Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. XX.[1] A Convenient Method for Synthesizing 5,6,7-Trihydroxyisoflavones and 5,6-Dihydroxy-7-methoxyisoflavones

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3′,6′-Bis(benzyloxy)-2′,4′-dimethoxychalcones, which were derived from dibenzyl ether of 3,6-dihydroxy-2,4-dimethoxyacetophenone, were oxidatively rearranged with thallium(III) nitrate (TTN) in methanol to give 2-aryl-1-[3,6-bis(benzyloxy)-2,4-dimethoxyphenyl]-3,3-dimethoxypropan-1-ones; these products were converted into 6-hydroxy-5,7-dimethoxyisoflavones by hydrogenolysis followed by cyclization. The 5-methoxy group in the acetates of the isoflavones was selectively cleaved with 5% (w/v) anhydrous aluminum bromide in acetonitrile to give quantitatively the corresponding 5-hydroxyisoflavones, which were hydrolyzed to 5,6-dihydroxy-7-methoxyisoflavones. The acetates were also demethylated to 5,6,7-trihydroxyisoflavones with 30% (w/v) anhydrous aluminum chloride in acetonitrile at 70 °C for 36—48 h. The spectral properties of these isoflavones were examined and some natural isoflavones were identified.

Key words 5,6,7-trihydroxyisoflavone; 5,6-dihydroxy-7-methoxyisoflavone; 6-hydroxy-5,7-dimethoxyisoflavone; oxidative rearrangement; thallium(III) nitrate; selective demethylation

In previous papers,[2,3] we have reported that 5,6,7-trihydroxyflavones can be synthesized from 6-hydroxy-5,7-dimethoxyflavones or their acetates by demethylation with anhydrous aluminum chloride or bromide in acetonitrile. We considered that 5,6,7-trihydroxyisoflavones (**1**) and 5,6-dihydroxy-7-methoxyisoflavones (**2**) might be easily synthesized from 6-hydroxy-5,7-dimethoxyisoflavones (**3**) by similar demethylation. Although the isolation of these isoflavones from the natural sources has been reported,[4-7] their general properties are not yet known. Thus, the demethylation of **3** and the corresponding acetates was examined in order to clarify the physical and biological properties of these compounds. In this paper, we wish to report a convenient method for synthesizing **1** and **2**, 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 trinitrate (TTN) is the most convenient one.[8] We have examined the reaction in detail in order to clarify its scope and limitations, and found that the reaction of 2′-methoxychalcones with electron-donating groups on the B ring proceeds smoothly to give the corresponding acetals.[9] The results show that 6-hydroxy-5,7-dimethoxyisoflavones (**3**) are easily synthesized from 3′,6′-bis(benzyloxy)-2′,4′-dimethoxychalcones (**6**), as shown in Chart 1.

Condensation of the dibenzyl ether (**5**) of 3,6-dihydroxy-2,4-dimethoxyacetophenone (**4**) with 4-methoxybenzaldehyde in the presence of potassium hydroxide afforded 3′,6′-bis(benzyloxy)-2′,4,4′-trimethoxychalcone (**6a**). The chalcone **6a** was oxidatively rearranged with TTN in methanol, and the mixture was treated with sodium sulfite in dilute hydrochloric acid at 0 °C to give a crude acetal (**7a**). Hydrogenolysis of the crude acetal **7a** with palladium on charcoal afforded the hydroxyacetal **8a** in a favorable yield without hydrogenation of the carbonyl group.[10] The acetal **8a** was easily cyclized with dilute hydrochloric acid into the desired 6-hydroxy-4′,5,7-trimethoxyisoflavone (**3a**), which was led to the acetate A**3a**. The process is usable for the synthesis of isoflavones that have no electron-withdrawing group,[9] and six 6-hydroxy-5,7-dimethoxyisoflavones (**3a—f**) were easily obtained.

Demethylation of 6-hydroxy-5,7-dimethoxyflavones with anhydrous aluminum chloride in acetonitrile afforded a mixture of 5,6-dihydroxy-7-methoxyflavone and 5,6,7-trihydroxyflavone, but that of 6-acetoxy-5,7-dimethoxyflavones proceeded with increasing reaction time and afforded 5,6,7-trihydroxyflavone as a main product after 48 h.[2,3] When the 6-acetoxyflavones were demethylated with anhydrous aluminum chloride or bromide in acetonitrile under mild conditions, the 5-methoxy group was selectively cleaved to give quantitatively the corresponding 5-hydroxyflavones.[1] The results suggest that the demethylation of the isoflavones **3** proceeds by a similar mechanism[2] to that of the 6-hydroxy-5,7-dimethoxyflavones, and that the isoflavones **1** and **2** can also be synthesized by the demethylation of **3**. Therefore, the demethylation of the acetates A**3** of **3** was examined as follows.

