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SYNTHESIS OF 5-HYDROXY-6- AND 8-METHYLFLAVONES AND THEIR ULTRAVIOLET SPECTRAL DIFFERENTIATION

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Key Word Index—6-methylflavones; 8-methylflavones; 8-(*p*-hydroxybenzyl)flavones; UV spectral properties; synthesis.

Abstract—Ultraviolet spectra of fifteen natural or synthetic 6- and 8-methylflavones, with hydroxy group at C-5 and hydroxy or methoxy groups at C-7, were recorded in methanol and in presence of neutral or acidic aluminium chloride. Several spectral characteristics may be deduced which are typical of the *C*-methyl group position and distinguish these compounds from their 6-and 8-methoxy homologues. Moreover, for flavones of each the above-mentioned groups, B-ring substitution at C-4′, C-3′,4′ and C-3′,4′,5′ (hydroxy and/or methoxy groups) may be differentiated. On the other hand, spectral differences are unimportant between 8-methylflavones and 8-(*p*-hydroxybenzyl)flavones, in a similar manner mono- or disubstituted at C-4′ or C-3′,4′. During this work three 6-methylflavones and four 8-methylflavones were newly synthesized.

INTRODUCTION

In our previous paper on ultraviolet spectral analysis of 151 flavones [1], we defined twenty groups according to substitution pattern-spectrum relationships elaborated by studying spectra in methanol (MeOH) alone and with neutral or acidic aluminium chloride ($+AlCl_3+HCl$). Bathochromic shifts, locations, shapes and heights of four major peaks Ia and Ib, IIa and IIb were compared. Thus, distinguishing 6- and 8-methoxy- or methylflavones with hydroxy group at C-5 and hydroxy or methoxy group at C-7, spectral characteristics were attempted but from a few compounds belonging to groups 5 (**1**) and 6 (**12**) i.e. 8- and 6-methylflavones, respectively. A series of fifteen such natural or synthetic compounds **1**–**7** and **11**–**18** being today available, we improved the above-mentioned analysis and compared with them three natural 8-(*p*-hydroxybenzyl)flavones **8**–**10** (group 5′) [2]. Seven flavones were newly synthesized: **4**, **5**, **7**, **15**, **16**, **18** and **20**.

RESULTS AND DISCUSSION

The synthesis of isomeric 8- and 6-methylflavone mixtures **2** and **13**, **3** and **14**, **4** and **15**, **5** and **16**, was carried out in a three-step procedure, by dehydration treatment (Step 3) of the crude products obtained by the Baker-Venkataraman rearrangement [3, 4] (Step 2) of the corresponding *C*-methylphloracetophenone triaroyl esters (Step 1). Each mixture was resolved by recrystallization from acetic acid giving the 6-methylflavone (**13** [5, 6], **14** [6, 7], **15** or **16**) whereas the 8-methyl isomer (**2** [5, 6], **3** [6, 7], **4** or **5**) was recovered from the mother-liquors after concentration to dryness and recrystallization from pyridine. Following demethylation of each of the above-mentioned flavone pairs, their hydroxylated homologues were obtained **1** [8] and **11** [8], **6** [9] and **17** [7, 9], **7** and **18**, each mixture being resolved by preparative TLC, but yielding a small quantity of flavone **18** which was finally prepared according to the 8-methylluteolin synthesis procedure [9] i.e. by demethylation of flavone **20** obtained from the ester **19**.

The spectral data are listed in Table 1. All spectra, after addition of both $AlCl_3$ and HCl, exhibit the two bands Ia and Ib characteristic of flavones of class II whereas flavones of class I such as 6-methoxyflavones exhibit a single band Ib, as previously defined [1] (Table 2). The band Ia of 8-methyl- (group 5), 6-methyl- (group 6) and phloroglucinol-like A-ring flavones (group 7) is lower than 396 nm whereas for 8-methoxyflavones (group 15) this band is higher than 397 nm.

