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Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. XI. A New Convenient Method for Synthesizing 3,5,7-Trihydroxy-8-methoxyflavones from 7-Hydroxy-3,5,8-trimethoxyflavones[1)]

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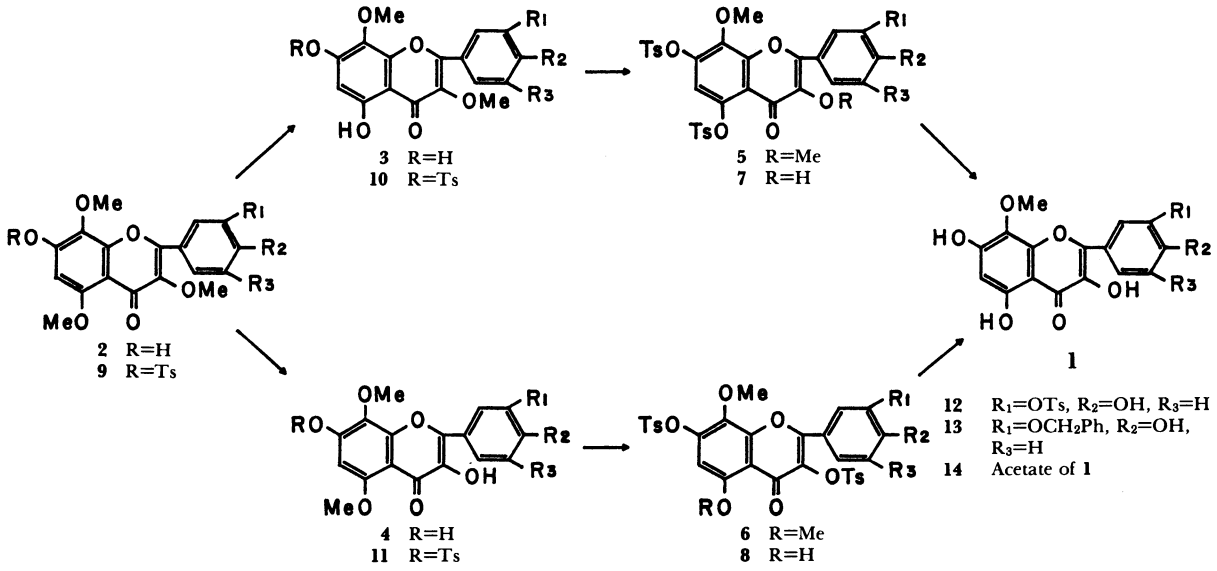
The 3- or 5-methoxyl group in the ditosylates of 5,7-dihydroxy-3,4′,8-trimethoxy- and 3,7-dihydroxy-4′,5,8-trimethoxyflavones was quantitatively demethylated with anhydrous aluminum bromide in acetonitrile to give the corresponding monohydroxyflavones, which were easily hydrolyzed into 3,5,7-trihydroxy-4′,8-dimethoxyflavone. On the basis of the results, the following convenient method for synthesizing 3,5,7-trihydroxy-8-methoxyflavones from 7-hydroxy-3,5,8-trimethoxyflavones was established. 7-Hydroxy-3,5,8-trimethoxyflavones or their tosylates were demethylated with 5% w/v anhydrous aluminum bromide in acetonitrile to give a mixture of the corresponding 3- and 5-hydroxyflavones. The mixture was tosylated and the resultant mixture was demethylated under the same conditions. The demethylated products were hydrolyzed with anhydrous potassium carbonate in methanol to give the desired 3,5,7-trihydroxy-8-methoxyflavones in high yields.

Generally, the selective cleavage of the 5-methoxyl group in flavones with free 3-hydroxyl and 8-methoxyl groups is not possible and the syntheses of 3,5,7-trihydroxy-8-methoxyflavones (**1**) from 7-hydroxy-3,5,8-trimethoxyflavones (**2**) by the selective demethylation have not also been successful.[2)] Therefore, the 3,5,7-trihydroxyflavones have been synthesized by the four following routes which bypassed the difficulty of the selective demethylation, albeit in low yields: (1) oxidative demethylation of the dibenzyl ether of 3,7-dihydroxy-5,8-dimethoxyflavones (**4**),[3)] (2) partial *O*-alkylation and dealkylation of 3,5,7,8-tetrahydroxyflavones,[4)] (3) Allan-Robinson reaction of ω-benzoyloxy-2,4,6-trihydroxy-3-methoxyacetophenone,[5)] and (4) nuclear oxidation of 3,7-bis(benzyloxy)-5-hydroxyflavones.[6)]

In previous papers, we reported that the demethylation of 7-hydroxy-3,5,8-trimethoxyflavones (**2**) with anhydrous aluminum bromide in acetonitrile afforded quantitatively a mixture of 5,7-dihydroxy-3,8-dimethoxyflavones (**3**) and 3,7-dihydroxy-5,8-dimethoxyflavones (**4**),[1)] and that 3-hydroxy-5,7,8-trimethoxyflavones were demethylated to 3,5-dihydroxy-7,8-dimethoxyflavones via the corresponding sulfonates.[7)] The results show that 3,5,7-trihydroxyflavones (**1**) are easily synthesized from **2** when the respective 3- and 5-methoxyl groups in tosylates of **3** and **4** are selectively cleaved and the tosyloxyl groups