The 5-methoxy group in the acetate A**3a** was selectively cleaved with 5% (w/v) anhydrous aluminum bromide in acetonitrile to give quantitatively 6-acetoxy-5-hydroxy-4′,7-dimethoxyisoflavone (**9a**), which was hydrolyzed with dilute hydrochloric acid to afford the desired 5,6-dihydroxy-7-methoxyisoflavone (**2a**). When the acetate A**3a** was demethylated with 30% (w/v) anhydrous aluminum chloride at 70 °C for 36—48 h, the 5- and 7-methoxy groups were simultaneously cleaved to give 5,6,7-trihydroxy-4′-methoxyisoflavone (**1a**) containing a small amount of **2a**, which was easily removed by preparative high-performance liquid chromatography (HPLC). The

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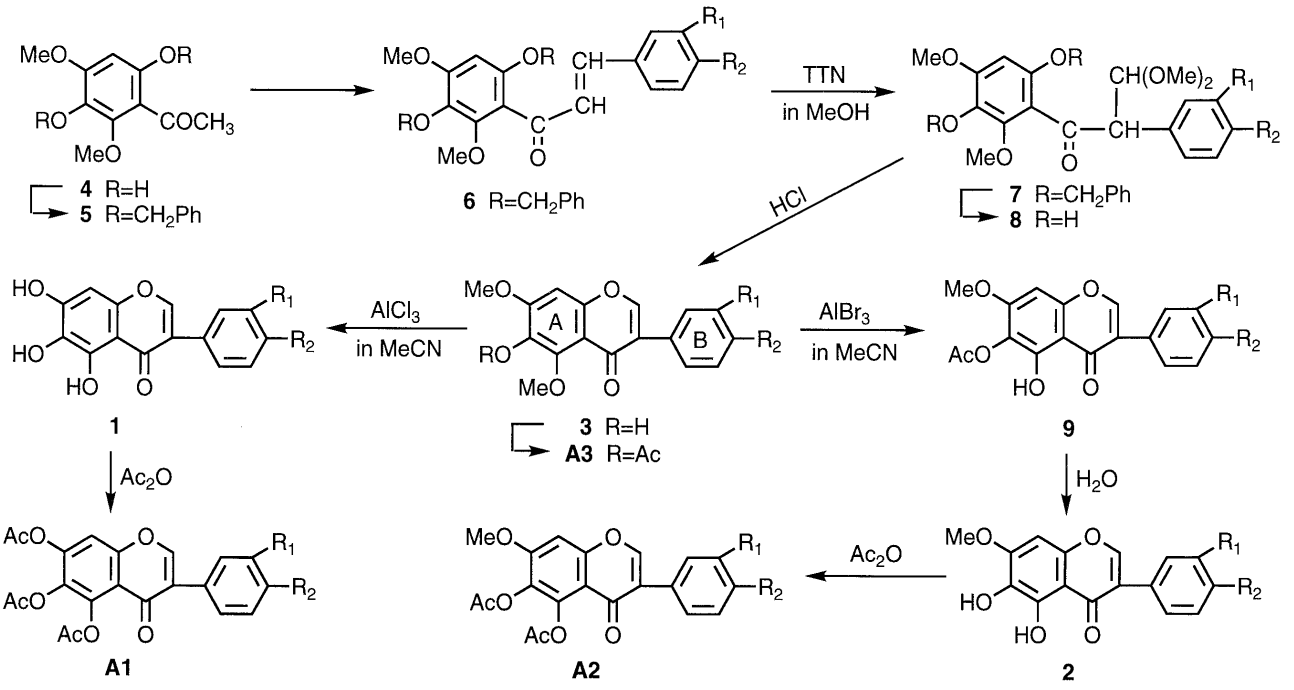

1, **2**, **3**, and **8**
a R_1=H, R_2=OMe **b** R_1=H, R_2=OH **c** R_1=R_2=OMe **d** R_1=OMe, R_2=OH **e** R_1=OH, R_2=OMe **f** R_1=R_2=OH
A1, **A2**, **A3**, and **9**
a R_1=H, R_2=OMe **b** R_1=H, R_2=OAc **c** R_1=R_2=OMe **d** R_1=OMe, R_2=OAc **e** R_1=OAc, R_2=OMe **f** R_1=R_2=OAc
6 and **7**
a R_1=H, R_2=OMe **b** R_1=H, R_2=OCH_2Ph **c** R_1=R_2=OMe **d** R_1=OMe, R_2=OCH_2Ph **e** R_1=OCH_2Ph, R_2=OMe **f** R_1=R_2=OCH_2Ph

Chart 1

method was convenient for synthesizing **1** and **2**, and the isoflavones **1b—f** and **2b—f** were readily obtained. The isoflavone **1a** was also obtained by the direct demethylation of **3a** with anhydrous aluminum bromide in acetonitrile. The method, however, was less suitable than the demethylation of acetates **A3** as a general method for synthesizing **1**, since the neighboring two methoxy groups on the B ring in **3c** were partly cleaved.

