Studies of the Selective *O*-Alkylation and Dealkylation of Flavonoids. XXIII.[1] Demethylation Behaviors of 6-Hydroxy-4′,7-dimethoxy-5-tosyloxyflavones with Anhydrous Aluminum Halides in Acetonitrile

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In the demethylation of 6-hydroxy-3,4′,7-trimethoxy-5-tosyloxyflavone (1) with anhydrous aluminum bromide ($AlBr_3$) or anhydrous aluminum chloride–sodium iodide ($AlCl_3$–NaI) in acetonitrile, the elimination of the 5-tosyloxy group proceeded after demethylation to give 8-bromo-3,6,7-trihydroxy-4′-methoxyflavone (6) or 3,6,7-trihydroxy-4′-methoxyflavone (5) as a main product. The demethylation of 6-hydroxy-4′,7-dimethoxy-5-tosyloxyflavone (2) with $AlCl_3$–NaI also afforded 6,7-dihydroxy-4′-methoxyflavone (12), but that with $AlBr_3$ afforded 8-bromo-5,6,7-trihydroxy-4′-methoxyflavone (13) as a main product. The demethylation of 1 with anhydrous aluminum chloride ($AlCl_3$) was accompanied by migration of the tosyl group to give a mixture of 3,6-dihydroxy-7,4′-dimethoxy-5-tosyloxyflavone (3) and 5-hydroxy-3,4′,7-trimethoxy-6-tosyloxyflavone (9), but that of 2 proceeded after the cleavage of the 5-tosyloxy group to give a mixture of 5,6-dihydroxy-7,4′-dimethoxy- (14) and 5,6,7-trihydroxy-4′-methoxyflavones (15) other than the corresponding 6-tosyloxyflavone (16). In the demethylation of the acetates of 1 and 2 with $AlCl_3$, the cleavage of the 5-tosyloxy group proceeded prior to the demethylation to afford the corresponding 5,6,7-trihydroxyflavones (8 and 15), although the demethylation of the former acetate was accompanied by formation of 3,5,7-trihydroxy-4′-methoxy-6-tosyloxyflavone (10). Mechanisms are proposed for these reactions.

Key words 5-tosyloxyflavone; abnormal demethylation; mechanism; anhydrous $AlCl_3$–MeCN; anhydrous $AlBr_3$–MeCN; anhydrous $AlCl_3$–NaI–MeCN

In a previous paper,[2] we reported that the demethylation of 6-hydroxy-3,4′,7-trimethoxy-5-tosyloxyflavone (**1**) with anhydrous aluminum bromide in acetonitrile is accompanied by elimination of the 5-tosyloxy group to give 8-bromo-3,6,7-trihydroxy-4′-methoxyflavone (**6**) as a main product, while that of the acetate (**A1**) with anhydrous aluminum chloride affords 5,6,7-trihydroxy-3,4′-dimethoxyflavone (**8**) accompanied by cleavage of the 5-tosyloxy group. The result suggests that the demethylation of 6-hydroxy-4′,7-dimethoxy-5-tosyloxyflavone (**2**) with the bromide would also afford 8-bromo-6,7-dihydroxy-4′-methoxyflavone. The demethylation of **2**, however, did not give the flavone, but afforded 8-bromo-5,6,7-trihydroxy-4′-methoxyflavone (**13**) as a main product. The elucidation of these unique reactions may be useful to survey the scope and limitations of the application of these reagents to the flavonoid synthesis. Therefore, we reexamined the demethylation of the 5-tosyloxyflavones (**1** and **2**) with anhydrous aluminum halides in acetonitrile in detail.

Results

The demethylation of 6-hydroxy-7-methoxy-5-tosyloxyflavones, **1** and **2**, was greatly affected by the nature of the reagent, such as anhydrous aluminum bromide ($AlBr_3$), anhydrous aluminum chloride ($AlCl_3$), or anhydrous aluminum chloride–sodium iodide ($AlCl_3$–NaI)[2,3] in acetonitrile, as well as by the reaction conditions, and afforded various products as summarized in Chart 1. The structures of these products were supported by their ^{1}H-NMR and UV spectral data as shown in Tables 1 and 2.

