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SYNTHESIS OF 5,8-DIHYDROXY-6,7-DIMETHOXYFLAVONES AND REVISED STRUCTURES FOR SOME NATURAL FLAVONES*

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Key Word Index—*Scutellaria baicalensis*; Labiatae; *Helichrysum* species; *Gnaphalium gaudichaudianum*; Compositae; revised structures; pedunculin; 5,8-dihydroxy-6,7-dimethoxyflavones; 5,6-dihydroxy-7,8-dimethoxyflavones; 5,7-dihydroxy-6,8-dimethoxyflavones.

Abstract—Six 5,8-dihydroxy-6,7-dimethoxyflavones and three 8-hydroxy-5,6,7-trimethoxyflavones were synthesized from 2′,5′-dihydroxy-3′,4′,6′-trimethoxyacetophenone by adapting the selective *O*-alkylation and dealkylation, and the differentiation between the flavones and their isomeric 6-hydroxyflavones was clarified by ^{1}H NMR and UV spectra. Four natural flavones proposed as 5,8-dihydroxy-6,7-dimethoxyflavones, must have other structures and three are shown to be the isomeric 5,7-dihydroxy-6,8-dimethoxyflavones. A flavone, isolated from *Ageratum conyzoides*, is correctly identified as 8-hydroxy-5,6,7,3′,4′,5′-hexamethoxyflavone, but the structure of a flavone, isolated from *Helichrysum*, is revised to the isomeric 7-hydroxy-5,6,8-trimethoxyflavone.

INTRODUCTION

We have been studying the selective *O*-alkylation and dealkylation of flavonoids to establish new, convenient methods for synthesizing polyhydroxyflavones [1] and have reported some revised structures of natural flavones [2, 3]. Naturally occurring 5,8-dihydroxy-6,7-dimethoxyflavones (**1**) and 8-hydroxy-5,6,7-trimethoxyflavones (**2**) can be synthesized from 2′,5′-dihydroxy-3′,4′,6′-trimethoxyacetophenone by adapting the selective *O*-alkylation and dealkylation. The differentiation between the 5,8-dihydroxyflavones **1** and 5,6-dihydroxy-7,8-dimethoxyflavones (**3**) is difficult by NMR techniques [4, 5] and Barberán *et al.* have proposed a technique for the elucidation of these flavones by means of chromatographic and UV spectrometric comparisons between the flavone and its isomer obtained by acidic treatment (Wessely–Moser rearrangement) [6–8]. The properties for the 5,8-dihydroxyflavones, however, are not always clear because of lack of synthetic evidence and the structures of some natural flavones are still in doubt. Hence, we established an unambiguous method for synthesizing 8-hydroxyflavones, **1** and **2**, and differentiating between the flavones and their isomers, **3** and 6-hydroxy-5,7,8-trimethoxyflavones (**4**), and propose revised structures for a few natural flavones, which were assumed to be 8-hydroxyflavone derivatives.

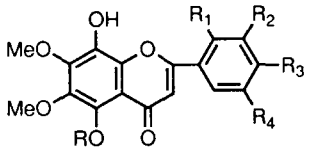
*17 in the series: 'Studies of the selective *O*-alkylation and dealkylation of flavonoids'. For Part 16 see ref. [1].

RESULTS AND DISCUSSION

Synthesis of 5,8-dihydroxy-6,7-dimethoxyflavones (**1**) *and 8-hydroxy-5,6,7-trimethoxyflavones* (**2**)

In a previous paper, we reported that cleavage of the 2′-alkoxy group in acetophenones is greatly affected by the steric factor between the alkoxy group and the reagent, and the 2′-methoxy group in 6′-isopropoxy-2′,4′-dimethoxyacetophenone is selectively cleaved with anhydrous aluminium bromide in acetonitrile [1]. This result shows that the 6′-methoxy group in the diisopropyl ether (**6**) of 2′,5′-dihydroxy-3′,4′,6′-trimethoxyacetophenone (**5**) is selectively cleaved with anhydrous aluminum bromide in acetonitrile. Actually, the demethylation of the diisopropyl ether **6** proceeded smoothly to give 2′-hydroxy-3′,6′-diisopropoxy-4′,5′-dimethoxyacetophenone (**7**) in high yield. The 2′-methoxy group in 3′-benzyloxy-6′-isopropoxy-2′,4′,5′-trimethoxyacetophenone (**9**) derived from the monobenzyl ether (**8**) of **5** was also selectively cleaved, without cleavage of the 3′-benzyloxy group, under similar conditions to give 3′-benzyloxy-2′-hydroxy-6′-isopropoxy-4′,5′-dimethoxyacetophenone (**10**) (Scheme 1).

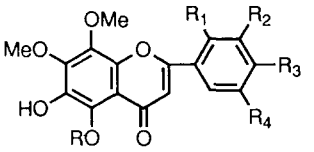
The acetophenone (**7**) was converted into 5,8-diisopropoxy-6,7,4′-trimethoxyflavone (**12b**) via the diketone **11b**. The 5-isopropoxy group in **12b** was easily cleaved with anhydrous aluminium chloride in acetonitrile to give 5-hydroxy-8-isopropoxy-6,7,4′-trimethoxyflavone, but the 8-isopropoxy group was hardly cleaved under mild conditions. This result shows that the 3′-benz-



