Table II. Dehydration of 3-(1-Hydroxyalkyl)-1-tosylpyrroles 4a–d to 3-Ethenyl-1-tosylpyrroles 7a–d with DMSO at 160 °C

starting material			product			
entry	compd	reaction time, min	compd	yield,[a] %	mp,[b] °C	purification process
1	**4a**	30	**7a**	94	81–83	CC;[c] hexane–$CHCl_3$ (1:1)
2	**4b**	20	**7b**	69	55–56[d]	CC; hexane–$CHCl_3$ (1:1)
3	**4c**	7	**7c**	65	204–205[e]	CC; hexane–CH_2Cl_2 (1:1)
4	**4d**	60	**7d**	93	105–107	cryst; pentane–Et_2O

[a] Yield of pure isolated product 7 based on 4. [b] Uncorrected. [c] CC = Column chromatography: the stationary phase was silica gel. [d] 80:20 trans/cis mixture determined by ^1H NMR spectroscopy. [e] Pure trans isomer.

Table III. Detosylation of 3-Ethenyl-1-tosylpyrroles 7a–d to 3-Ethenylpyrroles 8a–d with 5 N NaOH

starting material				product		
entry	compd	solvent	reaction time, h	compd	yield,[a] %	purification process
1	**7a**	*i*-PrOH	8.0	**8a**	82 (54)	oil;[b] distillation
2	**7b**	*i*-PrOH[c]	9.0	**8b**	75 (35)	oil;[d] CC;[e] C_6H_6–CCl_4 (2:3)
3	**7c**	dioxane[f]	8.5	**8c**	80 (37)	solid;[g,h] CC; hexane–THF (2:1)
4	**7d**	*i*-PrOH	15.0	**8d**	73 (33)	oil;[i] distillation

[a] Yield of pure isolated product 8 based on 7. Numbers in parentheses are overall yields based on 3. [b] Bp 30 °C, 6×10^{-3} torr. [c] In the presence of diphenylamine (5% w/w) as polymerization inhibitor. [d] 80/20 trans/cis mixture determined by ^1H NMR spectroscopy. [e] CC = Column chromatography: the stationary phase was silica gel and the eluent mixture was NH_3-saturated. [f] Dioxane was used as the solvent due to the low solubility of **7c** in 2-propanol. [g] The product decomposed under mp determination conditions. [h] Pure trans isomer. [i] Bp 38–40 °C, 6×10^{-3} torr.

3.32 Hz, H4), 3.15 (h, 1 H, J = 6.88 Hz, CH), 2.42 (s, 3 H), 1.16 (d, 6 H, J = 6.88 Hz, $(CH_3)_2$); MS *m/e* 291 (M^+, 6.22), 248 (90.54), 155 (66.5), 91 (100), 65 (36.1), 41 (45.7), 39 (60.5). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.54; H, 5.63; N, 4.73.

3-(1-Hydroxyalkyl)-1-tosylpyrroles. General Procedure. 3-(1-Hydroxyethyl)-1-tosylpyrrole (4a). To a solution of 3-acetyl-1-tosylpyrrole (**3a**) (10.0 g, 0.038 mol) in dioxane (320 mL) were added $NaBH_4$ (0.76 g, 0.020 mol) and 2-propanol (3.3 mL, 0.043 mol). The reaction suspension was refluxed for 6.5 h, and then it was cooled to room temperature, treated with 5 M aqueous ammonium chloride solution (150 mL), and extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were treated with water (1000 mL), and then the aqueous phase was extracted with Et_2O (5 × 150 mL). The organic extracts were dried over anhydrous sodium sulfate, and the solvents were evaporated under reduced pressure to give a yellow-orange residue which was chromatographed on silica gel, by eluting with 70:30 chloroform/ethyl acetate to afford 3-(1-hydroxyethyl)-1-tosylpyrrole (**4a**) (7.02 g, 0.026 mol, 70% yield) as a pale yellow oil: ^1H NMR δ 7.74 (d, 2 H, J = 8.14 Hz), 7.28 (d, 2 H, J = 8.14 Hz), 7.12–7.07 (m, 2 H, H2, H5), 6.29 (dd, 1 H, J = 1.71, 3.14 Hz, H4), 4.76 (q, 1 H, J = 6.40 Hz, CH), 2.40 (s, 3 H), 2.00–1.90 (br s, 1 H, OH), 1.42 (d, 3 H, J = 6.40 Hz, CH_3); MS *m/e* 265 (M^+, 21), 250 (43.5), 155 (37.1), 132 (12.9), 91 (100), 65 (24.2). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.73; H, 5.71; N, 5.27.

