[Chem. Pharm. Bull. 34(4)1656—1662(1986)]

Flavonoids Synthesis. I. Synthesis and Spectroscopic Properties of Flavones with Two Hydroxy and Five Methoxy Groups at C-2′,3′,4′,5,6,6′,7 and C-2′,3,4′,5,5′,6,7

MUNEKAZU IINUMA,* YOSHINOBU MATOBA, TOSHIYUKI TANAKA and MIZUO MIZUNO

Gifu Pharmaceutical University, 6–1 Mitahora-higashi 5-chome, Gifu 502, Japan

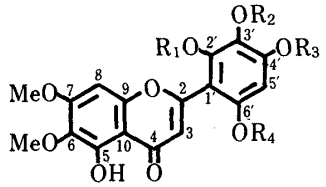
(Received July 29, 1985)

Four flavones oxygenated at C-2′,3′,4′ and 6′, and seven flavonols oxygenated at C-2′,4′ and 5′, each with a 5,6,7-trioxygenated structure in ring A, were synthesized for comparison with brickellin and apulein. The structures of brickellin and apulein were thus confirmed to be 2′,5-dihydroxy-3,4′,5′,6,7-pentamethoxyflavone and 2′,5′-dihydroxy-3,4′,5,6,7-pentamethoxyflavone, respectively. The differences between flavones oxygenated at 2′,3′,4′ and 6′, and flavonols oxygenated at C-2′,4′,5′ are discussed on the basis of spectroscopic data.

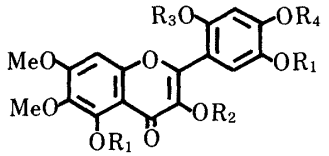
Keywords——flavone synthesis; 2′,5-dihydroxy-3,4′,5′,6,7-pentamethoxyflavone; 2′,5′-dihydroxy-3,4′,5,6,7-pentamethoxyflavone; brickellin; apulein; ^{13}C-NMR

We have already shown that the proposed structure for brickellin (**4**), isolated from *Brickellia veronicaefolia* and *B. chlorolepis* by Roberts *et al.*,[1] is not correct on the basis of a comparison with the synthesized flavone (**4**) and the related compounds, 2′,5-dihydroxy-3′,4′,6,6′,7-pentamethoxy- (**1**) and 3′,5-dihydroxy-2′,4′,6,6′,7-pentamethoxyflavone (**2**).[2] After a re-investigation of the spectral data and comparison with other possible synthetic flavones, the structure of brickellin was revised to 2′,5-dihydroxy-3,4′,5′,6,7-pentamethoxyflavone (**7**).[3] Usually, flavonoids possess many oxygenated groups in their skeleton, and their structures are not easy to determine. In this paper, we describe the process of structure revision of brickellin and confirm that 2′,5′-dihydroxy-3,4′,5,6,7-pentamethoxyflavone is the correct structure for apulein, which was isolated from *Apuleia leiocarpa*. The spectral characteristics of various synthetic flavones are also discussed.

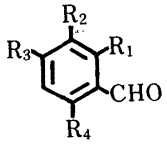
The requisite aldehydes for the preparation of flavones tetraoxygenated at C-2′, 3′, 4′ and 6′, *i.e.*, 2-isopropyloxy-3,4,6-tetramethoxy- (**13**), 3-benzyloxy-2,4,6-trimethoxy- (**14**), 4-benzyloxy-2,3,6-trimethoxy- (**15**), and 6-isopropyloxy-2,3,4-trimethoxybenzaldehyde (**16**), were synthesized from 3,5-dimethoxy-1,4-diphenol for **13**, **14** and **16**, or 3,5-dibenzyloxy-1,4-dephenol for **15** by usual methylation or benzylation, followed by the Vilsmeier reaction and dealkylation.[2] On the other hand, the aldehydes (**17**—**23**) required for preparation of flavonols trioxygenated at C-2′, 4′, and 5′ were synthesized according to our previous paper.[5] The respective aldehydes were condensed with 2-hydroxy-4,5,6-trimethoxyacetophenone (**35**) in the presence of potassium hydroxide to give the corresponding chalcones (**24**)—(**34**). Treatment of 2′-hydroxy-2-isopropyloxy-3,4,4′,5′,6,6′-hexamethoxychalcone (**24**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[6] in dry dioxane under reflux afforded 2′-isopropyloxy-3′,4′,5,6,6′,7-hexamethoxyflavone (**24a**) in 68% yield, and **24a** was allowed to react with boron trichloride[7] to give **1** in 82% yield. Analogous treatment of 3-benzyloxy-2′-hydroxy-2,4,4′,5′,6,6′-hexamethoxy- (**25**), 4-benzyloxy-2′-hydroxy-2,3,4′,5′,6,6′-hexamethoxy- (**26**) and 2′-hydroxy-6-isopropyloxy-2,3,4,4′,5′,6′-hexamethoxychalcone (**27**) gave 3′-



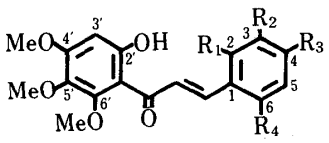
1: $R_1=H$, $R_2=R_3=R_4=Me$
2: $R_2=H$, $R_1=R_3=R_4=Me$
3: $R_3=H$, $R_1=R_2=R_4=Me$
4: $R_4=H$, $R_1=R_2=R_3=Me$



