Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. XV.[1] A Convenient Synthesis of 3,5,6-Trihydroxy-7-methoxyflavones and Revised Structures of Two Natural Flavones

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A mixture of 6-hydroxy-3,4′,5,7-tetramethoxy- and 5,6-dihydroxy-3,4′,7-trimethoxyflavone was converted into 6-acetoxy-5-hydroxy-3,4′,7-trimethoxyflavone by acetylation and following dealkylation. The 3-methoxyl group in the tosylate of the 5-hydroxyflavone was selectively cleaved with anhydrous aluminum bromide in acetonitrile to give 6-acetoxy-3-hydroxy-4′,7-dimethoxy-5-(tosyloxy)flavone. 3,6-Dihydroxy-4′,7-dimethoxy-5-(tosyloxy)flavone, a deacetylated product of the flavone, was easily hydrolyzed to the desired 3,5,6-trihydroxy-4′,7-dimethoxyflavone in high yield via the corresponding 6-methoxymethyl ether. Eight 3,5,6-trihydroxy-7-methoxyflavones were synthesized by this method and their properties were clarified. Additionally, two 3,5,8-trihydroxy-7-methoxyflavones were synthesized by a similar method and the structures of two natural flavones which were proposed as 3,5,6-trihydroxy-7-methoxyflavone derivatives were revised to be 4′,7-dimethoxy- and 3′,4′,7-trimethoxy-3,5,8-trihydroxyflavones.

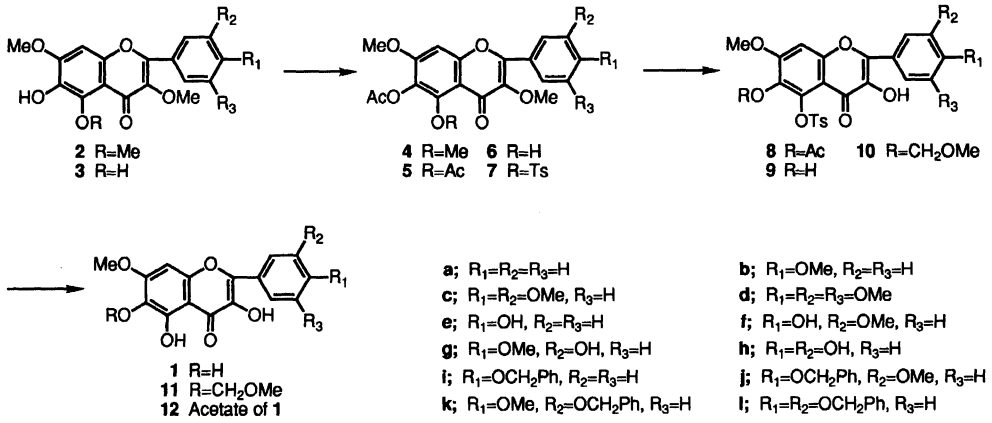
We have been studying the selective *O*-alkylation and dealkylation of flavonoids in order to establish a new, convenient method for synthesizing polyhydroxyflavones;[1] the inhibitory activities of the products against some enzymes were concurrently examined.[2,3] In these studies we found that the 3- and 5-methoxyl groups in the 3,5-dimethoxyflavone derivatives can be selectively cleaved with anhydrous aluminum bromide in acetonitrile.[4—6] The results suggest that 3,5,6-trihydroxy-7-methoxyflavones (**1**) are easily synthesized from 6-hydroxy-3,5,7-trimethoxyflavones (**2**) by selective demethylation. Wagner et al.[7] have reported that 3,4′,5,6-tetrahydroxy-3′,7-dimethoxyflavone (**1f**), one of these flavones, could be synthesized from the corresponding chalcone in low yield by the Algar–Flynn–Oyamada reaction[8] and sequential demethylation. The other flavones **1**, however, were not synthesized and their general properties have not yet been clarified. For the identification of some natural flavones[9—11] and a clarification of the physical and biological properties, a more convenient method for synthesizing 3,5,6-trihydroxy-7-methoxyflavones (**1**) is desired. Herein, we established a convenient method for synthesizing **1** by the selective demethylation of 6-hydroxy-3,5,7-trimethoxyflavones (**2**) and characterized their physical properties. The spectral data for two natural flavones,[9] proposed as **1b** and **1c**, however, are different from those for the synthetic ones, suggesting that the structures are 3,5,8-trihydroxy-7-methoxyflavones (**20b** and **20c**), isomers of **1**. Therefore, the two 3,5,8-trihydroxy-7-methoxyflavones were additionally synthesized by a similar method, and the structures of the natural flavones were revised.

Results and Discussion

In demethylation with anhydrous aluminum bromide or chloride in acetonitrile, the 5-methoxyl group in 5,6,7-trioxygenated flavones with free hydroxyl groups was selectively cleaved after protection of the hydroxyl groups with an acetyl group.[12] By contrast, the 3-methoxyl group in the 5-hydroxyflavones was also cleaved after protection of the 5-hydroxyl group with a tosyl group.[4—6] The results suggest that 3,5,6-trihydroxy-7-methoxyflavones (**1**) can be synthesized from 6-hydroxy-3,5,7-trimethoxyflavones (**2**), as shown in Scheme 1.