The ^{1}H-NMR spectra of the flavones **9** and **16** indicated the presence of chelated hydroxy and tosyl groups, and bands I and II in the UV spectra were bathochromically shifted upon the addition of aluminum chloride, showing that the structure is the 6-tosylate of **7**[5] or **14**,[6,7] respectively. The ^{1}H-NMR spectrum of the flavone **10** indicated the presence of chelated hydroxy, tosyl and methoxy groups, and the 8-proton signal at δ 6.95 in dimethyl sulfoxide-d_6 (DMSO-d_6) is paramagnetically shifted to δ 7.52 (in $CDCl_3$) by acetylation of the hydroxy groups (triacetate, **A10**). The large lower field shift is characteristic of flavones with a 7-hydroxy group,[6-8] and shows that the structure is 3,5,7-trihydroxy-4′-methoxy-6-tosyloxyflavone (**10**). This structure is supported by the fact that bands I and II in the UV spectra are bathochromically shifted upon the addition of aluminum chloride or sodium acetate (Table 2). The ^{1}H-NMR spectrum of the flavone **11** indicates the presence of tosyl, methoxy, and two hydroxy groups, and the 8-proton signal at δ 7.00 (in DMSO-d_6) is shifted to δ 7.54 (in $CDCl_3$) by acetylation of the hydroxy groups (diacetate, **A11**). Furthermore, the UV spectral behavior is similar to that of the flavone **12**, and band I is bathochromically shifted upon the addition of sodium acetate. These facts show that the structure of the flavone is 6,7-dihydroxy-4′-methoxy-5-tosyloxyflavone (**11**). The ^{1}H-NMR, UV, and MS data for the flavone **13** show that it is a 8- or 3-brominated derivative of 5,6,7-trihydroxy-4′-methoxyflavone (**15**).[6,7] The aromatic proton signal at δ 6.98 in the ^{1}H-NMR spectrum in DMSO-d_6 is not paramagnetically shifted by acetylation of the hydroxy groups (triacetate, **A13**), showing clearly that the structure is 8-bromo-5,6,7-trihydroxy-4′-methoxyflavone (**13**). The structure of 6,7-dihydroxy-4′-methoxyflavone (**12**) was suggested from the ^{1}H-NMR and UV spectral

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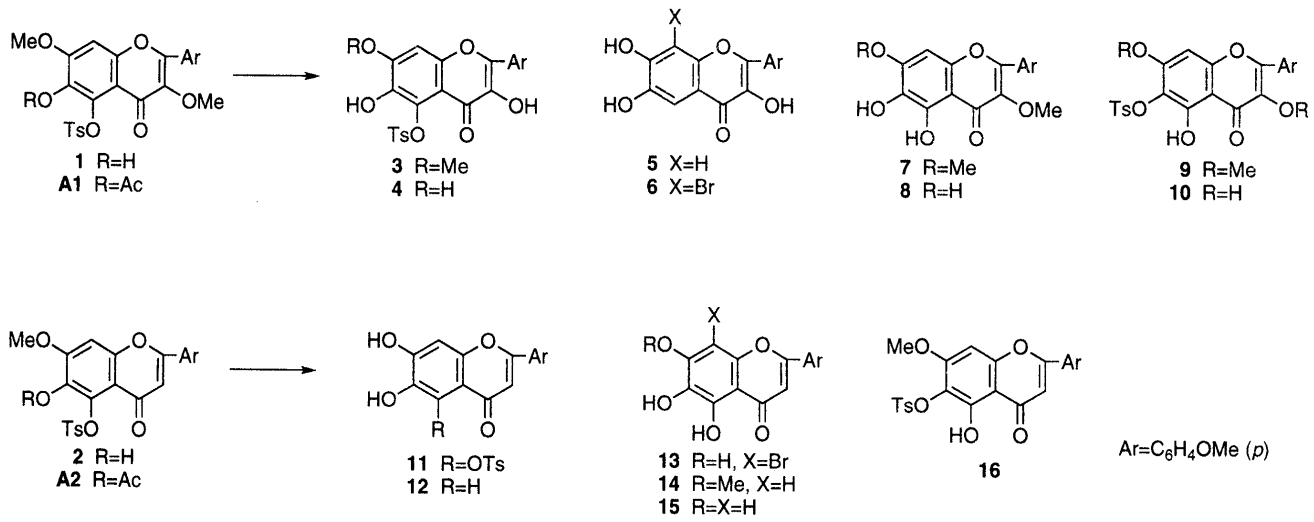

Chart 1

Table 1. ^{1}H-NMR Data for 5-Tosyloxyflavones and the Demethylated Products in DMSO-d_6, and Their Acetates in $CDCl_3$[a)]

