A Facile Synthesis of 2-Substituted Isoflavones for Immunoassay: Assembly of the Isoflavonoid Skeleton By Means of a Novel Cyclisation Reaction

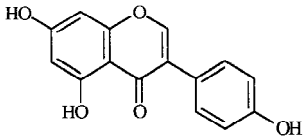
Andrew Pelter*, Robert S. Ward, Jacqueline L. Whalley
Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK
Fax +44(1792)295747; E-mail: A. Pelter@swansea.ac.uk
Received 1 April 1998; revised 5 June 1998

Abstract: For the purpose of the development of immunoassays for wide-scale screening, isoflavones suitable for attachment to a hapten were prepared. A new cyclisation reaction allowed the direct conversion of 2-(acyloxy)deoxybenzoins to 2-alkylisoflavones by treatment with chlorotrimethylsilane and triethylamine in dimethylformamide.

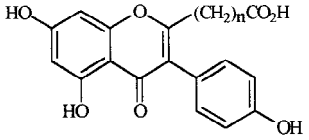
Key words: immunoassay, genistein, cyclisation, 2-(acyloxy)deoxybenzoins, 2-alkylisoflavones

The incidence of hormone-dependent cancers is high in the western world relative to the rates for populations in Asia. Breast cancer rates among Japanese women are one fifth of those in the UK,[1] but are rising rapidly as the population adopts a more westernised lifestyle.[2,3] In Europe and the USA, prostate cancer is the second most common cause of cancer death in males, whereas it is relatively rare in the Far East. It has been proposed that isoflavonoids, such as genistein **(1)**, act as protective factors against the development of hormone dependent cancers.[4] It has been discovered that primates other than man have a low incidence of cancer and that they excrete high levels of isoflavonoids,[5] presumably derived from their diet of seeds, fruits and vegetables which are major sources of isoflavones. These plant phytoestrogens have been identified and measured in a variety of biological fluids by gas chromatography–mass spectrometry, a technique which is time consuming, labour intensive and requires sophisticated and expensive instrumentation. To study these compounds in large population based studies requires the development of faster and more efficient analytical methods; radioimmunoassay offers the advantages of speed and high throughput, with the potential for automation.

This paper describes the synthesis of isoflavones, suitable for use in the development of an immunoassay for the wide-scale screening of genistein **(1)** in clinical samples. The aim was to prepare isoflavones containing the key features of **1**, but containing side chains which are capable of attachment to a carrier protein and which perturb the stereochemistry and/or the electronics of the system as little as possible. In particular, the side chain should carry a carboxylic acid group.



1



2

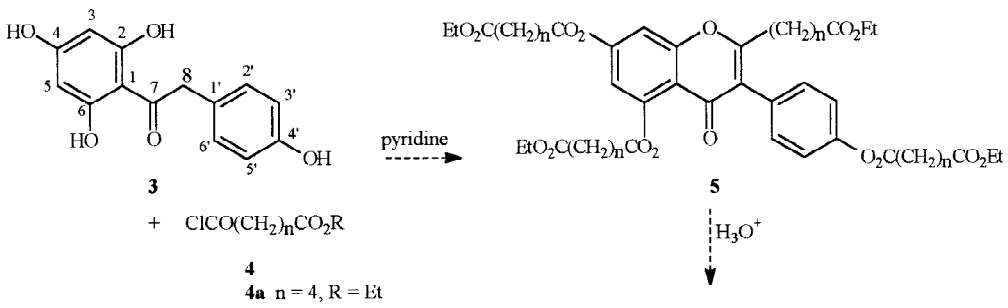
As a result of the requirements given above it was decided that compounds **2** were suitable target molecules. The advantages of **2** are that the phenolic hydroxy groups of genistein, on which activity is thought to depend, are intact, the electronics of the system are left relatively unperturbed, and the acid group is remote from the main nucleus so that its binding to the protein will not affect the isoflavone system.

Initially, it was anticipated that the target molecules **2** could be made by variation of a known procedure for isoflavone synthesis in which a deoxybenzoin reacts with ethyl oxalyl chloride (**4**, n = 0).[6] This strategy would involve the reaction of 4 equivalents of acid chloride **4** with deoxybenzoin **3** in pyridine (Scheme 1). The ester groups would be cleaved by hydrolysis with aqueous acid to give **2**. However, the reaction has never been reported with $n \neq 0$.

