Synthesis of 7-Vinylflavone and 7-Aminoflavone by Palladium-Catalyzed Coupling Reactions

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Keywords: Flavone / Palladium / Cross coupling / Triflate / Aminations

Palladium-catalyzed cross-coupling reactions of flavone triflates **2a–c**, **4a** with tetravinyltin give the corresponding vinylflavones **5a–d**, whereas reactions with benzophenone imine, followed by cleavage, afford the corresponding aminoflavone.

Introduction

Flavonoids are natural products with many biological and pharmacological activities.[1] Antiviral,[2][3] antitumour,[4–6] antioxidant,[7][8] and antiinflammatory[9] properties, as well as inhibition of HIV proteinase,[10] HIV integrase,[11][12] reverse transcriptase,[13][14] xanthine oxidase,[15] and protein tyrosine kinase[16] have been demonstrated. In most cases, pronounced structure−activity relationships have been defected. For example, some studies have indicated that the presence of a 3-methoxy group in the flavone skeleton is essential for antipicornavirus activity.[17–19]

In the last ten years, the scope of the application of aryl triflates in highly regioselective cross-coupling reactions with various organometallic compounds under mild conditions has broadened enormously.[20][21] We have attempted to introduce triflyloxy and vinyl groups on ring A of flavone in order to obtain useful synthons. The vinyl group can be transformed into numerous other groups.[22][23]

A few aminoflavones have been synthesized and, as far as their biological activities have been examined, analogous activities have been found as for the corresponding hydroxyflavones.[24–26] Aminoflavones are normally synthesized by reduction of the corresponding nitroflavones. Obviously, this method has limited applicability since the nitroflavones are difficult to obtain. We attempted to synthesize flavones aminated at ring A by palladium-catalyzed amination, which would be a practical complementary method for synthesizing aminoflavone. In this paper, the synthesis of 7-vinylflavones and 7-aminoflavone from 7-triflyloxyflavones is described and their antiviral activities are reported.

Results and Discussion

The triflate of flavone **1a** was synthesized by treating **1a** with triflic anhydride in the presence of pyridine, as outlined in Scheme 1.

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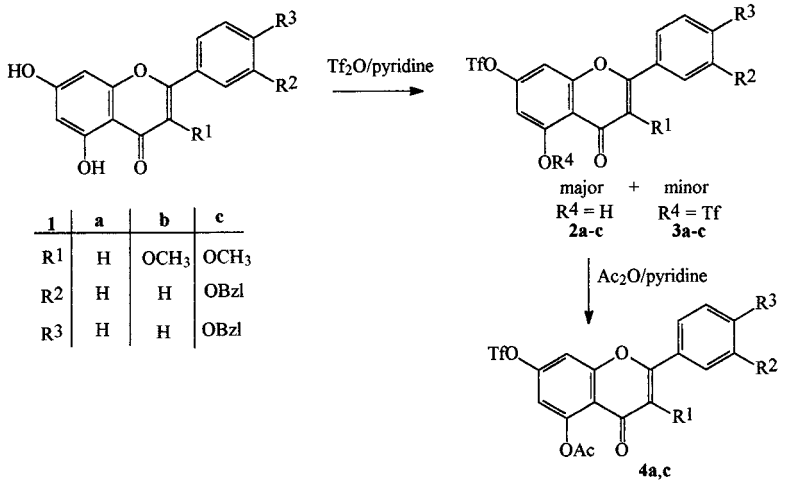
Stille et al.[27] have reported the synthesis of 5-hydroxy-7-triflyloxyflavone (**2a**) in good yield from 5,7-dihydroxyflavone (**1a**) using triflic anhydride in pyridine. However, when we carried out this reaction as originally described, we found that some starting material invariably remained in the reaction mixture. On the other hand, the separation of the mono- and ditriflates of flavone by regular column chromatography proved very tedious (see the TLC R_f values). Several modifications aimed at reducing the formation of ditriflates were tested. On reducing the amount of triflic anhydride and on decreasing the reaction time, only the amount of recovered starting material increased. We found that by treating the reaction mixture with Ac_2O/pyridine, to convert compounds **2a** and **2c** into acetylated compounds **4a** and **4c**, respectively, the separations of **3a**, **4a** and **3c**, **4c** became much easier (cf. the relevant R_f values).

The palladium-catalyzed cross coupling of organotin reagents with organic electrophiles is known as the Stille reaction.[28][29] Since tetravinyltin is cheaper than tributylvinyltin, and use of the former avoids the introduction of a butyl group, we used tetravinyltin as our organotin reagent rather than the tributylvinyltin employed by Stille and other authors.

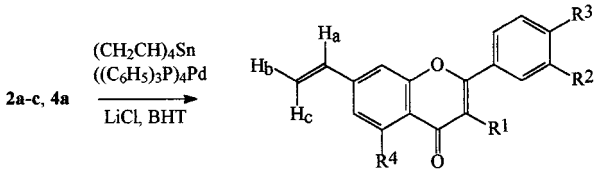
The palladium-catalyzed cross-coupling reaction for the conversion of 5-hydroxy-7-triflyloxyflavone (**2a**) to **5a** was studied under various conditions (Table 1). When the reaction was carried out under Stille's conditions[30] (Entry 1), some black material appeared in the reaction mixture after about 2.5 h, possibly due to decomposition of the catalyst. Even when the reaction was allowed to proceed for 24 h, 18% of the starting material was recovered. When 10 mol-% of the ligand PPh_3 was added to the mixture, the reaction afforded a yield of 52% within a few hours (Entry 2), although some black material was also observed in the reaction mixture after about 3 h. The yield of the coupling reaction was further improved when the amounts of catalyst and ligand were increased (Entry 4), and in this case no black material was seen. When triphenylarsane or tris(2-furyl)phosphane was used as the ligand,[31] the yield was fairly good (Entries 5 and 6). Nevertheless, after 1 h and 1.5 h, respectively, some black material was again found. Some unsuccessful attempts to promote the coupling included the addition of $Cu^{I}I$[32] (Entry 3) and the use of