Compd.	C_3-H	C_5-H	C_8-H	$C_{3',5'}$-H	$C_{2',6'}$-H	Ts (arom. H)		Ts-Me	OMe	OH or OAc
1[2)]			7.31 s	7.13 d (2H)	8.02 d (2H)	7.41 d (2H)	7.75 d (2H)	2.40 s	3.62 s 3.86 s 3.94 s	9.49 s
3[4)]			7.31 s	7.12 d (2H)	8.17 d (2H)	7.42 d (2H)	7.80 d (2H)	2.42 s	3.85 s 3.94 s	9.29 s 9.20 s
9			6.98 s	7.16 d (2H)	8.08 d (2H)	7.49 d (2H)	7.83 d (2H)	2.46 s	3.66 s 3.82 s 3.87 s	12.89 s
10			6.95 s	7.11 d (2H)	8.12 d (2H)	7.42 d (2H)	7.79 d (2H)	2.42 s	3.84 s	11.19 s 9.16 s 9.14 s
5[2)]		7.31 s	6.97 s	7.10 d (2H)	8.12 d (2H)				3.84 s	10.42 br 9.74 br 9.01 br s
6[2)]		7.37 s		7.15 d (2H)	8.23 d (2H)				3.95 s	10.62 br s (2H) 9.32 br s
7[5)]			6.90 s	7.15 d (2H)	8.06 d (2H)				3.81 s 3.87 s 3.91 s	12.31 s 8.76 s
8[8)]			6.53 s	7.13 d (2H)	8.02 d (2H)				3.79 s 3.86 s	12.46 s 10.56 s 8.08 s
2	6.67 s		7.36 s	7.11 d (2H)	8.02 d (2H)	7.41 d (2H)	7.77 d (2H)	2.42 s	3.86 s 3.95 s	9.43 s
11	6.60 s		7.00 s	7.09 d (2H)	7.97 d (2H)	7.41 d (2H)	7.77 d (2H)	2.42 s	3.85 s	11.13 s 9.25 s
16	7.04 s		7.03 s	7.14 d (2H)	8.10 d (2H)	7.50 d (2H)	7.83 d (2H)	2.46 s	3.68 s 3.87 s	13.22 s
12	6.73 s	7.29 s	7.01 s	7.01 d (2H)	7.99 d (2H)				3.85 s	10.03 br (2H)
14[6,7)]	6.90 s		6.95 s	7.13 d (2H)	8.07 d (2H)				3.87 s 3.92 s	12.61 s 8.74 s
15[6,7)]	6.84 s		6.60 s	7.11 d (2H)	8.03 d (2H)				3.86 s	12.76 s 10.50 s 8.77 s
13	6.98 s			7.16 d (2H)	8.10 d (2H)				3.89 s	12.89 s 10.86 s 9.54 s
A10			7.52 s	7.00 d (2H)	7.79 d (2H)	7.35 d (2H)	7.91 d (2H)	2.47 s	3.88 s	2.13 s 2.29 s 2.31 s
A5[2)]		8.02 s	7.52 s	7.02 d (2H)	7.83 d (2H)				3.89 s	2.34 s 2.34 s 2.35 s
A6[2)]		8.03 s		7.05 d (2H)	7.98 d (2H)				3.90 s	2.34 s 2.38 s 2.42 s
A11	6.56 s		7.54 s	7.01 d (2H)	7.79 d (2H)	7.38 d (2H)	7.96 d (2H)	2.47 s	3.89 s	2.20 s 2.33 s
A12	6.71 s	7.51 s	8.00 s	7.02 d (2H)	7.85 d (2H)				3.89 s	2.34 s 2.35 s
A13	6.61 s			7.04 d (2H)	7.92 d (2H)				3.90 s	2.34 s 2.41 s 2.43 s

a) s, singlet; br s, broad singlet; br, broad; d, doublet (J=8.5—9.0 Hz).

Table 2. UV Spectral Data for 5-Tosyloxyflavones and Their Demethylated Products

Compd.	λ_{max} nm (log ε)[a)]		
	MeOH	MeOH–$AlCl_3$	MeOH–NaOAc
1	265 (4.18) 330 (4.46)	No shift	295 (4.30) 330 (4.34) 380 sh (3.79)
3	261 (4.28) 347 (4.41)	274 (4.40) 418 (4.52)	261 (4.28) 283 (4.25) 352 (4.38)
5	259 (4.12) 348 (4.45)	273 (4.25) 280 sh (4.22) 418 (4.55)	265 (4.18) 376 (4.36)
6	265 (4.12) 358 (4.33)	274 (4.25) 315—325 (3.73) 422 (4.55)	268 (4.19) 304 (4.03) 380 (4.35)
9	269 (4.37) 340 (4.38)	278 (4.37) 300 sh (4.13) 360 (4.38) 390 sh (4.33)	No shift
10	261 (4.16) 349 (4.40)	249 (4.27) 275 (4.32) 420 (4.53)	267 (4.22) 372 (4.38)
2	274 (4.23) 321 (4.49)	No shift	307 (4.46) 387 (3.79)
11	275 (4.21) 323 (4.46)	291 (4.30) 410 sh (3.91)	279 (4.37) 360 (4.26)
12	274 (4.14) 325 (4.40)	293 (4.28) 420 (4.20)	281 (4.33) 370 (4.25)
13	292 (4.30) 336 (4.31)	314 (4.38) 387 (4.33)	282 (4.37) 372 (4.16)
16	271 (4.30) 330 (4.42)	280 (4.29) 300 (4.23) 354 (4.43) 373 i (4.36)	No shift

a) sh, shoulder; i, inflection point.

Table 3. Demethylation Conditions of 5-Tosyloxyflavones (**1** and **2**) and Their Products

