University is gratefully acknowledged. We thank the Midwest Center of Mass Spectrometry, an NSF Regional Instrument Facility (CHE-8211164), for obtaining mass spectral data and the National Institutes of Health (RR-02314) for the purchase of a 400-MHz NMR spectrometer used in these studies. In addition we thank Mark A. Russell for initial experiments and Bernard J. Banks for helpful discussions.

Registry No. **1**, 60595-16-6; **2**, 67808-91-7; **4a**, 5661-55-2; **4b**, 96746-26-8; **4d**, 109975-75-9; **4e**, 74373-13-0; **5b**, 109975-72-6; **6a**, 96746-23-5; **6b**, 109996-04-5; **6c**, 96746-27-9; **6d**, 109975-73-7; **6e**, 109975-74-8; **6f**, 109975-76-0; **6g**, 109975-77-1; **6h**, 109996-05-6; **6i**, 109996-06-7; **8a**, 96746-29-1; **9**, 96746-30-4; **10a**, 96746-32-6; **11a**, 96746-33-7; **16**, 28562-53-0; **17a**, 79196-83-1; **17b**, 109975-83-9; **18a**, 109975-78-2; **18b**, 109975-79-3; **18c**, 109975-80-6; **18d**, 109996-07-8; **18e**, 96746-34-8; **18f**, 96746-35-9; **18g**, 109975-84-0; **18h**, 109996-08-9; **19a**, 109975-81-7; **19c**, 96746-37-1; **20a**, 109975-82-8; **20c**, 96746-38-2; **23**, 109975-85-1; **24a**, 109975-86-2; **24b**, 109975-87-3; **24c**, 109975-88-4; **24d**, 109996-09-0; **24e**, 109975-89-5; **24f**, 109975-90-8; **25a**, 109975-91-9; **25b**, 110043-15-7; **26**, 109975-92-0; $ClSO_2NCO$, 1189-71-5; 1,6-heptadiene, 3070-53-9; 2-methyl-2-buten-2-ol, 4675-87-0; 2-methylene-1,3-propanediol, 3513-81-3.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, and bond distances and angles for hydroxyoxacepham **25a** (6 pages). Ordering information is given on any current masthead page.

Studies of the Selective O-Alkylation and Dealkylation of Flavonoids. 10. Selective Demethylation of 7-Hydroxy-3,5,8-trimethoxyflavones with Anhydrous Aluminum Halide in Acetonitrile or Ether[1]

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Demethylation of five 7-hydroxy-3,5,8-trimethoxyflavones and their acetates with anhydrous aluminum halides in acetonitrile or ether was studied and the following results were found. (1) The demethylation was apparently influenced by both solvents and afforded 5,7-dihydroxy-3,8-dimethoxyflavones in acetonitrile and 3,7-dihydroxy-5,8-dimethoxyflavones in ether as main products. (2) The demethylation with 5% w/v anhydrous aluminum bromide in acetonitrile proceeded quantitatively to give a mixture of the corresponding 5- and 3-hydroxyflavones, but that of 7-hydroxy-3,4′,5,8-tetramethoxyflavone and its acetate with 10% anhydrous aluminum chloride in acetonitrile afforded 6-acetyl-5,7-dihydroxy-3,4′,8-trimethoxyflavone as a byproduct along with the 5- and 3-hydroxyflavones. (3) The demethylation of the acetates proceeded more smoothly than that of hydroxyflavones and was superior to that of the flavones with a hydroxy group. (4) These demethylations are available for the syntheses of 3- or 5-hydroxyflavones with no substituent at 6-position.

In a previous paper, we reported a convenient method for synthesizing 3,5-dihydroxy-7,8-dimethoxyflavones from ω-(aroyloxy)-2-hydroxy-3,4,6-trimethoxyacetophenones via the corresponding 3-hydroxyflavones.[1] However, the yield of the 3-hydroxyflavones in this method is low and the improvement of the yield elevates the utility of the method. Generally, cleavage of the 5-methoxy group in 3,5-dimethoxyflavone derivatives is easier than the others. For example, the partial demethylation of 7-hydroxy-3,5,8-trimethoxyflavones **1** was employed for the synthesis of naturally occurring 5,7-dihydroxy-3,8-dimethoxyflavones **2**.[2,3] However, the demethylation of 4′,7-dihydroxy-3,5,8-trimethoxyflavone with anhydrous aluminum chloride in boiling ether does not give the corresponding 5-hydroxyflavone but gives 3,4′,7-trihydroxy-5,8-dimethoxyflavone as a main product.[4] The facts suggest that the 5- or 3-methoxy group on **1** was selectively cleaved by variation of the demethylating conditions.

Therefore, we studied the partial demethylation of 7-hydroxy-3,5,8-trimethoxyflavones **1**, and it was found that the demethylation was affected by the solvents and that the corresponding 5- or 3-hydroxyflavones were obtained as main products in acetonitrile or ether, respectively. In this paper, we report the selective demethylation of the 5- or 3-methoxy group in 3,5-dimethoxyflavones with no substituent at the 6-position and the characterization of the demethylated products.

Results and Discussion

Demethylation of 7-Hydroxy-3,4′,5,8-tetramethoxyflavone (1a) with Anhydrous Aluminum Chloride in Acetonitrile. Anhydrous aluminum chloride in acetonitrile is a most suitable demethylating reagent and the selective demethylation of the 5-methoxy group in 5,6,7-[5] and 5,7,8-trioxygenated flavones[6] affords quantitatively the corresponding 5-hydroxyflavones. Therefore, the selective demethylation of 7-hydroxy-3,5,8-trimethoxyflavones **1** was studied first.

Demethylation of 7-hydroxy-3,5,8-trimethoxyflavone (**1a**) with anhydrous aluminum chloride in acetonitrile required reaction times for 7–10 h and afforded 5,7-dihydroxy-3,4′,8-trimethoxyflavone (**2a**) as a main product, 3,7-dihydroxy-4′,5,8-trimethoxyflavone (**3a**), and 6-

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Table I. Demethylation of 7-Hydroxy-3,5,8-trimethoxyflavones 1 and Their Acetates 5 with 5% w/v Anhydrous Aluminum Bromide in Acetonitrile[a]

startng matl	product (rel yield) 2	3	startng matl	product (rel yield) 2	3
1a	65	35	**5a**	61	39
1b	69	31	**5b**	57	43
1c	65	35	**5c**	56	44
1d	76	24	**5d**	74	26
1e[b]	65	35	**5e**	82	18

[a] Conditions: room temperature (25–28 °C) for 2 h. [b] This dissolved slowly into the reagent to give a homogeneous solution after 30–40 min.

