

Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids.

XIX.¹⁾ A Convenient Method for Synthesizing 3,5,6,7,8-Pentaoxygenated Flavones

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The methoxymethyl ethers of 6-hydroxy-5,7,8-trimethoxyflavones, which were derived from 2',5'-dihydroxy-3',4',6'-trimethoxyacetophenone, were oxidized with dimethyldioxirane to give the corresponding 3-hydroxyflavones. Selective *O*-alkylation and dealkylation of the 3-hydroxyflavones were examined and a convenient method for synthesizing the following ten kinds of 3,5,6,7,8-pentaoxygenated flavones was established: 3-hydroxy-5,6,7,8-tetramethoxyflavones, 3,5-dihydroxy-6,7,8-trimethoxyflavones, 3,6-dihydroxy-5,7,8-trimethoxyflavones, 3,5,6-trihydroxy-7,8-dimethoxyflavones, 3,5,6,7-tetrahydroxy-8-methoxyflavones, and their 3-methyl ethers. Furthermore, 3,5,8-trihydroxy-4',6,7-trimethoxyflavone, 3,8-dihydroxy-4',5,6,7-tetramethoxyflavone, and 5,8-dihydroxy-3,6,7-trimethoxyflavones were similarly synthesized and their spectral properties were examined. Additionally, the proposed structures of three natural flavones were revised.

Key words 3,5,6,7,8-pentaoxygenated flavone; ¹³C-NMR; selective demethylation; oxidation with dimethyldioxirane; synthesis; revised structure

In a previous paper,²⁾ we have reported an unambiguous method for synthesizing 5,8-dihydroxy-6,7-dimethoxyflavones and we revised the structures of four natural flavones which had been proposed to have the above structures to the isomeric 5,7-dihydroxy-6,8-dimethoxyflavones. The structural elucidation of flavones such as 3,5,6,7,8-pentaoxygenated flavones by ¹H-NMR is generally difficult due to lack of aromatic protons in the A-ring^{2,3)} and ¹³C-NMR may be the preferred approach. Convenient methods for synthesizing these flavones, however, have not been established so far and their general properties are not always clear, although some have been synthesized by using the Allan–Robinson reaction^{4,5)} or oxidative cyclization of chalcones with hydrogen peroxide⁶⁾ (AFO reaction).

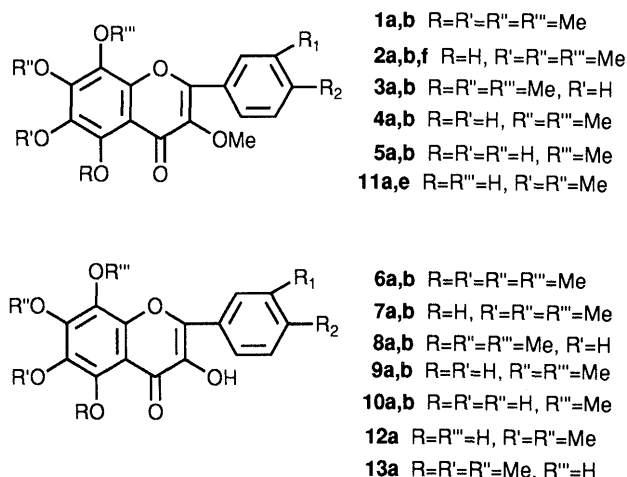
We have been trying to develop convenient methods for synthesizing polyhydroxyflavones by the application of selective *O*-alkylation and dealkylation in order to clarify their general properties and to survey their biological activities,⁷⁾ and we reported in the previous paper that 3,5,6,7-tetrahydroxyflavones are easily synthesized from 6-hydroxy-5,7-dimethoxyflavones.¹⁾ The method may also be applicable for the synthesis of various 3,5,6,7,8-pentaoxygenated flavones from flavones such as 6-hydroxy-5,7,8-trimethoxyflavones (17).^{2,8)} Here we describe a convenient method for synthesizing several kinds of 3,5,6,7,8-pentaoxygenated flavones (1–13) and isomeric flavone derivatives,²⁾ and we discuss their spectral properties. Additionally, we have revised the structures of two natural flavones,^{9,10)} proposed to be 8-hydroxyflavone derivatives, and a flavone,¹¹⁾ isolated from *Anisomeles ovata* and proposed to have the structure 2b.

Results and Discussion

Synthesis of 3,5,6,7,8-Pentaoxygenated Flavones In our synthetic study of polyhydroxyflavones, the following results have been obtained: (1) 3-hydroxy-5,7-dimethoxy-6-methoxymethoxyflavones¹⁾ can be conveniently synthe-

sized from 5,7-dimethoxy-6-(methoxymethoxy)flavones by oxidation with dimethyldioxirane; (2) the 5- or 3-methoxy group in 3-hydroxy-5-methoxy- or 5-hydroxy-3-methoxyflavones is quantitatively cleaved with anhydrous aluminum bromide in acetonitrile *via* the corresponding tosylate^{12,13)}; (3) the 5- and 7-methoxy groups in 6-hydroxy-5,7-dimethoxyflavones^{14,15)} and 6-hydroxy-5,7,8-trimethoxyflavones⁸⁾ can be selectively cleaved. The results suggest that the several 3,5,6,7,8-pentaoxygenated flavones may be conveniently synthesized from 6-hydroxy-5,7,8-trimethoxyflavone (17). Therefore, a method for synthesizing the flavones (1–5) with the 3-methoxy group was examined first according to the process shown in Chart 1.

The mono(methoxymethyl) ether (15) of 2',5'-dihydroxy-3',4',6'-trimethoxyacetophenone (14)¹⁶⁾ was benzoylated with substituted benzoyl chloride and then transformed with potassium hydroxide in pyridine to give a diketone



a; R₁=H, R₂=OMe b; R₁=OMe, R₂=OH

e; R₁=R₂=H f; R₁=OH, R₂=OMe

Fig. 1

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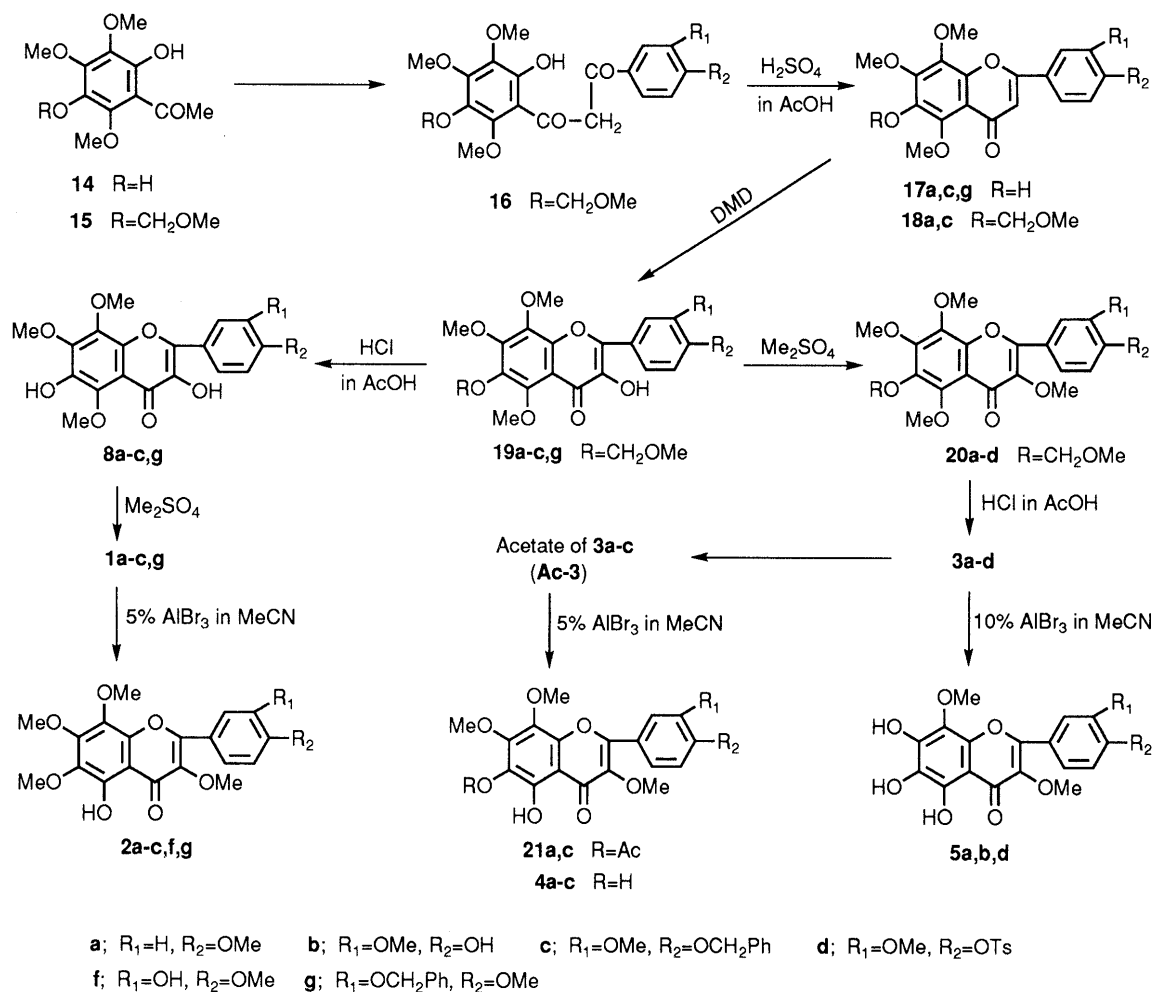


Chart 1

derivative (**16a,c**). Cyclization of the diketone **16** with a small amount of sulfuric acid in acetic acid afforded 6-hydroxy-5,7,8-trimethoxyflavone (**17a,c**) accompanied with demethoxymethylation. The methoxymethyl ether (**18a,c**) of **17** was converted into 3-hydroxy-5,7,8-trimethoxy-6-(methoxymethoxy)flavone (**19a,c**) in high yield by oxidation with dimethyldioxirane (DMD) followed by treatment with a small amount of *p*-toluenesulfonic acid.¹⁷⁾ The flavone **19b** was obtained from **19c** by hydrogenolysis with palladium on charcoal.