1 R=H **2** R=Me

A1 Acetate of **1**

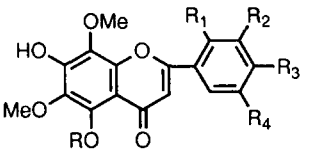
A2 Acetate of **2**



3 R=H **4** R=Me

A3 Acetate of **3**

A4 Acetate of **4**

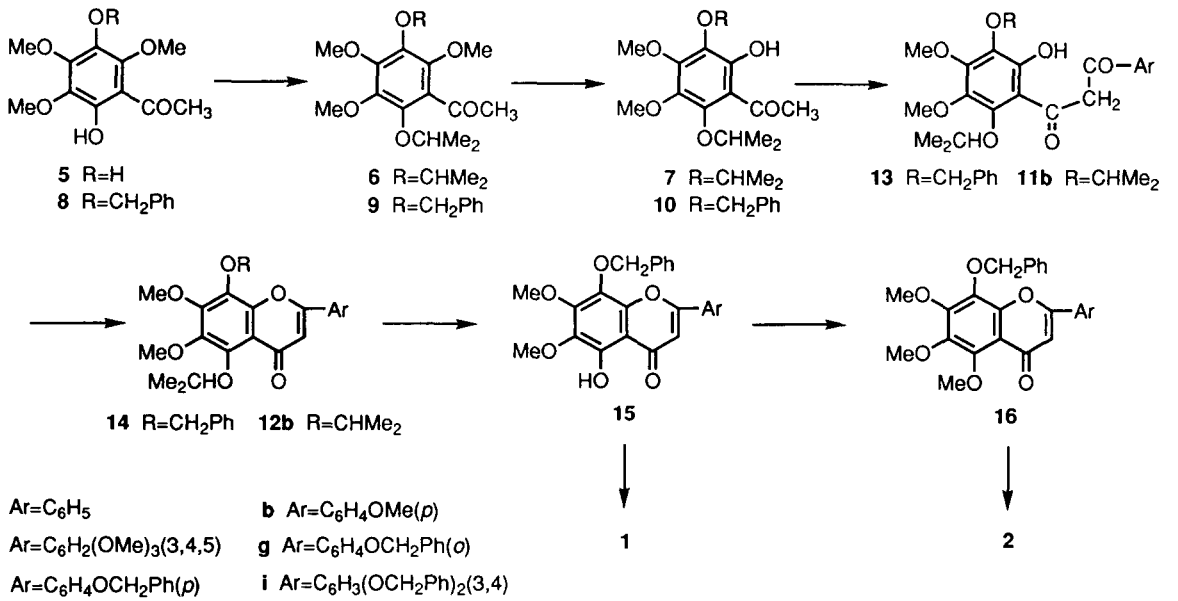


17 R=H

18 R=Me

a $R_1=R_2=R_3=R_4=H$ **b** $R_1=R_2=R_4=H$, $R_3=OMe$ **c** $R_1=H$, $R_2=R_3=R_4=OMe$

d $R_1=OH$, $R_2=R_3=R_4=H$ **e** $R_1=R_2=R_4=H$, $R_3=OH$ **f** $R_1=R_4=H$, $R_2=R_3=OH$



5 R=H
8 R=CH_2Ph

6 R=$CHMe_2$
9 R=CH_2Ph

7 R=$CHMe_2$
10 R=CH_2Ph

13 R=CH_2Ph **11b** R=$CHMe_2$

14 R=CH_2Ph **12b** R=$CHMe_2$

15

16

a Ar=C_6H_5 **b** Ar=$C_6H_4OMe(p)$

c Ar=$C_6H_2(OMe)_3(3,4,5)$ **g** Ar=$C_6H_4OCH_2Ph(o)$

h Ar=$C_6H_4OCH_2Ph(p)$ **i** Ar=$C_6H_3(OCH_2Ph)_2(3,4)$

Scheme 1

yloxyacetophenone, **10**, is more suitable than **7** as the starting material for synthesis of **1** and **2**.

The benzoates of the acetophenone **10** were converted into the corresponding oily diketones (**13**) by the Baker–Venkataraman transformation with potassium hydroxide in pyridine. In the reaction, only the crude 2-benzyloxybenzoate of **10** was transformed with anhydrous potassium carbonate in boiling acetone, since the transformation of the benzoate was accompanied by many by-products. The diketones **13** were easily cyclized with sulphuric acid in acetic acid to give 8-benzyloxy-5-isopropoxy-6,7-dimethoxyflavones (**14**). The 5-isopropoxy group in **14a** was selectively cleaved with anhydrous aluminium chloride in acetonitrile without the cleavage of the 8-benzyloxy group to give quantitatively the corresponding 5-hydroxyflavones (**15a**), which led to methyl ethers (**16a**). Hydrogenolysis of the benzyloxyflavones **15a** and **16a** afforded quantitatively the desired flavones **1a** and **2a**, respectively. The method was useful as an unambiguous one for synthesizing **1** and **2**, and the 5,8-dihydroxyflavones (**1a**–**1f**) and 8-hydroxyflavones (**2a**–**2c**) were synthesized by this method. These flavones **1** and **2** were converted into the corresponding acetates **A1** and **A2**. The flavone **1b** corresponds to the one synthesized from 5,6,7,8,4′-pentamethoxyflavone by oxidative demethylation with nitric acid by Chaliha *et al.* [9], but the melting points differ.

The flavones **3** and **4**, isomers of **1** and **2**, were synthesized from the 5-benzyl **8** [10] or the methoxymethyl ether of **5** by a similar method to that described above.

Differentiation between the 8*-hydroxyflavones,* **1** *and* **2**, *and their isomers,* **3** *and* **4**

The UV spectra for the 8-hydroxyflavones with no free hydroxy group at the B ring in methanol have a tendency to fuse the bands I and II, and exhibit, characteristically, an aggregated band, or two bands I and II which are flatter than those of the corresponding 6-hydroxyflavones (Table 1). The same effect was apparent in the

Table 1. UV spectral data for 5,8-dihydroxy-6,7-dimethoxyflavones (**1**), 8-hydroxy-5,6,7-trimethoxyflavones (**2**) and their isomers (**3** and **4**)*

Compound	λ_{max} nm (log ε)		
	MeOH	MeOH–$AlCl_3$	MeOH–NaOAc
1a	286 (4.50) 370 (3.44)	311 (4.48) 445 (3.48)	290 (4.41)
3a	284 (4.51) 317i (4.06)	300 (4.44) 344 (4.15)	284 (4.44) 310i (4.19)
1b	306 (4.46) 328sh (4.32)	325 (4.48) 356 (4.40) 430 (3.59)	315 (4.48)
3b	298 (4.43) 332 (4.38)	313 (4.41) 361 (4.46)	301 (4.42) 325 (4.37)
1c	300 (4.36) 331i (4.21)	326 (4.36) 455 (4.26)	311 (4.39)
3c	297 (4.37) 333 (4.31)	316 (4.34) 364 (4.37)	303 (4.37) 327 (4.35)
1d	282 (4.45) 332 (4.12)	291 (4.36) 302 (4.36) 359 (4.27) 433 (3.59)	283 (4.34) 322sh (4.05) 398 (3.73)
3d	281 (4.42) 337 (4.20)	291 (4.38) 362 (4.30) 425sh (3.48)	283 (4.35) 333 (4.07) 400 (3.82)
1e	306 (4.37) 330 (4.28)	295sh (4.11) 324 (4.39) 360 (4.38) 415 (3.66)	315 (4.25) 385 (4.30)
3e	298 (4.36) 335 (4.37)	313 (4.36) 365 (4.45)	298 (4.23) 340 (4.21) 386 (4.26)
1f	256 (4.09) 288 (4.23) 346 (4.27)	278–285 (4.19) 317 (4.13) 434 (4.36)	282 (4.13) 340 (4.13) 404 (4.16)
3f	256 (4.12) 291 (4.29) 351 (4.37)	276 (4.17) 310 (4.21) 435 (4.46)	285 (4.18) 403 (4.27)
2a	276 (4.56)		286 (4.52)
4a	276 (4.51) 308 (4.16)		277.5 (4.47) 300i (4.27)
2b	278 (4.36) 294sh (4.35) 322 (4.50)		307 (4.53)
4b	283 (4.37) 324 (4.43)		295sh (4.38) 314 (4.42)
2c	280 (4.33) 322 (4.30)		304 (4.47)
4c	285 (4.31) 325 (4.37)		295i (4.34) 314 (4.40)