Run	Starting material	Reaction conditions			Total yield (%)	Product ratio (%)						
		Reagent[a]	Temp. (°C)	Time (h)		**3**	**5**	**6**	**7**	**8**	**9**	**10**
1	**1**	$AlBr_3$	70	32	quant.		10	90				
2	**1**	$AlBr_3$	30	24	quant.	100						
3	**1**	$AlCl_3$–NaI	30	5	quant.		100					
4	**1**	$AlCl_3$	70	6	quant.	84					16	
5	**A1**	$AlCl_3$	70	6	quant.	22			39	39		
6	**A1**	$AlCl_3$	70	48	quant.					79		21
7	**3**	$AlCl_3$	70	48	quant.							100
						11	**12**	**13**	**14**	**15**	**16**	
8	**2**	$AlBr_3$	70	48	80[b]		18	82				
9	**2**	$AlBr_3$	30	42	65[b]	100						
10	**2**	$AlCl_3$–NaI	30	5	quant.		100					
11	**2**	$AlCl_3$	70	6	quant.				18	44	38	
12	**A2**	$AlCl_3$	70	6	quant.				50	50		
13	**A2**	$AlCl_3$	70	48	quant.					100		

a) Reagent: $AlBr_3$ = 10% (w/v) $AlBr_3$–MeCN (10 eq); $AlCl_3$–NaI = 10% (w/v) $AlCl_3$–NaI–MeCN (10 eq); $AlCl_3$ = 30% (w/v) $AlCl_3$–MeCN (30 eq). *b*) The yield was that after treatment with hot methanol.

data and confirmed by synthesis. For identification of the other products, **3**,[4] **5**,[2] **6**,[2] **7**,[5] **8**,[8] **14**,[6] and **15**,[6] we used authentic samples synthesized previously.

The analysis of these products by high-performance liquid chromatography was difficult because of their low solubility in the eluting solvent. On the other hand, the signals of the protons at the 8- and/or 3-positions in the ^{1}H-NMR spectra of the products were affected by the substituents on the A ring and were observed in the ranges of δ 6.53 to 7.36 and of δ 6.60 to 7.04 as sharp singlets which did not overlap with the other signals, suggesting that the ratio of the products can be estimated by using these signals (Table 1). Therefore, the product ratios in this experiment were estimated from the intensities of the 8-proton signals, although the 3-proton signals were used for the analysis when 8-brominated compounds were involved. The results are shown in Table 3.

Namely, the demethylation of **1** with $AlBr_3$ afforded a mixture of **6** and a small amount of **5**, accompanied by elimination of the 5-tosyloxy group, but 3,6-dihydroxy-4′,7-dimethoxy-5-tosyloxyflavone (**3**) was also formed instead when the demethylation was carried out under mild conditions (Table 3; runs 1 and 2). The demethylation of **1** with $AlCl_3$–NaI quantitatively afforded the flavone **5** (run 3). The results suggest that the flavones **5** and **6** were produced *via* 3,6,7-trihydroxy-4′-methoxy-5-tosyloxyflavone (**4**), which was not isolated. The demethylation of **1** with $AlCl_3$ also afforded **3** as a main product, although the flavone **9** was partly produced by migration of the 5-tosyl group (run 4). In the demethylation of its acetate **A1** with $AlCl_3$, however, the cleavage of the 5-tosyloxy group proceeded predominantly to give a mixture of 5,6-dihydroxy-3,4′,7-trimethoxyflavone (**7**) and the further demethylated product **8** other than **3**, and these products were converted into a mixture of **8** and 3,5,7-trihydroxy-4′-methoxy-6-tosyloxyflavone (**10**) after 48 h (runs 5 and 6). The results show that the flavone **3** is converted into **10** by demethylation and simultaneous migration of a tosyl group. Indeed, the demethylation of **3** with $AlCl_3$ quantitatively afforded the flavone **10** (run 7).

In contrast to the above results, the demethylation of **2** with no substituent at the 3-position with $AlBr_3$ under mild conditions quantitatively afforded 6,7-dihydroxy-4′-methoxy-5-tosyloxyflavone (**11**), and the product was converted into a mixture of 8-bromo-5,6,7-trihydroxy-4′-methoxyflavone (**13**) as a main product and 6,7-dihydroxy-4′-methoxyflavone (**12**) at 70 °C for 48 h (runs 8 and 9). In the demethylation with $AlCl_3$–NaI, however, the detosyloxylated product **12** was quantitatively obtained (run 10). On the other hand, the demethylation of **2** with $AlCl_3$ afforded two detosylated products, **14** and **15**, and an appreciable amount of the isomerized product **16** (run 11). In the demethylation of its acetate **A2** with $AlCl_3$, the cleavage of the 5-tosyloxy group proceeded prior to the demethylation to give a mixture of **14** and **15** without formation of the isomerized product **16**, and the products were converted into **15** after 48 h (runs 12 and 13).

Discussion

Our results show that demethylation with $AlBr_3$ and $AlCl_3$–NaI proceeds prior to the elimination or cleavage of the 5-tosyloxy group, and $AlCl_3$ mainly cleaves the 5-tosyloxy group prior to demethylation. The phenomena can be considered to be caused by differences in the interaction between the bulky 5-tosyloxy group and the reagents, based on our previous paper:[9] the 5-tosyloxyl oxygen atom can interact with $AlCl_3$ coordinated to the 4-carbonyl group and the tosyloxy group is cleaved prior to the demethylation, but the interaction with bulky $AlBr_3$ is difficult and the elimination or cleavage of the 5-tosyloxy group proceeds after demethylation. The reason why a combined reagent such as $AlCl_3$–NaI demethylates prior to detosyloxylation is presumed to be an acceleration of the demethylation relative to the detosylation. On the basis of the above considerations, the mechanism of these unique demethylations is considered to be as shown in Charts 2 and 3.