The flavones of group 7, without *C*-methyl groups

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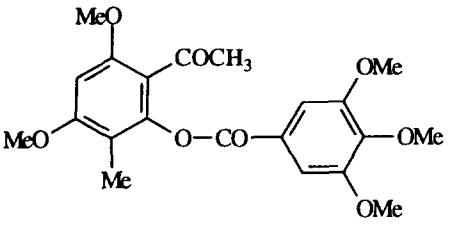

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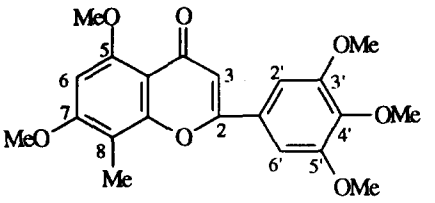

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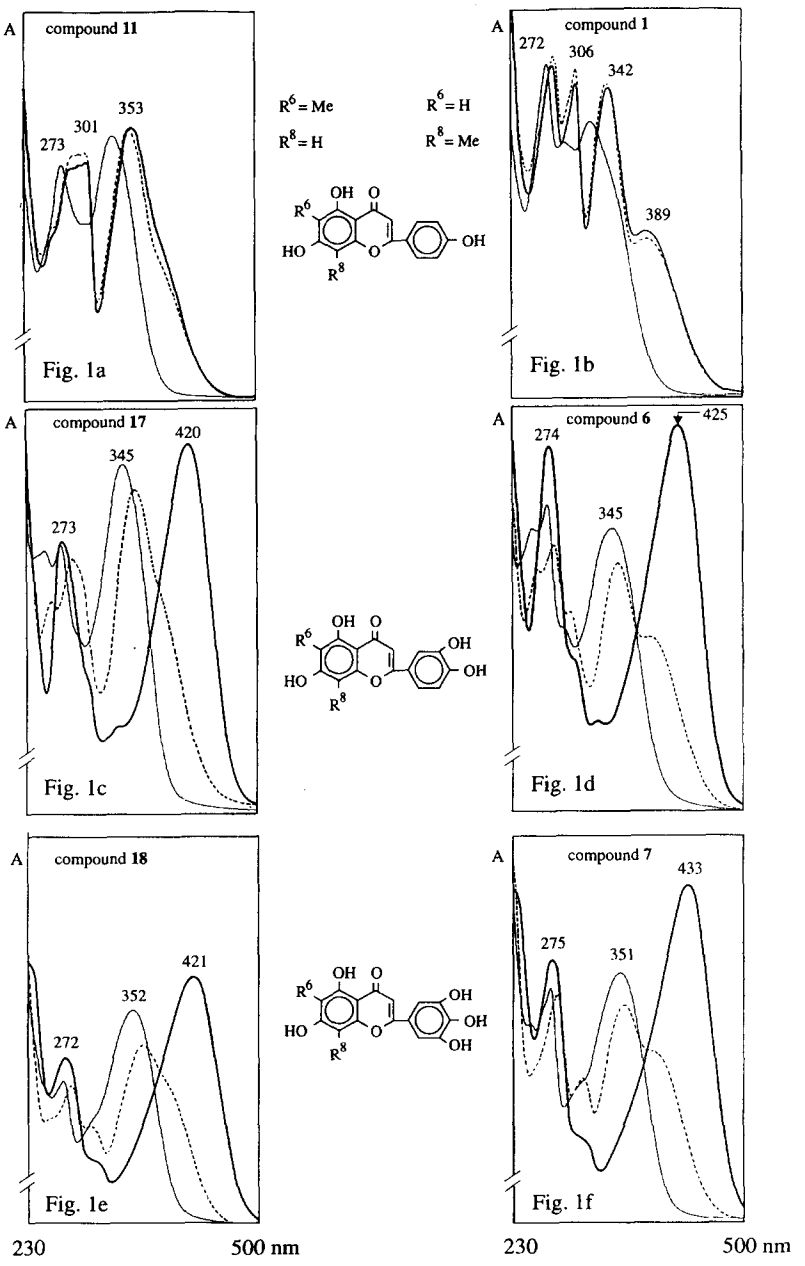


Fig. 1. UV spectra of isomer flavones **1** and **11**, **6** and **17**, **7** and **18** in MeOH (—), MeOH + $AlCl_3$(—) and MeOH + $AlCl_3$ + HCl (– – –).

[1], and their corresponding *C*-methyl derivatives of groups 5 (8-Me) and 6 (6-Me) may be discriminated by the spectral properties grouped together in Table 2 corroborating previous results [1, 10]. Moreover, the flavones may be differentiated on the basis of the following subheadings.