Table II. Demethylation of 7-Hydroxy-3,5,8-trimethoxyflavones 1 and Their Acetates 5 with 10% w/v Anhydrous Aluminum Chloride in Anhydrous Ether[a]

startng matl (% recvry)	product (rel yield) 2	3	startng matl (% recvry)	product (rel yield) 2	3
1a (8)	31	69	**5a** (<1)	28	72
1b (3)	29	71	**5b** (2)	27	73
1c[b] (12)	28	72	**5c**[b] (<1)	23	77
1d (49)	59	41	**5d** (<1)	41	59
1e[c]			**5e** (<1)	35	65

[a] Conditions: reflux for 8–10 h. [b] The product contains ca. 10% of demethylated products that were formed by the demethylation of the methoxy groups on ring B in **2** or **3**, other than **1**, **2**, and **3**. [c] This was hardly demethylated.

acetyl-5,7-dihydroxy-3,4′,8-trimethoxyflavone (**4a**). The 6-*C*-acetyl compound (**4a**) seems to be produced from **2a** by acetylation such as the Hoesch reaction, because the amount of **4a** increases with longer reaction times. In the demethylation of the acetate (**5a**) of **1a** or 7-hydroxy-3,3′,4′,5,8-pentamethoxyflavone (**1b**), the 6-*C*-acetyl compounds (**4a** or **4b**) were also isolated. These results show that the formation of 6-*C*-acetyl compounds is attributable to the fundamental properties of the reagent and **2** and cannot be suppressed by varying the conditions.

Demethylation of 7-Hydroxy-3,5,8-trimethoxyflavones 1 with Anhydrous Aluminum Bromide in Acetonitrile. Anhydrous aluminum bromide in acetonitrile as a demethylating reagent is very powerful and cleaves simultaneously the 5-methoxy and other methoxy groups on the flavone skeleton,[6] but the selective cleavage of the 5-methoxy group is also possible only under mild conditions.[1,7] Actually, the demethylation of **1a** with 10% w/v anhydrous aluminum bromide in acetonitrile at 50 °C for 1 h afforded quantitatively only a mixture of **2a** and **3a**. However, the demethylation of **1c** and **1d** under these conditions was accompanied by the cleavage of the methoxy groups on ring B. Therefore, the demethylation of **1** was reexamined by high performance liquid chromatography (HPLC)[8] and the following optimum conditions were found: a large excess of 5% w/v anhydrous aluminum bromide in acetonitrile at room temperature (25–28 °C). The demethylation of the four flavones **1a–d** under these conditions afforded quantitatively a mixture of the corresponding **2** and **3**, and no other byproducts were detected by HPLC. However, the demethylation of **1e** having two hydroxy groups adjacent to each other did not proceed as smoothly as the demethylation of the others because of the low solubility of the flavone **1e**.

In the demethylation of polyhydroxyflavone derivatives, the protection of hydroxy groups by acetyl groups is useful for prevention of the reagent consumption and of the cleavage of the methoxy groups adjacent to hydroxy groups.[5,9] Thus, the demethylation of the acetates **5a–e** was also examined and it was found that all acetates **5** were more smoothly demethylated than hydroxyflavones **1** to give quantitatively a mixture of the corresponding **2** and **3** by the subsequent hydrolysis of the demethylated products. The ratios of **2** and **3** in these demethylated products were calculated from the peak areas in the chromatograms and the molar extinction coefficients at 340 nm as shown in Table VII. The values in Table I are consistent with the yield of each product, since the products are quantitatively isolated from the reaction mixtures.

In these demethylations, the hydroxy or acetoxy group on ring B suppresses the cleavage of the 3-methoxy group and increases the yield of **2**. The protection of the 7-hydroxy group on ring A by an acetyl group tends to decrease the yield of **2**. On the other hand, the difference of the properties between **2** and **3** is large and both compounds are easily separated to each component by chromatography. The results show that the demethylation of the acetates is useful for the syntheses of **2** and for the methodology of chemical modification.

Demethylation of 1 with Anhydrous Aluminum Chloride in Ether. The demethylation of **1a** with anhydrous aluminum chloride or bromide in ether proceeded under heterogeneous conditions because of the low solubility of the aluminum complex in the solvent. Therefore, we studied the demethylation of **1** and **5** with anhydrous aluminum chloride in ether. The products were analyzed by HPLC and the results are shown in Table II. The demethylation is remarkably influenced by the properties of the aluminum chloride complex which is formed from **1** in the initial step. For example, the demethylation of the hydroxyflavones **1d** and **1e** does not proceed smoothly because of the separation of aluminum complexes in the solid state, but the demethylation of the acetates **5** proceeds more smoothly than that of hydroxyflavones **1** (Table II).

The demethylation of **1a–c** and **5** afforded the corresponding 3-hydroxyflavones as main products in contrast with the demethylation in acetonitrile. In the demethylation, the acetoxy groups on ring B increased the yield of 5-hydroxyflavones and the 7-acetoxy group on ring A tended to decrease the yield of 5-hydroxyflavones as observed in the demethylation in acetonitrile. In all demethylations except for that of **1c** and **5c**, HPLC of the products exhibited the presence of **2**, **3**, and the starting materials, but no other demethylated products. However, the methoxy groups on ring B of **1c** and **5c** are partly cleaved to form ca. 10% of more demethylated products other than **2** and **3**, since the cleavage of the 4′-methoxy group is promoted by two neighboring methoxy groups.[6]

These results show that the demethylation of the acetates with aluminum chloride in ether is useful for the syntheses of 3,7-dihydroxy-5,8-dimethoxyflavones **3**.

Characterization of the Demethylated Products. The flavones **2a**,[10] **2d**,[11] and **2e**[12] among the synthesized

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Table III. ^{1}H NMR Spectral Data for 7-Hydroxy-3,5,8-trimethoxyflavones 1, 5,7-Dihydroxy-3,8-dimethoxyflavones 2, 3,7-Dihydroxy-5,8-dimethoxyflavones 3, and 6-Acetyl-5,7-dihydroxy-3,8-dimethoxyflavones 4a and 4b in DMSO-d_6[a]

