Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. XIV.[1] A Convenient Method for Synthesizing 5,6,7-Trihydroxy-3-methoxyflavones from 6-Hydroxy-3,5,7-trimethoxyflavones

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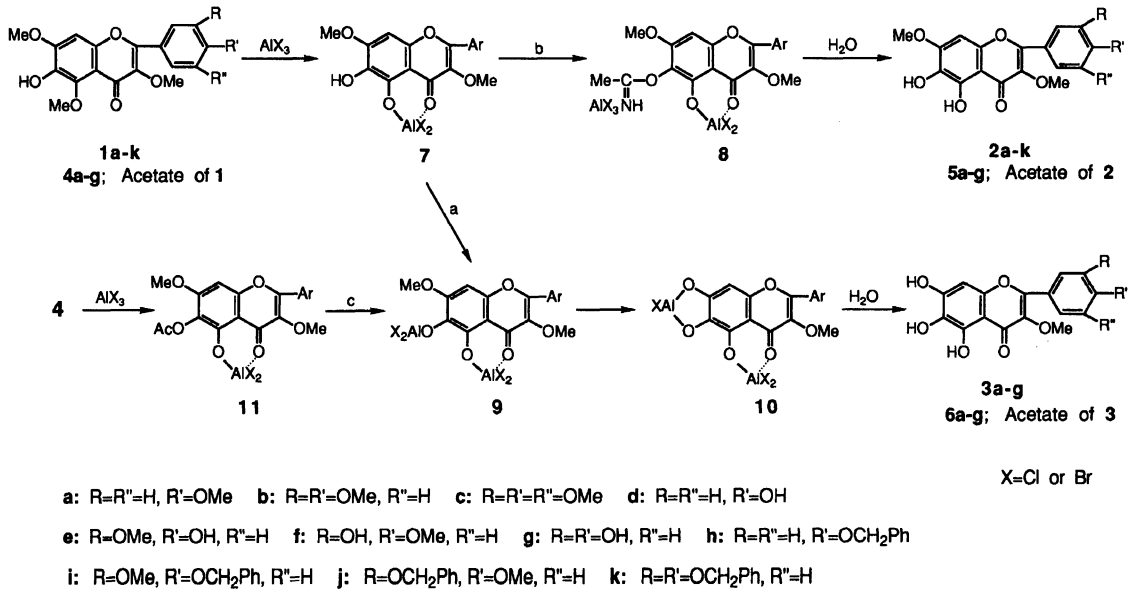
Demethylation of 6-hydroxy-3,5,7-trimethoxyflavones and their acetates was studied and the following results were found. Demethylation of 6-hydroxy-3,4′,5,7-tetramethoxyflavone with 30% anhydrous aluminum chloride in acetonitrile afforded a mixture of 5,6-dihydroxy-3,4′,7-trimethoxyflavone and 5,6,7-trihydroxy-3,4′-dimethoxyflavone, but demethylation of its acetate formed the 5,6,7-trihydroxyflavone as a main product. The latter reaction was applicable as a general method for synthesizing 5,6,7-trihydroxy-3-methoxyflavones. On the other hand, the demethylation of 6-hydroxy-3,4′,5,7-tetramethoxyflavone with 10% anhydrous aluminum bromide in acetonitrile afforded the 5,6,7-trihydroxyflavone as a main product without cleavage of the 4′-methoxyl group and the reaction was more conveniently applicable for the synthesis of the 5,6,7-trihydroxyflavones. The method, however, was not adapted to the synthesis of the flavones with methoxyl groups adjacent to the hydroxyl group on the B ring, since the benzyloxyl group and the methoxyl group adjacent to the hydroxyl group were simultaneously cleaved under demethylating conditions. Seven 5,6,7-trihydroxy-3-methoxyflavones were synthesized by these methods and their properties were clarified.