The 5-acetoxyl group in 5,6-diacetoxy-3,4′,7-trimethoxyflavone (**5b**) was also selectively cleaved with anhydrous aluminum bromide in acetonitrile to give 6-acetoxy-5-hydroxy-3,4′,7-trimethoxyflavone (**6b**) quantitatively. The result shows that the flavones **6** are synthesized from a mixture of **2** and 5,6-dihydroxy-3,7-dimethoxyflavones (**3**), which was easily obtained from 3′,6′-dihydroxy-2′,4′,α-trimethoxyacetophenone by the Allan–Robinson reaction.[4] Actually, dealkylation of a mixture of acetates **4** and **5** with anhydrous aluminum bromide in acetonitrile proceeded smoothly without any cleavage of the 6-acetoxyl group to give **6**, which led to the tosylate **7**. The 3-methoxyl group in the tosylates **7** was selectively cleaved with 10% (w/v) anhydrous aluminum bromide in acetonitrile to give the 3-hydroxyflavones (**8**) quantitatively. The simultaneous hydrolysis of the acetoxyl and tosyloxyl groups in **8b** with anhydrous potassium carbonate in methanol afforded colored by-products; the desired product **1b** was not obtained in high yield. The result suggests that side reactions are induced due to the existence of neighboring 5,6-dihydroxyl groups in **1**, and can be suppressed by exchanging the 6-acetyl group to other protecting groups which are stable in basic media.

Hydrolysis of the 6-acetoxyl group in **8b** with hydrochloric acid in methanol proceeded slowly due to a steric hindrance of the substituents at the 5- and 7-positions. However, that with a dilute methanolic potas-



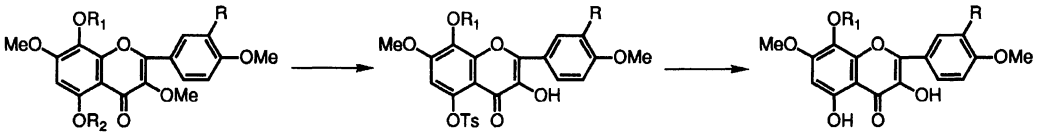
Scheme 1.

sium hydroxide at 0—5 °C proceeded rapidly without hydrolysis of the tosyloxyl group to give the 6-hydroxyflavone **9b** in high yield. The methoxymethylation of **9b** with methoxymethyl chloride and *N,N*-diisopropylethylamine in dichloromethane afforded the 6-methoxymethyl ether **10b** containing a small amount of 3,6-bis(methoxymethyl ether). The 5-tosyloxyl group in the crude methoxymethyl ether was smoothly hydrolyzed with potassium carbonate in methanol, and the desired 3,5,6-trihydroxy-7-methoxyflavone (**1b**) was easily obtained by hydrolysis of the resultant product with hydrochloric acid in acetic acid. Since the benzyloxyl groups on the B ring were hardly cleaved under the demethylating conditions, and easily removed by hydrogenolysis with palladium on charcoal, this method is useful as a general one for synthesizing **1**; eight flavones **1** were synthesized by this method. In the synthetic route, although the protection of the 6-hydroxyl group in **9b** with a benzyl group was additionally examined, this protecting group was unsuitable, since benzylation with benzyl chloride and potassium carbonate in *N,N*-dimethylformamide was accompanied by side reactions.

The results also show that the 3,5,8-trihydroxy-7-methoxyflavones (**20**), isomers of **1**, can be easily synthesized from 3,5,7,8-tetramethoxyflavones[5] (**13**) by a similar method. Thus, two 3,5,8-trihydroxy-7-methoxyflavones (**20b** and **20c**) were synthesized, as shown in Scheme 2, in connection with the identification of natural flavones (see Identification of Natural Flavones). 3,5,7,8-Tetramethoxyflavones (**13**) were converted into the corresponding 5,8-dihydroxyflavones (**14**) by using oxidative demethylation with nitric acid.[13] The 8-hydroxyl group in **14** was selectively methoxymethylated to **15** in high yield. The cleavage of the 3-methoxyl group in the tosylates **16** of the flavones **15** with 10% (w/v) anhydrous aluminum bromide in acetonitrile was accompanied by simultaneous demethoxymethylation to give the 3,8-dihydroxyflavones (**17**) quantitatively. Although the direct hydrolysis of the tosyloxyl group in **17** was also unsuitable because of the formation of by-products, their 8-methoxymethyl ethers **18** were smoothly hydrolyzed to **19** with potassium carbonate in methanol. The resultant compounds **19** were converted into the desired flavones **20** by hydrolysis with hydrochloric acid in acetic acid.

