Studies of the Selective O-Alkylation and Dealkylation of Flavonoids. XXIV.[1] A Convenient Method for Synthesizing 6- and 8-Methoxylated 5,7-Dihydroxyisoflavones

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2′,4′-Bis(benzyloxy)-3′,6′-dimethoxychalcones (5), which were obtained from the dibenzyl ether of 2,4-dihydroxy-3,6-dimethoxyacetophenone (3), were oxidatively rearranged with thallium (III) nitrate in methanol and the resultant products were converted into 7-hydroxy-5,8-dimethoxyisoflavones (8) by hydrogenolysis, followed by cyclization. The isoflavones were quantitatively demethylated to 5,7-dihydroxy-8-methoxyisoflavones (2) *via* their acetates. The isomeric 5,7-dihydroxy-6-methoxyisoflavones (1) were also synthesized from the chalcones, obtained from 2,3-dimethoxy- (16) or 2-isopropoxy-3-methoxy-4,6-bis(benzyloxy)acetophenones (21), by a similar method. On the other hand, the isoflavones with two hydroxy groups at the 2′- and 4′-positions were easily synthesized by the following method. Treatment of the rearranged product from 2,2′,4,4′-tetrakis(benzyloxy)-3′6′-dimethoxychalcone (5f) with hydrochloric acid (HCl) in acetic acid afforded 2′,4′,7-tris(benzyloxy)-5,8-dimethoxyisoflavone (10f). The 5-methoxy group in the isoflavone was quantitatively cleaved to give the corresponding 5-hydroxyisoflavone (11f), which was isomerized to 2′,4′,7-tris(benzyloxy)-5-hydroxy-6-methoxyisoflavone (25f) in the presence of anhydrous potassium carbonate. Hydrogenolysis of the two 5-hydroxyisoflavones proceeded smoothly to give 2′,4′,5,7-tetrahydroxy-8- (2f) and 6-methoxyisoflavones (1f), respectively. The ^{13}C-NMR spectra of these isoflavones supported the proposed structures of polyhydroxyisoflavones. The proposed structures of two natural isoflavones were revised.

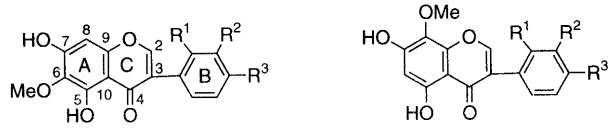
Key words 5,7-dihydroxy-6-methoxyisoflavone; 5,7-dihydroxy-8-methoxyisoflavone; ^{13}C-NMR; structural revison; iristectorigenin A; iristectorigenin B

In a previous paper,[2] we described a method for synthesizing 5,6,7-trihydroxyisoflavones and 5,6-dihydroxy-7-methoxyisoflavones from 3,6-dihydroxy-2,4-dimethoxyacetophenone *via* the corresponding 6-hydroxy-5,7-dimethoxyisoflavones and showed that the 8-proton signal in the ^{1}H-NMR spectrum of the acetate of a natural isoflavone,[3] proposed to be 4′,5,6,7-tetrahydroxy-3′-methoxyisoflavone, is consistent with that of isomeric 5,7-dihydroxy-6-methoxyisoflavones (**1**) rather than that of the synthetic compound. Although these isoflavones **1** have been isolated from numerous plant sources[4] and some have been synthesized,[5-7] no convenient method for synthesizing **1** has been established so far and the general properties of these compounds are not always clear. Therefore, we examined the synthesis of **1** and isomeric 5,7-dihydroxy-8-methoxyisoflavones (**2**) from 2,4-dihydroxy-3,6-dimethoxyacetophenone (**3**) in order to clarify their physical and biological properties. In this paper, we wish to report a convenient method for synthesizing **1** and **2**, in addition to their characterization and the identification of some natural isoflavones.

Results and Discussion

In the synthesis of polyhydroxyisoflavones, a method based on the oxidative rearrangement of 2′-hydroxychalcones with thallium (III) nitrate (TTN) is the most convenient one.[8] We have examined the reaction in detail in connection with isoflavonoid synthesis, and found that the reaction of 2′-alkoxychalcones without an electron-withdrawing group on the B ring proceeded smoothly to give the corresponding acetals,[9] which were easily cyclized to isoflavones. On the other hand, 6,7-dioxygenated 5-hydroxyisoflavones can be synthesized by isomerization of 7,8-dioxygenated 5-hydroxyisoflavones with potassium ethoxide[5] or potassium carbonate.[6] Therefore, the syntheses of 5,7-dihydroxy-8-methoxyisoflavones (**2**) were examined first according to the procedures shown in Chart 1.

Synthesis of 5,7-Dihydroxy-8-methoxyisoflavones (2) The dibenzyl ether (**4**)[10] of **3** was condensed with substituted benzaldehydes in the presence of potassium hydroxide in ethanol to give the chalcones (**5**) in high yields. The chalcones **5** were oxidatively rearranged with (TTN) in methanol, and the mixture was treated with sodium sulfite in dilute hydrochloric acid at 0 °C to give the crude acetals **6**. The acetals **6** were hydrogenolyzed with palladium on charcoal and the resultant products (**7**) were directly cyclized with hydrochloric acid to give 7-hydroxy-5,8-dimethoxyisoflavones (**8**) in favorable yields. The 5-methoxy group of the acetates **A8** was selectively cleaved with anhydrous aluminum bromide in acetonitrile to give the corresponding 5-hydroxyisoflavones (**9**), which were hydrolyzed to the desired isoflavones **2**. The process



1a-g **2a-f**

a R^1=R^2=H, R^3=OMe; **b** R^1=R^2=H, R^3=OH; **c** R^1=H, R^2=OMe, R^3=OH **d** R^1=H, R^2=OH, R^3=OMe; **e** R^1=H, R^2=R^3=OH; **f** R^1=R^3=OH, R^2=H; **g** R^1=R^3=OMe, R^2=H

Fig. 1

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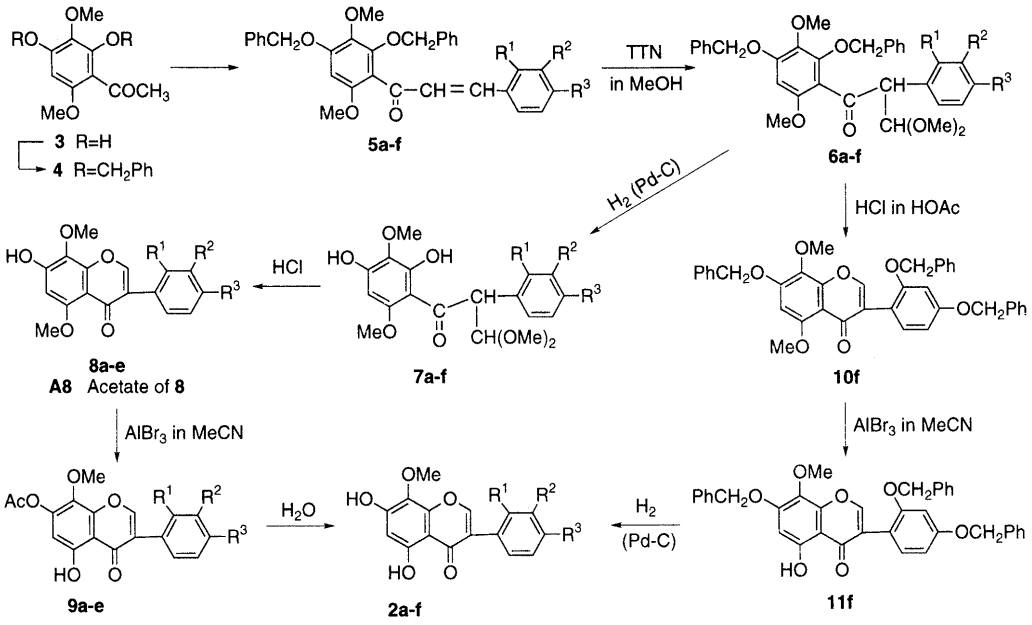


2, **7**, and **8**
a, $R^1=R^2=H$, $R^3=OMe$; **b**, $R^1=R^2=H$, $R^3=OH$; **c**, $R^1=H$, $R^2=OMe$, $R^3=OH$; **d**, $R^1=H$, $R^2=OH$, $R^3=OMe$; **e**, $R^1=H$, $R^2=R^3=OH$; **f**, $R^1=R^3=OH$, $R^2=H$

5 and **6**
a, $R^1=R^2=H$, $R^3=OMe$; **b**, $R^1=R^2=H$, $R^3=OCH_2Ph$; **c**, $R^1=H$, $R^2=OMe$, $R^3=OCH_2Ph$; **d**, $R^1=H$, $R^2=OCH_2Ph$, $R^3=OMe$; **e**, $R^1=H$, $R^2=R^3=OCH_2Ph$; **f**, $R^1=R^3=OCH_2Ph$, $R^2=H$

Chart 1

is useful as a general method for synthesizing **2** without a hydroxy group at the 2′-position, and the five isoflavones **2a**—**e** were easily synthesized.