In previous papers, we reported that the 5- and 7-methoxyl groups in the acetates of 6-hydroxy-5,7-dimethoxyflavones were selectively cleaved with anhydrous aluminum chloride–acetonitrile to give the corresponding 5,6,7-trihydroxyflavones in high yields[1] and that the 5-methoxyl group in 3,5,6,7-tetramethoxyflavones was quantitatively cleaved without cleavage of the 3-methoxyl group.[2] The results showed that 5,6,7-trihydroxy-3-methoxyflavones (**3**) could also be synthesized from 6-hydroxy-3,5,7-trimethoxyflavones (**1**) or 5,6-dihydroxy-3,7-dimethoxyflavones (**2**) by demethylation. A few natural flavones have been proposed as 5,6,7-trihydroxy-3-methoxyflavones (**3**) or their glycosides on the basis of their spectral data,[3—6] but the structures have not always been correct because of the small differences in the properties between the flavones and their isomers. For example, in order to confirm the two natural flavones, assumed to be quercetagetin 3′- and 4′-methyl ethers,[3] Wagner et al.[7] synthesized the two proposed flavones from 3′,4′,6′-trihydroxy-2′,α-dimethoxyacetophenone by the Allan-Robinson reaction[8] and revised them as quercetagetin 3,7-dimethyl ether and axillarin, respectively. The method seemed to be a general one for synthesizing **3**, but the yield was poor and an efficient method is desired to clarify their physical and biological properties. In view of these points, demethylation of 6-hydroxy-3,5,7-trimethoxyflavones (**1**) and their acetates (**4**) was examined. In this paper, we wish to report a convenient method for synthesizing **3** and their subsequent characterization.

Results and Discussion

Demethylation of 6-hydroxy-5,7-dimethoxyflavones with anhydrous aluminum chloride in acetonitrile afforded a mixture of the corresponding 5,6-dihydroxy- and 5,6,7-trihydroxyflavones, but demethylation of their acetates formed 5,6,7-trihyroxyflavones as main products.[1] On the other hand, demethylation of 3,5,6,7-tetramethoxyflavones afforded the corresponding 5-hydroxyflavones quantitatively.[2] These results suggest that demethylation of 6-hydroxy-3,5,7-trimethoxyflavones (**1**) or 5,6-dihydroxy-3,7-dimethoxyflavones (**2**) and their acetates (**4** and **5**) proceeds by the process shown in Scheme 1 similarly to the case of the demethylation of 6-hydroxy-5,7-dimethoxyflavones and their acetates. Generally, in the cleavage of a methoxyl group adjacent to a carbonyl group, anhydrous aluminum bromide whose bromine atom is a softer base than a chlorine atom accelerates the cleavage more than anhydrous aluminum chloride does.[9] One of the reasons may be as follows: The formation of an aluminum–oxygen bond by elimination of a bromide anion is easier than by elimination of a chloride anion because the aluminum atom is a hard acid and the formation of an aluminum complex such as **9** in Scheme 1 is greatly accelerated as a result. In the demethylation of the 6-hydroxyflavones **1**, reasoning suggests that the use of anhydrous aluminum bromide accelerates path a in Scheme 1 and the acetimidoylation (path b) by the reaction with acetonitrile is suppressed as a result; the 5,6,7-trihydroxyflavones (**3**) may be easily synthesized from **1** or **2** without the 6-hydroxyl group being protected by an acetyl group. Therefore, demethylation of 6-hydroxy-3,4′,5,7-tetramethoxyflavone (**1a**) and its acetate (**4a**) with anhydrous aluminum chloride and bromide in acetonitrile was studied first and the time conversion curves are shown in Figs. 1 and 2.

In the demethylation of **1a** with 30% (w/v) anhydrous aluminum chloride–acetonitrile, the 5- and/or 7-methoxyl groups were selectively cleaved without cleav-



Scheme 1.