  1434−193X/99/1010−2683 $ 17.50+.50/0



1	a	b	c
R1	H	OCH_3	OCH_3
R2	H	H	OBzl
R3	H	H	OBzl

Scheme 1. Synthesis of 7-triflyloxyflavones



5	a	b	c	d
R1	H	CH_3O	CH_3O	H
R2	H	H	BzlO	H
R3	H	H	BzlO	H
R4	OH	OH	OH	AcO

Scheme 2. Synthesis of 7-vinylflavones

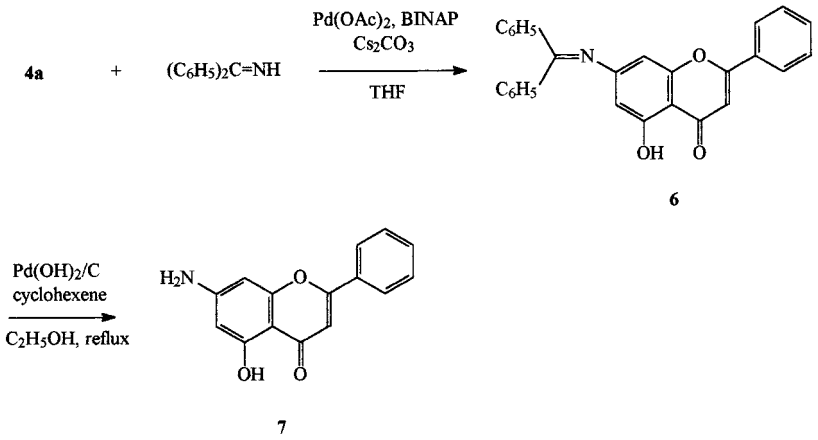
$Pd_2(dba)_3$ (Entry 7). These results indicate that PPh_3 (40%) and $Pd(PPh_3)_4$ (10%) (Entry 4) are likely to provide the optimum catalyst for the synthesis of 7-vinylflavones.

The 3-methoxy-7-vinylflavones **5b**, **c** (Scheme 2) were also synthesized in good yields under these reaction conditions. 5-Acetoxy-7-triflyloxyflavone (**4a**) was chosen for use in a coupling reaction with tetravinyltin under the same conditions, which led to the isolation of 5-acetoxy-7-vinylflavone (**5d**) (47%) and some free 5-hydroxy-7-vinylflavone (**5a**) (3.3%). Partially deacetylated products of both the starting material and the coupling product were also observed by Echavarren et al.[33] The synthesis of 7-amino-5-hydroxyflavone **7** was attempted as illustrated in Scheme 3.[34] 5-Acetoxy-7-triflyloxyflavone (**4a**) was coupled with benzophenone imine in the presence of palladium acetate, BINAP, and cesium carbonate to give the diphenyl ketimine adduct **6** with a free hydroxy group in the 5-position, which was recrystallized from MeOH/acetone (5:2). The diphenyl ketimine adduct **6** was then hydrogenolyzed using $Pd(OH)_2$ on carbon in the presence of cyclohexene to give 7-amino-5-hydroxyflavone **7** in good yield. The utility of this method in the synthesis of aminoflavones will be investigated further.

The antiviral potencies of compounds **2**−**5** against Coxsakie B2 (COXB2) and Poliomyelitis virus type 1 (POLIO I) as well as human rhinovirus type 30 (HRV 30) or human rhinovirus type 81 (HRV 81) were determined by the end-point titration technique (EPTT) as described elsewhere.[18] The inhibitory effects of the compounds on virus replication were monitored by the virus strength reduction factor (RF) in the presence of the maximum nontoxic dose of the compound. The results of the tests are presented in Table 2. A reduction factor of 10^3 to 10^4 or more indicates a pronounced antiviral activity, constituting a selection criterion for further investigation. However, analysis of the results for compounds **2**−**5** indicates that these compounds show insufficient activity.

Table 1. Effects of various reaction conditions on the coupling reaction of compound **2a**; catalyst A, $Pd(PPh_3)_4$; catalyst B, $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium(0); NMP = 1-methylpyrrolidinone; BHT = 2,6-di-*tert*-butyl-4-methylphenol; P(*o*-Fu)$_3$ = tri(2-furyl)phosphane

Entry	1	2	3	4	5	6	7
$(CH_2CH)_4Sn$ (equiv.)	1.15	1.25	1.25	1.45	1.15	1.20	1.30
Catalyst (mol-%)	5.0 A	5.0 A	5.0 A	10 A	10 A	10 A	5.0 B
LiCl (equiv.)	3	3	3	3	3	3	3
Cu^II (mol-%)	0	0	10	0	0	0	0
Ligand (mol-%)	0	10 PPh_3	10 PPh_3	40 PPh_3	40 $AsPh_3$	40 P(*o*-Fu)$_3$	20 $AsPh_3$
Solvent	dioxane	dioxane	dioxane	dioxane	dioxane	dioxane	NMP
Reaction temp.	reflux	reflux	reflux	reflux	reflux	reflux	room temp.
Reaction time [h]	24	4	24	5	4	4	7
Yield (%)	38	52	9.5	55	45	45.5	no reaction
Recovered material%	18	5	53	0	6	6	