Scheme 1.

are easily hydrolyzed. Therefore, we studied the selective demethylation of ditosylates (**5a** and **6a**) of 5,7-dihydroxy-3,4′,8-trimethoxyflavone (**3a**) and 3,7-dihydroxy-4′,5,8-trimethoxyflavone (**4a**) and the hydrolysis of the resultant 3- and 5-hydroxyflavones, and consequently established a convenient method for synthesizing 3,5,7-trihydroxy-8-methoxyflavones (**1**) from 7-hydroxy-3,5,8-trimethoxyflavones (**2**). In this paper, we report on a general method for synthesizing **1** and their characterization.

Results and Discussion

Selective Demethylation of 5,7-Dihydroxy-3,4′,8-trimethoxyflavone (3a) and 3,7-Dihydroxy-4′,5,8-trimethoxyflavone (4a). The outline of the demethylation of the dihydroxyflavones **3a** and **4a** to **1a** was as follows. The 3-methoxyl group of the ditosylate **5a**, which was easily synthesized from **3a** by the tosylation, was selectively cleaved with 5% w/v anhydrous aluminum bromide in acetonitrile to give quantitatively 3-hydroxy-4′,8-dimethoxy-5,7-bis(tosyloxy)flavone (**7a**). The tosyloxyl groups in **7a** were smoothly hydrolyzed with potassium carbonate in methanol and the desired 3,5,7-trihydroxy-4′,8-dimethoxyflavone (**1a**) was easily obtained. On the other hand, the 3-hydroxyflavone **4a** was also demethylated to **1a** under similar conditions via the corresponding ditosylates **6a** and **8a**. All of the reactions proceeded quantitatively and no side reaction products were detected by TLC. The results show that **1a** was easily synthesized by the demethylation of 7-hydroxy-3,4′,5,8-tetramethoxyflavone (**2a**) as shown in Scheme 1.

A Method for Synthesizing 3,5,7-Trihydroxy-8-methoxyflavones (1). The demethylation of **2a** with anhydrous aluminum bromide in acetonitrile gave quantitatively a mixture of **3a** and **4a**.[1] The condensation of the mixture with *p*-toluenesulfonyl chloride in the presence of potassium carbonate afforded a mixture of tosylates **5a** and **6a**. The mixture of tosylates was selectively demethylated with anhydrous aluminum bromide in acetonitrile to give the monohydroxyflavones **7a** and **8a**, which were hydrolyzed to the desired **1a** with anhydrous potassium carbonate in methanol under nitrogen atmosphere. The overall yield of **1a** was 72%. The flavones **1b** and **1c** with no hydroxyl groups on the B ring were easily synthesized from the corresponding 7-hydroxyflavones **2b** and **2c** by this method.

On the other hand, the tosylates **9l** and **9m** of hydroxyflavones **2e** and **2g** as starting materials were used for syntheses of the 3,5,7-trihydroxyflavones **1e** and **1g** with hydroxyl groups on the B ring, since the selective demethylation of flavones with no hydroxyl group proceeded more smoothly than that of flavones with hydroxyl groups.[1,8] 3,4′,5,7-Tetrahydroxy-3′,8-dimethoxyflavone (**1e**) was easily synthesized from the tosylate **9l**. The tosylate **9m** of **2g** was also demethylated under similar conditions to give a mixture of two monohydroxyflavones **10m** and **11m**. The mixture was converted into a mixture of 3-hydroxy-8-methoxy-3′,4′,5,7-tetrakis(tosyloxy)flavone (**7m**) and 5-hydroxy-8-methoxy-3,3′,4′,7-tetrakis(tosyloxy)flavone (**8m**) by tosylation and subsequent demethylation. However, these tosylates were not easily hydrolyzed with potassium carbonate in methanol, and a mixture (ca. 1/1) of **1g** and its 3′-tosylate **12** was obtained in the hydrolysis for 10 h.

The results show that the 3-, 4′-, 5-, and 7-tosyloxyl groups which are associated with the carbonyl group in the flavone skeleton are easily hydrolyzed under mild conditions, but that hydrolysis of the tosyloxyl groups at the other positions is difficult. It is desired that the alkaline hydrolysis is carried out under as mild conditions as possible in the flavone synthesis, since the stability of flavones in alkaline media generally decreases with increasing the number of hydroxyl groups. Therefore, an alternative method for the protection of the hydroxyl groups on the B ring was studied in order to establish a general method for synthesizing 3,5,7-trihydroxy-8-methoxyflavones (**1**).