Characterization of 3,5,6-Trihydroxy-7-methoxyflavones (1). The flavones **1** were converted into the corresponding acetates **12** by acetylation with hot acetic anhydride–pyridine. The ^{1}H NMR spectra for **1** and their acetates **12** are shown in Table 1. The chemical shifts of the C_8-protons of the hydroxyflavones **1** in DMSO-d_6 are similar to those of their acetates **12** in $CDCl_3$; signals appear in the $\delta=6.82$—6.94 range. This behavior is also observed in the spectra of the 7-methylated 5,6,7-trihydroxyflavone derivatives, such as 3,5-dihydroxy-6,7-dimethoxylflavones[4] and 5,6-dihydroxy-3,7-dimethoxyflavones.[1] The aromatic proton signals on the B ring of **1** and their acetates **12** exhibit a characteristic splitting pattern corresponding to the respective structures, and the chemical shifts are also similar to those of the corresponding 6,7-dimethoxy-[4] and 7,8-dimethoxy-3,5-dihydroxyflavones,[5] 3,5,7-trihydroxy-8-methoxyflavones,[6] and their acetates. The ^{13}C NMR spectral data for the flavones **1** fully support the assigned structures, and the characteristic spectral pattern for the 3,5,6-trihydroxy-7-methoxyflavone structure is observed in the signals of the carbons at the 2 to 10-positions, as shown in Table 2.

The UV spectra for **1a**—**h** comprise a band I at 357—362 nm and two splitting bands II at 255—260 and 275—278 nm; these bands are characteristically shifted by the addition of aluminum chloride or sodium acetate (Table 3). The absorption patterns of the flavones **1** bearing the same oxygenated pattern on the B ring are very similar to each other (**1b** and **1e**; **1c**, **1f**, **1g**, and **1h**). Especially, band I shifts bathochromically in ca. 30 nm upon the addition of sodium acetate in all cases; the effect of the 4′-hydroxyl group on the B ring has not been clearly observed. Although the behavior has been observed in the UV spectra for 6,7-dimethoxy-[4]



Scheme 2.

Table 1. ^{1}H NMR Data for 3,5,6-Trihydroxy-7-methoxyflavones (**1**) in DMSO-d_6 and Their Acetates (**12**) in $CDCl_3$

Compd	Aromatic H						OMe	OH or OAc
	C_8-H	$C_{3'}$-H	$C_{5'}$-H	$C_{4'}$-H	$C_{2'}$-H	$C_{6'}$-H		
1a	6.91s	7.57t (2H)		7.52d	8.20d (2H)		3.92s	12.00s 8.69s 9.64s
1b	6.89s	7.12d (2H)		—	8.18d (2H)		3.85s 3.92s	12.09s 8.65s 9.47s
1c	6.92s	—	7.15d	—	7.78d′	7.86dd	3.85s (6H) 3.93s	12.08s 8.66s 9.49s
1d	6.94s	—	—	—	7.54s (2H)		3.76s 3.87s (6H) 3.94s	12.01s 8.69s 9.62s
1e	6.86s	6.93d (2H)		—	8.08d (2H)		3.91s	12.13s 8.63s 9.36s 10.10s
1f	6.90s	—	6.94d	—	7.78d′	7.75dd	3.86s 3.92s	12.12s 8.63s 9.39s 9.74s
1g	6.85s	—	7.09d	—	7.72d′	7.69dd	3.86s 3.92s	12.10s 8.64s 9.30s 9.42s
1h	6.82s	—	6.89d	—	7.73d′	7.57dd	3.91s	12.14s 8.62s 9.27s 9.32s 9.60s
12a	6.93s	7.48—7.56m (3H)			7.79dd (2H)		3.95s	2.30s 2.34s 2.44s
12b	6.92s	7.01d (2H)		—	7.78d (2H)		3.89s 3.95s	2.31s 2.34s 2.43s
12c	6.92s	—	6.97d	—	7.32d′	7.44dd	3.94s 3.955s 3.960s	2.31s 2.34s 2.43s
12d	6.93s	—	—	—	7.02s (2H)		3.91s (6H) 3.93s 3.96s	2.32s 2.35s 2.44s
12e	6.92s	7.25d (2H)		—	7.83d (2H)		3.95s	2.31s 2.34s 2.35s 2.43s
12f	6.91s	—	7.17d	—	7.37d′	7.40dd	3.89s 3.95s	2.31s 2.34s 2.35s 2.43s
12g	6.92s	—	7.06d	—	7.54d′	7.71dd	3.91s 3.95s	2.32s 2.34s 2.36s 2.43s
12h	6.92s	—	7.35d	—	7.67d′	7.70dd	3.95s	2.33s 2.337s (6H) 2.340s 2.43s

s, Singlet; d, doublet (J=9 Hz); d′, doublet (J=2 Hz); dd, double doublet (J=9, 2 Hz); t, triplet (J=9 Hz); m, multiplet.

and 7,8-dimethoxy-3,5-dihydroxyflavones,[5] the shift ranges are smaller (4—15 nm). The results suggest that any structural elucidation of natural flavones using the UV spectral method must be carried out with scruplous care.