Scheme 3. Synthesis of 7-aminoflavones

Table 2. Antiviral activities; N = precipitation of the sample; T = toxicity; T/2 = less toxic; T/4 = very low toxicity; the product concentrations (e.g. 100−5) are given in μg/mL; test concentration: (for viruses) starting from 100 μg/mL, dilutions of 50 μg/mL, 25 μg/mL, 10 μg/mL, and 1 μg/mL were used

No.	COXB2 conc. [μg/mL]		POLIO I conc. [μg/mL]		HRV30 conc. [μg/mL]		HRV81 conc. [μg/mL]	
2a	100−10	T	100−25	T	100−50	T		
	1	RF 1	10	T/2	25	T/2		
			1	RF 1	10−1	RF 1		
2b	100−50	N	100−25	N	100−50	N		
	100−1	RF1	100−50	T	100	T/2		
				RF 1	50	T/4		
					50−1	RF 1		
2c	100−25	N	100−25	N, T			100−50	N
	100−50	T	10−1	RF 1			100−1	RF 1
	25	T/4						
	25−1	RF 1						
3a	100−25	N	100−25	N	100−50	N		
	100−50	T	100	T/2	100−1	RF 1		
	25−1	RF 1	50	T/4				
			100−1	RF 1				
3b	100−50	N	100	T/2			100−1	RF 1
	100	T/4	100−1	RF 1				
	100−1	RF 1						
4a	100−50	N	100−1	RF 1	100−50	N, RF 10		
	100−1	RF 1			25−1	RF 1		
4c	100−50	N	100	N			100−50	N
	100−25	T	100−1	RF 1			100−1	RF 1
	10−1	RF 1						
5a	100−50	N	100	N			100−25	N
	100−1	RF 1	100−1	RF 1			50	RF 10^2
							25	RF 10
							10−1	RF 1
5b	100−25	N	100−50	N			100−50	N
	100	T/4	100	T/2			50−1	RF 1
	100−25	RF 10^2	100−1	RF 1				
	25−1	RF 1						
5c	100−1	RF 1	100	N			100	N
			100−1	RF 1			100−1	RF 1

Experimental Section

General Remarks: Melting points were determined in glass capillaries with a Tottoli apparatus and are uncorrected. − ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian Unity 400 spectrometer and DCI mass spectra with a Ribermag R10−10B quadrupole mass spectrometer; ammonia was used as reagent gas; accurate mass measurements were made using a VG-SEQ hybrid mass spectrometer equipped with a cesium ion gun (Micromass, Manchester, U.K.) and were performed on protonated molecules generated by LSI-MA. Samples were analyzed at 5,000 resolution by linear-accelerating voltage scanning. The data were acquired in the multichannel analyzer mode by measuring the mass of the unknown peak against two mass references originating from the calibrant and averaging 25 scans. As calibrant, a mixture of glycerol and polyethylene glycol 300 or 600 was used. − Column chromatography was

performed on Kieselgel 60 (Merck), 0.040−0.063 mm (230−400 mesh ASTM). − TLC analyses were performed on Alugram Sil G/UV_{254} (Macherey−Nagel) with CH_2Cl_2/MeOH (50:1) (R_f denoted as R_{f1}) and heptane/EtOAc (8:1) (R_f denoted as R_{f2}) as eluents. − Dichloromethane, dimethylformamide, and *N*-methylpyrrolidinone (NMP)[35] were distilled from CaH_2 and stored over activated molecular sieves (4 Å). Lithium chloride was dried for about 12 h in a vacuum oven at 120°C. Dioxane was treated with solid potassium hydroxide, refluxed in the presence of Na, and distilled under N_2. 5,7-Dihydroxy-3-methoxyflavone (**1b**) and 3′,4′-bis(benzyloxy)-5,7-dihydroxy-3-methoxyflavone (**1c**) were synthesized according to a published method.[36]

5-Hydroxy-7-triflyloxyflavone (2a): To a solution of 5,7-dihydroxyflavone (**1a**) (1.02 g, 4.0 mmol) in 30 mL of dichloromethane and 10 mL of pyridine at 0°C was slowly added trifluoromethanesulfonic anhydride (0.75 mL, ca. 4.5 mmol) in 1 mL of dichloromethane. The mixture was allowed to warm to room temperature and then stirred for 22.5 h. Thereafter, it was concentrated and the residue was chromatographed (heptane/EtOAc, 8:1) to give 5-hydroxy-7-triflyloxyflavone (**2a**) as pale-yellow needles (1.13 g, 73%; m.p. 133.5−134°C, ref.[27] 129−130°C; R_{f1} = 0.82, R_{f2} = 0.16), 5,7-bis(triflyloxy)flavone (**3a**) as white crystals (98 mg, 5%; m.p. 206.5−207.5°C, ref.[27] 206−207°C; R_{f1} = 0.76, R_{f2} = 0.06), and starting material (20 mg, 2%).

2a: ^{1}H NMR ($CDCl_3$, TMS): δ = 12.92 (s, 1 H, 5-OH), 7.90 (m, 2 H, 2′,6′-H), 7.57 (m, 3 H, 3′,4′,5′-H), 6.98 (d, 1 H, $J_{6,8}$ = 2.28 Hz, 8-H), 6.87 (s, 1 H, 3-H), 6.74 (d, 1 H, $J_{6,8}$ = 2.28 Hz, 6-H). − ^{13}C NMR ($CDCl_3$, TMS): δ = 182.6 (C-4), 165.4 (C-2), 162.7 (C-5), 156.8 (C-9), 153.4 (C-7), 132.6 (C-4′), 130.6 (C-1′), 129.3 (C-3′,5′), 126.6 (C-2′,6′), 118.7 (7-SO_2CF_3), 110.5 (C-10), 106.5 (C-3), 105.2 (C-6), 100.8 (C-8). − DCI MS; *m/z*: 387 [M + H]$^+$. − HR MS; [M + H]$^+$: found 387.017; calcd. 387.015.