	aromatic H						
compd	C_6-H	$C_{3'}$-H	$C_{5'}$-H	$C_{2'}$-H	$C_{6'}$-H	OMe	5-OH
1a	6.44 s	7.11 d (2 H)		8.00 d (2 H)		3.73 s (3 H) 3.77 s (3 H) 3.81 s (3 H) 3.83 s (3 H)	
1b	6.47 s		7.16 d	7.66 s	7.72 dd	3.78 s (3 H) 3.79 s (3 H) 3.86 s (9 H)	
1c	6.46 s			7.40 s (2 H)		3.78 s (3 H) 3.80 s (6 H) 3.88 s (9 H)	
1d	6.45 s		6.97 d	7.67 s	7.60 dd	3.76 s (3 H) 3.78 s (3 H) 3.87 s (6 H)	
1e	6.43 s		6.91 d	7.58 s	7.49 dd	3.73 s (3 H) 3.76 s (3 H) 3.82 s (3 H)	
2a	6.29 s	7.15 d (2 H)		8.02 d (2 H)		3.82 s (6 H) 3.86 s (3 H)	12.29 s
2b	6.28 s		7.15 d	7.64 s	7.71 dd	3.84 s (6 H) 3.86 s (6 H)	12.26 s
2c	6.28 s			7.39 s (2 H)		3.78 s (3 H) 3.85 s (3 H) 3.87 s (9 H)	12.17 s
2d	6.27 s		6.98 d	7.69 s	7.60 dd	3.83 s (6 H) 3.86 s (3 H)	12.32 s
2e	6.26 s		6.91 d	7.61 s	7.48 dd	3.80 s (3 H) 3.82 s (3 H)	12.33 s
3a	6.43 s	7.12 d (2 H)		8.10 d (2 H)		3.80 s (3 H) 3.82 s (6 H)	
3b	6.45 s		7.14 d	7.75 s	7.82 dd	3.84 s (6 H) 3.86 s (6 H)	
3c	6.43 s			7.51 s (2 H)		3.75 s (3 H) 3.80 s (3 H) 3.87 s (9 H)	
3d	6.45 s		6.96 d	7.79 s	7.72 dd	3.82 s (3 H) 3.88 s (6 H)	
3e	6.42 s		6.88 d	7.68 d′	7.55 dd	3.80 s (3 H) 3.85 s (3 H)	
4a[b]		7.01 d (2 H)		8.13 d (2 H)		3.88 s (6 H) 3.92 s (3 H) 2.78 s (3 H)[c]	14.17 s 14.73 s
4b[b]			7.00 d	7.78 s	7.84 dd	3.90 s (3 H) 3.93 s (3 H) 3.96 s (6 H) 2.80 s (3 H)[c]	14.23 s 14.73 s

[a] s, singlet; d, doublet (J = 8.5 Hz); d′, doublet (J = 2.5 Hz); dd, doublet of doublets (J = 8.5, 2.5 Hz). [b] Measured in $CDCl_3$. [c] This is the signal of the *C*-acetyl group.

flavones were identical with the corresponding authentic samples that had been synthesized from 2,4,6-trihydroxy-3,ω-dimethoxyacetophenone by the Allan–Robinson reaction. The properties of **3a** agreed also with the flavone that was synthesized by Nagarajan et al.[13] However, the melting point of the flavone **2b**, which had already been synthesized from **1b** by the demethylation with anhydrous aluminum chloride in acetonitrile by Krishnamurti et al.,[3] agreed with that of **3b** but not with that of **2b**, which was synthesized in our laboratory. The physical properties of **2c** were identical with those of the flavone that was isolated from *Conyza stricta* by Sen et al.[14] and by Tandon et al.,[15] although the melting point of the acetate **6c** was strikingly different from that of the natural ones.

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(15) Tandon, S.; Pastogi, R. P. *Phytochemistry* **1977**, *16*, 1455–1456.

The ^{1}H NMR data for the hydroxyflavones **1**, **2**, and **3** (in DMSO-d_6) and their acetates **5**, **6**, and **7** (in $CDCl_3$) are shown in Tables III and IV. The signals of C_6-protons in 3,7-dihydroxy-5,8-dimethoxyflavones **3** and their acetates **7** appear in the ranges of δ 6.42 to 6.45 and of 6.50 to 6.54, respectively, and the ranges are similar to those of the starting materials **1** and their acetates **5**. On the other hand, the signals of C_6-protons in 5,7-dihydroxy-3,8-dimethoxyflavones **2** are in the range of δ 6.26 to 6.29, which is at higher field than that in **3**, but the signals of their acetates **6** shift to ca. 0.5 ppm lower field than those of **2** and are exhibited in the range of δ 6.74 to 6.77.

In the UV spectra for **2** and **3**, bands I and II are seen at 360 to 380 and 260 to 280 nm, but band I of **3** appears at ca. a 10 nm longer wavelength than that of **2** (Table V). These bands undergo typical bathochromic shifts by the addition of aluminum chloride or sodium acetate, because of the presence of 5,7- or 3,7-dihydroxy groups. In the presence of aluminum chloride, the intensity of band I for **3** is similar to that of band II, but that for **2** is markedly lower than that of band II, although band I for both flavones **2** and **3** shifts bathochromically by 50 to 60 nm. The

Table IV. ^{1}H NMR Spectral Data for 7-Acetoxy-3,5,8-trimethoxyflavones 5, 5,7-Diacetoxy-3,8-dimethoxyflavones 6, and 3,7-Diacetoxy-5,8-dimethoxyflavones 7 in $CDCl_3$[a]

	aromatic H						
compd	C_6-H	$C_{3'}$-H	$C_{5'}$-H	$C_{2'}$-H	$C_{6'}$-H	OMe	OAc
5a	6.49 s	6.99 d (2 H)		8.10 d (2 H)		3.88 s (6 H) 3.92 s (6 H)	2.37 s (3 H)
5b	6.50 s		6.98 d	7.77 d′	7.83 dd	3.89 s (3 H) 3.94 s (12 H)	2.36 s (3 H)
5c	6.51 s			7.50 s (2 H)		3.92 s (9 H) 3.94 s (9 H)	2.38 s (3 H)
5d	6.51 s		7.18 d	7.85 s	7.79 dd	3.90 s (3 H) 3.91 s (6 H) 3.95 s (3 H)	2.33 s (3 H) 2.37 s (3 H)
5e	6.50 s		7.32 d	8.03 d′	8.08 dd	3.90 s (6 H) 3.93 s (3 H)	2.32 s (6 H) 2.38 s (6 H)
6a	6.75 s	7.00 d (2 H)		8.08 d (2 H)		3.80 s (3 H) 3.88 s (3 H) 3.98 s (3 H)	2.36 s (3 H) 2.43 s (3 H)
6b	6.76 s		7.00 d	7.72 s	7.80 dd	3.81 s (3 H) 3.95 s (6 H) 4.00 s (3 H)	2.36 s (3 H) 2.44 s (3 H)
6c	6.77 s			7.43 s (2 H)		3.83 s (3 H) 3.91 s (3 H) 3.93 s (6 H) 4.00 s (3 H)	2.36 s (3 H) 2.43 s (3 H)
6d	6.77 s		7.16 d	7.79 s	7.74 dd	3.82 s (3 H) 3.89 s (3 H) 3.97 s (3 H)	2.33 s (3 H) 2.36 s (3 H) 2.44 s (3 H)
6e	6.74 s		7.30 d	7.95 d′	8.01 dd	3.81 s (3 H) 3.94 s (3 H)	2.31 s (6 H) 2.34 s (3 H) 2.43 s (3 H)
7a	6.52 s	6.99 d (2 H)		7.86 d (2 H)		3.86 s (3 H) 3.92 s (6 H)	2.36 s (6 H)
7b	6.53 s		6.98 d	7.48 s	7.57 dd	3.92 s (12 H)	2.37 s (6 H)
7c	6.54 s			7.18 s (2 H)		3.90 s (3 H) 3.93 s (12 H)	2.38 s (6 H)
7d	6.53 s		7.14 d	7.4–7.7 m (2 H)		3.87 s (3 H) 3.90 s (6 H)	2.34 s (6 H) 2.37 s (3 H)
7e	6.50 s		7.28 d	7.6–7.9 m (2 H)		3.89 s (6 H)	2.30 s (6 H) 2.36 s (6 H)

[a] s, singlet; d, doublet (J = 8.5 Hz); d′, doublet (J = 2.5 Hz); dd, doublet of doublets (J = 8.5, 2.5 Hz).

differences in the UV and ^{1}H NMR spectra would be useful for the distinction of 3- and 5-hydroxyflavones.