Distinction of 6- *and* 8-*methylflavones from spectra in MeOH*

In the case of 6-methylflavones, the absorbance ratio values of bands I and II is higher than that for their 8-methyl isomer (Table 2).

Distinction of 6- *and* 8-*methylflavones from spectra in MeOH* + $AlCl_3$ + *HCl*

Spectra of 6-methylflavones show band Ia (389–395 nm) as a shoulder whereas 8-methylflavones generally give a peak.

Distinction of 6- *and* 8-*methylflavones with differing B-ring oxygenation*

The substitution positions at C-4′, C-3′,4′ or C-3′,4′,5′ by hydroxy and/or methoxy groups are recognized for each flavone group. Thus, when a such substituent is present at C-4′, the bands IIa and IIb (+ $AlCl_3$ + HCl) are fused in a broad single peak at ca 300 nm for 6-methylflavones **11** (Fig. 1a), **12** and **13** and well separated for 8-methylflavones **1** (Fig. 1b) and **2**, band IIa being at 306 nm and the main peak of band IIb at ca 280 nm.

When substituents are present at C-3′,4′, band IIa occurs as a slight shoulder at 296 nm and band IIb as two peaks at 255 nm and 286 nm for 6-methylflavones **14** and **17** (Fig. 1c), whereas for 8-methylflavones **3** and **6** (Fig. 1d) band IIa occurs as a peak (**6**) or a shoulder (**3**) at ca 300 nm and double band IIb as a main peak in the 280–283 nm region and another peak in the range 255–261 nm.

When substituents are present at C-3′,4′,5′, band IIa appears as a peak between 300 and 304 nm for 6-methylflavones **15**, **16** and **18** (Fig. 1e) and between 305 and 312 nm for 8-methylflavones **4**, **5** and **7** (Fig. 1f).

On the other hand, no obvious spectral difference is observed which distinguishes 8-(*p*-hydroxybenzyl)flavones **8**, **9** and **10** from the 8-methylflavones similarly substituted on B-ring at C-4′ or C-3′,4′ i.e. from flavones **1**, **2** and **6**.

Distinction of 6-*methoxy- and* 6-*methylflavones*

The 6-methoxyflavones (group 1 [1]) and 6-methylflavones (group 6) may be easily recognized from the absence or presence of band Ia (+ $AlCl_3$ + HCl) respectively, whereas band IIa provides information on B-ring substitution. Thus, substituents at C-4′, C-3′,4′ and C-3′,4′,5′ agree with band IIa as a main peak at ca 300 nm, a shoulder between 292 and 298 nm and a peak between 300 and 308 nm, respectively.

Distinction of 8-*methoxy- and* 8-*methylflavones*

The 8-methoxyflavones (group 15 [1]) and 8-methylflavones (group 5) may be recognized from band Ia (+ $AlCl_3$ + HCl) which is higher and lower than 397 nm, respectively, whereas their B-ring substitution may be established from bands IIa and IIb. Thus, substituents at C-3′,4′ agree with band IIa as a shoulder or a peak at ca 300 nm and with double band IIb as a main peak and a shoulder in 280–285 nm and 255–264 nm ranges, respectively. Substituents at C-4′ and C-3′,4′,5′ agree with a similar band IIa between 305 and 312 nm but with a value lower or higher than 0.6 for the ratio below [1], respectively

$$\frac{A_1 - A}{A_2 - A}$$

A_1 = Band IIa absorbance,
A_2 = Band IIb absorbance,
A = Absorbance at 320 nm (λ_{min}).

EXPERIMENTAL

General

M.p.s. are uncorr. NaOH beads, 20–40 mesh (Sigma) or KOH powder (Merck) were used for Baker-Venkataraman rearrangement. TLC and prep. TLC (0.2 mm and 1 mm layers, respectively) were carried out on Merck F_{254} silica gel with solvent systems: (A) CH_2Cl_2–Me_2CO (19:1); (B) CH_2Cl_2–MeOH (9:1); (C) CH_2Cl_2–MeOH (17:3), (D) C_6H_6–Me_2CO–Hexane (8:1:1) or (E) C_6H_6–MeOH (4:1). The spots or bands were visualized under UV light (254 and 360 nm) and by spraying *bis*-diazotized benzidine followed by heating at 110°. Prep. TLC bands were eluted with MeOH. UV spectra were recorded on Uvikon 860 Kontron spectrophotometer according to the previously described procedures [1]. MS-FAB$^+$ spectra were recorded on VG ZAB2-SEQ spectrometer. ^{13}C NMR spectra were recorded at 50 MHz on AC 200 Bruker spectrometer.