5: $R_1=R_2=H$, $R_3=R_4=R_5=Me$
6: $R_2=R_3=H$, $R_1=R_4=R_5=Me$
7: $R_1=R_3=H$, $R_2=R_4=R_5=Me$
8: $R_2=R_4=H$, $R_1=R_3=R_5=Me$
9: $R_1=R_4=H$, $R_2=R_3=R_5=Me$
10: $R_3=R_5=H$, $R_1=R_2=R_4=Me$
11: $R_3=R_4=H$, $R_1=R_2=R_5=Me$
12: $R_2=H$, $R_1=R_3=R_4=R_5=Me$



13: $R_1=O\text{–}<$, $R_2=R_3=R_4=OMe$
14: $R_2=OBz$, $R_1=R_3=R_4=OMe$
15: $R_3=OBz$, $R_1=R_2=R_4=OMe$
16: $R_4=O\text{–}<$, $R_1=R_2=R_3=OMe$
17: $R_1=H$, $R_2=R_3=R_4=OMe$
18: $R_1=H$, $R_4=OBz$, $R_2=R_3=OMe$
19: $R_1=H$, $R_4=O\text{–}<$, $R_2=R_4=OMe$
20: $R_1=H$, $R_3=OBz$, $R_2=R_4=OMe$
21: $R_1=H$, $R_3=O\text{–}<$, $R_2=R_4=OMe$
22: $R_1=H$, $R_2=R_4=OBz$, $R_3=OMe$
23: $R_1=H$, $R_2=R_4=O\text{–}<$, $R_3=OMe$
$Bz=CH_2C_6H_5$



24: $R_1=O\text{–}<$, $R_2=R_3=R_4=OMe$
25: $R_2=OBz$, $R_1=R_3=R_4=OMe$
26: $R_3=OBz$, $R_1=R_2=R_4=OMe$
27: $R_4=O\text{–}<$, $R_1=R_2=R_3=OMe$
28: $R_1=H$, $R_2=R_3=R_4=OMe$
29: $R_1=H$, $R_4=OBz$, $R_2=R_3=OMe$
30: $R_1=H$, $R_4=O\text{–}<$, $R_2=R_4=OMe$
31: $R_1=H$, $R_3=OBz$, $R_2=R_4=OMe$
32: $R_1=H$, $R_3=O\text{–}<$, $R_2=R_4=OMe$
33: $R_1=H$, $R_2=R_4=OBz$, $R_3=OMe$
34: $R_1=H$, $R_2=R_4=O\text{–}<$, $R_3=OMe$
$Bz=CH_2C_6H_5$

Chart 1

benzyloxy-2′,4′,5,6,6′,7-hexamethoxy- (**25a**), 4′-benzyloxy-2′,3′,5,6,6′,7-hexamethoxy- (**26a**) and 6′-isopropyloxy-2′,3′,4′,5,6,7-hexamethoxyflavone (**27a**), which were transformed to **2**, **3** and **4** by a combination of deisopropylation, partial demethylation or debenzylation.

On the other hand, 2′-hydroxy-2,4,4′,5,5′,6′-hexamethoxychalcone (**28**) was converted by means of the Algar–Flynn–Oyamada method (AFO method)[8] to 3-hydroxy-2′,4′,5,5′,6,7-hexamethoxyflavone (2′,4′,5,5′,6,7-hexamethoxyflavonol) in 42% yield. The flavone **12** was methylated with dimethyl sulfate and 50% potassium hydroxide to give 2′,3,4′,5,5′,6,7-heptamethoxyflavone. The resulting flavone was allowed to react with boron trichloride at −60 °C to afford 5-hydroxy-2′,3,4′,5′,6,7-hexamethoxyflavone as a result of partial demethylation at C-5. Our experiment showed the methoxyl group at C-5 was predominantly demethylated with BCl_3, while that at C-3 was not demethylated. Analogous treatment of 2-benzyloxy-2′-hydroxy-4,4′,5,5′,6′-pentamethoxy- (**29**), 2′-hydroxy-2-isopropyloxy-4,4′,5,5′,6′-pentamethoxy- (**30**), 4-benzyloxy-2′-hydroxy-2,4′,5,5′,6′-pentamethoxy- (**31**), 2′-hydroxy-4-isopropyloxy-2,4′,5,5′,6′-pentamethoxy- (**32**), 2,5-dibenzyloxy-2′-hydroxy-4,4′,5′,6′-tetramethoxy- (**33**) and 2,4-dibenzyloxy-2′-hydroxy-4′,5,5′,6′-tetramethoxychalcone (**34**) gave the corresponding flavonols **29a**, **30a**, **31a**, **32a**, **33a** and **34a**, respectively. These flavonols were alkylated and dealkylated as described in the experimental section to