The method, however, may be unsuitable for the synthesis of isoflavones with a hydroxy group at the 2′-position because a large amount of benzofuran derivative is produced in the cyclization of the hydroxyacetal,[11] such as **7f**. Therefore, the selective cleavage of the 2-benzyloxy group adjacent to the carbonyl group in **6f** was examined, since the 2-benzyloxy group in **4** was selectively cleaved under very mild conditions.[10,12] It was found that the 2-benzyloxy group in **6f** was cleaved with hydrochloric acid in acetic acid and the resultant compound was simultaneously cyclized to give 2′,4′,7-tris(benzyloxy)-5,8-dimethoxyisoflavone (**10f**), although the yield (*ca.* 50%) was lower than that in the case of the synthesis of hydroxyisoflavones **8** from **6**. The 5-methoxy group in **10f** was quantitatively cleaved with anhydrous aluminum bromide in acetonitrile to give a 5-hydroxyisoflavone **11f**. Hydrogenolysis of **11f** proceeded smoothly without hydrogenation of the double bond at the C ring and the desired product **2f** was easily obtained. This process may be useful as a general method for synthesizing **2** with hydroxy groups at the 2′- and/or 6′-positions.

Synthesis of 5,7-Dihydroxy-6-methoxyisoflavones (1) Although the above results suggest that the isoflavones **1** can also be synthesized from **4** *via* **2**, the synthesis of protected isoflavones such as **10f** is more difficult than that of the hydroxyisoflavones **8**, which are not always suitable as starting materials for **1**. Therefore, an unambiguous process is preferred for the synthesis of **1**, as shown in Chart 2.

4-Benzyloxy-6-hydroxy-3-methoxy-2-tosyloxyacetophenone (**12**),[10] which was easily obtained from the dibenzyl ether **4**, was hydrolyzed with anhydrous potassium carbonate in methanol to give quantitatively 2,6-dihydroxyacetophenone (**13**). The 2-benzyloxy group of the dibenzyl ether (**14**) of **13** was selectively cleaved with hydrochloric acid in acetic acid to give 4,6-bis(benzyloxy)-2-hydroxy-3-methoxyacetophenone (**15**), which was converted into the methyl ether **16**. The chalcones **17** obtained from **16** and substituted benzaldehydes were oxidatively rearranged with TTN to give the corresponding acetals **18**, which were converted into 7-hydroxy-5,6-dimethoxyisoflavones (**19**) by hydrogenolysis with palladium on charcoal, followed by cyclization with hydrochloric acid. The isoflavones **19** were quantitatively demethylated to the desired isoflavones **1** *via* the acetates A**19**.

The benzyl ether (**21**), of 4-benzyloxy-6-hydroxy-2-isopropoxy-3-methoxyacetophenone (**20**),[10] obtained from **4**, was easily converted into chalcones (**22**). The chalcones (**22**) were also cyclized to the corresponding isoflavones **24** *via* **23** by using a similar method to that described above, and the isoflavones **24** were directly deisopropylated to the desired isoflavones **1** by using anhydrous aluminum chloride in acetonitrile.

The method is useful as a general one for synthesizing **1** without a hydroxy group at the 2′- and/or 6′-positions. For the synthesis of **1f** with two hydroxy groups at the 2′- and 4′-positions, 4,4′,6′-tris(benzyloxy)-2-isopropoxy-2′,3′-dimethoxychalcone (**17h**) was used as a starting material, because the selective cleavage of the 6-benzyloxy group in the acetals (**18**) was difficult, in contrast to the case of that in **6**.[12] The 5-methoxy and 2′-isopropoxy groups in the isoflavone **19h**, which was obtained from **17h** *via* **18h**, were cleaved simultaneously with hydro-

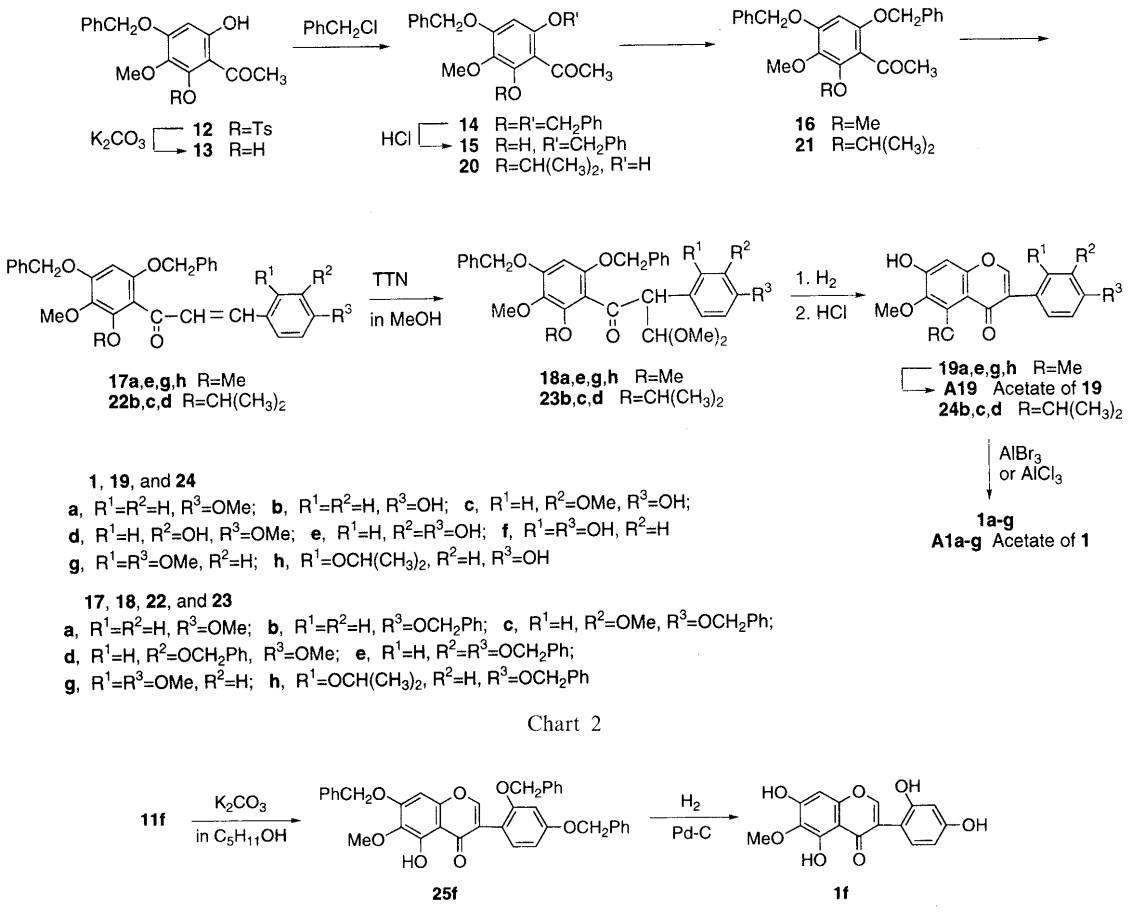


Chart 2

Chart 3

Table 1. UV Spectral Data for 5,7-Dihydroxy-6-methoxyisoflavones (**1**) and 5,7-Dihydroxy-8-methoxyisoflavones (**2**)