Identification of Natural Flavones. Two flavones were isolated from *Citrus medica* L. var *sarcodactylis* (Noot.) Swingle by He and Ling;[9] the structures were assumed to be 3,5,6-trihydroxy-4′,7-dimethoxyflavone (**1b**) and 3,5,6-trihydroxy-3′,4′,7-trimethoxyflavone (**1c**), respectively, on the basis of their spectral data. The UV and ^{1}H NMR spectral data and melting points for the natural flavones, however, are different from those for synthetic flavones, as shown in Table 4. In the ^{1}H NMR spectra for the natural flavones in DMSO-d_6 and their acetates in $CDCl_3$, although the signals assigned to the B-ring protons are similar to those of the B ring in the synthetic flavones (**1b** and **1c**) and their acetates (**12b** and **12c**), the C_8-proton signals are different. The signals at δ=6.55 in the natural flavones were observed in a higher field than those of the C_8-protons of 5,6-dihydroxy-3,7-dimethoxyflavones[1] and 3,5-dihydroxy-6,7-dimethoxyflavones,[4] and shifted to a lower field at δ=6.71 by acetylation. The behavior is similar to those of the C_6-proton signals of 3,5-dihydroxy-7,8-dimethoxyflavones[5] and 5,8-dihydroxy-7-methoxyflavones.[14] Futhermore, band I for 3,5-dihydroxy-7,8-dimethoxyflavones[5] is observed at a longer wavelength than that for the corresponding 3,5-dihydroxy-6,7-dimethoxyflavones.[4] The results suggest that the structures of the two natural flavones are 4′,7-dimethoxy- and 3′,4′,7-trimethoxy-3,5,8-trihydroxyflavones, isomers of **1b** and **1c**, respectively. Actually, the physical data concerning the natural flavones

Table 2. ^{13}C NMR Data for 3,5,6-Trihydroxy-7-methoxyflavones (**1**) in DMSO-d_6

	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**
C_2	145.87	146.38	146.29	145.68	146.96	146.74	146.47	146.96
C_3	136.92	135.90	136.08	136.65	135.50	135.66	135.95	135.55
C_4	176.35	176.02	175.99	176.15	175.91	175.86	175.95	175.82
C_5	144.90	144.93	144.91	144.84	144.93	144.90	144.91	144.93
C_6	129.24	129.17	129.19	129.26	129.11	129.13	129.13	129.08
C_7	154.88	154.62	154.64	154.81	154.52	154.53	154.61	154.52
C_8	90.76	90.69	90.78	90.89	90.64	90.73	90.58	90.53
C_9	148.97	148.75	148.74	148.81	148.68	148.66	148.70	148.63
C_{10}	104.44	104.30	104.28	104.33	104.22	104.21	104.24	104.19
$C_{1'}$	131.03	123.33	123.39	126.32	121.74	122.04	123.50	122.04
$C_{2'}$	127.47 (2C)	129.22 (2C)	110.72	105.43 (2C)	129.41 (2C)	111.56	114.63	115.12
$C_{6'}$			121.44			121.73	119.62	119.82
$C_{4'}$	129.86	160.40	150.31	139.12	159.11	147.31	149.23	147.58
$C_{3'}$	128.46 (2C)	113.92 (2C)	148.32	152.65 (2C)	115.32 (2C)	148.32	146.10	144.97
$C_{5'}$			111.36			115.42	111.63	115.45
OMe	56.25	55.29	55.58 (2C)	56.02 (2C)	56.18	55.74	55.52	56.16
		56.22	56.25	56.31		56.20	56.18	
				60.15				

Table 3. UV Spectral Data for 3,5,6-Trihydroxy-7-methoxyflavones (**1**)

Compd		λ_{max} nm (log ε)			
1a	EtOH		277 (4.27)	335 (4.26)	375sh (3.93)
	EtOH–$AlCl_3$	252 (4.18)	288 (4.28)	364 (4.31)	430sh (3.73)
	EtOH–NaOAc		272 (4.15)	377 (4.16)	
1b	EtOH	257 (4.17)	276 (4.25)	347 (4.36)	
	EtOH–$AlCl_3$	263 (4.15)	292 (4.23)	378 (4.41)	437sh (3.92)
	EtOH–NaOAc		265 (4.25)	382 (4.23)	
1c	EtOH	257 (4.22)	277 (4.16)	355 (4.33)	
	EtOH–$AlCl_3$	264 (4.21)	288 (4.16)	387 (4.38)	
	EtOH–NaOAc		262 (4.24)	386 (4.23)	
1d	EtOH	258sh (4.13)	279 (4.18)	348 (4.34)	
	EtOH–$AlCl_3$	264 (4.14)	293 (4.17)	380 (4.38)	439sh (3.87)
	EtOH–NaOAc		259 (4.25)	384 (4.26)	
1e	EtOH	257 (4.15)	276 (4.21)	351 (4.33)	
	EtOH–$AlCl_3$	264 (4.13)	287 (4.19)	383 (4.38)	
	EtOH–NaOAc		267 (4.18)	382 (4.13)	
1f	EtOH	258 (4.24)	277 (4.17)	360 (4.35)	
	EtOH–$AlCl_3$	266 (4.23)	286 (4.18)	392 (4.39)	
	EtOH–NaOAc		285 (4.22)	392 (4.39)	
1g	EtOH	257 (4.25)	275 (4.18)	355 (4.36)	
	EtOH–$AlCl_3$	266 (4.24)	287 (4.19)	388 (4.39)	
	EtOH–NaOAc		262 (4.25)	384 (4.20)	
1h	EtOH	260 (4.23)	275sh (4.17)	363 (4.33)	
	EtOH–$AlCl_3$	270 (4.25)	285sh (4.21)	393 (4.36)	
	EtOH–NaOAc		283 (4.18)	390 (4.00)	

sh, Shoulder.

and their acetates were identical with those of the synthesized 3,5,8-trihydroxy-7-methoxyflavones (**20b** and **20c**), as shown in Table 4. Consequently, the structures of the two natural flavones were revealed to be 3,5,8-trihydroxy-4′,7-dimethoxyflavone (**20b**) and 3,5,8-trihydroxy-3′,4′,7-trimethoxyflavone (**20c**), respectively. Flavone **20b** has been isolated as its acetate and butyrate from *Notholeana affinis* by Wollenweber et al.;[15] the aglycone of the natural products is identical with the synthetic one.