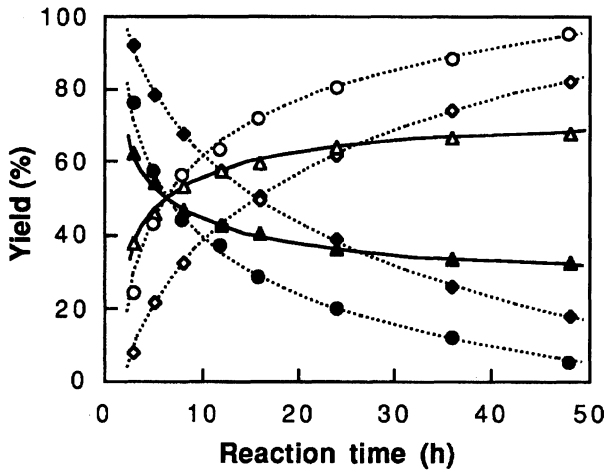


Fig. 1. Time conversion of the demethylation of **1a** (—) and its acetate **4a** (---) (each 100 mg) with 30% (w/v) anhydrous aluminum chloride in acetonitrile (3 ml) containing water (6 μl) at 70°C (**3a**, ○ and △; **2a**, ● and ▲) and 10% (w/v) anhydrous aluminum bromide in acetonitrile (5 ml) at 50°C (3a, ◇; 2a, ◆).

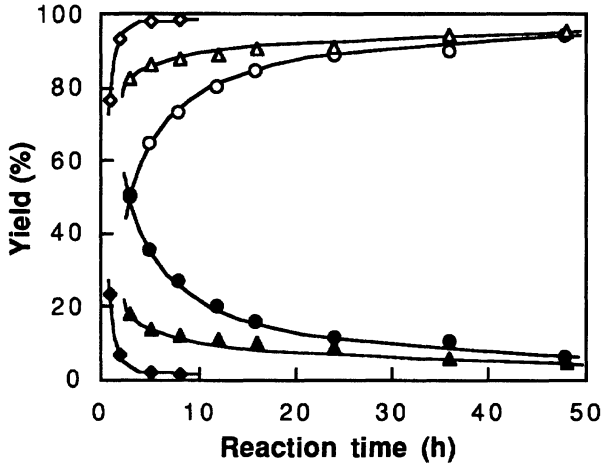


Fig. 2. Time conversion of the demethylation of **1a** (100 mg) with 10% (w/v) anhydrous aluminum bromide in acetonitrile (5 ml at 50°C; **3a**, ○ and **2a**, ●: 5 ml at 70°C; **3a**, △ and **2a**, ▲: 15 ml at 70°C; **3a**, ◇ and **2a**, ◆).

age of the 3-methoxyl group to give a mixture of the corresponding 5,6-di- and 5,6,7-trihydroxyflavones (**2a** and **3a**), but demethylation of its acetate (**4a**) afforded the 5,6,7-trihydroxyflavone (**3a**) as a main product (Fig. 1). The behavior is similar to that seen in the demethylation of 6-hydroxy-5,7-dimethoxyflavones and their acetates, showing that the demethylations proceed by the process shown in Scheme 1 and the demethylation of the acetates (**4**) is also applicable as a general method for synthesizing 5,6,7-trihydroxy-3-methoxyflavones (**3**).

The time conversion curve of the demethylation of the acetate (**4a**) with anhydrous aluminum bromide at 50°C is similar to that with the chloride at 70°C, but the formation rate of **3** is smaller than with the chloride (Fig. 1). This result shows that the exchange reaction of the acetyl group by aluminum bromide is slower than that by the chloride and bromide use is not advantageous. In the demethylation of **1a** with anhydrous aluminum bromide at 50°C, however, the acetimidoylation of the 6-hydroxyl group is suppressed as expected and **3a** is formed as a main product without cleavage of the 3- and 4′-methoxyl groups. Furthermore, raising the reaction temperature to 70°C accelerated the rate of **3a** formation and an increase of the reagent amount increased the ratio of **3a** as shown in Fig. 2. This result shows that the demethylation is more convenient than that of the acetates (**4**) in order to synthesize the flavones **3** from **1**. Therefore, demethylation of