3-(1-Hydroxypropyl)-1-tosylpyrrole (4b): ^1H NMR δ 7.73 (d, 2 H, J = 8.63 Hz), 7.28 (d, 2 H, J = 8.63 Hz), 7.12–7.06 (m, 2 H, H2, H5), 6.27 (dd, 1 H, J = 1.64, 3.16 Hz, H4), 4.49 (t, 1 H, J = 6.22 Hz, CH), 2.40 (s, 3 H), 1.78–1.64 (m, 3 H, CH_2, OH), 0.88 (t, 3 H, J = 7.41 Hz, CH_3); MS *m/e* 277 (M^+, 20.8), 250 (41.7), 248 (100), 207 (10.4). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.63; H, 5.46; N, 5.05. Found: C, 60.51; H, 5.48; N, 5.03.

3-(1-Hydroxy-2-phenylethyl)-1-tosylpyrrole (4c): ^1H NMR δ 7.71 (d, 2 H, J = 8.30 Hz), 7.28 (d, 2 H, J = 8.30 Hz), 7.26–7.20 (m, 5 H), 7.14–7.03 (m, 2 H, H2, H5), 6.29 (m, 1 H, H4), 4.79 (t, 1 H, J = 6.20 Hz, CH), 3.02–2.89 (m, 2 H, CH_2), 2.41 (s, 3 H), 2.02 (br s, 1 H, OH); MS *m/e* 323 (M^+ – 18, 24.7), 250 (41.9), 168 (100), 167 (89.7), 155 (45.3), 141 (69.3), 115 (30.0), 91 (90.2), 65 (23.0), 39 (21.3). Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 67.05; H, 5.48; N, 4.25.

3-(1-Hydroxy-2-methylpropyl)-1-tosylpyrrole (4d): ^1H NMR δ 7.73 (d, 2H, J = 8.12 Hz), 7.28 (d, 2H, J = 8.12 Hz), 7.10 (t, 1H, J = 2.20 Hz, H2), 7.06 (m, 1 H, H5), 6.25 (dd, 1 H, J = 1.72, 3.24 Hz, H4), 4.30 (d, 1 H, J = 6.22 Hz, C*H*OH), 2.40 (s, 3 H), 1.76–1.92 (m, 2 H, C*H*CH_3, OH), 0.91 (d, 3 H, J = 6.74 Hz, CH_3), 0.79 (d, 3 H, J = 6.74 Hz, CH_3); MS *m/e* 275 (M^+ – 18, 27.2), 250 (38.8), 155 (34.8), 120 (39.3), 93 (41.1), 91 (100), 65 (32.7), 51 (24.8), 41 (44.4), 39 (56.4). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.55; H, 6.71; N, 4.69.

3-Ethenyl-1-tosylpyrroles. General Procedure. 3-Vinyl-1-tosylpyrrole (7a). 3-(1-Hydroxyethyl)-1-tosylpyrrole (**4a**) (13.5 g, 0.051 mol) and DMSO (47 mL, 0.67 mol) were stirred under a nitrogen atmosphere at 160 °C for 0.5 h. After cooling to room temperature, water was added and the mixture extracted thoroughly with Et_2O (5 × 50 mL). The combined ethereal extracts were dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to give a residue which was chromatographed on silica gel by eluting with 1:1 chloroform/hexane to afford 3-vinyl-1-tosylpyrrole (**7a**) (11.9 g, 0.048 mol, 94% yield) as a colorless solid: mp 81–83 °C; ^1H NMR δ 7.74 (d, J = 8.60 Hz, 2 H), 7.28 (d, J = 8.60 Hz, 2 H), 7.10 (d, 2 H, J = 2.40 Hz, H2, H5), 6.49 (dd, 1 H, J = 10.80, 17.60 Hz, CHα), 6.45 (d, 1 H, J = 2.40 Hz, H4), 5.44 (dd, 1 H, J = 1.22, 17.60 Hz, CHβ cis), 5.10 (dd, 1 H, J = 1.22, 10.80 Hz, CHβ trans), 2.4 (s, 3 H); MS *m/e* 247 (M^+, 50), 155 (42.9), 135 (14.3), 91 (100), 65 (21.4), 39 (17.9). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 62.95; H, 5.32; N, 5.64.

