Synthesis of C−C-Bridged Bis-Isoflavones

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Unique C−C-bridged bis-isoflavones **5**, **8**, and **9** were obtained by reaction of 2-bromomethyl-7,4′-dimethoxyisoflavone **4** with ethyl cyanoacetate anion or tetraethylammonium cyanide or by Pd-catalyzed ethoxycarbonylation, respectively. The phenolic carboxylic acid **7** is available from **5** in two steps.

Introduction

We have recently reported[1,2] the synthesis of isoflavone C-conjugates, containing an alkyl chain appendage with a terminal carboxy group for radioimmunoassay (RIA). Continuing this work, we have now come across the very facile formation of bridged bis-isoflavones **5**, **8**, and **9** during reaction of the allylic C-2 bromomethyl derivative of an isoflavone **4** with ethyl cyanoacetate anion or cyanide anion or by Pd-catalyzed ethoxycarbonylation, respectively. Although biflavonoids are fairly commonly encountered in nature,[3] there is only one report[4] involving the discovery of *directly* C−C-linked isoflavone (daidzein) dimers in yeast-treated *Pueraria lobata*. No C−C-*bridged* bis-isoflavones have been described previously, and **5**, **8**, and **9** are the first synthetic bis-isoflavones of any kind.

Cyanation of allyl and benzyl halides can be generally accomplished by alkali cyanide[5,6] or tetraalkylammonium cyanide[6,7] or by HCN/NaCN for nitrobenzyl halides.[8] The products of these reactions possess a doubly activated CH_2 group that might be expected to be prone toward a second alkylation. In practice, however, bis products are seldom seen except with nitrobenzyl halides, which may react with NaCN to give 2,3-bis(nitroaryl)propionitriles. Various cyanide reagents even give from 4-nitrobenzylbromide the *trimeric* 1,2,3-triaryl-2-cyanopropane.[8,9] Benzyl chloride reacts with NaCN in DMSO mainly to give benzyl cyanide accompanied by a small amount of 2,3-diphenylpropionitrile.[5]

Results and Discussion

For the synthesis of 2-bromomethyl-7,4′-dimethoxyisoflavone **4**, a Friedel−Crafts reaction of resorcinol and 4-hydroxyphenylacetic acid in refluxing $BF_3{\cdot}Et_2O$ provided 2,4,4′-trihydroxydeoxybenzoin **1** in excellent yield. Treatment of **1** with $BF_3{\cdot}Et_2O$ and methanesulfonyl chloride in *N*,*N*-dimethylacetamide gave 7,4′-dihydroxy-2-methylisoflavone **2** in 77% yield. Methylation of **2** with potassium *tert*-butoxide/methyl iodide provided the isoflavone **3** in 93% yield. Bromination of **3** by NBS and a catalytic amount of dibenzoyl peroxide under irradiation gave 2-bromomethyl-7,4′-dimethoxyisoflavone **4** in 82% yield.

Nucleophilic substitution of the allylic bromine in **4** by either ethyl cyanoacetate anion,[10] cyanide anion, or Pd-catalyzed ethoxycarbonylation[11] resulted in bridged bis-isoflavones **5**, **8**, and **9** (Scheme 1). Stirring **4** with the enolate anion of ethyl cyanoacetate, prepared by the reaction of K_2CO_3 and ethyl cyanoacetate, at ambient temperature for 4 h gave **5** in good yield. Acidic hydrolysis of compound **5** yielded **6** in 76% yield. Demethylation of **6** to **7** was carried out using an excess of BBr_3 in CH_2Cl_2 in 79% yield. The bis-isoflavone **8** was obtained by treatment of **4** with tetraethylammonium cyanide in CH_2Cl_2 at ambient temperature in 68% yield. For the synthesis of compound **9** (71%), 2-bromomethyl-7,4′-dimethoxyisoflavone **4** was treated with a mixture of K_2CO_3 and $Pd(OAc)_2$ in ethanol under carbon monoxide atmosphere.