3a: ^{1}H NMR ($CDCl_3$, TMS): δ = 7.89 (m, 2 H, 2′,6′-H), 7.63 (d, 1 H, $J_{6,8}$ = 2.28 Hz, 8-H), 7.57 (m, 3 H, 3′,4′,5′-H), 7.15 (d, 1 H, $J_{6,8}$ = 2.28 Hz, 6-H), 6.83 (s, 1 H, 3-H). − ^{13}C NMR ($CDCl_3$, TMS): δ = 174.6 (C-4), 163.4 (C-2), 157.5 (C-9), 150.9 (C-7), 147.9 (C-5), 132.6 (C-4′), 130.2 (C-1′), 129.4 (C-3′,5′), 126.4 (C-2′,6′), 118.8, 118.7 (5-SO_2CF_3, 7-SO_2CF_3), 117.8 (C-10), 113.2 (C-6), 112.3 (C-8), 109.1 (C-3). − DCI MS; *m/z*: 519 [M + H]$^+$. − HR MS; [M+H]$^+$: found 518.967; calcd. 518.964.

5-Acetoxy-7-triflyloxyflavone (4a): To a solution of 5,7-dihydroxyflavone (**1a**) (2.54 g, 10 mmol) in 100 mL of dichloromethane and 25 mL of pyridine at 0°C was slowly added trifluoromethanesulfonic anhydride (1.73 mL, 10.3 mmol). The mixture was stirred at 0°C for 3 h and at room temperature for 0.5 h, then mixed with 200 mL of 5% aqueous hydrochloric acid and the resulting mixture was stirred for a few minutes. The dichloromethane phase was separated and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined dichloromethane phases were then dried ($MgSO_4$) and concentrated. The residue was chromatographed (hexane/EtOAc, 8:1) to give a mixture of 5-hydroxy-7-triflyloxyflavone and 5,7-bis(triflyloxy)flavone. This mixture was acetylated with acetic anhydride/pyridine (5:1), worked up, and separated by column chromatography (CH_2Cl_2/MeOH, 50:1) to furnish 5-acetoxy-7-triflyloxyflavone (**4a**) (2.76 g, 68%; m.p. 178.5−179°C; R_{f1} = 0.30, R_{f2} = 0.03) and 5,7-bis(triflyloxy)flavone (**3a**) (0.31 g, 3%).

4a: ^{1}H NMR ($CDCl_3$, TMS): δ = 7.87 (m, 2 H, 2′,6′-H), 7.54 (m, 3 H, 3′,4′,5′-H), 7.45 (d, 1 H, $J_{6,8}$ = 2.38 Hz, 8-H), 6.70 (s, 1 H, 3-H), 6.99 (d, 1 H, $J_{6,8}$ = 2.38 Hz, 6-H), 2.46 (s, 3 H, CH_3CO). − ^{13}C NMR ($CDCl_3$, TMS): δ = 175.7 (C-4), 169.0 (*C*OCH_3), 163.0 (C-2), 151.4, 151.2 (C-7, C-5), 157.7 (C-9), 132.2 (C-4′), 130.6 (C-1′), 129.2 (C-3′,5′), 126.3 (C-2′,6′), 118.7 (7-SO_2CF_3), 117.1 (C-10), 113.3 (C-6), 109.4 (C-8), 109.0 (C-3), 21.0 (*C*H_3CO). − DCI MS; *m/z*: 429 [M + H]$^+$. − HR MS; [M + H]$^+$: found 429.028; calcd. 429.026. − $C_{18}H_{11}F_3O_7S$ (428.34): calcd. C 50.47, H 2.59, S 7.48; found C 50.35, H 2.72, S 7.13.

5-Hydroxy-3-methoxy-7-triflyloxyflavone (2b): To a solution of 5,7-dihydroxy-3-methoxyflavone (**1b**) (0.70 g, 2.5 mmol) in 20 mL of dichloromethane and 8 mL of pyridine at 0°C was slowly added trifluoromethanesulfonic anhydride (0.5 mL, ca. 3.0 mmol). The resulting mixture was stirred at 0°C for 10 min., allowed to warm to room temperature, and then stirred for 23 h. It was then concentrated and the residue was chromatographed (heptane/EtOAc, 8:1) to give 5-hydroxy-3-methoxy-7-triflyloxyflavone (**2b**) (recrystallized from heptane, 0.59 g, 56%; m.p. 124.5°C; R_{f1} = 0.76, R_{f2} = 0.20) and 3-methoxy-5,7-bis(triflyloxy)flavone (**3b**) (recrystallized from heptane/EtOAc, 8:1, 56 mg, 4%; m.p. 171.5−172.5°C; R_{f1} = 0.80, R_{f2} = 0.13).

2b: ^{1}H NMR ($CDCl_3$, TMS): δ = 12.80 (s, 1 H, 5-OH), 8.07 (m, 2 H, 2′,6′-H), 7.54 (m, 3 H, 3′,4′,5′-H), 6.95 (d, 1 H, $J_{6,8}$ = 2.10 Hz, 8-H), 6.72 (d, 1 H, $J_{6,8}$ = 2.10 Hz, 6-H), 3.90 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$, TMS): δ = 179.3 (C-4), 162.5 (C-5), 157.5 (C-2), 155.7 (C-9), 153.3 (C-7), 140.4 (C-3), 131.7 (C-4′), 129.8 (C-1′), 128.8 (C-3′,5′), 128.6 (C-2′,6′), 118.7 (7-SO_2CF_3), 110.9 (C-10), 104.4 (C-6), 100.7 (C-8), 60.5 (OCH_3). − DCI MS; *m/z*: 417 [M + H]$^+$. − HR MS; [M + H]$^+$: found 417.028; calcd. 417.026. − $C_{17}H_{11}F_3O_7S$ (416.32): calcd. C 49.05, H 2.66, S 7.70; found C 49.01, H 2.47, S 7.76.