5,7-*Dihydroxy*-2-(4-*hydroxy*-3,5-*dimethoxy*)*phenyl*-8-*methyl*-4*H*-1-*benzopyran*-4-*one* (**4**) *and* 6-*methyl isomer* (**15**). (a) Step 1: To a soln of *C*-methylphloracetophenone [11] (0.5 g, 2.7 mmol) in anhydrous pyridine (ca 7 ml), (4-acetyloxy-3,5-dimethoxy)benzoyl chloride (2.5 g, 10 mmol) was slowly added and then 4-(dimethylamino)pyridine catalytic amount (ca 10 mg). The mixture was stirred for 5 h at room temp., poured into an ice-water mixture (ca 150 ml) and then neutralized with 12 M HCl. The gummy product was poured off, triturated with satd $NaHCO_3$ soln (2 × 100 ml) and then washed until the filtrate was neutral. (b) Step 2: The dry solid was dissolved in DMSO and stirred with NaOH bead suspension

Table 1. UV spectral data of flavones **1**–**18**

Compound	Substitution pattern			Trivial name	λ_{max}^{MeOH} nm (band II)		λ_{max}^{MeOH} nm (band I)		$\lambda_{max}^{MeOH}+AlCl_3$ nm						$\lambda_{max}^{MeOH}+AlCl_3+HCl_{nm}$						$\Delta\lambda$ band I $AlCl_3$	$\Delta\lambda$ band I $AlCl_3+HCl$
	Group 5	OH	OMe	Me																		
1		5,7,4′	—	8	8-methylapigenin		272 (1.00)*	294 *s* (0.76)	323 (0.83)	260 *s* (0.72)	279 (1.00)	297 *s* (0.82)	306 (0.94)	344 (0.92)	389 (0.50)						66	
										260 *s* (0.76)	280 (1.00)		306 (0.96)	342 (0.91)	389 (0.46)						66
2		5,7	4′	8	8-methylacacetin		274 (1.00)	282 (0.83)	319 (0.80)	260 *s* (0.50)	281 (0.88)	297 *s* (0.83)	307 (1.00)	343 (0.93)	394 (0.47)						75	
										260 *s* (0.54)	282 (0.88)	297 *s* (0.88)	306 (1.00)	339 (0.85)	393 (0.39)						74
3		5,7	3′,4′	8		251 *s* (0.88)	274 (1.00)	294 *s* (0.74)	332 (0.94)	256 (0.75)	283 (0.98)		298 *s* (0.87)	350 (1.00)	392 (0.68)						60	
										255 (0.77)	283 (0.95)		298 *s* (0.84)	349 (1.00)	389 (0.62)						57
4		5,7,4′	3′,5′	8	8-methyltricin	244 (0.80)	273 (0.83)	302 *s* (0.56)	348 (1.00)	255 (0.60)	282 (0.86)		312 (0.57)	360 (1.00)	392 (0.74)						44	
										255 (0.66)	281 (0.89)		312 (0.61)	357 (1.00)	392 (0.63)						44
5		5,7	3′,4′,5′	8			275 (1.00)	295 *s* (0.76)	322 (0.80)	251 *s* (0.52)	284 (1.00)		306 (0.73)	345 (0.94)	395 (0.48)						73	
										254 *s* (0.50)	285 (1.00)		305 (0.93)	342 (0.89)	395 (0.41)						73
6		5,7,3′,4′	—	8	8-methylluteolin	256 (0.92)	272 (1.00)	292 (0.60)	345 (0.92)		274 (0.95)	302 (0.39)	330 (0.23)			425 (1.00)					80	
										261 (0.90)	280 (1.00)		300 (0.74)	354 (0.92)	389 (0.64)						44
7		5,7,3′,4′,5′	—	8	8-methyltricetin	262 *s* (0.85)	274 (0.94)	309 *s* (0.57)	351 (1.00)		275 (0.77)	305 *s* (0.26)	315 (0.23)			433 (1.00)					82	
										258 *s* (0.70)	282 (1.00)		310 (0.63)	359 (0.95)	392 (0.75)						41
	Group 5′	OH	OMe	*p*-OH benzyl																		
8		5,7,4′	—	8	8-(*p*-OHbenzyl) apigenin		274 (1.00)		326 (0.81)	262 (0.64)	280 (1.00)		308 (0.85)	350 (0.88)	396 (0.52)						70	
										257 (0.67)	280 (1.00)		308 (0.85)	346 (0.85)	392 (0.47)						66
9		5,7,3′	4′	8	8-(*p*-OHbenzyl) diosmetin	253 (0.82)	274 (1.00)		338 (0.83)	262 *s* (0.82)	280 (1.00)		301 (0.68)	359 (0.82)	396 (0.61)						58	
										262 (0.79)	282 (1.00)		299 *s* (0.71)	353 (0.83)	394 (0.51)						56