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

Compd	Arom. H					OMe		C_5-OH or OAc	
	C_8-H	$C_{3'}$-H	$C_{5'}$-H	$C_{2'}$-H	$C_{6'}$-H				
3a	6.55s	7.10d(2H)		8.01d(2H)		3.80s(3H)	3.85s(3H)	12.46s	
3b	6.59s	—	7.12d	7.62d′	7.66dd	3.82s(3H)	3.85s(6H)	12.46s	
3c	6.60s	—	—	7.33s(2H)		3.77s(3H)	3.83s(3H)	12.37s	
						3.87s(6H)			
3d	6.54s	6.92d(2H)		7.91d(2H)		3.78s(3H)		12.56s	
Nat. **3d**[b,5)]	6.50s	6.90d(2H)		7.95d(2H)		3.84s(3H)			
3e	6.57s	—	6.95d	7.63d′	7.56dd	3.80s(3H)	3.86s(3H)	12.49s	
3f	6.52s	—	7.10d	7.53d′	7.54dd	3.78s(3H)	3.85s(3H)	12.47s	
3g	6.50s	—	6.90d	7.53d′	7.43dd	3.78s(3H)		12.51s	
Nat. **3g**[c,4)]	6.28s		6.65d	7.39bs	7.41d				
6a	7.42s	6.99d(2H)		8.02d(2H)		3.78s(3H)	3.86s(3H)	2.31s(6H)	2.44s(3H)
6b	7.43s	—	6.95d	7.64d′	7.69dd	3.76s(3H)	3.94s(6H)	2.33s(6H)	2.45s(3H)
6c	7.43s	—	—	7.32s(2H)		3.80s(3H)	3.92s(9H)	2.32s(6H)	2.45s(3H)
6d	7.41s	7.21d(2H)		8.05d(2H)		3.80s(3H)		2.32s(9H)	2.44s(3H)
6e	7.42s	—	7.14d	7.71d′	7.65dd	3.80s(3H)	3.89s(3H)	2.32s(9H)	2.45s(3H)
6f	7.45s	—	7.08d	7.81d′	8.03dd	3.80s(3H)	3.92s(3H)	2.33s(3H)	2.37s(3H)
								2.35s(3H)	2.47s(3H)
6g	7.39s	—	7.29d	7.87d′	7.95dd	3.80s(3H)		2.31s(12H)	2.45s(3H)

a) s, Singlet; d, doublet (J=8.5—9.0 Hz); d′, doublet (J=2.5 Hz); dd, double doublet (J=8.5 and 2.5 Hz). b) Reported data for the TMS ether in CCl_4. c) Measured in CCl_4; the data seem to be those for its TMS ether although the description is not shown.

the other 6-hydroxyflavones with anhydrous aluminum bromide–acetonitrile was studied.

Demethylation of the 6-hydroxyflavones (**1b** and **1c**) with no hydroxyl group on the B ring proceeded as in the case of **1a** to give the corresponding 5,6,7-trihydroxyflavones (**3b** and **3c**). The benzyloxyl groups on the B ring, however, were cleaved under the demethylating conditions and the flavones **3** with benzyloxyl groups were only obtained in small amounts. Actually, the demethylation of 4′-benzyloxy-6-hydroxy-3,5,7-trimethoxyflavone (**1h**) afforded 4′,5,6,7-tetrahydroxy-3-methoxyflavone (**3d**) and that of 4′-benzyloxy-6-hydroxy-3,3′,5,7-tetramethoxyflavone (**1i**) formed 3′,4′,5,6,7-pentahydroxy-3-methoxyflavone (**3g**) via **3e** because the cleavage of the 3′-methoxyl group was accelerated by the neighboring 4′-hydroxyl group.

These results show that the demethylation of the acetates (**4** and **5**) with anhydrous aluminum chloride is applicable as a general method for synthesizing 5,6,7-trihydroxy-3-methoxyflavones (**3**). Flavones **3** with no methoxyl groups adjacent to the hydroxyl group on the B ring were synthesized by demethylation of the 6-hydroxyflavones (**1a**—**c**, **1h**, and **1k**) with 10% (w/v) anhydrous aluminum bromide–acetonitrile. Practically, for the synthesis of **3**, demethylation of a mixture of the hydroxyflavones **1** and **2** or of their acetates **4** and **5** is more convenient instead of using flavone **1** or **2** solely, since the synthesis of **1** by the Allan–Robinson reaction is usually accompanied by the demethylation of the 5-methoxyl group and a mixture of **1** and **2** is easily obtained from the reaction mixture.