TABLE I. Elemental Analysis and Mass Spectral Data for Synthetic Flavones

Compound	Found[a]		MS (*m/z*) (rel. int.)
	C	H	
1	59.25	5.01	404 (100), 389 (81), 375 (24), 361 (11), 359 (24), 209 (16), 181 (19), 173 (14), 165 (19), 153 (21)
2	59.40	5.01	404 (100), 389 (86), 375 (19), 361 (8), 359 (18), 345 (9), 209 (13), 181 (18), 179 (14), 153 (19)
3	59.20	5.16	404 (100), 389 (71), 375 (14), 359 (12), 331 (6), 209 (9), 193 (11), 181 (14), 153 (13)
4	59.25	4.95	404 (100), 389 (72), 375 (17), 361 (8), 359 (17), 209 (17), 193 (16), 181 (28), 153 (21)
5	59.31	4.95	404 (100), 390 (6), 373 (30), 361 (24), 355 (17), 343 (6), 331 (10), 303 (5), 206 (33), 197 (24), 179 (42)
6	59.14	4.95	404 (100), 389 (74), 387 (17), 371 (26), 369 (17), 331 (13), 206 (26), 167 (17)
8	59.30	5.12	404 (22), 389 (20), 373 (9), 198 (100), 192 (14), 183 (92), 181 (15), 167 (14), 155 (26)
9	59.22	4.93	404 (100), 389 (61), 373 (42), 371 (14), 361 (15), 355 (21), 343 (18), 315 (15), 194 (14), 181 (16), 179 (19), 173 (21)
10	59.25	5.12	404 (100), 389 (86), 387 (64), 373 (62), 371 (7), 357 (7), 355 (11), 211 (14), 195 (16), 188 (15), 179 (21), 167 (46)
11	59.55	5.12	404 (52), 389 (100), 387 (32), 373 (26), 371 (13), 361 (10), 343 (10), 331 (16), 211 (6), 195 (11), 188 (10), 179 (13), 173 (6), 167 (19)
12	60.01	5.36	418 (94), 403 (100), 387 (66), 369 (16), 357 (20), 345 (18), 211 (36), 206 (97), 195 (22), 191 (19), 179 (22)

a) $C_{20}H_{20}O_9$ requires C, 59.40; H, 4.99% for **1**—**11**, and $C_{21}H_{22}O_9$ requires C, 60.28; H, 5.30% for **12**.

TABLE II. Melting Points and ^{1}H-NMR Spectral Data for Synthetic Flavones

Compound	mp (°C)	^{1}H-NMR (ppm)					
		OMe	H-3	H-8	H-3′	H-5′	H-6′
1	187—188	3.83 3.87 3.91 (2) 3.93	6.12	6.45		6.37	
2	198—199	3.76 3.85 3.91 (2) 3.95	6.32	6.45		6.37	
3	193—194	3.74 3.85 3.88 3.92 (2)	6.29	6.45		6.46	
4	177—178	3.79 3.85 3.87 (2) 3.91	6.39	6.53		6.46	
5	159	3.85 (2) 3.91 (2) 3.94		6.46	6.48		7.09
6	208—210	3.78 3.81 (2) 3.89 3.93		6.92	6.48		7.03
8	166—167	3.81 3.92 (2) 3.94 4.03		6.72	6.70		7.08
9	175	3.79 3.80 3.91 (3)		6.67	6.43		6.94
10	196—198	3.92 (2) 3.95 (2) 4.00		6.75	6.60		7.21
11	166—167	3.88 3.92 3.96 3.99 4.02		6.74	6.69		7.10
12	189—191	3.83 (2) 3.87 3.91 (2) 4.00		6.71	6.63		7.08

All spectra were measured in $CDCl_3$. The numbers in parentheses are the numbers of methoxyl groups.

afford 2′,3-dihydroxy-4′,5,5′,6,7-pentamethoxy- (**6**), 2′,5-dihydroxy-3,4′,5′,6,7-pentamethoxy- (**7**), 3,4′-dihydroxy-2′,5,5′,6,7-pentamethoxy- (**8**), 4′,5-dihydroxy-2′,3,5′,6,7-pentamethoxy- (**9**), 2′,5′-dihydroxy-3,4′,5,6,7-pentamethoxy- (**10**), and 2′,4′-dihydroxy-3,4,4′,6,7-pentamethoxyflavone (**11**). Tables I, II and III list the physical and spectroscopic data of the flavonoids thus obtained.

It was suggested that the structure proposed for brickellin was incorrect based on a

TABLE III. UV Spectral Data for Synthetic Flavones in the Presence of Shift Reagents

Compound	λ_{max}^{MeOH} nm (log ε)	$\lambda_{max}^{+AlCl_3}$	$\lambda_{max}^{+AlCl_3+HCl}$	λ_{max}^{+NaOMe}
1	264 (4.2) 312 (4.1)	274 299 361	276 295sh 344	262 291sh 340
2	263 (4.3) 300 (4.0) 331sh (4.0)	276 326 379	276 322 371	269 360
3	263 (4.2) 323 (4.0)	274 297sh 364	275 295sh 351	269 372
4	262 (4.3) 326 (4.1)	275 293sh 368	275 296sh 356	264 380
5	259 (4.3) 304sh (3.8) 356 (4.1)	269 327 414	272 327sh 410	266 394
6	255 (4.5) 304sh (4.1) 353 (4.3)	270 335 425	268 332 422	262 310 334 399
8	253 (4.2) 303sh (3.9) 332 (3.9)	266 324 410	265 321 408	270sh 295sh 395 (dec.)
9	260 (4.5) 303 (3.1) 345 (4.2)	275 323 396	274 317 383	267 301sh 396
10	252 (4.5) 307 (4.2)	252 307	252 307	246 290 310sh (dec.)
11	253 (4.3) 324 (4.1)	253 324	253 324	263sh 290 313sh 401
12	252 (4.4) 305sh (4.0) 388 (4.1)	265 325 406	264 322 403	265 378

comparison of the natural product with the synthetic flavones **1**, **2**, **3** and **4**. Finally the structure of brickellin was revised as reported in our previous paper.[3] The spectral properties of **11** agreed well with those of apulein,[4] which confirmed the proposed structure for apulein, 2′,5′-dihydroxy-3,4′,5,6,7-pentamethoxyflavone.[12]

