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

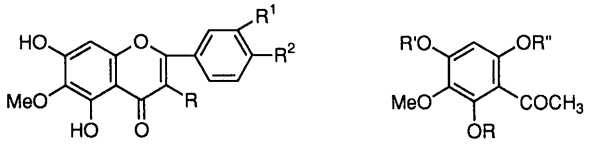
Tokunaru HORIE,* Kenichi SHIBATA, Kazuyo YAMASHITA, Yasuhiko KAWAMURA, and Masao TSUKAYAMA

Department of Chemical Sciences and Technology, Faculty of Engineering, The University of Tokushima, Minami-jousanjima-cho, Tokushima 770, Japan. Received August 8, 1996; accepted November 6, 1996

The demethylation of 3,4-dioxygenated 6-methoxy-2-isopropoxyacetophenones was studied and it was found that 4-benzyloxy-6-hydroxy-3-methoxy-2-isopropoxyacetophenone was easily obtained from 4-benzyloxy-3,6-dimethoxy-2-isopropoxyacetophenone by selective demethylation with anhydrous aluminum bromide–sodium iodide in acetonitrile. The acetophenone was converted into 7-benzyloxy-3-hydroxy-6-methoxy-5-isopropoxyflavones by cyclization followed by oxidation with dimethyldioxirane. The isopropoxy group in the flavones was selectively cleaved with anhydrous aluminum chloride *via* the corresponding tosylates to give 7-benzyloxy-3,5-dihydroxy-6-methoxyflavones, which were converted into the desired 3,5,7-trihydroxy-6-methoxyflavones by hydrogenolysis. The process was suitable as a general method for synthesizing 3,5,7-trihydroxy-6-methoxyflavones and five flavones were synthesized. We also examined the ^{13}C-NMR spectra of twelve kinds of 3,5,6,7-tetraoxygenated 4′-methoxyflavones and revised the proposed structure of a natural flavone.

Key words 3,5,7-trihydroxy-6-methoxyflavone; selective demethylation; ^{13}C-NMR; 2,3,4,6-tetraoxygenated acetophenone; synthesis; revised structure

In the previous paper,[1] we established a method for synthesizing 3,5,7-trihydroxy-6,8-dimethoxyflavones and their 3-methyl ethers from 2,4-dihydroxy-3,5,6-trimethoxyacetophenone *via* 7-benzyloxy-5,6,8-trimethoxyflavones. The result suggested that 3,5,7-trihydroxy-6-methoxyflavones (**1**) could be conveniently synthesized from the corresponding 5,7-dihydroxy-6-methoxyflavones (**2**) by oxidation with dimethyldioxirane, followed by selective dealkylation. Although these flavones **1** have been isolated from numerous plant sources and their structures proposed on the basis of spectral data,[2] there have been few synthetic studies and no convenient method for synthesizing **1** is available. For example, flavones such as beturetol (**1a**), spinacetin (**1c**), and patuletin (**1e**) have been synthesized from α-benzoyloxy-2,4,6-trihydroxy-3-methoxyacetophenone[3,4] or 4′-benzyloxy-6′-hydroxy-2′,3′,4-trimethoxychalcone[5] by using the Allan–Robinson or Algar–Flym–Oyamada reaction, and patuletin (**1e**) has also been synthesized from quercetagitrin by using selective methylation and demethylation,[6] but the yields are very low. On the other hand, the flavones **2**, the starting materials of **1**, are easily synthesized from 4-benzyloxy-6-hydroxy-2,3-dimethoxy- (**3**)[7] or 2,4-bis(benzyloxy)-6-hydroxy-3-methoxyacetophenones (**4**).[8] The synthesis of these acetophenones, however, is much more difficult than that of 2,4-dihydroxy-3,6-dimethoxyacetophenone (**5**).[9] Therefore, we examined the selective demethylation of the 6-methoxy group in **5** first, and then established a convenient method for synthesizing **1** in order to clarify their physical and biological properties. We also examined the ^{13}C-NMR spectra of twelve kinds of 3,5,6,7-tetraoxygenated 4′-methoxyflavones and revised the structure of a natural flavone, isolated from *Eupatorium glandulosum* and proposed to be **1a**,[10] to 3,5,4′-trihydroxy-6,7-dimethoxyflavone (**20b**).