Compd.	λ_{max} nm (log ε)[a]						
	MeOH		MeOH–$AlCl_3$			MeOH–NaOAc	
1a	265.4 (4.52)		277.5 (4.51)	312 sh (3.92)	383 (3.54)	272.5 (4.52)	340 (4.11)
1b	265 (4.47)		277 (4.47)	312 sh (3.88)	383 (3.50)	272 (4.47)	338 (4.06)
1c	267.5 (4.47)	288 i (4.24)	278 (4.46)	313 sh (4.00)	384 (3.55)	272 (4.47)	338 (4.10)
1d	266 (4.40)	289 i (4.19)	278 (4.43)	312 sh (3.97)	385 (3.51)	272 (4.45)	338 (4.09)
1e	267 (4.46)	289 i (4.21)	278 (4.42)	309 i (4.11)	387 (3.51)	272 (4.46)	338 (4.09)
1f	264 (4.39)	286 i (4.15)	274 (4.38)	313 (3.97)	380 (3.52)	271 (4.40)	340 (4.07)
1g	262 (4.41)	274 i (4.14)	274 (4.42)	314 (3.99)	379 (3.55)	269 (4.45)	338 (4.16)
2a	265 (4.56)	335 (3.62)	280 (4.60)		398 (3.61)	281 (4.57)	331 (3.92)
2b	265 (4.56)	337 (3.60)	279 (4.60)		397 (3.59)	280 (4.57)	330 (3.88)
2c	267 (4.53)		280 (4.57)		398 (3.60)	280 (4.55)	329 sh (3.91)
2d	266 (4.52)		280 (4.56)		398 (3.61)	280 (4.55)	328 sh (3.92)
2e	266 (4.52)		280 (4.52)		399 (3.59)	279 (4.53)	327 sh (3.94)
2f	264 (4.46)		277 (4.50)		395 (3.57)	279 (4.49)	328 i (3.92)

a) sh, shoulder; i, inflection point.

chloric acid in acetic acid to give the desired isoflavone **1f** in a low yield (38%). The isopropoxy group, however, is hardly cleaved with anhydrous aluminum chloride or bromide in acetonitrile under mild conditions and the process is not always suitable for the synthesis of 2′-hydroxyisoflavones.

On the other hand, the isomerization of 2′,4′,7-tris-(benzyloxy)-5-hydroxy-8-methoxyisoflavones (**11f**) proceeded in the presence of anhydrous potassium carbonate in pentanol to give an isomeric isoflavone **25f**, which was easily converted into the desired **1f** by hydrogenolysis with palladium on charcoal (Chart 3). The result shows that the process using the isomerization is useful as a convenient method for synthesizing **1** with hydroxy groups at the 2′- and/or 6′-positions.

Characterization of 5,7-Dihydroxy-6- (1) and -8-methoxyisoflavones (2) The UV spectra of the isoflavones **1** and **2** in methanol exhibit a strong band in the range of 262 to 267.5 nm, and the spectral patterns for those with the same oxygenated substituents on the A ring are very similar to each other, being little influenced by the oxygenated group on the B ring, as shown in Table 1.

Table 2. ^{1}H-NMR Data for 5,7-Dihydroxy-6-methoxyisoflavones (**1**), 5,7-Dihydroxy-8-methoxyisoflavones (**2**) in DMSO-d_6, and Their Acetates (A**1** and A**2**) in $CDCl_3$[a]

Compd.	Arom. H							OMe	OH or OAc
	C_2-H	$C_{6\text{ or }8}$-H	$C_{2'}$-H	$C_{6'}$-H	$C_{3'}$-H	$C_{5'}$-H	C_4-H		
1a	8.39 s	6.52 s	7.50 d (2H)		7.01 d (2H)			3.75 s 3.79 s	13.03 s 10.80 s
1b	8.33 s	6.51 s	7.38 d (2H)		6.83 d (2H)			3.76 s	13.07 s 10.78 s 9.61 s
1c	8.37 s	6.51 s	7.14 d′	6.99 dd		6.84 d		3.76 s 3.81 s	13.09 s 10.79 s 9.18 s
1d	8.35 s	6.52 s	7.04 d′	6.94 dd		6.98 d		3.76 s 3.80 s	13.08 s 10.82 s 9.10 br
1e	8.31 s	6.50 s	7.00 d′	6.80 dd		6.77 d		3.75 s	13.11 s 10.79 s 9.10 s 9.04 s
1f	8.17 s	6.50 s		6.97 d	6.37 d′	6.27 dd		3.75 s	13.10 s 10.74 s 9.40 s 9.31 s
1g	8.19 s	6.51 s		7.15 d	6.65 d′	6.58 dd		3.72 s 3.75 s 3.80 s	13.00 s 10.79 s
2a	8.46 s	6.33 s	7.51 d (2H)		7.01d (2H)			3.78 s 3.80 s	12.63 s 10.86 s
2b	8.41 s	6.32 s	7.38 d (2H)		6.83 d (2H)			3.77 s	12.65 s 10.82 s, 9.60 s
2c	8.45 s	6.32 s	7.15 d′	7.00 dd		6.84 d		3.78 s 3.80 s	12.67 s 10.83 s 9.17 s
2d	8.42 s	6.33 s	7.04 d′	6.94 dd		6.98 d		3.77 s 3.80 s	12.67 s 10.85 s 9.10 s
2e	8.39 s	6.32 s	7.02 s	6.82 dd		6.79 d		3.78 s	12.71 s 10.84 s 9.11 s 9.04 s
2f	8.23 s	6.32 s		6.97 d	6.38 d′	6.27 dd		3.77 s	12.67 s 9.36 br (2H)
A**1a**	7.85 s	7.19 s	7.40 d (2H)		6.96 d (2H)			3.83 s 3.87 s	2.39 s 2.47 s
A**1b**	7.88 s	7.20 s	7.49 d (2H)		7.15 d (2H)			3.87 s	2.32 s 2.39 s 2.47 s
A**1c**	7.89 s	7.20 s	7.13 d′	6.99 dd		7.08 d		3.86 s 3.87 s	2.33 s 2.39 s 2.47 s
Nat.[b]	7.84 s	7.16 s	7.20 d′	7.33 dd		6.98 d		3.83 s (6H)	2.30 s 2.36 s 2.45 s
A**1d**	7.87 s	7.18 s	7.20 d′	7.33 dd		7.01 d		3.86 s 3.86 s	2.33 s 2.39 s 2.47 s
Nat.[c]	7.87 s	7.18 s		6.97—7.15 m (3H)				3.85 s (6H)	2.32 s 2.37 s 2.46 s
A**1e**	7.91 s	7.20 s	7.36 d′	7.36 dd		7.25 d		3.87 s	2.31 s (6H) 2.39 s 2.47 s
A**1f**	7.81 s	7.20 s		7.28 d	7.06 d′	7.06 dd		3.87 s	2.17 s 2.31 s 2.40 s 2.44 s
A**1g**	7.81 s	7.17 s		7.19 d	6.53 d′	6.54 dd		3.75 s 3.83 s 3.86 s	2.39 s 2.44 s
A**2a**	7.93 s	6.81 s	7.41 d (2H)		6.97 d (2H)			3.99 s 3.84 s	2.39 s 2.40 s
A**2b**	7.96 s	6.83 s	7.50 d (2H)		7.16 d (2H)			3.99 s	2.32 s 2.39 s 2.40 s
A**2c**	7.97 s	6.83 s	7.13 d′	7.00 dd		7.09 d		3.87 s 3.99 s	2.33 s 2.39 s 2.41 s
A**2d**	7.95 s	6.82 s	7.21 d′	7.33 dd		7.02 d		3.86 s 3.98 s	2.33 s 2.39 s 2.40 s
A**2e**	7.98 s	6.83 s	7.37 d′	7.37 dd		7.25 d		3.99 s	2.31 s (6H) 2.39 s 2.40 s
A**2f**	7.89 s	6.83 s		7.29 d	7.08 s	7.06 dd		4.00 s	2.18 s 2.31 s 2.37 s 2.39 s

a) s, singlet; br, broad; d, doublet (J=8.0—9.0 Hz); d′, doublet (2.0—3.0 Hz); dd, double doublet (J=8.0—9.0, 2.0—3.0 Hz). *b*) Reported data for the acetate of iristectorigenin B (proposed to be A**1c**), isolated from *Iris tecorium*.[14] *c*) Reported data for the acetate of iristectorigenin A (proposed to be A**1d**), isolated from *Iris tecorium*.[15]

Upon the addition of aluminum chloride or sodium acetate, the spectral patterns are changed characteristically by the effect of the hydroxy groups on the A ring, and little effect of the substituents on the B ring is observed.