Isolation of two flavones, which were assumed to be 3,4′,5,6-tetrahydroxy-7-methoxyflavone (**1e**) and 3,3′,4′,5,6-pentahydroxy-7-methoxyflavone (**1h**) from natural sources (*Balsamorhiza deltoidea*[10] and *Balsamorhiza sagittata*[11]), had been reported by Bohm et al. However, identification of the natural flavones was impossible because little information had been reported concerning their physical data.

Experimental

The melting points were determined in glass capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a

Table 4. Comparison of the Two Natural Flavones with 3,5,6-Trihydroxy-7-methoxyflavones (**1**) and 3,5,8-Trihydroxy-7-methoxyflavones (**20**)

	3,5,6-Trihydroxy-7-methoxyflavones	Natural flavones	3,5,8-Trihydroxy-7-methoxyflavones
	1b		**20b**
Mp (°C)	240—241.5	234—235	227—228.5
^{1}H NMR in DMSO-d_6 (δ)	6.89s 7.12d 8.18d 3.85s 3.92s 12.09s	6.55s 7.13d 8.23d 3.85s 3.90s 11.95s	6.53s 7.11d 8.23d 3.84s 3.90s 11.91s
UV: λ_{max} nm (log ε)	(EtOH) 257 276 347 ($AlCl_3$) 272 377 (NaOAc) 265 382	(MeOH) 255sh 287 330 388 ($AlCl_3$) 269 285 364 451 (NaOAc) 272 378	(EtOH) 255sh (4.10) 278 (4.33) 329 (4.18) 388 (4.08) ($AlCl_3$) 267 (4.25) 284 (4.28) 360 (4.20) 451 (4.14) (NaOAc) 276 (4.33) 383 (4.13)
Triacetate	**12b**		**21b**
Mp (°C)	217	239	224.5—226
^{1}H NMR in $CDCl_3$ (δ)	6.92s 7.01d 7.78d 3.89s 3.95s 2.31s 2.34s 2.43s	6.71s 6.98d 7.71d 3.88s 3.94s 2.32s 2.40s 2.44s	6.68s 6.94d 7.69d 3.83s 3.91s 2.29s 2.37s 2.41s
	1c		**20c**
Mp (°C)	168 and 196	272 (decomp)	277—278.5 (decomp)
^{1}H NMR in DMSO-d_6 (δ)	6.92s 7.15d 7.78d′ 7.86dd 3.85s (6H) 3.92s 12.08s	6.55s 7.16d 7.73—8.01m (2H) 3.83s 3.85s 3.90s 11.94s	6.57s 7.17d 7.86d′ 7.90dd 3.83s 3.85s 3.91s 11.97s
UV: λ_{max} nm (log ε)	(EtOH) 257 277 355 ($AlCl_3$) 264 288 387 (NaOAc) 262 386	(MeOH) 260 281 338 390 ($AlCl_3$) 273 286sh 372 451 (NaOAc) 275 384	(EtOH) 260 (4.29) 279 (4.27) 338 (4.12) 391 (4.13) ($AlCl_3$) 272 (4.37) 288sh (4.20) 368 (4.18) 453 (4.18) (NaOAc) 275 (4.29) 385 (4.19)
Triacetate	**12c**		**21c**
Mp (°C)	204.5—206	170	166—167.5
^{1}H NMR in $CDCl_3$ (δ)	6.92s 6.97d 7.32d′ 7.44dd 3.84s 3.955s 3.960s 2.31s 2.23s 2.43s	6.71s 7.02d 7.28d′ 7.39dd 3.93s 3.95s (6H) 2.33s 2.41s 2.45s	6.73s 6.97d 7.30d′ 7.41dd 3.92s 3.95s 3.96s 2.33s 2.40s 2.45s

Hitachi R-24B (60 MHz) or a JEOL EX-400 (400 MHz) NMR spectrometer using tetramethylsilane as an internal standard; the chemical shifts are given in δ values. The ^{13}C NMR spectra were recorded on a JEOL EX-400 (100.4 MHz) NMR spectrometer. UV spectra were recorded on a Hitachi 124 spectrophotometer. Elemental analyses were performed with a Yanaco CHN Corder (MT-5). Column chromatography was carried out with a Merck Kieselgel 60 (230—400 mesh). Acetonitrile was distilled over phosphorus pentaoxide.

6-Acetoxy-5-hydroxy-3,7-dimethoxyflavone (6). A mixture of flavones **2** and **3** (ca. 3 g), which was prepared from 3′,6′-dihydroxy-2′,4′, α-trimethoxyacetophenone by the Allan–Robinson reaction,[4,16] was acetylated with hot acetic anhydride–pyridine to give a mixture of acetates (**4** and **5**). The mixture of the acetates was dissolved in cold 10% (w/v) anhydrous aluminum bromide in acetonitrile (40—50 ml) and allowed to stand at 0 °C for 1 h. The solution was poured into 2% hydrochloric acid and heated at 50—60 °C for 10 min. The separated precipitates were collected and recrystallized from chloroform–methanol to give **6** as pale-yellow needles, with yields greater than 80% (Table 5).