1 R=OH
2 R=H

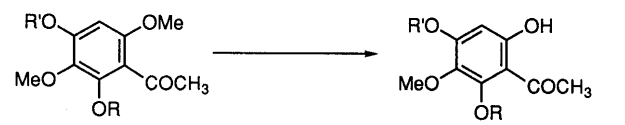
3 R=Me, R′=CH_2Ph, R″=H
4 R=R′=CH_2Ph, R″=H
5 R=R′=H, R″=Me

a, R^1=H, R^2=OMe; b, R^1=H, R^2=OH; c, R^1=OMe, R^2=OH
d, R^1=OH, R^2=OMe; e, R^1=R^2=OH

Fig. 1

Results and Discussion

The 6-methoxy group in a tosylate (**7**) of the 4-benzyl ether (**6**)[11] of **5** was selectively cleaved with anhydrous aluminum bromide in acetonitrile to give 4-benzyloxy-6-hydroxy-3-methoxy-2-tosyloxyacetophenone (**8**), as expected from our previous studies,[12] but the benzylation of the 6-hydroxy group in the product did not proceed smoothly. On the other hand, in the dealkylation of 2,4-dimethoxy-6-isopropoxy-[13] or 3-benzyloxy-2,4,5-trimethoxy-6-isopropoxyacetophenones,[14] anhydrous aluminum bromide selectively cleaves the 2-methoxy group, although less bulky reagents such as anhydrous aluminum chloride quantitatively cleave the 6-isopropoxy group. The result suggests that the isopropyl ether (**9**) of **6** is converted



6 R=H, R′=CH_2Ph
7 R=Ts, R′=CH_2Ph
9 R=$CH(CH_3)_2$, R′=CH_2Ph
11 R=$CH(CH_3)_2$, R′=Me
12 R=H, R′=Me

8 R=Ts, R′=CH_2Ph
10 R=$CH(CH_3)_2$, R′=CH_2Ph
13 R=$CH(CH_3)_2$, R′=Me

Chart 1

* To whom correspondence should be addressed.

into 4-benzyloxy-6-hydroxy-3-methoxy-2-isopropoxyacetophenone (**10**) by treatment with anhydrous aluminum bromide. Therefore, the dealkylation of 3,4,6-trimethoxy-2-isopropoxyacetophenone (**11**) was examined first as a representative example and the results are shown in Table 1.

The isopropoxy group in **11** was quantitatively cleaved by anhydrous aluminum chloride and the cleavage was suppressed by using anhydrous aluminum bromide to give a mixture of **12** and **13** (about 1 : 1). The suppression, however, is less than in the case of the other 2-isopropoxyacetophenones because the cleavage of the 2-alkoxy group is greatly accelerated by the neighboring 3-methoxy group.[13] The result suggests that a more powerful and bulky demethylating reagent, such as anhydrous aluminum iodide, is needed for the selective cleavage of the 6-methoxy group in **11**. Therefore, demethylation with the anhydrous aluminum bromide–sodium iodide system was examined and it was found that the product ratio of **13** increased above 90% at 0 °C for 10 min (Table 1). The demethylation of **9** under similar conditions proceeded smoothly without cleavage of the 4-benzyloxy group and the desired acetophenone **10** was easily obtained in about 75% yield. Thus, a method for synthesizing flavones **1** from **10** through the route shown in Chart 2 was examined.

The crude benzoates of **10** were treated with potassium hydroxide in pyridine to give diketone derivatives **14**, which were quantitatively converted into 7-benzyloxy-6-methoxy-5-isopropoxyflavones (**15**) by cyclization with a small amount of sulfuric acid in acetic acid. The oxidation of **15** with dimethyldioxirane (DMD)[15] at 0 °C afforded the corresponding 3-hydroxyflavones (**16**) in favorable yields. The 5-isopropoxy group in **16** was hardly cleaved with 5% (w/v) anhydrous aluminum chloride or the chloride–sodium iodide in acetonitrile at room temperature because of the existence of the 3-hydroxy group,[12] but that in the tosylates (**17**) was selectively cleaved with anhydrous aluminum chloride without cleavage of the benzyloxy groups on the A and B rings to give the 5-hydroxyflavones (**18**) in high yield. The 3-tosyloxy group in **18** was easily hydrolyzed with potassium carbonate in methanol to give the 3,5-dihydroxyflavones **19**. Hydrogenolysis of the flavones **19** afforded quantitatively the desired flavones **1**, which were led to the acetates **A1**.

Table 1. Dealkylation of 3,4,6-Trimethoxy-2-isopropoxyacetophenone (**11**)[a]

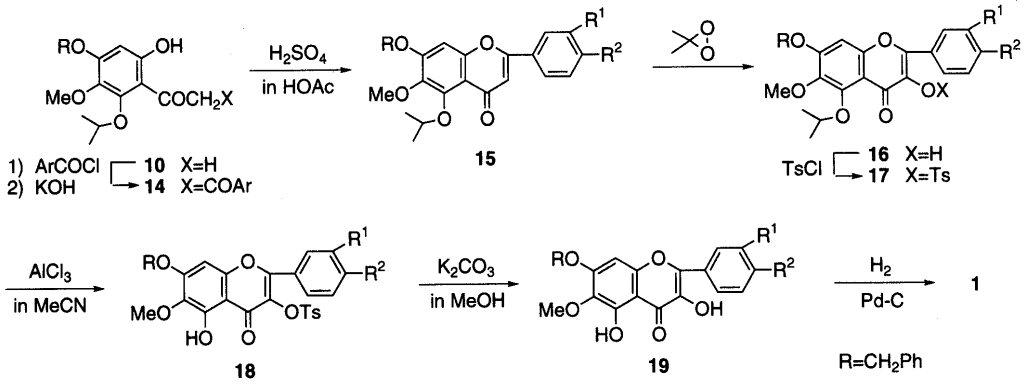
Reaction conditions			Product (%)		
Reagent	Temp. (°C)	Time (min)	**11**	**12**	**13**
5%(w/v) $AlCl_3$–MeCN	0	30	0	100	0
5%(w/v) $AlBr_3$–MeCN	0	90	3	45	52
5%(w/v) $AlBr_3$–NaI–MeCN	0	10	0	6	94

a) Acetophenone **11**, 0.37 mmol (100 mg); reagent, 1.12 mmol.