The ^{1}H NMR spectrum of **4a** shows a singlet at δ 2.78 for an acetyl group and two singlets at δ 14.27 and 14.83 for the two chelated hydroxy groups but does not exhibit a singlet for the C_6-proton in the flavone skeleton (Table III). The results show that the structure of **4a** is 6-acetyl-5,7-dihydroxy-3,4′,8-trimethoxyflavone, 6-C-acetate of **1a**.

Mechanism of the Demethylation. In the demethylation of polyhydroxyflavones with anhydrous aluminum halides, the cleavage of the 5-methoxy group is remarkably promoted by the oxygenated groups adjacent to the methoxy group (see the following scope and limitation). Therefore, the 5-methoxy groups in flavones with an oxygenated substituent at the 6-position[5,9] are cleaved more easily than those in flavones with no substituent at the 6-position[6] and the formation of 3-hydroxyflavones has not been recognized in the demethylation of 3,5,6-trioxygenated flavones.[16]

In the reaction mechanism, it is generally considered that the reaction proceeds via the cyclic aluminum complex as shown in Scheme I.[6,17] Therefore, the ease of the reaction depends on whether such complexes can be formed feasibly or not. For instance, the 2-methoxy groups in ω-aroyl-2,3,4,6-tetramethoxy-[1] and ω-aroyl-2,3,5,6-tetramethoxyacetophenones[16] are easily cleaved with anhydrous

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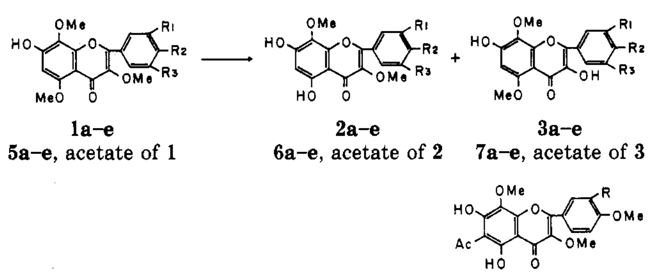
Scheme I



1a–e, **5a–e**, acetate of 1 — **2a–e**, **6a–e**, acetate of 2 — **3a–e**, **7a–e**, acetate of 3

4a: R = H
4b: R = OMe

a: $R_1 = R_3$ = H, R_2 = OMe
b: $R_1 = R_2$ = OMe, R_3 = H
c: $R_1 = R_2 = R_3$ = OMe
d: R_1 = OMe, R_2 = OH, R_3 = H
e: $R_1 = R_2$ = OH, R_3 = H

aluminum chloride in acetonitrile, whereas the 2-methoxy group in 2,3,4,6,ω-pentamethoxyacetophenone is not cleaved,[18] presumably because of the interference of the formation of the corresponding aluminum complex by an alternative formation of that between ω-methoxy and carbonyl groups.

The above facts suggest that the solvent dependency as observed in the demethylation of **1** and **5** (solvent effect) appears when there is a slight difference of demethylation rates between 3- and 5-methoxy groups and that the solvent affects the initial stage of the formation of the alu-

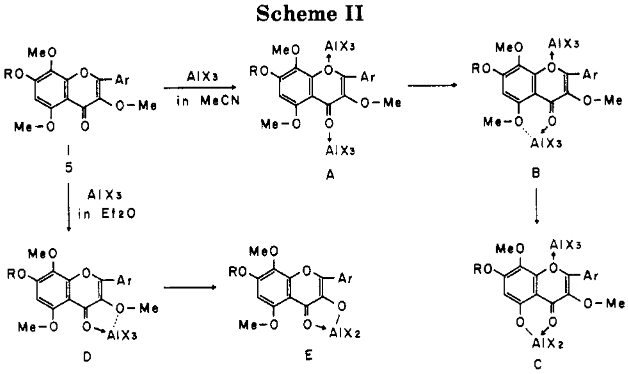
(18) Horie, T., Unpublished work.

Table V. UV Spectral Data for 5,7-Dihydroxy-3,8-dimethoxyflavones 2, 3,7-Dihydroxy-5,8-dimethoxyflavones 3, and 6-Acetyl-5,7-dihydroxy-3,8-dimethoxyflavones 4a and 4b[a]

compd		λ_{max} nm (log ε)				
2a	EtOH		275 (4.35)	301 sh (4.20)		364 (4.09)
	$EtOH-AlCl_3$		282 (4.26)	311 (4.17)	344 (4.18)	419 (4.04)
	EtOH-NaOAc		283 (4.48)	303 i (4.27)		386 (4.05)
2b	EtOH	257 (4.19)	277 (4.34)	329 (4.15)		359 (4.12)
	$EtOH-AlCl_3$	261 (4.17)	285 (4.28)		355 (4.23)	415 (3.99)
	EtOH-NaOAc		285 (4.46)	318 (4.18)		387 (4.05)
2c	EtOH		280 (4.35)	305 sh (4.19)		360 sh (4.02)
	$EtOH-AlCl_3$		288 (4.27)	313 (4.16)	348 (4.18)	417 (3.89)
	EtOH-NaOAc		286 (4.50)	306 i (4.23)		392 (4.00)
2d	EtOH	257 (4.21)	276 (4.28)	338 i (4.16)		367 (4.19)
	$EtOH-AlCl_3$	265 (4.18)	285 (4.24)		360 (4.25)	415 (4.06)
	EtOH-NaOAc		284 (4.40)	325 (4.16)		395 (4.13)
2e	EtOH	262 (4.33)	274 (4.32)			368 (4.25)
	$EtOH-AlCl_3$		283 (4.36)	305 sh (4.08)	363 (4.21)	418 (4.16)
	EtOH-NaOAc		283 (4.39)	329 (4.09)		397 (4.14)
3a	EtOH		272 (4.26)	308 (4.07)		373 (4.22)
	$EtOH-AlCl_3$	265 (4.37)			340 (3.77)	428 (4.39)
	EtOH-NaOAc		280 (4.43)			387 (4.17)
3b	EtOH	255 (4.26)	273 (4.22)	326 (4.04)		375 (4.26)
	$EtOH-AlCl_3$	265 (4.44)			348 (3.70)	432 (4.42)
	EtOH-NaOAc		281 (4.40)	323 (4.13)		392 (4.20)
3c	EtOH		281 (4.25)	310 (4.08)		374 (4.17)
	$EtOH-AlCl_3$	264 (4.35)			344 (3.77)	428 (4.37)
	EtOH-NaOAc		283 (4.45)	309 (4.15)		393 (4.16)
3d	EtOH	255 (4.27)	273 (4.17)	327 (3.99)		377 (4.29)
	$EtOH-AlCl_3$	265 (4.41)	288 sh (3.95)		350 (3.67)	435 (4.42)
	EtOH-NaOAc		281 (4.39)	324 (4.13)		391 (4.25)
3e	EtOH	257 (4.30)	273 (4.27)	328 (4.02)		379 (4.29)
	$EtOH-AlCl_3$	267 (4.48)			350 (3.63)	435 (4.47)
	EtOH-NaOAc		280 (4.27)	328 (4.18)		390 (4.05)
4a	EtOH		290 (4.43)	315 (4.35)		350 i (4.20)
	$EtOH-AlCl_3$	275 (4.31)		307 (4.50)		355 i (4.22)
	EtOH-NaOAc			302 (4.48)		388 (4.00)
4b	EtOH		288 (4.36)		344 (4.19)	370 i (4.16)
	$EtOH-AlCl_3$	270 sh (4.29)	292 (4.35)	300 i (4.32)	358 (4.25)	
	EtOH-NaOAc	277 sh (4.35)	295 (4.37)			390 (4.07)