The ^{1}H-NMR spectra of the isoflavones (**1** and **2**) in dimethyl sulfoxide-d_6 (DMSO-d_6) and those of their acetates (A**1** and A**2**) in $CDCl_3$ exhibit a characteristic signal in the ranges of δ 8.17 to 8.46 and δ 7.81 to 7.98, respectively, for the C_2-proton (Table 2). The C_8- or C_6-proton signals in **1** and **2** (in DMSO-d_6) appear in the ranges of δ 6.50 to 6.52 and δ 6.32 to 6.33, respectively, and are shifted paramagnetically by acetylation of the hydroxy groups (acetates A**1** and A**2**; in $CDCl_3$) to the ranges of δ 7.17 to 7.20 ($\Delta\ \delta$ 0.66—0.70) and δ 6.81 to 6.83 ($\Delta\ \delta$ 0.48—0.51), respectively. These features are similar to those in the ^{1}H-NMR spectra of the 3,5,7-trihydroxy-6-methoxyflavones[10] and 3,5,7-trihydroxy-8-methoxyflavones,[13] and this property is useful for differentiation between **1** and **2**. The signals of the aromatic protons on the B ring of the hydroxyisoflavones (**1** and **2**) and their acetates (A**1** and A**2**) exhibit characteristic splitting patterns.

The ^{13}C-NMR spectra of the hydroxyisoflavones (**1** and **2**) fully support the respective structures (Table 3), and the signals at the 5- to 10-positions in the isoflavones bearing the same oxygenated pattern on the A ring are superimposable on each other. Although the ^{13}C-NMR spectra of polyhydroxyflavonoids exhibit a diagnostic pattern reflecting the substituent pattern, the assignment is generally difficult because of the decreasing number of aromatic protons, and the spectral data are not always useful for structure elucidation. We therefore examined the ^{13}C-NMR spectra of polyhydroxyflavones and flavonols in detail, and found that the chemical shifts of the A ring carbon could be correctly estimated from the data for analogous compounds and the substituent effects.[19] If the substituent effects obtained from flavones are adapted to the assignment of the ^{13}C-NMR signals of isoflavones, the structures of polyhydroxyisoflavones may be correctly assessed from the ^{13}C-NMR spectra. Therefore, the ^{13}C-NMR spectra of ten different 5,6,7- and 5,7,8-trioxygenated 4′-methoxyisoflavones were compared with those of the corresponding flavones.

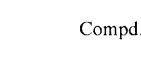
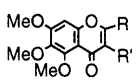
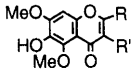
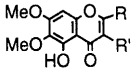
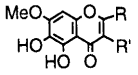
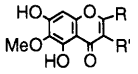
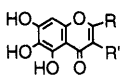
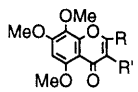
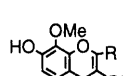
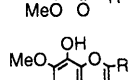
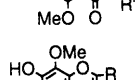
As shown in Table 4, a regular relationship is observed between the isoflavones and flavones bearing the same substituents. Thus, the ^{13}C-NMR chemical shifts of C_5 to C_{10} (A ring carbons) of the isoflavones can be easily estimated from those of the corresponding flavones or analogous isoflavones by using the shift ranges between isoflavones and flavones or the substituent effects[19] obtained from flavones. For example, the chemical shifts of the A ring carbons of **19a** were calculated from those in **26** or **1a** and the substituent effects obtained from flavones,[19] and the values accord well with the observed ones, as shown in Table 5. Furthermore, the chemical shifts of the A ring carbons of 4′,5,7-trihydroxy-6,8-dimethoxyisofla-

Table 3. ^{13}C-NMR Data for 5,6,7- and 5,7,8-Trioxygenated Isoflavones in DMSO-d_6[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		
1a	154.3	121.4	180.4	153.2	131.4	157.5	93.9	152.7	104.8	122.9	130.1		113.6		159.1	59.9	55.1	
1b	154.0	121.7	180.5	153.2	131.3	157.3	93.8	152.7	104.8	121.1	130.1		115.0		157.4	59.9		
1c	154.2	121.8	180.4	153.2	131.3	157.4	93.8	152.6	104.8	121.6	115.2	121.6	147.2	113.2	146.6	59.9	55.6	
1d	154.3	121.5	180.4	153.2	131.3	157.4	93.8	152.6	104.7	123.2	116.3	119.7	146.0	111.9	147.6	59.9	55.5	
Nat[b]	154.2	121.8	180.5	153.0	131.4	157.5	93.9	152.7	104.7	121.9	115.3	121.8	147.3	113.3	146.7	60.0	55.8	
1e	153.9	121.8	180.5	153.2	131.3	157.4	93.7	152.6	104.8	121.6	115.3	119.9	144.8	116.5	145.4	59.9		
1f	155.3	119.9	180.8	153.1	131.3	157.2	93.8	152.7	104.9	108.6	156.4	132.1	102.6	106.2	158.6	59.9		
1g	155.2	119.7	180.4	153.1	131.4	157.4	93.9	152.7	104.7	112.0	158.4	132.0	98.6	104.7	160.9	59.9	55.2	55.5
2a	154.2	121.7	180.2	156.6	99.1	157.1	127.3	149.8	104.2	122.8	130.1		113.6		159.1	60.8	55.1	
2b	153.9	122.1	180.3	156.6	99.0	157.0	127.3	149.8	104.2	121.0	130.1		115.0		157.4	60.8		
2c	154.1	122.1	180.3	156.6	99.0	157.0	127.3	149.8	104.2	121.6	115.2	121.5	147.2	113.2	146.7	60.8	55.6	
2d	154.1	121.9	180.2	156.6	99.0	157.0	127.3	149.8	104.2	123.2	116.3	119.7	146.0	111.9	147.6	60.8	55.5	
2e	153.9	122.2	180.3	156.6	99.0	156.9	127.3	149.8	104.2	121.5	115.3	119.9	144.8	116.5	145.5	60.8		
2f	155.1	120.2	180.4	156.5	99.0	157.2	127.4	149.8	104.0	108.5	156.4	132.1	102.5	106.1	158.5	60.7		
19a	151.3	124.3	173.7	152.5	139.4	156.0	99.4	153.8	111.7	123.6	130.2		113.4		158.8	61.6	60.8	55.0

a) The ^{13}C-NMR data for **1a** and **1b** are consistent with those for the natural flavones isolated from *Podocarpus amarus* by Carman *et al.*[16] and tectorigenin.[17] *b*) Reported data for an isoflavone isolated from *Iris spuria* and identified as iristectorigenin A by Shawl *et al.*[18]: the assignment of the carbon signals has been partly revised to facilitate comparison.

Table 4. Relationship of the ^{13}C-NMR Data between 5,6,7- and 5,7,8-Trioxygenated Isoflavones and the Corresponding Flavones in DMSO-d_6