Hydrolysis of **19a** with hydrochloric acid in acetic acid afforded quantitatively 3,6-dihydroxy-4',5,7,8-tetramethoxyflavone (**8a**), which was converted into 3,4',5,6,7,8-hexamethoxyflavone (**1a**) by methylation. The demethylation of **1a** with 5% (w/v) anhydrous aluminum bromide in acetonitrile afforded 5-hydroxy-3,4',6,7,8-pentamethoxyflavone (**2a**). The flavone **19a** was also converted into 6-hydroxy-3,4',5,7,8-pentamethoxyflavone (**3a**) via its methyl ether (**20a**). Although the direct demethylation of **3a** to **4a** was accompanied with the formation of 5,6,7-trihydroxy-3,4',8-trimethoxyflavone (**5a**), the 5-methoxy group in the acetate (Ac-**3a**) of **3a** was selectively cleaved to give quantitatively 6-acetoxy-5-hydroxy-3,4',7,8-tetramethoxyflavone (**21a**), which was easily hydrolyzed to **4a**, as in the case of the demethylation of 6-hydroxy-5,7,8-trimethoxyflavones.⁸⁾ On the other hand, the 5- and 7-methoxy groups in **3a** were simultaneously cleaved with

10% (w/v) anhydrous aluminum bromide in acetonitrile at 50 °C to give **5a** in high yield.

In all the synthetic reactions except for the demethylation of **3a** to **5a**, the benzyloxy group at the B-ring in the flavone skeleton was stable. Therefore, the flavones (**1c—4c**) with a benzyloxy group in the B-ring could be synthesized from **19c** by the same method, and the desired flavones (**1b—4b**) were easily obtained from these by hydrogenolysis with palladium on charcoal. In the demethylation of **3c** with 10% (w/v) aluminum bromide in acetonitrile, however, the cleavage of the 3'-methoxy group proceeded with participation of the neighboring 4'-hydroxy group formed by the debenzoylation to afford a large amount of a further demethylated product of **5b** with increasing reaction time. Therefore, 4',5,6,7-tetrahydroxy-3,3',8-trimethoxyflavone (**5b**) was synthesized as follows. That is, 4'-hydroxy-3,3',5,7,8-pentamethoxy-6-(methoxymethoxy)flavone (**20b**), which was obtained from **20c** by hydrogenolysis, was converted into 6-hydroxy-3,3',5,7,8-pentamethoxy-4'-tosyloxyflavone (**3d**) by tosylation, followed by demethoxymethylation. The demethylation of **3d** proceeded smoothly to give the 5,6,7-trihydroxyflavone (**5d**) in high yield. Although the direct hydrolysis of **5d** to **5b** was not achieved,^{1,13)} the 4'-tosyloxy group in the crude methoxymethyl ether obtained from **5d** by methoxymethylation [main product; 6,7-bis(methoxymethyl) ether] was smoothly hydrolyzed

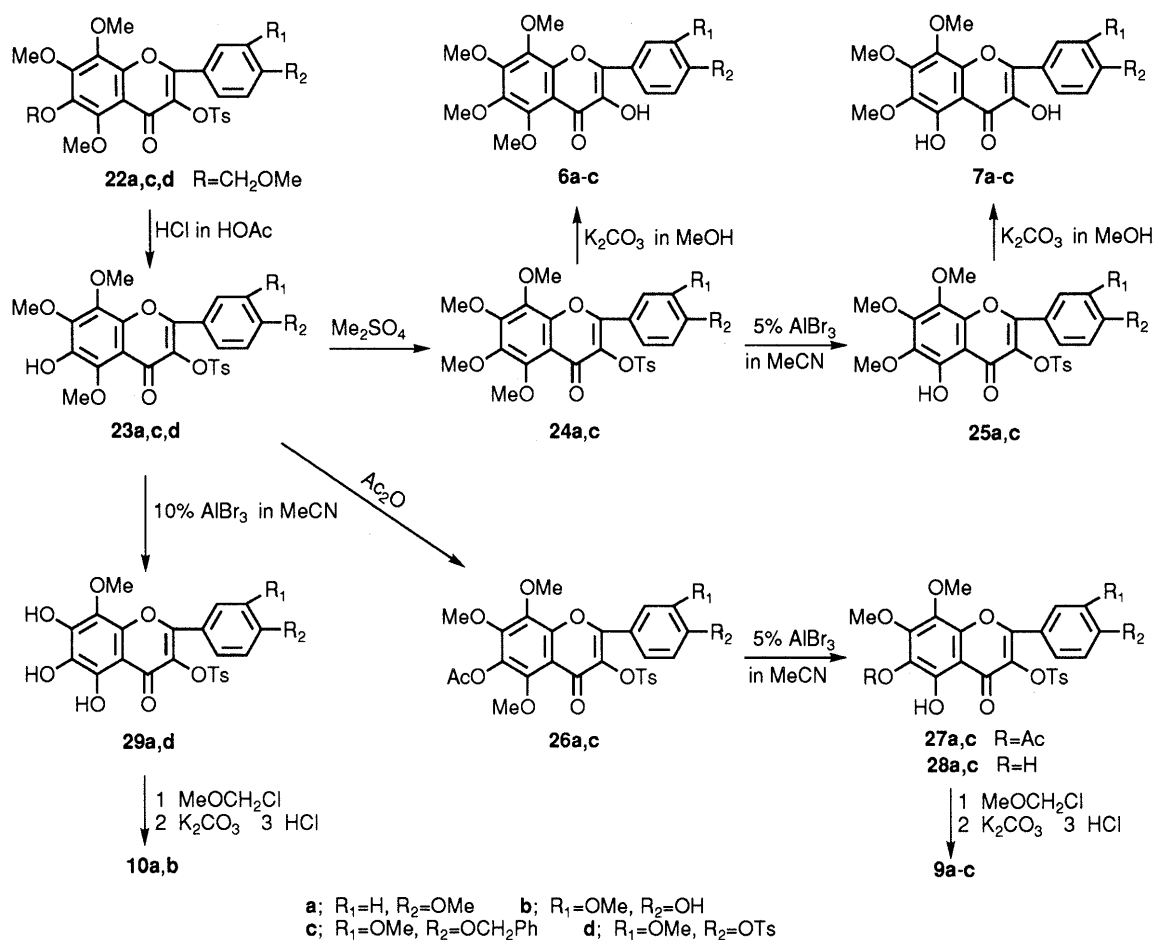


Chart 2

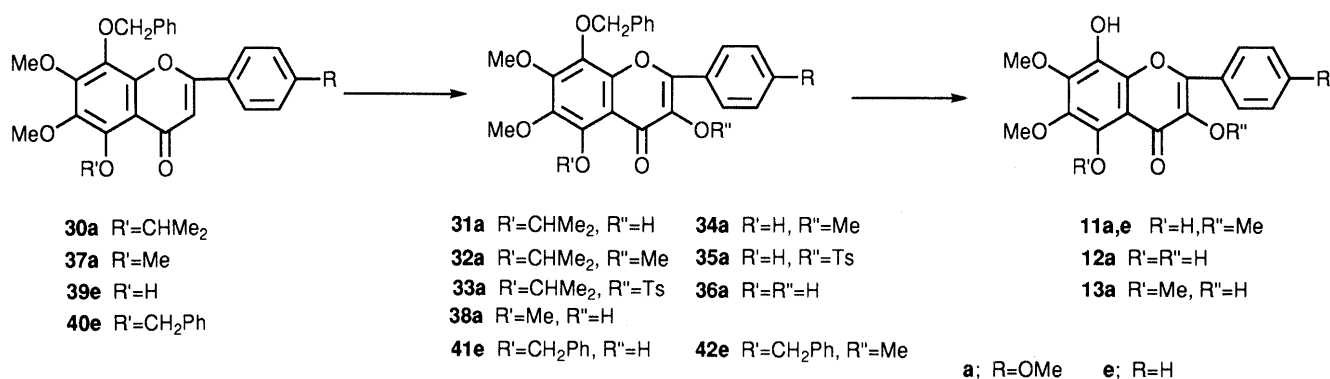


Chart 3

with potassium carbonate in methanol and the resultant compound was demethoxymethylated with hydrochloric acid in acetic acid to give the desired **5b** without the formation of by-product, in contrast to the deprotection of 3,5-dihydroxy-4'-methoxy-6,7-bis(methoxymethoxy)-flavone.¹⁾

The flavones (**6**–**10**) with the 3-hydroxy group were also synthesized by a similar method (Chart 2). That is, the 3-tosyloxyflavones (**22a, c, d**) which were obtained from **19a, c, b** by tosylation were demethoxymethylated to give **23a, c, d**. The flavones **23a, c** were converted into 5-hydroxyflavones **25a, c** and **28a, c** via their methyl ethers (**24a, c**) or acetates (**26a, c**). The direct demethylation of **23a, d** with 10% (w/v) anhydrous aluminum bromide in

acetonitrile afforded the 5,6,7-trihydroxyflavones **29a, d** in high yield. The 3-tosyloxy group in **24a, c** and **25a, c** was directly hydrolyzed with potassium carbonate in methanol to give **6a, c** and **7a, c**. The tosyloxy groups in **28a, c** and **29a, d** were hydrolyzed via their methoxymethyl ethers as in the case of the hydrolysis of **5d** to **5b**, to give **9a, c** and **10a, b**, respectively. The benzyloxyflavones (**6c, 7c, 8c**, and **9c**) were quantitatively converted into the corresponding hydroxyflavones (**6b, 7b, 8b**, and **9b**).