A General Method for Synthesizing 3,5,7-Trihydroxy-8-methoxyflavones (1) from 7-Hydroxy-3,5,8-trimethoxyflavones (2). In the demethylation, a benzyl group seems to be the most suitable protecting group of the hydroxyl groups when the 3- or 5-methoxyl group in the 3,5-dimethoxyflavone derivatives with benzyloxyl groups on the B ring is selectively cleaved without the cleavage of benzyloxyl groups. However, the demethylation of the 5-methoxyl group in the 5,7,8-trioxygenated flavones by anhydrous aluminum chloride in acetonitrile is generally more difficult than that in 5,6,7-trioxygenated flavones, and that the 5-methoxyl group in 8-hydroxy-5,7-dimethoxyflavones with benzyloxyl groups on the B ring is not demethylated selectively with anhydrous aluminum chloride because of the simultaneous cleavage of the benzyloxyl groups.[1,9] On the other hand, anhydrous aluminum bromide as a demethylating reagent can be expected to be much more selective than aluminum chloride.[7,10] Therefore, the demethylation of tosylates **9i** and **9k** of **2i** and **2k** was examined. The 3- or 5-methoxyl group in the tosylate **9i** with a benzyloxyl group on the B ring was selectively cleaved with 5% w/v anhydrous aluminum bromide in acetonitrile for 1 h at room temperature without debenzylation to give a mixture of the two monohydroxyflavones **10i** and **11i**, which was easily converted into **1i** via the corresponding tosylates by the demethylation and hydrolysis. The tosylate **9k** with two adjacent benzyloxyl groups on the B ring was also selectively demethylated under similar conditions, but a little amount of debenzylated products were detected by TLC. And the mixture of the tosylates of the demethylated products was converted into **1k** and a little

amount of 3′-benzyl ether **13** of **1g**.

The results show that the demethylation of the 7-tosyloxyflavones (**9**) (as shown in Scheme 1) is generally applicable for the synthesis of 3,5,7-trihydroxy-8-methoxyflavones (**1**). Actually, the 3- and 5-methoxyl groups in all of the 7-tosyloxyflavones **9a—c** and **9h—k** were selectively demethylated by this method to give the corresponding **1** in good yields (Table 5). The benzyloxyflavones obtained (**1h—k**) were easily debenzylated by hydrogenolysis with palladium on charcoal to give the desired flavones **1d—g**, which were converted into the corresponding acetates by the acetylation with acetic anhydride-pyridine at room temperature.

Characterization of 3,5,7-Trihydroxy-8-methoxyflavone Derivatives (1). The ^{1}H NMR spectra of **7a**

Table 1. ^{1}H NMR Data for 3,5,7-Trihydroxy-8-methoxyflavones (**1**, **12**, and **13**) and Ditosylates of **1a** (**7a** and **8a**) in DMSO-d_6[a]

Compd.	Arom. H					OMe	C_5-OH	OCH_2Ph or SO_2PhMe
	C_6-H	$C_{3'}$-H	$C_{5'}$-H	$C_{2'}$-H	$C_{6'}$-H			
1a	6.28s	7.13d(2H)		8.15d(2H)		3.82s(6H)	12.11s	—
1b	6.28s	—	7.15d	7.77s	7.84dd	3.85s(9H)	12.06s	—
1c	6.28s	—	—	7.53s(2H)		3.76s(3H) 3.86s(9H)	11.99s	—
1d	6.24s	6.92d(2H)		8.02d(2H)		3.82s(3H)	12.04s	—
1e	6.26s	—	6.93d	7.74d′	7.67dd	3.86s(6H)	12.07s	—
1f	6.28s	—	7.10d	7.55—7.8m(2H)		3.85s(6H)	12.07s	—
1g[b]	6.27s	—	6.91d	7.72d′	7.59dd	3.84s(3H)	12.16s	—
1h	6.26s	7.17d(2H)		8.12d(2H)		3.82s(3H)	12.07s	5.17s(2H)
1i	6.23s	—	7.17d	7.73d′	7.78dd	3.82s(6H)	11.98s	5.14s(2H)
1j	6.23s	—	7.12d	7.6—7.9m(2H)		3.78s(3H) 3.84s(3H)	11.96s	5.10s(2H)
1k	6.25s	—	*[c]	7.84s	7.78dd	3.79s(3H)	12.01s	5.16s(2H) 5.20s(2H)
12[b]	6.28s	—	7.05d	8.00d′	8.00dd	3.79s(3H)	12.06s	2.41s(3H)
13	6.26s	—	*[c]	*[c]	*[c]	3.81s(3H)	12.02s	5.18s(2H)
7a	6.90s	*[c]		*[c]		3.89s(3H) 3.99s(3H)	—	2.49s(6H)
8a	6.51s	*[c]		*[c]		3.88s(6H)	11.83s	2.43s(3H) 2.48s(3H)

a) s, singlet; d, doublet (J=8.5 Hz); d′, doublet (J=2.5 Hz); dd, double doublet (J=8.5, 2.5 Hz); m, multiplet. b) This was measured with a Bruker 400 spectrometer. c) Overlapped with the benzyl or tosyl aromatic protons.