In these reactions, a double alkylation occurs leading to the formation of **5**, **8**, and **9** in preference to the monomeric products. For example, in the last-mentioned case, the second step is apparently distinctly faster than the initial ethoxycarbonylation, judging from the product distribution [bis/mono product weight ratio = 3.4:1, indicating that approximately 60% of the first-formed ethyl (2-isoflavonyl)acetate **10** has undergone further alkylation]. As noted in the Introduction, allyl or benzyl halides do not normally give bis products with the cyanide anion[5−8] with the exception of nitrobenzyl halides. Obviously, in this case the acidity of the intermediate nitrobenzyl cyanide is increased due to the electron-

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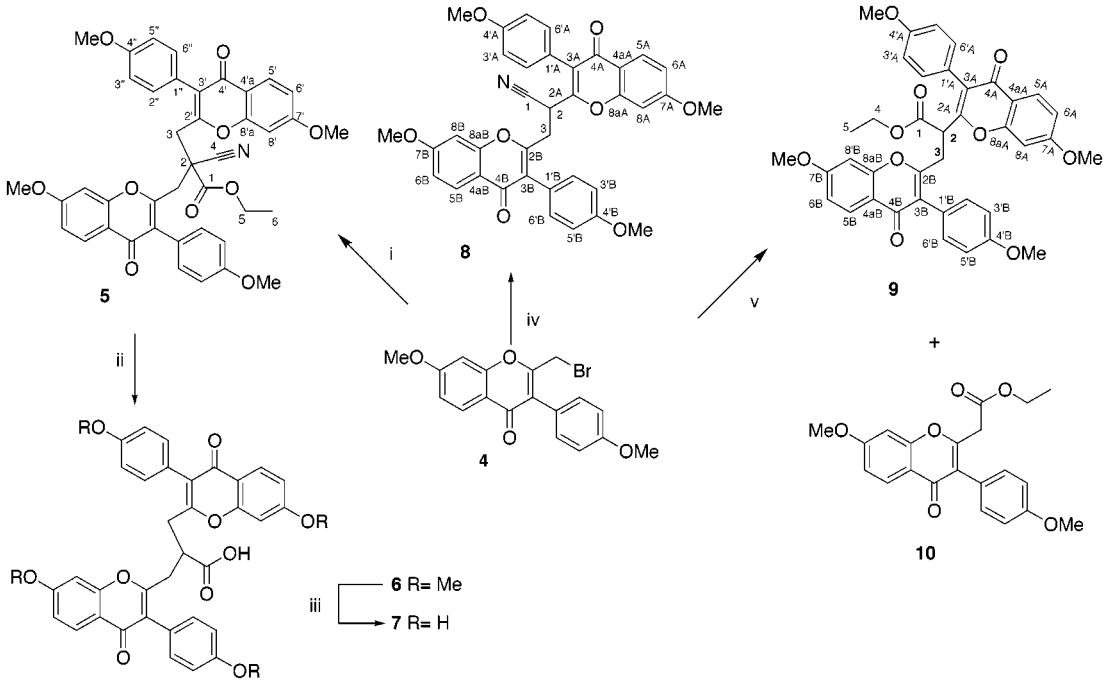
Scheme 1[a]



[a] Reagents and conditions: (i) ethyl cyanoacetate, K_2CO_3, DMF, rt, 4 h; (ii) AcOH, aq H_2SO_4, reflux, 4 h; (iii) BBr_3, CH_2Cl_2, rt, 72 h; (iv) tetraethylammonium cyanide, CH_2Cl_2; (v) CO, $Pd(OAc)_2$, K_2CO_3, absolute EtOH, 50 °C, 10 h.

withdrawing nitro group. An analogous situation occurs in the reaction **4** → **8** where again the intermediate monoalkylation product is more acidic than HCN as the nitrile CH_2 is now attached to the electron-withdrawing isoflavone enone system. As for **5**, the product from the first alkylation is slightly but sufficiently more acidic than the starting material owing to the presence of the alkyl substituent at the acidic site. Thus, in the latter two cases the initially formed monoalkylation product is rapidly converted to the enolate and alkylated for the second time, overcoming any steric congestion at the reacting enolate site.

The X-ray structure shows that in the solid state the molecule adopts a head-to-tail arrangement in such a way that each 4-methoxyphenyl ring lies more or less parallel to the benzopyrone system of the other half of the molecule. The angle between the planes of the A-methoxyphenyl and B-benzopyrone ring is 9°, with an interplanar distance of ca. 3.8 Å, and that between the B-methoxyphenyl and A-benzopyrone ring is 32° (see Figure 1). The stacking of the A-methoxyphenyl and B-benzopyrone rings is, however, not extensive. The minimized structure of the entire molecule is very similar to the X-ray structure except that the angle between the B-methoxyphenyl and A-benzopyrone ring is 9° instead of 32°. The difference may be due to crystal packing effects being operative in the solid state but not in the MM2 calculation,[12] which in principle involves a gas-phase molecule. Overall, the structure of the bis compound is so congested that no rotation about the bridge C−C bonds is possible. This is also seen in the ^{1}H NMR spectrum where the coupling between H3a and H2 (11.7 Hz) is much larger than that between H3b and H2 (3.3 Hz), approximating values suggested by the Karplus relationship (12.2 and 2.2 Hz, respectively). This strongly favored conformation means that all the oxygen atoms are more or less on the same face of the molecule, six of them (O1−O4, O7, and O8) relatively close to each other in space that may lead to interesting coordination chemistry of this molecule.