Characterization of the 5,6,7-Trihydroxy-3-methoxyflavones (3) and Identification of Natural Flavones. The ^{1}H NMR spectral data for the 5,6,7-trihydroxyflavones **3** and their acetates **6** are shown in Table 1. The C_8-proton signals in **3** (in DMSO-d_6) and their acetates **6** (in $CDCl_3$) appear in the ranges of δ=6.50 to 6.60 and of δ=7.39 to 7.45, respectively, and the ranges are similar to those in the 5,6,7-trihydroxyflavones (**12**)[1,10)] with no substituent at the 3-position, and their acetates. Furthermore, the chemical shifts of the aromatic protons in **3** agree with those in the corresponding **12** within 0.1 ppm. Similar phenomena are observed in the comparison between the acetates **6** and the corresponding acetates of **12**, but the chemical shifts of the $C_{2'}$- and $C_{6'}$-protons in **6** appear in the lower field of 0.2 to 0.6 ppm than those of the acetates of **12** by the influence of the C_3-methoxyl group.

In the UV spectra for flavones **3**, bands I and II are seen in narrow ranges at 346 to 360 nm and 277 to 279 nm and the bands exhibit a similar characteristic shift upon the addition of aluminum chloride and sodium acetate as shown in Table 2. Especially, the absorption patterns of the flavones (**3**) with the same oxygenated pattern on the B ring are very similar to each other (**3a** and **3d**; **3b**, **3e**, **3f**, and **3g**) and the characteristic shift attributed to the hydroxyl group at the 4′-position by the addition of sodium acetate is not observed in contrast to the other flavones such as 5,7-dihydroxy-3,6-dimethoxyflavones. The phenomena are observed in the spectra of 5,6,7-trihydroxyflavones (**12**)[1,10)] and the absorption pattern is similar to that of the corresponding **3**. These results show that the structural elucida-

tion of the natural flavones by the UV spectral method requires more attention. The UV spectral data for **3e** and **3f** are not fully in accordance with those for the flavones (**3e** and **3f**) synthesized by Wagner et al.,[7] although the ^{1}H NMR data are consistent with our data, respectively. The ambiguity seems to be caused by the insufficient purity of the flavone they synthesized in a low yield.

Some flavones were isolated as glycosides and/or aglycone from *Chrysosplenium tetrandrum* by Bohm et al.[4] and from *Neurolaena oaxacana* by Ulubelen et al.,[5] and the structures of their aglycones were assumed to be **3d** and **3g** on the basis of their spectral data. The ^{1}H NMR data for the trimethylsilyl ether of the natural flavone (**3d**), isolated from *N. oaxacana*, in CCl_4 agreed with the data for **3d** in DMSO-d_6, and the UV data in methanol also agreed with the data for the synthetic flavone, although the UV data upon the addition of sodium acetate was different. This result suggests that the natural flavone is 4′,5,6,7-tetrahydroxy-3-methoxyflavone. On the other hand, the UV data for the aglycone of the natural flavone which was isolated from *N. oaxacana* and assumed to be a 7-glucoside of **3g** was different from the UV data for the synthetic flavone (Table 2). The melting point (218—220°C) of the aglycone of the natural flavone which was isolated from *C. tetrandrum* and assumed to be a 6-glucoside of **3g** was markedly lower than that of the synthetic flavone and the C_8-proton signal at δ=6.28 in the ^{1}H NMR spectra was in a higher field than that of 5,6,7-trioxygenated flavones with a 7-hydroxyl group. The results show that the structural elucidation of the natural flavones only by the data described in the literature is difficult, and further study is required for the accurate determination of their structures.