The process is useful as a general method for synthesizing not only 3,5,7-trihydroxy-6-methoxyflavones (**1**), but also 5,7-dihydroxy-6-methoxyflavones and 5,7-dihydroxy-3,6-dimethoxyflavones. Desmethoxycentauridin (**2d**)[16] and centaureidin (3-methyl ether of **1d**)[17] were easily synthesized from **15d** and **16d**, for example.

The UV spectra of the flavones **1a**—**e** comprise bands I and II at 364—373 and 255—258 nm, and these bands are bathochromically shifted by the addition of aluminum chloride or sodium acetate (Table 2). The absorption patterns of the flavones **1** bearing the same pattern of oxygenation on the B ring are similar to each other (**1a**, **1b**; **1c**, **1d**, **1e**). In particular, the spectral patterns upon the addition of sodium acetate are similar to each other and no effect of the 4′-hydroxy group on the B ring is observed, as in the cases of other 3-hydroxyflavones.[1,18–20]

In the ^{1}H-NMR spectra, the C_8-proton signals in the hydroxyflavones **1** (in dimethyl sulfoxide (DMSO)-d_6) and their acetates **A1** (in $CDCl_3$) appear in the ranges of δ 6.52 to 6.58 and of δ 7.26 to 7.27, respectively; these ranges are similar to those in the 5,7-dihydroxy-3,6-dimethoxyflavones[17,21] and 5,7-dihydroxy-6-methoxyflavones,[16] and their acetates. The chemical shifts of the other aromatic protons on the B ring in **1** and **A1** agree with those in the corresponding 5,6,7-trioxygenated flavones with the 3-hydroxy group and their acetates[19,20] (Table 3). The ^{13}C-NMR spectra of **1** exhibit a characteristic spectral pattern and fully support the assigned structure (Table 4). The precise assignment of the carbon signals in these polyhydroxyflavones, however, is difficult because of the decreased number of aromatic protons, and because the reported data are not always consistent.[22] Therefore, we examined the signal assignments of twelve kinds of synthetic 3,5,6,7-tetraoxygenated 4′-methoxyflavones; the



a R^1=H, R^2=OMe; **b** R^1=H, R^2=OCH_2Ph; **c** R^1=OMe, R^2=OCH_2Ph; **d** R^1=OCH_2Ph, R^2=OMe; **e** R^1=R^2=OCH_2Ph

Chart 2

Table 2. UV Spectral Data for 3,5,7-Trihydroxy-6-methoxyflavones (**1**)

Compd.		λ_{max} nm (log ε)[a]			
1a	MeOH	255 (4.17)	269 (4.22)	343 sh (4.26)	364 (4.31)
	+$AlCl_3$	272 (4.34)	302 sh (3.85)	374 sh (4.12)	426 (4.40)
	+NaOAc	274 (4.32)	299 (4.11)	309 i (4.09)	378 (4.30)
1b	MeOH	257 i (4.17)	269 (4.21)	345 i (4.25)	367 (4.31)
	+$AlCl_3$	272 (4.32)	301 sh (3.82)	375 sh (4.11)	429 (4.40)
	+NaOAc	274 (4.30)	299 (4.08)	309 sh (4.07)	380 (4.30)
1c	MeOH	256 (4.26)			370 (4.33)
	+$AlCl_3$	267 (4.34)			434 (4.34)
	+NaOAc	267 (4.22)	298 i (3.93)	320 (4.02)	384 (4.30)
1d	MeOH	256 (4.32)			367 (4.36)
	+$AlCl_3$	266 (4.41)			433 (4.44)
	+NaOAc	264 (4.29)	300 (4.02)	321 (4.07)	381 (4.34)
1e	MeOH	258 (4.30)			373 (4.35)
	+$AlCl_3$	273 (4.33)			453 (4.46)
	+NaOAc	263 (4.26)	300 i (3.94)	323 (4.02)	385 (4.32)

a) sh, shoulder; i, inflection point.