Compd.	Ar = 		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	
																A rin	B ring
	**26**	R=H, R'=Ar	151.5	124.1	173.7	152.0	139.8	157.4	96.8	154.0	112.6	123.9	130.2	113.4	158.8	61.6	60.9 56.4 55.0
		$\delta\Delta$	+8.7	−18.0	+1.9	−0.4	−0.1	0	+0.5	−0.1	−0.6						
	26F[19]	R=Ar, R'=H	160.2	106.1	175.6	151.6	139.7	157.4	97.3	153.9	112.0	123.0	127.8	114.4	161.8	61.8	61.0 56.4 55.5
	**27**[2,a]	R=H, R'=Ar	151.4	124.4	173.8	144.5	137.6	153.3	96.2	150.8	112.5	123.6	130.2	113.4	158.8	61.0	56.2 55.1
		$\delta\Delta$	+8.6	−18.5	+1.9	−0.3	−0.1	−0.1	+0.4	−0.1	−0.6						
	27F[19]	R=Ar, R'=H	160.0	105.9	175.7	144.2	137.5	153.2	96.6	150.7	111.9	123.2	127.6	114.4	161.7	61.2	56.2 55.4
	**28**	R=H, R'=Ar	154.7	121.7	180.5	152.4	131.9	158.8	91.1	152.9	105.8	122.7	130.1	113.6	159.1	59.9	56.4 55.1
		$\delta\Delta$	+8.8	−18.5	+1.6	−0.4	−0.1	−0.2	+0.4	−0.4	−0.8						
	28F[19]	R=Ar, R'=H	163.5	103.2	182.1	152.0	131.8	158.6	91.5	152.5	105.0	122.6	128.2	114.5	162.3	59.9	56.3 55.5
	**29**[2]	R=H, R'=Ar	154.5	121.4	180.3	146.4	130.0	154.4	90.7	149.9	105.7	123.0	130.1	113.6	159.0		56.2 55.1
		$\delta\Delta$	+8.7	−18.4	+1.8	−0.3	−0.1	−0.1	+0.4	−0.3	−0.7						
	29F[19]	R=Ar, R'=H	163.2	103.0	182.1	146.1	129.9	154.3	91.1	149.6	105.0	122.9	128.1	114.4	162.2		56.2 55.4
	**1a**	R=H, R'=Ar	154.3	121.4	180.4	153.2	131.4	157.5	93.9	152.7	104.8	122.9	130.1	113.6	159.1		59.9 55.1
		$\delta\Delta$	+9.0	−18.4	+1.7	−0.5	−0.1	−0.2	+0.3	−0.3	−0.7						
	1F[19]	R=Ar, R'=H	163.3	103.0	182.1	152.7	131.3	157.3	94.2	152.4	104.1	122.8	128.2	114.5	162.2		59.9 55.5
	**30**[2]	R=H, R'=Ar	154.1	121.1	180.2	147.3	129.2	153.5	93.5	150.0	104.7	123.2	130.1	113.6	159.0		55.1
		$\delta\Delta$	+8.9	−18.3	+1.7	−0.3	−0.1	−0.2	+0.3	−0.4	−0.7						
	30F[19]	R=Ar, R'=H	163.0	102.8	181.9	147.0	129.1	153.3	93.8	149.6	104.0	123.0	128.1	114.4	162.1		55.4
	**31**	R=H, R'-Ar	150.9	124.2	173.9	156.1	93.6	156.1	129.4	151.2	108.6	124.1	130.2	113.4	158.8	56.2	56.3 60.8 55.0
		$\delta\Delta$	+8.5	−18.0	+1.9	−0.5	−0.1	+0.1	+0.4	−0.3	−0.8						
	31F[19]	R=Ar, R'-H	159.4	106.2	175.8	155.6	93.5	156.2	129.8	150.9	107.8	123.1	127.5	114.5	161.7	56.1	56.3 60.9 55.4
	**8a**	R=H, R'=Ar	150.6	124.3	173.7	154.6	96.7	155.8	128.3	151.9	107.9	124.1	130.2	113.4	158.8	55.8	60.7 55.0
		$\delta\Delta$	+8.6	−18.0	+2.0	+0.3	−0.1	−0.4	+0.4	−0.2	−0.6						
	8F[19]	R=Ar, R'=H	159.2	106.3	175.7	154.9	96.6	155.4	128.7	151.7	107.3	123.2	127.4	114.5	161.7	55.7	60.9 55.4
	**32**[20]	R=H, R'=Ar	150.9	124.4	174.2	151.3	94.1	152.4	127.7	146.9	108.7	123.7	130.2	113.3	158.7	56.2	56.4 55.0
		$\delta\Delta$	+8.7	−18.5	+2.0	+0.5	−0.1	−0.4	+0.2	−0.1	−0.7						
	32F[19]	R=Ar, R'=H	159.6	105.9	176.2	151.8	94.0	152.0	127.9	146.8	108.0	123.2	127.8	114.3	161.7	56.2	56.3 55.4
	**2a**	R=H, R'=Ar	154.2	121.7	180.2	156.6	99.1	157.1	127.3	149.8	104.2	122.8	130.1	113.6	159.1		60.8 55.1
		$\delta\Delta$	+8.8	−18.4	+1.6	−0.4	−0.2	0	+0.3	−0.4	−0.7						
	2F[19]	R=Ar, R'=H	163.0	103.3	181.8	156.2	98.9	157.1	127.6	149.4	103.5	122.9	128.0	114.6	162.3		60.9 55.5
	Average (shift range)	$\delta\Delta$	+8.8	−18.2	+1.8	−0.3	−0.1	−0.2	+0.4	−0.2	−0.7						

a) The assignment of the carbon signals has been partly revised.

Table 5. Calculated and Observed A Ring ^{13}C-NMR Signals of Two Isoflabones

	7(OH)/5,6(OMe)			5,7(OH)/6,8(OMe)	
	Calcd.[a] from		Obs. (**19a**)	Calcd.[b]	Obs.[c]
	26	**1a**			
C_5	152.8	153.0	152.5	148.6	148.7
C_6	139.2	139.2	139.4	131.6	131.5
C_7	156.3	156.4	156.0	151.0	150.7
C_8	99.5	99.5	99.4	127.5	127.5
C_9	153.9	153.9	153.8	145.5	145.7
C_{10}	111.6	111.8	111.7	103.6	103.7

a) By using the substituent effects obtained from polyhydroxyflavones.[19] *b*) Calculated from the ^{13}C-NMR data for 5,7-dihydroxy-4′,6,8-trimethoxyflavone[19] and the shift range shown in Table 4. *c*) The data are the reported values for 4′,5,7-trihydroxy-6,8-dimethoxyisoflavone isolated from *Polygala virgata* by Bashir *et al.*,[21] the assignment of the carbon signals has been partly revised to facilifate comparison.

vone, isolated from *Polygala virgata* by Bashir *et al.*,[21] are also consistent with the values calculated from those of 5,7-dihydroxy-4′,6,8-trimethoxyflavone[19] and the shift ranges shown in Table 4. The results show that the A ring carbon signals of polyhydroxyisoflavones can be estimated from those of the corresponding flavones or analogous isoflavones, and the structures can be correctly evaluated from the ^{13}C-NMR spectra.

The isoflavones **1a—d and 2a—e** isolated from natural sources exhibit properties consistent with those of the corresponding synthesized isoflavones (Table 8). However, the melting points of two natural isoflavones, iristectorigenin A (proposed as **1d**, mp 231 °C; triacetate, mp 206—208 °C)[15] and iristectorigenin B (proposed as **1c**, mp 153—155 °C; triacetate, mp 160—163 °C),[14] isolated from *Iris tectorum* by Morita *et al.*, are greatly different from those of the synthetic isoflavones **1d** (mp 175—176 °C; triacetate, mp 158—159 °C) and **1c** (mp 237—238 °C; triacetate, mp 207—208 °C), albeit the structures have been proposed on the basis of spectral and degradation studies. The ^{1}H-NMR spectral data for the acetate of iristectorigenin A are similar to those of A**1c** rather than those for A**1d** (Table 2). The ^{13}C-NMR spectral data for a natural isoflavone, which has been isolated from *Iris spuria* and confirmed to be iristectorigenin A by direct comparison by Shawl *et al.*,[18] are not consistent with those for **1d**, but do coincide with those of **1c** (Table 3). On the other hand, the ^{1}H-NMR spectral data for the acetate of iristectorigenin B are consistent with those for A**1d** (Table 2). The results show clearly that the structures of iristectorigenins A and B must be revised to 5,7,4′-trihydroxy-6,3′-dimethoxyisoflavone (**1c**) and 5,7,3′-trihydroxy-6,4′-dimethoxyisoflavone (**1d**), respectively.

The melting point (257 °C) of a natural isoflavone, which has been isolated from *Iris milesii* and proposed to be 4′,5,6,7-tetrahydroxy-3′-methoxyisoflavone by Agarwal *et al.*,[3] corresponded well to that of the isomeric isoflavone **1e** (mp 251—253 °C) rather than that of the proposed compound (mp 209—211 °C).[2] The UV spectra of the isoflavone and the chemical shifts of the B ring aromatic protons in ^{1}H-NMR spectra of its acetate, however, are different from those of the synthetic **1e** and A**1e**, and the structure can not be confirmed on the basis of the reported data.

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 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. Column chromatography was carried out with Merck Kieselgel 60 (230—400 mesh). Elemental analyses were performed with a Yanaco CHN corder Model MT-5.

4-Benzyloxy-2-isopropoxybenzaldehyde 2,4-Bis(benzyloxy)benzaldehyde (2.0 g) was partially debenzylated with 5% (w/v) anhydrous $AlCl_3$ in MeCN (84 ml) containing NaI (5.0 g) at 0 °C for 1 h. The mixture was diluted with dilute HCl containing a small amount of Na_2SO_3, warmed at 60—70 °C for 10 min, and then concentrated under reduced pressure. The separated precipitates were collected and chromatographed over a silica gel column with $CHCl_3$ to give 4-benzyloxy-2-hydroxybenzaldehyde, mp 62—63 °C (from MeOH), yield 1.1 g (76%). *Anal.* Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.48; H, 5.32.