Characterization of 5,6,7-Trioxygenated Isoflavones (1 and 2) and Identification of Some Natural Isoflavones The isoflavones **1** and **2** were converted into the corresponding acetates **A1** and **A2** by acetylation with hot acetic anhydride–pyridine. The ^{1}H-NMR spectra of the hydroxyisoflavones (**1** and **2**) in dimethyl sulfoxide-d_6 (DMSO-d_6) and their acetates (**A1** and **A2**) in $CDCl_3$ exhibit a characteristic signal in the ranges of δ 8.3 to 8.45 and 7.8—7.9 for the C_2-proton, respectively; other signals are shown in Table 1. The C_8-proton signals in **1** (in DMSO-d_6) and their acetates **A1** (in $CDCl_3$) appear in the ranges of δ 6.48 to 6.50 and δ 7.38 to 7.41, respectively, and those in **2** (δ *ca.* 6.8 in DMSO-d_6) and their acetates **A2** (δ *ca.* 6.85 in $CDCl_3$) appear in similar ranges. These features are similar to those in the ^{1}H-NMR spectra of the 5,6,7-trihydroxyflavones[2,3,11] and 5,6-dihydroxy-7-methoxyflavones.[2,11,12] The ^{13}C-NMR spectra of the hydroxyisoflavones (**1—3**) fully support the respective structures as shown in Table 2, and the signals at the 2- to 10-positions in the isoflavones bearing the same oxygenation pattern at the A ring are superimposable on each other. These features in the NMR may be useful for the structural elucidation of the 5,6,7-trioxygenated isoflavones.

The UV spectra of **1**, **2**, and **3** exhibit a strong band in the range of 264 to 275 nm and a weak band in the range of 325 to 347 nm, and the spectral patterns for those with the same oxygenated substituents at the A ring are very similar to each other, being little influenced by the oxygenated groups on the B ring, as shown in Table 3. 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, except in the case of **3f** upon the addition of aluminum chloride. Only the spectra of the 5,6,7-trihydroxyisoflavones **1** showed remarkable behavior upon the addition of sodium acetate: with the passage of time, the bands at about 270 and 345 nm shifted hypochromically with decreasing intensity and a new band appeared at about 420 nm; the rate also accelerated with increasing concentration of the reagent (an example is shown in Table 3). These results suggest that the UV spectral method is useful for the structural elucidation of the oxygenation pattern at the A ring.

The isoflavones **2b** and **2d** correspond to the natural ones isolated from *Gaillardia suavis* by Herz *et al.*,[6] and the ^{1}H-NMR spectra of the latter are consistent with those of the synthetic samples, as shown in Table 1. This shows that the structures proposed for the two natural isoflavones are correct. A natural isoflavone, isolated from *Baptisia hirsuta*, has been proposed to have the structure **1b** (6-hydroxygenistein) on the basis of spectral

Table 1. ^{1}H-NMR Spectral Data for 5,6,7-Trioxygenated Isoflavones (**1** and **2**) and Their Acetates (A**1** and A**2**)[a]