3b: ^{1}H NMR ($CDCl_3$, TMS): δ = 8.07 (m, 2 H, 2′,6′-H), 7.60 (d, 1 H, $J_{6,8}$ = 2.38 Hz, 8-H), 7.55 (m, 3 H, 3′,4′,5′-H), 7.14 (d, 1 H, $J_{6,8}$ = 2.38 Hz, 6-H), 3.92 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$, TMS): δ = 171.9 (C-4), 156.3 (C-2), 155.7 (C-9), 150.6 (C-7), 147.9 (C-5), 142.4 (C-3), 131.6 (C-4′), 129.5 (C-1′), 128.8 (C-3′,5′), 128.5 (C-2′,6′), 118.9, 118.7 (5-SO_2CF_3, 7-SO_2CF_3), 117.9 (C-10), 112.7 (C-6), 112.1 (C-8), 60.3 (OCH_3). − DCI MS; *m/z*: 548 [M + H]$^+$. − HR MS; [M + H]$^+$: found 548.978; calcd. 548.975.

3′,4′-Bis(benzyloxy)-5-hydroxy-3-methoxy-7-triflyloxyflavone (2c): To a solution of 3′,4′-bis(benzyloxy)-5,7-dihydroxy-3-methoxyflavone (**1c**) (0.50 g, 1.0 mmol) in 15 mL of dichloromethane and 3 mL of pyridine at 0°C was slowly added trifluoromethanesulfonic anhydride (0.16 mL, ca. 0.95 mmol). The resulting mixture was stirred at 0°C for 3.5 h, allowed to warm to room temperature, stirred for a further 2.5 h, and then mixed with 20 mL of water. The dichloromethane phase was separated, washed twice with dilute HCl solution, and concentrated to afford a yellow residue. Chromatography (CH_2Cl_2/MeOH, 50:1) of this residue gave 3′,4′-bis(benzyloxy)-5-hydroxy-3-methoxy-7-triflyloxyflavone (**2c**) (0.27 g, 44%; m.p. 132−133°C; R_{f1} = 0.85, R_{f2} = 0.09) and the starting material 3′,4′-bis(benzyloxy)-5,7-dihydroxy-3-methoxyflavone (0.22 g, 44%).

2c: ^{1}H NMR ($CDCl_3$, TMS): δ = 12.84 (s, 1 H, 5-OH), 7.73 (d, 1 H, $J_{2',6'}$ = 2.10 Hz, 2′-H), 7.69 (dd, 1 H, $J_{2',6'}$ = 2.10 Hz, $J_{5',6'}$ = 8.60 Hz, 6′-H), 7.47 (m, 4 H, 2′′,2′′′,6′′,6′′′-H), 7.39 (m, 4 H, 3′′,3′′′,5′′,5′′′-H), 7.33 (m, 2 H, 4′′,4′′′-H), 7.04 (d, 1 H, $J_{5',6'}$ = 8.60 Hz, 5′-H), 6.85 (d, 1 H, $J_{6,8}$ = 2.19 Hz, 8-H), 6.68 (d, 1 H, $J_{6,8}$ = 2.19 Hz, 6-H), 5.28, 5.26 (s, 4 H, 2CH_2), 3.73 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$, TMS): δ = 178.9 (C-4), 162.5 (C-5), 157.1 (C-2), 155.4 (C-9), 153.1 (C-7), 152.1 (C-4′), 148.5 (C-3′), 139.6 (C-3), 136.9, 136.5 (C-1′′,1′′′), 128.7 (C-3′′,5′′,3′′′,5′′′), 128.1, 128.0 (C-4′′,4′′′), 127.2 (C-2′′,2′′′,6′′,6′′′), 123.0 (C-6′), 122.4 (C-1′), 118.7 (7-SO_2CF_3), 115.4 (C-2′), 113.9 (C-5′), 110.7 (C-10), 104.2 (C-6), 100.6 (C-8), 71.6, 71.0 (2CH_2), 60.1 (3-OCH_3). − DCI MS; *m/z*: 629 [M + H]$^+$. − HR MS; [M + H]$^+$: found 629.111; calcd.

629.109. − $C_{31}H_{23}F_3O_9S$ (628.57): calcd. C 59.24, H 3.69, S 5.10; found 59.01, H 3.57, S 4.84.

5-Acetoxy-3′,4′-bis(benzyloxy)-3-methoxy-7-triflyloxyflavone (4c): To a solution of 3′,4′-bis(benzyloxy)-5,7-dihydroxy-3-methoxyflavone (**1c**) (0.50 g, 1.0 mmol) in 10 mL of dichloromethane and 3 mL of pyridine at 0°C was slowly added trifluoromethanesulfonic anhydride (0.2 mL, ca. 1.19 mmol). The resulting mixture was stirred at 0°C for 3 h, then mixed with 20 mL of water. The dichloromethane phase was separated, washed with 6% HCl (45 mL), and concentrated to leave a yellow residue. Chromatography (CH_2Cl_2/MeOH, 50:1) of this residue afforded a yellow mixture, which was treated with Ac_2O/pyridine (5:1) and worked-up to give 5-acetoxy-3′,4′-bis(benzyloxy)-3-methoxy-7-triflyloxyflavone (**4c**) (0.21 g, 31%; m.p. 140.5−141.5°C; R_{f1} = 0.50, R_{f2} = 0.01) and 3′,4′-bis(benzyloxy)-3-methoxy-5,7-bis(triflyloxy)flavone (**3c**) (0.27 g, 35%).

