Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. XXI.[1)]

A Convenient Method for Synthesizing 3,5,7-Trihydroxy-6,8-dimethoxyflavones and 5,7-Dihydroxy-3,6,8-trimethoxyflavones

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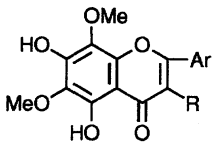
The Friedel–Crafts acetylation with boron trifluoride was studied and it was found that 1-(2,4-dihydroxy-3,5,6-trimethoxyphenyl)ethanone was conveniently synthesized from 2,3,5,6-tetramethoxyphenyl acetate in a mixture of acetic anhydride and acetic acid. 1-[2-Hydroxy-3,5,6-trimethoxy-4-(methoxymethoxy)phenyl]ethanone was cyclized to 7-hydroxy-5,6,8-trimethoxyflavone by using the Baker–Venkataraman transformation. The 7-benzyl ether of the flavone was oxidized with dimethyldioxirane and then treated with a small amount of *p*-toluenesulfonic acid to give 7-benzyloxy-3-hydroxy-5,6,8-trimethoxyflavone, which was converted into the methyl ether and tosylate. The 5-methoxy group in the methyl ether or tosylate was selectively cleaved with anhydrous aluminum bromide in acetonitrile under mild conditions to give the corresponding 5-hydroxyflavones and the latter compound with a 3-tosyloxy group was smoothly converted into the 3,5-dihydroxyflavone by hydrolysis with potassium carbonate in methanol. The hydrogenolysis of the 7-benzyloxy-3,5-dihydroxyflavone and its 3-methyl ether afforded quantitatively 3,5,7-trihydroxy-6,8-dimethoxyflavone and its 3-methyl ether. The process was suitable as a general method for synthesizing 3,5,7-trihydroxy-6,8-dimethoxyflavones and their 3-methyl ethers and the six flavones were synthesized for the clarification of their ^{1}H and ^{13}C NMR, MS, and UV spectral properties.

3,5,7-Trihydroxy-6,8-dimethoxyflavones (**1**) and their 3-methyl ethers (**2**) have been isolated from numerous plant sources and their structures are proposed on the basis of their spectral data,[2)] and a few among the ones has been synthesized by using the Allan–Robinson reaction of 2-benzoyloxy-1-(2,4,6-trihydroxy-3,5-dimethoxyphenyl)ethanone[3,4)] or 1-(2,4-dihydroxy-3,5,6-trimethoxyphenyl)-2-methoxyethanone,[5)] or oxidative cyclization of the chalcone derivatives with hydrogen peroxide (AFO reaction),[6)] but the yields in the synthesis of the starting materials and in the cyclization to flavonols are generally very low and the methods are not suitable for the synthesis of **1** or **2** (Chart 1). On the other hand, we have been studying the selective *O*-alkylation and dealkylation of flavonoids to establish new, convenient methods for synthesizing polyhydroxyflavone derivatives and to survey their inhibitory activities,[7)] and reported that several 3,5,6,7,8-pentaoxygenated flavones can be easily synthesized from 6-hydroxy-5,7,8-trimethoxyflavones by using the oxidation with dimethyldioxirane and selective demethylation.[8)] The result shows that the naturally occurring flavones **1** and **2** are easily synthesized from 1-(2,4-dihydroxy-3,5,6-trimethoxyphenyl)ethanone (**4**) via the derivatives of 5,7-dihydroxy-6,8-dimethoxyflavones (**3**) by a similar method. The 4-benzyloxy derivative of **4** has already been synthesized by Lee and Tan,[9)] but the method is not suitable because of the low yield. Thus, we examined the convenient synthesis of **4** first, then established a general method for synthesizing the flavones **1** and **2**, and clarified their properties.



1 R=OH
2 R=OMe
3 R=H

Chart 1.

Results and Discussion

Synthesis of 1-(2,4-Dihydroxy-3,5,6-trimethoxyphenyl)ethanone Derivatives. In a previous paper,[10)] we had examined the synthesis of 1-(2,4-dihydroxy-3,5,6-trimethoxyphenyl)ethanone (**4**) to establish a method for synthesizing **3** and obtained the following results: (1) the ethanone **4** was not obtained by the Friedel–Crafts reaction of 2,3,5,6-tetramethoxyphenol (**5**), and its acetate (**A5**) or benzyl ether with acetyl chloride and anhydrous aluminum chloride in ether (Chart 2); (2) the reaction of the isopropyl ether of **5** afforded the corresponding ethanone **4** in low yield (about 10%). The Friedel–Crafts reaction of polymethoxyben-

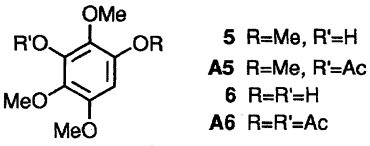
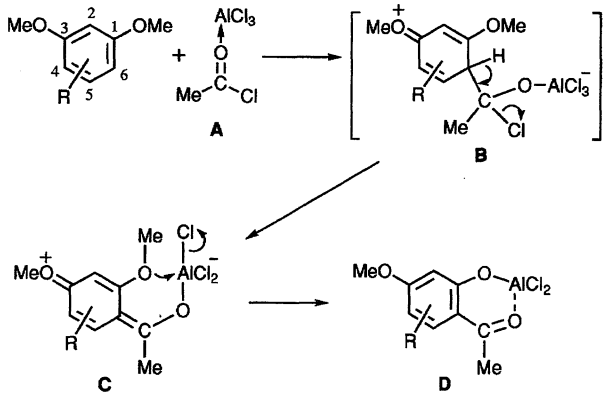


Chart 2.

zenes with two methoxy groups at the 1- and 3-positions is generally accelerated by increasing the number of methoxy groups.[11] Actually, the reaction of 1,2,3,5-tetramethoxybenzene proceeds under mild conditions to give the acetylated product in high yield,[7] but the yield of the product from pentamethoxybenzene is low (about 33%).[11] The behavior is similar to that of the demethylation of 1-(2-methoxyphenyl)ethanone with anhydrous aluminum halogenide in acetonitrile.[12] These results suggest that the reaction proceeds via an intermediate such as **B** to form a complex **C**, which is demethylated to a stable complex **D**, as shown in Scheme 1. That is, a reason for the low reactivity of pentamethoxybenzene is the decreasing of the resonance between the 3-methoxyl oxygen atom and benzene skeleton by the steric hindrance of the neighboring 2,4-dimethoxy groups and the steric hindrance between the substrate and a reagent such as the complex **A**. Thus, the reaction of 1,2,4,5-tetramethoxybenzene with no substituent at the 3-position does not proceed.[11] This consideration suggests that **4** can be synthesized from **5** or 1,3-dihydroxy-2,4,5-trimethoxybenzene (**6**) when a smaller reagent such as boron trifluoride is used.