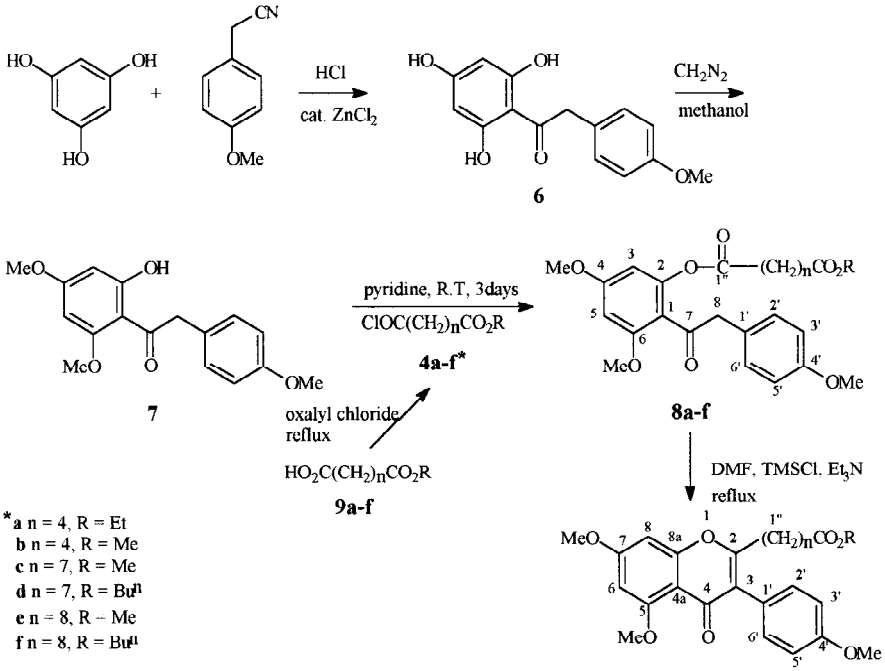
Deoxybenzoin **3** was prepared by an established procedure[7] (Scheme 1) in moderate to poor yields. The attempted reaction of deoxybenzoin **3** with ethyl 4-(chlorocarbonyl)pentanoate **(4a)** in pyridine unfortunately did not provide the isoflavone and, instead, a complex product mixture was recovered. Attention, therefore, turned to undertaking a "two step" acylation/cyclisation process in which the acid chlorides **4a–f** react solely with the 2-OH group. This would require protection of the 4-, 6- and 4′-OH groups, then cyclisation of the deoxybenzoin esters **8a–f** by treatment with acid or base. It was decided to use a methyl group for the necessary protection.

Deoxybenzoin **6** (Scheme 2) has been previously prepared by saturation of the reaction mixture with HCl[8] or by a standard Hoesch reaction[9] employing 1 molar equivalent of zinc chloride. In our hands, these methods provided only moderate yields of the deoxybenzoins. However, by using a catalytic amount of zinc chloride (10% molar equivalent) the reaction was optimised to consistently provide deoxybenzoin **6** in yields of ≥90%. Selective protection of the 4- and 6-OH groups was effected by addition of an excess of diazomethane[10] in methanol. Monoethyl and monomethyl esters **9a** and **9b** are both commercially available. The monobutyl esters **9d** and **9f** were prepared according to Nishiguchi,[11] while the monomethyl esters **9c** and **9e** were prepared by a modification on the Nishiguchi method. Monoesters **9a–f** and excess oxalyl chloride were heated at reflux to give the desired acid chlorides **4a–f**, which, when added to a pyridine solution of **6** gave **8a–f** which were isolated in good yields.