In the ^{1}H-nuclear magnetic resonance (NMR) spectra of these flavones the proton at C-5′ of 2′,3′,4′,6′-tetraoxygenated flavones was observed at 6.35—6.46 ppm, as is also the case for the flavones with four methoxy groups at the 2′,3′,4′ and 6′.[9] On the other hand, the protons at C-3′ and 6′ of 2′,4′,5′-trioxygenated flavones were observed at 6.43—6.70 ppm (H-3′) and 6.92—7.21 ppm (H-6′), which is also in agreement with our previous data.[5] In the mass spectra (MS) of **1**—**4**, the significant fragment was *m/z* 209 ($C_{11}H_{13}O_{14}$), produced by cleavage through pathway II ($B_1^{\cdot +}$) and transfer of $H^{\cdot}$.[10]

In **5**—**12**, which possess O-functions at C-3 and C-2′, *m/z* 387 ($M^+ - 17$) and 373 ($M^+ - 31$) were characteristically produced through stable 5-membered heterocyclic ring formation between rings B and C.[10] ^{13}C-NMR spectral data of the present flavones are summarized in Table IV. All carbons were assigned by calculation based on the extensive additivity rules,[11] and substituent chemical shifts of methoxy or hydroxy groups. The shifts of C-2′ and C-3 in **5**—**12** were determined by comparison with those of the following model flavones; 2′,3-dihydroxy- (**36**), 2′-methoxy-3-hydroxy- (**37**), 2′-hydroxy-3-methoxy- (**38**) and 2′,3-dimethoxyflavone (**39**). The chemical shifts of methoxyl carbons reflect the surroundings, and methoxyl carbons sandwiched between other methoxy and/or hydroxyl groups, and those at C-3 were observed at lower field (60 ppm). The results were applicable to all the present flavones except **10**. The exception can be explained by assuming that **10** isomerizes to 6,6′-dihydroxy-2′,3,3′,4′,7-pentamethoxyflavone in solution through a kind of Wessely–Moser rearrangement. Further studies on the rearrangement and stability of the flavones oxygenated at C-2′, and on the abnormal spectroscopic properties of the flavones oxygenated at C-2′, 3, 6′ are in progress.

Experimental

Melting points were determined on a Buchi melting-point apparatus and are uncorrected. ^{1}H-NMR spectra were determined with a Hitachi-Perkin-Elmer R-20B 60 MHz instrument, using tetramethylsilane as an internal standard. ^{13}C-NMR were obtained on a JEOL FX 60 FT spectrometer (25.15 MHz, spectral width 4000 Hz, 4096 data points). MS were taken on a JEOL JMS-D300 machine operating at 70 eV. The ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrophotometer. Elemental analyses were carried out at the Microanalytical Laboratory of our University.

2′,5-Dihydroxy-3′,4′,6,6′,7-pentamethoxyflavone (1)——1,2,3,5-Tetramethoxybenzene (10 g, 51 mmol), derived from 3,5-dimethoxy-1,4-diphenol by the usual methylation, was allowed to react with the Vilsmeier reagent prepared

TABLE IV. ^{13}C-NMR Spectral Data for Synthetic Flavones

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1	160.7	112.6	182.8	152.9	130.0	158.6	90.7	152.9	106.3
2	161.1	112.6	182.7	150.0	132.5	158.8	92.2	151.0	106.3
3	161.0	112.8	182.8	152.5	132.6	158.8	94.9	152.5	106.4
4	162.0	112.0	182.9	151.9	132.4	159.0	96.8	151.9	105.9
5	143.7	136.6	175.8	151.8	132.4	159.4	90.8	159.0	105.1
6	140.0	138.4	172.1	153.2	140.0	158.0	96.2	154.0	113.3
8	140.6	138.1	171.5	154.0	139.8	158.0	96.2	154.3	110.2
9	155.4	140.4	179.0	153.0	132.6	158.7	90.6	155.4	113.1
10	154.3	140.0	170.5	153.0	135.1	158.4	96.1	154.3	110.8
11	154.0	140.3	172.3	153.5	138.6	158.0	96.2	154.0	110.4
12	143.2	138.2	171.5	152.6	139.9	158.0	96.2	154.4	113.8
36	147.5	138.9	172.8	124.8	124.4	133.4	118.4	155.1	122.0
37	146.1	138.9	173.3	125.6	124.4	133.4	118.6	156.1	124.4
38	155.6	141.9	174.8	126.8	124.5	133.1	118.0	155.6	124.5
39	154.4	141.6	174.4	125.4	124.2	132.9	117.8	155.7	124.2