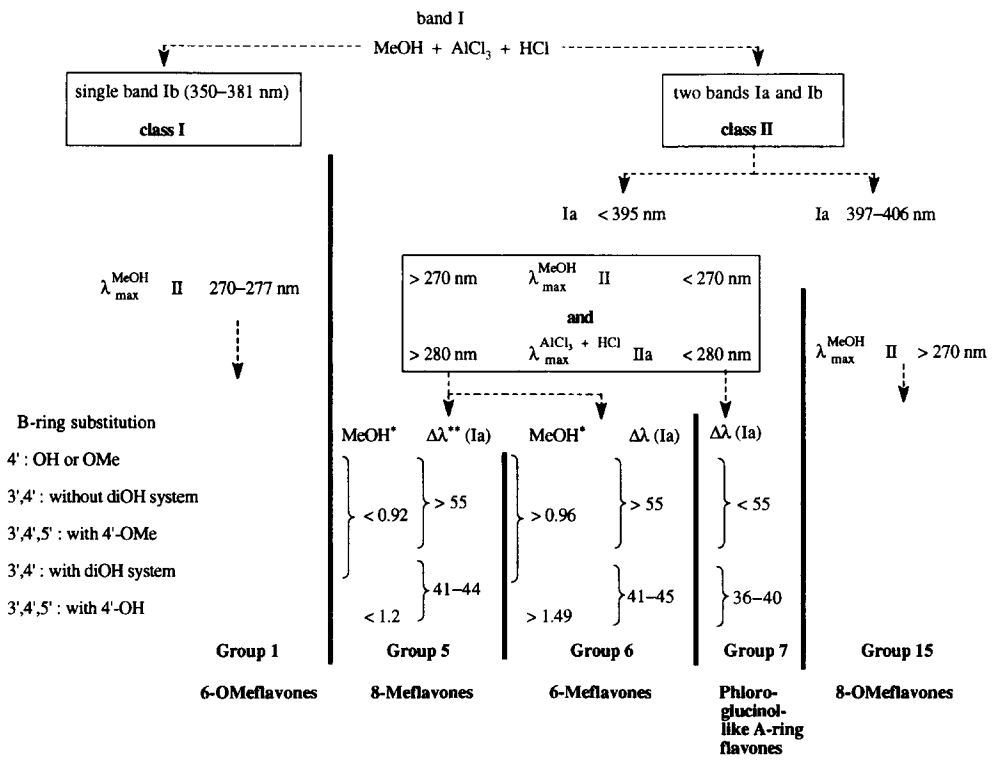
10		5,7,3′,4′	—	8	8-(*p*-OHbenzyl) luteolin	256 (0.75)	278 (1.00)		346 (0.92)		279 (0.98)		306 *s* (0.43)	335 *s* (0.22)		430 (1.00)	84	
										265 (0.82)	284 (0.99)		301 *s* (0.76)	362 (1.00)	394 *s* (0.45)			48
	Group 6	OH	OMe	Me														
11		5,7,4′	—	6	6-methylapigenin		273 (0.88)		331 (1.00)	260 *s* (0.60)	281 (0.83)	292 *s* (0.85)	301 (0.87)	353 (1.00)	392 *s* (0.56)		61	
										260 *s* (0.63)	282 (0.91)	292 *s* (0.91)	299 (0.92)	349 (1.00)	392 *s* (0.51)			61
12†		5,4′	7	6	6-methyl genkwanin		274 (0.85)		332 (1.00)	263 *s* (0.48)	288 (0.84)		301 (0.87)	351 (1.00)	390 *s* (0.45)		58	
										—	—		—	—	—			—
13		5,7	4′	6	6-methyl acacetin		274 (1.00)	306 (0.74)	328 (0.96)	261 *s* (0.45)	285 *s* (0.89)	295 (0.95)	303 (0.95)	349 (1.00)	394 *s* (0.46)		66	
										260 (0.50)	284 *s* (0.95)	291 (1.00)	301 (1.00)	345 (1.00)	389 *s* (0.41)			61
14		5,7	3′,4′	6		251 *s* (0.70)	274 (0.79)		336 (1.00)	257 (0.63)	286 (0.76)		297 *s* (0.72)	360 (1.00)	396 *s* (0.50)		60	
										255 (0.69)	286 (0.81)		296 *s* (0.77)	356 (1.00)	394 *s* (0.49)			56
15		5,7,4′	3′,5′	6	6-methyltricin		273 (0.43)		348 (1.00)	254 (0.46)	283 (0.59)		302 (0.51)	363 (1.00)	394 (0.65)		46	
										254 (0.44)	284 (0.50)		302 (0.51)	362 (1.00)	392 (0.66)			44
16		5,7	3′,4′,5′	6			274 (0.98)		329 (1.00)	253 (0.55)	285 (0.76)		303 (0.77)	353 (1.00)	395 *s* (0.49)		66	
										253 (0.69)	288 (0.94)		300 (0.94)	348 (1.00)	394 *s* (0.37)			65
17		5,7,3′,4′	—	6	6-methylluteolin	251 (0.75)	271 (0.77)		345 (1.00)		273 (0.74)	289 *s* (0.38)		338 (0.26)		420 (1.00)	75	
										260 (0.67)		285 (0.78)	297 *s* (0.94)	358 (1.00)	390 *s* (0.66)			45
18		5,7,3′,4′,5′	—	6	6-methyltricetin	262 *s* (0.64)	271 (0.67)	307 *s* (0.44)	352 (1.00)		272 (0.67)	280 (0.65)	310 (0.28)			421 (1.00)	69	
										255 (0.69)	281 (0.78)	304 (0.66)		367 (1.00)	393 *s* (0.79)			41