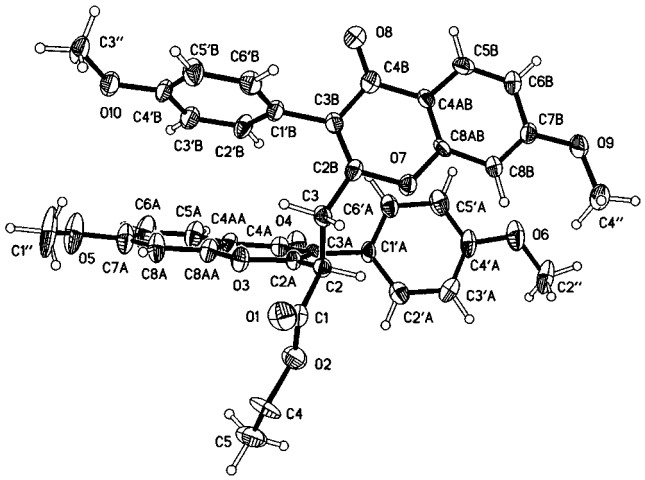


Figure 1. Perspective view of the X-ray crystal structure of **9**.

In view of the highly topical biological properties of isoflavonoids, including those related to hormone-based cancers, osteoporosis, and coronary heart disease,[13] we are now looking into the biological activity and also possible application in RIA of the new dimeric compounds. In this connection, it is significant that health claims of soy foods, rich in isoflavonoids, have now received FDA authorization.[13]

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Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. NMR spectra were recorded on a 200 or 300 MHz spectrometer with $SiMe_4$ as an internal standard. The NMR spectra were assigned using 2D COSY, GHSQCTOCSY, and GHMBC techniques. Mass spectra were obtained using EI ionization at 70 eV. Samples were introduced by a direct inlet probe. IR spectra were recorded from KBr disks. All compounds were homogeneous on TLC. Combustion analysis were performed by the Analytische Laboratorien, Lindlar, Germany.

2,4,4′-Trihydroxydeoxybenzoin (1). Dry resorcinol (11 g, 0.10 mol) and 4-hydroxyphenylacetic acid (13.21 g, 0.09 mol) in $BF_3{\cdot}Et_2O$ (35.5 mL, 0.3 mol) were stirred under reflux for 15 min under Ar. The reaction vessel was then cooled in an ice bath and the reaction mixture poured into an excess of ice−water. The resulting yellow precipitate was collected by filtration and washed with $CHCl_3$ to give **1** (19.72 g, 90%): mp 189−191 °C (lit.[14] mp 192 °C).

7,4′-Dihydroxy-2-methylisoflavone (2). $BF_3{\cdot}Et_2O$ (14.1 mL, 0.114 mol) was added to 2,4,4′-trihydroxydeoxybenzoin (**1**) (7 g, 28.68 mmol) in freshly distilled *N*,*N*-dimethylacetamide (DMA, 40 mL) under Ar and the reaction mixture heated to 50 °C. Methanesulfonyl chloride (6.69 mL, 86 mmol in 10 mL of DMA) was added dropwise and the mixture stirred at 75 °C for 3 h. The dark brown solution was cooled and the viscous product poured over crushed ice to afford an orange precipitate. The solid was collected by filtration, washed with cold water, and recrystallized from aqueous ethanol to give **2** as a white solid (5.9 g, 77%): mp 315−317 °C (lit.[15] mp 315−317 °C); δ_H (DMSO-d_6) 10.77 (7-OH), 9.56 (4′-OH), 7.93 (d, 1H, J = 8.6 Hz, H-5), 7.13 (d, 2H, J = 8.5 Hz, H-2′,6′), 6.95 (dd, 1H, J = 8.6, 2.2, H-6), 6.88 (d, 1H, J = 2.2 Hz, H-8), 6.88 (d, 2H, J = 8.5 Hz, H-3′,5′), 2.29 (s, 3H, $-CH_3$); δ_C 175.0 (C-4), 162.2 (C-7, 8a), 156.9 (C-4′), 156.6 (C-2), 131.6 (C-2′,6′), 127.1 (C-5), 123.6 (C-3), 121.9 (C-1′), 115.6 (C-4a), 114.8 (C-3′,5′), 114.6 (C-6), 101.8 (C-8), 19.2 (CH_3); HRMS $C_{16}H_{12}O_4$ requires 268.0735, found 268.0740.