Therefore, the Friedel–Crafts reaction[13] of the two compounds **5** and **6** with boron trifluoride were examined (Chart 2). The reaction in acetic acid was not done by accompanying many side reactions such as demethylation, but that in a mixture of acetic acid and acetic anhydride afforded

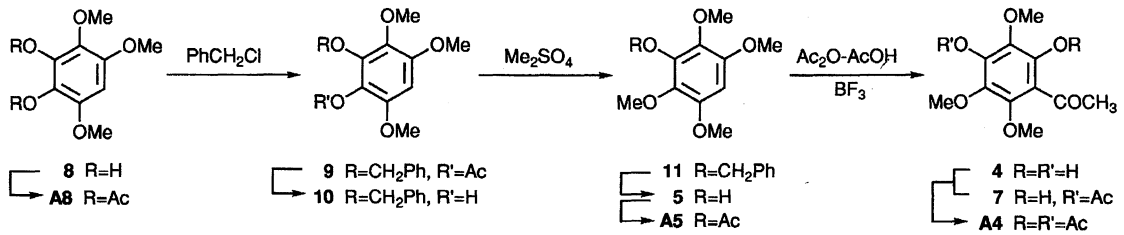


Scheme 1.

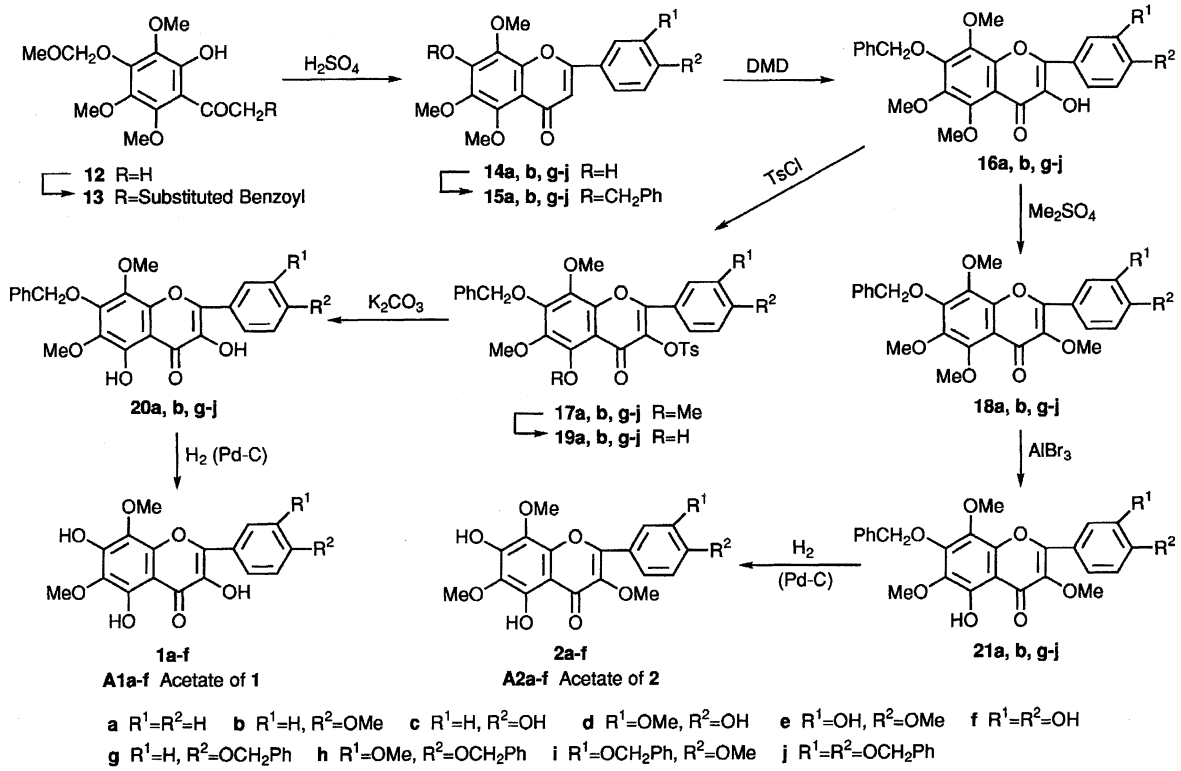
the desired ethanone **4** in low yield. The result suggests that **4** can be synthesized from their acetates (**A5** and **A6**), since the protection of the hydroxy groups in **5** or **6** suppresses the formation of the boron trifluoride complex with the hydroxy groups and the cleavage of the methoxy group adjacent to the hydroxy group.[14] Actually, the reaction of the acetate (**A5**) of **5** proceeded under mild conditions to give a mixture of **4** and its acetate (**7**), and the desired product **4** was easily obtained as a diacetate (**A4**) in 65% yield, although the reaction of the diacetate (**A6**) of **6** produced many by-products and the yield was low.

The phenol **5** had been obtained from 1,2-dihydroxy-3,4,6-trimethoxybenzene (**8**) by the partial methylation, but the yield was low (about 30%).[10] Therefore, the synthetic method of **5** was reexamined and it was found that **5** was easily synthesized from the diacetate (**A8**) of **8**[15] by a process shown in Scheme 2. That is, benzylation of the diacetate **A8** with benzyl chloride and anhydrous potassium carbonate in a mixture of acetone and *N*,*N*-dimethylformamide (DMF) proceeded selectively to give 2-benzyloxy-3,4,6-trimethoxyphenyl acetate (**9**) in favorable yield (77%). The acetate **9** was converted into 1-benzyloxy-2,3,5,6-tetramethoxybenzene (**11**) by the hydrolysis and following methylation. Hydrogenolysis of **11** with palladium on charcoal proceeded quantitatively to give the phenol **5**, which was converted into the diacetate **A4** via its acetate (**A5**).

Synthesis of 3,5,7-Trihydroxy-6,8-dimethoxyflavones (1) and Their 3-Methyl Ethers (2). The flavones **1** and **2** were synthesized from **4** by a process via a methoxymethyl ether (**12**) as shown in Scheme 3, since the selectivity in the partial benzylation of **4** was lower than that in partial methoxymethylation. That is, the crude compound **4** which was obtained from its diacetate **A4** by hydrolysis was converted into the methoxymethyl ether (**12**) with methoxymethyl chloride and *N*,*N*-diisopropylethylamine in dichloromethane. The crude **12** was benzoylated with substituted benzoyl chloride in pyridine and then transformed with powdered potassium hydroxide in pyridine to give oily diketone derivatives (**13**). Cyclization of the diketones with a small amount of concd sulfuric acid in acetic acid afforded the flavones **14** accompanied by demethoxymethylation. The benzyl ethers (**15**) of **14** were oxidized with dimethyldioxirane (DMD)[16] to give the corresponding 3-hydroxyflavones (**16**) in high yield. The flavones **16** were easily converted into the tosylates (**17**) and methyl ethers (**18**). Although the selective cleavage of the 5-methoxy group in the 3-hydroxyflavones **16** is difficult,[17] the 5-methoxy group in **17** and **18** with



Scheme 2.