Compd.	Solvent	C_2-H	C_8-H	$C_{3'}$-H	$C_{5'}$-H	$C_{2'}$-H	$C_{6'}$-H	OMe	OH
1a	DMSO	8.35 s	6.50 s	7.00 d (2H)		7.51 d (2H)		3.79 s	12.76 s 10.55 br s 8.80 br s
1b	DMSO	8.31 s	6.49 s	6.82 d (2H)		7.38 d (2H)		—	12.80 s 10.54 s 9.58 s 8.80 br s
1c	DMSO	8.38 s	6.50 s	—	7.01 d	7.18 d′	7.12 dd	3.79 s (6H)	12.78 s 10.55 s 8.81 s
1d	DMSO	8.34 s	6.49 s	—	6.82 d	7.14 d′	6.99 dd	3.80 s	12.81 s 10.53 s 9.14 s 8.80 s
1e	DMSO	8.31 s	6.49 s	—	6.97 d	7.04 d′	6.94 dd	3.79 s	12.80 s 10.53 s 9.05 s 8.79 s
1f	DMSO	8.27 s	6.48 s	—	6.77 d	7.01 d′	6.80 dd	—	12.84 s 10.52 s 9.04 s 8.98 s 8.77 s
2a	DMSO	8.45 s	6.81 s	7.01 d (2H)		7.52 d (2H)		3.91 s 3.79 s	12.62 s 8.76 br s
2b	DMSO	8.40 s	6.80 s	6.82 d (2H)		7.40 d (2H)		3.91 s	1.266 s 9.58 s 8.74 s
	$CDCl_3$[b]	7.90 s	6.51 s	6.93 d (2H)		7.37 d (2H)		3.99 s	
Nat.[6]	$CDCl_3$	7.93 s	6.49 s	6.90 d (2H)		7.40 d (2H)		3.97 s	
2c	DMSO	8.48 s	6.82 s	—	7.02 d	7.20 d′	7.15 dd	3.92 s 3.79 s (6H)	12.64 s 8.76 s
2d	DMSO	8.45 s	6.81 s	—	6.83 d	7.16 d′	7.01 dd	3.91 s 3.80 s	12.68 s 9.16 s 8.76 s
	$CDCl_3$	7.92 s	6.52 s	—	6.98 d	7.16 d′	6.96 dd	3.95 s 3.91 s	12.64 s
Nat.[6]	$CDCl_3$	7.91 s	6.44 s	—	6.95 d	7.10 d′	6.92 dd	3.95 s 3.91 s	12.38 s 5.32 s
2e	DMSO	8.42 s	6.81 s	—	6.98 d	7.06 d′	6.95 dd	3.91 s 3.80 s	12.67 s 9.08 s 8.76 s
2f	DMSO	8.38 s	6.79 s	—	6.78 d	7.03 d′	6.82 dd	3.91 s	12.70 s 9.09 s 9.02 s 8.75 s
A1a	$CDCl_3$	7.87 s	7.38 s	6.96 d (2H)		7.39 d (2H)		3.83 s	2.42 s 2.34 s 2.33 s
A1b	$CDCl_3$	7.90 s	7.40 s	7.15 d (2H)		7.48 d (2H)		—	2.42 s 2.35 s 2.34 s 2.32 s
A1c	$CDCl_3$	7.89 s	7.40 s	—	6.91 d	7.01 d′	6.98 dd	3.91 s 3.90 s	2.42 s 2.35 s 2.34 s
A1d	$CDCl_3$	7.91 s	7.41 s	—	7.08 d	7.11 d′	6.98 dd	3.86 s	2.42 s 2.35 s 2.34 s 2.33 s
Nat.[4]	$CDCl_3$	7.8 s	7.20 s	—	7.17—7.23 m (2H)		7.03 br s	3.8 s	2.33 s 2.18 s 2.17 s 2.16 s
A1e	$CDCl_3$	7.89 s	7.39 s	—	7.01 d	7.19 d′	7.32 dd	3.85 s	2.42 s 2.34 s 2.33 s 2.33 s
A1f	$CDCl_3$	7.93 s	7.40 s	—	7.25 d	7.35 br s	7.36 dd	—	2.42 s 2.35 s 2.34 s 2.30 (6H)
A2a	$CDCl_3$	7.81 s	6.85 s	6.95 d (2H)		7.39 d (2H)		3.94 s 3.83 s	2.42 s 2.34 s
A2b	$CDCl_3$	7.84 s	6.86 s	7.14 d (2H)		7.48 d (2H)		3.94 s	2.42 s 2.35 s 2.31 s
A2c	$CDCl_3$	7.83 s	6.85 s	—	6.91 d	7.02 d′	6.98 dd	3.95 s 3.91 s 3.90 s	2.42 s 2.35 s
A2d	$CDCl_3$	7.86 s	6.87 s	—	7.07 d	7.13 d′	6.98 dd	3.95 s 3.86 s	2.42 s 2.35 s 2.33 s
A2f	$CDCl_3$	7.84 s	6.85 s	—	7.01 d	7.19 d′	7.33 dd	3.94 s 3.85 s	2.42 s 2.35 s 2.32 s
A2g	$CDCl_3$	7.88 s	6.87 s	—	7.24 d	7.36 br s	7.37 dd	3.95 s	2.42 s 2.35 s 2.30 s (6H)

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*) Five drops of DMSO-d_6 were added.

Table 2. ^{13}C-NMR Spectral Data for 5,6,7-Trioxygenated Isoflavones (**1**—**3**) in DMSO-d_6