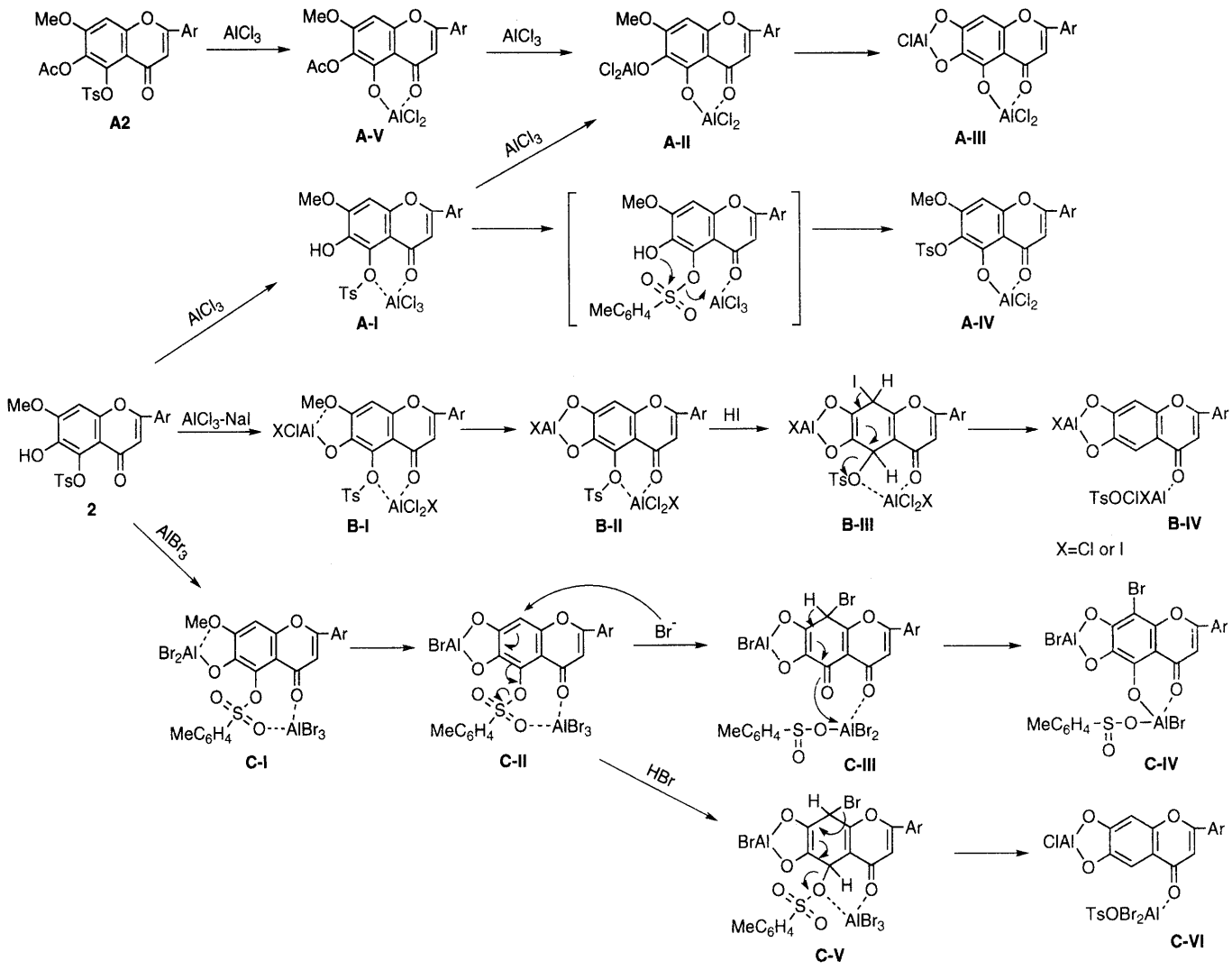

Chart 2

Demethylation of 6-Hydroxy-4′,7-dimethoxy-5-tosyloxyflavone (2) and Its Acetate (A2) (Chart 2) Since $AlCl_3$ coordinated to the 4-carbonyl group in **2** is able to interact with the 5-tosyloxyl oxygen atom, the first-formed complex **A-I** is detosylated to a cyclic aluminum complex **A-II**, which is further demethylated to **A-III**, accompanied by migration of the tosyl group to **A-IV** with the participation of the neighboring 6-hydroxy group. In the demethylation of its acetate **A2** with $AlCl_3$, the migration is completely suppressed because of protection of the 6-hydroxy group and **A2** is demethylated to **A-III** *via* **A-V** and **A-II** *via* a similar pathway to that in the case of the demethylation of 6-acetoxy-5,7-dimethoxyflavones with $AlCl_3$.[7,8] In contrast to this, a combined reagent such as $AlCl_3$–NaI greatly accelerates the formation of the aluminum–oxygen bond and cleavage of the methoxy group adjacent to a carbonyl or hydroxy group.[2,9] Therefore, in the demethylation of **2** with $AlCl_3$–NaI, the 7-methoxy group is cleaved under mild conditions *via* **B-I** prior to the detosyloxylation to form a cyclic aluminum complex **B-II**. The carbon atom at the 8-position in **B-II** is attacked by an iodide ion because of the electron-withdrawing nature of the 5-tosyloxy group to form an adduct **B-III**, which is quantitatively converted into **B-IV** by elimination of the iodo and tosyloxy groups.