*sh, shoulder; i, inflection point.

spectra upon addition of aluminium chloride. In particular the UV spectra for 6- and 8-hydroxyflavones shifted characteristically upon addition of sodium acetate, albeit the flavones have no hydroxy group at the 7-position and the bands for the 8-hydroxyflavones (**1a**–**1c** and **2a**–**2c**) with no hydroxy group at the B ring were observed as an aggregated band, in contrast to those for the 6-hydroxyflavones (**3a**–**3c** and **4a**–**4c**). These phenomena can only be used for differentiation between the two isomers that lack a free hydroxy group in the B ring.

In the ^{1}H NMR spectra for the hydroxyflavones in $CDCl_3$, the methoxyl signals at the 7-position were exhibited at a fairly low field in the range δ4.12–4.16 and can be used to distinguish from the isomeric 7-hydroxyflavones, as shown in Table 2. Although the difference between the 6- and 7-methoxyl signals was similar to that between the 7- and 8-methoxyls, the 6-methoxyl group was more affected than the 8-methoxyl group by the solvent, and the difference ($\Delta\delta$0.11–0.16) between the 6- and 7-methoxyl signals was larger than that ($\Delta\delta$0.02–0.06) between the 7- and 8-methoxyl, when the spectra were measured in DMSO-d_6: the chemical shifts and differences may be used for differentiation.

These phenomena were also observed in the ^{1}H NMR spectra for the acetate, in $CDCl_3$ (Table 3). When the spectra were measured in benzene-d_6, however, the methoxyl groups were greatly affected by the solvent and exhibited characteristic spectral patterns corresponding to the respective 8- and 6-acetoxy isomers (Table 3). That is, the 7-methoxyl signals in the 5,8-diacetoxy isomers (**A1**) were seen at a range of δ3.58–3.64, at lower field than those (δ3.32–3.44) in the 5,6-diacetoxy isomers (**A3**), and the difference ($\Delta\delta$0.08–0.09) between the 6- and 7-methoxyl signals was much smaller than that ($\Delta\delta$0.31–0.39) between the 7- and 8-methoxyl signals. Similar phenomena were observed in the spectra for the 8- (**A2**) and 6-acetoxy-5-methoxyflavones (**A4**). The results showed that the 8-hydroxyflavones (**1** and **2**) were clearly distinguished from the 6-hydroxyflavones (**3** and **4**) by comparing the characteristic properties of their acetates.

Identification and revised structures of some natural flavones

Two natural flavones, isolated from *Helichrysum* sp., have been proposed as **1a** and **2a** on the basis of the spectral data reported by Bohlmann *et al.* [11]. Furthermore, a natural flavone, which is identical with the former flavone **1a**, has also been isolated from *Scutellaria baicalensis* Georgi [12] and *Gnaphalium gaudichaudianum* [13]. The spectral data for the two natural flavones, however, are not compatible with those for the synthetic flavones **1a** and **2a** (Tables 4 and 5). The ^{1}H NMR data for the natural flavones exhibit no 7-methoxyl signal (δ4.12–4.15) and the UV spectra are shifted bathochromically upon addition of sodium acetate. This behaviour shows that the structures of the two natural flavones are 5,7-dihydroxy-6,8-dimethoxyflavone (**17a**) and 7-hydroxy-5,6,8-trimethoxyflavone (**18a**), isomers of **1a** and **2a**. Therefore, the flavones **17a** and **18a** were synthesized by a method described by Lee and Tan [14] and compared with the natural flavones. The mp, UV, ^{1}H NMR and ^{13}C NMR data for the natural flavones were completely consistent with the synthetic compounds (Tables 4 and 5). Thus, the two natural flavones must be revised to **17a** and **18a**, respectively.

Table 2. ^{1}H NMR data for 8-hydroxy-5,6,7-trioxygenated flavones (**1** and **2**) and 6-hydroxy-5,7,8-trioxygenated flavones (**3** and **4**)*