Table 2. ^{1}H NMR Data for 3,5,7-Triacetoxy-8-methoxyflavones (**14**) in $CDCl_3$[a]

Compd.	Arom. H					OMe	OAc
	C_6-H	$C_{3'}$-H	$C_{5'}$-H	$C_{2'}$-H	$C_{6'}$-H		
14a	6.78s	6.97d(2H)		7.82d(2H)		3.87s(3H) 3.97s(3H)	2.32s(3H) 2.36s(3H) 2.40s(3H)
14b	6.78s	—	6.95d	7.42s	7.51dd	3.91s(3H) 3.94s(3H) 3.98s(3H)	2.34s(3H) 2.36s(3H) 2.41s(3H)
14c	6.82s	—	—	7.14s(2H)		3.90s(6H) 3.92s(3H) 4.00s(3H)	2.34s(3H) 2.36s(3H) 2.42s(3H)
14d	6.75s	7.19d(2H)		7.82d(2H)		3.93s(3H)	2.30s(6H) 2.34s(3H) 2.39s(3H)
14e	6.80s	—	7.13d	7.43d′	7.46dd	3.85s(3H) 3.95s(3H)	2.32s(6H) 2.34s(3H) 2.40s(3H)
14f	6.73s	—	7.00d	7.52d′	7.70dd	3.87s(3H) 3.93s(3H)	2.31s(3H) 2.33s(6H) 2.38s(3H)
14g	6.77s	—	7.28d	7.69d′	7.70dd	3.94s(3H)	2.30s(6H) 2.32s(6H) 2.39s(3H)

a) s, singlet; d, doublet (J=8.5 Hz); d′, doublet (J=2.5 Hz); dd, double doublet (J=8.5, 2.5 Hz).

Table 3. UV Spectral Data for 3,5,7-Trihydroxy-8-methoxyflavones (**1**, **12**, and **13**) and Ditosylates of **1a** (**7a** and **8a**)[a)]

Compd.		λ_{max}/nm(log ε)			
1a	EtOH		274(4.31)	321(4.10)	377(4.19)
	EtOH-$AlCl_3$		271(4.31)	353(4.06)	435(4.28)
	EtOH-NaOAc		283(4.39)	307(4.15)	396(4.10)
1b	EtOH	257(4.25)	275(4.20)	335(4.05)	379(4.21)
	EtOH-$AlCl_3$		268(4.32)	362(4.01)	438(4.29)
	EtOH-NaOAc		284(4.31)	325(4.08)	398(4.10)
1c	EtOH		277(4.24)	315(4.11)	380(4.13)
	EtOH-$AlCl_3$		276(4.31)	355(4.05)	436(4.25)
	EtOH-NaOAc		286(4.36)	310(4.11)	415(4.13)
1d	EtOH		274(4.31)	325(4.09)	379(4.23)
	EtOH-$AlCl_3$		272(4.33)	355(4.09)	436(4.32)
	EtOH-NaOAc		282(4.40)	312(4.14)	401(4.14)
1e	EtOH	259(4.29)	270sh(4.26)	340i(4.00)	386(4.17)
	EtOH-$AlCl_3$		268(4.36)	365(4.03)	440(4.33)
	EtOH-NaOAc		284(4.30)	329(4.14)	408(4.01)
1f	EtOH	259(4.31)	274(4.25)	339i(4.04)	381(4.23)
	EtOH-$AlCl_3$		269(4.40)	365(3.97)	438(4.33)
	EtOH-NaOAc		283(4.37)	327(4.11)	397(4.15)
1g	EtOH	260(4.30)	272i(4.20)		383(4.28)
	EtOH-$AlCl_3$		270(4.37)	367(3.88)	443(4.36)
	EtOH-NaOAc	263sh(4.16)	281(4.25)	328(4.03)	394(4.15)
1h	EtOH		275(4.34)	320(4.16)	378(4.20)
	EtOH-$AlCl_3$		271(4.35)	353(4.14)	435(4.33)
	EtOH-NaOAc		283(4.42)	305sh(4.19)	404(4.12)
1i	EtOH	258(4.27)	276(4.25)	331(4.10)	380(4.22)
	EtOH-$AlCl_3$		266(4.38)	361(4.06)	438(4.34)
	EtOH-NaOAc		284(4.36)	324(4.13)	410(4.14)
1j	EtOH	258(4.28)	276(4.23)	332(4.07)	379(4.19)
	EtOH-$AlCl_3$		267(4.33)	360(4.04)	437(4.28)
	EtOH-NaOAc		284(4.34)	324(4.10)	395(4.12)
1k	EtOH	258(4.29)	277(4.25)	329(4.10)	382(4.18)
	EtOH-$AlCl_3$		265(4.37)	360(4.07)	438(4.31)
	EtOH-NaOAc		284(4.36)	322(4.12)	407(4.12)
12	EtOH		275(4.30)	320(4.10)	378(4.20)
	EtOH-$AlCl_3$		268(4.31)	353(4.07)	435(4.30)
	EtOH-NaOAc		282(4.32)	307i(4.07)	407(4.20)
13	EtOH	258(4.30)	275(4.25)	334(4.16)	381(4.23)
	EtOH-$AlCl_3$		269(4.40)	363(4.04)	438(4.34)
	EtOH-NaOAc		284(4.35)	325(4.10)	405(4.08)
7a	EtOH		262(4.27)		365(4.24)
	EtOH-$AlCl_3$		265sh(4.27)		437(4.40)
	EtOH-NaOAc		262(4.27)	366(4.13)	427(3.84)
8a	EtOH	268(4.31)	298(4.10)	332(4.23)	
	EtOH-$AlCl_3$	275(4.28)	320(4.20)	348(4.21)	410(3.89)
	EtOH-NaOAc	268(4.30)	300(4.17)	322(4.17)	