4c: ^{1}H NMR ($CDCl_3$, TMS): δ = 7.68 (d, 1 H, $J_{2',6'}$ = 2.02 Hz, 2′-H), 7.62 (dd, 1 H, $J_{2',6'}$ = 2.02 Hz, $J_{5',6'}$ = 8.61 Hz, 6′-H), 7.44 (m, 4 H, 2″,2‴,6″,6‴-H), 7.34 (m, 4 H, 3″,3‴,5″,5‴-H), 7.28 (m, 2 H, 4″,4‴-H), 6.99 (d, 1 H, $J_{5',6'}$ = 8.61 Hz, 5′-H), 7.28 (d, 1 H, $J_{6,8}$ = 2.47 Hz, 8-H), 6.90 (d, 1 H, $J_{6,8}$ = 2.47 Hz, 6-H), 5.20, 5.19 (s, 4 H, 2CH_2), 3.65 (s, 3 H, OCH_3), 2.44 (s, 3 H, $COCH_3$). − ^{13}C NMR ($CDCl_3$, TMS): δ = 172.3 (C-4), 168.7 (*C*OCH_3), 156.1 (C-2), 154.7 (C-9), 151.5 (C-4′), 150.9, 150.8 (C-5, C-7), 148.3 (C-3′), 141.3 (C-3), 136.8, 136.4 (C-1″,1‴), 128.4 (C-3″,5″,3‴,5‴), 127.9, 127.8 (C-4″,4‴), 127.0 (C-2″,2‴,6″,6‴), 122.4 (C-6′,1′), 118.5 (7-SO_2CF_3), 117.0 (C-10), 115.0 (C-2′), 113.6 (C-5′), 112.3 (C-6), 109.0 (C-8), 71.2, 70.7 (2CH_2), 59.6 (3-OCH_3), 20.8 (CO*C*H_3). − DCI MS; *m*/*z*: 671 [M + H]$^+$. − HR MS; [M + H]$^+$: found 671.125; calcd. 671.120. − $C_{33}H_{25}F_3O_{10}S$ (670.61): calcd. C 59.10, H 3.76, S 4.78; found C 58.93, H 3.62, S 4.36.

3c: ^{1}H NMR ($CDCl_3$, TMS): δ = 7.71 (d, 1 H, $J_{2',6'}$ = 2.20 Hz, 2′-H), 7.67 (dd, 1 H, $J_{2',6'}$ = 2.2 Hz, $J_{5',6'}$ = 8.60 Hz, 6′-H), 7.48 (d, 1 H, $J_{6,8}$ = 2.20 Hz, 8-H), 7.47 (m, 4 H, 2″,2‴,6″,6‴-H), 7.39 (m, 4 H, 3″,3‴,5″,5‴-H), 7.33 (m, 2 H, 4″,4‴-H), 7.09 (d, 1 H, $J_{6,8}$ = 2.20 Hz, 6-H), 7.04 (d, 1 H, $J_{5',6'}$ = 8.60 Hz, 5′-H), 5.26, 5.25 (s, 4 H, 2CH_2), 3.75 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$, TMS): δ = 171.6 (C-4), 156.1 (C-2), 155.3 (C-9), 152.0 (C-4′), 150.4 (C-7), 148.5 (C-3′), 147.8 (C-5), 141.7 (C-3), 136.9, 136.5 (C-1″,1‴), 128.7 (C-3″,5″,3‴,5‴), 128.1, 128.0 (C-4″,4‴), 127.3, 127.2 (C-2″,2‴,6″,6‴), 122.9 (C-6′), 122.2 (C-1′), 118.8, 118.2 (7-SO_2CF_3, 5-SO_2CF_3), 115.4 (C-2′), 113.9 (C-5′), 117.8 (C-10), 112.5 (C-6), 112.0 (C-8), 71.6, 71.0 (2CH_2), 60.0 (3-OCH_3). − DCI MS; *m*/*z*: 761 [M + H]$^+$.

5-Hydroxy-7-vinylflavone (5a): An oven-dried three-necked flask was charged with a mixture of 5-hydroxy-7-triflyloxyflavone (**2a**), the chosen palladium catalyst and ligand, and anhydrous lithium chloride or copper(I) iodide in NMP or dioxane under argon (Table 1). A few crystals of 2,6-di-*tert*-butyl-4-methylphenol were also added to the mixture. After stirring for a few minutes, tetravinyltin was added. The mixture was either stirred at room temperature or refluxed for several hours and cooled, then treated with 5% aqueous potassium fluoride solution and extracted with diethyl ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$), concentrated, and separated by column chromatography (CH_2Cl_2).

5a: M.p. 141.5−142.5°C. − ^{1}H NMR ($CDCl_3$, TMS): δ = 12.48 (s, 1 H, 5-OH), 7.90 (m, 2 H, 2′,6′-H), 7.54 (m, 3 H, 3′,4′,5′-H), 7.02 (d, 1 H, $J_{6,8}$ = 1.38 Hz, 8-H), 6.86 (d, 1 H, $J_{6,8}$ = 1.38 Hz, 6-H), 6.71 (s, 1 H, 3-H), 6.70 (q, 1 H, J_{ac} = 17.58 Hz, J_{ab} = 10.80 Hz, H_a), 5.71 (d, 1 H, J_{ac} = 17.58 Hz, H_c), 5.47 (d, 1 H, J_{ab} = 10.80 Hz, H_b). − ^{13}C NMR ($CDCl_3$, TMS): δ = 183.1 (C-4), 164.6 (C-2), 160.8 (C-5), 156.7 (C-9), 144.9 (C-7), 135.8 (*C*HCH_2), 132.0 (C-4′), 131.3 (C-1′), 129.1 (C-3′,5′), 126.4 (C-2′,6′), 118.2 (CH*C*H_2), 110.3 (C-10), 109.0 (C-6), 106.2 (C-8), 104.9 (C-3). − DCI MS; *m*/*z*: 265 [M + H]$^+$. − HR MS; [M + H]$^+$: found 265.086; calcd. 265.086.