A mixture of the benzaldehyde (1.0 g), iso-PrBr (2.5 ml), KI (0.7 g) and K_2CO_3 (6.1 g) in *N*,*N*-dimethylformamide (DMF) (10 ml) was heated with stirring at 100 °C for 1 h, then diluted with H_2O, concentrated, and extracted with Et_2O. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from Et_2O–hexane to give the desired benzaldehyde, mp 46—47 °C, yield 0.85 g (72%). *Anal.* Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.72; H, 6.66.

4-Benzyloxy-2,6-dihydroxy-3-methoxyacetophenone (13) A mixture of 4-benzyloxy-6-hydroxy-3-methoxy-2-tosyloxyacetophenone (**12**)[10] (5.0 g) and anhydrous K_2CO_3 (16.0 g) in MeOH (100 ml) was refluxed with stirring for 2 h. The mixture was acidified with dilute HCl and then concentrated under reduced pressure. The separated crystals were collected and recrystallized from MeOH to give **13**, mp 149—150 °C, yield 3.1 g (94%). *Anal.* Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.80; H, 5.58.

4,6-Bis(benzyloxy)-2-hydroxy-3-methoxyacetophenone (15) A mixture of **13** (2.5 g), $PhCH_2Cl$ (4.0 ml), and anhydrous K_2CO_3 (11.5 g) in DMF (10 ml) was heated with vigorous stirring at 150—160 °C for 10 min. Excess $PhCH_2Cl$ was removed by steam distillation, and the separated oily material was collected by extraction with ether to give a crude dibenzyl ether (**14**) of **13**. The crude ether **14** was dissolved in AcOH (15 ml), a mixture of concentrated HCl (6 ml) and AcOH (15 ml) was added, and the whole was allowed to stand at room temperature for *ca.* 50 min, then diluted with H_2O. The precipitate was collected and recrystallized from $CHCl_3$–MeOH to give **15**, mp 137—138 °C (lit.[30] mp 140—141 °C), yield 2.7 g (82%). *Anal.* Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 72.87; H, 5.90.

4,6-Bis(benzyloxy)-2,3-dimethoxyacetophenone (16) A mixture of **15** (2.5 g), Me_2SO_4 (1.9 ml), and anhydrous K_2CO_3 (9.0 g) in Me_2CO (30 ml) was refluxed for 1—2 h, diluted with H_2O, and additionally refluxed for 20—30 min. The solvent was distillated off, and the separated crystals were collected and recrystallized from MeOH to give **16**, mp 74.5—75.5 °C, yield 2.4 g (92%). *Anal.* Calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.25; H, 6.20.

4,6-Bis(benzyloxy)-2-isopropoxy-3-methoxyacetophenone (21) A mixture of 4-benzyloxy-6-hydroxy-2-isopropoxy-3-methoxyacetophenone (**20**)[10] (2.0 g), $PhCH_2Cl$ (1.2 ml), and K_2CO_3 (4.5 g) in DMF (10 ml) was heated with vigorous stirring at 150—160 °C for 10 min. Excess $PhCH_2Cl$ was removed by steam distillation, then the precipitate was collected and recrystallized from MeOH to give **21**, mp 79—80 °C, yield 2.3 g (87%). *Anal.* Calcd for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.03; H, 6.72.

2′,4′-Bis(benzyloxy)-3′,6′-dimethoxychalcones (5a—f), 4′,6′-Bis(benzyloxy)-2′,3′-dimethoxychalcones (17a, e, g, h), and 4′,6′-Bis(benzyloxy)-2′-isopropoxy-3′-methoxychalcones (22b—d) A solution of **4** (2.0 g, 5.1 mmol), **16** (2.0 g, 5.1 mmol), or **21** (2.1 g, 5.1 mmol) and substituted benzaldehyde (5.6—5.7 mmol) in EtOH (*ca.* 30 ml) was treated with KOH (1.7 g, 30 mmol), then the mixture was warmed with stirring at 40 °C for 1—1.5 h and diluted with H_2O. The separated oily material (or precipitate) was extracted with $CHCl_3$ and the extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized to give the chalcone **5**, **17**, or **22** (Table 6).

Table 6. Syntheses of 2′,4′-Bis(benzyloxy)-3′,6′-dimethoxychalcones (**5**), 4′,6′-Bis(benzyloxy)-2′,3′-dimethoxychalcones (**17**), and 4′,6′-Bis(benzyloxy)-2′-isopropoxy-3′-methoxychalcones (**22**)[a]

Compd.	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Found (%)		Calcd (%)	
					C	H	C	H
5a	87—89	$CHCl_3$–MeOH	82	$C_{32}H_{30}O_6$	75.02	5.92	75.27	5.92
5b	106—108	$CHCl_3$–MeOH	84	$C_{38}H_{34}O_6$	78.00	5.90	77.79	5.84
5c	125—127	$CHCl_3$–MeOH	83	$C_{39}H_{36}O_7$	75.90	5.86	75.95	5.88
5d	115—117	$CHCl_3$–MeOH	79	$C_{39}H_{36}O_7$	75.66	5.94	75.95	5.88
5e	94—96	$CHCl_3$–MeOH	81	$C_{45}H_{40}O_7$	77.95	5.78	78.01	5.82
5f	133—135	$CHCl_3$–MeOH	93	$C_{45}H_{40}O_7$	78.22	5.90	78.01	5.82
17e	75—77	EtOAc	97	$C_{45}H_{40}O_7$	77.85	5.79	78.01	5.82
17g	98—99	MeOH	95	$C_{33}H_{32}O_7$	73.20	5.89	73.31	5.97
22b	84—86	$CHCl_3$–MeOH	84	$C_{40}H_{38}O_6$	77.92	6.30	78.15	6.23
22c	103—105	$CHCl_3$–MeOH	93	$C_{41}H_{40}O_7$	76.10	6.20	76.37	6.25
22d	100—102	$CHCl_3$–MeOH	80	$C_{41}H_{40}O_7$	76.08	6.27	76.37	6.25

a) **17a** and **17h**, oily material.

Table 7. Syntheses of 7-Hydroxy-5,8-dimethoxyisoflavones (**8**), 7-Hydroxy-5,6-dimethoxyisoflavones (**19**), 7-Acetoxy-5,8-dimethoxyisoflavones (A**8**), 7-Acetoxy-5,6-dimethoxyisoflavones (A**19**), and 7-Acetoxy-5-hydroxy-8-methoxyisoflavones (**9**)

Compd.	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Found (%)		Calcd (%)	
					C	H	C	H
8a	245—247	MeOH	65	$C_{18}H_{16}O_6$	65.59	4.84	65.85	4.91
8b	274—276	MeOH	70	$C_{17}H_{14}O_6$	64.69	4.53	64.96	4.49
8c	229—231	MeOH	81	$C_{18}H_{16}O_7$	62.51	4.75	62.79	4.68
8d	263—265	MeOH	70	$C_{18}H_{16}O_7$	62.54	4.69	62.79	4.68
8e	253—255	Aq. MeOH	72	$C_{17}H_{14}O_7 \cdot 3H_2O$	52.94	5.07	53.12	5.25
19a	228—230	MeOH	72	$C_{18}H_{16}O_6$	65.88	4.89	65.85	4.91
19e	238—239	MeOH	71	$C_{17}H_{14}O_7$	61.56	4.27	61.82	4.27
19g	265—267	DMF	63	$C_{19}H_{18}O_7$	63.40	5.00	63.68	5.06
19h	211—213	MeOH	78	$C_{20}H_{20}O_7 \cdot H_2O$	61.80	5.85	61.53	5.68
A**8a**	139—140	$CHCl_3$–MeOH	Quant.	$C_{20}H_{18}O_7$	64.92	4.88	64.86	4.90
A**8b**	162—164	$CHCl_3$–MeOH	Quant.	$C_{21}H_{18}O_8$	63.16	4.63	63.31	4.55
A**8c**	105—107	MeOH	Quant.	$C_{22}H_{20}O_9 \cdot 3/2H_2O$	58.23	5.03	58.00	5.09
A**8d**	190—192	$CHCl_3$–MeOH	Quant.	$C_{22}H_{20}O_9$	61.42	4.67	61.68	4.71
A**8e**	180—182	$CHCl_3$–MeOH	Quant.	$C_{23}H_{20}O_{10}$	60.41	4.41	60.52	4.42
A**19a**	152—153	MeOH	Quant.	$C_{20}H_{18}O_7$	64.80	4.80	64.86	4.90
A**19e**	143—144	MeOH	Quant.	$C_{23}H_{20}O_{10}$	60.59	4.40	60.52	4.42
A**19g**	135—136	MeOH	Quant.	$C_{21}H_{20}O_8$	62.91	4.99	62.99	5.04
A**19h**	148—149	MeOH	Quant.	$C_{24}H_{24}O_9$	63.17	5.27	63.15	5.30
9a	129—130	$CHCl_3$–MeOH	93	$C_{19}H_{16}O_7$	63.90	4.47	64.04	4.53
9b	180—182	$CHCl_3$–MeOH	82	$C_{20}H_{16}O_8$	62.70	4.32	62.50	4.20
9c	174—176	$CHCl_3$–MeOH	83	$C_{21}H_{18}O_9$	60.74	4.35	60.87	4.38
9d	169—171	$CHCl_3$–MeOH	91	$C_{21}H_{18}O_9$	60.63	4.35	60.87	4.38
9e	172—174	MeOH	78	$C_{22}H_{18}O_{10}$	59.75	4.18	59.73	4.10