Scheme 3.

no free hydroxy group at the 3-position was quantitatively cleaved with anhydrous aluminum bromide in acetonitrile to give the corresponding 5-hydroxyflavones (**19** and **21**) without the cleavage of the benzyloxy groups on the flavone skeleton. The 3-tosyloxy group in **19** was smoothly hydrolyzed to the 3,5-dihydroxyflavones (**20**) with anhydrous potassium carbonate in methanol. The benzyloxy groups in the benzyloxyflavones **20** and **21** were quantitatively cleaved by hydrogenolysis with palladium on charcoal to give the desired hydroxyflavones **1** and **2**. The flavones **1d**,[3] **2a**,[5] and **2b**[5,6] had been synthesized previously.

The process is not only usable for a general method for synthesizing **1** and **2** but for 5,7-dihydroxy-6,8-dimethoxyflavones, since the 5-methoxy group in the flavones **14** or **15** is selectively cleaved.

Characterization of 3,5,7-Trihydroxy-6,8-dimethoxyflavones (1) and Their 3-Methyl Ethers (2). The Flavones **1** and **2** were converted into the corresponding acetates **A1** and **A2** with hot acetic anhydride–pyridine. The ^{1}H NMR spectra for these flavones have the characteristic splitting pattern attributed to the B-ring substituents and support well the respective structures as shown in Table 1. The 2′,6′-proton signals in the 3-hydroxyflavones (**1**) appear in a lower field by a range of 0.11 to 0.14 ppm than those in the corresponding 3-methoxyflavones (**2**) by the effect of the 3-hydroxy group, although the other signals on the B-ring are similar to each other. In contrast to the behavior, the signals in their acetates (**A1**) are observed in a higher field by a range of 0.25 to 0.30 ppm than those in the corresponding acetates (**A2**). On the other hand, the ^{13}C NMR spectra for the hydroxyflavones **1** and **2** have a characteristic spectral pattern reflecting the respective substitution patterns and the signals at 2- to 10-positions in the flavones bearing the same oxygenated pattern at the A and C rings are superimposable on each other as shown in Table 2. In the comparison of the ^{13}C NMR spectra between **1** and **2**, the carbon signals at the 2- to 10-positions in **1** are paramagnetically shifted by methylation of the 3-hydroxy group (conversion to **2**) and the shift ranges of the signals decreased in the order of 2- (8.6—9.2 ppm), 4- (1.9—2.1 ppm), 3- (1.6—1.9 ppm), 10-positions (1.1—1.2 ppm): The tendency corresponds well to the relation between the 6,7,8-trioxygenated 3,5-dihydroxyflavones and their 3-methyl ethers.[8]

The MS spectral pattern for **1** is different from that for **2** by the effect of the 3-hydroxy group, but the respective spectral patterns are similar to each other and the influence of the substituents on the B ring is hardly observed. That is, the MS spectra for **1** have a molecular ion peak and three major fragment peaks, $[M-Me]^+$ as the base peak, $[M-Me-CO]^+$, and $[M-2Me-CO]^+$, and those for **2** show only the two peaks, a molecular ion and $[M-Me]^+$ as the base peak, as shown in Table 2.

In the UV spectral comparison with natural flavones, we found that the spectra for these flavones in methanol are not always consistent with those in ethanol. Therefore, the difference between ethanol and methanol as a solvent was examined first and the following results were obtained. The respective spectral patterns for the flavones **1** and **2** in methanol was fairly different from that in ethanol, but both spectral patterns, upon the addition of aluminum chloride or sodium acetate, were similar to each other except for that for **1f** and **2f**. Although both UV spectra for **1** and **2** have a

Table 1. ^{1}H NMR Spectral Data for 3,5,7-Trihydroxy-6,8-dimethoxyflavones (**1**), 5,7-Dihydroxy-3,6,8-trimethoxyflavones (**2**), and Their Acetates (**A1** and **A2**) [a]