The method is useful as a general one for synthesizing 3,5,6,7,8-pentaoxygenated flavones and the 8-hydroxyflavones (**11**–**13**) can be synthesized by a similar process (Chart 3). The oxidation of 8-benzyloxy-5-isopropoxy-4',6,7-trimethoxyflavone (**30a**)²⁾ with dimethyldioxirane

Table 1. UV Spectral Data for 3,5,6,7,8-Pentaoxygenated Flavones^{a)}

Compd.	λ_{\max} nm (log ϵ)								
	EtOH			EtOH-AlCl ₃			EtOH-NaOAc		
1a	268 (4.31)	330 (4.37)							
2a	279 (4.31)	334 (4.32)	290 (4.26)	311 (4.26)	355 (4.37)	420 (3.86)	279 (4.33)	334 (4.32)	
3a	276 (4.30)	330 (4.38)					282 (4.28)	332 (4.35)	
4a	292 (4.33)	334 (4.27)		311 (4.36)	364 (4.39)	430sh (3.61)	297 (4.32)		
11a	290—302 (4.35)	333 (4.26)	300sh (4.25)	322 (4.37)	357 (4.33)	445 (3.70)	300 (4.36)		
5a	281 (4.29)	375i (3.96)		307 (4.32)	379 (4.30)		272 (4.31)	376 (4.02)	
6a	260 (4.30)	362 (4.31)	271 (4.38)			429 (4.43)	261 (4.31)	366 (4.25)	415i (3.71)
7a	258 (4.17)	278 (4.26)	339 (4.23)	380 (4.20)	265 (4.22)	286 (4.21)	368 (4.26)	438 (4.21)	262 (4.34)
8a	262 (4.30)	270sh (4.28)	347 (4.35)			272 (4.44)	428 (4.42)	261 (4.26)	296 (4.16)
13a	273 (4.29)	339 (4.21)	365 (4.21)	269 (4.41)	375sh (4.05)	431 (4.39)	277 (4.22)	291 (4.22)	320 (4.20)
9a	258 (4.12)	283 (4.24)	345 (4.30)	383i (4.05)	295 (4.20)	379 (3.89)	432sh (4.23)	274 (4.23)	385 (4.20)
12a	258 (4.14)	283 (4.32)	340 (4.27)	388 (4.06)	268 (4.27)	288 (4.27)	373 (4.28)	445 (4.13)	280 (4.34)
10a	279 (4.25)	305 (4.11)	380 (4.13)		280 (4.21)	307sh (4.09)	397 (4.35)	278 (4.17)	387 (4.00)
1b	254 (4.34)	267i (4.26)	347 (4.37)				254 (4.31)	350 (4.21)	414 (4.10)
2b	261 (4.26)	279 (4.25)	356 (4.29)	270 (4.20)	289 (4.24)	372 (4.33)	415i (4.04)	270 (4.27)	430 (4.26)
3b	258 (4.27)	274 (4.25)	346 (4.39)				258 (4.26)	350 (4.29)	407 (4.04)
4b	261 (4.15)	288 (4.25)	351 (4.32)	265 (4.11)	302 (4.25)	378 (4.38)		288 (4.17)	352 (4.18)
5b	278 (4.27)	325 (4.18)	370 (4.14)	266 (4.17)	296 (4.21)	390 (4.38)		271 (4.23)	328 (4.15)
6b	257 (4.38)	371 (4.36)		267 (4.43)		436 (4.47)	257 (4.35)	377 (4.27)	420sh (3.92)
7b	261 (4.35)	277i (4.21)	384 (4.29)	271 (4.31)		381 (4.26)	442 (4.25)	262 (4.39)	432 (4.21)
8b	261 (4.32)		366 (4.35)	272 (4.43)		435 (4.45)	260 (4.40)	367 (4.39)	415i (4.21)
9b	263 (4.14)	286 (4.18)	357 (4.14)	268 (4.18)	294 (4.18)	391 (4.39)	440i (4.05)	293 (4.22)	386 (4.01)
10b	260 (4.15)	320 (4.09)	365i (3.98)	274 (4.21)		406 (4.35)		272 (4.09)	327 (4.02)

a) sh, Shoulder; i, inflection point.

afforded the 3-hydroxyflavone **31a**, which was converted into the methyl ether (**32a**) and tosylate (**33a**). The 5-isopropoxy group in **32a** and **33a** was selectively cleaved with anhydrous aluminum chloride in acetonitrile at room temperature without the cleavage of the 8-benzyloxy group to give the 5-hydroxyflavones (**34a** and **35a**). The flavone **34a** was debenzylated to the 5,8-dihydroxyflavone (**11a**), which had been synthesized by the oxidative demethylation of **1a** with nitric acid by Herz *et al.*,⁶⁾ and the flavone **35a** was also converted into **12a** via **36a**. The 3,8-dihydroxyflavone **13a** was synthesized from 8-benzyloxy-4',5,6,7-tetramethoxyflavone (**37a**)²⁾ via **38a**. 5,8-Dihydroxy-3,6,7-trimethoxyflavone (**11e**) was also synthesized from 8-benzyloxy-5-hydroxy-6,7-dimethoxyflavone (**39e**)²⁾ via **40e**, **41e**, and **42e**.

Characterization of the 3,5,6,7,8-Pentaoxygenated Flavones and Identification of Some Natural Flavones The UV spectra of the synthesized flavones (**1**—**13**) exhibit a characteristic absorption pattern corresponding to the respective structures and the absorption bands of the hydroxyflavones are characteristically shifted upon the addition of aluminum chloride or sodium acetate, as shown in Table 1. In the spectra, the bathochromic shift of band I for the 3-hydroxyflavones is greater than that for the 3-methoxyflavones upon addition of aluminum chloride and a clear absorption band appears at 400—440 nm. Upon the addition of sodium acetate, the UV spectra of 3-methoxyflavones (**3a**, **4a**, and **11a**) with a hydroxy group at the 6- or 8-position change to a characteristic absorption pattern without the bathochromic