		OMe						Arom. H			
Compound	Solvent	3′,5′-	4′-	5-	6-	7-	8-	3-	2′- 6′-	3′- 5′- 4′	5-OH
1a	$CDCl_3$	—	—	—	3.98	4.15	—	6.68 *s*	7.92–7.97 *m* (2H)	7.51–7.58 *m* (3H)	12.24 *br s*
3a	$CDCl_3$	—	—	—	—	4.15	4.00	6.70 *s*	7.93–7.96 *m* (2H)	7.52–7.59 *m* (3H)	
2a	$CDCl_3$	—	—	3.93	3.99	4.13	—	6.82 *s*	7.94–7.96 *m* (2H)	7.50–7.54 *m* (3H)	—
4a	$CDCl_3$	—	—	4.00	—	4.16	4.05	6.86 *s*	7.94–7.96 *m* (2H)	7.52–7.55 *m* (3H)	—
1b	$CDCl_3$	—	3.89	—	3.98	4.14	—	6.58 *s*	7.91 *d* (2H)	7.02 *d* (2H) —	12.34 *s*
3b	$CDCl_3$	—	3.90	—	—	4.14	4.00	6.61 *s*	7.90 *d* (2H)	7.04 *d* (2H) —	
2b	$CDCl_3$	—	3.89	3.92	3.98	4.12	—	6.65 *s*	7.89 *d* (2H)	7.02 *d* (2H) —	—
4b	$CDCl_3$	—	3.89	4.00	—	4.14	4.04	6.62 *s*	7.88 *d* (2H)	7.03 *d* (2H) —	—
1c	$CDCl_3$	3.96	3.93	—	3.98	4.14	—	6.61 *s*	7.17 *s* (2H)	— — —	
3c	$CDCl_3$	3.96	3.94	—	—	4.15	4.00	6.64 *s*	7.17 *s* (2H)	— — —	
2c	$CDCl_3$	3.95	3.92	3.99	3.93	4.12	—	6.62 *s*	7.15 *s* (2H)	— — —	—
4c	$CDCl_3$	3.96	3.94	4.00	—	4.16	4.05	6.80 *s*	7.18 *s* (2H)	— — —	—
1a	DMSO	—	—	—	3.84	3.95	—	7.04 *s*	8.17–8.19 *m* (2H)	7.56–7.64 *m* (3H)	12.30 *s*
3a	DMSO	—	—	—	—	3.97	3.93	7.04 *s*	8.08–8.10 *m* (2H)	7.60–7.65 *m* (3H)	12.37 *s*
1b	DMSO	—	3.83	—	3.87	3.95	—	6.93 *s*	8.14 *d* (2H)	7.14 *d* (2H) —	12.41 *s*
3b	DMSO	—	3.87	—	—	3.96	3.92	6.93 *s*	8.05 *d* (2H)	7.16 *d* (2H) —	12.48 *s*
1c	DMSO	3.91	3.76	—	3.83	3.95	—	7.14 *s*	7.45 *s* (2H)	— — —	12.33 *s*
3c	DMSO	3.91	3.77	—	—	3.97	3.95	7.15 *s*	7.37 *s* (2H)	— — —	12.37 *s*
1d	DMSO	—	—	—	3.83	3.94	—	7.15 *s*	— 8.04 *dd*	7.07 *br d* 7.07 *br t* 7.42 *td*	12.36 *s*
3d	DMSO	—	—	—	—	3.96	3.90	7.09 *s*	— 7.87 *dd*	7.08 *br t* 7.05 *br t* 7.43 *td*	12.43 *s*
1e	DMSO	—	—	—	3.82	3.94	—	6.84 *s*	8.03 *d* (2H)	6.94 *d* (2H) —	12.45 *s*
3e	DMSO	—	—	—	—	3.95	3.92	6.84 *s*	7.94 *d* (2H)	6.96 *d* (2H) —	12.52 *s*
1f	DMSO	—	—	—	3.83	3.94	—	6.73 *s*	7.52 *br s* 7.51 *dd*	— 6.90 *d* —	12.48 *s*
3f	DMSO	—	—	—	—	3.95	3.93	6.73 *s*	7.46 *br s* 7.45 *dd*	— 6.91 *d* —	12.54 *s*

*s, Singlet; *br s*, broad singlet; *d*, doublet (J = 8.8 Hz); *dd*, double doublet (J = 8.0, 2.0 Hz); *br d*, broad doublet (J = 8.0 Hz); *br t*, broad triplet (J = 8.0 Hz); *td*, triplet doublet (J = 8.0, 2.0 Hz).

Table 3. ^{1}H NMR data for acetates (**A1**, **A2**, **A3** and **A4**) of 8-hydroxyflavones (**1** and **2**) and 6-hydroxyflavones (**3** and **4**) in $CDCl_3$ and C_6D_6*

		OAc				OMe						Arom. H		
Compound	Solvent	5-	6-	8-	others	3',5'-	4'-	5-	6-	7-	8-	3-	2'- 6'-	3'- 5'- 4'
A1a	$CDCl_3$	2.492		2.489	—	—	—	—	3.90	4.05	—	6.60 *s*	7.76–7.78 *m*	7.48–7.56 *m*
A3a	$CDCl_3$	2.44	2.37		—	—	—	—	—	4.08	4.06	6.65 *s*	7.90–7.92 *m*	7.51–7.56 *m*
A1b	$CDCl_3$	2.49		2.49	—	—	3.89	—	3.90	4.04	—	6.51 *s*	7.72 *d*	7.01 *d* —
A3b	$CDCl_3$	2.43	2.36		—	—	3.89	—	—	4.07	4.05	6.57 *s*	7.86 *d*	7.03 *d* —
A1c	$CDCl_3$	2.49		2.46	—	3.93	3.90	—	3.92	4.05	—	6.53 *s*	6.99 *s*	— —
A3c	$CDCl_3$	2.44	2.37		—	3.96	3.94	—	—	4.08	4.06	6.59 *s*	7.14 *s*	— —
A2a	$CDCl_3$	—		2.48	—	—	—	3.99	3.96	4.05	—	6.66 *s*	7.77–7.80 *m*	7.48–7.55 *m*
A4a	$CDCl_3$	—	2.40		—	—	—	3.91	—	4.07	4.04	6.78 *s*	7.93–7.95 *m*	7.51–7.56 *m*
A2b	$CDCl_3$	—		2.49	—	—	3.89	3.96	3.98	4.05	—	6.57 *s*	7.73 *d*	7.01 *d* —
A4b	$CDCl_3$	—	2.40		—	—	3.896	3.902	—	4.06	4.03	6.63 *s*	7.88 *d*	7.04 *d* —
A2c	$CDCl_3$	—		2.46	—	3.94	3.92	3.99	3.97	4.05	—	6.60 *s*	7.02 *s*	— —
A4c	$CDCl_3$	—	2.40		—	3.96	3.94	3.91	—	4.07	4.04	6.69 *s*	7.17 *s*	— —
A1a	C_6D_6	2.35		1.94	—	—	—	—	3.70	3.61	—	6.34 *s*	7.32–7.35 *m*	6.96–7.04 *m*
A3a	C_6D_6	2.34	1.90		—	—	—	—	—	3.40	3.75	6.47 *s*	7.45–7.48 *m*	7.00–7.04 *m*
A1b	C_6D_6	2.36		1.98	—	—	3.20	—	3.71	3.62	—	6.35 *s*	7.33 *d*	6.61 *d* —
A3b	C_6D_6	2.36	1.90		—	—	3.21	—	—	3.44	3.76	6.48 *s*	7.46 *d*	6.62 *d* —
A1c	C_6D_6	2.35		1.90	—	3.33	3.82	—	3.72	3.63	—	6.47 *s*	6.72 *s*	— —
A3c	C_6D_6	2.35	1.91		—	3.35	3.82	—	—	3.43	3.78	6.60 *s*	6.86 *s*	— —
A1d	C_6D_6	2.31		1.98	1.78	—	—	—	3.66	3.58	—	6.27 *s*	7.00 *dd*	6.86 *br d* 6.73 *td* 6.94 *td*
A3d	C_6D_6	2.31	1.88		1.77	—	—	—	—	3.32	3.71	6.50 *s*	7.31 *dd*	6.88 *br d* 6.82 *td* 6.96 *td*
A1e	C_6D_6	2.35		1.93	1.71	—	—	—	3.70	3.61	—	6.28 *s*	7.27 *d*	6.93 *d* —
A3e	C_6D_6	2.35	1.90		1.71	—	—	—	—	3.40	3.75	6.41 *s*	7.41 *d*	6.97 *d* —
A1f	C_6D_6	2.35		2.08	1.75 1.75	—	—	—	3.70	3.61	—	6.21 *s*	7.45 *d'* 6.95 *dd*	— 6.91 *d* —
A3f	C_6D_6	2.34	1.89		1.74 1.76	—	—	—	—	3.43	3.74	6.35 *s*	7.56 *d'* †	— 7.00 *d* —
A2a	C_6D_6	—		1.98	—	—	—	3.96	3.79	3.63	—	6.49 *s*	7.44–7.47 *m*	7.00–7.05 *m*
A4a	C_6D_6	—	1.93		—	—	—	4.05	—	3.49	3.78	6.57 *s*	7.56–7.59 *m*	7.04–7.07 *m*
A2b	C_6D_6	—		2.02	—	—	3.21	3.99	3.81	3.64	—	6.50 *s*	7.45 *d*	6.64 *d* —
A4b	C_6D_6	—	1.94		—	—	3.21	4.08	—	3.54	3.79	6.58 *s*	7.57 *d*	6.65 *d* —
A2c	C_6D_6	—		1.95	—	3.34	3.83	3.99	3.82	3.64	—	6.62 *s*	6.84 *s*	— —
A4c	C_6D_6	—	1.95		—	3.37	3.83	4.09	—	3.53	3.81	6.70 *s*	6.97 *s*	— —