Compound	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	OMe
1	106.3	154.2	132.4	154.8	88.8	152.9	61.3 60.8 56.3 (2) 56.0
2	109.0	153.0	132.9	154.2	90.7	151.0	61.3 60.8 56.6 56.4 56.3
3	108.5	153.1	133.7	154.5	90.7	152.5	61.2 (2) 60.9 56.3 56.2
4	106.7	154.2	136.0	156.0	91.0	152.6	61.7 61.2 60.9 56.4 56.1
5	110.8	151.8	98.2	152.2	143.7	111.0	60.9 56.7 56.3 56.2 56.0
6	109.8	152.3	102.1	153.2	140.2	112.7	62.1 61.4 56.3 56.0 (2)
8	108.4	152.9	100.5	151.9	140.6	110.2	62.1 61.5 56.6 56.4 56.3
9	107.1	152.9	99.9	152.9	140.4	110.2	60.9 60.6 56.8 56.4 56.3
10	109.8	151.7	103.0	152.3	143.5	112.7	62.2 61.4 56.8 56.4 55.9
11	109.0	151.2	105.9	152.4	141.5	112.8	62.2 61.8 61.6 56.7 56.4
12	110.3	151.8	98.3	152.6	143.2	111.0	62.2 61.6 57.1 56.7 56.3 56.1
36	118.7	155.4	116.6	131.5	118.7	130.9	— —
37	118.6	157.5	112.0	132.1	120.7	131.0	— 56.1
38	118.0	156.4	113.1	131.8	120.6	130.9	60.3 —
39	117.8	157.0	111.1	131.6	120.1	130.1	60.0 55.4

All spectra were measured in $CDCl_3$. The numbers in parentheses are numbers of methoxyl groups.

from phosphorus oxychloride (9.2 g, 60 mmol) and *N,N*-dimethylformamide (DMF) (24 g, 330 mmol) at room temperature overnight. The reaction mixture was poured into 2 M sodium hydroxide (100 ml) and extracted with AcOEt to give 2,3,4,6-tetramethoxybenzaldehyde (7 g) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.27 (1H, s, H-5),

10.09 (1H, s, CHO). Boron trichloride (100 mmol) in dichloromethane (20 ml) was added to a solution of the resulting aldehyde (7 g) in dichloromethane (30 ml) at −60 °C. The mixture was allowed to stand for 1 h, then poured into water (300 ml), and extracted with AcOEt. The extract gave 2-hydroxy-3,4,6-trimethoxybenzaldehyde (4.5 g) as colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 5.90 (1H, s, H-5), 10.08 (1H, s, CHO), 12.18 (1H, s, OH). This aldehyde (4.5 g, 21 mmol) was isopropylated with isopropyl bromide (6.2 g, 50 mmol) and potassium carbonate (5.9 g, 40 mmol) in DMF (50 ml) to give 2-isopropyloxy-3,4,6-trimethoxybenzaldehyde (**13**) (4 g) as a pale yellow oil. ^{1}H-NMR (CCl_4) δ: 1.27 (6H, d, J=6 Hz, $(CH_3)_2CH$), 3.69, 3.80, 3.89 (3H, each s, 3×OMe), 4.55 (1H, heptet, CH), 6.26 (1H, s, H-5), 10.15 (1H, s, CHO). MS (*m/z*) (rel. int.): 254 [M^+] (39), 197 (100). The aldehyde **13** (1.2 g, 4.3 mmol) and 2-hydroxy-4,5,6-trimethoxyacetophenone (**35**) (1 g, 4.3 mmol) were added to ethanol (100 ml) containing potassium hydroxide (10 g), and the mixture was stirred overnight. The reaction mixture was poured into 1 N HCl (300 ml) and extracted with AcOEt to give 2′-hydroxy-2-isopropyloxy-3,4,4′,5′,6,6′-hexamethoxychalcone (**24**) (1.8 g) as a red oil. ^{1}H-NMR (CCl_4) δ: 6.12, 6.20 (1H, each s, H-3′,5′), 8.12 (2H, s, COCH=CH), 13.80 (1H, s, OH). A chalcone (**24**) (900 mg, 2 mmol) was refluxed in dry dioxane (30 ml) containing DDQ (450 mg, 2 mmol) for 7 h. The reaction mixture was subjected to column chromatography on silica gel (eluent: C_6H_{14}–AcOEt=3:2) to give 2′-isopropyloxy-3′,4′,5,6,6′,7-hexamethoxyflavone (**24a**) (550 mg) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 6.28, 6.32, 6.70 (3H, each s, H-3, 5′, 8). **24a** (500 mg) was deisopropylated in the same way as described above to give **1** (350 mg) as pale yellow needles after purification by column chromatography (eluent, C_6H_6: acetone=5:1).