a) sh, shoulder; i, inflection point.

and **8a** show the presence of two tosyloxyl groups and the UV spectra exhibit the characteristic properties for 3- or 5-hydroxyflavones, suggesting that the structure of **7a** and **8a** are the 5,7- and 3,7-ditosylates of **1a**, respectively (Tables 1 and 3).

The properties of five of the synthesized flavones **1** agreed with those of the flavones **1a**,[3)] **1d**,[6)] **1e**,[5)] **1g**,[4)] and **1i**[5)] which had been synthesized by the alternative routes, respectively. Also, the flavones **1a—g** afforded the corresponding acetates **14a—g** by the acetylation with acetic anhydride-pyridine. The ^{1}H NMR data for these flavones are shown in Tables 1 and 2. Signals of C_6-protons in **1** (in DMSO-d_6) are in the range of δ 6.23 to 6.28 and those in the acetates **14** (in $CDCl_3$) of **1** shift paramagnetically into the range of δ 6,75 to 6.82. The signals of C_6-protons in 5,7-

dihydroxy-3,8-dimethoxyflavones (**3**) and their acetates are appeared in a similar range,[1] respectively. The chemical shifts of the aromatic protons on the B ring are affected by the 3-hydroxyl or acetoxyl groups; these signals were similar to those in 3,7-dihydroxy-5,8-dimethoxyflavones (**4**) and their acetates.[1]

In the UV spectral data for **1**, Bands I and II are seen at 375 to 385 and 260 to 275 nm, respectively (Table 3). These Bands I shift bathochromically about 60 nm by the addition of aluminum chloride, but the bathochromic shift of Bands II is not observed. On the other hand, Bands I and II in all 3,5,7-trihydroxy-8-methoxyflavones shift bathochromically upon the addition of sodium acetate and the characteristic shift attributed to the 4′-hydroxyl group could not be found. These properties in the UV spectra are useful for a distinction from the other flavones, such as 3,5-dihydroxy-7,8-dimethoxyflavones,[7] but are shown to be applicable for the assignment of 4′-hydroxyl group in 3,5,7-trihydroxy-8-methoxyflavones in contrast to that in 5,7,8-trioxygenated flavones with no hydroxyl group at the 3-position.[9]

The ^{1}H NMR spectrum for **12** shows the presence of a methoxyl and a tosyloxyl group, suggesting that the structure is a monotosylate of **1g**. In a comparison of the ^{1}H NMR spectra for **1g** and **12**, the aromatic protons at 2′- and 6′-positions in **12** are more largely influenced by the tosyloxyl group than that at the 5′-position; both signals appeared at δ 8.00. The results show that the structure of **12** is the 3′-*O*-tosylate of **1g**. The ^{1}H NMR spectrum for **13** shows the presence of a benzyl group and the UV spectral data are similar to those for **12**, suggesting that the structure of **13** is the 3′-*O*-benzyl ether of **1g**.

Identification of a Natural Flavone (1f). During the survey of the flavonoids in the *Primulaceae*, Harborne proposed originally that the structure of Primula F 3A, which was isolated from an acid hydrolysate of several yellow-flowered Primula species, was a methyl ether of quercetagetin.[11] The author later revised its structure: Primula F 3A could be the as yet unknown 8,4′-dimethyl ether of gossypetin; however, further studies are required.[12] The UV spectral data for the flavone are essentially identical with those for the synthetic flavone (**1f**) and it shows that the proposed structure is correct. However, a direct comparison between the natural and synthetic flavones is required for a more accurate determination of the structure since the UV spectral data for the 3,5,7-trihydroxyflavones having 3,3′,4′,5,7,8-hexaoxygenated structure are similar to each other (Table 3).