6-Acetoxy-3,7-dimethoxy-5-(tosyloxy)flavone (7). A mixture of **6** (1.5 mmol), *p*-toluenesulfonyl chloride (340 mg; 1.8 mmol) and anhydrous potassium carbonate (2 g; 14.5 mmol) in acetone (30 ml) was refluxed with stirring until the starting material disappeared (2—3 h). After potassium carbonate was filtered off, the filtrate was acidified with 2% hydrochloric acid and evaporated under reduced pressure. The separated precipitates were collected and recrystallized from chloroform–methanol to give **7** as colorless needles. Only flavone **7i** was recrystallized from acetone–methanol, since **7i** was solvated with chloroform ($C_{33}H_{28}O_{10}S \cdot 1/3CHCl_3$) (Table 6).

6-Acetoxy-3-hydroxy-7-methoxy-5-(tosyloxy)flavone (8). To a cold solution of **7** (1.2 mmol) in acetonitrile (5 ml), 20% (w/v) anhydrous aluminum bromide in acetonitrile (5 ml; 3.7 mmol) was added. The mixture was allowed to stand at 0 °C for 1 h, poured into 2% hydrochloric acid, and heated at 50—60 °C for 10 min. The separated crystals were collected and recrystallized from chloroform-methanol to give **8** as pale-yellow needles (Table 6).

3,6-Dihydroxy-7-methoxy-5-(tosyloxy)flavone (9). (A) To a cold suspension of **8** (1 mmol) in methanol (20 ml), 10% aqueous potassium hydroxide (2 ml; 3.6 mmol) was added with stirring at 0 °C (changed rapidly to yellow solution). The solution was additionally stirred at 0°C for 1—1.5 h and acidified with 10% hydrochloric acid. The separated precipitates were collected and passed through a short column of silica gel using chloroform–ethyl acetate (10 : 1) as an eluent. The eluate was evaporated, and the residue was recrystallized from methanol or chloroform–methanol to give **9** as colorless prisms (Table 6).

(B) A mixture of flavone **8b** (530 mg; 1 mmol) and concd hydrochloric acid (3 ml) in methanol (40 ml) was refluxed for 10 h. The mixture was concentrated under reduced pressure and diluted with water. The separated crystals were collected and recrystallized to give **9b** (443 mg; 91%).

3,5,6-Trihydroxy-7-methoxyflavones (1). A mixture of **9** (0.8 mmol), *N*,*N*-diisopropylethylamine (0.4 ml; 2.3 mmol), and methoxymethyl chloride (0.13 ml; 1.7 mmol) in dichloromethane (25 ml) was stirred at room tempera-

Table 5. 6-Acetoxy-5-hydroxy-3,7-dimethoxyflavones (**6**)

Compd	Mp	^{1}H NMR	Formula	Found(%)		Calcd(%)	
	°C	C_8-H		C	H	C	H
6a	186—188	6.48s	$C_{19}H_{16}O_7$	63.94	4.45	64.04	4.53
6b	192—194	6.46s	$C_{20}H_{18}O_8$	61.96	4.73	62.18	4.70
6c	187—188	6.46s	$C_{21}H_{20}O_9$	60.35	4.74	60.58	4.84
6d	190.5—192	6.48s	$C_{22}H_{22}O_{10}$	58.91	4.97	59.19	4.97
6i	181.5—182.5	6.53s	$C_{26}H_{22}O_8$	67.40	4.80	67.53	4.79
6j	187—188	6.44s	$C_{27}H_{24}O_9$	65.59	4.87	65.85	4.91
6k	139—141	6.40s	$C_{27}H_{24}O_9$	65.60	4.83	65.85	4.91
6l	149.5—151.5	6.38s	$C_{33}H_{28}O_9$	69.63	4.88	69.71	4.96

Table 6. 6-Acetoxy-3,7-dimethoxy-5-(tosyloxy)flavones (**7**), 6-Acetoxy-3-hydroxy-7-methoxy-5-(tosyloxy)flavones (**8**), and 3,6-Dihydroxy-7-methoxy-5-(tosyloxy)flavones (**9**)