Table 3. ^{1}H-NMR Spectral Data for 3,5,7-Trihydroxy-6-methoxyflavones (**1**) in DMSO-d_6 and Their Acetates (**A1**) in $CDCl_3$[a]

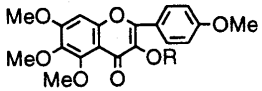
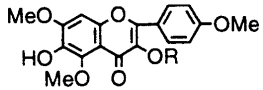
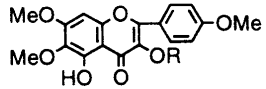
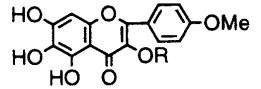
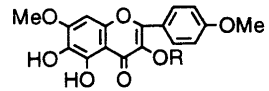
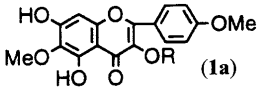
Compd.	Arom. H					OMe	5-OH or OAc
	C_8-H	$C_{2'}$-H	$C_{6'}$-H	$C_{3'}$-H	$C_{5'}$-H		
1a	6.57 s	8.14 d (2H)		7.12 d (2H)		3.76 s 3.84 s	12.53 s
Nat.[b]	6.8 s	8.04 d (2H)		7.0 d (2H)		3.7 s 3.78 s	
Nat.[c]	6.90 s	8.10 d (2H)		6.94 d (2H)		3.74 s 3.92 s	12.45 br s
20b[24]	6.84 s	8.10 d (2H)		6.94 d (2H)		3.75 s 3.92 s	12.44 s
1b	6.56 s	8.06 d (2H)		6.94 d (2H)		3.78 s	12.59 s
1c	6.58 s	7.77 d′	7.70 dd		6.95 d	3.78 s 3.86 s	12.55 s
1d	6.54 s	7.67 d′	7.66 dd		7.07 d	3.76 s 3.85 s	12.54 s
1e	6.52 s	7.69 d′	7.55 dd		6.90 d	3.77 s	12.59 s
A1a	7.26 s	7.79 d (2H)		7.01 d (2H)		3.87 s 3.89 s	2.33 s 2.39 s 2.49 s
ANat.[c]	6.88 s	7.83 d (2H)		7.27 d (2H)		3.85 s 3.99 s	2.32 s 2.35 s 2.48 s
A20b[24]	6.89 s	7.86 d (2H)		7.24 d (2H)		3.86 s 3.98 s	2.31 s 2.34 s 2.48 s
A1b	7.26 s	7.83 d (2H)		7.25 d (2H)		3.87 s	2.32 s 2.34 s 2.39 s 2.49 s
A1c	7.27 s	7.37 d′	7.40 dd		7.17 d	3.87 s 3.89 s	2.32 s 2.35 s 2.39 s 2.49 s
A1d	7.27 s	7.54 d′	7.71 dd		7.07 d	3.86 s 3.91 s	2.33 s 2.36 s 2.39 s 2.48 s
A1e	7.27 s	7.67 d′	7.70 dd		7.35 d	3.87 s	2.34 s (9H) 2.39 s 2.49 s

a) s, Singlet; br s, broad singlet; d, doublet (J=8.0—9.0 Hz); d′, doublet (J=2.0—3.0 Hz); dd, double doublet (J=8.0—9.0, 2.0—3.0 Hz). *b*) Reported data for a flavone isolated from *Lantana camara*.[23] *c*) Reported data for a flavone isolated from *Eupatorium glandulosum*.[10]

results are summarized in Table 4. The ^{13}C-NMR spectra of these flavones exhibit characteristic spectral patterns reflecting the substituent patterns on the A and C rings. In a comparison between the 3-methoxyflavones and 3-hydroxyflavones bearing the same oxygenation pattern on the A ring, the carbon signals at the 6- to 9-positions are similar to each other, but those at the 2-, 3-, 4-, 5-, and 10-positions are diamagnetically shifted by removal of the 3-methyl group (conversion to 3-hydroxyflavones). The shift ranges of the respective signals in the flavones with the 5-methoxy group are slightly different from those with the 5-hydroxy group, suggesting that those signals in the 3-hydroxyflavones are slightly affected by hydrogen bonding between the 3-hydroxy and 4-carbonyl groups.[18] That is, in the cases of 5-methoxyflavones, the shift ranges at the 2-position are the largest ($\Delta\delta$ 9.7—9.8) and those at the other positions decrease in the order of the 3- and 10- ($\Delta\delta$ 2.2—2.3), 4- ($\Delta\delta$ 1.2), and 5-positions ($\Delta\delta$ 0.3—0.5), while the ranges in the cases of 5-hydroxyflavones decrease in the order of the 2- ($\Delta\delta$ 8.8—8.9), 4- ($\Delta\delta$ 2.0—2.1), 3- ($\Delta\delta$ 1.8—1.9), 10- ($\Delta\delta$ 1.2—1.3), and 5-positions ($\Delta\delta$ 0.6—0.7) (Table 4). These features may be useful for the structural assignment of 3,5,6,7-tetraoxygenated flavones.