3-(1-Propenyl)-1-tosylpyrrole (7b): ^1H NMR δ 7.83–7.79 (m 2 H), 7.37–7.34 (m, 2 H), 7.16 (m, 1 H, H2), 7.05 (m, 1 H, H5), 6.46 (m, 1 H, H4), 6.27 (*trans*-**7b** d, 1 H, J = 16.00 Hz, CHα), 6.03 (*trans*-**7b** dq, 1 H, J = 6.90, 16.00 Hz, CHβ), 5.74 (*cis*-**7b** dq, 1 H, J = 7.10, 11.60 Hz, CHβ), 2.48 (s, 3 H), 1.94 (*cis*-**7b** dd, 3 H, J = 1.80, 7.10 Hz, CH_3), 1.88 (*trans*-**7b** dd, 3 H, J = 1.80, 6.90 Hz, CH_3); MS *m/e* *trans*-**7b** 261 (M^+, 45.1), 155 (27.1), 106 (43.0), 91 (100), 79 (44.4), 65 (29.2), 51 (27.1), 39 (17.4), 31 (93). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.16; H, 5.80; N, 5.34.

3-(2-Phenylethenyl)-1-tosylpyrrole (7c): ^1H NMR δ 7.86 (d, 2 H, J = 8.45 Hz), 7.52–7.43 (m, 8 H), 7.23 (dd, 1 H, J = 2.35, 3.31 Hz, H5), 6.99 (d, 1 H, J = 16.17 Hz, CHα or CHβ), 6.88 (d, 1 H, J = 16.17 Hz, CHβ or CHα), 6.63 (dd, 1 H, J = 1.65, 3.31 Hz, H4), 2.50 (s, 3 H); MS *m/e* 323 (M^+, 23.9), 168 (100), 167 (88.8), 141 (69.8), 115 (27.7), 91 (33.2), 39 (11.7). Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.71; H, 5.52; N, 4.18.

3-(2-Methyl-1-propenyl)-1-tosylpyrrole (7d): ^1H NMR δ 7.73 (d, 2 H, J = 8.05 Hz), 7.27 (d, 2 H, J = 8.05 Hz), 7.10–7.03 (m, 2 H, H2, H5), 6.28 (dd, 1 H, J = 1.67, 6.34 Hz, H4), 5.94 (br s, 1 H, CH), 2.40 (s, 3 H), 1.83 (s, 6 H, $(CH_3)_2$); MS *m/e* 275 (M^+, 27.2), 250 (38.8), 155 (34.8), 120 (39.3), 93 (41.1), 91 (100), 65 (32.7), 51 (24.8), 41 (44.4), 39 (56.4). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.17; H, 6.02; N, 5.31.

3-Ethenylpyrroles. General Procedure. 3-Vinylpyrrole (8a). A mixture of 3-vinyl-1-tosylpyrrole (**7a**) (8.0 g, 0.032 mol) in 2-propanol (200 mL) was stirred with 150 mL of 5 N aqueous NaOH under reflux for 8 h. After cooling to room temperature, 2-propanol was removed at reduced pressure and the aqueous residue extracted with Et_2O (3 × 30 mL). The combined extracts were washed with water, dried over Na_2SO_4 and concentrated to

give a red-orange oil which was distilled at reduced pressure to afford 3-vinylpyrrole (**8a**) (2.44 g, 0.026 mol, 82% yield) as a yellowish oil: bp 30 °C, 6×10^{-3} torr; ^{1}H NMR δ 8.11 (br s, 1 H, NH), 6.80–6.72 (m, 2 H, H2, H5), 6.64 (dd, 1 H, J = 10.80, 17.50 Hz, CHα), 6.40 (q, 1 H, J = 2.72, 4.29 Hz, H4), 5.42 (dd, 1 H, J = 1.69, 17.50 Hz, CHβ cis), 4.97 (dd, 1 H, J = 1.69, 10.80 Hz, CHβ trans); MS m/e 93 (M^+, 100), 92 (36.7), 65 (16.8), 41 (19.0), 39 (60.0), 31 (37.0). Anal. Calcd for C_6H_7N: C, 77.58; H, 7.58; N, 15.04. Found: C, 77.35; H, 7.60; N, 14.99.