[a] sh, shoulder; i, inflection point.

Scheme II



minum complex. Therefore, based on the assumption that 3-methoxy group cleavage is slightly easier than cleavage of the 5-methoxy group, the solvent effect is explained as follows (Scheme II).

In the demethylation in acetonitrile, anhydrous aluminum halides coordinate with the carbonyl oxygen atom at the 4-position and the etheric oxygen atom at the 1-position, and the complex such as A in Scheme II is formed, because the nitrile group of the solvent is a softer base than an etheric oxygen atom. The complex A gives preferentially the cyclic complex B, since the electron density of the 3-methoxyl oxygen atom in the complex A decreases by resonance between the etheric oxygen atoms at 1- and 3-positions. The 5-methoxy group in the complex B is easily cleaved to give the complex C, which is subsequently converted into 5-hydroxyflavone by hydrolysis. Therefore, the demethylation of **1** and **5** in acetonitrile affords the 5-hydroxyflavone as a main product.

In the demethylation of **1** and **5** in ether, anhydrous aluminum halides coordinate hardly at all to the etheric oxygen atom at the 1-position and form preferentially the cyclic complex D between the carbonyl and 3-methoxyl oxygen atoms, since the electron density of the 3-methoxyl oxygen atom is higher than that of the 5-methoxyl oxygen atom. That is, the 3-methoxy group in **1** and **5** is cleaved more easily than the 5-methoxy group.

The effects of substituents in A and B rings are explained on the basis of the change of electron densities at the 3- or 5-methoxy group under the demethylating conditions. Namely, the demethylation of the flavones **1d**, **5d**, and **5e** with a hydroxy or acetoxy group on ring B increases the yield of 5-hydroxyflavones, because these groups which are coordinated with aluminum halide decrease the electron density of the 3-methoxyl oxygen atom by resonance. On the other hand, the demethylation of **5** tends to decrease the yield of **2** more than that of **1**, suggesting that the 7-acetoxy group slightly reduces the electron density of the 5-methoxyl oxygen atom.

Scope and Limitation. We studied additionally the demethylation of the following flavones (**8**,[19] **11**,[20] and **14**[21]) of three types as shown in Scheme III in order to find the scope and limitation of the demethylation and the results are shown in Figure 1 and Table VI. The difference of the rates in the demethylation of **8** and **11** could not be recognized and the both rates were remarkably lower than

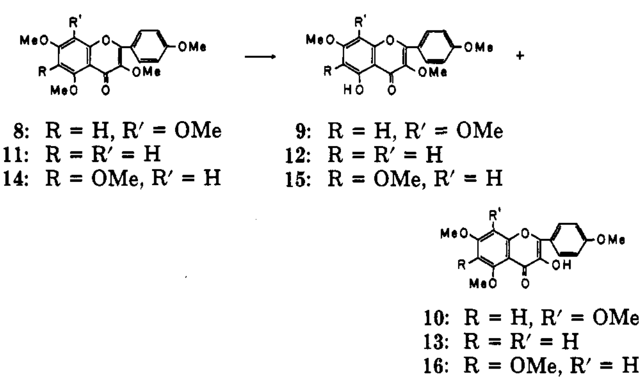
(19) Goldsworthy, L. J.; Robinson, R. *J. Chem. Soc.* **1938**, 56–58.
(20) Rao, K. V.; Seshadri, T. R. *J. Chem. Soc.* **1947**, 122–124.
(21) Row, L. R.; Seshadri, T. R. *Proc. Indian Acad. Sci.* **1946**, *23A*, 23–36.

Table VI. Demethylation of 3,5-Dimethoxyflavone Derivatives 8, 11, and 14

			product (yield, %)	
startng matl (% recvry)	reagent	conditions	5-hydroxyflavone	3-hydroxyflavone
8 (0)	5% w/v $AlBr_3$–MeCN	room temp, 2 h	62	38
8 (0)	10% w/v $AlCl_3$–MeCN	70 °C, 8 h	86	14
8 (1)	10% w/v $AlCl_3$–Et_2O	reflux, 8 h	20	80
11 (0)	5% w/v $AlBr_3$–MeCN	room temp, 2 h	50	50
11 (0)	10% w/v $AlCl_3$–MeCN	70 °C, 8 h	83	17
11[a] (>99)	10% w/v $AlCl_3$–Et_2O	reflux, 8 h		
14 (0)	5% w/v $AlBr_3$–MeCN	room temp, 0.5 h	100	
14 (0)	5% w/v $AlCl_3$–MeCN	60 °C, 1.5 h	100	
14 (0)	10% w/v $AlCl_3$–Et_2O	reflux, 3 h	100	

[a] This was hardly demethylated because the aluminum complex formed was separated from the reaction mixture as a solid.