*s, Singlet; *br s*, broad singlet; *d*, doublet (J = 8.8 Hz); *dd*, double doublet (J = 8.0, 2.0 Hz); *br d*, broad doublet (J = 8.0 Hz); *td*, triplet doublet (J = 8.0, 2.0 Hz).
†Overlapped with the aromatic proton signals of benzene.

Table 4. Comparisons of natural flavones with synthetic and isomeric flavones

	Synthetic	Natural	Isomeric*
5,8-Dihydroxy-6,7-dimethoxyflavone (**1a**) [11–13]			**17a** [14]
Mp (°)	180–182	232 [11]; 235–236 [12]	229–231; 235–237 [14]
^{1}H NMR in $CDCl_3$	3.98 *s*, 4.15 *s*, 6.68 *s*, 12.24 *br s*	4.03 *s*, 4.05 *s*, 6.69 *s*, 12.71 *s* [11]	4.03 *s*, 4.05 *s*, 6.68 *s*
in DMSO	3.84 *s*, 3.95 *s*, 7.04 *s*, 12.30 *s*	3.77 *s*, 3.87 *s*, 6.95 *s*, 12.60 *br s* [12]	3.78 *s*, 3.88 *s*, 7.00 *s*, 12.68 *s*
UV: λ_{max} nm MeOH		269 318 [11]	
MeOH	286 370 (weak)	250sh 279 322 [12]	251i (4.11) 278 (4.49) 321 (4.04)
+ $AlCl_3$	311 445 (weak)	255sh 295 347 [12]	256 (4.06) 297 (4.44) 343 (4.12) 408 (3.58)
+ NaOAc	290	270 286sh 375 [12]	270 (4.42) 283 (4.41) 375 (4.00)
Diacetate		**A1a**	**A17a**
Mp (°)	170–171	oil [11]	165–166.5
^{1}H NMR in $CDCl_3$	2.48 *s*, 2.49 *s*, 3.90 *s*, 4.05 *s*, 6.60 *s*	2.43 *s*, 2.48 *s*, 3.88 *s*, 4.06 *s*, 6.66 *s*	2.44 *s*, 2.48 *s*, 3.87 *s*, 4.05 *s*, 6.66 *s*
8-Hydroxy-5,6,7-trimethoxyflavone (**2a**) [11]			**18a** [14]
Mp (°)	199–200	oil	182–183 186–188 [14]
^{1}H NMR in $CDCl_3$	3.93 *s*, 3.99 *s*, 4.13 *s*, 6.82 *s*	3.96 *s*, 4.03 *s*, 4.07 *s*, 6.70 *s*	3.96 *s*, 4.05 *s*, 4.08 *s*, 6.88 *s*
Acetate		**A2a**	**A18a**
Mp (°)	157–158	oil	125–127
^{1}H NMR in $CDCl_3$	2.48 *s*, 3.97 *s*, 3.99 *s*, 4.05 *s*, 6.66 *s*	2.43 *s*, 3.94 *s*, 3.96 *s*, 4.06 *s*, 6.73 *s*	2.44 *s*, 3.94 *s*, 3.96 *s*, 4.02 *s*, 6.74 *s*
5,8-Dihydroxy-6,7,4′-trimethoxyflavone (pedunculin) (**1b**) [15]			**17b** [16, 17]
^{1}H NMR in $CDCl_3$	3.89 *s*, 3.98 *s*, 4.14 *s*, 6.58 *s*, 7.02 *d*, 7.91 *d*	3.89 *s*, 4.01 *s*, 4.04 *s*, 6.75 *s*, 7.02 *d*, 7.88 *d*	3.90 *s*, 4.02 *s*, 4.05 *s*, 6.59 *s*, 7.04 *d*, 7.90 *d*
UV: λ_{max} nm MeOH	306 328sh	282 332	286 (4.33) 331 (4.29)
+ $AlCl_3$	325 356sh 430	288 312 358 390sh	263 (3.69) 311 (4.38) 356 (4.33) 403i (3.87)
+ NaOAc	315	282 374	283 (4.43) 298i (4.36) 373 (4.11)
5,8,2′-Trihydroxy-6,7-dimethoxyflavones (**1d**) [18]			**17d**
Mp (°)	267–270 decomp.	282–283	267–268 decomp.
^{1}H NMR in DMSO	3.83 *s*, 3.94 *s*, 7.15 *s*, 12.36 *s*	3.83 *s*, 3.90 *s*, 7.08 *s*, 12.76 *s*	3.78 *s*, 3.84 *s*, 7.07 *s*, 12.74 *s*
UV: λ_{max} nm MeOH	282 (4.45) 332 (4.12)	277 (4.42) 338 (4.19)	275 (4.40) 337 (4.18)
+ $AlCl_3$	250sh (4.00) 291 (4.36) 302 (4.36) 359 (4.27) 4.33 (3.59)	257 (4.08) 290 (4.39) 360 (4.24)	256 (4.05) 289 (4.38) 358 (4.24)
+ NaOAc	283 (4.34) 323sh (4.05) 398 (3.73)	276 (4.39) 349 (4.06)	268 (4.34) 279sh (4.34) 380 (4.07)
8-Hydroxy-5,6,7,3′,4′,5′-hexamethoxyflavone (**2c**) [19]			**4c**
^{1}H NMR in $CDCl_3$	3.92 *s*, 3.93 *s*, 3.95 *s* (6H), 3.99 *s*, 4.12 *s*, 5.73 *s* (OH), 6.62 *s*, 7.16 *s*	3.92 *s*, 3.93 *s*, 3.95 *s* (6H), 3.98 *s*, 4.12 *s*, 5.70 *br s* (OH), 6.61 *s*, 7.16 *s*	3.94 *s*, 3.96 *s* (6H), 4.01 *s*, 4.05 *s*, 4.16 *s*, 6.80 *s*, 7.18 *s*
UV: λ_{max} nm MeOH	281 323	290 310	285 325
+ NaOAc	304	290 305	295i 314
5,8,3′,4′-Tetrahydroxy-6,7-dimethoxyflavone (**1f**) [6]			**3f**
UV: λ_{max} nm MeOH	256 288 346	254 285 298sh 341	256 291 351
+ $AlCl_3$	278–285 317 434	275 314 432	276 310 435
+ NaOAc	282 340 404	275 336 395	285 403
EIMS: 70 eV	346 (89; M^+) 345 (9) 332 (18)	346 (32; M^+) 345 (4) 332 (9)	346 (53; M^+) 345 (4) 332 (18)
m/z (rel. int.)	331 (100) 313 (23) 197 (48)	331 (41) 313 (14) 213 (7) 197 (100)	331 (100) 313 (23) 197 (48)
	169 (19) 137 (9)	185 (23) 183 (27) 169 (68) 137 (55)	169 (14) 137 (6)
	135 (16) 134 (13)	134 (89) 109 (41)	135 (12) 134 (9)