3-(1-Propenyl)pyrrole (8b). Prepared according to the general procedure except that diphenylamine (5% weight) as polymerization inhibitor was used: ^{1}H NMR δ 8.40–7.80 (br s, 1 H, NH), 6.65 (m, 2 H, H2, H5), 6.40–6.25 (*trans*-**8b** m, 2 H, H4, CHα), 5.94 (*trans*-**8b** dq, 1 H, J = 6.50, 17.10 Hz, CHβ), 1.88 (*cis*-**8b** dd, 3 H, J = 1.76, 7.09 Hz, CH_3), 1.80 (*trans*-**8b** dd, 3 H, J = 1.62, 6.50 Hz, CH_3); MS m/e *trans*-**8b** 107 (M^+, 57.9), 92 (53.9), 67 (38.2), 65 (34.4), 53 (22.8), 52 (25.9), 51 (37.6), 41 (30.4), 39 (100). Anal. Calcd for C_7H_9N: C, 78.45; H, 8.47; N, 13.08. Found: C, 78.21; H, 8.49; N, 13.04.

3-(2-Phenylethenyl)pyrrole (8c). Prepared according to the general procedure except that dioxane was used as a solvent: ^{1}H NMR δ 8.30–8.05 (br s, 1 H, NH), 7.47–6.83 (m, 8 H), 6.78 (m, 1 H, H5), 6.49 (m, 1 H, H4); MS m/e 169 (M^+, 97.1), 168 (100), 141 (29.9), 139 (17.3), 115 (31.0), 84 (24.1), 83 (23.0), 39 (18.1). Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.22. Found: C, 85.42; H, 6.37; N, 8.27.

3-(2-Methyl-1-propenyl)pyrrole (8d): ^{1}H NMR δ 8.30–7.75 (br s, 1 H, NH), 6.73–6.71 (m, 2 H, H2, H5), 6.25 (dd, 1 H, J = 2.20, 4.60 Hz, H4), 6.11 (br s, 1 H, CH), 1.89 (s, 3 H, CH_3), 1.87 (s, 3 H, CH_3); MS m/e 121 (M^+, 100), 106 (69.9), 80 (53.2), 51 (25.7), 41 (21.8), 39 (45.3). Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.18; H, 9.36; N, 11.70.

A Convenient Large-Scale Synthesis of 5-Methoxyflavone and Its Application to Analog Preparation

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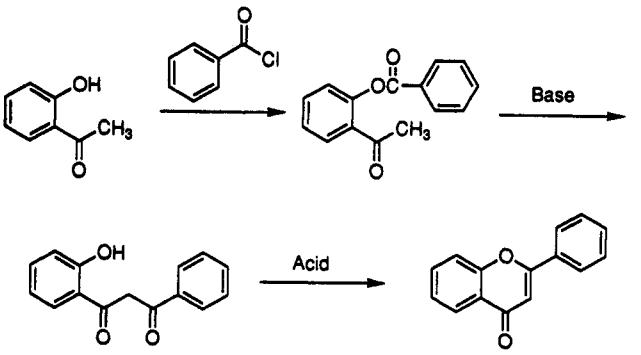
Introduction

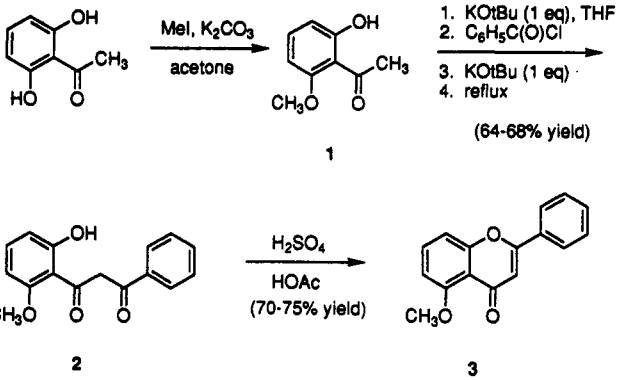
Flavonoids are a group of naturally occurring, low molecular weight compounds that are widely distributed in the plant kingdom and represent a significant part of the average Western daily diet.[2] Many types of compounds comprise the flavonoids, one of the most abundant being the flavones. Members of the flavone class have been associated with a wide variety of biological activities[3] and may be useful in the treatment of certain diseases.[4] Our interest in the biological properties of the compound 5-methoxyflavone (3) prompted us to pursue a synthesis of this material which could be readily executed on a several hundred-gram scale.