Attempts to initiate intramolecular cyclisation of **8a** employing lithium diisopropylamide or lithium bis(trimethylsilyl)amide resulted in cleavage of the ester to give deoxybenzoin **7** quantitatively. Due to the failure of the



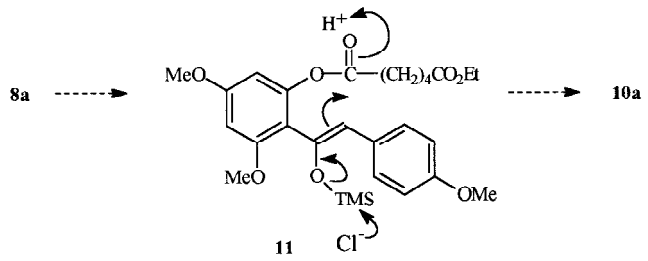
Scheme 1



Scheme 2

basic reaction conditions, our attention turned to the use of acidic conditions to initiate cyclisation. Treatment of deoxybenzoin **8a** with a variety of acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, and 4-toluenesulfonic acid (*p*-TSA) again resulted only in cleavage of the ester link.

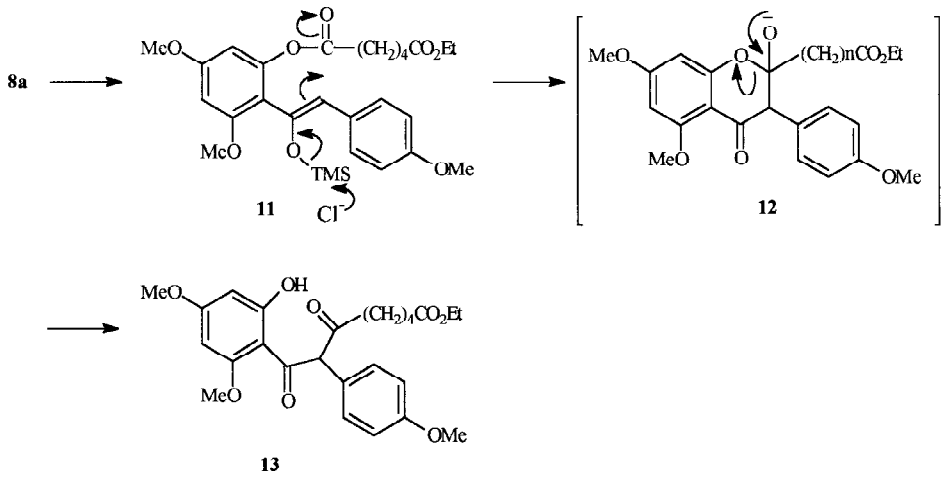
Obviously, different conditions were required in order to prevent the cleavage of the ester before enolisation/cyclisation could occur. We proposed that cyclisation could occur by formation of the silyl enolate **11** and subsequent mild cyclisation leading to isoflavone **10a** (Scheme 3).



Scheme 3

The production of a silyl enol ether under mild conditions using ethyl (trimethylsilyl)acetate (ETSA) and catalysed by tetrabutylammonium fluoride has been described.[12] This procedure should circumvent problems, such as the formation of large amounts of inorganic salts or amine–HCl salts, as well as the aqueous workup usually associated with the standard methodology.[13,14] When this method was applied to **8a** the diketone **13** was isolated as the sole product. Thus the cyclic intermediate **12** had broken down as shown to give **13** (Scheme 4). This was, however, an advance as **13** contains all the carbon atoms of **10a** and **2a** with the right connectivity.

The diketone **13** was identified by the presence of signals at $\delta = 13.65$ for the hydrogen bonded HO group, $\delta = 5.78$ identified as the CH of the β-diketone in the ^{1}H NMR, and $\delta = 198.9$ and 204.4 due to the two ketone groups, as well as by the replacement of the CH_2 peak of the deoxybenzoin by a CH at $\delta = 70.31$ in the ^{13}C NMR. Further investigation led to a procedure employing chlorotrimethylsilane and triethylamine in dimethylformamide[15] to form the required trimethylsilyl enol ethers. When this reaction was carried out at 120 °C a mixture of the previously ob-

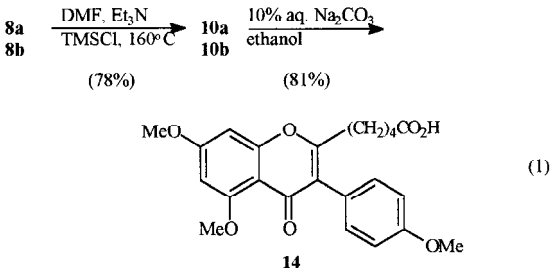


Scheme 4

served **13** (45%) and the desired C-2 substituted isoflavone **10a** (33%) was obtained. Furthermore, HPLC indicated that **13** underwent an intramolecular cyclisation to provide **10a** when treated with polyphosphoric acid, but that under these conditions some degradation of the isoflavone was observed before conversion was complete. However, **13** upon treatment with *p*-TSA in dichloromethane afforded the required isoflavone **10a** in good yield. The *p*-TSA reaction could be carried out on the crude product mixture, mainly **13**, to give **10a** in an overall yield of 72% from **8a**.