7,4′-Dimethoxy-2-methylisoflavone (3). 7,4′-Dihydroxy-2-methylisoflavone (**2**) (5 g, 18.65 mmol) and potassium *tert*-butoxide (4.39 g, 39.2 mmol) were stirred in dry DMF (40 mL) under Ar for 2 h. After addition of methyl iodide (5.955 g, 39.2 mmol), the mixture was stirred at 80 °C overnight, cooled to rt, and poured into water, and the crude product was filtered and recrystallized from absolute ethanol to give **3** (5.1 g, 92%): mp 166−167 °C (lit.[15] mp 166−168 °C); δ_H ($CDCl_3$) 8.13 (d, J = 8.9 Hz, 1H, H-5), 7.22 (d, J = 8.9 Hz, 2H, H-2′, H-6′), 6.97 (d, J = 8.9 Hz, 2H, H-3′, H-5′), 6.95 (dd, J = 8.9, 2.4 Hz, 1H, H-6), 6.83 (d, J = 2.4 Hz, 1H, H-8), 3.91 (s, 3H, 7-OMe), 3.84 (s, 3H, 4′-OMe), 2.29 (3H, s, $-CH_3$); δ_C 176.3 (C-4), 163.6 (C-7), 162.5 (C-4′), 158.9 (C-8a), 157.4 (C-2), 131.5 (C-2′, C-6′), 127.5 (C-5), 125.2 (C-3), 122.8 (C-1′), 117.2 (C-4a), 113.9 (C-6), 113.7 (C-3′, C-5′), 99.7 (C-8), 55.7 (7-OCH_3), 55.2 (4′-OCH_3), 19.4 (CH_3); MS m/z relative intensity 296 (M^+, 100), 146 (17); HRMS $C_{18}H_{16}O_4$ requires 296.1049, found 296.1048.

2-(Bromomethyl)-7,4′-dimethoxyisoflavone (4). *N*-Bromosuccinimide (0.992 g, 5.57 mmol), dibenzoyl peroxide (1 mg), and the isoflavone **3** (1.5 g, 5 mmol) in CCl_4 (100 mL) were heated under reflux for 6 h under irradiation (Hg lamp, Osram HQL-R 250). The mixture was then filtered hot to remove the resultant succinimide and the solvent removed to give an orange gummy product. The dichloromethane-soluble materials were chromatographed over silica gel using CH_2Cl_2/EtOAc (9:1) as eluent to give **4** (1.55 g, 82%): mp 152−154 °C; δ_H ($CDCl_3$) 8.13 (d, J = 8.8 Hz, 1H, H-5), 7.33 (d, J = 8.5 Hz, 2H, H-2′, H-6′), 7.00 (d, J = 8.5 Hz, 2H, H-3′, H-5′), 6.97 (dd, J = 8.8, 2.2 Hz, 1H, H-6), 6.91 (d, J = 2.2 Hz, 1H, H-8), 4.27 (s, 2H, CH_2Br), 3.94 (s, 3H, 7-OMe), 3.86 (s, 3H, 4′-OMe); δ_C 176.3 (C-4), 164.2 (C-7), 159.4 (C-4′), 158.4 (C-8a), 157.4 (C-2), 131.0 (C-2′, C-6′), 127.6 (C-5), 123.9 (C-3), 123.5 (C-1′), 117.2 (C-4a), 114.7 (C-6), 113.9 (C-3′, C-5′), 99.8 (C-8), 55.8 (7-OCH_3), 55.2 (4′-OCH_3), 27.4 (CH_2Br); MS m/z relative intensity 376 and 374 (M^+, 24), 295 (100), 279 (27); HRMS $C_{18}H_{15}BrO_4$ requires 374.0153, found 374.0165.