Compd	Solv.	OMe					Arom. H					OH or OAc				
		C_3	C_6	C_8	$C_{3'}$	$C_{4'}$	$C_{2'}$	$C_{6'}$	$C_{3'}$	$C_{5'}$	$C_{4'}$	C_3	C_5	C_7	$C_{3'}$	$C_{4'}$
1a	DMSO	—	3.81s	3.88s	—	—	8.18d (2H)		7.59t (2H)		7.52t	9.74s	12.19s	10.46s	—	—
	$CDCl_3$	—	4.03s	4.06s	—	—	8.25d (2H)		7.55t (2H)		7.49t	6.70s	11.62s	6.47s	—	—
Lit,[18]	$CDCl_3$	—	4.03s	4.06s	—	—	8.23m (2H)		7.5m (3H)			6.72s	11.62s	6.48s	—	—
2a	DMSO	3.80s	3.83s	3.85s	—	—	8.03—8.05m (2H)		7.61—7.63m (3H)			—	12.41s	10.52b	—	—
	$CDCl_3$	3.88s	3.99s	4.05s	—	—	8.12—8.15m (2H)		7.53—7.56m (3H)			—	12.54s	6.43s	—	—
Lit,[19]	$CDCl_3$	3.79s	3.90s	3.95s	—	—	8.05m (2H)		7.45m (3H)			—	10.56s	6.55s	—	—
1b	DMSO	—	3.80s	3.86s	—	3.87s	8.17d (2H)		7.16d (2H)		—	9.61s	12.29s	10.43s	—	—
2b	DMSO	3.79s	3.81s	3.85s	—	3.87s	8.04d (2H)		7.17d (2H)		—	—	12.49s	10.50s	—	—
	$CDCl_3$	3.87s	3.99s	4.04s	—	3.90s	8.14d (2H)		7.05d (2H)		—	—	12.61s	6.40s	—	—
Lit,[19]	$CDCl_3$	3.79s	3.90s	3.95s	—	3.82s	8.03d (2H)		6.95d (2H)		—	—	10.45s	6.34s	—	—
1c	DMSO	—	3.81s	3.88s	—	—	8.09d (2H)		6.98d (2H)		—	9.47s	12.33s	10.38s	—	10.17s
2c	DMSO	3.80s	3.81s	3.86s	—	—	7.97d (2H)		7.00d (2H)		—	—	12.54s	10.45b	—	10.33b
1d	DMSO	—	3.80s	3.87s	3.89s	—	7.79d′	7.76dd	—	6.99d	—	9.51s	12.29s	10.38s	—	9.81s
2d	DMSO	3.78s	3.82s	3.87s	3.87s	—	7.67bs	7.63dd	—	7.00d	—	—	12.50s	10.44b	—	9.98s
1e	DMSO	—	3.81s	3.87s	—	3.89s	7.74bs	7.72dd	—	7.14d	—	9.44s	12.29s	10.39s	9.53s	—
2e	DMSO	3.80s	3.81s	3.87s	—	3.88s	7.60d′	7.61dd	—	7.15d	—	—	12.51s	10.46b	9.54s	—
1f	DMSO	—	3.81s	3.89s	—	—	7.74d′	7.62dd	—	6.94d	—	9.44s	12.34s	10.37s	9.42s	9.63s
2f	DMSO	3.78s	3.80s	3.86s	—	—	7.60d′	7.50dd	—	6.94d	—	—	12.55s	10.42b	9.50b	9.80b
A1a	$CDCl_3$	—	3.86s	4.00s	—	—	7.83—7.86m (2H)		7.50—7.54m (3H)			2.32s	2.47s	2.42s	—	—
A2a	$CDCl_3$	3.81s	3.87s	4.01s	—	—	8.08—8.11m (2H)		7.52—7.53m (3H)			—	2.51s	2.43s	—	—
A1b	$CDCl_3$	—	3.86s	4.00s	—	3.89s	7.84d (2H)		7.02d (2H)		—	2.34s	2.47s	2.43s	—	—
A2b	$CDCl_3$	3.80s	3.86s	4.00s	—	3.90s	8.10d (2H)		7.03d (2H)		—	—	2.50s	2.42s	—	—
A1c	$CDCl_3$	—	3.86s	3.98s	—	—	7.88d (2H)		7.27d (2H)		—	2.33s	2.47s	2.42s	—	2.35s
A2c	$CDCl_3$	3.82s	3.86s	3.99s	—	—	8.14d (2H)		7.26d (2H)		—	—	2.50s	2.43s	—	2.35s
A1d	$CDCl_3$	—	3.86s	3.99s	3.88s	—	7.46bs	7.47dd	—	7.18d	—	2.33s	2.47s	2.42s	—	2.36s
A2d	$CDCl_3$	3.83s	3.87s	4.00s	3.91s	—	7.79d′	7.74dd	—	7.19d	—	—	2.51s	2.43s	—	2.36s
A1e	$CDCl_3$	—	3.85s	3.99s	—	3.92s	7.58d′	7.76dd	—	7.09d	—	2.34s	2.47s	2.42s	2.35s	—
A2e	$CDCl_3$	3.81s	3.86s	3.99s	—	3.92s	7.87d′	8.04dd	—	7.10d	—	—	2.50s	2.42s	2.36s	—
A1f	$CDCl_3$	—	3.86s	3.98s	—	—	7.73d′	7.75dd	—	7.36d	—	2.33s	2.47s	2.42s	2.34s	2.35s
A2f	$CDCl_3$	3.84s	3.86s	3.99s	—	—	8.01d′	8.04dd	—	7.36d	—	—	2.50s	2.42s	2.34s	2.34s

a) s, Singlet; bs, broad singlet; b, broad; d, doublet (J = 8.0—9.0 Hz); d′, doublet (J = 2.0—2.5 Hz); dd, doublet doublet (J = 8.0—9.0, 2.0—2.5 Hz); t, triplet (J = 8.0 Hz).

characteristic absorption pattern corresponding to the respective structures and the absorption band is characteristically shifted upon the addition of the two shift reagents, the UV spectral data in methanol were used here for comparison with the natural flavones (Table 3).

In the spectra for **1**, the band I at 371—378 nm is bathochromically shifted upon the addition of aluminum chloride and the characteristically split two bands are observed at 357—385 and 430—440 nm. Although the similar phenomena are also observed in the spectra for **2**, the intensity of the longer wavelength at about 410 nm in the two split bands is very weak. The behavior in the spectra for **1f** and **2f**, however, is different from that for the other flavones **1** and **2**, and both spectral patterns upon the addition of aluminum chloride are similar. The particular behavior disappeared when the spectra was measured in ethanol and the two split bands were observed as shown in Table 3. Upon the addition of sodium acetate, the spectra for **1** and **2** change to the characteristic spectral pattern with two clear bands at 280—285 and 380—400 nm and the characteristic bathochromic shift attributed to the 4′-hydroxy group is not observed in all cases.

The flavones **1a**, **1d**—**1f**, and **2a**—**2f** have been isolated from the natural sources[2] and the UV, ^{1}H NMR, and/or ^{13}C NMR spectral data are consistent with those for the corresponding synthesized flavones as shown in Tables 1, 2, and 3. The results support that the structures of the natural flavones are correct.

Experimental

All melting points were measured in glass capillaries and are uncorrected. ^{1}H NMR (at 400 MHz or 60 MHz) and ^{13}C NMR (at 100.4 MHz) spectra were recorded on a JEOL EX400, using tetramethylsilane as an internal standard, and chemical shifts are given in δ values. UV and MS spectra were recorded on a Hitachi 124 spectrophotometer and on a Shimadzu QP 1000 spectrometer, respectively. Column chromatography was done on Kiesel-gel 60 (70—230 mesh; Merck). Elemental analyses were done with a Yanaco CHN corder Model MT-5.

2-Benzyloxy-3,4,6-trimethoxyphenyl Acetate (9). To a solution of 1-(2-hydroxy-3,4,6-trimethoxyphenyl)ethanone[15] (30 g) in MeOH (300 ml)–aq 4% NaOH (150 ml), a cooled aq 6% H_2O_2 (270 ml) was added, the mixture was stirred at 50 °C for 2 h and then acidified with HCl. After the separated precipitate was filtered off, the filtrate was concentrated and extracted with ether to give

Table 2. ^{13}C NMR and MS Spectral Data for 3,5,7-Trihydroxy-6,8-dimethoxyflavones (1) and Their 3-Methyl Ethers (2)[a]