Currently there are a number of methods available to synthesize flavones,[5] including the Allan–Robinson synthesis,[6] the Baker–Venkataraman method,[7] synthesis from chalcones,[8,9] and synthesis via an intramolecular Wittig strategy.[10] At the outset, it appeared the Baker–Venkataraman approach, shown generically in Scheme I, would be the most convenient route to the synthesis of 3. In this process, a 2-hydroxyacetophenone is first converted into a benzoyl ester. This species is then isolated and treated with base (usually potassium hydroxide or potassium carbonate) to effect an intramolecular Claisen condensation, forming a 1,3-diketone. Acid treatment induces a dehydrative cyclization to the desired flavone. Unfortunately, we found that the conventional Baker–Venkataraman approach[11] was not suitable for synthesizing large amounts of 3 since low yields and product isolation

Scheme I



Scheme II



complications were encountered in the benzoylation and Claisen condensation steps, respectively. In addition, newer methods for directly converting hydroxyacetophenones into the required diketones, such as potassium carbonate,[12] organolithium reagents,[13,14] or phase-transfer catalysis,[15] proved to be ineffective or impractical for large-scale use. In this Note, we describe a simple and convenient large-scale synthesis of 5-methoxyflavone (3), which employs potassium *tert*-butoxide (KOtBu) in a modified Baker–Venkataraman process.

Results and Discussion

The synthesis of 3 is shown on Scheme II. The starting material, 2-hydroxy-6-methoxyacetophenone (1), was readily prepared, several moles at a time, from commercially available 2,6-dihydroxyacetophenone using methyl iodide and potassium carbonate in acetone according to established procedures.[16] Transformation of 1 into its potassium phenoxide anion with 1.1 equiv of KOtBu was followed by treatment with benzoyl chloride to form the benzoyl ester. To this reaction mixture was directly added a second 1.1 equiv of KOtBu which, after refluxing overnight, provided crystalline diketone 2 in 64–68% isolated yield. Treatment of 2 with sulfuric acid in refluxing acetic acid afforded 5-methoxyflavone (3) in 70–

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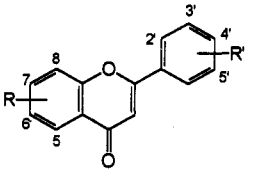
Table I. Flavones Synthesized



compound	R	R′	method[a]	yield (%)[b]
4	7-OMe	3′-CF_3	A	30
5	7-OMe	2′-Cl	A	23
6	5-OMe	4′-CF_3	A	41
7	5-F	H	A	18
8	H	2′-Me	A	49
9	H	4′-Me	A	45
10	H	2′-F	A	40
11	7-OMe	4′-F	A	25
12	5-OMe	3′,5′-diF	B	33
13	5-OMe	3′,5′-diCF_3	B	20
14	5-OMe	4′-F	B	38
15	5-OMe	4′-Me	B	42
16	5-OMe	4′-Cl	B	37

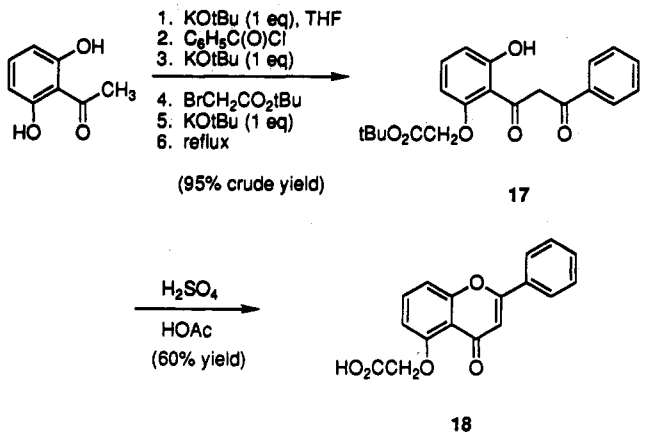
[a] In Method A, the hydroxyacetophenone is treated with 2.2 equiv of KOtBu, followed by addition of the benzoyl chloride and heating. In method B, the hydroxyacetophenone is treated sequentially with 1.1 equiv of KOtBu, the benzoyl chloride, a second 1.1 equiv of KOtBu and heating. See text for more details. [b] Yield of purified flavone from the starting acetophenone.

75% yield. The overall yield for this process from 1 was about 46%, and we have found it can be easily accomplished on a several hundred-gram scale.