Conclusion

The method for synthesizing 3,5,7-trihydroxy-8-methoxyflavones consists of the following three fundamental reactions which proceed quantitatively:

1. The 3- or 5-methoxyl group in 7-hydroxy-3,5,8-trimethoxyflavones (**2**) and their tosylates (**9**) was selectively cleaved with 5% w/v anhydrous aluminum bromide in acetonitrile at room temperature for 1—2 h to give a mixture of the corresponding 3- and 5-hydroxyflavones, and the benzyloxyl groups on the B ring were hardly cleaved under the conditions.
2. The respective 3- and 5-methoxyl groups in the 3-methoxy-5-tosyloxy- and 5-methoxy-3-tosyloxyflavone derivatives were also cleaved selectively under similar conditions.
3. The tosyloxyl groups at the 3-, 4′-, 5-, and 7-positions which are associated with the carbonyl group in the flavone skeleton are hydrolyzed under mild conditions such as potassium carbonate in methanol.

It seems that the reactions can not be attributed to the characteristic properties for 3,5,7,8-tetraoxygenated flavones. Therefore, the method would be widely applied to the syntheses of 3,5-dihydroxyflavone derivatives.

Experimental

All melting points were determined in glass capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi R-24 spectrometer (60 MHz), using tetramethylsilane as an internal standard, and chemical shifts were given in δ values. UV spectra were recorded on a Hitachi 124 spectrometer. Thin-layer chromatography was carried out with silica-gel plates (Merck, Kiesel gel 60 F_{254}) using chloroform–ethyl acetate as an eluent. Elemental analyses were performed with a Yanaco CHN corder model MT-2.

7-Hydroxy-3,5,8-trimethoxyflavones (2). Flavones **2** were synthesized from 2,4-dihydroxy-3,6,ω-trimethoxyacetophenone by the Allan-Robinson reaction according to the method described in a previous paper.[1] 4′-Benzyloxy-7-hydroxy-3,5,8-trimethoxyflavone (**2h**): mp 238—240 °C (from ethyl acetate); (lit,[13] mp 240—242 °C); yield 55%. 3′-Benzyloxy-7-hydroxy-3,4′,5,8-tetramethoxyflavone (**2j**): mp 214—216 °C (from methanol); (lit,[14] mp 215—217 °C); yield 52%.

3-Hydroxy-4′,8-dimethoxy-5,7-bis(tosyloxy)flavone (7a). The flavone **5a** (85 mg) was dissolved in a solution of 5% w/v anhydrous aluminum bromide in acetonitrile (10 cm^3) and allowed to stand for 2 h. The mixture was poured into 2% hydrochloric acid and heated at 70—80 °C for 20 min and diluted with water. After the mixture was concentrated under reduced pressure, the crystals separated as yellow needles were collected, washed with water and dried to give **7a**: mp 173—174 °C; yield 80 mg (96%). Found: C, 58.15; H, 3.89%. Calcd for $C_{31}H_{26}O_{11}S_2$: C, 58.31; H, 4.08%.

5-Hydroxy-4′,8-dimethoxy-3,7-bis(tosyloxy)flavone (8a). The flavone **6a** (85 mg) was demethylated and treated under the same conditions as described above to give **8a** as pale yellow plates: mp 173—174 °C; yield 77 mg (93%). Found: C, 58.10; H, 3.89%. Calcd for $C_{31}H_{26}O_{11}S_2$: C, 58.31; H, 4.08%.

3,5,7-Trihydroxy-4′,8-dimethoxyflavone (1a). A mixture of **7a** (70 mg) and anhydrous potassium carbonate (0.5 g) in methanol (25 cm^3) was refluxed with stirring for 2 h. The mixture was acidified with diluted hydrochloric acid; then the methanol was evaporated under reduced pressure. The

separated crystals were recrystallized from aq methanol to give **1a** as yellow needles, yield 30 mg (83%). The flavone **1a** was also synthesized from **8a** (60 mg) by the hydrolysis described above, yield 25 mg (80%).

3,5,8-Trimethoxy-7-tosyloxyflavones 9a—c and 9h—k. A mixture of 7-hydroxy-3,5,8-trimethoxyflavone (**2**) with no hydroxyl groups on the B ring (1 mmol), *p*-toluenesulfonyl chloride (285 mg; 1.5 mmol), and anhydrous potassium carbonate (1.5—2 g; 8—11 mmol) in acetone (30—50 cm^3) was refluxed with stirring until the starting material disappeared (2—3 h). The cooled reaction mixture was poured into diluted hydrochloric acid and then concentrated under reduced pressure. The separated precipitate was collected, washed with water and a little amount of ether, and then recrystallized to give **9** as colorless prisms or needles. The results are shown in Table 4.

3,4′,8-Trimethoxy-5,7-bis(tosyloxy)flavone (5a), 4′,5,8-Trimethoxy-3,7-bis(tosyloxy)flavone (6a), and 3,3′,5,8-Tetramethoxy-4′,7-bis(tosyloxy)flavone (9l). A mixture of the flavone[1] (**3a**, **4a**, or **2e**) (0.3 mmol), *p*-toluenesulfonyl chloride (190 mg; 1 mmol), and anhydrous potassium carbonate (1.5 g; 10 mmol) in acetone (20—30 cm^3) was refluxed with stirring for 3—5 h. The reaction mixture was treated by the method described above to give the ditosylate as colorless needles or prisms (Table 4).