3′,5-Dihydroxy-2′,4′,6,6′,7-pentamethoxyflavone (2)——2,5-Dibenzyloxy-1,3-dimethoxybenzene (9 g, 26 mmol) derived from 3,5-dimethoxy-1,4-diphenol by the usual benzylation was subjected to the Vilsmeier reaction as described above to give 3,6-dibenzyloxy-2,4-dimethoxybenzaldehyde (6 g). The resulting aldehyde (6.8 g) was debenzylated with Pd–C/H_2 (atmospheric pressure) in ethanol for 0.6 h to give 3,6-dihydroxy-2,4-dimethoxybenzaldehyde (2.4 g), mp 131—133 °C (C_6H_6–C_6H_{14}), ^{1}H-NMR ($CDCl_3$) δ: 5.31 (1H, brs, OH), 6.17 (1H, s, CHO), 10.00 (1H, s, CHO), 11.81 (1H, s, OH), and 3-benzyloxy-6-hydroxy-2,4-dimethoxybenzaldehyde (1.5 g) as a pale yellow oil, ^{1}H-NMR (CCl_4) δ: 4.80 (2H, s, $OC\underline{H}_2C_6H_5$), 6.40 (1H, s, H-5), 9.90, 11.95 (2H, each s, OH and CHO), after purification by column chromatography (eluent: $CHCl_3$). The latter aldehyde was methylated with $(CH_3)_2SO_4$ and 50% KOH to give 3-benzyloxy-2,4,6-trimethoxybenzaldehyde (**14**) as a colorless oil. ^{1}H-NMR (CCl_4) δ: 3.80 (3H, s, OMe), 3.84 (6H, s, 2×OMe), 4.85 (2H, s, $CH_2C_6H_5$), 6.15 (1H, s, H-5), 7.15—7.42 (5H, m, C_6H_5), 10.12 (1H, s, CHO). MS (*m/z*) (rel. int.): 302 [M^+] (6), 211 (100). In the same manner, the aldehyde **14** (1.25 g, 5 mmol) was condensed with **35** (1.1 g, 5 mmol) to give 3-benzyloxy-2′-hydroxy-2,4,4′,5′,6,6′-hexamethoxychalcone (**25**) (1.9 g) as orange-red needles (MeOH). mp 142—143 °C. ^{1}H-NMR ($CDCl_3$) δ: 4.88 (2H, s, $C\underline{H}_2C_6H_5$), 6.11, 6.20 (2H, each s, H-3′, 5), 7.21—7.40 (5H, m, C_6H_5), 7.94 (1H, d, J=16 Hz, H-α), 8.21 (1H, d, J=16 Hz, H-β), 13.78 (1H, s, OH). Oxidation of **25** (1.9 g) followed by debenzylation afforded 3′-hydroxy-2′,4′,5,6,6′,7-hexamethoxyflavone (210 mg) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 6.33, 6.36, 6.82 (3H, each s, H-3, 5′, 8). This flavone was partially demethylated with BCl_3 to give **2** as brown rectangles.

4′,5-Dihydroxy-2′,3′,6,6′,7-pentamethoxyflavone (3)——2,4-Dibenzyloxy-3,6-dimethoxybenzaldehyde (8.6 g) [derived from 3,5-dibenzyloxy-1,4-diphenol by methylation and the Vilsmeier reaction] was debenzylated with Pd–C/H_2 (1 atm) in AcOEt for 0.5 h to give 2,4-dihydroxy-3,6-dimethoxybenzaldehyde (2.5 g) as pale yellow needles, mp 187—188 °C (MeOH). ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 5.97 (1H, s, H-5), 10.93 (1H, s, CHO), 10.14, 12.14 (1H, each s, OH), and 4-benzyloxy-2-hydroxy-3,6-dimethoxybenzaldehyde (3.7 g) as pale yellow needles, mp 117—118 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 5.20 (2H, s, $OC\underline{H}_2C_6H_5$), 5.95 (1H, s, H-5), 7.35 (5H, s, C_6H_5), 10.05 (1H, s, CHO), 12.20 (1H, s, OH), after purification by column chromatography (eluent, C_6H_6). The latter aldehyde was methylated to give 4-benzyloxy-2,3,6-trimethoxybenzaldehyde (**15**) as a colorless oil. ^{1}H-NMR (CCl_4) δ: 3.81, 3.85, 3.94 (9H, each s, 3×OMe), 5.18 (2H, s, $OC\underline{H}_2C_6H_5$), 6.32 (1H, s, H-5), 6.40 (5H, s, C_6H_5). MS (*m/z*) (rel. int.): 302 [M^+] (100). By the usual condensation of **15** (1.2 g, 4.3 mmol) with **35** (1 g, 4.3 mmol), 4-benzyloxy-2′-hydroxy-2,3,4′,5′,6,6′-hexamethoxychalcone (1.6 g) was obtained as red needles, mp 144—145 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 6.25, 6.30 (2H, each s, H-3′, 5), 8.09 (1H, d, J=16 Hz, H-α), 8.35 (1H, d, J=16 Hz, H-β), 13.88 (1H, s, OH). Oxidation of the chalcone (**26**) (980 mg), followed by debenzylation gave 4′-hydroxy-2′,3′,5,6,6′,7-hexamethoxyflavone (340 mg) as colorless prisms, mp 84—85 °C (AcOEt–C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 6.27, 6.40, 6.70 (3H, each s, H-3, 5′, 8). This flavone (300 mg) was partially demethylated in the manner described for **1** to give **3** (180 mg) as pale yellow needles.