s = shoulder

* In parentheses, absorbance ratio value relative to the highest peak.

† E. Wollenweber's spectra [13] and Ref. [14].

Table 2. Spectral differences between flavones of groups 1, 5, 6, 7 and 15



* Absorbance ratio value of bands I and II.

** Band I bathochromic shift (nm), with both $AlCl_3$ and HCl, in relation to B-ring substitution.

(6 g, 0.15 mol) for 1 h at room temp. The mixture poured into an ice-water mixture (ca 150 ml) was kept at room temp. for 3 h and then neutralized with HOAc giving a precipitate which was filtered off, washed with water and then dried. (c) Step 3: The solid in HOAc (ca 8 ml) and 3 drops of 18 M H_2SO_4 were refluxed for 15 min before pouring into ice. The precipitate, filtered off, was recrystallized three times from HOAc yielding **15** (15 mg), m.p. 290–293° dec; R_f 0.29, solvent system (B); MS-FAB$^+$ *m/z*: 345 $[M+H]^+$. The mother-liquors were concd to dryness. The residue recrystallized three times from pyridine afforded **4** (11 mg), m.p. 298–303° dec; R_f 0.24, solvent system (B); MS-FAB$^+$ *m/z*: 345 $[M+H]^+$.

5,7-*Dihydroxy*-2-(3,4,5-*trimethoxyphenyl*)-8-*methyl*-4*H*-1-*benzopyran*-4-*one* (**5**) *and* 6-*methyl isomer* (**16**). The procedure described above for the preparation of **4** and **15** was repeated from *C*-methylphloracetophenone [11] (0.5 g, 2.7 mmol) and 3,4,5-trimethoxybenzoyl chloride (2.3 g, 10 mmol), yielding **16** (13 mg), m.p. 286–288°; R_f 0.48, solvent system (A); MS-FAB$^+$ *m/z*: 359 $[M+H]^+$ and **5** (10 mg), m.p. 275–277°; R_f 0.31, solvent system (A); MS-FAB$^+$ *m/z*: 359 $[M+H]^+$.

5,7-*Dihydroxy*-2-(3,4,5-*trihydroxyphenyl*)-8-*methyl*-4*H*-1-*benzopyran*-4-*one* (**7**). A mixture of **20** (0.1 g, 0.2 mmol) and anhydrous $AlCl_3$ (0.4 g, 3 mmol) in dry toluene (10 ml) was refluxed for 30 min. After 4 M HCl addition (4 ml), the mixture was refluxed for 10 min and then toluene was evaporated. After water addition (ca 20 ml), the precipitate was filtered off, washed with water and recrystallized from Me_2CO–H_2O (ca 2:1) and then twice from MeOH to give **7** (25 mg, 30%), m.p. > 355° dec; R_f 0.72, solvent system (C); MS-FAB$^+$ *m/z*: 317 $[M+H]^+$; ^{13}C NMR (DMSO-d_6): δ 7.56 (CH_3-8), 98.1 (C-6), 101.9 (C-8), 103.2 (C-3), 103.5 (C-10), 154.4 (C-9), 158.7 (C-5), 161.8 (C-7), 163.8 (C-2), 181.9 (C-4).