A simple modification was to heat the reaction mixture of **8a**, triethylamine and chlorotrimethylsilane in DMF, to 160 °C, which gave **10a** in 78% yield. This reaction also provided isoflavones **10b–f** in good to excellent yields.

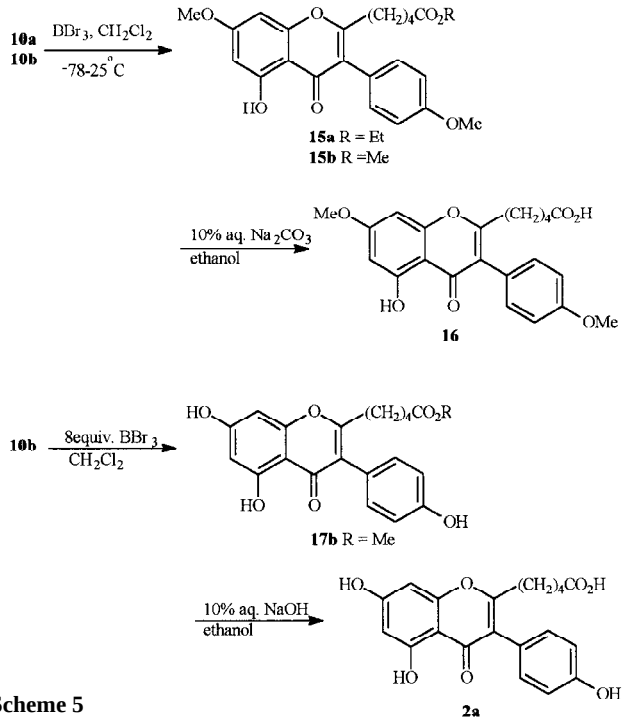
Hydrolysis of ethyl ester **10a** or methyl ester **10b** with aqueous sodium carbonate in ethanol gave acid **14** (equation 1).



(1)

Unfortunately attempts to generate the desired trihydroxy acid **2a** from **14** failed. However, treatment of **10a** and **10b** with one equivalent of boron tribromide at low temperature cleanly gave **15a** and **15b**, which were in turn hydrolysed to give acid **16** (Scheme 5), a potentially useful compound as a model to establish a routine procedure for the attachment of the target isoflavones to a carrier protein and hence the development of immunoassay techniques.

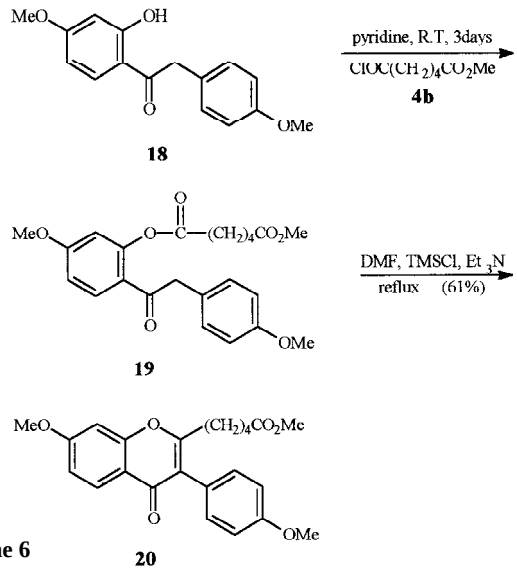
Treatment of **10a** with eight equivalents of boron tribromide at room temperature gave the required target molecule **2a** in 75% yield. Sequential removal of the methyl ether and ester groups was observed by HPLC and occurred in the order 5-OMe, then 7-OMe and 4′-OMe together, followed by the alkyl residue of the ester. A more reproducible procedure involved demethylation as far as the trihydroxy ester **17** followed by hydrolysis of the ester using aqueous sodium hydroxide (Scheme 5).