Table 5. ^{13}C NMR data for 5,6,7,8-tetraoxygenated flavones in DMSO-d_6

Carbon No.	**1a**	Natural [12]	**17a**	**3a**	**1d**	Natural [18]	**17d**	**3d**
2	163.5	163.4	162.9	163.5	161.5	161.5	161.2	161.6
3	104.6	104.9	104.6	104.6	108.6	108.7	108.6	108.5
4	183.0	182.6	182.4	183.0	183.0	182.4	182.5	182.7
5	144.6	145.8	145.5	144.6	144.5	145.6	145.6	142.9
6	128.4	132.1	132.0	136.2	130.6	131.7	131.5	134.0
7	141.4	151.3	151.1	141.4	141.5	150.8	151.0	142.0
8	136.2	128.5	128.0	130.7	136.0	128.2	127.9	132.9
9	148.2	148.5	148.3	148.2	148.0	148.2	148.3	148.1
10	106.5	103.6	103.1	106.5	106.3	103.2	103.0	106.0
1′	130.7	131.2	130.8	130.6	117.1	117.8	117.4	117.4
2′					156.9	156.7	156.8	156.8
	126.6	126.4	126.2	126.6				
6′					128.7	128.3	128.2	128.2
3′					117.0	117.3	117.1	117.1
	129.0	129.3	129.2	129.0				
5′					119.4	119.6	119.6	119.6
4′	132.1	132.1	131.6	132.1	132.9	132.6	132.9	132.9
OMe	60.4	60.3	60.1	60.4	60.4	60.1	60.2	60.9
OMe	61.1	61.3	61.2	61.1	61.1	61.2	61.2	61.8

A natural flavone, pedunculin, isolated from *Tithonia pedunculata*, has been proposed as **1b** on the basis of ^{1}H NMR and UV data by La Duke [15]. The spectral data were not compatible with those of the synthetic **1b**, but showed that the structure of pedunculin is 5,7-dihydroxy-6,8,4′-trimethoxyflavone (**17b**) [16], an isomer of **1b**. Actually, the ^{1}H NMR and UV data for pedunculin were consistent with those for the synthetic flavone **17b** [17] (Table 4) and the structure of pedunculin was revealed to be **17b**, an isomer of **1b**.

A natural flavone, isolated from *Scutellaria baicalensis* Georgi, has been proposed as **1d** on the basis of spectral data, by Takagi *et al.* [18]. In the ^{1}H NMR data for the natural flavone, the difference ($\Delta\delta$0.07) between the two methoxyl signals was smaller than that ($\Delta\delta$0.11) in **1d** and consistent with that ($\Delta\delta$0.06) in **3d**, but the chemical shifts of the two methoxy groups appeared at a higher field than those in **3d** (Tables 2 and 4). The UV data were also similar to those of **3d** rather than **1d** (Tables 1 and 4), but the identification was difficult because the UV spectral patterns of the two isomeric flavones **1d** and **3d** are similar to each other. In the ^{13}C NMR spectra for the natural flavone, however, the carbon signals at the 6-, 7-, and 8-positions were consistent with those in **17a** rather than those in flavones, **1d** and **3d** (Table 5), suggesting that the natural compound was 5,7,2′-trihydroxy-6,8-dimethoxyflavone (**17d**). Therefore, the flavone **17d** was synthesized from 4′-benzyloxy-2′-hydroxy-3′,5′,6′-trimethoxyacetophenone [14] by using the Baker–Venkataraman transformation and compared with the natural product. The properties of the natural flavone were identical to those of the synthetic **17d** (Tables 4 and 5). Consequently, the structure of the natural flavone must be **17d**.

A natural flavone, isolated from *Ageratum conyzoides*, has been proposed as **2c** on the basis of spectral data, by González *et al.* [19]. Although the UV data for the natural flavone were different from those for synthetic **2c**, the proposed structure seems to be correct in that the ^{1}H NMR data were consistent with those for the synthetic compound (Table 4).