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	OMe C_6	OMe C_8	OMe $C_{3'}$	OMe $C_{4'}$
1a	145.8	136.8	176.7	147.3	131.0	150.8	127.7	144.7	102.5	131.1	127.3		128.6		128.6	—	60.1	61.1	—	—
1b	146.2	135.8	176.4	147.3	130.9	150.5	127.6	144.4	102.3	123.4	129.1		114.1		160.5	—	60.1	61.1	—	55.3
1c	146.9	135.4	176.3	147.2	130.9	150.4	127.6	144.4	102.3	121.8	129.3		115.5		159.2	—	60.1	61.1	—	—
1d[b]	146.5	135.6	176.2	147.2	130.9	150.5	127.6	144.3	102.3	122.1	111.2	121.6	148.8	115.6	147.3	—	60.1	61.0	55.5	—
1e	146.3	135.9	176.3	147.2	130.9	150.5	127.6	144.4	102.3	123.6	111.9	119.6	146.2	114.4	149.4	—	60.1	61.1	—	55.5
1f[b]	146.8	135.4	176.2	147.2	130.9	150.4	127.6	144.3	102.2	122.1	114.8	119.9	145.1	115.6	147.7	—	60.1	61.1	—	—
2a	155.0	138.4	178.6	147.9	131.4	151.0	127.8	144.8	103.7	131.0	128.0		128.9		130.2	59.9	60.1	61.1	—	—
2b	155.0	137.5	178.4	147.9	131.3	150.8	127.7	144.6	103.5	122.3	129.8		114.3		161.3	59.7	60.1	61.1	—	55.4
2c[c]	155.5	137.3	178.3	147.9	131.3	150.7	127.7	144.5	103.4	120.7	130.0		115.7		160.2	59.6	60.1	61.1	—	—
2d[c]	155.2	137.4	178.3	147.9	131.3	150.7	127.6	144.4	103.4	122.0	111.6	120.9	149.7	115.7	147.4	59.6	60.1	61.1	55.4	—
2e	155.1	137.7	178.4	147.9	131.3	150.8	127.7	144.5	103.5	122.4	112.0	120.2	146.4	114.8	150.3	59.6	60.1	61.2	—	55.4
2f[c]	155.4	137.3	178.3	147.8	131.2	150.6	127.7	144.4	103.4	120.9	115.2	120.5	145.2	115.8	148.7	59.5	60.1	61.2	—	—
EIMS (70 eV):		**1a;**	330 (M^+, 84),		315 (M^+–Me, 100),			287 (M^+–Me–CO, 31),			272 (M^+–2Me–CO, 20):					**2a;**	344 (M^+, 72),		329 (M^+–Me, 100)	
m/z (rel intensity)		**1b;**	360 (M^+, 82),		345 (M^+–Me, 100),			317 (M^+–Me–CO, 32),			302 (M^+–2Me–CO, 27):					**2b;**	374 (M^+, 63),		359 (M^+–Me, 100)	
		1c;	346 (M^+, 97),		331 (M^+–Me, 100),			303 (M^+–Me–CO, 26),			288 (M^+–2Me–CO, 20):					**2c;**	360 (M^+, 82),		345 (M^+–Me, 100)	
		1d;	376 (M^+, 83),		361 (M^+–Me, 100),			333 (M^+–Me–CO, 32),			318 (M^+–2Me–CO, 28):					**2d;**	390 (M^+, 64),		375 (M^+–Me, 100)	
		1e;	376 (M^+, 89),		361 (M^+–Me, 100),			333 (M^+–Me–CO, 22),			318 (M^+–2Me–CO, 16):					**2e;**	390 (M^+, 77),		375 (M^+–Me, 100)	
		1f;	362 (M^+, 92),		347 (M^+–Me, 100),			319 (M^+–Me–CO, 27),			304 (M^+–2Me–CO, 21):					**2f;**	376 (M^+, 76),		361 (M^+–Me, 100)	

a) ^{13}C NMR spectra were measured in DMSO-d_6. b) The data are completely consistent with those for the natural flavone isolated from Gutierrezia microcephala by Roitman and James,[20] although the assignment is slightly different. c) The data are completely consistent with those for the natural flavone isolated from Gutierrezia microcephala by Roitman and James.[20]

a crude **8**. The method by using aq MeOH as a solvent was more convenient than the one described by Baker.[15] The crude **8** was acetylated with acetic anhydride-pyridine to give the diacetate **A8**; mp 141—142 °C (from $CHCl_3$–MeOH) (lit,[10] mp 146—147.5 °C); yield, 25.0 g (57%).

A mixture of **A8** (28.7 g), benzyl chloride (20 ml), and anhydrous K_2CO_3 (140 g) in Me_2CO (200 ml)-*N*,*N*-dimethylformamide (50 ml) was refluxed until the starting material disappeared on the TLC (about 50 h). The mixture was filtered and the excess benzyl chloride was removed by steam distillation. The separated precipitate was collected and recrystallized from MeOH to give **9**; mp 76—77 °C; yield, 25.1 g (77%). Found: C, 65.14; H, 6.03%. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07%.

1-Benzyloxy-2,3,5,6-tetramethoxybenzene (11). The acetate **9** (25.1 g) was hydrolyzed with aq 10% NaOH (100 ml) in methanol (300 ml) at room temperature for 30 min and then acidified with HCl. The MeOH was evaporated and extracted with ether to give a crude phenol **10** as an oil. A mixture of the phenol **10**, Me_2SO_4 (14.5 ml), and anhydrous K_2CO_3 (100 g) in Me_2CO (200 ml) was refluxed for 2—3 h, then diluted with H_2O, and additionally refluxed for 15—20 min. After Me_2CO was distilled off, the separated precipitate was collected and recrystallized from MeOH to give **11**; mp 68—68.5 °C (lit,[10] mp 67—68 °C); yield, 22.3 g (96%).

2,3,5,6-Tetramethoxyphenyl Acetate (A5). The compound **11** (22.3 g) was hydrogenolyzed with 10% Pd–C in MeOH (200 ml)–EtOAc (20 ml) at room temperature to give a phenol **5**. The phenol **5** was acetylated with acetic anhydride–pyridine and then recrystallized from methanol to give **A5**; mp 97—98 °C (lit,[10] mp 94—95 °C); yield, 18.1 g (97%).

1-(2,4-Diacetoxy-3,5,6-trimethoxyphenyl)ethanone (A4). A solution of **A5** (6.5 g) in acetic anhydride–acetic acid (1 : 1; 16 ml) was saturated with BF_3 gas at 10—15 °C and then heated with stirring at 50—60 °C for 5 h. The mixture was poured into a mixture of ice and concd HCl and extracted with ether. The extract was washed with aq $NaHCO_3$ and H_2O, dried over Na_2SO_4, and concentrated to give a mixture of **4** and **7**. The mixture was acetylated with hot acetic anhydride–pyridine and then recrystallized from $CHCl_3$–hexane to give **A4**; mp 82—84 °C; yield, 5.4 g (65%). Found: C, 55.47; H, 5.71%. Calcd for $C_{15}H_{18}O_8$: C, 55.21; H, 5.56%. ^1H NMR: ($CDCl_3$) $\delta = 3.67$ (3H, s, OMe), 3.77s (6H, s, 2×OMe), 2.23 and 2.33 (each 3H, s, OAc), 2.45 (3H, s, Ac).