5-Hydroxy-3-methoxy-7-vinylflavone (5b): A three-necked flask was charged with a mixture of tetravinyltin (0.20 g, 0.9 mmol), 5-hydroxy-3-methoxy-7-triflyloxyflavone (**2b**) (0.25 g, 0.6 mmol), triphenylphosphane (0.06 g, 0.24 mmol), tetrakis(triphenylphosphane)palladium (0.07 g, 0.06 mmol), lithium chloride (0.08 g, 1.8 mmol), and dioxane (15 mL) under argon. A few crystals of 2,6-di-*tert*-butyl-4-methylphenol were also added to the mixture, which was stirred at reflux under argon for 4 h. After workup as described in the case of compound **5a**, 5-hydroxy-3-methoxy-7-vinylflavone (**5b**) (0.11 g, 62%; m.p. 105−106°C; R_{f1} = 0.81, R_{f2} = 0.32) was obtained.

5b: ^{1}H NMR ($CDCl_3$, TMS): δ = 12.36 (s, 1 H, 5-OH), 8.09 (m, 2 H, 2′,6′-H), 7.53 (m, 3 H, 3′,4′,5′-H), 6.99 (d, 1 H, $J_{6,8}$ = 1.28 Hz, 8-H), 6.86 (d, 1 H, $J_{6,8}$ = 1.28 Hz, 6-H), 6.71 (q, 1 H, J_{ac} = 17.40 Hz, J_{ab} = 10.80 Hz, H_a), 5.92 (d, 1 H, J_{ac} = 17.40 Hz, H_c), 5.47 (d, 1 H, J_{ab} = 10.80 Hz, H_b), 3.89 (s, 3 H, 3-OCH_3). − ^{13}C NMR ($CDCl_3$, TMS): δ = 179.5 (C-4), 160.8 (C-5), 156.6, 155.8 (C-2, C-9), 144.8 (C-7), 140.1 (C-3), 135.8 (*C*HCH_2), 131.1 (C-4′), 130.5 (C-1′), 128.7 (C-3′,5′), 128.5 (C-2′,6′), 118.2 (CH*C*H_2), 110.8 (C-10), 108.1 (C-6), 105.0 (C-8), 60.3 (3-O*C*H_3). − DCI MS; *m*/*z*: 295 [M + H]$^+$. − HR MS; [M + H]$^+$: found 295.097; calcd. 295.097.

3′,4′-Bis(benzyloxy)-5-hydroxy-3-methoxy-7-vinylflavone (5c): This compound was synthesized from 3′,4′-bis(benzyloxy)-5-hydroxy-3-methoxy-7-triflyloxyflavone (**2c**) according to the procedure used for **5b**. **5c** (0.094 g, 61%; m.p. 89.5−90.5°C; R_{f1} = 0.84, R_{f2} = 0.12).

5c: ^{1}H NMR ($CDCl_3$, TMS): δ = 12.39 (s, 1 H, 5-OH), 7.77 (d, 1 H, $J_{2',6'}$ = 2.10 Hz, 2′-H), 7.69 (dd, 1 H, $J_{2',6'}$ = 2.10 Hz, $J_{5',6'}$ = 8.60 Hz, 6′-H), 7.47 (m, 4 H, 2″,2‴,6″,6‴-H), 7.38 (m, 4 H, 3″,3‴,5″,5‴-H), 7.32 (m, 2 H, 4″,4‴-H), 7.03 (d, 1 H, $J_{5',6'}$ = 8.60 Hz, 5′-H), 6.90 (d, 1 H, $J_{6,8}$ = 1.46 Hz, 8-H), 6.81 (d, 1 H, $J_{6,8}$ = 1.46 Hz, 6-H), 6.67 (q, 1 H, J_{ac} = 17.58 Hz, J_{ab} = 10.81 Hz, H_a), 5.89 (d, 1 H, J_{ac} = 17.58 Hz, H_c), 5.44 (d, 1 H, J_{ab} = 10.81 Hz, H_b), 5.26, 5.25 (s, 4 H, 2CH_2), 3.72 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$, TMS): δ = 178.2 (C-4), 159.7 (C-5), 155.2, 154.5 (C-2, C-9), 150.6 (C-4′), 147.4 (C-3′), 143.5 (C-7), 138.5 (C-3), 136.0, 135.6, 134.8 (C-1″, *C*HCH_2, C-1‴), 127.6 (C-3″,5″,3‴,5‴), 127.0 (C-4″,4‴), 126.2 (C-2″,2‴,6″,6‴), 122.3 (C-6′), 121.8 (C-1′), 116.9 (C-2′), 114.4 (CH*C*H_2), 112.8 (C-5′), 109.6 (C-10), 107.0 (C-6), 103.9 (C-8), 70.5, 70.0 (2CH_2), 59.1 (3-OCH_3). − DCI MS; *m*/*z*: 507 [M + H]$^+$. − HR MS; [M + H]$^+$: found 507.183; calcd. 507.181.