In the demethylation of **2** with $AlBr_3$, the first-formed complex **C-I** is demethylated to a cyclic complex **C-II** under mild conditions and stabilized, since interaction between the 5-tosyloxyl oxygen atom and bulky $AlBr_3$ coordinated to the 4-carbonyl group is difficult owing to the steric hindrance of the tosyl group. It seems that the stability of **C-II** is a result of the interaction between $AlBr_3$ coordinated to the 4-carbonyl group and the 5-tosyl oxygen atom (**C-I** or **C-II**), and the interaction also accelerates elimination of the 5-tosyl group: with raising the reaction temperature, the complex **C-II** is mainly converted into an adduct **C-III** by attack of a bromide ion on the carbon atom at the 8-position, and the adduct **C-III** is aromatized to a stable complex **C-IV**. In this case, the formation pathway of the detosyloxylated product **C-VI** as a minor product is assumed as follows: the complex **C-II** is partly converted into an adduct **C-V** by addition of hydrogen bromide accompanied by isomerization of the complex and then detosyloxylated.

Demethylation of 6-Hydroxy-3,4′,7-trimethoxy-5-tosyloxyflavone (1) and Its Acetate (A1) (Chart 3) In the demethylation of **1** with $AlBr_3$, the 3-methoxy group in the complex **D-I** is quantitatively demethylated by inter-