Compd.	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	$C_{1'}$	$C_{2'}$	$C_{6'}$	$C_{3'}$	$C_{5'}$	$C_{4'}$	OMe		
																C_5	C_7	B-ring
1a	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
1b	153.7	121.5	180.3	147.3	129.1	153.5	93.4	149.9	104.7	121.5	130.1		114.9		157.2	—	—	—
1c	154.2	121.2	180.2	147.3	129.2	153.5	93.5	149.9	104.7	121.3	112.8	123.5	148.3	111.5	148.6	—	—	55.5 55.5
1d	154.0	121.5	180.2	147.3	129.1	153.5	93.4	149.9	104.6	121.6	113.2	121.9	147.2	115.2	146.5	—	—	55.6
1e	154.0	121.3	180.2	147.3	129.2	153.5	93.4	149.9	104.7	119.7	111.9	123.6	146.0	116.3	147.5	—	—	55.6
1f	153.7	121.9	180.3	147.3	129.1	153.4	93.4	149.9	104.7	121.6	115.3	119.9	144.8	116.5	145.3	—	—	—
2a	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
2b	154.5	121.3	180.4	146.5	129.9	154.1	90.7	149.9	105.7	121.7	130.1		115.0		157.3	—	56.2	—
2c	154.5	121.5	180.3	146.5	130.0	154.6	90.7	149.9	105.7	121.3	112.7	123.3	148.3	111.5	148.7	—	56.3	55.5 55.5
2d	154.5	121.8	180.4	146.6	129.9	154.4	90.7	149.9	105.7	121.7	113.2	121.8	147.2	115.2	146.5	—	56.2	55.7
2e	154.5	121.6	180.4	146.5	129.9	154.4	90.7	149.9	105.7	119.7	111.9	123.5	146.0	116.4	147.6	—	56.3	55.6
2f	154.4	121.8	180.4	146.5	129.9	154.1	90.6	149.9	105.7	121.9	116.5	119.9	144.8	115.3	145.4	—	56.2	—
3a	153.3	124.4	173.8	144.5	137.6	151.4	96.2	150.8	112.5	123.6	130.2		113,4		158.8	61.0	56.2	55.1
3b	153.3	123.9	173.9	144.5	137.5	151.1	96.1	150.8	112.5	122.7	130.2		114.8		156.9	61.0	56.2	—
3c	153.3	124.8	173.7	144.6	137.6	151.6	96.1	150.8	112.5	121.4	113.0	123.7	148.2	111.4	148.4	61.0	56.2	55.5 (2C)
3d	153.2	123.9	173.8	144.5	137.5	151.3	96.1	150.8	112.4	121.7	113.4	123.2	147.0	115.0	146.2	61.0	56.2	55.6
3e	153.3	124.9	173.7	144.5	137.5	151.3	96.1	150.8	112.5	119.7	111.8	123.8	145.9	116.6	147.3	61.0	56.2	55.6
3f	153.2	124.0	173.8	144.5	137.5	151.0	96.1	150.7	112.5	123.2	116.8	119.9	144.6	115.1	145.0	61.0	56.1	—

and chemical evidence.[5] Although the UV spectral data are similar to those for synthetic **1b**, the spectral data upon the addition of aluminum chloride or sodium acetate are not consistent with those for **1b**. The data upon the addition of sodium acetate, however, are consistent with those for **1b** after standing for a long period (Table 3), suggesting that the proposed structure is correct.

A natural isoflavone, isolated from *Iris milesii*, has been proposed to have the structure **1d** on the basis of the spectral data.[4] The UV spectral data in methanol are similar to those for synthetic **1d**, but those upon the addition of aluminum chloride or sodium acetate are not (Table 3). Although the ^{1}H-NMR data for the acetate are also similar to those for the synthetic A**1d**, the signal at

Table 3. UV Spectral Data for 5,6,7-Trihyroxyisoflavones (**1**), 5,6-Dihydroxy-7-methoxyisoflavones (**2**), and 6-Hydroxy-5,7-dimethoxyisoflavones (**3**) in Methanol[a)]

Compd.	λ_{max} nm (log ε)								
	MeOH		MeOH–$AlCl_3$				MeOH–NaOAc		
1a	272 (4.41)	345i (3.57)	241 (4.42)	287 (4.23)	356 (4.03)	420sh (3.32)	273 (4.36)	345 (4.07)	
1b[b)]	272 (4.41)	345i (3.55)	241 (4.44)	291 (4.22)	357 (4.09)	420sh (3.33)	272 (4.37)	345 (4.07)	
Lit.[5)]	245sh 269	340sh	238 274	297sh	352		248sh 301	325sh 416	
1c	273 (4.36)	345i (3.55)	238 (4.42)	293 (4.24)	357 (4.07)	420sh (3.32)	273 (4.31)	345 (4.08)	
1d	273 (4.39)	345i (3.54)	237 (4.43)	295 (4.28)	358 (4.09)	420sh (3.29)	272 (4.35)	345 (4.09)	
Lit.[4)]	278	320sh		312	340sh		292	325	
1e	273 (4.34)	345i (3.52)	235 (4.44)	295 (4.26)	357 (4.08)	420sh (3.23)	272 (4.32)	345 (4.07)	
1f	273 (4.34)	343i (3.57)	234 (4.44)	297 (4.26)	356 (4.03)	420i (3.26)	272 (4.27)	347 (4.06)	
2a	268 (4.49)	340sh (3.55)		281 (4.46)	320i (3.95)	400 (3.33)	268 (4.44)	340i (3.57)	
2b	273 (4.46)	345sh (3.55)		286 (4.44)	325i (3.92)	402 (3.38)	273 (4.41)	345i (3.57)	
2c	271 (4.46)	340sh (3.56)		284 (4.47)		398 (3.31)	271 (4.41)	340i (3.60)	
2d	275 (4.43)	345sh (3.55)		289 (4.41)		406 (3.30)	275 (4.32)	340i (3.54)	
2e	275 (4.42)	345sh (3.57)		290 (4.43)		405 (3.41)	275 (4.39)	343i (3.56)	
2f	275 (4.43)	347 (3.54)		291 (4.42)		405 (3.43)	274 (4.41)	346i (3.59)	
3a	264 (4.51)	326 (3.87)					262 (4.49)	323sh (3.80)	370i (3.51)
3b	264 (4.49)	326 (3.85)					263 (4.47)	325sh (3.82)	375i (3.23)
3c	265 (4.47)	326 (3.89)					263 (4.45)	323sh (3.82)	372i (3.51)
3d	266 (4.42)	326 (3.83)					264 (4.41)	323sh (3.80)	375i (3.33)
3e	264 (4.39)	326 (3.82)					262 (4.37)	323sh (3.74)	373i (3.38)
3f	265 (4.38)	325 (3.83)		270 (4.29)	293i (4.18)	325i (3.83)	263 (4.36)	325sh (3.80)	372i (3.42)