Table 2. ¹H-NMR Spectral Data for 3,5,6,7,8-Pentaoxygenated Flavones^{a)}

Compd.	Solv.	OMe						Arom. H				OH or OAc					
		C ₃	C ₅	C ₆	C ₇	C ₈	B ring	C _{3'}	C _{5'}	C _{2'}	C _{6'}	C ₃	C ₅	C ₆	C ₇	C ₈	C _{4'}
1a	DMSO	3.75	3.71	3.79	3.95	3.87	3.79	7.02 d (2H)	7.89 d (2H)	—	—	—	—	—	—	—	—
2a	DMSO	3.77	—	3.77	3.97	3.83	3.82	7.10 d (2H)	7.98 d (2H)	—	12.31	—	—	—	—	—	—
3a	DMSO	3.74	3.74	—	3.93	3.89	3.83	7.07 d (2H)	7.95 d (2H)	—	—	9.20	—	—	—	—	—
4a	DMSO	3.79	—	—	3.94	3.87	3.85	7.11 d (2H)	8.00 d (2H)	—	12.08	9.01 brs	—	—	—	—	—
11a	DMSO	3.81	—	3.87	3.94	—	3.84	7.16 d (2H)	8.13 d (2H)	—	12.13	—	—	—	9.30	—	—
5a	DMSO	3.80	—	—	—	3.86	3.83	7.17 d (2H)	8.03 d (2H)	—	12.21	9.05 br	10.26 br	—	—	—	—
6a	DMSO	—	3.78	3.78	3.96	3.89	3.78	7.01 d (2H)	8.01 d (2H)	9.00 brs	—	—	—	—	—	—	—
7a	DMSO	—	—	3.77	3.96	3.84	3.79	7.05 d (2H)	8.07 d (2H)	9.60 brs	12.09	—	—	—	—	—	—
8a	DMSO	—	3.73	—	3.92	3.89	3.78	7.05 d (2H)	8.04 d (2H)	9.08	—	8.90	—	—	—	—	—
13a	DMSO	—	3.86	3.88	3.94	—	3.81	7.14 d (2H)	8.24 d (2H)	9.65	—	—	—	—	9.17	—	—
9a	DMSO	—	—	—	3.92	3.85	3.80	7.06 d (2H)	8.14 d (2H)	9.47	11.91	8.95 brs	—	—	—	—	—
12a	DMSO	—	—	3.86	3.95	—	3.85	7.15 d (2H)	8.26 d (2H)	9.66	11.95	—	—	—	9.26	—	—
10a	DMSO	—	—	—	—	3.85	3.85	7.16 d (2H)	8.15 d (2H)	9.45	11.97	8.94	10.22	—	—	—	—
1b	DMSO	3.82	3.80	3.85	4.03	3.96	3.88	—	7.00 d	7.67 d'	7.62 dd	—	—	—	—	—	9.89
2b	DMSO	3.83	—	3.83	4.03	3.91	3.88	—	7.01 d	7.69 d'	7.65 dd	—	12.46	—	—	—	10.03
2f	DMSO	3.83	—	3.82	4.03	3.91	3.88	—	7.15 d	7.61 brs	7.62 dd	—	12.45	—	—	—	9.55 ^{b)}
3b	DMSO	3.79	3.77	—	3.97	3.95	3.88	—	6.99 d	7.67 d'	7.61 dd	—	—	9.29	—	—	9.85
4b	DMSO	3.83	—	—	3.96	3.92	3.88	—	7.01 d	7.69 d'	7.65 dd	—	12.21	9.12	—	—	10.00
5b	DMSO	3.83	—	—	—	3.88	3.87	—	7.00 d	7.68 d'	7.63 dd	—	12.25	9.01 brs	10.23 brs	—	9.95
6b	DMSO	—	3.84	3.86	4.04	3.99	3.87	—	6.98 d	7.78 d'	7.75 dd	9.15	—	—	—	—	9.72
7b	DMSO	—	—	3.84	4.03	3.94	3.87	—	6.99 d	7.79 brs	7.78 dd	9.66	12.27	—	—	—	9.85
8b	DMSO	—	3.80	—	3.984	3.98	3.87	—	6.98 d	7.77 d'	7.74 dd	9.24 brs	—	9.02	—	—	9.70 brs
9b	DMSO	—	—	—	3.97	3.94	3.87	—	6.99 d	7.79 brs	7.78 dd	9.51	11.99	9.02 brs	—	—	9.83
10b	DMSO	—	—	—	—	3.89	3.87	—	6.99 d	7.79 d'	7.75 dd	9.36	11.99	8.90 brs	10.18	—	9.77
Ac-2a	CDCl ₃	3.75	—	3.84	4.04	3.97	3.84	6.95 d (2H)	8.04 d (2H)	—	2.45	—	—	—	—	—	—
Ac-3a	CDCl ₃	3.85	3.90	—	4.01	3.98	3.86	6.98 d (2H)	8.07 d (2H)	—	—	2.38	—	—	—	—	—
Ac-4a	CDCl ₃	3.77	—	—	4.01	3.99	3.85	6.95 d (2H)	8.02 d (2H)	—	2.41	2.30	—	—	—	—	—
Ac-11a	CDCl ₃	3.77	—	3.89	4.03	—	3.89	7.01 d (2H)	7.95 d (2H)	—	2.51	—	—	—	2.46	—	—
Ac-5a	CDCl ₃	3.72	—	—	—	3.93	3.80	6.88 d (2H)	7.92 d (2H)	—	2.40	2.33	2.29	—	—	—	—
Ac-6a	CDCl ₃	—	3.88	3.88	4.03	3.92	3.81	6.93 d (2H)	7.82 d (2H)	2.33	—	—	—	—	—	—	—
Ac-7a	CDCl ₃	—	—	3.83	4.04	3.96	3.83	6.91 d (2H)	7.73 d (2H)	2.30	2.43	—	—	—	—	—	—
Ac-8a	CDCl ₃	—	3.84	—	3.97	3.93	3.84	6.93 d (2H)	7.79 d (2H)	2.34	—	2.34	—	—	—	—	—
Ac-13a	CDCl ₃	—	3.96	3.98	4.04	—	3.88	7.00 d (2H)	7.74 d (2H)	2.35	—	—	—	—	2.42	—	—
Ac-9a	CDCl ₃	—	—	—	3.98	3.94	3.81	6.92 d (2H)	7.74 d (2H)	2.29	2.37	2.29	—	—	—	—	—
Ac-12a	CDCl ₃	—	—	3.89	4.04	—	3.88	7.00 d (2H)	7.72 d (2H)	2.32	2.47	—	—	—	2.42	—	—
Ac-10a	CDCl ₃	—	—	—	—	3.96	3.82	6.93 d (2H)	7.77 d (2H)	2.29	2.37	2.32	2.29	—	—	—	—
Ac-1b	CDCl ₃	3.90	3.95	3.98	4.10	3.99	3.92	—	7.19 d	7.88 d'	7.80 dd	—	—	—	—	—	2.36
Ac-2b	CDCl ₃	3.83	—	3.89	4.10	4.02	3.92	—	7.19 d	7.83 d'	7.77 dd	—	2.51	—	—	—	2.36
Ac-3b	CDCl ₃	3.89	3.93	—	4.05	3.99	3.92	—	7.19 d	7.87 d'	7.79 dd	—	—	2.40	—	—	2.37
Ac-4b	CDCl ₃	3.82	—	—	4.07	4.02	3.92	—	7.19 d	7.82 d'	7.76 dd	—	2.46	2.36	—	—	2.36
Ac-5b	CDCl ₃	3.82	—	—	—	4.02	3.91	—	7.19 d	7.78 d'	7.73 dd	—	2.45	2.37	2.34	—	2.36
Ac-6b	CDCl ₃	—	3.95	3.94	4.10	3.98	3.90	—	7.18 d	7.53 brs	7.52 dd	2.37	—	—	—	—	2.36
Ac-7b	CDCl ₃	—	—	3.88	4.10	4.01	3.89	—	7.18 d	7.48 brs	7.49 dd	2.34	2.47	—	—	—	2.36
Ac-8b	CDCl ₃	—	3.90	—	4.06	3.98	3.89	—	7.19 d	7.52 d'	7.52 dd	2.37	—	2.40	—	—	2.36
Ac-9b	CDCl ₃	—	—	—	4.07	4.01	3.89	—	7.19 d	7.47 brs	7.48 dd	2.33	2.42	2.35	—	—	2.36
Ac-10b	CDCl ₃	—	—	—	—	4.01	3.88	—	7.19 d	7.45 brs	7.46 dd	2.33	2.41	2.37	2.33	—	2.36

a) brs, broad singlet; br, broad; d, doublet ($J=8.5$ Hz); d', doublet ($J=2.5$ Hz); dd, double doublet ($J=8.5, 2.5$ Hz). b) 3'-Hydroxyl proton.

shift of band I and a bathochromic shift attributed to the 4'-hydroxy group is observed as in the spectra of **1b—4b**, but this characteristic shift is not clearly observed in the spectra for all 3-hydroxyflavones because the shift is also caused by the 3-hydroxy group. These features are usable for the structural elucidation of natural flavones, but care is needed in interpretation.

The ¹H-NMR spectra of the flavones and their acetates supported the structures assigned, as shown in Table 2. The oxygenation pattern of the B-ring in the flavones can be evaluated from the spectral data, but the assignment of the substitution pattern in the A-ring, except for the 5-hydroxy group, is difficult, since the methoxyl or acetoxyl signals appear in a narrow range and the aromatic protons in the A-ring are also substituted. On the other

hand, the ¹³C-NMR spectra show a characteristic pattern reflecting the respective substitution pattern and the signals are assigned as shown in Table 3. The carbon signals at the 2- to 10-positions are less affected by the substituents in the B-ring and reflect well the substitution pattern in the A- and C-rings. In a comparison between the 3-methoxyflavones (**1a, b—5a, b** and **11a**) and 3-hydroxyflavones (**6a, b—10a, b** and **12a**) bearing the same oxygenation pattern on the A-ring, the carbon signals at the 2- to 10-positions in the 3-methoxyflavones are diamagnetically shifted by removal of the 3-methyl group (conversion to the 3-hydroxyflavones) and the shift ranges of the respective carbon signals are similar to those of the corresponding 3-hydroxyflavones (Table 3). That is, the shift ranges of the carbon signals at the 2-position are the