3,5,8-Trimethoxy-3′,4′,7-tris(tosyloxy)flavone (9m). The flavone **2g** (180 mg) was tosylated with *p*-toluenesulfonyl chloride (450 mg), and anhydrous potassium carbonate (2 g) in acetone to give **9k** as colorless needles (Table 4).

A General Method for Synthesizing 3,5,7-Trihydroxy-8-methoxyflavones (1) from 3,5,8-Trimethoxy-7-tosyloxyflavones (9). The flavone **9** (1 mmol) was dissolved in a solution of 5% w/v anhydrous aluminum bromide in acetonitrile (25—30 cm^3; 4.5—5.5 mmol) and the solution is allowed to stand at room temperature (25—28 °C) for 2 h. The reaction times in the demethylation of the flavones **1h—k** with benzyloxyl groups on the B ring were reduced to 1 h. The reaction mixture was poured into 2% hydrochloric acid

Table 4. 3,5,8-Trimethoxy-7-tosyloxyflavones (**9**) and 5,7- and 3,7-Ditosyloxyflavones (**5a** and **6a**)

Compd.	Mp θ_m/°C	Recrystn. solvent	Yield %	^{1}H NMR in $CDCl_3$ C_6-H	Ph-Me	Formula	Found (%) C	H	Calcd (%) C	H
9a	201—202	$CHCl_3$-MeOH	95	6.47s	2.45s	$C_{26}H_{24}O_9S$	60.94	4.61	60.93	4.72
9b	170—171	$CHCl_3$-MeOH	96	6.43s	2.45s	$C_{27}H_{26}O_{10}S$	59.50	5.02	59.77	4.83
9c	205—205.5	$CHCl_3$-MeOH	83	6.43s	2.46s	$C_{28}H_{28}O_{11}S$	58.52	5.06	58.73	4.93
9h	194—195	$CHCl_3$-MeOH	95	6.49s	2.45s	$C_{32}H_{28}O_9S$	65.05	4.69	65.29	4.80
9i	140—141	EtOAc-MeOH	90	6.43s	2.44s	$C_{33}H_{30}O_{10}S$	63.78	4.79	64.07	4.89
9j	134—136	Me_2CO-EtOAc	85	6.44s	2.44s	$C_{33}H_{30}O_{10}S$	64.29	4.81	64.07	4.89
9k	151—152	EtOAc-Et_2O	86	6.42s	2.42s	$C_{39}H_{34}O_{10}S$	67.32	4.89	67.42	4.93
9l	159—160	EtOAc-MeOH	85	6.51s	2.47s(6H)	$C_{33}H_{30}O_{12}S_2$	57.86	4.24	58.05	4.43
9m	149—150	EtOAc-MeOH	90	6.54s	2.46s(9H)	$C_{39}H_{34}O_{14}S_3$	56.64	4.04	56.92	4.16
5a	160—161	EtOAc-MeOH	87	6.86s	2.42s 2.46s	$C_{32}H_{28}O_{11}S_2$	58.60	4.12	58.88	4.32
6a	176—177	EtOAc	82	6.54s	2.39s 2.46s	$C_{32}H_{28}O_{11}S_2$	58.89	4.13	58.88	4.32

Table 5. 3,5,7-Trihydroxy-8-methoxyflavones (**1**, **12**, and **13**)

Compd.	Starting material	Mp θ_m/°C	Recrystn. solvent	Yield %	Formula	Found(%) C	H	Calcd (%) C	H
1a	**2a**	206—207	MeOH	72	$C_{17}H_{14}O_7$	61.53	4.48	61.82	4.27
	9a	(lit,[3] 207—208)		75					
1b	**2b**	246—248	aq MeOH	70	$C_{18}H_{16}O_8$	59.90	4.32	60.00	4.48
	9b			79					
1c	**2c**	220—221	EtOAc	75	$C_{19}H_{18}O_9$	58.54	4.57	58.46	4.65
	9c			76					
1d	**1h**	276—278	MeOH	97	$C_{16}H_{12}O_7$	60.82	3.71	60.76	3.82
		(lit,[6] 269—270)							
1e	**1i**	269—271	aq MeOH	85	$C_{17}H_{14}O_8$	59.10	4.11	58.96	4.08
	9l	(lit,[5] 269—271)		60					
1f	**1j**	242—243	AcOH	95	$C_{17}H_{14}O_8$	58.76	4.06	58.96	4.08
1g	**1k**	274—276	aq MeOH	91	$C_{16}H_{12}O_8$	57.71	3.62	57.83	3.64
		(lit,[4] 273—275)							
1h	**9h**	192—193	MeOH	88	$C_{23}H_{18}O_7$	68.07	4.53	67.97	4.46
1i	**9i**	238—240	AcOH	80	$C_{24}H_{20}O_8$	65.89	4.49	66.05	4.62
		(lit,[5] 247—249)							
1j	**9j**	187—189	MeOH	85	$C_{24}H_{20}O_8$	66.18	4.65	66.05	4.62
1k	**9k**	183—185	MeOH	75	$C_{30}H_{24}O_8$	70.21	4.78	70.30	4.72
12	**9m**	220—222	MeOH	25[a] 27	$C_{23}H_{18}O_{10}S$	56.47	4.02	56.79	3.73
13[b]	**9k**	228—230	MeOH	2	$C_{23}H_{18}O_8$	65.25	4.20	65.40	4.30

a) This is the yield of **1g**. b) This is a byproduct in the synthesis of **1k** from **9k**.