7-Hydroxy-5,8-dimethoxyisoflavones (8a—e), 7-Hydroxy-5,6-dimethoxyisoflavones (19a, e, g, h), and 7-Hydroxy-5-isopropoxy-6-methoxyisoflavones (24b—d) A solution of a chalcone (**5**, **17**, or **22**) (2.5 mmol) and TTN·$3H_2O$ (2.2 g, 5.0 mmol) in MeOH–$CHCl_3$ (4 : 1) (80—100 ml) was stirred at 30 °C for 16—20 h (the reaction time in the cases of the 2,4-dioxygenated chalcones **5f**, **17g** and **17h** was 20—30 min). The mixture was cooled, Na_2SO_3 (1.5 g) and 3—4% HCl (15—20 ml) were added and the whole was stirred at 0 °C for 1—2 h. The precipitate was filtered off, and the filtrate was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and then passed through a short column of silica gel with $CHCl_3$. The eluate was evaporated under reduced pressure to give a crude acetal (**6a—f**, **18a, e, g, h**, or **23b—d**).

The crude acetals except for **6f** were hydrogenolyzed with 10% Pd–C (100—200 mg) in MeOH, until the absorption of H_2 ceased, to give crude hydroxyacetals. A solution of a hydroxyacetal in MeOH (60 ml) was refluxed with aqueous 10% HCl (6 ml) for 1.5—2 h, diluted with H_2O and concentrated under reduced pressure. The separated crystals were corrected and recrystallized to give the corresponding 7-hydroxyisoflavone (**8a—e** or **19a, e, g, h**) (Table 7). The purification of 5-isopropoxyisoflavones **23** was not carried out at this stage, since the products were obtained as semisolid materials by extraction with EtOAc. The isoflavones **8** and **19** were quantitatively converted into the acetates (A**8** and A**19**) with hot acetic anhydride–pyridine (Table 7).

5,7-Dihydroxy-8-methoxyisoflavones (2a—e) and 5,7-Dihydroxy-6-methoxyisoflavones (1a—e, g) Method A: A 20% (w/v) solution of anhydrous $AlBr_3$ in MeCN (5.0 ml) was added to a solution of the 7-acetoxyisoflavone (A**8** or A**19**) (0.6 mmol) in acetonitrile (15 ml) with stirring. The mixture was allowed to stand at room temperature (*ca.* 20 °C) for 30—40 min, then diluted with 2—3% aqueous HCl, and warmed at 50—60 °C for 20 min. The separated crystals were collected and recrystallized to give the corresponding 5-hydroxyisoflavone, such as **9** (Table 7). A solution of the crude isoflavone in MeOH (*ca.* 50 ml) was refluxed with ca. 16% aqueous HCl (5 ml) for 1—2 h, then diluted with H_2O, and concentrated. The separated crystals were collected and recrystallized to give a 5,7-dihydroxyisoflavone (**2a—e** or **1a, e, g**) (Table 8).

Method B: The crude 7-hydroxy-5-isopropoxyisoflavone (**23b—d**) (0.6 mmol) was deisopropylated with 10% (w/v) anhydrous $AlCl_3$ in MeCN (33 ml) at room temperature (*ca.* 25 °C) for 1.5 h, then diluted with 2—3% aqueous HCl, warmed at 50—60 °C for 20 min, and concentrated. The separated crystals were collected and recrystallized to

Table 8. Syntheses of 5,7-Dihydroxy-6-methoxyisoflavones (**1**) and 5,7-Dihydroxy-8-methoxyisoflavones (**2**), and Their Acetates (**A1** and **A2**)

Compd.	mp (°C9	Lit. mp (°C)	Recrystn. solvent	Yield (%)	Formula	Found (%)		Calcd (%)	
						C	H	C	H
1a	187—188	200—203[16] 195—196[22]	MeOH	98	$C_{17}H_{14}O_6$	65.27	4.44	64.96	4.49
1b	225—226	226—227[5] 226[23]	MeOH	50[a]	$C_{16}H_{12}O_6$	64.18	4.30	64.00	4.03
1c	237—238	237—240[24]	MeOH–EtOAc	53[a]	$C_{17}H_{14}O_7$	61.82	4.42	61.82	4.27
1d	175—176[b]	163—166[24] 93—94[25] 176[26]	MeOH	55[a]	$C_{17}H_{14}O_7 \cdot H_2O$	58.47	4.74	58.62	4.63
1e	251—253		MeOH	85	$C_{16}H_{12}O_7$	60.52	3.87	60.76	3.82
1f	215—217		MeOH	80	$C_{16}H_{12}O_7 \cdot H_2O$	57.33	4.29	57.49	4.22
1g	187—188		MeOH	93	$C_{18}H_{16}O_7$	62.69	4.77	62.79	4.68
2a	164—166	141—149[21]	Aq. MeOH	82	$C_{17}H_{14}O_6$	64.70	4.58	64.96	4.49
2b	240—242d	238—239[27] 245[28]	Aq. MeOH	85	$C_{16}H_{12}O_6$	63.74	4.30	64.00	4.03
2c	264—266	202—204[29]	Aq. MeOH	85	$C_{17}H_{14}O_7$	61.77	4.26	61.82	4.27
2d	174—175[c]	197—198[26] 200—201[6]	Aq. MeOH	98	$C_{17}H_{14}O_7$	61.88	4.27	61.82	4.27
2e	253—255	252[28]	MeOH	98	$C_{16}H_{12}O_7 \cdot H_2O$	57.32	4.17	57.49	4.22
2f	224—226		Aq. MeOH	82	$C_{16}H_{12}O_7 \cdot H_2O$	57.52	4.34	57.49	4.22
A1a	210—212	224[16] 162—163[22]	$CHCl_3$–MeOH	Quant.	$C_{21}H_{18}O_8$	63.27	4.57	63.31	4.55
A1b	190—192	190—191[5] 188—190[23]	$CHCl_3$–MeOH	Quant.	$C_{22}H_{18}O_9$	61.86	4.26	61.97	4.26
A1c	207—208		$CHCl_3$–MeOH	Quant.	$C_{23}H_{20}O_{10}$	60.51	4.41	60.52	4.42
A1d	158—159	166—167[25] 159[26]	$CHCl_3$–MeOH	Quant.	$C_{23}H_{20}O_{10}$	60.31	4.38	60.52	4.42
A1e	165—166		MeOH	Quant.	$C_{24}H_{20}O_{11}$	59.27	4.13	59.50	4.16
A1f	125—126		MeOH	Quant.	$C_{24}H_{20}O_{11}$	59.23	4.14	59.50	4.16
A1g	148—149		MeOH	Quant.	$C_{22}H_{20}O_9$	61.51	4.74	61.68	4.71
A2a	126—127		$CHCl_3$–MeOH	Quant.	$C_{21}H_{18}O_8$	63.11	4.51	63.31	4.55
A2b	157—159	167[27]	$CHCl_3$–MeOH	Quant.	$C_{22}H_{18}O_9$	61.92	4.21	61.97	4.26
A2c	196—198	168—170[29]	$CHCl_3$–MeOH	Quant.	$C_{23}H_{20}O_{10}$	60.31	4.35	60.52	4.42
A2d	141—142	144[26]	MeOH	Quant.	$C_{23}H_{20}O_{10}$	60.38	4.45	60.52	4.42
A2e	131—132		MeOH	Quant.	$C_{24}H_{20}O_{11}$	59.37	4.08	59.50	4.16
A2f	114—116		MeOH	Quant.	$C_{24}H_{20}O_{11}$	59.52	4.17	59.50	4.16

a) Overally yield from **22**. *b*) 100—110 °C sintered, then solidified. *c*) 143—147 °C sintered, then solidified.

give a 5,7-dihydroxyisoflavone (**1b—d**) (Table 8).