Scheme 5

Attempts to fully remove the O-alkyl groups from isoflavones **10c–f** were largely unsuccessful. It is thought in these cases the initial cleavage of the 5-OMe group is followed by cleavage of the ester group to form the acid prior to complete cleavage of the methyl ethers. We had previously observed that boron tribromide demethylations of the acid **14** had been fruitless.

The new methodology proved suitable for the preparation of 2-substituted daidzein **20** from 2-hydroxyphenyl 4-methoxybenzyl ketone **(18)** via the ester **19** (Scheme 6).



Scheme 6

In conclusion, new methodology has been introduced for the synthesis of 2-substituted isoflavones and this methodology has been used to synthesise a wide variety of such compounds including our target molecule **2a**.

IR and UV spectra were recorded on a Perkin–Elmer FT 1725X and Phillips PU 8720 spectrophotometers, respectively. UV spectra were measured as MeOH solutions. IR spectra were measured using KBr discs unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 spectrometer in $CDCl_3$ unless otherwise stated. MS were recorded on a VG12-250 low resolution quadrupole mass spectrometer while a ZAB-E high resolution double-focusing instrument was used for accurate mass measurements. Mps were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

TLC analysis was carried out on Merck 5785 Kiesegel 60F_{254} fluorescent plates and reversed phase TLC on Whatman 1803–800 KC_{18} with UV_{254} fluorescent indicator. Column chromatography (normal phase and reversed phase) was performed on silica gel (Fisons matrex, 35–70 μ) and ODS silica (Fluka 100 C_{18} Reversed Phase), respectively. Analytical HPLC was carried out on a Milton Roy system using a 3100 Spectromonitor, 3000 ConstaMetric pump and CI 4100 integrator.

Et_2O and CH_2Cl_2 were dried by passing down an alumina column and distilling from CaH_2. EtOAc was dried over K_2CO_3 and distilled from CaH_2. THF was passed down a dry alumina column and distilled from Na/benzophenone.

4-Methoxybenzyl 2,4,6-Trihydroxyphenyl Ketone (6):
To a vigorously stirred solution of (4-methoxyphenyl)acetonitrile (1.00 g, 6.80 mmol) and 1,3,5-trihydroxybenzene (1.53 g, 12.14 mmol) in anhyd Et_2O (40 mL) under argon was added freshly fused $ZnCl_2$ (100 mg, 0.073 mmol) via a dry addition funnel. The argon inlet was then replaced with a $CaCl_2$ drying tube and the mixture saturated with dry HCl at 0 °C for 6 h. After allowing the mixture to warm to r.t. it was stirred for 24 h, during which time a solid crust had formed on the edge of the reaction vessel. The Et_2O layer was decanted and the residue washed twice with Et_2O (20 mL). 0.1 N aq HCl was added to the residue and the solution heated at reflux for 2 h under argon, it was then cooled and the resultant solid was filtered off and recrystallised from MeOH/H_2O. The product was dried (P_2O_5) to afford deoxybenzoin **6** as a white solid; yield: 1.70 g (91%); mp 198–200 °C (lit.[16] mp 198–200 °C).
UV: λ_{max} (log ε) = 288 nm (4.299).
^{1}H NMR(CD_3OD): δ = 3.74 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2), 5.78 (s, 2H, H-3, H-5), 6.78 and 7.12 (d, 4H, J = 8.6 Hz, H-2′, H-3′).
^{13}C NMR (CD_3OD): δ = 49.6 (CH_2), 55.7 (OCH_3), 95.9 (C-3, C-5), 105.3 (C-1), 114.6 (C-3′, C-5′), 129.2 (C-1′), 131.8 (C-2′, C-6′), 159.6(C-4), 165.8 (C-2, C-6), 166.2 (C-4′), 204.6 (*C*=O).