Table 3. ¹³C-NMR Data for 3,5,6,7,8-Pentaoxygenated Flavones in DMSO-*d*₆

Compd.	C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	C ₉	C ₁₀	C _{1'}	C _{2'}	C _{6'}	C _{3'}	C _{5'}	C _{4'}	OMe					
																C ₃	C ₅	C ₆	C ₇	C ₈	B ring
1a	152.5	137.4	172.2	147.2	146.2	150.8	139.8	143.2	114.4	122.5	129.5	114.3	161.0	59.2	61.7	61.3	61.8	61.5	55.3		
<i>Δδ</i>	-9.7	0	-1.0	-0.3	-0.1	-0.1	-2.1	-0.2	-2.2	+1.0	-0.8	-0.2	-0.8								
6a	142.8	137.4	171.2	146.9	146.1	150.7	137.7	143.0	112.2	123.5	128.7	114.1	160.2	—	61.7	61.3	61.9	61.5	55.3		
2a	155.7	137.8	178.6	148.1	135.4	152.3	132.5	144.4	106.7	122.1	129.9	114.4	161.5	59.7	—	60.5	61.8	61.4	55.4		
<i>Δδ</i>	-8.6	-1.6	-2.0	-0.7	-0.5	-0.2	-0.1	-0.2	-1.1	+1.1	-0.6	-0.3	-0.8								
7a	147.1	136.2	176.6	147.4	134.9	152.1	132.4	144.2	105.6	123.2	129.3	114.1	160.7	—	—	60.5	61.7	61.4	55.3		
3a	152.5	137.6	172.3	141.0	139.7	146.4	140.4	142.8	114.4	122.7	129.5	114.2	160.9	59.2	61.4	—	61.7	60.8	55.3		
<i>Δδ</i>	-9.6	-0.1	-1.1	-0.4	-2.2	+0.1	-0.5	0	-2.3	+1.0	-0.8	-0.1	-0.8								
8a	142.9	137.5	171.2	140.6	137.5	146.5	139.9	142.8	112.1	123.7	128.7	114.1	160.1	—	61.4	—	61.6	60.8	55.2		
4a	155.6	137.7	178.5	141.0	133.8	148.0	132.7	142.4	106.7	122.3	129.8	114.3	161.4	59.7	—	—	61.7	60.9	55.4		
<i>Δδ</i>	-8.7	-1.8	-2.0	0	-0.6	0	0	-0.6	-1.2	+1.1	-0.5	-0.2	-0.8								
9a	146.9	135.9	176.5	141.0	133.2	148.0	132.7	141.8	105.5	123.4	129.3	114.1	160.6	—	—	—	61.7	60.9	55.3		
5a	154.8	137.5	178.2	142.2	129.3	147.2	127.7	141.7	103.4	122.5	129.7	114.3	161.2	59.7	—	—	—	61.1	55.4		
<i>Δδ</i>	-8.9	-1.9	-2.1	-0.7	-0.6	-0.1	-0.1	0	-1.2	+1.0	-0.7	-0.2	-0.9								
10a	145.9	135.6	176.1	141.5	128.7	147.1	127.6	141.7	102.2	123.5	129.0	114.1	160.3	—	—	—	—	61.0	55.3		
11a	155.7	137.7	178.8	140.7	135.8	147.8	130.5	144.2	106.9	122.2	130.2	114.2	161.4	59.7	—	60.4	61.1	—	55.4		
<i>Δδ</i>	-8.7	-1.7	-2.1	0	-0.5	-0.3	-0.1	-0.7	-1.2	+1.1	-0.6	-0.2	-0.8								
12a	147.0	136.0	176.7	140.7	135.3	147.5	130.4	143.5	105.7	123.3	129.6	114.0	160.6	—	—	60.4	61.1	—	55.3		
13a	143.1	137.6	171.4	142.7	142.4	145.3	135.7	143.0	112.3	123.6	129.0	113.9	160.1	—	61.4	61.0	61.9	—	55.2		
1b	152.6	137.4	172.2	147.2	146.1	150.7	139.7	143.2	114.4	121.1	111.4	121.7	149.3	115.7	147.4	59.2	61.7	61.3	61.8	61.4	55.4
6b	143.3	137.3	171.1	146.9	146.0	150.6	137.5	142.8	112.1	122.2	110.8	121.2	148.4	115.6	147.4	—	61.6	61.3	61.9	61.5	55.5
2b ^{a)}	155.8	137.7	178.5	148.0	135.4	152.3	132.4	144.3	106.7	120.7	111.6	122.3	150.0	115.7	147.5	59.6	—	60.5	61.7	61.4	55.4
7b	147.4	136.0	176.4	147.4	134.9	152.0	132.4	144.1	105.5	121.9	111.2	121.9	149.0	115.6	147.4	—	—	60.5	61.6	61.4	55.5
3b	152.6	137.5	172.3	140.9	139.6	146.4	140.4	142.7	114.3	121.3	111.4	121.6	149.2	115.6	147.4	59.2	61.4	—	61.6	60.8	55.4
8b	143.1	137.3	171.1	140.5	137.4	146.5	139.9	142.8	112.1	122.4	110.8	121.1	148.3	115.6	147.4	—	61.4	—	61.6	60.9	55.4
4b	155.7	137.5	178.5	140.9	133.7	148.0	132.7	142.5	106.6	120.9	111.6	122.2	149.9	115.7	147.4	59.6	—	—	61.7	60.9	55.4
9b	147.2	135.7	176.3	140.9	133.1	148.0	132.6	141.8	105.4	122.1	111.2	121.8	148.9	115.6	147.3	—	—	—	61.6	60.9	55.5
5b	154.9	137.3	178.1	142.2	129.2	147.2	127.7	141.6	103.3	121.1	111.5	121.9	149.6	115.7	147.4	59.6	—	—	—	61.0	55.4
10b	146.2	135.4	176.0	141.5	128.8	147.1	127.6	141.6	102.2	122.3	111.1	121.5	148.6	115.6	147.3	—	—	—	—	61.0	55.5
2f	155.8	137.9	178.6	148.0	135.4	152.3	132.4	144.3	106.7	120.4	112.0	122.2	146.4	114.8	150.5	59.6	—	60.5	61.8	61.4	55.6

a) The data were consistent with those for the natural flavone isolated by Roitmann and James.²¹⁾

largest (*ca.* $\Delta\delta$ -8.7) and those at the other positions decrease in the order of the 4-, 3-, and 10-positions. In the flavones with the 5-methoxy group (**1a** vs. **6a** and **3a** vs. **8a**), however, the tendency changes slightly because of the effect of the newly formed hydrogen bond between the 3-hydroxy group and 4-carbonyl group. These features may be useful for the assignment of 3,5,6,7,8-pentaoxygenated flavones.

The three flavones synthesized are corresponding to the natural ones, **2a**,^{18,19)} **2b**,^{20,21)} and **7b**,²²⁾ and their properties are consistent with those of the synthetic ones, respectively, showing that the assigned structures of the natural products are correct. However, a flavone, isolated from *Gutierrezia resinosa* and proposed to be **2b** by Bittner *et al.*,¹¹⁾ and two natural ones,^{9,10)} proposed to be 8-hydroxyflavone derivatives, were not consistent with the synthetic products, as shown in Table 4.

The UV spectral data for the former natural flavone are similar to those for the synthetic compound, but no bathochromic shift attributed to the 4'-hydroxy group is observed upon the addition of sodium acetate. Although the ¹H-NMR signals of the natural flavone diacetate are also similar to those of the synthetic one, the 6'-proton signal at δ 8.07 is at lower field than that at δ 7.77 in **Ac-2b** and the spectral pattern of the protons of the B-ring is similar to that in 5,6,7,3'-tetraacetoxy-3,4'-dimethoxyflavones.¹⁵⁾ The result suggests that the structure of the natural flavone is an isomeric 5,3'-dihydroxy-3,4',6,7,8-

pentamethoxyflavone (**2f**) which has been isolated from *Polanisia trachysperma* by Wollenweber *et al.*¹⁹⁾ Therefore, the flavone **2f** was also synthesized by the method shown in Chart 1 and the properties of the natural flavone were compared with those of the synthesized **2f** and **2b**. As shown in Table 4, the spectral data for the natural flavone and its acetate are not consistent with those of **2b** and **Ac-2b**, but coincide well with those of **2f** and **Ac-2f**. Consequently, the structure of the natural flavone was revealed to be **2f**.

A flavone, eriostemin, isolated from *Eriostemon* species, has been proposed to be **13a** on the basis of the spectral data reported by Lassak and Southwell.⁹⁾ Although the properties of the natural flavone and its acetate are not consistent with those of the synthetic compounds, the ¹H-NMR spectral data are similar to each other (Table 4), suggesting that the natural product is an isomeric flavone. In the ¹H-NMR data for the natural flavone in CDCl₃, the signal at δ 11.51 is attributed to the 5-hydroxyl proton and the signal at δ 4.12 shows the existence of the 7-methoxy group.²⁾ Furthermore, the UV spectrum of the natural flavone exhibited a large bathochromic shift upon the addition of sodium acetate, as seen with the flavone **7a**. The result suggests that the structure of the natural flavone **7a**, an isomer of **13a**, and the properties coincide well with those of the synthesized **7a**, as shown in Table 4. Consequently, the structure of the natural flavone, is concluded to be 3,5-dihydroxy-4',6,7,8-tetramethoxyfla-

Table 4. Comparisons of the Natural Flavones with the Synthetic and Isomeric Flavones^{a)}

	Synthetic	Natural	Isomeric
	5,4'-Dihydroxy-3,3',6,7,8-pentamethoxyflavone (2b) (Isolated from <i>Gutierrezia resinosa</i> ¹¹⁾)		5,3'-Dihydroxy-3,4',6,7,8-pentamethoxyflavone (2f)
mp (°C)	170—171	174—176	169—170
UV λ_{\max} nm MeOH	(EtOH) 261 279 356	260 278 350	(EtOH) 261 (4.30) 278 (4.28) 351 (4.28)
+ AlCl ₃	270 289 372 415i	273 286 305sh 374	272i (4.22) 286 (4.24) 367 (4.27)
+ NaOAc	270 430	260 278 348	262 (4.30) 278 (4.28) 351 (4.26)
MS m/z (rel. int. %)	404 (M ⁺ , 57) 389 (100) 374 (5) 373 (5) 359 (5) 331 (6) 211 (9) 202 (5)	404 (M ⁺) 389 (100) 374 359 202 84	404 (M ⁺ , 67) 389 (100) 374 (5) 373 (6) 371 (4) 359 (3) 211 (7) 202 (5)
¹ H-NMR for the diacetate in CDCl ₃	2.36 s 2.51 s 3.83 s 3.89 s 3.92 s 4.02 s 4.10 s 7.19 d 7.83 d' 7.77 dd	2.37 s 2.51 s 3.82 s 3.89 s 3.93 s 4.02 s 4.10 s 7.10 d 7.89 d' 8.07 dd	2.37 s 2.50 s 3.81 s 3.89 s 3.92 s 4.01 s 4.09 s 7.10 d 7.89 d' 8.07 dd
	3,8-Dihydroxy-4',5,6,7-tetramethoxyflavone (13a) ⁹⁾		7a
mp (°C)	142—143	167—168	161—163
¹ H-NMR in CDCl ₃	3.89 s 3.96 s 3.99 s 4.12 s 5.71 s (OH) 7.05 d 8.24 d	3.88 s 3.96 s 3.98 s 4.12 s 6.76 s (OH) 7.01 d 8.21 d 11.51 s (OH)	3.90 s 3.96 s 3.98 s 4.13 s 6.20 s (OH) 7.06 d 8.25 d 11.53 s (OH)
UV λ_{\max} nm MeOH	(EtOH) 273 (4.27) 339 (4.21) 365 (4.21)	258 (4.22) 278 (4.28) 337 (4.23) 376 (4.28)	258 (4.17) 278 (4.26) 339 (4.23) 380 (4.20)
+ AlCl ₃	269 (4.41) 375sh (4.05) 431 (4.39)	270 (4.35) 283 (4.29) 312 (3.72) 374 (4.17) 436 (4.28)	265 (4.22) 286 (4.21) 310i (3.88) 368 (4.26) 438 (4.21)
+ NaOAc	277 291 320 342	262 (4.37) 275 (4.26) 340 (3.82) 420 (4.16)	262 (4.34) 275i (4.24) 342 (4.00) 427 (4.16)
MS m/z (rel. int. %)	374 (M ⁺ , 100) 359 (87) 356 (50) 345 (7) 331 (10)	374 (M ⁺ , 100) 359 (90) 345 (5) 331 (26)	374 (M ⁺ , 83) 359 (100) 345 (4) 331 (23)
Diacetate: mp (°C)	140—141	123—124	148—149
¹ H-NMR for the diacetate in CDCl ₃	2.35 s 2.42 s 3.88 s 3.94 s 3.98 s 4.04 s 7.00 d 7.74 d	2.33 s 2.46 s 3.89 s 4.02 s 4.10 s (4 × OMe) 7.04 d 7.87 d	2.34 s 2.47 s 3.88 s 3.89 s 4.02 s 4.10 s 7.02 d 7.85 d
	5,8-Dihydroxy-3,6,7-trimethoxyflavone (11e) ¹⁰⁾		5,7-Dihydroxy-3,6,8-trimethoxyflavone (43) ²³⁾
mp (°C)	206—207	177—178	172—174
¹ H-NMR in CDCl ₃	3.87 s 3.98 s 4.14 s 5.40 br s (OH) 7.53 m (3H) 8.14 m (2H) 12.10 s (OH)	3.88 s 3.98 s 4.03 s 6.58 br s (OH) 7.46 m (2H) 8.08 m (3H) 11.30 br s (OH)	3.88 s 3.99 s 4.05 s 6.43 s (OH) 7.53—7.56 m (3H) 8.12—8.15 m (2H) 12.54 (OH)
UV λ_{\max} nm MeOH	(EtOH) 287 (4.46) 372 (3.55)	277 324sh 375sh	278 (4.43) 322 (4.00)
+ AlCl ₃	305 (4.45) 345i (3.89) 450 (3.53)	252sh 291 341 420sh	293 (4.42) 347 (4.13) 422 (3.65)
+ NaOAc	289 (4.41)	280 375	283 (4.44) 380 (4.03)
MS m/z (rel. int. %)	344 (M ⁺ , 100) 329 (80) 325 (11) 311 (18) 301 (4)	344 (M ⁺ , 81) 329 (100) 301 (12.5)	344 (M ⁺ , 72) 329 (100) 325 (5) 311 (7) 301 (9)