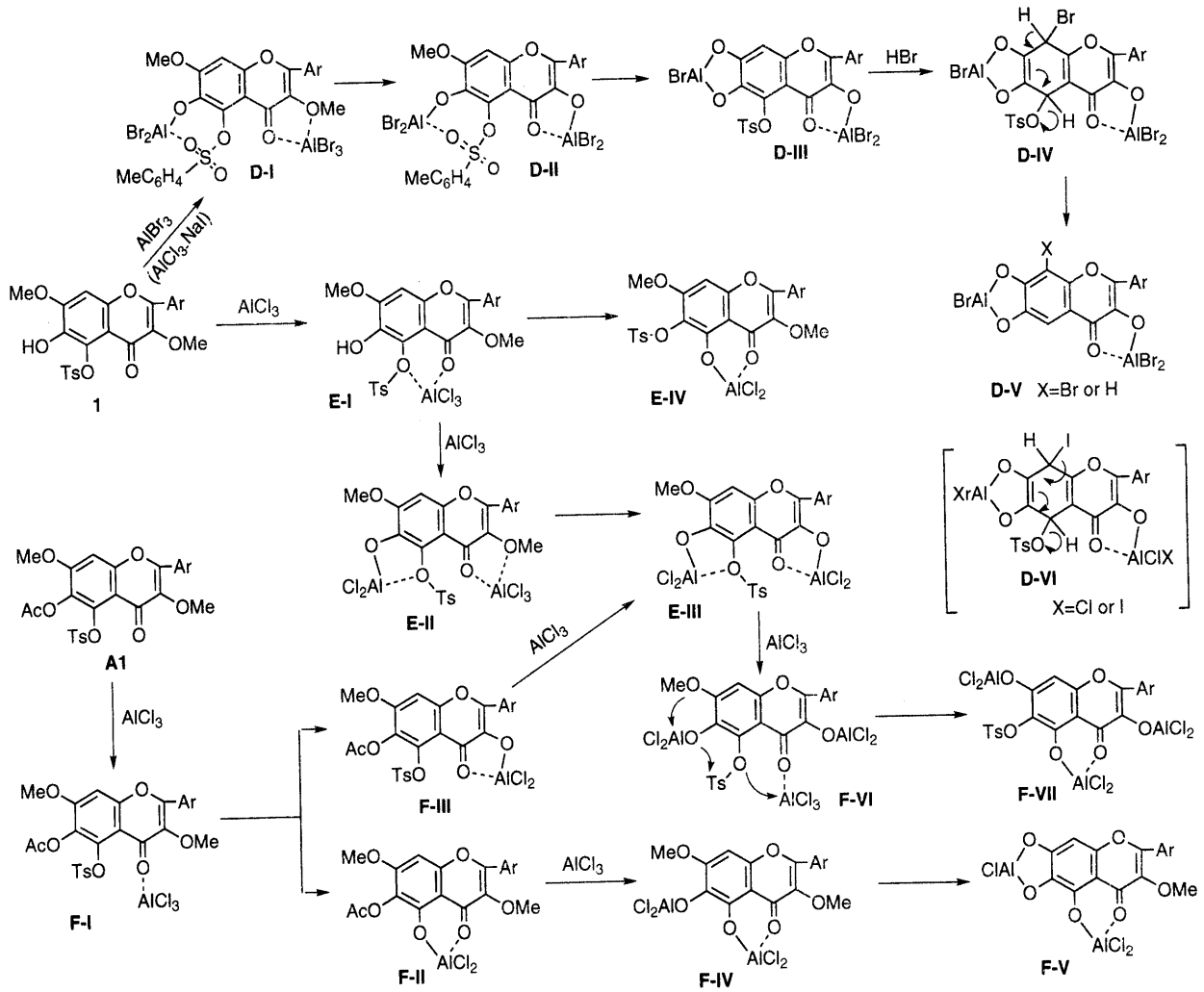

Chart 3

action with the neighboring $AlBr_3$ coordinated to the 4-carbonyl group to form a cyclic complex **D-II**, but the 7-methoxy group in **D-II** is not cleaved under mild conditions in contrast to the demethylation of **2** (from **C-I** to **C-II**), suggesting that the stability of **D-II** is enhanced by interaction between the aluminum atom bonded to the 6-hydroxy group and the 5-tosyl oxygen atom. The complex **D-II** is further demethylated to an unstable cyclic aluminum complex **D-III** with raising the reaction temperature. The carbon atom at the 8-position in **D-III** is attacked by a bromide ion to form an adduct **D-IV**, which is mainly converted into a complex **D-V** (X=Br) by elimination of *p*-toluenesulfonic acid. The demethylation of **1** with $AlCl_3$–NaI proceeds *via* a similar pathway under mild conditions *via* an adduct **D-VI** to form quantitatively a cyclic aluminum complex such as **D-V** (X=H).

In the demethylation of **1** with $AlCl_3$, the interaction between the 5-tosyloxyl oxygen atom and $AlCl_3$ coordinated to the 4-carbonyl oxygen atom in the complex **E-II** formed *via* **E-I** is suppressed by interaction of the aluminum atom bonded to the 6-hydroxy group with the 5-tosyloxyl oxygen atom: the 3-methoxy group is therefore predominantly cleaved without cleavage of the 5-tosyloxy group to form complex **E-III**, although the migration of the tosyl group proceeds simultaneously *via* **E-I** to form the complex **E-IV** as a minor product.

On the other hand, in the demethylation of the acetate **A1** with $AlCl_3$, the cleavages of the 5-tosyloxy group, as a main reaction, and the 3-methoxy group proceed simultaneously *via* the complex **F-I** to give a mixture of **F-II** and **F-III**, since $AlCl_3$ coordinated to the 4-carbonyl group in **F-I** is able to interact with the 5-tosyloxyl and 3-methoxyl oxygen atoms. With increasing reaction time, the complex **F-II** is further demethylated to **F-V** *via* **F-IV**,[8] but the complex **F-III** is slowly converted into **F-VI** by an excess of $AlCl_3$ *via* **E-III**, which is converted into the complex **F-VII** by cleavage of the 7-methoxy group and simultaneous migration of the 5-tosyl group, since the complex **E-III** with a five-membered ring is less stable than the complex **F-IV** or **F-V** with a six-membered ring:[2] the demethylation product after 48 h becomes a mixture of **F-V** and **F-VII**.

Experimental

All melting points were determined in glass capillaries and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL EX 400 NMR spectrometer in DMSO-d_6, using tetramethylsilane as an internal standard, and chemical shifts are given in δ values. UV and MS spectra were recorded on a Hitachi 124 spectrophotometer in MeOH and on a Shimadzu QP 1000 spectrometer, respectively. High-performance liquid chromatography (HPLC) was carried out with a Hitachi 635 instrument, using a column (2.1 × 500 mm) packed with Hitachi gel No. 3011, MeOH (0.5 ml min^{-1}) as an eluent, and a UV monitor set at 340 nm. Column

Table 4. Melting Points and Analytical Data for 5-Tosyloxyflavones and Their Demethylated Products

Compd.	mp (°C)[a]	Recrystn. solvent	Formula	Analysis (%) Found C	Found H	Calcd C	Calcd H
2	201—202 d	$CHCl_3$–MeOH	$C_{24}H_{20}O_8S$	61.37	4.31	61.53	4.30
A2	200—202	$CHCl_3$–MeOH	$C_{26}H_{22}O_9S$	60.95	4.36	61.17	4.34
9	169—170	$CHCl_3$–MeOH	$C_{25}H_{22}O_9S$	60.02	4.53	60.24	4.45
10	182—183 d[b]	$CHCl_3$–MeOH	$C_{23}H_{18}O_9S \cdot H_2O$	57.02	4.22	56.56	4.13
A10	190—191	$CHCl_3$–MeOH	$C_{29}H_{24}O_{12}S$	58.21	3.90	58.38	4.06
11	208—209 d	DMF–H_2O	$C_{23}H_{18}O_8S$	60.68	4.18	60.79	3.99
A11	161—162	$CHCl_3$–MeOH	$C_{27}H_{22}O_{10}S$	60.30	3.94	60.22	4.12
12	271 d	DMF–H_2O	$C_{16}H_{12}O_5$	67.43	4.31	67.60	4.25
A12	183—184	MeOH	$C_{20}H_{16}O_7$	65.40	4.48	65.20	4.38
13	235 d[c]	DMF–H_2O	$C_{16}H_{11}O_6Br$	50.43	3.22	50.68	2.92
A13	272—273	$CHCl_3$–MeOH	$C_{22}H_{17}O_9Br$	52.06	3.33	52.30	3.39
16	222—224	$CHCl_3$–MeOH	$C_{24}H_{20}O_8S$	61.27	4.21	61.53	4.30

a) d, decomposition. *b*) The compound sintered at 120—125 °C and then solidified at about 160 °C. *c*) The compound darkened at 215—220 °C.