5,6′-Dihydroxy-2′,3′,4′,6,7-pentamethoxyflavone (4)——3,6-Dihydroxy-2,4-dimethoxybenzaldehyde (2 g), obtained in the preparation of **14**, was partially methylated with CH_3I (1.5 ml) and potassium carbonate (3 g) in acetone to give 6-hydroxy-2,3,4-trimethoxybenzaldehyde as a pale yellow oil (1.8 g). ^{1}H-NMR (CCl_4) δ: 3.68, 3.82, 3.97 (9H, each s, 3×OMe), 6.04 (1H, s, H-5), 9.90 (1H, s, CHO). The above aldehyde (**15**) (1.2 g) was isopropylated to give 6-isopropyloxy-2,3,4-trimethoxybenzaldehyde (**16**) (1 g) as a yellow oil. ^{1}H-NMR (CCl_4) δ: 1.29 (6H, d, J=6 Hz, $(\underline{CH}_3)_2CH$), 3.66 (3H, s, OMe), 3.80 (6H, s, 2×OMe), 4.39 (1H, heptet, CH<), 6.23 (1H, s, H-5), 10.12 (1H, s, CHO). MS (*m/z*) (rel. int.): 254 [M^+] (27), 197 (100). **16** (800 mg, 3 mmol) was condensed with **35** (670 mg, 3 mmol) to give 2′-hydroxy-6-isopropyloxy-2,3,4,4′,5′,6′-hexamethoxychalcone (**27**) (600 mg) as an orange-yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 6.27, 6.31 (2H, each s, H-3′, 5), 8.10 (1H, d, J=15.6 Hz, H-α), 8.42 (1H, d, J=15.6 Hz, H-β), 13.81 (1H, s, OH), which was oxidized with DDQ to give 6′-isopropyloxy-2′,3′,4′,5,6,7-hexamethoxyflavone (**27a**) as a brown oil after purification by column chromatography (eluent, C_6H_{14}: AcOEt=3:2). ^{1}H-NMR ($CDCl_3$) δ:

6.34, 6.37, 6.71 (3H, each s, H-3, 5′, 8). The flavone (**27a**) (160 mg) was deisopropylated to give **4** (85 mg) as pale yellow needles.

3,5-Dihydroxy-2′,4′,5′,6,7-pentamethoxyflavone (5)——Usual condensation of **35** (500 mg, 2.2 mmol) with 2,4,5-trimethoxybenzaldehyde (**17**) (434 mg, 2.2 mmol) gave 2′-hydroxy-2,4,4′,5,5′,6′-hexamethoxychalcone (**28**) (800 mg), which was dissolved in EtOH (60 ml) and treated according to Farkas *et al.*[8] to give 3-hydroxy-2′,4′,5′,5,6,7-hexamethoxyflavone (**12**) (350 mg) as yellow needles. The flavone (**12**) (320 mg) was partially demethylated with BCl_3 to give **5** (210 mg) as yellow needles.

2′,3-Dihydroxy-4′,5,5′,6,7-pentamethoxyflavone (6)——Condensation of 2-benzyloxy-4,5-dimethoxybenzaldehyde (**18**) (1.2 g, 4.4 mmol) with **35** (1 g, 4.4 mmol) gave 2-benzyloxy-2′-hydroxy-4,4′,5,5′,6′-pentamethoxychalcone (**29**) (1.9 g) as orange-yellow prisms, mp 149—151 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 6.28, 6.52, 7.28 (3H, each s, H-3, 3′, 6), 7.85 (1H, d, J=15.5 Hz, H-α), 8.22 (1H, d, J=15.5 Hz, H-β), 13.83 (1H, s, OH), which was transformed to 2′-benzyloxy-3-hydroxy-4′,5,5′,6,7-pentamethoxyflavone (**29a**) (1.2 g), yellow needles, mp 131—133 °C (C_6H_6–C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 6.53, 7.31, 7.38 (3H, each s, H-3′, 6′, 8), 10.47 (1H, s, OH). MS (*m/z*) (rel. int.): 494 [M^+] (33), 375 (100). Debenzylation of **29a** (1 g) gave **6** (650 mg) as pale yellow prisms.

3,4′-Dihydroxy-2′,5,5′,6,7-pentamethoxyflavone (8)——Condensation of **35** (830 mg, 3.7 mmol) with 4-benzyloxy-2,5-dimethoxybenzaldehyde (**20**) (1 g, 3.7 mmol) gave 4-benzyloxy-2′-hydroxy-2,4′,5,5′,6′-pentamethoxychalcone (**31**) (1.6 g) as red needles, mp 160—161 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 6.30, 6.56, 7.19 (3H, each s, H-3, 3′, 6), 7.89 (1H, d, J=16 Hz, H-α), 8.21 (1H, d, J=16 Hz, H-β), 13.89 (1H, s, OH). MS (*m/z*) (rel. int.): 480 [M^+] (44), 403 (71), 91 (100). This chalcone (1.5 g) was treated in the same way as **30** to give 4′-benzyloxy-3-hydroxy-2′,5,5′,6,7-pentamethoxyflavone (**31a**) (700 mg). **31a** (720 mg) was debenzylated to give **8** (480 mg) as pale yellow needles after purification by column chromatography (eluent, AcOEt : C_6H_{14} = 1 : 1).