a) s, singlet; sh, shoulder; i, inflection point.

vone (**7a**).

A flavone, isolated from *Gnaphalium gaudichaudianum*, has been proposed to be **11e** on the basis of the spectral data reported by Guerreiro *et al.*¹⁰⁾ Although the ¹H-NMR spectral data are similar to those for the synthetic flavone **11e**, the signal at δ 4.10—4.15 attributed to the 4'-methoxy group²⁾ is not observed. Furthermore, the UV spectral data are greatly different from those for **11e** and band I is bathochromically shifted upon the addition of sodium acetate. The behavior suggests that the structure of the natural flavone is 5,7-dihydroxy-3,6,8-trimethoxyflavone (**43**), an isomer of **11e**. The physical data for the flavone coincide well with those for our synthetic flavone **43**,²³⁾ as shown in Table 4. Thus, the structure of the natural flavone must be revised to **43**, which has been isolated as araneol from *Anaphalis araneosa* by Ali *et al.*²⁴⁾

Experimental

All melting points were determined in glass capillaries and are uncorrected. ¹H-NMR (at 400 MHz or 60 MHz) and ¹³C-NMR (at 100.4 MHz) spectra were recorded on a JEOL EX400 or Hitachi R-24B spectrometer, using tetramethylsilane as an internal standard, and chemical shifts are given in δ values. UV spectra and MS were recorded on a Hitachi 124 spectrophotometer and on a Shimadzu QP 1000 spectrometer, respectively. Column chromatography was carried out on Kiesel-gel 60 (70—230 mesh; Merck). Elemental analyses were performed

with a Yanaco CHN corder Model MT-5.

6-Hydroxy-5,7,8-trimethoxyflavones (17a, c, g) A mixture of 2',5'-dihydroxy-3',4',6'-trimethoxyacetophenone (**14**) (5.0 g; 20.6 mmol), MeOCH₂Cl (2.2 ml; 30 mmol), and *N,N*-diisopropylethylamine (10 ml) in CH₂Cl₂ (80 ml) was stirred at room temperature till the starting material disappeared (3—4 h). The mixture was washed with cooled 2—3% HCl, aqueous NaHCO₃, and water, dried over Na₂SO₄, and evaporated to give a crude methoxymethyl ether (**15**).

To a solution of the crude ether **15** in pyridine (15 ml), a substituted benzoyl chloride (25—30 mmol) was added. The mixture was heated at 60—80 °C for 2 h and poured into a mixture of ice and HCl. The separated oily materials were extracted with EtOAc and the extract was washed with cooled 2—3% HCl, aqueous K₂CO₃ and water, dried over Na₂SO₄ and evaporated to give a crude benzoate. A mixture of the crude benzoate and freshly powdered KOH (12 g) in pyridine (25 ml) was heated with stirring at 60—70 °C for 2 h and poured into a mixture of ice and HCl. The separated oily materials were extracted with EtOAc and the extract was washed with aqueous K₂CO₃, dried over Na₂SO₄, and evaporated to give a crude oily diketone (**16**). The diketone **16** was warmed in AcOH (25 ml) containing a small amount of H₂SO₄ at 50 °C for 1 h, diluted with a saturated aqueous solution of NaHCO₃ and extracted with CHCl₃. The extract was washed with aqueous NaHCO₃, dried over Na₂SO₄, and concentrated. The residue was chromatographed over a silica gel column with CHCl₃—EtOAc (5:1) and the product was recrystallized from CHCl₃—MeOH to give **17**. Flavone **17a**: mp 180—182 °C; yield, 5.2 g (70%). *Anal.* Calcd for C₁₉H₁₈O₇: C, 63.68; H, 5.06%. Found: C, 63.50; H, 5.13%. Flavone **17c**: mp 172—173 °C; yield, 6.4 g (67%). *Anal.* Calcd for C₂₆H₂₄O₈: C, 67.23; H, 5.21. Found: C, 67.20; H, 5.26. Flavone **17g**: mp 187—189 °C; yield, 4.6 g (48%). *Anal.* Calcd for C₂₆H₂₄O₈: C, 67.23; H, 5.21. Found: C, 67.09; H, 5.23.

3-Hydroxy-5,7,8-trimethoxy-6-methoxymethoxyflavones. (19a—c, f)

Table 5. 3,6-Dihydroxy-5,7,8-trimethoxyflavone Derivatives

Compd.	Starting material	mp (°C)	Recystn. solvent	Formula	Found (%)		Calcd (%)	
					C	H	C	H
8c	19c	161—162	CHCl ₃ -MeOH	C ₂₆ H ₂₄ O ₉	64.76	4.86	65.00	5.03
8g	19g	138—139	MeOH	C ₂₆ H ₂₄ O ₉	64.87	5.08	65.00	5.03
1c	8c	126—127	CHCl ₃ -MeOH	C ₂₈ H ₂₈ O ₉	65.96	5.59	66.13	5.55
1g	8g	124—125	CHCl ₃ -MeOH	C ₂₈ H ₂₈ O ₉	66.05	5.52	66.13	5.55
2c	1c	93—95	MeOH	C ₂₇ H ₂₆ O ₉ · 1/2H ₂ O	64.39	5.23	64.41	5.40
2g	1g	102—103	MeOH	C ₂₇ H ₂₆ O ₉	65.61	5.27	65.58	5.30
20a	19a	107—108	aq. MeOH	C ₂₂ H ₂₄ O ₉	61.06	5.56	61.11	5.59
20b	20c	148—149	MeOH	C ₂₂ H ₂₄ O ₁₀	59.07	5.48	58.93	5.39
20c	19c	102—103	MeOH	C ₂₉ H ₃₀ O ₁₀	64.88	5.55	64.68	5.61
20d	20b	103—105	MeOH	C ₂₉ H ₃₀ O ₁₂ S	57.75	5.02	57.80	5.02
3c	20c	138—139	CHCl ₃ -MeOH	C ₂₇ H ₂₆ O ₉	65.36	5.27	65.58	5.30
3d	20d	170—171	MeOH	C ₂₇ H ₂₆ O ₁₁ S	58.14	4.75	58.06	4.69
Ac-3c	3c	144—145	CHCl ₃ -MeOH	C ₂₉ H ₂₈ O ₁₀	64.88	5.40	64.92	5.26
21a	Ac-3a	170—172	CHCl ₃ -MeOH	C ₂₁ H ₂₀ O ₉	60.76	4.85	60.58	4.84
21c	Ac-3c	142—143	CHCl ₃ -MeOH	C ₂₈ H ₂₆ O ₁₀	64.09	4.92	64.36	5.02
4c	21c	135—136	CHCl ₃ -MeOH	C ₂₆ H ₂₄ O ₉	64.80	5.03	65.00	5.03
5d	3d	178—180	Me ₂ CO-hexane	C ₂₅ H ₂₂ O ₁₁ S	56.40	4.07	56.60	4.18
22a	19a	118—120	CHCl ₃ -MeOH	C ₂₈ H ₂₈ O ₁₁ S	58.46	4.86	58.73	4.93
22c	19c	139—140	CHCl ₃ -MeOH	C ₃₅ H ₃₄ O ₁₂ S	61.71	4.97	61.94	5.05
22d	19b	136—137	CHCl ₃ -MeOH	C ₃₅ H ₃₄ O ₁₄ S ₂	58.15	4.38	58.37	4.31
23a	22a	169—170	CHCl ₃ -MeOH	C ₂₆ H ₂₄ O ₁₀ S · 1/2H ₂ O	58.25	4.87	58.09	4.69
23c ^{a)}	22c	156—157	CHCl ₃ -MeOH	C ₃₃ H ₃₀ O ₁₁ S	62.35	4.77	62.45	4.76
23d	22d	193—194	CHCl ₃ -MeOH	C ₃₃ H ₃₀ O ₁₃ S ₂	52.75	3.77	52.47	3.85
24a	23a	137—138	CHCl ₃ -MeOH	C ₂₇ H ₂₆ O ₁₀ S	59.64	4.78	59.77	4.83
24c	23c	180—182	CHCl ₃ -MeOH	C ₃₄ H ₃₂ O ₁₁ S	62.87	4.88	62.95	4.97
6c	24c	158—159	CHCl ₃ -MeOH	C ₂₇ H ₂₆ O ₉	65.37	5.23	65.58	5.30
25a	24a	157—159	CHCl ₃ -MeOH	C ₂₆ H ₂₄ O ₁₀ S	58.88	4.36	59.09	4.58
25c	24c	176—178	CHCl ₃ -MeOH	C ₃₃ H ₃₀ O ₁₁ S	62.28	4.68	62.45	4.76
7c	25c	152—153	CHCl ₃ -MeOH	C ₂₆ H ₂₄ O ₉	64.71	5.04	65.00	5.03
26a	23a	133—134	MeOH	C ₂₈ H ₂₆ O ₁₁ S	58.81	4.54	58.94	4.59
26c	23c	181—182	CHCl ₃ -MeOH	C ₃₅ H ₃₂ O ₁₂ S	61.95	4.69	62.12	4.77
27a	26a	188—190	CHCl ₃ -MeOH	C ₂₇ H ₂₄ O ₁₁ S	58.01	4.16	58.27	4.35
27c	26c	170—171	CHCl ₃ -MeOH	C ₃₄ H ₃₀ O ₁₂ S	61.39	4.58	61.63	4.56
28a	27a	112—114	CHCl ₃ -MeOH	C ₂₅ H ₂₂ O ₁₀ S · 1/2H ₂ O	57.19	4.47	57.36	4.43
28c	27c	170—171	CHCl ₃ -MeOH	C ₃₂ H ₂₈ O ₁₁ S · 3/2H ₂ O	59.20	4.86	59.35	4.82
29a	23a	113—115	CHCl ₃ -MeOH	C ₂₄ H ₂₀ O ₁₀ S · H ₂ O	55.43	3.99	55.60	4.28
29d	23d	227—228	Me ₂ CO-MeOH	C ₃₁ H ₂₆ O ₁₃ S ₂	55.43	3.99	55.60	4.28