a) sh, shoulder; i, inflection point. *b*) UV spectral data for **1b** (2.34×10^{-5} mol/l) upon the addition of NaOAc. Final concentration of NaOAc, 0.084 mol/l: after 0 min: 247sh (4.30), 272 (4.37), 345 (4.07); after 15 min: 248 (4.30), 272 (4.33), 343 (4.06), 420i (3.23); after 30 min: 248 (4.29), 271 (4.27), 340 (4.04), 420sh (3.38); after 18 h: 249 (4.27), 303 (4.17), 335i (3.98), 420 (3.75). Final concentration of NaOAc, 0.20 mol/l: after 0 min: 248sh (4.31), 272 (4.35), 344 (4.10); after 15 min: 248 (4.31), 271 (4.28), 340 (4.07), 420sh (3.54); after 30 min: 249 (4.29), 301 (4.13), 333sh (4.04), 420 (3.66); after 18 h; 249 (4.27), 303 (4.15), 333i (3.96), 420 (3.73).

Table 4. 2′,5′-Bis(benzyloxy)-4′,6′-dimethoxychalcones (**6**)

Compd.	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Calcd (%)		Found (%)	
					C	H	C	H
6a	70—72	MeOH	86	$C_{32}H_{30}O_6$	75.27	5.92	75.50	5.87
6b	91—93	Et_2O–MeOH	87	$C_{38}H_{34}O_6$	77.79	5.84	77.99	5.98
6c	108—109	$CHCl_3$–MeOH	90	$C_{33}H_{32}O_7$	73.32	5.97	73.04	5.69
6d	106—108	$CHCl_3$–MeOH	91	$C_{39}H_{36}O_7$	75.96	5.88	75.90	5.94
6e	109—110	EtOAc–MeOH	83	$C_{39}H_{36}O_7$	75.96	5.88	75.93	5.80
6f	103—105	EtOAc–MeOH	93	$C_{45}H_{40}O_7$	78.01	5.82	78.29	5.84

δ 7.20 for the C_8-proton is not consistent with that in 5,6,7-triacetoxyisoflavones (**A1d**) but rather, resembles that in 5,7-diacetoxy-6-methoxyisoflavones[13)] (Table 1). This result suggests that the natural isoflavone is an isomer of **1d**, but its structure can not yet be identified.

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, using tetramethylsilane as an internal standard, and chemical shifts are given in δ values. UV spectra were recorded on a Hitachi 124 spectrophotometer. HPLC was carried out with a Hitachi 635 instrument, using a column (2.1 × 500 mm) packed with Hitachi gel No. 3011, with MeOH (0.5 ml min^{-1}) as an eluent, and UV monitoring at 280 nm. For the separation of demethylated products, a column (20 × 600 mm) packed with Hitachi gel No. 3019 using methanol as an eluent was employed. Column chromatography was carried out on Kiesel-gel 60 (70—230 mesh, Merck). Elemental analyses were performed with a Yanaco CHN corder Model MT-5.

3′,6′-Bis(benzyloxy)-2′,4′-dimethoxychalcones (6) A mixture of 3,6-dihydroxy-2,4-dimethoxyacetophenone (**4**) (20 g), benzyl chloride (29 g), and anhydrous potassium carbonate (63 g) in *N*,*N*-dimethylformamide (60 ml) was heated with vigorous stirring at 160 °C for 10 min. The mixture was diluted with water and the excess of benzyl chloride was removed by steam distillation. The separated precipitate was collected and recrystallized from MeOH to give the dibenzyl ether **5**: mp 68—69 °C; yield, 32.4 g (88%). *Anal.* Calcd for $C_{24}H_{24}O_5$: C, 73.46; H, 6.16%. Found: C, 73.47; H, 6.21%.