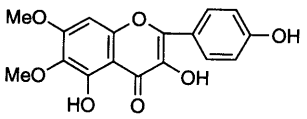
The ^{13}C-NMR data for natural flavones which have been proposed to have 3,5,7-trihydroxy-6-methoxyflavone structures are consistent with those for the synthetic flavones (Table 4). However, the ^{1}H- and ^{13}C-NMR data for the aglycone of a natural flavone glycoside, which was isolated from *Eupatorium glandulosum* and proposed to be **1a** by Nair and Sivakumar,[10] are not consistent with those for the synthetic **1a**. In the ^{1}H-NMR spectrum of the aglycone, the signal at δ 6.90, assigned to the C_8-proton, is at lower field than that for **1** and is not paramagnetically shifted by acetylation of the hydroxy groups (triacetate), showing that the C_7-hydroxy group is methylated. Furthermore, the ^{1}H and ^{13}C-NMR data attributed to the B ring are consistent with those for **1b** and 5,6,7-trioxygenated 3,4′-dihydroxyflavones.[19,20] The results show that the structure of the natural flavone should be revised to 3,5,4′-trihydroxy-6,7-dimethoxyflavone (**20b**), an isomer of **1a**, and the ^{1}H- and ^{13}C-NMR

Table 4. ^{13}C-NMR Data for 3,5,6,7-Tetraoxygenated 4′-Methoxyflavones and 3,5,7-Trihydroxy-6-methoxyflavones (**1a**—**e**) in DMSO-d_6[a]

Compd.	R		C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	$C_{1'}$	$C_{2'}$	$C_{6'}$	$C_{3'}$	$C_{5'}$	$C_{4'}$	OMe				
																		C_3	C_5	C_6	C_7	$C_{4'\text{ or }3'}$
	Me[24]		152.3	139.8	172.1	151.3	139.5	157.4	96.9	153.0	112.1	122.4	129.6		114.0		160.9	59.2	61.8	60.9	56.4	55.3
		$\Delta\delta$	−9.7	−2.2	−1.2	−0.3	−0.3	0	−0.1	−0.1	−2.2	+1.0	−0.8		−0.1		−0.8					
	H[27]		142.6	137.6	170.9	151.0	139.2	157.4	96.8	152.9	109.9	123.4	128.8		113.9		160.1		61.9	61.0	56.4	55.2
	Me[24]		152.2	139.8	172.1	143.9	137.3	153.4	96.3	149.9	112.1	122.7	129.5		114.0		160.8	59.2	61.2		56.2	55.3
		$\Delta\delta$	−9.8	−2.3	−1.2	−0.5	−0.3	+0.2	−0.1	0	−2.3	+0.9	−0.8		−0.1		−0.8					
	H[19]		142.4	137.5	170.9	143.4	137.0	153.6	96.2	149.9	109.8	123.6	128.7		113.9		160.0		61.2		56.2	55.2
	Me[21,24]		155.4	137.9	178.2	151.6	131.6	158.6	91.3	151.8	105.6	122.0	130.0		114.2		161.4	59.7		60.0	56.4	55.4
		$\Delta\delta$	−8.8	−1.8	−2.0	−0.6	−0.4	−0.1	−0.2	−0.3	−1.3	+1.1	−0.7		−0.3		−0.9					
	H[24]		146.6	136.1	176.2	151.0	131.2	158.5	91.1	151.5	104.3	123.1	129.3		113.9		160.5			60.0	56.3	55.3
	Me[28]		154.9	137.5	178.0	146.5	128.9	153.5	93.6	148.9	104.6	122.4	129.8		114.1		161.2	59.7				55.3
		$\Delta\delta$	−8.9	−1.9	−2.1	−0.7	−0.4	+0.1	−0.3	0	−1.3	+1.0	−0.6		−0.2		−0.9					
	H[19]		146.0	135.6	175.9	145.8	128.5	153.6	93.3	148.9	103.3	123.4	129.2		113.9		160.3					55.3
	Me[24]		155.2	137.7	178.1	145.6	129.6	154.5	90.9	148.8	105.6	122.3	129.9		114.1		161.2	59.6			56.2	55.4
		$\Delta\delta$	−8.8	−1.8	−2.1	−0.7	−0.4	+0.1	−0.2	0	−1.3	+1.0	−0.7		−0.2		−0.8					
	H[20]		146.4	135.9	176.0	144.9	129.2	154.6	90.7	148.8	104.3	123.3	129.2		113.9		160.4				56.2	55.3
	Me[b,21]		155.2	137.5	178.2	152.3	131.1	157.4	94.0	151.5	104.6	122.1	129.9		114.2		161.3	59.7		59.9		55.4
		$\Delta\delta$	−8.9	−1.8	−2.0	−0.6	−0.3	−0.2	−0.2	−0.1	−1.2	+1.1	−0.6		−0.3		−0.9					
	(1a) H		146.3	135.7	176.2	151.7	130.8	157.2	93.8	151.4	103.4	123.2	129.3		113.9		160.4			59.9		55.3
	Nat.[c]		146.2	135.9	177.0	150.1	132.3	158.1	94.0	151.0	102.9	122.8	127.7		114.9		163.1					
	Nat.[d]		148.1	135.6	176.1	151.5	131.5	158.5	91.8	152.0	104.5	122.2	129.5		115.4		159.3			60.1	57.0	
	20b[24]		147.2	135.7	176.0	150.9	131.2	158.4	91.1	151.5	104.3	121.5	129.5		115.4		159.3			60.0	56.3	
	1b		146.9	135.3	176.1	151.7	130.8	157.2	93.7	151.4	103.3	121.7	129.5		115.4		159.2			59.9		
	1c[e]		146.5	135.4	175.9	151.6	130.9	157.8	93.9	151.4	103.1	121.6	111.6	121.9	148.7	115.5	147.3			59.9		55.7
	1d		146.3	135.7	176.0	151.6	130.7	157.2	93.6	151.3	103.3	123.3	114.4	119.6	146.0	111.6	149.2			59.9		55.4
	1e[e]		146.8	135.3	175.9	151.6	130.7	157.2	93.5	151.3	103.2	121.9	114.9	119.9	145.0	115.5	147.6			59.9		