Scheme III



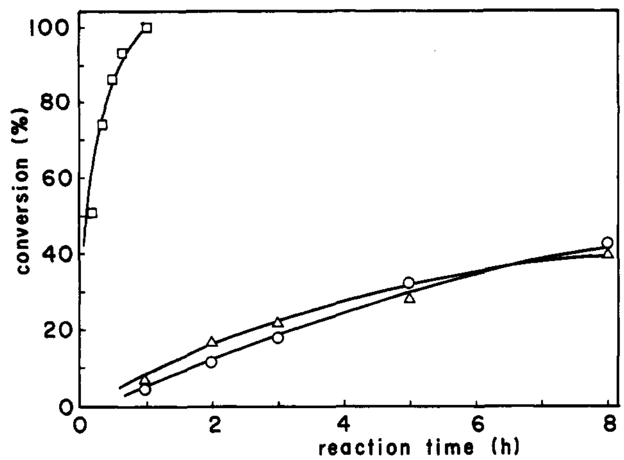


Figure 1. Demethylation of 3,5-dimethoxyflavone derivatives 8, 11, and 14 (50 mg) with 5% w/v anhydrous aluminum chloride in acetonitrile (20 mL) at 50 °C: ○, 8; △, 11; □, 14.

that of 14 with a methoxy group at the 6-position (Figure 1). The demethylation of 8 and 11 afforded also a mixture of the corresponding 3- and 5-hydroxyflavones and was influenced by the demethylating solvents (Table VI). On the other hand, the demethylation of 14 with the 6-methoxy group afforded the 5-hydroxyflavone 15 only without the influence of the solvents, again indicating the fact that the cleavage of the 5-methoxy group was remarkably promoted by the adjacent 6-oxygenated group. In the comparison of the two demethylating reagents, the selectivity in the demethylation of 8 and 11 with anhydrous aluminum chloride in acetonitrile was apparently higher than that with the bromide. The 6-*C*-acetyl derivatives like 4a were not found in the demethylation of these flavones with no free hydroxy group at the 7-position.

These results show that the demethylation is useful for the synthesis of the 3- or 5-hydroxyflavones with no substituent at the 6-position as a general method, and the important points are summarized as follows.

1. Protection of the hydroxy groups by acetyl groups is a most promising method for the selective demethylation of the 3- or 5-methoxy group in 3,5-dimethoxyflavones with free hydroxy groups.

2. Anhydrous aluminum bromide or chloride in acetonitrile as demethylating reagents cleaves preferentially the 5-methoxy group to give 5-hydroxyflavone as a main product. Although the selectivity in the demethylation with the bromide is lower than that with the chloride, the bromide is useful for the demethylation of the flavones with the 7-hydroxy or 7-acetoxy group because of no formation of byproduct.

3. For the synthesis of 3-hydroxyflavones, demethylation with anhydrous aluminum chloride in ether is useful, but that with anhydrous aluminum bromide in acetonitrile is also available when the demethylation hardly proceeds in ether.

Experimental Section

All melting points were determined in glass capillaries and are uncorrected. ^1H NMR spectra were recorded on a Hitachi R-24 spectrometer (60 MHz), using tetramethylsilane as an internal standard and chemical shifts were given in δ values. UV spectra were recorded on a Hitachi 124 spectrophotometer. The high performance liquid chromatographic analysis was carried out with a Hitachi 635 instrument, using a column (2.1 × 1000 mm) packed with Hitachi gel No. 3011, methanol (0.4 mL/min) as an eluent, and a UV monitor at 340 nm. For the separation of demethylated products, a column (20 × 600 nm) packed with Hitachi gel No. 3019 using methanol was employed. Column chromatography was carried out on Kiselgel 60 (70–230 mesh; Merck). Elemental analyses were performed with a Yanako CHN recorder Model MT-2. Acetonitrile and ether as demethylating solvents were obtained by distillation over phosphorus pentoxide and sodium wire, respectively.

7-Hydroxy-3,5,8-trimethoxyflavones 1. All of the 7-hydroxyflavones were synthesized from 2,4-dihydroxy-3,6,ω-trimethoxyacetophenone by the Allan–Robinson reaction as follows.

A mixture of the acetophenone (2.4 g, 10 mmol), substituted benzoic anhydride (37–40 mmol), and potassium benzoate (20 mmol) was heated at 170–180 °C for 8 h under reduced pressure and then the mixture was dissolved in methanol–acetone–water (ca. 3:1:1; 250–400 mL). The solution was refluxed with a solution of potassium hydroxide (7.0 g, 125 mmol) in water (20 mL) for 15–20 min under a nitrogen atmosphere and diluted with water. After the solvent was evaporated under reduced pressure, the solution was saturated with carbon dioxide and the separated phenolic products were collected by filtration and by extraction with ethyl acetate. The combined products were recrystallized to give the 7-hydroxyflavones. Only 3′,4′-bis(benzyloxy)-7-hydroxy-3,5,8-trimethoxyflavone was separated from 3,4-bis(benzyloxy)benzoic acid by fractional recrystallization with ethyl acetate and chloroform, since the crude products contained a large amount of the acid which was not dissolved in sodium hydrogencarbonate solution.

7-Hydroxy-3,4′,5,8-tetramethoxyflavone (1a): yellow needles from ethyl acetate; mp 267–268 °C (lit.[19] mp 269–270 °C); yield 45%.

7-Hydroxy-3,3′,4′,5,8-pentamethoxyflavone (1b): yellow

Table VII. Molar Extinction Coefficients at 340 nm in Ethanol and Retention Times in Methanol for Hydroxyflavones[a]

	a	b	c	d	e	others					
1	13 400 (23.6)	15 400 (22.2)	11 600 (21.0)	14 200 (13.1)	11 800 (9.8)	8	17 800 (13.6)	11	21 500 (16.8)	14	21 700 (13.3)
3	9300 (26.2)	10 000 (24.3)	8800 (22.7)	9900 (14.9)	10 000 (10.1)	10	10 700 (15.0)	13	17 800 (20.0)		
2	10 900 (32.2)	13 600 (30.8)	12 200 (28.8)	14 500 (16.8)	14 300 (11.1)	9	13 400 (27.1)	12	17 400 (32.0)	15	22 500 (22.3)

[a] Retention times (min) are shown in parentheses. Conditions in 1, 2, and 3: column, 2.1 × 1,000 mm; flow rate, 0.4 mL/min. In the others: column, 2.1 × 500 mm; flow rate, 0.7 mL/min.

needles from chloroform; mp 249–250 °C (lit.[3] mp 253–254 °C); yield 53%.

7-Hydroxy-3,3′,4′,5,5′,8-hexamethoxyflavone (1c): yellow plates from ethyl acetate–chloroform; mp 229–230 °C; yield 50%. Anal. Calcd for $C_{21}H_{22}O_9$: C, 60.26; H, 5.26. Found: C, 59.98; H, 5.34.