7-Hydroxy-5,6,8-trimethoxyflavones (14). The diacetate **A4** (2.5 g; 7.65 mmol) was hydrolyzed with aq 10% NaOH (15 ml) in MeOH (50 ml) at room temperature for 10—15 min to give a crude **4**. To a solution of the crude **4** in CH_2Cl_2 (40 ml), *N*,*N*-diisopropylethylamine (4 ml; 23.0 mmol) and $MeOCH_2Cl$ (0.9 ml; 11.5 mmol) was added under ice cooling, then the mixture was stirred below 5 °C for 40—50 min and poured into a mixture of ice and dil HCl. The organic layer was collected, washed with water, dried over Na_2SO_4, and evaporated to give a crude methoxymethyl ether **12**.

The crude ether **12** was benzoylated with a substituted benzoyl chloride (10.5—11.5 mmol) in pyridines (10—15 ml) at 60—70 °C for 2—3 h to give a crude benzoate which contained an appreciable amount of the benzoic anhydride. To a solution of the dried benzoate in pyridine (15—20 ml), a freshly powdered KOH (4—4.5 g) was added, the mixture was stirred at 60 °C for 2 h and poured into a mixture of ice and HCl. The separated oily materials were extracted with EtOAc. The extract was washed with aq K_2CO_3 and H_2O, dried over Na_2SO_4, and then concentrated to give a crude diketone derivative **13**. A solution of the diketone **13** in HOAc (10 ml) was warmed with a few drops of concd H_2SO_4 at 50 °C for 1 h

Table 3. UV Spectral Data for 3,5,7-Trihydroxy-6,8-dimethoxyflavones (**1**) and Their 3-Methyl Ethers (**2**)[a)]

Compd	λ_{max} /nm (log ε)										
	MeOH				MeOH–$AlCl_3$				MeOH–NaOAc		
1a		276 (4.36)	325 (4.10)	371 (4.01)	284 (4.29)		357 (4.17)	430 (4.02)	284 (4.38)		397 (4.07)
Lit,[18)]		277 (4.31)	323 (4.06)	370 (3.97)							
1b	256 (4.14)	275 (4.28)	337 (4.23)	374 (4.21)	282 (4.25)	315 (3.98)	371 (4.26)	435 (4.22)	281 (4.38)	306 (4.18)	395 (4.18)
1c	256 (4.16)	274 (4.27)	338 (4.22)	375 (4.23)	280 (4.25)	315 (3.95)	373 (4.24)	435 (4.24)	280 (4.36)	312 (4.14)	398 (4.21)
1d	259 (4.28)	274sh (4.21)		377 (4.29)	270 (4.32)		385 (4.22)	440 (4.30)	282 (4.31)	326 (4.13)	401 (4.22)
Lit,[20)]	262 (0.99)	276 (0.88)	315sh 345sh	380 (1.00)	272 (1.00)	320sh	375sh (0.50)	440 (0.96)	280 (1.00)	330 (0.70)	388 (0.97)
1e	259 (4.30)	275 (4.23)		375 (4.27)	270 (4.34)		382 (4.22)	438 (4.28)	282 (4.35)	325 (4.13)	395 (4.22)
Lit,[21)]	260	276—350		375	271	381		441	282	325 (low)	401
1f	260 (4.31)	272i (4.22)		378 (4.29)	281 (4.36)			463 (4.42)	281 (4.29)	328 (4.10)	400 (4.21)
Lit,[20)]	264 (1.00)	280sh (0.89)	345sh	382sh (0.88)	280 (0.86)			468 (1.00)	280 (0.93)	329 (0.52)	392 (0.80)
(EtOH)	262 (4.18)	275sh (4.16)		385 (4.14)	273 (4.24)		379 (4.13)	440 (4.21)	281 (4.01)	349 (4.09)	410sh (3.83)
2a		278 (4.43)	322 (4.00)		293 (4.42)		347 (4.13)	422 (3.65)	283 (4.44)		380 (4.03)
Lit,[19)]		278	328	375sh	290		345	430sh	282		385
2b		278 (4.33)	334 (4.27)		290 (4.25)	312 (4.26)	362 (4.34)	410sh (3.94)	283 (4.47)	300i (4.28)	380 (4.13)
Lit,[19)]		280	336	365sh	284	305	385		290 317	367	420sh
2c		277 (4.31)	337 (4.28)		287 (4.24)	312 (4.22)	366 (4.34)	410i (4.02)	282 (4.43)	305sh (4.17)	395 (4.22)
Lit,[20)]		280 (1.00)	340 (0.81)		288 (0.83)	314 (0.76)	366 (1.00)	425sh (0.47)	282 (1.00)	310sh (0.65)	366 (0.54)
2d	258 (4.22)	278 (4.27)	350 (4.30)		268 (4.19)	288 (4.24)	377 (4.33)	415i (4.11)	282 (4.30)	323 (4.12)	382 (4.14)[b)]
Lit,[22)]	257	277	353		265	286 306sh	377	420sh	280		378
2e	258 (4.27)	278 (4.31)	348 (4.29)		268 (4.22)	288 (4.27)	374 (4.31)	412i (4.06)	282 (4.41)	320 (4.13)	381 (4.17)
Lit,[23)]	258	278	350		271	288 308sh	375	420sh	280	315sh	380
2f	261 (4.26)	277 (4.28)	355 (4.29)			283 (4.40)		449 (4.42)	281 (4.38)	330 (4.09)	403 (4.25)
Lit,[20)]	264sh (0.92)	278 (1.00)	360 (0.86)			284 (0.93)	314sh (0.32)	448 (1.00)	282 (1.00)	330 (0.53)	402 (0.64)
(EtOH)		278 (4.34)	370 (4.17)		270i (4.21)	287 (4.27)	373 (4.27)	412sh (4.11)	281 (4.38)	328 (4.08)	406 (4.24)

a) sh, Shoulder; i, inflection point. b) The spectra were taken immediately after the addition of NaOAc (50 mg) to the solution (25 ml), since only the spectra were greatly affected by increasing the time after the addition of the reagent or by increasing an amount of the reagent and varied as follows: the band at 282 nm decreased greatly, that at 323 nm collapsed, and that at 382 nm shifted hypochromically to about 360 nm.