2-Hydroxy-4,6-dimethoxyphenyl 4-Methoxybenzyl Ketone (7):
A solution of **6** (5.00 g, 18.25 mmol) in MeOH (40 mL) was treated with a large excess of diazomethane in Et_2O at 0 °C. When the reaction was complete by HPLC the mixture was concentrated under reduced pressure and the solid residue recrystallised from MeOH to give **7** as a white solid; yield: 4.88 g (80%); mp 139–140 °C (lit.[17] mp 140 °C).
UV: λ_{max} (log ε) = 286.1 nm (4.320).
^{1}H NMR: δ = 3.67–3.85 (3 × s, 9H, 3 × OCH_3), 4.20 (s, 2H, CH_2), 5.81, 5.94 (2 × s, 2H, H-3 and H-5), 6.73 and 7.03 (d, 4H, J = 9.0 Hz, H-2′, H-3′), 13.4 (brs, 1H, O*H*).

Preparation of Monobutyl Esters 9d and 9f:
To a solution of the diacid (1.0 mmol) in petroleum ether (bp 100–120 °C, 9 mL) was added consecutively, butyl formate (1 mL) then Dowex 50W-X2 resin (1 g) and the slurry heated to reflux with vigorous stirring. After 4.5 h, the resin was filtered off from the hot solution and the filtrate, when cooled, extracted with sat. $NaHCO_3$ (3 × 100 mL). The aqueous layers were acidified with concd HCl to pH 1, then extracted with EtOAc (5 × 100 mL). The combined EtOAc layers were dried ($MgSO_4$), filtered, then concentrated to afford the monobutyl ester.

8-(Butoxycarbonyl)octanoic Acid **(9d)**: oily white solid; yield: 2.45 g (95%); bp 220 °C/760 Torr; mp 68–70 °C (lit.[18] mp 68–69 °C).
^{1}H NMR: δ = 0.93 (t, 3H, J = 7.4 Hz, CH_3), 1.32–1.39 (m, 8H, 4 × CH_2), 1.59–1.64 (m, 6H, 3 × CH_2), 2.28–2.36 (m, 4H, 2 × CH_2), 4.07 (t, 2H, J = 6.7 Hz, OCH_2).
^{13}C NMR: δ = 13.62 (*C*H_3), 19.1 (*C*H_2), 24.5 (*C*H_2), 24.8 (*C*H_2), 28.79 (*C*H_2), 28.83 (*C*H_2), 30.6 (*C*H_2), 34.0 (*C*H_2), 34.2 (*C*H_2), 64.1 (O*C*H_2), 173.9 (*C*O_2Bu), 179.9 (*C*O_2H).

9-(Butoxycarbonyl)nonanoic Acid **(9f)**: oily white solid; yield: 4.83 g (74%); bp 159 °C/0.1 Torr; mp 73–74 °C (lit.[19] mp 74–75 °C).
^{1}H NMR: δ = 0.95 (t, 3H, J = 7.4 Hz, CH_3), 1.32–1.42 (m, 10H, 5 × CH_2), 1.57–1.64 (m, 6H, 3 × CH_2), 2.26–2.39 (m, 4H, 2 × CH_2), 4.06 (t, 2H, J = 6.7 Hz, OCH_2).
^{13}C NMR: δ = 14.79 (*C*H_3), 20.37, 26.10, 26.18, 30.29, 30.35, 31.88, 35.3, 35.53 (*C*H_2) 65.51 (O*C*H_2), 175.7 (*C*O_2Bu), 177.8 (*C*O_2H).

Preparation of the Monomethyl Esters 9c and 9e:
To a solution of the diacid (10.0 mmol) in petroleum ether (bp 100–120 °C, 90 mL) was added consecutively, methyl butyrate (85.0 mmol) then Dowex 50W-X2 resin (10 g) and the slurry heated to reflux with vigorous stirring. After 4 h the resin was filtered off from the hot solution and the filtrate was cooled and extracted with sat. $NaHCO_3$ (3 × 100 mL). The aqueous layers were acidified with concd HCl to pH 1, then extracted with EtOAc (5 × 100 mL). The combined EtOAc layers were dried ($MgSO_4$), filtered, then concentrated to afford the monomethyl ester.