a) The ^{13}C-NMR data for **1b** and **1e** are consistent with those for the natural flavones isolated from *Arnica* species by Merfort and Wendisch,[25] and *Veronica filiformis* by Chari *et al.*,[26] respectively. *b*) The data are consistent with those for the natural flavone isolated from *Artemisia incanescens* by Barberá *et al.*[29] *c*) Reported data for a flavone isolated from *Lantana camara*.[23] *d*) Reported data for a flavone isolated from *Eupatorium glandulosum*[10]; the assignment of the carbon signals has been partly revised for the comparison. *e*) The data are consistent with those for the natural flavone isolated from *Spinacia oleracea* by Aritomi *et al.*,[30] although the assignment is slightly different.

data for the aglycone are consistent with those for the synthetic flavone **20b**[24] (Tables 3, 4). Consequently, the structure of the aglycone is revealed to be **20b** and that of its glycoside[10] must be revised to the 3-*O*-galactoside of **20b**.



20b
A20b (Triacetate of **20b**)

Fig. 2

The aglycone of a flavone glucoside, camaraside, isolated from *Lantana camara*, has also been proposed to be **1a** by Mahato *et al.*[23] However, the ^{1}H- and ^{13}C-NMR data are slightly different from those for synthesized **1a**, as shown in Tables 3 and 4, so the structure of the aglycone should be re-examined.

Experimental

All melting points were determined in glass capillaries and are uncorrected. ^{1}H-NMR (at 400 MHz) and ^{13}C-NMR (at 100.4 MHz) spectra were recorded on a JEOL EX400 spectrometer, using tetramethylsilane as an internal standard, and chemical shifts are given in δ values. UV spectra were recorded on a Hitachi 124 spectrophotometer. Gas chromatographic analyses were done at 110—180 °C using a glass column (3.2 i.d. × 2100 mm) packed with Silicon OV-101 (GL Science Co., Ltd.). Column chromatography was carried out with Merck Kieselgel 60 (230—400 mesh). Elemental analyses were performed with a Yanaco CHN corder Model MT-5. The values of all crystalline compounds in this paper were within 0.3% of theoretical values.

Preparation of the Acetophenones (7, 9, 11) Although the acetophenone (**6**) had been synthesized from **5** by partial benzylation, it was more conveniently synthesized by the following method: the dibenzyl ether of **5**, which was easily obtained from **5** by benzylation with $PhCH_2Cl$ and anhydrous K_2CO_3 in *N*,*N*-dimethylformamide (DMF) at 150 °C for 5—10 min, was hydrolyzed with concentrated HCl–HOAc (1:20) at room temperature for 45—60 min to give quantitatively **6**: mp 107—108 °C.

A mixture of **6** (2.0 g), TsCl (2.0 g), and anhydrous K_2CO_3 (9.5 g) in acetone (30 ml) was refluxed with stirring for 2—3 h and the precipitates were filtered off. The filtrate was evaporated and the residue was recrystallized from MeOH to give **7** ($C_{24}H_{24}O_7S$): mp 106—108 °C; yield, 2.4 g (86%).

A mixture of **6** (3.0 g), Me_2CHBr (5.6 ml), anhydrous K_2CO_3 (20 g), and KI (1.65 g) in acetone (40 ml)–DMF (30 ml) was refluxed with stirring till the starting material disappeared to give **9** ($C_{20}H_{24}O_5$): mp 74—75 °C (from hexane), yield, 2.85 g (83%). The acetophenone **11** [($C_{14}H_{20}O_5$): mp 69—71 °C (from hexane)] was also synthesized from **12** by a similar method.

Demethylation of the Acetophenones (7, 9, 11) Twenty percent (w/v) anhydrous $AlBr_3$ in MeCN (12 ml; 9.0 mmol) was stirred with dried NaI (1.32 g; 8.8 mmol) for 30 min and then cooled at 0 °C. To this solution, a cooled solution of **9** (1.0 g; 2.9 mmol) in MeCN (12 ml) was added with stirring, and the mixture was allowed to stand at 0 °C for 10—15 min. The mixture was diluted with about 3% aqueous HCl and warmed with a small amount of Na_2SO_3 at 60—70 °C for 20—30 min. The MeCN was evaporated under reduced pressure, and the separated oily material was extracted with Et_2O and chromatographed over a silica-gel column with $CHCl_3$ to give **10** ($C_{19}H_{22}O_5$): mp 69—70 °C (MeOH); yield, 720 mg (75%).

