calcd for $C_{20}H_{18}O_5$, H_2O: C, 67.39; H, 5.66. Found: C, 67.68; H, 5.62.

REFERENCES

1. J.B. Harborne, "The Flavonoids, Advances in Research since 1986", Chapman & Hall, London, 1994.
2. G. Delle Monache, J.F. de Mello, F. Delle Monache, G.B. Marini-Bettolo, O. Gonçalves de Lima, and J. Sidney de Barros Coêlho, *Gazz. Chim. Ital.*, 1974, **104**, 861.
3. T. Saitoh and S. Shibata, *Tetrahedron Lett.*, 1975, 4461.
4. M. Caffaratti, M.G. Ortega, M.E. Scafaria, L. Ariza Espinar, and H.R. Juliani, *Phytochemistry*, 1994, **36**, 1083.
5. T. Fukai, J. Ikuta, and T. Nomura, *Chem. Pharm. Bull.*, 1986, **34**, 1987.
6. M. Kaouadji and P. Ravanel, *Phytochemistry*, 1990, **29**, 1348.
7. M. Kaouadji, S. Chiron, J. Garcia, F. Thomasson, M. Tissut, and P. Ravanel, *Phytochemistry*, 1992, **31**, 2131.
8. P. Ravanel, M. Tissut, and R. Douce, *Plant Physiol.*, 1986, **80**, 500.
9. S. Creuzet, P. Ravanel, M. Tissut, and M. Kaouadji, *Phytochemistry*, 1988, **27**, 3093.
10. P. Ravanel, S. Creuzet, and M. Tissut, *Phytochemistry*, 1990, **29**, 441.
11. D. Barron, S. Jolivet, J.M. Crouzet, and A.M. Mariotte, *Tetrahedron Lett.*, 1992, **33**, 7137.
12. D. Barron and A.M. Mariotte, *Nat. Prod. Lett.*, 1994, **4**, 21.
13. D. Barron, C. El Aidi, and A.M. Mariotte, *Phytochem. Anal.*, 1994, **5**, 309.
14. A review on Claisen rearrangement in organic synthesis: R.P. Lutz, *Chem. Rev.*, 1984, **84**, 205.

15. For a rapid overview on the synthesis of flavones, see: H. Wagner and L. Farkas, "Synthesis of Flavonoids", *in* The Flavonoids, ed. by J.B. Harborne, T.J. Mabry and H. Mabry, Chapman and Hall, London, 1975, pp. 127-213.
16. A selection of papers on the dibenzoylmethane route: a) A.J. Kalra, M. Krishnamurti, and T.R. Seshadri, *Indian J. Chem.*, 1975, **13**, 779; b) D. Roy and R.N. Khanna, *Indian J. Chem.*, 1979, **18B**, 552; c) P.K. Jain, J.K. Makrandi, and S.K. Grover, *Synthesis*, 1982, 221; d) M. Iinuma, T. Tanaka, and S. Matsuura, *Chem. Pharm. Bull.*, 1984, **32**, 2296; e) S. Saxena, J.K. Makrandi, and S.K. Grover, *Synthesis*, 1985, 697; f) M. Cushman and D. Nagarathnam, *Tetrahedron Lett.*, *1990*, **31**, *6497*; g) D. Nagarathnam and M. Cushnam, *J. Org. Chem.*, 1991, **56**, 4884.
17. A selection of papers on the chalcone route: a) T. Patonay, G.Y. Litkei, E. Peli, V.P. Khilya, and A. Aitmambetov, *Pharmazie*, 1987, **42**, 662; b) K. Imafuku, M. Honda, and J.F.W. Mc.Omie, *Synthesis*, 1987, 199; c) M. Iinuma, T. Tanaka, K. Ito, and M. Mizuno, *Chem. Pharm. Bull.*, 1987, **35**, 660.
18. D. Noungoue-Tchamo, D. Barron, and A.M. Mariotte, *Nat. Prod. Lett.*, 1995, **7**, 73.
19. M.K. Anwer and A.F. Spatola, *Synthesis*, 1980, 929.
20. W. Lasek and M. Makosza, *Synthesis*, 1993, 780.
21. A.C. Jain and P.K. Bambah, *Indian J. Chem.*, 1987, **26B**, 488.

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