Table 2. UV Spectral Data for 5,6,7-Trihydroxy-3-methoxyflavones (**3**)[a]

Compd		λ_{max}/nm (log ε)		
3a	EtOH		278(4.35)	349(4.23)
	EtOH–$AlCl_3$		297(4.31)	372(4.39)
	EtOH–NaOAc		275(4.37)	366(4.25)
3b	EtOH		278(4.29)	356(4.27)
	EtOH–$AlCl_3$	258(4.20)	288(4.20)	380(4.40)
	EtOH–NaOAc		275(4.31)	367(4.27)
3c	EtOH		279(4.33)	355(4.20)
	EtOH–$AlCl_3$		297(4.25)	374(4.37)
	EtOH–NaOAc		272(4.31)	367(4.25)
3d	EtOH		279(4.27)	346(4.33)
	EtOH–$AlCl_3$		297(4.29)	374(4.41)
	EtOH–NaOAc		275(4.34)	367(4.27)
Nat. **3d**[5]	MeOH		281[0.9]	340[1.0]
	MeOH–$AlCl_3$		302[0.8]	375[1.0]
	MeOH–NaOAc	285[1.2]	342[1.0]	410sh
3e	EtOH		278(4.24)	360(4.29)
	EtOH–$AlCl_3$	262(4.18)	291(4.18)	383(4.43)
	EtOH–NaOAc	277(4.23)	313(4.10)	371(4.28)
3f	EtOH		277(4.26)	356(4.27)
	EtOH–$AlCl_3$	263(4.20)	291(4.21)	380(4.39)
	EtOH–NaOAc	277(4.28)	325(4.14)	367(4.28)
3g	EtOH		278(4.18)	357(4.32)
	EtOH–$AlCl_3$	266(4.17)	289(4.16)	386(4.35)
	EtOH–NaOAc		276(4.23)	372(4.23)
Nat. **3g**[5]	MeOH	258[0.9]	270sh	350[1]
	MeOH–$AlCl_3$	274[1.1]	305[0.5]	426[1]
	MeOH–NaOAc		260[1.3]	374[1]

a) Numbers in square brackets denote relative absorptivities from the literature.

Experimental

All melting points were determined in glass capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-24 or JEOL EX-400 spectrometer, using tetramethylsilane as an internal standard, and chemical shifts are given in δ values. UV spectra were recorded on a Hitachi 124 spectrophotometer. The high-performance liquid chromatography (HPLC) was carried out by the method described in previous papers[1,11] with a UV monitor at 340 nm and a column (2.1 i.d. ×500 mm) packed with Hitachi gel No. 3011; methanol (0.5 ml min^{-1}) was used as an eluent. For the separation of demethylated products, a column (20 i.d. ×600 mm) packed with Hitachi gel No. 3019 using methanol as an eluent was employed. Column chromatography was carried out on Kieselgel 60 (70—230 mesh; Merck). Elemental analyses were performed with a Yanaco CHN corder Model MT-2. Acetonitrile as a demethylating solvent was obtained by distillation over CaH_2.

Synthesis of 6-Hydroxy-3,5,7-trimethoxyflavones (1) and 5,6-Dihydroxy-3,7-dimethoxyflavones (2). A mixture of **1** and **2** was synthesized from 3′,6′-dihydroxy-2′,4′,α-trimethoxyacetophenone by the method described in a previous paper[2] and separated to **1** and **2** by recrystallization and silica-gel column chromatography with chloroform–ethyl acetate as an eluent. Benzyloxyflavones (**1h**—**1k**) were debenzylated with 10% Pd–C in methanol or methanol–ethyl acetate in the usual manner. The acetates were obtained by the acetylation of **1** with hot acetic anhydride–pyridine.

Analysis of the Demethylated Product from 1a and Its Acetate (4a). In a test tube (1.8 i.d. ×150 mm) fitted with a calcium chloride tube was dissolved flavone **1a** or **4a** in a 30% (w/v) solution of anhydrous aluminum chloride–acetonitrile or a 10% (w/v) solution of anhydrous aluminum bromide–acetonitrile, and the solution was heated to an appropriate temperature in a thermostated oil bath. Small amounts of the reaction mixture (0.1—0.2 ml) were removed at intervals, diluted with 1—2% hydrochloric acid (2—3 ml), and heated at 60—70°C for 20—30 min. The mixtures were allowed to stand in a refrigerator until the aqueous layers became colorless. The separated crystals were collected, washed with water, dissolved in methanol (ca. 4 ml) containing 10% hydrochloric acid (0.5 ml), and refluxed for 1—2 h. The solutions (or the concentrated solutions) were directly analyzed by HPLC and the yields of the products were calculated from the chromatogram by incorporating the molar extinction coefficients (ε at 340 nm: **2a**, 24200; **3a**, 16400).