4′-(Benzyloxy)-7-hydroxy-3,3′,5,8-tetramethoxyflavone: yellow prisms from ethyl acetate–chloroform; mp 243–243.5 °C; yield 51%. Anal. Calcd for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21. Found: C, 67.06; H, 5.19. The flavone (460 mg) was hydrogenated with 10% palladium on charcoal (100 mg) in methanol–ethyl acetate (ca. 1:1; 200 mL) and the product was recrystallized from ethyl acetate to give 4′,7-dihydroxy-3,3′,5,8-tetramethoxyflavone (**1d**) as pale yellow needles: mp 244–246 °C; yield 340 mg (91%). Anal. Calcd for $C_{19}H_{18}O_8$: C, 60.90; H, 5.05. Found: C, 60.96; H, 4.81. Its dibenzyl ether had been synthesized by Farkas et al.[22]

3′,4′-Bis(benzyloxy)-7-hydroxy-3,5,8-trimethoxyflavone: pale yellow needles from methanol; mp 208–208.5 °C; yield 75%. Anal. Calcd for $C_{32}H_{28}O_8$: C, 71.10; H, 5.22. Found: C, 71.34; H, 5.25. The flavone was hydrogenated by the method described above to give 3′,4′,7-trihydroxy-3,5,8-trimethoxyflavone (**1d**); pale yellow needles from aqueous methanol; mp 268.5–270 °C (lit.[2] mp 268–270 °C); yield 95%. Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.44. Found: C, 59.82; H, 4.32.

Demethylation of 1a with Anhydrous Aluminum Chloride in Acetonitrile. Flavone **1a** (200 mg, 0.56 mmol) was dissolved in a solution of anhydrous aluminum chloride (2 g) in acetonitrile (20 mL) and heated at 70 °C for 10 h. The solution was poured into 2% hydrochloric acid (40 mL), heated at 70–80 °C for 20–30 min, diluted with water (40 mL), and concentrated to ca. 50 mL under reduced pressure. The crystals separated were filtered, washed with water, and dried. The product was chromatographed on a silica gel column eluting with chloroform and chloroform–ethyl acetate (10:1). 6-Acetyl-5,7-dihydroxy-3,4′,8-trimethoxyflavone (**4a**) was obtained from the first eluate: mp 203–205 °C (yellow needles from chloroform–methanol); yield 33 mg (15%). From the second and third eluates, **2a** and **3a** were obtained in 40% and 23% yields, respectively.

6-Acetyl-5,7-dihydroxy-3,3′,4′-trimethoxyflavone (4b) was obtained from **1b** by a similar procedure: mp 216–218 °C (yellow needles from chloroform–methanol); yield 10%.

General Method for Demethylation with Anhydrous Aluminum Bromide in Acetonitrile. A. Demethylation of 3,5-Dimethoxyflavones with No Acetoxy Groups. Flavone **1**, **8**, **11**, or **14** (20 mg) was dissolved in 5% w/v anhydrous aluminum bromide in acetonitrile solution (2 mL) (**1d**, 3 mL; **1e**, 4 mL) and allowed to stand at room temperature (25–28 °C) for 2 h (**14**, 30 min). The solution was poured into 2% hydrochloric acid (3 mL) (**1d**, 4 mL; **1e**, 6 mL), heated at 70–80 °C for 20–30 min, and diluted with water. The acetonitrile was evaporated under reduced pressure and the mixture was allowed to stand in a refrigerator. The yellow crystals separated were filtered (the mother liquor was colorless or slightly yellowish color), washed with water, and dried to give quantitatively demethylated products.

B. Demethylation of Acetoxyflavones 5. Acetate **5** (20 mg) was demethylated with 5% w/v anhydrous aluminum bromide in acetonitrile (2 mL) under the same conditions as described above. The reaction mixture was poured into 2% hydrochloric acid (3 mL), heated at 70–80 °C for 10–15 min, and diluted with water. The precipitate separated was extracted with ethyl acetate and the extract was concentrated. The residue was dissolved in a mixture of 15% hydrochloric acid (1.5 mL) and methanol (5 mL) and refluxed for 4–5 h. The mixture was diluted with water, concentrated, and allowed to stand in a refrigerator. The crystals separated were collected to give quantitatively the demethylated products.

(22) Farkas, L.; Nógrádi, M. *Acta Chim. Acad. Sci. Hung.* **1968**, *58*, 93–95.

Table VIII. 5,7-Dihydroxy-3,8-dimethoxyflavones 2 and 3,7-Dihydroxy-5,8-dimethoxyflavone 3

compd	mp (°C)	recrystn solvent	formula	found C	found H	calcd C	calcd H
2a	170–171	$CHCl_3$–MeOH	$C_{18}H_{16}O_7$	62.48	4.61	62.79	4.68
(lit.[10] 171–172)							
2b	224–225	EtCOMe	$C_{19}H_{18}O_8$	60.87	4.92	60.96	4.85
(lit.[3] 243)							
2c	206–207	MeOH	$C_{20}H_{20}O_9$	59.10	4.85	59.40	4.99
(lit.[14] 204–205)							
(lit.[15] 209.5)							
2d	215–217	MeOH	$C_{18}H_{16}O_8$	59.96	4.43	60.00	4.48
(lit.[11] 217–219)							
2e	297–299	aqueous MeOH	$C_{17}H_{14}O_8$	58.84	3.98	58.96	4.08
(lit.[2] 300–302)							
(lit.[12] 297–299)							
3a	282–284	EtCOMe–MeOH	$C_{18}H_{16}O_7$	62.76	4.69	62.79	4.68
(lit.[13] 279–280)							
3b	245–246	EtCOMe–MeOH	$C_{19}H_{18}O_8$	60.70	4.77	60.96	4.85
3c	245–246	MeOH	$C_{20}H_{20}O_9$	59.15	4.83	59.40	4.99
3d	247–249	MeOH	$C_{18}H_{16}O_8$	60.10	4.69	60.00	4.48
3e	302–303	aqueous MeOH	$C_{17}H_{14}O_8$	58.95	3.97	58.96	4.08

General Method for Demethylation with Anhydrous Aluminum Chloride in Ether. Anhydrous aluminum chloride (10% w/v) in ether (3 mL) was added to flavone **1**, **5**, **8**, **11**, or **14**, and the separated aluminum complex was finely divided by a ultrasonic cleaner (Bransonic Model 12) for 5–10 min. The mixture was refluxed for 8–10 h and poured into 2% hydrochloric acid (5 mL), and the ether was evaporated off. The mixture was treated by the following two methods.

A. To the mixture from acetates **5** was added ethyl acetate, and the mixture was heated with stirring at 65–75 °C for 10–15 min. The mixture was extracted with ethyl acetate and the extract was concentrated. The residue was hydrolyzed with hydrochloric acid by the method described above to give quantitatively demethylated products.

B. To the reaction mixture from the other flavones was added methanol until the separated precipitate dissolved. The mixture was heated at 70–80 °C for 15–20 min and diluted with water. The solvent was evaporated and the mixture was allowed to stand in a refrigerator. The crystals separated were collected to give quantitatively demethylated products.

Analysis and Separation of the Demethylated Product. These demethylated products were analyzed by HPLC and the ratios of **2** and **3** were calculated from the peak areas and the molar extinction coefficient at 340 nm as shown in Table VII. The results are shown in Tables I and II.