5-Acetoxy-7-vinylflavone (5d): A 100-mL flask, equipped with a magnetic stirring bar, a septum inlet and a condenser, was charged with 5-acetoxy-7-triflyloxyflavone (**4a**) (2.14 g, 5 mmol), triphenylphosphane (0.52 g, 2 mmol), tetrakis(triphenylphosphane)-palladium (0.58 g, 0.5 mmol), lithium chloride (0.64 g, 15 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol in dioxane (40 mL), and flushed with argon. A solution of tetravinyltin (1.71 g, 75 mmol) in 10 mL of dioxane was then added. The resulting mixture was stirred at reflux under argon for 5 h. After workup, 5-acetoxy-7-vinylflavone (**5d**) (0.72 g, 47%) and 5-hydroxy-7-vinylflavone (**5a**) (0.04 g, 3.3%) were obtained.

5d: ^{1}H NMR ($CDCl_3$, TMS): δ = 7.87 (m, 2 H, 2′,6′-H), 7.52 (m, 3 H, 3′,4′,5′-H), 7.44 (d, 1 H, $J_{6,8}$ = 1.46 Hz, 8-H), 7.08 (d, 1 H, $J_{6,8}$ = 1.46 Hz, 6-H), 6.65 (s, 1 H, 3-H), 6.75 (q, 1 H, J_{ac} = 17.58 Hz, J_{ab} = 10.99 Hz, H_a), 5.94 (d, 1 H, J_{ac} = 17.58 Hz, H_c),

5.51 (d, 1 H, J_{ab} = 10.99 Hz, H_b), 2.45 (s, 3 H, $COCH_3$). − ^{13}C NMR ($CDCl_3$, TMS): δ = 176.8 (C-4), 169.8 ($COCH_3$), 162.5 (C-2), 157.7 (C-9), 149.5 (C-5), 143.2 (C-7), 134.8 ($CHCH_2$), 131.7 (C-4′), 131.4 (C-1′), 129.1 (C-3′,5′), 126.3 (C-2′,6′), 118.7 ($CHCH_2$), 116.7 (C-6), 116.3 (C-10), 113.7 (C-8), 108.8 (C-3), 21.2 ($COCH_3$). − DCI MS; *m/z*: 307 $[M + H]^+$.

7-Amino-5-hydroxyflavone (7): An oven-dried flask was charged with BINAP (11 mg, 0.02 mmol), palladium acetate (3 mg, 0.2 mmol), 5-acetoxy-7-triflyloxyflavone (**4a**) (86 mg, 0.2 mmol) and cesium carbonate (164 mg, 0.50 mmol) and then purged with argon. A solution of benzophenone imine (46 mg, 0.025 mmol) in 5 mL of THF was added and the mixture was stirred at reflux under argon for 3.5 h. After this period, DCI MS showed that the starting material had been consumed. The mixture was cooled to room temperature, diluted with diethyl ether (100 mL), filtered, and concentrated. The brown residue was purified by column chromatography (CH_2Cl_2/MeOH, 50:1) to give **6** (53 mg, 63%). The diphenyl ketimine adduct **6** was recrystallized from MeOH/acetone (5:2).

6: ^1H NMR ([D_6]acetone): δ = 12.71 (s, 1 H, 5-OH), 8.02 (m, 2 H, 2′,6′-H), 7.70−7.33 (m, 10 H, $2C_6H_5$), 7.58 (m, 3 H, 3′,4′,5′-H), 6.77 (s, 1 H, 3-H), 6.52 (d, 1 H, $J_{6,8}$ = 1.75 Hz, 8-H), 6.18 (d, 1 H, $J_{6,8}$ = 1.75 Hz, 6-H). − DCI MS; *m/z*: 418 $[M + H]^+$. − HR MS; $[M + H]^+$: found 418.145; calcd. 418.144. − A mixture of the diphenyl ketimine adduct **6** (42.7 mg, 0.10 mmol), palladium hydroxide on carbon (57 mg), cyclohexene (2 mL), and ethanol (5 mL) was heated under reflux for 2 h. After cooling to room temperature, the solution was passed through a short column of silica gel, which was eluted with dichloromethane. The eluate was collected, concentrated, and chromatographed (CH_2Cl_2/MeOH, 50:1) to yield 7-amino-5-hydroxyflavone (**7**) (23 mg, 79%).

7: ^1H NMR ([D_6]DMSO): δ = 12.80 (s, 1 H, 7-OH), 7.99 (m, 2 H, 2′,6′-H), 7.55 (m, 3 H, 3′,4′,5′-H), 6.79 (s, 1 H, 3-H), 6.44 (m, 2 H, NH_2), 6.19 (d, 1 H, $J_{6,8}$ = 1.84 Hz, 8-H), 5.96 (d, 1 H, $J_{6,8}$ = 1.84 Hz, 6-H). − ^{13}C NMR ([D_6]DMSO): δ = 180.5 (C-4), 162.0 (C-2), 161.1 (C-5), 157.7 (C-9), 156.0 (C-7), 131.5 (C-4′), 131.0 (C-1′), 128.9 (C-3′,5′), 126.0 (C-2′,6′), 104.8 (C-3), 101.3 (C-10), 95.9 (C-6), 90.4 (C-8). − DCI MS; *m/z*: 254 $[M + H]^+$. − HR MS; $[M + H]^+$: found 254.085; calcd. 254.082.

Acknowledgments

We thank Prof. M. Claeys for carrying out high-resolution mass measurements, Ir. J. Verreydt for recording the DCI mass spectra, and Ir. J. Aerts and Dr. A. De Groot for recording the NMR spectra. We are also grateful to Prof. D. A. Vanden Berghe for performing the biological tests. This work was supported by the Flemish government (Belgium) in a concerted action 92/94−9.

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Received October 19, 1998
[O98458]