General Method for Synthesizing 5,6,7-Trihydroxy-3-methoxyflavones (3a—g). The flavone acetate (**4** or **5**) (1.0 mmol) or 6-hydroxyflavone (**1**) (1.0 mmol) was

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

Compd	Starting material	Reagent	React. time	Mp θ_m/°C	Recrystn. solvent	Formula	Found (%) C	Found (%) H	Calcd (%) C	Calcd (%) H
3a	**4a**	$AlCl_3$	48	206—208	aq MeOH	$C_{17}H_{14}O_7$	61.75	4.20	61.82	4.27
	1a	$AlBr_3$	8							
3b	**4b**	$AlCl_3$	48	192—194	MeOH	$C_{18}H_{16}O_8$	59.86	4.72	60.00	4.48
	1b	$AlBr_3$	8							
3c	**4c**	$AlCl_3$	30	244—246	MeOH	$C_{19}H_{18}O_9$	58.33	4.73	58.46	4.65
	1c	$AlBr_3$	8							
3d	**4d**	$AlCl_3$	36	>300	aq MeOH	$C_{16}H_{12}O_7$	60.84	3.78	60.76	3.82
3e	**4e**	$AlCl_3$	24	256—258 lit,[7] 242—244	aq MeOH	$C_{17}H_{14}O_8$	58.70	4.14	58.96	4.08
3f	**5f**	$AlCl_3$	16	227—228 lit,[7] 226—228	MeOH	$C_{17}H_{14}O_8$	59.00	4.18	58.96	4.08
3g	**4g**	$AlCl_3$	36	283—285 lit,[4] 218—220	aq MeOH	$C_{16}H_{12}O_8$	57.58	3.63	57.83	3.64
	1j	$AlBr_3$	10							
6a				210—211	MeOH	$C_{23}H_{20}O_{10}$	60.43	4.32	60.52	4.42
6b				179—180	EtOAc–MeOH	$C_{24}H_{22}O_{11}$	59.40	4.53	59.26	4.56
6c				202—204	$CHCl_3$–MeOH	$C_{25}H_{24}O_{12}$	57.95	4.70	58.14	4.68
6d				214—215	MeOH	$C_{24}H_{20}O_{11}$	59.78	3.89	59.50	4.16
6e				202—204 lit,[7] 190—192	MeOH	$C_{25}H_{22}O_{12}$	58.11	4.05	58.37	4.31
6f				177—179 lit,[7] 168—170	MeOH	$C_{25}H_{22}O_{12}$	58.59	4.36	58.37	4.31
6g				214—216	MeOH	$C_{26}H_{22}O_{13}$	57.70	4.10	57.57	4.09

dissolved in a 30% (w/v) solution of anhydrous aluminum chloride in acetonitrile (15 ml; 30 mmol) containing water (30 μl) or a 10% (w/v) solution of anhydrous aluminum bromide in acetonitrile (20 ml; 7.5 mmol). The solution was heated at 70°C for 8—48 h, diluted with cooled ca. 2% hydrochloric acid, and warmed at 60—70°C for 20—30 min. The solvent was evaporated under reduced pressure, and the residue was allowed to stand in a refrigerator. The separated precipitates were collected, washed with water, and then recrystallized to give **3**. When acetate **4** was used as a starting material, the precipitates were dissolved in methanol–10% hydrochloric acid (10 : 1), and refluxed for 1—2 h. The solution was then diluted with water, the methanol was evaporated under reduced pressure, and the residue was allowed to stand in a refrigerator. The separated precipitates were collected, washed with water, and then recrystallized to give **3**. The product recovered from the mother liquor was separated by preparative HPLC to give an additional small amount of **3**. The total yield of **3** was higher than 80% in all cases and the melting point and reaction conditions are summarized in Table 3.

Acetates (6a—g) of 3. Flavone **3** was acetylated with hot acetic anhydride–pyridine to give **6**. (Table 3).

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