Compd	Mp	Yield	^{1}H NMR	Formula	Found(%)		Calcd(%)	
	°C	%	C_8-H		C	H	C	H
7a	190—192	55	6.93s	$C_{26}H_{22}O_9S$	60.98	4.35	61.17	4.34
7b	171—173	87	6.88s	$C_{27}H_{24}O_{10}S$	59.86	4.56	59.99	4.48
7c	174—175	90	6.90s	$C_{28}H_{26}O_{11}S$	58.72	4.58	58.94	4.59
7d	113—115, 164—165	77	6.91s	$C_{29}H_{28}O_{12}S$	57.76	4.77	58.00	4.70
7i	135—137, 184—185	89	6.86s	$C_{33}H_{28}O_{10}S$	64.08	4.80	64.28	4.58
7j	208—210	83	6.86s	$C_{34}H_{30}O_{11}S$	62.94	4.60	63.15	4.68
7k	106—108	80	6.77s	$C_{34}H_{30}O_{11}S$	62.96	4.62	63.15	4.68
7l	105.5—107	75	6.81s	$C_{40}H_{34}O_{11}S$	66.29	4.72	66.47	4.74
8a	197.5—198.5	88	6.93s	$C_{25}H_{20}O_9S$	60.21	4.05	60.48	4.06
8b	150—154	92	6.97s	$C_{26}H_{22}O_{10}S\cdot 1/2H_2O$	58.02	4.45	58.31	4.32
8c	122—124	79	6.89s	$C_{27}H_{24}O_{11}S$	57.99	4.28	58.27	4.35
8d	218	89	6.90s	$C_{28}H_{26}O_{12}S$	57.37	4.37	57.34	4.47
8i	173—175	86	6.92s	$C_{32}H_{26}O_{10}S$	63.63	4.43	63.78	4.35
8j	114—116	84	6.86s	$C_{33}H_{28}O_{11}S$	62.37	4.55	62.65	4.46
8k	168—170	85	6.82s	$C_{33}H_{28}O_{11}S$	62.39	4.41	62.65	4.46
8l	125—127	72	6.92s	$C_{39}H_{32}O_{11}S$	65.89	4.57	66.09	4.55
9a	194—195 (decomp)	89	6.80s	$C_{23}H_{18}O_8S$	60.67	4.01	60.79	3.99
9b	221—222 (decomp)	91	6.96s	$C_{24}H_{20}O_9S$	59.40	4.16	59.50	4.16
9c	197—198 (decomp)	80	6.85s	$C_{25}H_{22}O_{10}S$	58.07	4.22	58.36	4.31
9d	191—194 (decomp)	95	6.84s	$C_{26}H_{24}O_{11}S\cdot H_2O$	55.43	4.62	55.51	4.66
9i	196—197 (decomp)	74	6.95s	$C_{30}H_{24}O_9S$	64.09	4.29	64.28	4.32
9j	204—205 (decomp)	84	6.93s	$C_{31}H_{26}O_{10}S$	62.95	4.33	63.04	4.44
9k	176—180 (decomp)	87	6.76s	$C_{31}H_{26}O_{10}S$	63.02	4.43	63.04	4.44
9l	152—153.5	89	6.68s	$C_{37}H_{30}O_{10}S$	66.56	4.54	66.66	4.54

ture for 30 min, diluted with ice-water, and then acidified with 10% hydrochloric acid. The separated organic layer was washed with water and evaporated to give the 6-methoxymethyl ether (**10**) containing a small amount of the 3,6-bis(methoxymethyl ether). A mixture of the crude product and potassium carbonate (1.1 g; 8 mmol) in methanol (40 ml) was refluxed with stirring for 1—1.5 h, concentrated to ca. 1/4 volume, and acidified with 2% hydrochloric acid. The separated precipitates were extracted with chloroform, and the extract was evaporated under reduced pressure. The residue was passed through a short column of silica gel using chloroform–ethyl acetate (10 : 1) as an eluent to give crude **11**. A suspension of **11** in a mixture of hydrochloric acid (1 ml) and acetic acid (10 ml) was stirred at room temperature for 1 h and diluted with water. The separated crystals were collected and recrystallized to give **1**.

The obtained (benzyloxy)flavones **1i**—**l** were hydrogenolyzed with palladium on charcoal (10%; 0.25 g) in methanol or methanol–ethyl acetate (50—100 ml). After the catalyst was filtered off, the filtrate was evaporated, and the residue was recrystallized to give the corresponding hydroxyflavones **1e**—**h** (Table 7).

Acetates (12) of 1. Hydroxylfavones **1** were acetylated with hot acetic anhydride–pyridine to give the acetate **12** (Table 7).

3,7-Dimethoxy-8-methoxymethoxy-5-(tosyloxy)-flavones (16b, c). 3,5,7,8-Tetramethoxyflavone **13**[5] (3 mmol) was converted into 5,8-dihydroxy-3,7-dimethoxyflavone (**14**) by oxidative demethylation with nitric acid and the following reduction with sodium sulfite in acetic acid.[13] **14b**: Mp 191.5—193 °C (from acetone–methanol); yield 30%. Found: C, 62.50; H, 4.70%. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68%. **14c**: Mp 243—244 °C (decomp) (from chloroform) (lit,[13] mp 245—247 °C); yield 49%. The flavone **14** (1 mmol) was methoxymethylated with *N*,*N*-diisopropylethylamine (0.4 ml; 2.3 mmol) and methoxymethyl

Table 7. 3,5,6-Trihydroxy-7-methoxyflavones (**1**) and Their Acetates (**12**)