a) The compound was sintered at 95—97 °C then resolidified.

A flavone **17** was methoxymethylated with MeOCH₂Cl and *N,N*-diisopropylethylamine in CH₂Cl₂ to give quantitatively a methoxymethyl ether (**18a, c, g**). Flavone **18a**: mp 104—105 °C (from MeOH). *Anal.* Calcd for C₂₁H₂₂O₈: C, 62.68; H, 5.51. Found: C, 62.55; H, 5.54. Flavone **18c**: mp 136—137 °C (from CHCl₃-MeOH). *Anal.* Calcd for C₂₈H₂₈O₉: C, 66.13; H, 5.55. Found: C, 65.86; H, 5.59.

An acetone solution of dimethyldioxirane (*ca.* 0.1 mol/l; 40 ml) was added to a cooled solution of a flavone **18** (2.0 mmol) in CH₂Cl₂ (30 ml). The mixture was stirred at 0 °C for 10—12 h and the solvent was evaporated off under reduced pressure. The residue was dissolved in CH₂Cl₂ (5 ml), and the solution was stirred with a small amount of TsOH (5—10 mg) at 0 °C for 10—20 min, then diluted with CH₂Cl₂. The mixture was washed with aqueous NaHCO₃ and H₂O, dried over Na₂SO₄, and evaporated to give a 3-hydroxyflavone (**19a, c, g**). Flavone **19a**: mp 137—139 °C (from CHCl₃-MeOH); yield, 80%. *Anal.* Calcd for C₂₁H₂₂O₉: C, 60.28; H, 5.30. Found: C, 60.25; H, 5.22. Flavone **19c**: mp 161—162 °C (from CHCl₃-MeOH); yield, 83%. *Anal.* Calcd for C₂₈H₂₈O₁₀: C, 64.12; H, 5.38. Found: C, 63.87; H, 5.33. Flavone **19g**: mp 110—111 °C (from CHCl₃-MeOH); yield, 80% (from **17g**). *Anal.* Calcd for C₂₈H₂₈O₁₀: C, 64.12; H, 5.38. Found: C, 64.04; H, 5.35. Flavone **19b** was synthesized from **19c** by hydrogenolysis with 10% Pd-C in MeOH-EtOAc: mp 161—162 °C (from CHCl₃-MeOH); yield, 96%. *Anal.* Calcd for C₂₁H₂₂O₁₀: C, 57.47; H, 4.26. Found: C, 57.65; H, 4.13.

Synthesis of 3,5,6,7,8-Penta-oxygenated Flavones (1—10) The flavones **1—10** were synthesized from the flavones **19** by using the following procedures and the results are shown in Table 5. All reactions in this process proceeded quantitatively and the products were obtained in

more than 80% yield as a pure form.

Methylation: A mixture of hydroxyflavone (1 mmol), Me₂SO₄ (2—3 eq), and anhydrous K₂CO₃ (10—20 eq) in acetone (30—35 ml) was refluxed with stirring till the starting material disappeared. The mixture was diluted with H₂O, refluxed for 10—15 min to decompose the excess Me₂SO₄, and then treated in a usual way to give a methyl ether.

Tosylation: A mixture of hydroxyflavone (1 mmol), TsCl (1.3—1.5 eq), and anhydrous K₂CO₃ (10—20 eq) in Me₂CO (30—35 ml) was refluxed with stirring till the starting material disappeared. The mixture was diluted with cooled water and concentrated under reduced pressure. The precipitates were collected by filtration, washed with water, and recrystallized to give a tosylate.

Selective Demethylation of the 5-Methoxy Group A cooled solution of 5-methoxyflavone (1 mmol) in MeCN (8 ml) was treated with 10% (w/v) anhydrous AlBr₃-MeCN (8 ml; 3 mmol), and the mixture was allowed to stand at 0 °C for 30—40 min. It was then diluted with 2—3% HCl, warmed at 50—60 °C for 30 min and concentrated. The separated crystals were collected and recrystallized to give a 5-hydroxyflavone.

Selective Demethylation of the 5- and 7-Methoxy Groups A solution of 6-hydroxyflavone (**3a, d** or **23a, d**) (0.4 mmol) in MeCN (4 ml) was treated with 20% (w/v) anhydrous AlBr₃-MeCN (4 ml; 3.0 mmol). The mixture was heated at 50 °C for 5 h and treated as described above to give a 5,6,7-trihydroxyflavone.

Demethoxymethylation: Concentrated HCl (0.5—1.0 ml) was added to a solution of methoxymethoxyflavone (1—2 mmol) in HOAc (5—10 ml). The mixture was stirred at room temperature for 1—2 h. The separated precipitates were collected and recrystallized to give a hydroxyflavone.

Table 6. 3,5,6,7,8-Pentaoxygenated Flavones (1—10) and Their Acetate (Ac-1—Ac-10)