Ethyl 2-Cyano-2,2-bis[(7-methoxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-2-yl)methyl]acetate (5). Ethyl cyanoacetate (0.24 g, 2.1 mmol) was added slowly to a suspension of anhyd K_2CO_3 (0.294 g, 2.1 mmol) in freshly distilled DMF (10 mL) under Ar. After being stirred for 2 h at ambient temperature, the solution was transferred with a syringe to a solution of **4** (0.2 g, 0.533 mmol) in dry DMF (10 mL) at room temperature. The dark red solution was stirred for a further 4 h at room temperature and quenched with water and the crude product filtered. Recrystallization from ethanol gave **5** (0.12 g, 64%): mp 201−202 °C; IR 2250, 1737, 1647 cm^{-1}; λ_{max} (MeCN) nm (log ϵ) 232 (4.67), 240 (4.66), 248 (4.62), 296 (4.30), 306 (4.27); δ_H ($CDCl_3$) 8.01 (d, J = 9.3 Hz, 2H, H-5′), 6.96 (d, J = 9.0 Hz, 4H, H-2″,6″), 6.88 (dd, J = 9.3, 2.4 Hz, 2H, H-6′), 6.74 (d, J = 9 Hz, 4H, H-3″,5″), 6.59 (d, J = 2.4 Hz, 2H, H-8′), 4.23 (q, J = 7.2 Hz, 2H, H-5), 3.80 (s, 6H, 7′-OMe), 3.71 (s, 6H, 4″-OMe), 3.12 (AB quartet, 4H, H-3a,3b), 1.15 (t, J = 7.2 Hz, 3H, H-6); δ_C 175.8 (C-4′), 167.1 (C-1), 164.1 (C-7′), 159.3 (C-4″), 157.3 (C-2′), 156.9 (C-8a′), 131.3 (C-2″, C-6″), 127.6 (C-5′), 125.4 (C-3′), 123.2 (C-1″), 117.1 (C-4), 117.0 (C-4a′), 114.4 (C-6′), 113.9 (C-3″, C-5″), 99.6 (C-8′), 63.5 (C-5), 55.7 (7′-OMe), 55.1 (4″-OMe), 45.5 (C-2), 37.9 (C-3), 13.9 (C-6); MS m/z relative intensity 701 (M^+, 9), 405 (42), 376 (41), 332 (65), 295 (100); HRMS $C_{41}H_{35}NO_{10}$ requires 701.2261, found 701.2247. Anal. Calcd for $C_{41}H_{35}NO_{10}$: C, 70.18; H, 5.03; N, 2.00. Found: C, 69.84; H, 4.96; N, 1.91.

2,2-Bis-[(7-methoxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-2-yl)methyl]acetic Acid (6). Concentrated H_2SO_4 (2 mL) was added slowly with stirring to a mixture of **5** (0.3 g, 0.43 mmol), acetic acid (2 mL), and water (2 mL). After being refluxed for 4 h, the reaction mixture was poured into ice−water (300 mL) and kept overnight at 5 °C. The precipitate was filtered off and dissolved in warm 5% sodium hydrogen carbonate solution (50−60 °C), and the solution was washed with ether. After filtration, the cooled aqueous solution was acidified with concentrated HCl, and the precipitate was filtered, washed thoroughly with water, dried, and crystallized from ethanol to give 0.21 g (76%) of **6**: mp 265−66 °C; IR 3500−2462, 1714, 1636 cm^{-1}; λ_{max} (MeCN) nm (log ϵ) 231 (4.77), 240 (4.78), 247 (4.76), 292 (4.41), 303 (4.37); δ_H (DMSO-d_6) 7.90 (d, J = 9.1 Hz, 2H, H-5′), 7.04 (dd, J = 9.1, 2.4 Hz, 2H, H-6′), 6.98 (d, J = 8.8 Hz, 4H, H-2″, H-6″), 6.90 (d, J = 2.4 Hz, 2H, H-8′), 6.81 (d, J = 8.8 Hz, 4H, H-3″, 5″); 3.88 (s, 6H, 7-OMe); 3.70 (s, 6H, 4″-OMe); 3.28 (quintet, J = 7.1, 1H, H-2), 2.86 (dd, J = 15.4, 7.1 Hz, 2H, H-3a), 2.74 (dd, J = 15.4, 7.3 Hz, 2H, H-3b); δ_C 175.2 (C-4′), 174.3 (C-1), 163.6 (C-7′), 162.4 (C-2′), 158.5 (C-4″),156.7 (C-8a′), 131.4 (C-2″, C-6″), 126.7 (C-5′), 124.2 (C-3′), 122.8 (C-1″), 116.3 (C-4a′), 114.5 (C-6′), 113.3 (C-3″, 5″), 99.9 (C-8′), 55.9 (7′-OMe), 54.9 (4″-OMe), 40.2 (C-2), 33.2 (C-3). For MS measurements, 5 mg of the acid **6** was derivatized to the corresponding methyl ester with diazomethane: MS m/z relative intensity 662 (M^+, 20), 366 (54), 307 (100), 295 (30); HRMS $C_{39}H_{34}O_{10}$ requires 662.2152, found 662.2131.