A flavone glycoside was isolated from *Sideritis leucantha* and the structure of the aglycone was assumed to be **1f** on the basis of UV and MS data and the chromatographic behaviour of the hydrolytic products by Barberán *et al.* [6]. The UV data for the aglycone were consistent with those for synthetic **1f** (Table 4). The chromatographic behaviour of **1f** was also similar to that of the natural flavone: the R_f values of flavones **1** were higher than those of the corresponding **3**, and flavone **1f** was partly isomerized to **3f** in 8N hydrochloric acid–ethanol (3:1, 80°). These results support the proposed structure of the aglycone, although the MS data for the aglycone were slightly different from those for the synthetic flavone **1f** (Table 4).

EXPERIMENTAL

All mps were determined in glass capillaries and are uncorr. ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100.4 MHz) spectra were recorded using TMS as an int. standard (chemical shifts in δ). Elemental analyses (C, H) were performed with a Yanaco CHN corder Model MT-5 and the values of all compounds in this paper were within 0.3% of theoretical values.

2′-Hydroxy-3′,6′-diisopropoxy-4′,5′-dimethoxyacetophenone (**7**). A mixt. of 2′,5′-dihydroxy-3′,4′,6′-trimethoxyacetophenone (**5**) (2.0 g), isopropyl bromide (3.2 g) and dry K_2CO_3 in Me_2CO (15 ml)–*N*,*N*-dimethylformamide (DMF) (15 ml) was heated at 100° for 8 hr. The crude product was chromatographed on a silica gel column with hexane–EtOAc (20:1) and recrystallized from hexane to give **6**; mp 60°; yield, 1.6 g (59%). Compound

Table 6. 5,8-Dihydroxy-6,7-dimethoxyflavones (**1**), 8-hydroxy-5,6,7-trimethoxyflavones (**2**) and their derivatives*

Compound	Mp (°)	Recrystallization solvent	Yield (%)	Formula	Compound	Mp (°)	Recrystallization solvent	Yield (%)	Formula
1a	180–182	aq. MeOH†	95	$C_{17}H_{14}O_6$	**A1a**	170–171	$CHCl_3$–MeOH	quant	$C_{21}H_{18}O_8$
1b	199–200	MeOH	80	$C_{18}H_{16}O_7$	**A1b**	186–187	MeOH	quant	$C_{22}H_{20}O_9$
1c	179–180	aq. MeOH†	92	$C_{20}H_{20}O_9$	**A1c**	164–165	$CHCl_3$–MeOH	quant	$C_{24}H_{24}O_{11}$
1d	267–270dec.	Me_2CO–MeOH	87	$C_{17}H_{14}O_7$	**A1d**	111–112	$CHCl_3$–MeOH	quant	$C_{23}H_{20}O_{10}$
1e	213–215	aq. MeOH†	85	$C_{17}H_{14}O_7 \cdot H_2O$	**A1e**	188–189	$CHCl_3$–MeOH	quant	$C_{23}H_{20}O_{10}$
1f	237–239dec.	aq. MeOH†	85	$C_{17}H_{14}O_8 \cdot H_2O$	**A1f**	185–186	$CHCl_3$–MeOH	quant	$C_{25}H_{22}O_{12}$
2a	199–200	aq. MeOH	80	$C_{18}H_{16}O_6$	**A2a**	157–158	aq. MeOH	quant	$C_{20}H_{18}O_7$
2b	149–150	EtOAc–Et_2O	60	$C_{19}H_{18}O_7$	**A2b**	123–124	MeOH	quant	$C_{21}H_{20}O_8$
2c	184–186	MeOH	62	$C_{21}H_{22}O_9$	**A2c**	151–152	MeOH	quant	$C_{23}H_{24}O_{10}$
14a	99–100	MeOH	74	$C_{27}H_{26}O_6$	**15a**	128–129	$CHCl_3$–MeOH	quant	$C_{24}H_{20}O_6$
14b	113–114	$CHCl_3$–MeOH	57	$C_{28}H_{28}O_7$	**15b**	148–150	$CHCl_3$–MeOH	quant	$C_{25}H_{22}O_7$
14c	110–111	MeOH	70	$C_{30}H_{32}O_9$	**15c**	168–169	MeOH	quant	$C_{27}H_{26}O_9$
14g	oil		45		**15g**	90– 91	$CHCl_3$–MeOH	quant	$C_{31}H_{26}O_7$
14h	119–121	$CHCl_3$–MeOH	68	$C_{34}H_{32}O_7$	**15h**	136–137	$CHCl_3$–MeOH	quant	$C_{31}H_{26}O_7$
14i	52– 55	$CHCl_3$–MeOH	59	$C_{41}H_{38}O_8$	**15i**	118–120	$CHCl_3$–MeOH	quant	$C_{38}H_{32}O_8$
12b	122–123	Hexane	40	$C_{24}H_{28}O_7$	**16a**	116–117	aq. MeOH	95	$C_{25}H_{22}O_6$
					16b	108–109	MeOH	80	$C_{26}H_{24}O_7$
					16c	133–134	MeOH	92	$C_{28}H_{28}O_9$

*Dec, decomposition.

†The solvent contained a small amount of HCl and $NaHSO_3$ in order to prevent air oxidation of the flavones **1** to the corresponding 5,8-quinones.

6 (0.73 g) was demethylated with 5% (w/v) anhydrous $AlBr_3$–MeCN (35 ml) at 0° for 20 min to give, quantitatively, **7** as an oily material. ^1H NMR (60 MHz, $CDCl_3$): δ1.31 (12H, *d*, J = 6.0 Hz, $OCH\underline{Me}_2$), 4.37, 4.77 (each 1H, *h*, J = 6.0 Hz, $OC\underline{H}Me_2$), 2.67 (3H, *s*, COMe), 3.77, 3.95 (each 3H, *s*, OMe), 12.75 (1H, *s*, OH).

3′-Benzyloxy-2′-hydroxy-6′-isopropoxy-4′,5′-dimethoxyacetophenone (**10**). A mixt. of benzyloxyacetophenone **8** (5.0 g) [10], isopropyl bromide (5.5 g) and dry K_2CO_3 in Me_2CO (25 ml)–DMF (25 ml) was heated with stirring at 100° for 8 hr and then diluted with H_2O. The sepd oily materials were extracted with ether. The extract was washed with H_2O and dilute HCl, dried over Na_2SO_4 and then evapd to dryness to give a crude isopropyl ether, **9**.