A solution of **5** (2.5 g; 6.4 mmol) and substituted benzaldehyde (7.0 mmol) in EtOH (15—20 ml) was treated with KOH (1.8—1.9 g), and the mixture was warmed at 50 °C for 2—3 h. The solvent was evaporated under reduced pressure, and the residue was diluted with water, then extracted with EtOAc. The extract was recrystallized to give the chalcone **6** (Table 4).

6-Hydroxy-5,7-dimethoxyisoflavones (3) A solution of **6** (4.5 mmol) and $Tl(NO_3)_3 \cdot 3H_2O$ (2.6—2.7 g, 6.7—7.0 mmol) in $CHCl_3$–MeOH (1 : 4, 120 ml) was stirred at 30 °C for 24 h. The mixture was cooled, Na_2SO_3 (2.6 g) and 5% HCl (*ca.* 10 ml) were added and the whole was stirred at 0 °C for 1—2 h. After the precipitate formed had been filtered off, the filtrate was diluted with water and extracted with $CHCl_3$. The extract was washed with water, 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 **7** (**7a**, mp 100—102 °C from MeOH). The crude **7** was hydrogenolyzed with 10% Pd–C (0.5 g) in MeOH or MeOH–EtOAc (*ca.* 100 ml) at room temperature to give a crude hydroxyacetal **8** (**8a**, mp 116—117 °C from Et_2O–hexane; **8c**, mp 164—166 °C from EtOAc–MeOH; **8d**, mp 167—169 °C from MeOH; the others, oil).

A solution of the crude **8** in methanol (*ca.* 60 ml) was refluxed with aqueous 10% HCl (6 ml) for 1—2 h, diluted with water, and concentrated

Table 5. 6-Hydroxy-5,7-dimethoxyisoflavones (**3**), 6-Acetoxy-5,7-dimethoxyisoflavones (**A3**), and 6-Acetoxy-5-hydroxy-7-methoxyisoflavones (**9**)

Compd.	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Calcd (%)		Found (%)	
					C	H	C	H
3a	178—180	MeOH	66	$C_{18}H_{16}O_6$	65.85	4.91	65.81	4.94
3b	284—285	MeOH	68	$C_{17}H_{14}O_6$	64.97	4.49	65.18	4.55
3c	209—210	$CHCl_3$–MeOH	76	$C_{19}H_{18}O_7$	63.68	5.06	63.48	5.05
3d	202—204	MeOH	77	$C_{18}H_{16}O_7 \cdot H_2O$	59.67	5.01	59.95	4.94
3e	173—174	MeOH	74	$C_{18}H_{16}O_7$	62.79	4.68	62.83	4.63
3f	217—218	EtOH	72	$C_{17}H_{14}O_7$	61.82	4.27	62.04	4.33
A3a	212—213	$CHCl_3$–MeOH	92	$C_{20}H_{18}O_7$	64.86	4.90	64.93	4.90
A3b	232—234	Aq. MeOH	96	$C_{21}H_{18}O_8$	63.32	4.55	63.09	4.56
A3c	224—225	$CHCl_3$–MeOH	96	$C_{21}H_{20}O_8$	63.00	5.04	63.10	5.08
A3d	178—179	$CHCl_3$–MeOH	93	$C_{22}H_{20}O_9$	61.68	4.71	61.66	4.75
A3e	191—192	$CHCl_3$–MeOH	95	$C_{22}H_{20}O_9$	61.68	4.71	61.49	4.75
A3f	210—211	$CHCl_3$–MeOH	90	$C_{23}H_{20}O_{10}$	60.53	4.42	60.33	4.40
9a	174—175	$CHCl_3$–MeOH	87	$C_{19}H_{16}O_7$	64.04	4.53	64.15	4.52
9b	206—208	$CHCl_3$–MeOH	85	$C_{20}H_{16}O_8$	62.50	4.20	62.23	4.22
9c	185—186	$CHCl_3$–MeOH	92	$C_{20}H_{18}O_8$	62.18	4.70	61.99	4.73
9d	186—187	$CHCl_3$–MeOH	87	$C_{21}H_{18}O_9$	60.87	4.38	60.59	4.43
9e	183—185	$CHCl_3$–MeOH	83	$C_{21}H_{18}O_9$	60.87	4.38	60.68	4.34
9f	179—181	$CHCl_3$–MeOH	94	$C_{22}H_{18}O_{10}$	59.73	4.10	59.64	4.34

Table 6. 5,6,7-Trihydroxyisoflavones (**1**) and 5,6-Dihydroxy-7-methoxyisoflavones (**2**)