Method C: A mixture of **19h** (300 mg) and concentrated HCl (15 ml) in HOAc (45 ml) was gently refluxed for 7 h and then diluted with H_2O. The HCl was neutralized with aqueous Na_2CO_3, and the mixture was extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized to give **1f** (100 mg, 38%).

2′,4′,7-Tris(benzyloxy)-5,8-dimethoxyisoflavone (10f) A mixture of concentrated HCl and HOAc (1 : 5, 20 ml) was added to a solution of the crude acetal **6f**, obtained from **5f** (1.73 g) by oxidative rearrangement with TTN, in HOAc (20 ml). The whole was allowed to stand at room temperature for 50—60 min, then diluted with H_2O (*ca.* 20 ml), and warmed at *ca.* 60 °C for 50—60 min. It was extracted with $CHCl_3$, then the extract was washed with aqueous Na_2CO_3 and evaporated. The residue was chromatographed over a silica gel column with $CHCl_3$ to give **10f** (lower *Rf* value), mp 131—133 °C (from $CHCl_3$–MeOH), yield 0.78 g (52%). *Anal.* Calcd for $C_{38}H_{32}O_7$: C, 75.98; H, 5.37. Found: C,75.78; H, 5.41.

2′,4′,7-Tris(benzyloxy)-5-hydroxy-8-methoxyisoflavone (11f) The isoflavone **10f** (1.2 g, 2.0 mmol) was demethylated with 5% (w/v) anhydrous $AlBr_3$ in MeCN (32 ml, 6 mmol) at room temperature (*ca.* 25 °C) for 30—40 min to give **11f**, mp 135—137 °C, yield 1.10 g (94%). *Anal.* Calcd for $C_{37}H_{30}O_7$: C, 75.75; H, 5.16. Found: C, 75.99; H, 5.21.

2′,4′,7-Tris(benzyloxy)-5-hydroxy-6-methoxyisoflavone (25f) A mixture of **11f** (300 mg) and anhydrous K_2CO_3 (1 g) in *n*-pentanol (40 ml) was refluxed for 2 h and then diluted with $CHCl_3$. The precipitates were filtered off, and the filtrate was washed with dilute HCl and H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from $CHCl_3$–MeOH to give **25f**, mp 128—130 °C, yield 225 mg (75%). *Anal.* Calcd for $C_{37}H_{30}O_7$: C, 75.75; H, 5.16. Found: C, 75.56; H, 5.11.

6-Methoxy- (1f) and 8-Methoxy-2′,4′,5,7-tetrahydroxyisoflavones (2f) The benzyloxyisoflavone **25f** or **11f** was hydrogenolyzed with 10% Pd–C in EtOAc–MeOH to give **1f** or **2f** (Table 8).

References and Notes

1) Part XXIII: Horie T., Ohtsuru Y., Minamimoto N., Yamashita K., Kawamura Y., Tsukayama M., *Chem. Pharm. Bull.*, **45**, 1573—1578 (1997).
2) Horie T., Sasagawa M., Torii F., Kawamura Y., Yamashita K., *Chem. Pharm. Bull.*, **44**, 486—491 (1996).
3) Agrawal V. K., Thappa R. K., Agrawal S. G., Mehra M. S., Dhar L., *Phytochemistry*, **23**, 2703—2704 (1984).
4) Wong E., "The Flavonoids," ed. by Harborne J. B., Mabry T. J., Mabry H., Chapman and Hall, London, 1975, pp. 743—761; Dewick P. M., "The Flavonoids: Advances in Research," ed. by Harborne J. B., Mabry T. J., Chapman and Hall, London, 1982, pp. 535—559; Dewick P. M., "The Flavonoids: Advances in Research Since 1980," ed. by Harborne J. B., Chapman and Hall, London, 1988, pp. 125—147; Dewick P. M., "The Flavonoids: Advances in Research Since 1986," ed. by Harborne J. B., Chapman and Hall, London, 1994, pp. 117—153.
5) Farkas L., Várady J., *Chem. Ber.*, **93**, 1269—1271 (1960).
6) Várady J., *Tetrahedron Lett.*, **1965**, 4273—4275.
7) Shaw S. C., Gupta A. K., Kumar R., *J. Indian Chem. Soc.*, **68**, 615—616 (1991).
8) McKillop A., Taylor E. C., "Comprehensive Organometallic Chemistry," Vol. 7, ed. by Wilkinson J., Pergamon, Oxford, 1982, pp. 474—480.
9) Horie T., Kawamura Y., Sakai C., Akita A., Kuramoto M., *J. Chem. Soc., Perkin Trans. 1*, **1994**, 753—759; Horie T., Kawamura Y., Sakai C., Akita A., Sasagawa M., Yamada T., *ibid.*, **1996**, 1987—1992.
10) Horie T., Shibata K., Yamashita K., Kawamura Y., Tsukayama M., *Chem. Pharm. Bull.*, **45**, 446—451 (1997).
11) Farkas L., Gottsegen A., Nógrádi M., Antus S., *J. Chem. Soc., Perkin Trans. 1*, **1974**, 305—312.
12) Kawamura Y., Takatsuki H., Torii F., Horie T., *Bull. Chem. Soc. Jpn.*, **67**, 511—515 (1994).
13) Horie T., Tsukayama M., Kawamura Y., Seno M., Yamamoto S., *Bull. Chem. Soc. Jpn.*, **61**, 441—447 (1988).
14) Morita N., Shimokoriyama M., Shimizu M., Arisawa M., *Yakugaku Zasshi*, **92**, 1052—1054 (1972).
15) Morita N., Shimokoriyama M., Shimizu M., Arisawa M., *Chem. Pharm. Bull.*, **20**, 730—733 (1972).
16) Carman R. M., Russell-Maynard J. K. L., Schumann R. C., *Aust. J. Chem.*, **38**, 485—496 (1985).

17) Konno C., Oshima Y., Hikino H., *Planta Medica*, **32**, 118—124 (1977).
18) Shawl A. S., Zaman V. A., Kalla A. K., *Phytochemistry*, **23**, 2405—2406 (1984).
19) Horie T., Ohtsuru Y., Shibata K., Yamashita K., Tsukayama M., Kawamura Y., *Phytochemistry*, in press.
20) Horie T., unpublished work (mp 179—181 °C, from $CHCl_3$–MeOH).
21) Bashir A., Hamburger M., Msonthi J. D., Hostettmann K., *Phytochemistry*, **31**, 309—311 (1992).
22) Prakash L., Zaman A., Kidwal A. R., *J. Org. Chem.*, **30**, 3561—3562 (1965).
23) Shawal A. S., Kumar T., *Phytochemistry*, **31**, 1399—1401 (1992).
24) Pailer M., Franke F., *Monatsch. Chem.*, **104**, 1394—1408 (1973).
25) Sethi M. L., Taneja S. C., Dhar K. L., Atal C. K., *Phytochemistry*, **22**, 289—292 (1981).
26) Chimura H., Sawa T., Kumada Y., Naganawa H., Matsuzaki M., Takita T., Hamada M., Takeuchi T., Umezawa H., *J. Antibiot.*, **28**, 619—626 (1975).
27) Kawase Y., Fujino Y., Ichioka Y., Fukui K., *Bull. Chem. Soc. Jpn.*, **30**, 689—691 (1957).
28) Umezawa H., Tobe H., Shibamoto N., Nakamura F., Nakamura K., Matsuzaki M., Takeuchi T., *J. Antibiot.*, **28**, 947—952 (1975).
29) Kawase A., Ohta N., Yagishita K., *Agric. Biol. Chem.*, **37**, 145—150 (1973).
30) Fukui K., Nakayama M., Horie T., *Bull. Chem. Soc. Jpn.*, **42**, 2327—2330 (1969).