The demethylation of **11** was carried out by a similar method to give **13** ($C_{13}H_{18}O_5$): mp 65—67 °C (from MeOH), yield, 80%.

The acetophenone **7** (2.50 g) was demethylated with anhydrous $AlBr_3$ (4.4 g) in MeCN (44 ml) at 0 °C for 1 h to give quantitatively **8** ($C_{23}H_{22}O_7S$): mp 94—95 °C (from MeOH).

α-Benzoyl-4-benzyloxy-6-hydroxy-3-methoxy-2-isopropoxyacetophenones (14) A mixture of **10** (1.65 g; 5.0 mmol) and a substituted benzoyl chloride (7—9 mmol) in pyridine (15—20 ml) was heated at 70—80 °C for 2 h and poured into a mixture of ice and HCl. The separated oily material was extracted with EtOAc and the extract was washed with dilute HCl, aqueous K_2CO_3, and H_2O, dried over Na_2SO_4, and evaporated. The residue was crystallized from MeOH to give a crude benzoate. A mixture of the crude benzoate and freshly powdered KOH (3.5—5.0 g) in pyridine (12—15 ml) was heated at 80 °C for 1—2 h, then poured into a mixture of ice and HCl. The separated oily material was extracted with EtOAc and the extract was washed with dilute HCl, aqueous K_2CO_3, and H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized to give a diketone derivative **14** (Table 5).

7-Benzyloxy-6-methoxy-5-isopropoxyflavones (15) A solution of **14** (2.5—3.0 mmol) in HOAc (10—15 ml) was warmed with a small amount of concentrated H_2SO_4 (5—6 drops) at 50 °C for 1 h under stirring and then diluted with H_2O. The separated precipitates were collected and recrystallized to give **15** (Table 5).

7-Benzyloxy-3-hydroxy-6-methoxy-5-isopropoxyflavones (16) An acetone solution of DMD (about 0.1 mol/l; 20—25 ml) was added to a cooled solution of **15** (1.0 mmol) in acetone (35—45 ml). The mixture was stirred at 0 °C for 5—7 h and then the solvent was distilled off under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 ml) and the solution was stirred in the presence of TsOH (5—10 mg) at 0 °C for 10—15 min, then diluted with CH_2Cl_2. The mixture was washed with aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated to give **16** (Table 5).

7-Benzyloxy-6-methoxy-5-isopropoxy-3-tosyloxyflavones (17) A mixture of **16** (0.5 mmol), TsCl (130—140 mg; 0.68—0.74 mmol), and

Table 5. Syntheses of α-Aroyl-4-benzyloxy-6-hydroxy-3-methoxy-2-isopropoxyacetophenones (**14**), 7-Benzyloxy-6-methoxy-5-isopropoxyflavones (**15**), 7-Benzyloxy-3-hydroxy-6-methoxy-5-isopropoxyflavones (**16**), 7-Benzyloxy-6-methoxy-5-isopropoxy-3-tosyloxyflavones (**17**), 7-Benzyloxy-5-hydroxy-6-methoxy-3-tosyloxyflavones (**18**), and 7-Benzyloxy-3,5-dihydroxy-6-methoxyflavones (**19**)

Compd.	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Compd.	mp (°C)	Recrystn. solvent	Yield (%)	Formula
14a	110—111	$CHCl_3$–MeOH	63	$C_{27}H_{28}O_7$	**15a**	156—157	MeOH	87	$C_{27}H_{26}O_6$
14b	101—103	$CHCl_3$–MeOH	64	$C_{33}H_{32}O_7$	**15b**	135—137	$CHCl_3$–MeOH	90	$C_{33}H_{30}O_6$
14c	122—124	$CHCl_3$–MeOH	68	$C_{34}H_{34}O_8$	**15c**	108—110	$CHCl_3$–MeOH	97	$C_{34}H_{32}O_7$
14d	125—126	$CHCl_3$–MeOH	55	$C_{34}H_{34}O_8$	**15d**	148—149	$CHCl_3$–MeOH	92	$C_{34}H_{32}O_7$
14e	126—128	$CHCl_3$–MeOH	62	$C_{40}H_{38}O_8$	**15e**	142—143	$CHCl_3$–MeOH	97	$C_{40}H_{36}O_7$
16a	136—137	$CHCl_3$–MeOH	71	$C_{27}H_{26}O_7$	**17a**	188—190	$CHCl_3$–MeOH	96	$C_{34}H_{32}O_9S$
16b	158—159	$CHCl_3$–MeOH	67	$C_{33}H_{30}O_7$	**17b**	157—158	$CHCl_3$–MeOH	92	$C_{40}H_{36}O_9S$
16c	154—156	$CHCl_3$–MeOH	56	$C_{34}H_{32}O_8$	**17c**	155—156	$CHCl_3$–MeOH	98	$C_{41}H_{38}O_{10}S$
16d	144—146	$CHCl_3$–MeOH	74	$C_{34}H_{32}O_8 \cdot H_2O$	**17d**	184—186	$CHCl_3$–MeOH	85	$C_{41}H_{38}O_{10}S$
16e	120—122	$CHCl_3$–MeOH	70	$C_{40}H_{36}O_8 \cdot H_2O$	**17e**	154—156	$CHCl_3$–MeOH	81	$C_{47}H_{42}O_{10}S$
18a	197—199	$CHCl_3$–MeOH	91	$C_{31}H_{26}O_9S$	**19a**	170—171	$CHCl_3$–MeOH	90	$C_{24}H_{20}O_7$
18b	190—191	$CHCl_3$–MeOH	93	$C_{37}H_{30}O_9S$	**19b**	190—191	$CHCl_3$–MeOH	60	$C_{30}H_{24}O_7$
18c	168—170	$CHCl_3$–MeOH	85	$C_{38}H_{32}O_{10}S$	**19c**	164—166	$CHCl_3$–MeOH	85	$C_{31}H_{26}O_8$
18d	173—175	$CHCl_3$–MeOH	83	$C_{38}H_{32}O_{10}S$	**19d**	179—181	$CHCl_3$–MeOH	88	$C_{31}H_{26}O_8$
18e	134—136	$CHCl_3$–MeOH	97	$C_{44}H_{36}O_{10}S \cdot 1/2H_2O$	**19e**	169—171	$CHCl_3$–MeOH	96	$C_{37}H_{30}O_8$