2,2-Bis-[(7-hydroxy-3-(4-hydroxyphenyl)-4-oxo-4*H*-chromen-2-yl)methyl]acetic Acid (7). An excess of 1 M BBr_3/CH_2Cl_2 (5.54 mL, 20 equiv) was added dropwise with stirring to a solution of **6** (0.18 g, 0.277 mmol) in CH_2Cl_2 (2 mL) under Ar at room temperature. The mixture was stirred for 72 h and then heated with water under reflux for 3 h. CH_2Cl_2 was evaporated, the resulting product was filtered off and recrystallized from aqueous ethanol to give **7** (0.13 g, 79%): mp 233−234 °C; IR 3500−2460, 1718, 1636 cm^{-1}; λ_{max} (MeCN) nm (log ϵ) 230 (4.65), 239 (4.65), 247 (4.62), 292 (4.30), 303 (4.26); δ_H (DMSO-d_6) 12.60 (br s, 1H, COOH), 10.77 (s, 2H, 7′-OH), 9.51 (s, 2H, 4″-OH), 7.91 (d, 2H, J = 8.8 Hz, H-5′), 6.96 (dd, 2H, J = 8.8, 1.8 Hz, H-6′), 6.95 (d, 4H, J = 8.4 Hz, H-2″, 6″), 6.80 (d, 2H, J = 1.8 Hz, H-8′), 6.77 (d, 4H, J = 8.4 Hz, H-3″ and 5″), 3.29 (quintet, 1H, J = 7.1 Hz, H-2), 2.89 (dd, 2H, J = 15.2, 7.7 Hz, H-3a), 2.77 (dd, 2H, J = 15.2, 6.8 Hz, H-3b); δ_C 175.1 (C-4′), 174.5 (C-1), 162.4 (C-7′), 161.9 (C-

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2′), 156.7 (C-8a′, 4″), 131.4 (C-2″, 6″), 127.1 (C-5′), 122.9 (C-3′, 1″), 115.6 (C-4a′), 114.9 (C-6′, C-3″, 5″), 101.8 (C-8′), 40.4 (C-2), 33.6 (C-3). For MS measurements, 5 mg of the acid was derivatized with diazomethane to the preceding pentamethyl derivative, affording mass spectra as reported above.