Compd	Mp	Recrystn.	Yield	Formula	Found(%)		Calcd(%)	
	°C	solvent	%		C	H	C	H
1a	175, 191—193	DMF–H_2O	56	$C_{16}H_{12}O_6$	63.77	4.15	64.00	4.03
1b	240—241.5	DMF–H_2O	62	$C_{17}H_{14}O_7$	61.83	4.30	61.82	4.27
1c	168, 196	DMF–H_2O	75	$C_{18}H_{16}O_8$	59.82	4.62	60.00	4.48
1d	225—226	DMF–H_2O	74	$C_{19}H_{18}O_9$	58.20	4.74	58.46	4.65
1e	>280	DMF–H_2O	72	$C_{16}H_{12}O_7$	60.65	3.86	60.76	3.82
1f	269—270 (decomp) (lit,[7] 266—268)	DMF–H_2O	61	$C_{17}H_{14}O_8$	58.78	4.10	58.96	4.07
1g	275—276 (decomp)	DMF–H_2O	61	$C_{17}H_{14}O_8$	59.07	4.09	58.96	4.07
1h	240—242	DMF–H_2O	73	$C_{16}H_{12}O_8$	58.00	3.71	57.84	3.64
12a	244—245	$CHCl_3$–MeOH	87	$C_{22}H_{18}O_9$	62.07	4.28	61.97	4.25
12b	217	$CHCl_3$–MeOH	94	$C_{23}H_{20}O_{10}$	60.33	4.53	60.53	4.42
12c	204.5—206	MeOH	90	$C_{24}H_{22}O_{11}$	58.98	4.58	59.26	4.56
12d	204—205	MeOH	81	$C_{25}H_{24}O_{12}$	57.95	4.68	58.14	4.68
12e	220—221	$CHCl_3$–MeOH	92	$C_{24}H_{20}O_{11}$	59.49	4.12	59.51	4.16
12f	218—220 (lit,[7] 221—223)	MeOH	88	$C_{25}H_{22}O_{12}$	58.09	4.29	58.37	4.31
12g	137—139, 202.5—203	MeOH	83	$C_{25}H_{22}O_{12}$	58.21	4.22	58.37	4.31
12h	206.5—207.5	$CHCl_3$–MeOH	80	$C_{26}H_{22}O_{13}$	57.39	4.12	57.57	4.09

chloride (0.1 ml; 1.3 mmol) in dichloromethane (20 ml) at room temperature for 1 h to give crude **15**. The product was tosylated with *p*-toluenesulfonyl chloride (0.3 g, 1.6 mmol) and anhydrous potassium carbonate (1 g; 7.2 mmol) in acetone (40 ml) to give **16** as colorless needles. **16b**: Mp 153—155 °C (from acetone–methanol); yield 87% (from **14b**). ^{1}H NMR ($CDCl_3$) δ=6.91 (1H, s, C_6-H). Found: C, 59.78; H, 4.81%. Calcd for $C_{27}H_{26}O_{10}S$: C, 59.77; H, 4.83%. **16c**: Mp 128—130 °C (from chloroform–methanol); yield 75% (from **14c**). ^{1}H NMR ($CDCl_3$) δ=6.96 (1H, s, C_6-H). Found: C, 58.59; H, 4.99%. Calcd for $C_{28}H_{28}O_{11}S$: C, 58.74; H, 4.93%.

3, 8-Dihydroxy-7-methoxy-5-(tosyloxy)flavones (17b, c). Flavones **16** (0.8 mmol) were demethylated with 10% (w/v) anhydrous aluminum bromide in acetonitrile (8 ml; 3 mmol) to give **17** as yellow needles. **17b**: Mp 181—182 °C (decomp) (from acetone–methanol); yield 86%. ^{1}H NMR ($CDCl_3$) δ=6.84 (1H, s, C_6-H). Found: C, 59.24; H, 4.20%. Calcd for $C_{24}H_{20}O_9S$: C, 59.50; H, 4.16%. **17c**: Mp 123—125 °C (decomp) (from chloroform–methanol); yield 97%. ^{1}H NMR ($CDCl_3$) δ=6.91 (1H, s, C_6-H). Found: C, 56.54; H, 4.76%. Calcd for $C_{25}H_{22}O_{10}S\cdot H_2O$: C, 56.39; H, 4.54%.

3, 5, 8- Trihydroxy- 7- methoxyflavones (20b, c). Flavones **17** (0.65 mmol) were methoxymethylated with methoxymethyl chloride (0.1 ml; 1.3 mmol) and *N,N*-diisopropylethylamine (0.5 ml; 2.9 mmol) in dichloromethane (20 ml) at room temperature for 1 h to give the crude monomethoxymethyl ether **18**. The product was hydrolyzed with potassium carbonate (0.9 g; 6.5 mmol) in boiling methanol (30 ml) for 2 h; the resultant product was demethoxymethylated with hydrochloric acid (1 ml) in acetic acid (10 ml) by a similar method (described in **1**) to give **20** as yellow needles. **20b**: Mp 227—228.5 °C (from acetone); yield 90%. Found: C, 61.61; H, 4.45%. Calcd for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27%. **20c**: Mp 277—278.5 °C (decomp) (from *N,N*-dimethylformamide–methanol); yield 79%. Found: C, 60.01; H, 4.50%. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48%.

Acetates (21b, c) of 19. Flavones **20** were acetylated with hot acetic anhydride–pyridine to give acetates **21** as colorless needles. **21b**: Mp 224.5—226 °C (from chloroform–methanol); yield 89%. Found: C, 60.21; H, 4.42%. Calcd for $C_{23}H_{20}O_{10}$: C, 60.53; H, 4.42%. **21c**: Mp 166—167.5 °C (from chloroform–methanol); yield 95%. Found: C, 58.99; H, 4.55%. Calcd for $C_{24}H_{22}O_{11}$: C, 59.26; H, 4.56%.

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