Table 6. Syntheses of 3,5,7-Trihydroxyflavones (**1**) and Their Acetates (**A1**)

Compd.	mp (°C)[a]	Recrystn. solvent	Yield (%)	Formula	Analysis (%) Found C	Found H	Calcd C	Calcd H
1a	220—221 Lit.[5] 222—224	aq. MeOH	90	$C_{17}H_{14}O_7$	61.61	4.36	61.82	4.27
1b	258—260 d Lit.[31] *ca.* 270	aq. MeOH	87	$C_{16}H_{12}O_7$	60.55	4.05	60.74	3.83
1c	220—222 Lit.[3] 228—232	aq. MeOH	76	$C_{17}H_{14}O_8 \cdot H_2O$	56.03	4.43	55.67	4.47
1d	249—251 Lit.[32] 255	aq. MeOH	89	$C_{17}H_{14}O_8$	58.74	4.19	58.91	4.08
1e	262—264 d Lit.[33] 260—261	aq. MeOH	74	$C_{16}H_{12}O_8 \cdot 2H_2O$	52.08	4.40	52.15	4.30
A1a	213—214 Lit.[5] 208—211	$CHCl_3$–MeOH	Quant.	$C_{23}H_{20}O_{10}$	69.61	6.03	69.81	6.08
A1b	142—144 Lit.[31] 145—148	$CHCl_3$–MeOH	Quant.	$C_{24}H_{20}O_{11}$	59.49	4.16	59.65	4.07
A1c	161—163	$CHCl_3$–MeOH	Quant.	$C_{25}H_{22}O_{12}$	58.23	4.27	58.32	4.31
A1d	202—203	$CHCl_3$–MeOH	Quant.	$C_{25}H_{22}O_{12}$	58.09	4.26	58.32	4.31
A1e	173—175 Lit.[33] 176—178	$CHCl_3$–MeOH	Quant.	$C_{27}H_{22}O_{13}$	58.21	4.00	58.47	4.00

a) d, decomposition point.

anhydrous K_2CO_3 (1.0 g) in acetone (25—35 ml) was refluxed with stirring till the starting material disappeared and then treated in the usual way to give **17** (Table 5).

7-Benzyloxy-5-hydroxy-6-methoxy-3-tosyloxyflavones (18) A solution of anhydrous $AlCl_3$ (0.5 g) in MeCN (5.0 ml) was added to a cooled solution of **17** (0.40 mmol) in MeCN (5.0 ml). The solution was allowed to stand at room temperature for 30 min, then diluted with 2—3% aqueous HCl, and warmed at 60—70 °C for 20—30 min. The separated precipitates were collected and recrystallized to give **18** (Table 5).

7-Benzyloxy-3,5-dihydroxy-6-methoxyflavones (19) A mixture of **18** (0.35 mmol) and anhydrous K_2CO_3 (500 mg) in MeOH (30 ml) was refluxed with stirring for 1.5 h and then acidified with dilute HCl. The mixture was concentrated under reduced pressure, and the separated precipitates were collected and recrystallized to give **19** (Table 5).

3,5,7-Trihydroxy-6-methoxyflavones (1) The flavone **19** (0.30 mmol) was hydrogenolyzed with Pd–C (10%; 50—60 mg) in MeOH–EtOAc (about 1 : 1) at room temperature to give **1**, which was converted to the corresponding acetate (**A1**) by the hot acetic anhydride–pyridine method (Table 6).

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