2,3-Bis[7-methoxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-2-yl]propionitrile (8). Tetraethylammonium cyanide (0.21 g, 1.34 mmol) in CH_2Cl_2 (2 mL) was added dropwise with stirring to a solution of **4** (0.5 g, 1.33 mmol) in 50 mL of anhyd CH_2Cl_2 at room temperature. The dark red solution was stirred for a further 10 h, washed with water, and dried and the solvent evaporated. The residue was purified by chromatography on silica gel (elution with CH_2Cl_2/EtOAc 8:2) and recrystallized from acetone to give **8** (0.28 g, 68%): mp 280−82 °C; IR 2250, 1636 cm^{-1}; λ_{max} (MeCN) nm (log ϵ) 232 (4.71), 240 (4.72), 298 (4.34), 304 (4.31); δ_H ($CDCl_3$) 8.06 (d, J = 9 Hz, 1H) and 8.05 (d, J = 9 Hz, 1H), H-5A and H-5B; 6.98 (dd, J = 9.0, 2.4 Hz, 1H) and 6.95 (dd, J = 9.0, 2.4 Hz, 1H), H-6A and H-6B; 6.96, 6.78 and 6.58 (three broad humps, 8H), H-2′A, H-2′B, H-3′A, H-3′B, H-5′A, H-5′B, H-6′A and H-6′B; 6.53 (d, J = 2.4 Hz, 1H) and 6.36 (d, J = 2.4 Hz, 1H), H-8A and H-8B; 4.47 (dd, J = 10.3, 4.2 Hz, 1H, H-2); 3.88 (s, 3H) and 3.84 (s, 3H),7A- or 7B−OMe; 3.71(s, 3H) and 3.70 (s, 3H), 4′A- or 4′B-OMe; 3.56 (dd, J = 13.9, 10.3 Hz, 1H, H-3b); 3.11 (dd, J = 13.9, 4.2 Hz, 1H, H-3a); δ_C 176.5 and 176.2 (C-4A or 4B); 165.1 and 164.6 (C-7A or C-7B); 160.3 and 159.9 (C-4′A or C-4′B); 158.1 and 158.0 (2C) (C-2A or C-2B or C-8aA or C-8aB); 154.6 (C-2A or C-2B); 131.6 (C-2′A, C-6′A, C-2′B, C-6′B); 128.4 and 128.3 (C-5A or C-5B); 126.1 and 126.0 (C-1′A or C-1′B); 123.8 and 123.1 (C-3A or C-3B); 117.7 and 117.6 (C-4aA or C-4aB); 117.4 (C-1); 116.1 and 115.6 (C-6A or C-6B); 114.5 (C-3′A, C-5′A, C-3′B, C-5′B); 100.4 and 100.2 (C-8A or C-8B); 56.6 and 56.4 (7A- or 7B-OMe); 55.8 and 55.7 (4′A- or 4′B-OMe); 34.5 (C-3), 32.7 (C-2); MS m/z relative intensity 615 (M^+, 29), 615 (70), 295 (100); HRMS $C_{37}H_{29}NO_8$ requires 615.1893, found 615.1913. Anal. Calcd for $C_{37}H_{29}NO_8$: C, 72.19; H, 4.75; N, 2.28. Found: C, 71.36; H, 4.74; N 2.17.

Ethyl 2,3-Bis[7-methoxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-2-yl]propanoate (9). $Pd(OAc)_2$ (12 mg, 2 mol %), isoflavone **4** (0.5 g, 1.33 mmol), and anhyd K_2CO_3 (0.55 g, 4 mmol) in absolute ethanol (5 mL) were stirred under CO for 10 h at 50 °C. After the mixture was cooled to room temperature, the solid was filtered and washed twice with CH_2Cl_2, and the volatiles were removed under reduced pressure. The resulting brown solid was dissolved in CH_2Cl_2 and the solution washed with water and dried over $MgSO_4$. The solvent was evaporated, and the residue was chromatographed over silica gel (eluent gradient CH_2Cl_2/EtOAc 9:1 to 8:2) to yield first 2-(ethoxycarbonylmethyl)-7,4′-dimethoxyisoflavone (**10**) (0.09 g) followed by the bis-isoflavone (**9**) as the major product (0.31 g, 71%): mp 201−202 °C; IR 1743, 1636 cm^{-1}; λ_{max} (MeCN) nm (log ϵ) 232 (4.74), 240 (4.75), 247 (4.72), 295 (4.36), 305 (4.34); δ_H ($CDCl_3$) 8.10 (d, J = 8.8 Hz, 1H) and 8.08 (d, J = 8.8 Hz, 1H), H-5A and H-5B; 6.98 (dd, J = 8.8, 2.4 Hz, 1H) and 6.97 (dd, J = 8.8, 2.4 Hz, 1H), H-6A and H-6B; 7.20, 6.79, 6.56 and 6.20 (four broad humps, 8H), H-2′A, H-2′B, H-3′A, H-3′B, H-5′A, H-5′B, H-6′A and H-6′B; 6.44 (d, J = 2.4 Hz, 1H) and 6.28 (d, J = 2.4 Hz, 1H), H-8A and H-8B; 4.39 (dd, J = 11.7, 3.3 Hz, 1H, H-2); 4.24 (q, J = 7.2 Hz, 2H, H-4); 3.88 (s, 3H) and 3.83 (s, 3H), 7A- or 7B−OMe; 3.69 (s, 3H) and 3.67 (s, 3H), 4′A- or 4′B−OMe; 3.46 (dd, J = 14.3, 11.7 Hz, 1H, H-3a); 3.16 (dd, J = 14.2, 3.3 Hz, 1H, H-3b); 1.25 (t, J = 7.2 Hz, 3H, H-5); δ_C 176.1 (C-4A, C-4B); 169.5 (C-1), 164.1 and 163.9 (C-7A or C-7B); 160.5 (C-2A or C-2B); 159.2 (C-4′A or C-4′B); 158.95 and 158.91 (C-2A or C-2B and C-4′A or C-4′B); 157.5 and 157.4 (C-8aA or C-8aB); 131.2 (C-2′A, C-6′A, C-2′B, C-6′B); 127.63 and 127.60 (C-5A or C-5B); 125.4 and 124.8 (C-3A or C-3B); 124.0 and 123.8 (C-1′A or C-1′B); 117.2 and 117.1 (C-4aA or C-4aB); 114.8 and 114.5 (C-6A or C-6B); 113.6 (C-3′A, C-5′A, C-3′B, C-5′B); 99.8 and 99.6 (C-8A or C-8B); 62.1 (C-4); 55.8 and 55.6 (7A- or 7B−OMe); 55.0 and 54.9 (4′A- or 4′B−OMe); 46.0 (C-3); 31.7 (C-2), 14.2 (C-5); MS m/z relative intensity 662 (M^+, 100), 589 (40), 295 (47); HRMS $C_{39}H_{34}O_{10}$ requires 662.2152, found 662.2126. Anal. Calcd for $C_{39}H_{34}O_{10}$: C, 70.69; H, 5.17. Found: C, 70.24; H, 5.25.