Compd.	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Calcd (%)		Found (%)	
					C	H	C	H
1a	210—211	Aq. MeOH	72	$C_{16}H_{12}O_6 \cdot H_2O$	60.38	4.43	60.37	4.46
1b	276—278	Aq. MeOH	70	$C_{15}H_{10}O_6 \cdot 1/2H_2O$	61.02	3.76	61.17	3.82
1c	262—264	MeOH	60	$C_{17}H_{14}O_7$	61.82	4.27	61.56	4.41
1d	209—211	MeOH	60	$C_{16}H_{12}O_7 \cdot 1/2H_2O$	59.08	4.03	59.21	3.90
1e	245—246	Aq. MeOH	65	$C_{16}H_{12}O_7$	60.75	3.83	60.54	3.83
1f	275—276	Aq. MeOH	55	$C_{15}H_{10}O_7 \cdot 3/4H_2O$	57.06	3.67	56.78	3.79
2a	220—221	MeOH	90	$C_{17}H_{14}O_6$	64.97	4.49	64.81	4.49
2b	269—271	MeOH	80	$C_{16}H_{12}O_6$	64.00	4.03	63.82	4.05
2c	186—187	MeOH	97	$C_{18}H_{16}O_7$	62.79	4.68	62.75	4.61
2d	225—227	MeOH	98	$C_{17}H_{14}O_7 \cdot H_2O$	58.62	4.63	58.79	4.80
2e	234—236	MeOH	91	$C_{17}H_{14}O_7$	61.82	4.27	61.59	4.37
2f	250—251	MeOH	87	$C_{16}H_{12}O_7$	60.76	3.82	60.57	3.92

Table 7. 5,6,7-Triacetoxyisoflavones (**A1**) and 5,6-Diacetoxy-7-methoxyisoflavones (**A2**)

Compd.	mp (°C)	Recrystn. solvent	Formula	Calcd (%)		Found (%)	
				C	H	C	H
A1a	174—175	$CHCl_3$–MeOH	$C_{22}H_{18}O_9$	61.97	4.26	61.70	4.27
A1b	224—226	$CHCl_3$–MeOH	$C_{23}H_{18}O_{10}$	60.80	3.99	61.00	3.97
A1c	116[a]	MeOH	$C_{23}H_{20}O_{10} \cdot 3/2H_2O$	58.79	4.61	58.70	4.58
A1d	203—205	EtOAc	$C_{24}H_{20}O_{11}$	59.51	4.16	59.27	4.16
A1e	197—198	EtOAc	$C_{24}H_{20}O_{11}$	59.51	4.16	59.30	4.07
A1f	145—148	$CHCl_3$–MeOH	$C_{25}H_{20}O_{12}$	58.60	3.93	58.45	3.94
A2a	214—216	$CHCl_3$–MeOH	$C_{21}H_{18}O_8$	63.32	4.55	63.17	4.55
A2b	192—194	$CHCl_3$–MeOH	$C_{22}H_{18}O_9$	61.97	4.20	61.99	4.26
A2c	197—199	$CHCl_3$–MeOH	$C_{22}H_{20}O_9$	61.68	4.71	61.71	4.77
A2d	192—193	MeOH	$C_{23}H_{20}O_{10}$	60.52	4.42	60.37	4.48
A2e	217—219	$CHCl_3$–MeOH	$C_{23}H_{20}O_{10}$	60.52	4.42	60.28	4.41
A2f	204—205	MeOH	$C_{24}H_{20}O_{11}$	59.50	4.16	59.49	4.22

a) Sintered at 85 °C.

under reduced pressure. The separated crystals were collected and recrystallized to give **3** (Table 5).

The isoflavones **3** were quantitatively converted into the acetates (**A3**) with hot acetic anydride–pyridine (Table 5).

5,6-Dihydroxy-7-methoxyisoflavones (2) and Their Acetates (9 and A2) To a cooled solution or suspension of the 6-acetoxyisoflavone (**A3**) (0.5 mmol) in MeCN (4.0 ml) was added 10% (w/v) anhydrous $AlBr_3$–MeCN (4.0 ml) with stirring. The mixture was allowed to stand

at 0 °C for 45 min, then diluted with aqueous 2—3% HCl and warmed at 50—60 °C for 15—20 min. The separated precipitate was collected and recrystallized to give **9** (Table 5). A solution of **9** in aqueous 15% HCl–MeOH (1 : 10) was refluxed for 2—3 h to give **2** (Table 6). The isoflavone **2** or **9** was easily converted into the acetate (A**2**) with hot acetic anhydride–pyridine (Table 7).

5,6,7-Trihydroxyisoflavones (1) The isoflavone A**3** (1.2 mmol) was dissolved in 30% (w/v) anhydrous $AlCl_3$–MeCN (12.0 ml). The solution was heated at 70 °C for 36—48 h, then diluted with aqueous 2—3% HCl, and warmed at 50—60 °C for 30—40 min. The separated precipitate was collected and purified by preparative HPLC to give **1** (Table 6), which was converted into the triacetate A**1** (Table 7).

The isoflavone **1a** was also synthesized from **3a** (400 mg) by demethylation with 10% (w/v) anhydrous $AlBr_3$–MeCN (16 ml) at 70 °C for 15 h.

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