The simple and convenient nature of this 5-methoxyflavone synthesis prompted us to examine its general utility for the synthesis of substituted flavones. Our results are collected in Table I. Two variations of the method could be employed. In method A, the hydroxyacetophenone was treated with 2.2 equiv of KOtBu. The benzoyl chloride was then added, and after heating, the diketone was obtained. Method B more closely parallels the 5-methoxyflavone synthesis. In this method, the hydroxyacetophenone was instead treated sequentially with 1.1 equiv of KOtBu, the benzoyl chloride, and then a second 1.1 equiv of KOtBu. After heating, the diketone was isolated. By either method, the diketones were generally obtained as crude oils that were directly cyclized without purification, although on occasion, the diketones were crystallized from ethanol. The methods are well suited for the synthesis of monosubstituted flavones substituted in either aromatic ring, as well as flavones substituted in both rings. Although the overall yields of purified products are slightly lower than that of the conventional Baker–Venkataraman sequence,[11] it should be noted that this new method takes far less time to execute, is operationally simple and, as noted with 5-methoxyflavone, is amenable to scaleup procedures.

This method can also be adapted to the synthesis of certain A-ring alkoxyflavones from dihydroxyacetophenones, an example of which is illustrated in Scheme III. Acylation of 2,6-dihydroxyacetophenone with benzoyl choride was followed by alkylation at the second phenolic oxygen with *tert*-butyl bromoacetate and KOtBu-induced acyl migration to provide diketone 17. Acid-catalyzed cyclization of 17 was accompanied by ester hydrolysis to afford the desired 5-(carboxymethoxy)flavone (18). This demonstrates the feasibility of converting a dihydroxyacetophenone into an A-ring alkoxyflavone using only two reaction vessels and without the need for rigorous purification of intermediates. It is reasonable to assume that

Scheme III



if one began with a nonsymmetrical dihydroxyacetophenone (such as 2,4-dihydroxyacetophenone), the same goal could be accomplished by simply reversing the order of the alkylation and benzoylation steps.

Conclusions

In summary, a convenient large-scale preparation of 5-methoxyflavone has been developed using a KOtBu-mediated diketone synthesis as the key step. This method has been successfully applied to the convenient synthesis of a number of flavone analogs. It has also been combined with a phenolic alkylation step, thereby providing a short and efficient means of transforming dihydroxyacetophenones into A-ring alkoxyflavones.

Experimental Section

Liquid chromatography was performed by (a) using flash chromatography conditions (silica gel, 50 × 60 μm, purchased from Amicon of Beverly, MA), or (b) filtering through a fritted glass funnel packed with a layer each of sand/flash silica gel/sand using a water aspirator vacuum (hereafter this method will be referred to as a vacuum column). Thin-layer chromatography (TLC) was accomplished using silica gel GHLF (250 μm) on prescored plates (10 × 20 cm) obtained from Analtech Inc., Newark, DE. THF was dried over sodium/benzophenone. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using $CDCl_3$ as a solvent except where noted. Melting points were uncorrected. Elemental analyses were obtained from Galbraith Laboratories, Inc., Knoxville, TN or Oneida Research Services, Whitesboro, NY.

Synthesis of 5-Methoxyflavone (3). KOtBu (157.5 g, 1.4 mol) was placed in a 5-L, three-necked round-bottom flask equipped with an agitator, immersion thermometer, addition funnel, and nitrogen inlet. Dry THF (700 mL) was added, and the mixture was cooled to 0–5 °C with stirring. 2-Hydroxy-6-methoxyacetophenone (1)[16] (200 g, 1.2 mol) in dry THF (700 mL) was added slowly to the reaction flask over 30 min while keeping the reaction temperature below 5 °C. The ice bath was removed, and the mixture was stirred at room temperature for 35 min. The mixture was recooled to 0–5 °C and benzoyl chloride (181.6 g, 150 mL, 1.29 mol) was added dropwise over 15 min while keeping the reaction temperature below 5 °C. After this addition was complete, the mixture was stirred at room temperature for 2 h, at which point TLC (20% EtOAc in hexane) revealed only a trace of starting acetophenone. The mixture was recooled to 5 °C and KOtBu (157.5 g, 1.4 mol) was added, resulting in an increase in the reaction temperature to 23 °C. A reflux condenser was attached. The mixture was heated at reflux overnight, cooled to room temperature, and 3N HCl was added until the pH of the mixture was 3. The mixture was concentrated to afford a reddish brown oil (372 g). The oil was dissolved in CH_2Cl_2 (450 mL), and the organic mixture was washed succes-