X-ray Crystal Structure Analysis. A colorless crystal with dimensions of 0.45 × 0.30 × 0.12 was mounted to the glass fiber using the oil-drop method.[16] The data were collected on a Rigaku AFC-7S diffractometer, graphite-monochromatizad Mo Kα radiation (λ = 0.710 73 Å), $\varpi-2\theta$ mode. Data reduction was done using the TEXSAN package.[17] The intensity data were corrected for Lorentz and polarization effects and for absorption and extinction. The structure was solved using direct methods. All non-H atoms were refined anisotropically. The carbon C5 was disordered and refined in two positions with population parameters of 0.4 and 0.6. H atoms were refined using a riding model. The final difference Fourier map had peak maxima of 0.220 and minima 0.221 eÅ-3. Programs from the Siemens SHELXTL- package[18] and SHELXL-97[19] were used for the solution, refinement and graphical representation of the structure. Full crystallographic data have been deposited at Cambridge Crystallographic Data Centre and are available as Supporting Information.

Crystal data for 9: ($C_{39}H_{34}O_{10}$) M = 662.2152, monoclinic $P2_1/c$ (no. 14), a = 10.767(2), b = 19.830(4), c = 16.049(3) Å, β = 105.71(3)°, V = 3299(1) Å^3, Z = 4, c = 1.330 g cm^{-3}, T = 193(1) K, μ(Mo Kα) = 0.096 mm^{-1}, F(000) = 1384, R_1 = 0.0965, wR_2 = 0.1894 with $I > 2\sigma(I)$, S = 1.048, 3445 data collected, 1935 $I > 2\sigma(I)$, 452 parameters.

2-(Ethoxycarbonylmethyl)-7,4′-dimethoxyisoflavone (10): white powder; mp 124−5 °C; δ_H ($CDCl_3$) 8.14 (1H, d, J = 9.0 Hz, H-5), 7.24 (2H, d, J = 8.8 Hz, H-2′, H-6′), 6.97 (1H, dd, J = 9.0, 2.3 Hz, H-6), 6.96 (2H, d, J = 8.8 Hz, H-3′, H-5′), 6.85 (1H, d, J = 2.3 Hz, H-8), 4.21 (2H, q, J = 7.1 Hz, CO_2CH_2-CH_3), 3.90 (3H, s, 7-OCH_3), 3.84 (3H, s, 4′-OCH_3), 3.60 (2H, s, H-1″), 1.27 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); δ_C 176.6 (C-4), 168.3 (C-2″), 164.1 (C-7), 159.4 (C-4′), 157.8 (C-2), 157.6 (C-8a), 131.5 (C-2′, C-6′), 127.7 (C-5), 124.9 (C-1′), 124.4 (C-3), 117.4 (C-4a), 114.6 (C-6), 114.0 (C-3′, C-5′), 99.9 (C-8), 61.6 (CO_2CH_2−), 55.8 (7-OCH_3), 55.3 (4′-OCH_3), 39.0 (C-1″), 14.2 (−CH_3); MS m/z relative intensity 368 (M^+, 87), 323 (20), 296 (100); HRMS $C_{21}H_{20}O_6$ requires 368.1260, found 368.1245.

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Supporting Information Available: Crystallograpic data for **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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