Table 4. 7-Hydroxy-5,6,8-trimethoxyflavones (**14**), 7-Benzyloxy-5,6,8-trimethoxyflavones (**15**), and 7-Benzyloxy-3-hydroxy-5,6,8-trimethoxyflavones (**16**)

Compd	Mp	Recrystn.	Yield	Formula	Found (%)		Calcd (%)	
	°C	solvent	%		C	H	C	H
14a	182—183	$CHCl_3$–MeOH	51	$C_{18}H_{16}O_6$	65.64	5.03	65.85	4.91
14b	159.5—161	$CHCl_3$–Et_2O	40	$C_{19}H_{18}O_7$	63.50	5.02	63.68	5.06
14g	154—156	$CHCl_3$–Et_2O	43	$C_{25}H_{22}O_7$	68.90	5.03	69.11	5.10
14h	157—159	$CHCl_3$–Et_2O	44	$C_{26}H_{24}O_8$	66.98	5.27	67.23	5.21
14i	147—148	$CHCl_3$–Et_2O	44	$C_{26}H_{24}O_8$	66.98	5.16	67.23	5.21
14j	172—173	$CHCl_3$–MeOH	47	$C_{32}H_{28}O_8$	71.35	5.34	71.10	5.22
15a	132—133	MeOH	97	$C_{25}H_{22}O_6$	71.84	5.42	71.76	5.30
15b	114—116	MeOH	98	$C_{26}H_{24}O_7$	69.79	5.33	69.63	5.39
15g	119—120	MeOH	86	$C_{32}H_{28}O_7$	73.05	5.42	73.27	5.38
15h	148—149	$CHCl_3$–MeOH	80	$C_{33}H_{30}O_8$	71.66	5.45	71.47	5.45
15i	128—129	$CHCl_3$–MeOH	90	$C_{33}H_{30}O_8$	71.36	5.48	71.47	5.45
15j	150—152	$CHCl_3$–MeOH	87	$C_{39}H_{34}O_8$	74.12	5.44	74.27	5.43
16a	129—130	$CHCl_3$–MeOH	73	$C_{25}H_{22}O_7$	69.02	5.09	69.11	5.10
16b	107—109	$CHCl_3$–MeOH	83	$C_{26}H_{24}O_8$	67.12	5.23	67.23	5.21
16g	159—161	$CHCl_3$–MeOH	85	$C_{32}H_{28}O_8$	70.90	4.99	71.10	5.22
16h	166—167	$CHCl_3$–MeOH	83	$C_{33}H_{30}O_9$	69.53	5.34	69.46	5.30
16i	142—144	$CHCl_3$–MeOH	88	$C_{33}H_{30}O_9$	69.21	5.28	69.46	5.30
16j	131.5—132.5	$CHCl_3$–MeOH	84	$C_{39}H_{34}O_9$	72.20	5.28	72.43	5.30

and then diluted with H_2O. The separated precipitate was collected and recrystallized to give **14** (Table 4).

7-Benzyloxy-5,6,8-trimethoxyflavones (15). A mixture of the flavone **14** (2.5 mmol), benzyl chloride (0.65 ml; 5.2 mmol), and anhydrous K_2CO_3 (3.0—4.0 g) in *N*,*N*-dimethylformamide (4—5 ml) was heated with vigorous stirring at 150 °C for 5 min and diluted with H_2O. After the excess benzyl chloride was removed by steam distillation, the separated crystals were collected and recrystallized to give **15** (Table 4).

7-Benzyloxy-3-hydroxy-5,6,8-trimethoxyflavones (16). To a cold solution of the flavone **15** (2.0 mmol) in CH_2Cl_2 (20—30 ml), a cold solution of dimethyldioxirane[16] in Me_2CO (concn 0.10—

Table 5. 7-Benzyloxy-5,6,8-trimethoxy-3-tosyloxyflavones (**17**), 7-Benzyloxy-3,5,6,8-tetramethoxyflavones (**18**), 7-Benzyloxy-5-hydroxy-6,8-dimethoxy-3-tosyloxyflavones (**19**), 7-Benzyloxy-3,5-dihydroxy-6,8-dimethoxyflavones (**20**), and 7-Benzyloxy-5-hydroxy-3,6,8-trimethoxyflavones (**21**)[a]

Compd	Mp	Recrystn.	Formula	Found (%)		Calcd (%)	
	°C	solvent		C	H	C	H
17a	169—171	MeOH	$C_{32}H_{28}O_9S$	65.50	4.77	65.30	4.80
17g	145—146.5	$CHCl_3$–MeOH	$C_{39}H_{34}O_{10}S$	67.17	4.87	67.42	4.93
17h	171—173	$CHCl_3$–MeOH	$C_{40}H_{36}O_{11}S$	66.03	4.99	66.28	5.01
18a	121—122	MeOH	$C_{26}H_{24}O_7$	69.59	5.38	69.63	5.39
18b	121—123	MeOH	$C_{27}H_{26}O_8$	67.89	5.49	67.77	5.48
18g	115—117	$CHCl_3$–MeOH	$C_{33}H_{30}O_8$	71.26	5.46	71.47	5.45
18h	122—123.5	$CHCl_3$–MeOH	$C_{34}H_{32}O_9$	70.05	5.54	69.85	5.52
18j	122—124	$CHCl_3$–MeOH	$C_{40}H_{36}O_9$	72.52	5.47	72.71	5.49
19a	146—148	$CHCl_3$–MeOH	$C_{31}H_{26}O_9S$	64.70	4.54	64.80	4.56
19h	185—187	$CHCl_3$–MeOH	$C_{39}H_{34}O_{11}S$	65.69	4.74	65.91	4.82
19i	151—153	MeOH	$C_{39}H_{34}O_{11}S$	65.69	4.90	65.91	4.82
20a	160—162	MeOH	$C_{24}H_{20}O_7$	68.29	4.88	68.56	4.80
20b	147—148.5	$CHCl_3$–MeOH	$C_{25}H_{22}O_8$	66.65	4.94	66.66	4.92
20g	157—159	$CHCl_3$–MeOH	$C_{31}H_{26}O_8$	70.54	5.03	70.71	4.98
20h	151—153	$CHCl_3$–MeOH	$C_{32}H_{28}O_9$	69.06	5.07	69.06	5.07
20i	144—146	MeOH	$C_{32}H_{28}O_9$	68.98	5.00	69.06	5.07
20j	172—173	$CHCl_3$–MeOH	$C_{38}H_{32}O_9 \cdot 1/2H_2O$	71.20	5.13	71.13	5.03
21a	112—115	$CHCl_3$–MeOH	$C_{25}H_{22}O_7$	68.84	5.07	69.11	5.10
21b	122—123	$CHCl_3$–MeOH	$C_{26}H_{24}O_8$	66.99	5.17	67.23	5.21
21g	118—120	$CHCl_3$–MeOH	$C_{32}H_{28}O_8$	70.85	5.24	71.10	5.22
21h	147—149	$CHCl_3$–MeOH	$C_{33}H_{30}O_9$	69.24	5.22	69.46	5.30
21i	128—130	$CHCl_3$–MeOH	$C_{33}H_{30}O_9$	69.64	5.34	69.46	5.30

a) The following compounds were hardly crystallized: **17b**, **17i**, **17j**, **18i**, **19b**, **19g**, **19j**, and **21j**.