Compd.	Starting material	mp (°C)	Recystn. solvent	Formula	Found (%)		Calcd (%)	
					C	H	C	H
1a	8a	123—125	MeOH	C ₂₁ H ₂₂ O ₈	62.47	5.42	62.68	5.51
1b	1c	187—188	CHCl ₃ -MeOH	C ₂₁ H ₂₂ O ₈	60.36	5.28	60.28	5.30
2a	1a	118—120	aq. MeOH	C ₂₀ H ₂₀ O ₈	61.71	5.21	61.85	5.19
2b	2c	170—171	CHCl ₃ -MeOH	C ₂₀ H ₂₀ O ₉	59.31	4.99	59.41	4.99
2f	2g	169—170	EtOAc	C ₂₀ H ₂₀ O ₉	59.39	5.02	59.41	4.99
3a	20a	160—162	MeOH	C ₂₀ H ₂₀ O ₈	61.90	5.21	61.85	5.19
3b	3c	166—167	aq. MeOH	C ₂₀ H ₂₀ O ₉	59.20	4.99	59.41	4.99
4a	21a	156—158	CHCl ₃ -MeOH	C ₁₉ H ₁₈ O ₈	60.76	4.84	60.96	4.85
4b	4c	174—175	aq. MeOH	C ₁₉ H ₁₈ O ₉	58.42	4.66	58.46	4.65
5a	3a	158—160	aq. EtOH	C ₁₈ H ₁₆ O ₈ ·H ₂ O	56.87	4.90	57.14	4.80
5b	5d	243—244	MeOH	C ₁₈ H ₁₆ O ₉	57.18	4.30	57.45	4.29
6a	24a	147—149	CHCl ₃ -MeOH	C ₂₀ H ₂₀ O ₈	61.74	5.12	61.85	5.19
6b	6c	171—172	CHCl ₃ -MeOH	C ₂₀ H ₂₀ O ₉	59.15	4.94	59.41	4.99
7a	25a	161—163	CHCl ₃ -MeOH	C ₁₉ H ₁₈ O ₈	60.75	4.79	60.96	4.85
7b	7c	165—166	CHCl ₃ -MeOH	C ₁₉ H ₁₈ O ₉	58.51	4.63	58.46	4.65
8a	19a	180—182	MeOH	C ₁₉ H ₁₈ O ₈	61.02	4.84	60.96	4.85
8b	8c	206—207	aq. Me ₂ CO	C ₁₉ H ₁₈ O ₉	58.18	4.54	58.46	4.65
9a	28a	172—174	aq. DMF	C ₁₈ H ₁₆ O ₈	59.81	4.53	60.00	4.48
9b	28c	183—185	aq. Me ₂ CO	C ₁₈ H ₁₆ O ₉	57.26	4.30	57.45	4.29
10a	29a	226—227	aq. Me ₂ CO	C ₁₇ H ₁₄ O ₈ ·1/2H ₂ O	57.65	4.13	57.47	4.26
10b	29d	257 dec.	aq. MeOH	C ₁₇ H ₁₄ O ₉	56.23	4.14	56.36	3.89
Ac-1b		113—114	aq. MeOH	C ₂₃ H ₂₄ O ₁₀	59.74	5.15	60.00	5.25
Ac-2a		140—141	CHCl ₃ -MeOH	C ₂₂ H ₂₂ O ₉	61.17	5.07	61.39	5.15
Ac-2b		133—134	CHCl ₃ -MeOH	C ₂₄ H ₂₄ O ₁₁	59.08	5.01	59.02	4.95
Ac-2f		130—131	aq. MeOH	C ₂₄ H ₂₄ O ₁₁	58.81	4.86	59.02	4.95
Ac-3a		127—128	CHCl ₃ -MeOH	C ₂₂ H ₂₂ O ₉	61.45	5.09	61.39	5.15
Ac-3b		149—150	CHCl ₃ -MeOH	C ₂₄ H ₂₄ O ₁₁	58.86	4.90	59.02	4.95
Ac-4b		166—167	CHCl ₃ -MeOH	C ₂₃ H ₂₂ O ₁₀	59.99	4.76	60.26	4.84
Ac-4c		166—168	CHCl ₃ -MeOH	C ₂₅ H ₂₄ O ₁₂	58.03	4.60	58.14	4.68
Ac-5a		177—179	CHCl ₃ -MeOH	C ₂₄ H ₂₂ O ₁₁	59.07	4.52	59.26	4.56
Ac-5b		175—176	CHCl ₃ -MeOH	C ₂₆ H ₂₄ O ₁₃	57.12	4.42	57.36	4.44
Ac-6a		130—131	CHCl ₃ -MeOH	C ₂₂ H ₂₂ O ₉	61.42	5.25	61.39	5.15
Ac-6b		117—118	MeOH	C ₂₄ H ₂₄ O ₁₁	58.76	5.06	59.02	4.95
Ac-7a		148—149	CHCl ₃ -MeOH	C ₂₃ H ₂₂ O ₁₀	59.99	4.95	60.26	4.84
Ac-7b		157—158	CHCl ₃ -MeOH	C ₂₅ H ₂₄ O ₁₂	57.97	4.58	58.14	4.68
Ac-8a		162—164	CHCl ₃ -MeOH	C ₂₃ H ₂₂ O ₁₀	60.28	4.89	60.26	4.84
Ac-8b		153—154	CHCl ₃ -MeOH	C ₂₅ H ₂₄ O ₁₂	58.00	4.59	58.14	4.68
Ac-9a		164—166	CHCl ₃ -MeOH	C ₂₄ H ₂₂ O ₁₁	59.28	4.62	59.26	4.56
Ac-9b		218—219	CHCl ₃ -MeOH	C ₂₆ H ₂₄ O ₁₃	57.10	4.35	57.36	4.44
Ac-10a		203—205	CHCl ₃ -MeOH	C ₂₅ H ₂₂ O ₁₂	58.15	4.38	58.37	4.31
Ac-10b		235—236	CHCl ₃ -MeOH	C ₂₇ H ₂₄ O ₁₄	56.45	4.16	56.65	4.23

Hydrolysis of the Tosyloxy Group A) Detosylation of the Flavones **24** and **25**: A mixture of a flavone (0.5 mmol) and anhydrous K₂CO₃ (0.8—1.0 g) in MeOH (30—35 ml) was refluxed with stirring for 1—2 h and then acidified with diluted HCl. The solvent was evaporated off and the separated crystals were collected and recrystallized to give a hydroxyflavone.

B) Detosylation of the Flavones (**5d**, **28**, **29**): A flavone (**5d**, **28**; 0.8 mmol; **29**; 0.6 mmol) was methoxymethylated with MeOCH₂Cl (0.20 ml) and *N,N*-diisopropylethylamine (1.0 ml) in CH₂Cl₂ (20—30 ml) at room temperature for 30—40 min to give a crude methoxymethyl ether. The crude ether was hydrolyzed according to method A and then demethoxymethylated with HCl in HOAc to give the desired flavone (**5b**, **9a**, **c**, or **10a**, **b**). The flavone **9c** was converted into **9b** by hydrolysis with Pd-C without purification.

Other Procedures Debenzylation: benzyloxyflavones were hydrogenolyzed with 10% Pd-C in MeOH-EtOAc. Acetylation: hot acetic anhydride-pyridine method. Hydrolysis of acetoxy group: acetates were hydrolyzed with 15% aqueous HCl-MeOH (1:10).

Synthesis of 3,5,8-Trihydroxy-4',6,7-trimethoxyflavone (12a) and Its 3- (11a) or 5-Methyl Ether (13a) 8-Benzyloxy-4',6,7-trimethoxy-5-isopropoxyflavone (**30a**) (715 mg; 1.5 mmol) was oxidized with dimethyldioxirane to give the 3-hydroxyflavone (**31a**): mp 113—114 °C (from Et₂O-hexane); yield, 595 mg (81%). *Anal.* Calcd for C₂₈H₂₈O₈: C, 68.28; H, 5.73. Found: C, 68.13; H, 5.74. Its methyl ether (**32a**): mp 107—108 °C (from MeOH). *Anal.* Calcd for C₂₉H₃₀O₈: C, 68.76; H,

5.97. Found: C, 68.82; H, 5.98. The methyl ether **32a** was dealkylated with 5% (w/v) anhydrous AlCl₃-MeCN at room temperature for 40 min to give quantitatively the 5-hydroxyflavone **34a**: mp 131—132 °C (from CHCl₃-MeOH). *Anal.* Calcd for C₂₆H₂₄O₈: C, 67.23; H, 5.21. Found: C, 67.11; H, 5.26. 5,8-Dihydroxy-3,4',6,7-tetramethoxyflavone (**11a**): mp 207—209 °C (from aq. MeOH containing SO₂) (lit.⁶⁾ mp 203—205 °C). *Anal.* Calcd for C₁₉H₁₈O₈: C, 60.96; H, 4.85. Found: C, 60.72; H, 4.76. Its acetate (**Ac-11a**): mp 158—159 °C (MeOH). *Anal.* Calcd for C₂₃H₂₂O₁₀: C, 60.26; H, 4.84. Found: C, 60.22; H, 4.81.

The crude tosylate **33a** obtained from **31a** was dealkylated with 5% (w/v) anhydrous AlCl₃-MeCN to give quantitatively the 5-hydroxyflavone **35a**: mp 145—146 °C (CHCl₃-MeOH). *Anal.* Calcd for C₃₂H₂₈O₁₀S: C, 63.57; H, 4.67. Found: C, 63.46; H, 4.70. 8-Benzyloxy-3,5-dihydroxy-4',6,7-trimethoxyflavone (**36a**): mp 145—146 °C (CHCl₃-MeOH). *Anal.* Calcd for C₂₅H₂₂O₈: C, 66.66; H, 4.92. Found: C, 66.66; H, 4.94. 3,5,8-Trihydroxy-4',6,7-trimethoxyflavone (**12a**): mp 181—182 °C (from aqueous MeOH). *Anal.* Calcd for C₁₈H₁₆O₈: C, 60.00; H, 4.48. Found: C, 59.95; H, 4.40. Its acetate (**Ac-12a**): mp 202—203 °C (from MeOH). *Anal.* Calcd for C₂₄H₂₂O₁₁: C, 59.26; H, 4.56. Found: C, 59.18; H, 4.57.

8-Benzyloxy-4',5,6,7-tetramethoxyflavone (**37a**)²⁾ was oxidized with dimethyldioxirane to give the flavone **38a**: mp 148—149 °C (from CHCl₃-MeOH); yield, 90%. *Anal.* Calcd for C₂₆H₂₄O₈: C, 67.23; H, 5.21. Found: C, 66.96; H, 5.20. 3,8-Dihydroxy-4',5,6,7-tetramethoxyflavone (**13a**): mp 142—143 °C (from CHCl₃-hexane). *Anal.* Calcd for

$C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.73; H, 4.82. Its acetate (Ac-13a): mp 140–141 °C (from MeOH). *Anal.* Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84. Found: C, 60.13; H, 4.82.

5,8-Dihydroxy-3,6,7-trimethoxyflavone (11e) A mixture of the flavone **39e**²⁾ (480 mg), $PhCH_2Cl$ (0.27 ml), and anhydrous K_2CO_3 (1.5 g) in *N,N*-dimethylformamide (5.0 ml) was heated with stirring at 150–160 °C for 10 min and then diluted with H_2O . The separated oily material was treated in a usual way to give the benzyl ether **40e**: mp 122–123 °C (from Me_2CO -MeOH); yield, 547 mg (93%). *Anal.* Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.28; H, 5.30. 5,8-Bis(benzyloxy)-3-hydroxy-6,7-dimethoxyflavone (**41e**): mp 140–141 °C (from $CHCl_3$ -MeOH). *Anal.* Calcd for $C_{31}H_{26}O_7$: C, 72.93; H, 5.13. Found: C, 72.66; H, 5.08. Its methyl ether (**42e**): mp 172–173 °C (from $CHCl_3$ -MeOH). *Anal.* Calcd for: $C_{32}H_{28}O_7$: C, 73.27; H, 5.38. Found: C, 73.03; H, 5.36. 5,8-Dihydroxy-3,6,7-trimethoxyflavone (**11e**): mp 206–207 °C (from EtOAc-MeOH). *Anal.* Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.50; H, 4.63. Its acetate (Ac-11e): mp 162–163 °C (from MeOH). *Anal.* Calcd for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71. Found: C, 61.56; H, 4.69.

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