For the separation of the demethylated products, 100–200 mg of starting materials were employed and the products were treated by the following method. The demethylated products from **1a–c**, **8**, and **11** were chromatographed on a silica gel column eluting

Table IX. 7-Acetoxy-3,5,8-trimethoxyflavones 5, 5,7-Diacetoxy-3,8-dimethoxyflavones 6, and 3,7-Diacetoxy-5,8-dimethoxyflavones 7

compd	mp (°C)	recrystn solvent	formula	found C	found H	calcd C	calcd H
5a	174–175	MeOH	$C_{21}H_{20}O_8$	62.95	4.99	62.99	5.04
5b	166–167	MeOH	$C_{22}H_{22}O_9$	61.04	5.01	61.39	5.15
5c	169–170	MeOH	$C_{23}H_{24}O_{10}$	60.02	5.18	60.00	5.25
5d	156–157	MeOH	$C_{23}H_{22}O_{10}$	60.36	4.92	60.26	4.84
5e	168–169	MeOH	$C_{24}H_{22}O_{11}$	59.19	4.43	59.26	4.56
(lit.[2] 172–173)							
6a	165–166	MeOH	$C_{22}H_{20}O_9$	61.63	4.68	61.68	4.71
(lit.[10] 166.5–167.5)							
6b	144–145	MeOH	$C_{23}H_{22}O_{10}$	60.35	4.83	60.26	4.84
6c	136–137	MeOH	$C_{24}H_{24}O_{11}$	58.89	4.88	59.01	4.95
(lit.[14] 165–167)							
(lit.[15] 152)							
6d	138–139	MeOH	$C_{24}H_{22}O_{11}$	59.26	4.65	59.26	4.56
(lit.[11] 140–141 and 147–148.5)							
6e	156–157	MeOH	$C_{25}H_{22}O_{12}$	58.10	4.25	58.37	4.31
(lit.[2] 158–160)							
(lit.[12] 157–158)							
7a	148–150	aqueous MeOH	$C_{22}H_{20}O_9$	61.58	4.91	61.68	4.71
(lit.[13] 154)							
7b	170–171	MeOH	$C_{23}H_{22}O_{10}$	60.24	4.62	60.26	4.84
7c	146–147	MeOH	$C_{24}H_{24}O_{11}$	58.93	4.78	59.01	4.95
7d	157–158	aqueous MeOH	$C_{24}H_{22}O_{11}$	59.00	4.58	59.26	4.56
7e	99–101	MeOH	$C_{25}H_{22}O_{12}$	58.08	4.56	58.37	4.31

with chloroform–ethyl acetate (10:1). The 5- and 3-hydroxyflavones were obtained from the first and second eluates, respectively. The demethylated products from **1d** and **1e** were separated by preparative HPLC using methanol as eluent. 5-Hydroxy-3,4′,7,8-tetramethoxyflavone (**9**):[10] yellow needles from methanol, mp 167–168 °C. 3-Hydroxy-4′,5,7,8-tetramethoxyflavone (**10**):[1] yellow prisms from methanol, mp 198–200 °C. 5-Hydroxy-3,4′,7-trimethoxyflavone (**12**): yellow prisms from ethyl acetate–hexane, mp 145–146.5 °C (lit.[23] mp 152–153 °C). 3-Hydroxy-4′,5,7-trimethoxyflavone (**13**): yellow needles from chloroform–ethyl acetate, mp 147.5–148.5 °C (lit.[23] mp 149–150 °C). 5-Hydroxy-3,4′,6,7-tetramethoxyflavone (**15**):[10] pale yellow prisms from chloroform–ethyl acetate, mp 168–169 °C. The other flavones **2** and **3** as yellow needles or prisms are shown in Table VIII.

Acetylation of the Hydroxyflavones. All of the hydroxyflavones were easily acetylated by the hot acetic anhydride–pyridine method to give the corresponding acetates as colorless needles. The results are shown in Table IX.

Registry No. **1a**, 85734-53-8; **1b**, 33554-63-1; **1c**, 110193-72-1; **1d**, 22109-96-2; **1e**, 7678-88-8; **2a**, 1570-09-8; **2b**, 42923-42-2; **2c**, 62953-00-8; **2d**, 14965-08-3; **2e**, 4988-22-1; **3a**, 95125-09-0; **3b**, 110193-74-3; **3c**, 110193-75-4; **3d**, 33554-57-3; **3e**, 110193-76-5; **4a**, 110193-77-6; **4b**, 110193-78-7; **5a**, 110193-79-8; **5b**, 110193-80-1; **5c**, 110193-81-2; **5d**, 23344-33-4; **5e**, 20972-77-4; **6a**, 5128-43-8; **6b**, 110193-82-3; **6c**, 62953-04-2; **6d**, 15085-75-3; **6e**, 4853-12-7; **7a**, 95626-26-9; **7b**, 110193-83-4; **7c**, 110193-84-5; **7d**, 110193-85-6; **7e**, 110193-86-7; **8**, 24027-55-2; **9**, 15486-34-7; **10**, 24027-55-2; **11**, 16692-52-7; **12**, 15486-34-7; **13**, 5631-70-9; **14**, 4472-73-5; **15**, 14787-34-9; 2,4-dihydroxy-3,6,ω-trimethoxyacetophenone, 42923-40-0; 4′-(benzyloxy)-7-hydroxy-3,3′,5,8-tetramethoxyflavone, 110205-36-2; 3′,4′-bis(benzyloxy)-7-hydroxy-3,5,8-trimethoxyflavone, 110193-73-2; 4-methoxybenzoic anhydride, 794-94-5; 3,4-dimethoxybenzoic anhydride, 24824-54-2; 3,4,5-trimethoxybenzoic anhydride, 1719-88-6; 4-(benzyloxy)-3-methoxybenzoic anhydride, 1592-47-8; 3,4-bis(benzyloxy)benzoic anhydride, 1592-48-9; potassium 4-methoxybenzoate, 52509-81-6; potassium 3,4-dimethoxybenzoate, 25635-53-4; potassium 3,4,5-trimethoxybenzoate, 29970-25-0; potassium 4-(benzyloxy)-3-methoxybenzoate, 110193-70-9; potassium 3,4-bis(benzyloxy)benzoate, 110193-71-0.

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Marine Alkaloids. 12.[1] Chartellines, Halogenated β-Lactam Alkaloids from the Marine Bryozoan *Chartella papyracea*

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The isolation and structure elucidation of three new β-lactam indole alkaloids, chartellines B and C and methoxydechlorochartelline A, from the marine bryozoan *Chartella papyracea* are described. The chartellines only differ in the number and position of the bromo substituents. Dechloro-3-methoxychartelline A is an artifact formed during the isolation procedure and is synthesized from chartelline A. All four alkaloids have the *S* configuration.

Bryozoans have lately emerged as a source of biologically active compounds. The prospect of identifying new interesting compounds from this large invertebrate phylum is thus quite encouraging. The limited number of studies reported so far[3] is at least in part due to difficulties in securing enough material for serious investigations to be performed. Many bryozoan species are adapted to an

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