5,7-*Hydroxy*-2-(3,4,5-*trihydroxyphenyl*)-6-*methyl*-4*H*-1-*benzopyran*-4-*one* (**18**). The crude product of **5** and **16** synthesis Step 3 (70 mg) was heated with anhydrous pyridine hydrochloride (2 g, 17 mmol) at 230–240°, under vacuum for 1 h. After water addition, the brown mixture was extracted with EtOAc (3 × 10 ml). The residue, obtained by concentration to dryness of all the EtOAc fractions, was recrystallized twice from MeOH to give a mixture of **7** and **18**. Prep. TLC gave **18** (8 mg), m.p. > 360° dec; R_f 0.62, solvent system (C); MS-FAB$^+$ *m/z*: 317 $[M+H]^+$; ^{13}C NMR (DMSO-d_6): δ 7.24 (CH_3-6), 92.7 (C-8), 102.7 (C-3), 102.9 (C-10), 103.3 (C-6), 154.8 (C-9), 158.5 (C-5), 162.0 (C-7), 163.7 (C-2), 181.4 (C-4).

1-[2-(3,4,5-*Trimethoxybenzoyloxy*)-4,6-*dimethoxy*-3-*methyl*]*ethanone* (**19**). A mixture of 3,4,6-tri-

methylphloracetophenone [12] (1 g, 48 mmol) and 3,4,5-trimethoxybenzoyl chloride (2 g, 87 mmol) in anhydrous pyridine (10 ml), was refluxed for 4 h. The gummy product, obtained after water addition and neutralization with 12 M HCl, was extracted with EtOAc (3 × 25 ml). The organic layer grouping was washed with satd $NaHCO_3$ soln (3 × 50 ml), with water until neutral pH and then concd to dryness. The residue was recrystallized twice from EtOAc to give **19** (1 g, 52%), m.p. 173–175°; R_f 0.30, solvent system (D).

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-8-methyl-4H-1-benzopyran-4-one (**20**). A stirred mixture of **19** (0.8 g, 2 mmol), KOH powder (0.8 g, 14 mmol) and anhydrous pyridine (ca 8 ml) was allowed to stand at room temp. for 30 min. Dilution and neutralization with HOAc gave a precipitate filtered off and then washed. The dry solid dissolved in HOAc (6 ml) and 18 M H_2SO_4 (20 μl) was refluxed for 15 min. The crystals, formed on keeping at room temp., were filtered off and then recrystallized twice for MeOH to give **20** (0.54 g, 70%), m.p. 221–222°C; R_f 0.56, solvent system (E); MS-FAB$^+$ m/z: 387 $[M+H]^+$.

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