4′,5-Dihydroxy-2′,3,5′,6,7-pentamethoxyflavone (9)——Condensation of **35** (1 g, 44 mmol) with 4-isopropyloxy-2,5-dimethoxybenzaldehyde (**21**) (991 mg, 44 mmol) gave 2′-hydroxy-4-isopropyloxy-2,4′,5,5′,6′-pentamethoxychalcone (**32**) (1.7 g) as a red oil. ^{1}H-NMR (CCl_4) δ: 6.40, 6.43, 7.19 (3H, each s, H-3, 3′, 6), 7.72 (1H, d, J=16 Hz, H-α), 8.06 (1H, d, J=16 Hz, H-β), 13.74 (1H, s, OH), and **32** was transformed to 3-hydroxy-4′-isopropyloxy-2′,5,5′,6,7-pentamethoxyflavone (**32a**). Pale yellow prisms, mp 168 °C (CCl_4–C_6H_{14}). ^{1}H-NMR ($CDCl_3$) δ: 6.64, 6.72, 7.11 (3H, each s, H-3′, 6′, 8). The flavone (**32a**) (700 mg) was methylated to give 4′-isopropyloxy-2′,3,5,5′,6,7-hexamethoxyflavone (650 mg), mp 157—158 °C (CCl_4) as pale yellow rectangles. ^{1}H-NMR ($CDCl_3$) δ: 6.65, 6.80, 6.99 (3H, each s, H-3′, 6′, 8). This flavone was treated with BCl_3 to give **9** (460 mg) as yellow needles.

2′,5′-Dihydroxy-3,4′,5,6,7-pentamethoxyflavone (10)——Condensation of **35** (1.1 g) with 2,5-dibenzyloxy-4-methoxybenzaldehyde (**22**) (1.8 g) gave 2,5-dibenzyloxy-2′-hydroxy-4,4′,5′,6′-tetramethoxychalcone (**33**) (2.3 g) as a red oil, which was transformed to 2′,5′-dibenzyloxy-3-hydroxy-4′,5,6,7-tetramethoxyflavone (**33a**). A yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 5.00, 5.06 (4H, each s, 2 × $OCH_2C_6H_5$), 6.43, 6.55, 7.20 (3H, each s, H-3′, 6′, 8). MS (*m/z*) (rel. int.): 570 [M^+] (22), 479 (24), 211 (100). **33a** was methylated to give 2′,5′-dibenzyloxy-3,4′,5,6,7-pentamethoxyflavone as a pale yellow oil. ^{1}H-NMR (CCl_4) δ: 6.41, 6.53, 6.99 (3H, each s, H-3′, 6′, 8). MS (*m/z*) (rel. int.): 584 [M^+] (35), 493 (100). The above flavone (200 mg) was debenzylated to give **10** (83 mg), mp 196—198 °C (apulein; lit.[4] mp 211—212 °C), as pale yellow prisms.

2′,4′-Dihydroxy-3,5,5′,6,7-pentamethoxyflavone (11)——Condensation of **35** (850 mg, 3.7 mmol) with 2,4-dibenzyloxy-5-methoxybenzaldehyde (**23**) (1.3 g, 3.7 mmol) gave 2,4-dibenzyloxy-2′-hydroxy-4′,5,5′,6′-tetramethoxychalcone (**34**) (1.9 g) as red prisms, mp 170—171 °C (MeOH), and **34** was led to 2′,4′-dibenzyloxy-3-hydroxy-5,5′,6,7-pentamethoxyflavone (**34a**) (950 mg), yellow rectangles, mp 159—160 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 6.62, 6.70, 7.20 (3H, each s, H-3′, 6′, 8). MS (*m/z*) (rel. int.): 570 [M^+] (44), 451 (55), 201 (100). The above flavone (570 mg) was methylated to give 2′,4′-dibenzyloxy-3,5,5′,6,7-pentamethoxyflavone as a pale yellow oil. This flavone (200 mg) was debenzylated in AcOEt with Pd–C/H_2 to give **11** (65 mg) as pale yellow needles.

References and Notes

1) M. F. Roberts, B. N. Timmermann, T. J. Mabry, R. Brown and S. A. Maltin, *Phytochemistry*, **23**, 163 (1984).
2) M. Iinuma, K. Iwashima, T. Tanaka and S. Matsuura, *Chem. Pharm. Bull.*, **32**, 4217 (1984).
3) M. Iinuma, M. F. Roberts, S. A. Maltin, V. E. Stacey, B. N. Temmermann, T. J. Mabry and R. Brown, *Phytochemistry*, **24**, 1367 (1985).
4) R. B. Filho and O. R. Gottlieb, *Phytochemistry*, **10**, 2433 (1971).
5) M. Iinuma, K. Iwashima and S. Matsuura, *Chem. Pharm. Bull.*, **32**, 4935 (1984).
6) T. Tanaka, K. Iwashima and S. Matsuura, *Yakugaku Zasshi*, **104**, 1306 (1984).
7) M. Iinuma, T. Tanaka, K. Iwashima and S. Matsuura, *Yakugaku Zasshi*, **104**, 691 (1984).
8) L. Farkas, L. Horhammer, H. Wagner, H. Rosler and G. Gurniak, *Chem. Ber.*, **96**, 610 (1964).
9) M. Iinuma, T. Tanaka and S. Matsuura, *Chem. Pharm. Bull.*, **32**, 3354 (1984).
10) T. J. Mabry and K. R. Markham, "The Flavonoids," ed. by J. B. Harborne, T. J. Mabry and H. Mabry, Academic Press, New York, 1975, Chapter 3.
11) M. Iinuma, S. Matsuura and K. Kusuda, *Chem. Pharm. Bull.*, **28**, 708 (1980).
12) Unfortunately, we could not obtain a sample of natural apulein.