Table 6. 3,5,7-Trihydroxy-6,8-dimethoxyflavones (**1**), 5,7-Dihydroxy-3,6,8-trimethoxyflavones (**2**), and Their Acetates (**A1** and **A2**)

Compd	Mp	Recrystn.	Formula	Found (%)		Calcd (%)	
	°C	solvent		C	H	C	H
1a	191—192.5	MeOH	$C_{17}H_{14}O_7$	61.93	4.34	61.82	4.27
1b	195—197	MeOH	$C_{18}H_{16}O_8$	59.81	4.52	60.00	4.48
1c	248—248.5	MeOH	$C_{17}H_{14}O_8 \cdot H_2O$	55.89	4.44	56.04	4.43
1d	212—214[a)]	aq MeOH	$C_{18}H_{16}O_9$	57.35	4.19	57.45	4.29
1e	229—231	MeOH	$C_{18}H_{16}O_9$	57.17	4.14	57.45	4.29
1f	277—278	aq MeOH	$C_{17}H_{14}O_9$	56.09	4.02	56.36	3.90
2a	172—174	$CHCl_3$–MeOH	$C_{18}H_{16}O_7$	62.55	4.69	62.79	4.68
2b	165—166	$CHCl_3$–MeOH	$C_{19}H_{18}O_8$	60.87	4.76	60.96	4.85
2c	237—239	MeOH	$C_{18}H_{16}O_8$	60.04	4.47	60.00	4.48
2d	164—165.5	MeOH	$C_{19}H_{18}O_9$	58.55	4.72	58.46	4.65
2e	182—184	MeOH	$C_{19}H_{18}O_9$	58.29	4.61	58.46	4.65
2f	244—245	aq MeOH	$C_{18}H_{16}O_9$	57.20	4.29	57.45	4.29
A1a	200—202	$CHCl_3$–MeOH	$C_{23}H_{20}O_{10}$	60.35	4.37	60.52	4.42
A1b	159—160.5	$CHCl_3$–MeOH	$C_{24}H_{22}O_{11}$	59.13	4.59	59.26	4.56
A1c	181—182	$CHCl_3$–MeOH	$C_{25}H_{22}O_{12}$	58.13	4.31	58.37	4.31
A1d	198.5—200	$CHCl_3$–MeOH	$C_{26}H_{24}O_{13}$	57.14	4.34	57.35	4.44
A1e	187—189	$CHCl_3$–MeOH	$C_{26}H_{24}O_{13}$	57.18	4.44	57.35	4.44
A1f	177—179	$CHCl_3$–MeOH	$C_{27}H_{24}O_{14}$	56.41	4.07	56.64	4.23
A2a	151—152	$CHCl_3$–MeOH	$C_{22}H_{20}O_9$	61.45	4.64	61.68	4.71
A2b	132—133	$CHCl_3$–MeOH	$C_{23}H_{22}O_{10}$	60.33	4.83	60.26	4.84
A2c	156—158	$CHCl_3$–MeOH	$C_{24}H_{22}O_{11}$	59.02	4.53	59.26	4.56
A2d	203—204	$CHCl_3$–MeOH	$C_{25}H_{24}O_{12}$	57.94	4.55	58.14	4.68
A2e	133—135	$CHCl_3$–MeOH	$C_{25}H_{24}O_{12}$	57.92	4.61	58.14	4.68
A2f	143—144	$CHCl_3$–MeOH	$C_{26}H_{24}O_{13}$	57.40	4.44	57.35	4.44

a) Sintered at 206—208 °C.

0.13 mol dm^{-3}; 45 ml; 4.5—5.8 mmol) was added. The mixture was stirred at 0 °C until the starting materials disappeared (about 12 h) and then the solvent was evaporated off under reduced pressure. The residue was dissolved in CH_2Cl_2 (5—10 ml), then stirred with *p*-TsOH (about 20 mg) at 0 °C for 30 min, and diluted with CH_2Cl_2. The mixture was washed with aq $NaHCO_3$ and H_2O, dried over Na_2SO_4, and then concentrated. The residue was recrystallized to give **16** (Table 4).

7-Benzyloxy-5,6,8-trimethoxy-3-tosyloxyflavones (17). A mixture of the flavone **16** (0.8 mmol), TsCl (0.3 g; 1.6 mmol), and anhydrous K_2CO_3 (0.5—1 g) in Me_2CO (30—40 ml) was refluxed with stirring until the starting material disappeared (about 2 h). After K_2CO_3 was filtered off, the filtrate was concentrated and the residue was recrystallized to give quantitatively **17** (Table 5).

7-Benzyloxy-3,5,6,8-tetramethoxyflavones (18). A mixture of the flavone **16** (0.8 mmol), Me_2SO_4 (0.3—0.4 ml; 3—4 mmol), and anhydrous K_2CO_3 (1.5 g) in Me_2CO (30—40 ml) was refluxed with stirring until the starting material disappeared (about 2 h), diluted with H_2O, and additionally refluxed for 15—20 min. After the Me_2CO was evaporated, the separated crystals were collected and recrystallized to give quantitatively **18** (Table 5).

Demethylation of the 5,6,8-Trimethoxyflavones (17) and 3,5,6,8-Tetramethoxyflavones (18). To a cold solution or suspension of the flavone **17** or **18** (0.7 mmol) in MeCN (9.0 ml), a 20% (w/v) solution of anhydrous $AlBr_3$ in MeCN (3.0 ml; 2.3 mmol) was added with stirring. The mixture was allowed to stand at 0 °C for 40—50 min, then diluted with 2—3% aq HCl, and warmed at 50—60 °C for 20 min. The separated crystals were collected and recrystallized to give quantitatively the corresponding 5-hydroxyflavone (**19** or **21**) (Table 5).

7-Benzyloxy-3,5-dihydroxy-6,8-dimethoxyflavones (20). A mixture of the flavone **19** (0.6 mmol) and anhydrous K_2CO_3 (0.5 g) in MeOH (30—40 ml) was heated with stirring at 60—70 °C for 30—40 min and then acidified with dil HCl. After MeOH was evaporated, the separated crystals were collected and recrystallized to give quantitatively **20** (Table 5).

3,5,7-Trihydroxy-6,8-dimethoxyflavones (1) and Their 3-Methyl Ethers (2). The flavone **20** or **21** (0.4 mmol) was hydrogenolyzed with 10% Pd–C (50—100 mg) in EtOAc–MeOH (1 : 1; about 30 ml) at room temperature until the absorption of hydrogen ceased to give quantitatively the flavone **1** or **2** (Table 6). The flavones **1** and **2** were easily acetylated by hot acetic anhydride–pyridine method (Table 6).

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