chromatography was carried out on Kiesel-gel 60 (70—230 mesh; Merck). Elemental analyses were performed with a Yanaco CHN corder Model MT-5.

6-Hydroxy-3,4′,7-trimethoxy-5-tosyloxyflavone (1) and 6-Hydroxy-4′,7-dimethoxy-5-tosyloxyflavone (2) The 5-tosyloxyflavones **1** and **2** were synthesized from the 5,6-dihydroxyflavone **7**[5] and **14**[6] by the following method. The flavone (**7** or **14**) (3.0 mmol) was methoxymethylated with $MeOCH_2Cl$ (0.4 ml; 5.0 mmol) and *N*,*N*-diisopropylethylamine (1.5 ml; 10.5 mmol) in CH_2Cl_2 (50 ml) at 5—10 °C for 2—3 h to give a crude 6-methoxymethyl ether. A mixture of the ether, TsCl (1.15 g; 6.0 mmol), and anhydrous K_2CO_3 (5.0—6.0 g) in acetone (40—50 ml) was refluxed with stirring until the starting material disappeared (2—3 h). The precipitates were filtered off, and the filtrate was evaporated to give a crude tosylate. This was dissolved in HOAc (20—25 ml), concentrated HCl (2.0 ml) was added, and the mixture was stirred at room temperature for 1—2 h then diluted with H_2O. The separated precipitates were collected and recrystallized to give the 5-tosyloxyflavone (**1**[2] or **2**) in more than 80% yield. The acetates **A1**[4] and **A2** were synthesized from **1** and **2** by the hot acetic anhydride-pyridine method, respectively (Table 4).

General Procedure for Demethylation of 5-Tosyloxyflavones (A) The tosylate (0.3 mmol) was dissolved in a 10% (w/v) solution of anhydrous $AlBr_3$ in MeCN (4.0 ml; 3.0 mmol) or a 30% (w/v) solution of anhydrous $AlCl_3$ in MeCN (4.0 ml; 9.0 mmol) and warmed in a thermostated oil bath under the conditions shown in Table 3. The reaction mixture was diluted with 2—3% aqueous HCl and then warmed at 60—70 °C for 20—30 min. The separated precipitates were collected, washed well with H_2O and dried to give quantitatively a demethylated product.

(B) Ten percent (w/v) anhydrous $AlCl_3$ in MeCN (4.0 ml; 3.0 mmol) was stirred with dried NaI (0.5 g; 3.0 mmol) for 30 min. The 5-tosyloxyflavone (0.3 mmol) was dissolved in the above solution stirring, and the resultant solution was warmed at 30 °C for 5 h. The reaction mixture was diluted with 2—3% aqueous HCl, and warmed with Na_2SO_3 (0.2—0.3 g) at 60—70 °C for 20—30 min, then the separated precipitates were collected.

(C) The demethylation of acetates (**A1** and **A2**) was carried out by using 30% (w/v) anhydrous $AlCl_3$ in MeCN containing 0.2% H_2O[7] (4.0 ml; 9.0 mmol) and the products were hydrolyzed with HCl in MeOH.

The product ratios in Table 3 were calculated from the signal intensities of the aromatic protons at the 8- or 3-position in the ^{1}H-NMR spectra of the products obtained here.

Isolation of the Demethylated Products Compounds **10**, **11**, and **12** were obtained from the products shown in Table 3, runs 7, 9, and 10, respectively, by recrystallization. These compounds were acetylated with hot acetic anhydride-pyridine to give the corresponding acetates (**A10**, **A11**, and **A12**). Compound **12** was identical with a synthetic sample obtained from 6,7-bis(benzyloxy)-4′-methoxyflavone[2] by hydrogenolysis with 10% Pd–C. Compound **13** was isolated from the product shown in Table 3, run 8 by acetylation and hydrolysis: the crude acetate which was obtained from the product by the hot acetic anhydride-pyridine method was purified by recrystallization and then hydrolyzed with methanolic HCl. EIMS; 20 eV, *m/z* (rel. int.): 380, 378 (M^+, each 100); 365, 363 (M^+-15, each 8); 300 ($M^+ + 1 - Br$, 6); 135 (10). Compounds **9** and **16** were isolated from the respective products shown in Table 3, runs 4 and 11: the $CHCl_3$-soluble materials were chromatographed over silica-gel with $CHCl_3$–EtOAc (5 : 1) and then recrystallized.

The melting points, recrystallization solvents, and analytical values for the compounds obtained here are summarized in Table 4.

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