8-(Methoxycarbonyl)octanoic Acid **(9c)**: oily white solid; yield: 1.26 g (60%); bp 159–160 °C/3 Torr (lit.[20] bp 158.5–159.5 °C); mp 22–24 °C, (lit.[20] mp 22–24 °C).
^{1}H NMR: δ = 1.33 (br. s, 6H, 3 × CH_2), 1.62–1.68 (m, 4H, 2 × CH_2), 2.29–2.40 (m, 4H, 2 × CH_2), 3.68 (s, 3H, OCH_3).
^{13}C NMR: δ = 20.1 (*C*H_2), 24.2 (*C*H_2), 24.4 (*C*H_2), 28.3 (*C*H_2), 28.4 (*C*H_2), 33.3 (*C*H_2), 35.0 (*C*H_2), 51.94 (O*C*H_3), 173.8 (*C*O_2Me), 178.6 (*C*O_2H).

9-(Methoxycarbonyl)nonanoic acid **(9e)**: oily white solid; yield: 1.22 g (58%); bp 168–170 °C/3 Torr; mp 41 °C (lit.[20] mp 40–41 °C).
^{1}H NMR: δ = 1.32 (br s, 8H, 4 × CH_2), 1.59–1.63 (m, 4H, 2 × CH_2), 2.27–2.33 (m, 4H, 2 × CH_2), 3.66 (s, 3H, OCH_3).
^{13}C NMR: δ = 20.37, 26.1, 26.18, 30.3, 30.35, 31.88, 35.28, 36.34 (*C*H_2), 175.73 (*C*O_2Me), 177.9 (*C*O_2H).

Formation of 4a–f; General Procedure:
To the monoester **9** (20 mmol) was added oxalyl chloride (30 mmol) under argon at r.t. Once evolution of gas had ceased (ca. 30 min), the mixture was heated to reflux for 2 h and then cooled. The excess oxalyl chloride was distilled off at atmospheric pressure and the remaining material distilled under high vacuum.

Ethyl 5-(Chlorocarbonyl)pentanoate **(4a)**: colourless liquid; yield: 2.82 g (73%); bp 71–72 °C/2 Torr.
IR: ν_{max} = 2982 (C–H), 1800 (COCl), 1733 cm^{-1} (C=O ester).
^{1}H NMR: δ = 1.22 (t, 3H, *J* = 6.7 Hz, OCH$_2$CH_3), 1.70 (q, 4H, *J* = 6.3 Hz, H-3, H-4), 2.28 (t, 2H, *J* = 8.7 Hz, H-5), 2.87 (t, 2H, *J* = 7.6 Hz, H-2), 4.16 (q, 2H, *J* = 6.7 Hz, CO$_2$CH_2CH$_3$).
^{13}C NMR: δ = 14.1 (*C*H$_3$), 23.5 (C-4), 24.3 (C-3), 33.5 (C-5), 46.6 (C-2), 60.3 (*C*H$_2$O), 172.8 (*C*O$_2$Et), 173.3 (*C*OCl).
MS (CI): *m/z* (%) = 192 (M$^+$, 23), 174 (100), 145 (32), 128 (35).

Methyl 5-(Chlorocarbonyl)pentanoate **(4b)**: colourless liquid; yield: 2.67 g (94%); bp 61 °C/0.1 Torr (lit.[21] bp 62 °C/0.1 Torr).
^{1}H NMR: δ = 1.50–1.88 (m, 4H, H-3, H-4), 2.35 (t, 2H, *J* = 6.98 Hz, H-5), 2.97 (t, 2H, *J* = 6.6 Hz, H-2), 3.11 (s, 3H, CO$_2$CH_3).

Methyl 8-(Chlorocarbonyl)octanoate **(4c)**: colourless liquid; yield: 3.58 g (81%); bp 84 °C/0.1 Torr (lit.[22] bp 177 °C/23 Torr).
^{1}H NMR: δ = 1.28–1.42 (m, 6H, H-4, H-5, H-6), 1.58–1.64 (m, 2H, H-7), 1.69–1.73 (m, 2H, H-3), 2.30 (t, 2H, *J* = 7.5 Hz, H-8), 2.89 (t, 2H, *J* = 7.6 Hz, H-2), 3.66 (s, 3H, CO$_2$CH_3).