Table 6. Acetates **14** of 3,5,7-Trihydroxy-8-methoxyflavones (**1**)

Compd.	Mp θ_m/°C	Recrystn. solvent	Formula	Found (%) C	Found (%) H	Calcd (%) C	Calcd (%) H
14a	203—204	EtOAc-MeOH	$C_{23}H_{20}O_{10}$	60.41	4.38	60.52	4.42
14b	167—168	MeOH	$C_{24}H_{22}O_{11}$	59.27	4.52	59.26	4.56
14c	131—133	aq MeOH	$C_{25}H_{24}O_{12}$	57.99	4.73	58.14	4.68
14d	155—157	MeOH	$C_{24}H_{20}O_{11}$	59.22	4.12	59.50	4.16
14e	173—175 (lit,[15] 155—156)	MeOH	$C_{25}H_{22}O_{12}$	58.45	4.43	58.37	4.31
14f	199—200	$CHCl_3$-MeOH	$C_{25}H_{22}O_{12}$	58.12	4.28	58.37	4.31
14g	142—144 (lit,[4] 142—144)	MeOH	$C_{26}H_{22}O_{13}$	57.35	4.20	57.57	4.09

(50—60 cm^3), heated at 70—80 °C for 15—30 min, and diluted with water. After the solvent was evaporated under reduced pressure, the separated yellow crystals were collected, washed with water, and dried to give a mixture of **10** and **11**.

The mixture was refluxed with *p*-toluenesulfonyl chloride (285 mg; 1.5 mmol) and anhydrous potassium carbonate (2 g; 11 mmol) in acetone (40—50 cm^3) with stirring until the hydroxyflavones disappeared (3—6 h). The mixture was poured into diluted hydrochloric acid and the solvent was evaporated under reduced pressure. The separated precipitate was collected, washed with water and dried to give a mixture of **5** and **6**.

However, the precipitate obtained from the flavone **1h—k** with benzyloxyl groups on the B ring was extracted with ethyl acetate, and the extract was washed with water and then concentrated to give a mixture of **5** and **6**. The mixture was contaminated with a small amount of *p*-toluenesulfonyl chloride; however, the following demethylation was not affected by the chloride.

The mixture of **5** and **6** was demethylated with 5% w/v anhydrous aluminum bromide in acetonitrile under the same conditions as described in the demethylation of **9**. The demethylated product was extracted with ethyl acetate, and the extract was washed with water and then concentrated to give a mixture of **7** and **8**. To the mixture, methanol (40—50 cm^3) and anhydrous potassium carbonate (3—4 g; 21—28 mmol) were added. The mixture was refluxed with stirring under nitrogen atmosphere for 2—3 h, and then poured into diluted hydrochloric acid. The methanol was evaporated under reduced pressure and the separated yellow crystals were collected to give a crude product **1**. All products except for **12** and **13** were purified by recrystallization to give **1** as yellow needles. The flavone **13** was obtained from the mother liquor of **1k** by silica-gel chromatography with chloroform.

Only the mixture of **7m** and **8m** was hydrolyzed for 10 h under conditions similar to that described above, and the products were separated by the preparative HPLC, using a column (20×600 mm) packed with Hitachi gel #3019 and methanol as an eluent, to give **1g** and **12**. The results are shown in Table 5.

3,5-Dihydroxyflavones (**1a**, **1b**, and **1c**) were also synthesized from the corresponding 7-hydroxyflavones **2a**, **2b**, and **2c** by a method similar to that described above.

3,5,7-Trihydroxy-8-methoxyflavones (1d—g) with Hydroxyl Groups on the B Ring. The benzyloxyflavones **1h—k** (200 mg) were hydrogenated over palladium on charcoal (10%; 100 mg) in ethyl acetate-methanol (1/2 volume ratio; 300 cm^3) until the uptake of hydrogen ceased. After the catalyst was filtered off, the filtrate was evaporated and the residue was recrystallized to give **1** as yellow needles (Table 5).

Acetates (14a—g) of 1. The flavone **1** (40 mg) was dissolved in acetic anhydride (0.4 cm^3)-pyridine (0.04 cm^3), and allowed to stand at room temperature for 1 day and then treated with water to give **14** as colorless needles. The results are shown in Table 6.

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