To a cold soln of **9**, in dry MeCN (100 ml), a solution of 10% (w/v) anhydrous $AlBr_3$–MeCN (100 ml) was added at 0°. The mixt. was stirred at 0° for 15 min, diluted with *ca* 3% HCl and then warmed at 50–60° for 15–20 min. After the solvent was concd under red. pres., the sepd oily materials were collected by extraction with ether and recrystallized from MeOH to give **10**; mp 76–77°; yield, 3.7 g (68%). ^1H NMR (60 MHz, $CDCl_3$): δ1.29 (6H, *d*, J = 7.0 Hz, $OCH\underline{Me}_2$), 4.76 (1H, *h*, J = 7.0 Hz, $OC\underline{H}Me_2$), 2.66 (3H, *s*, COMe), 3.73, 3.93 (each 3H, *s*, OMe), 4.99 (2H, *s*, $OC\underline{H}_2Ph$), 12.89 (1H, *s*, OH).

8-Benzyloxy-5-isopropoxy-6,7-dimethoxyflavones (**14**). A mixture of **10** (720 mg, 2.0 mmol) and substituted benzoyl chloride (2.5–3.0 mmol) in pyridine (3–5 ml) was heated at 50–80° for 2 hr. The cooled mixt. was poured into a mixt. of ice and HCl and then extracted with ether. The extract was washed with aq. K_2CO_3 and concd to dryness under red. pres. to give a crude benzoate which contained an appreciable amount of the benzoic anhydride. To a soln of the benzoate dried in pyridine (10 ml), freshly powdered KOH (3–5 g) was added. The mixt. was stirred at 60° for 1.5–2 hr, poured into a mixt. of ice and HCl and then extracted with EtOAc. The extract was washed with aq. K_2CO_3 and concd to dryness under red. pres. to give crude **13** as an oily material. In the synthesis of the diketone **13g**, the crude 2-benzyloxybenzoate of **10** was refluxed with dry K_2CO_3 (10 g) in Me_2CO (40 ml) for 48 hr to give **13g**, which contained an appreciable amount of **10**.

A soln of the diketone **13** in HOAc (10 ml) was warmed with a few drops of conc. H_2SO_4 at 50° for 1 hr, diluted with water and extracted with ether. The extract was washed with aq. K_2CO_3, concd and then recrystallized to give **14** (Table 6).

8-Benzyloxy-5-hydroxy-6,7-dimethoxyflavones (**15**). To a cold soln of **14** (0.70 mmol) in MeCN (10 ml), a soln of 10% (w/v) anhydrous $AlCl_3$–MeCN (10 ml) was added. The mixt. was allowed to stand at 30° for 30 min, diluted with *ca* 5% HCl and warmed at 50–60° for 15–20 min. After the acetonitrile was evapd under red. pres., the sepd ppt. was recrystallized to give, quantitatively, **15** (Table 6).

8-Benzyloxy-5,6,7-trimethoxyflavones (**16a–16c**). The flavone **15** (1.0 mmol) was methylated with Me_2SO_4 (0.3 ml) and K_2CO_3 (1.5 g) in boiling Me_2CO (35 ml) to give **16** (Table 6).

5,8-Dihydroxy-6,7-dimethoxyflavones (**1a–1g**) *and 8-hydroxy-5,6,7-trimethoxyflavones* (**2a–2c**). The flavone, **15** or **16**, (100–200 mg) was hydrogenolysed over 10% Pd–C (50–100 mg) in EtOAc–MeOH (1:1) (15–25 ml) until uptake of H_2 ceased. After the catalyst was filtered off, the filtrate was concd and the residue recrystallized to give, quantitatively, **1** or **2**. Their acetates were synthesized by the hot Ac_2O–pyridine method (Table 6).

5,6-Dihydroxy-7,8-dimethoxyflavones (**3b**, **3c** *and* **3d**) *6-hydroxy-5,7,8-trimethoxyflavones* (**4b** *and* **4c**). The acetophenone **5** (1.0 g) was methoxymethylated with methoxymethyl chloride (0.55 ml) and diisopropylethylamine (2.1 ml) in CH_2Cl_2 at room temp. The flavones **4b** (mp 180–182°; yield, 1.04 g; 70%) and **4c** (mp 175–176°; yield, 1.1 g; 64%) were directly obtained from the methoxymethyl ether by a similar method to that described in the synthesis of **14**. The acetate, **A4b** (mp 124–125°) or **A4c** (mp 144–145°), (300 mg) was dissolved into a cooled soln of 10% (w/v) anhydrous $AlBr_3$–MeCN (10 ml) and allowed to stand at 0° for 45 min. The mixt. was diluted with *ca* 5% aq. HCl, warmed at 50–60° for 20 min and concd. The sepd ppt. was collected and hydrolysed with methanolic HCl to give **3b** (mp 181–182°; yield, 240 mg; 93%) or **3c** (mp 188–189°; yield, 224 mg; 85%).

The flavone **3d** was synthesized as follows: the benzyl ether (**8**) (600 mg) of **5** was converted into oily 6,2′-bis(benzyloxy)-5,7,8-trimethoxyflavone and then the flavone was demethylated with 5% (w/v) anhydrous $AlBr_3$–MeCN at 0° for 20 min to give 6,2′-bis(benzyloxy)-5-hydroxy-7,8-dimethoxyflavone (mp 139–140°; yield, 350 mg; 38%). The hydrogenolysis of the 5-hydroxyflavone with 10% Pd–C in EtOAc–MeOH (1:1) afforded quantitatively, **3d** (mp 250–251°; its acetate **A3d**, mp 101–103°).

5,7,2′-Trihydroxy-6,8-dimethoxyflavone (**17d**). 2′-Hydroxy-4′-benzyloxy-3′,5′,6′-trimethoxyacetophenone [14] (500 mg) was benzoylated with 2-benzyloxybenzoyl chloride (1.0 g) in pyridine and then transformed with powdered KOH (2.0 g) in pyridine (5 ml) to a diketone derivative. The diketone was cyclized with a small amount of H_2SO_4 in HOAc and the product was chromatographed over a silica gel column with $CHCl_3$–EtOAc to give an oily flavone. The flavone was demethylated with 5% (w/v) anhydrous $AlBr_3$–MeCN (3 ml) at 0° for 30 min and the product hydrogenolysed with 10% Pd–C (100 mg) in MeOH to give **17d** (mp 267–268° decomp.; yield, 60 mg; 12%).

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