Butyl 8-(Chlorocarbonyl)octanoate **(4d)**: colourless liquid; yield: 4.04 g (92%); bp 145 °C/4 Torr.
^{1}H NMR: δ = 0.93 [t, 3H, *J* = 7.0 Hz, CO$_2$(CH$_2$)$_2$CH_3], 1.33–1.40 (m, 8H, 4 × CH_2), 1.58–1.64 (m, 4H, 2 × CH_2), 1.64–1.69 (m, 2H, CH_2), 2.29 (t, 2H, *J* = 7.6 Hz, H-8), 2.89 (t, 2H, *J* = 7.3 Hz, H-2), 4.07 (t, 2H, *J* = 6.7 Hz, OCH_2Pr).
^{13}C NMR: δ = 13.7 (*C*H$_3$), 19.2 (*C*H$_2$CH$_3$), 24.8 (C-5) 24.9 (C-4, C-6), 28.1 (OCH$_2$*C*H$_2$), 28.7 (C-3), 29.1 (C-7), 34.3 (C-8), 46.9 (C-2), 64.2 (O*C*H$_2$), 173.7 (*C*O$_2$Bu), 173.9 (*C*OCl).
MS (CI): *m/z* (%) = 262 (M$^+$, 98), 242 (100), 187 (30), 170 (21).
HRMS: obsd 262.7765. Calcd for $C_{13}H_{23}O_3Cl$, 262.7765.

Methyl 9-(Chlorocarbonyl)nonanoate **(4e)**: colourless liquid; yield: 4.42 g (94%); bp 158–160 °C (lit.[23] bp 158–160 °C).
^{1}H NMR: δ = 1.30–1.39 (m, 8H, H-4, H-5, H-6, H-7), 1.59–1.63 (m, 2H, H-8), 1.64–1.78 (m, 2H, H-3), 2.29 (t, 2H, *J* = 7.5 Hz, H-9), 2.87 (t, 2H, *J* = 7.3 Hz, H-2), 3.11 (s, 3H, CO$_2$CH_3).

Butyl 9-(Chlorocarbonyl)nonanoate **(4f)**: colourless liquid; yield: 4.25 g (83%); bp 165 °C/4 Torr.
^{1}H NMR: δ = 0.93 (t, 3H, *J* = 7.4 Hz, CH_3), 1.30–1.39 (m, 10H, 5 × CH_2), 1.57–1.63 (m, 4H, 2 × CH_2), 1.64–1.72 (m, 2H, CH_2), 2.29 (t, 2H, *J* = 7.6 Hz, H-9), 2.89 (t, 2H, *J* = 7.3 Hz, H-2), 4.07 (t, 2H, *J* = 6.7 Hz, OCH_2Pr).
^{13}C NMR: δ = 13.7 (*C*H$_3$), 19.2 (*C*H$_2$CH$_3$), 23.1 (C-5, C-6), 23.3 (C-4, C-7), 28.0 (OCH$_2$*C*H$_2$), 28.7 (C-3), 29.1 (C-8), 34.2 (C-9), 46.9 (C-2), 64.4 (O*C*H$_2$), 173.8 (*C*O$_2$Bu), 174.1 (*C*OCl).
MS (CI): *m/z* (%) = 276 (M$^+$, 67), 256 (50), 207 (35), 187 (21), 184 (23).
HRMS: obsd 276.8049. Calcd for $C_{14}H_{25}O_3Cl$, 276.8049.

Synthesis of 8a–f; General Procedure:
To a stirred solution of deoxybenzoin **7** (1.20 g, 4.0 mmol) in anhyd pyridine (10 mL) under argon at 0 °C was added the acid chloride **4** (4.80 mmol) dropwise. The mixture was stirred for 2 d at r.t., the pyridine was removed in vacuo and the resultant residue dissolved in $CHCl_3$ (20 mL), washed with water (2 × 10 mL), and dried (anhyd $MgSO_4$). Filtration and concentration provided an oil which was purified by flash chromatography (Et_2O/hexane 3:2) to afford the pure substituted deoxybenzoin. (For ^{13}C NMR data of substituted deoxybenzoins and isoflavones see Tables 1 and 2).

2-[5-(Ethoxycarbonyl)pentanoyloxy]-4,6-dimethoxyphenyl 4-Methoxybenzyl Ketone **(8a)**: colourless oil; yield: 1.15 g (72%).
UV: λ_{max} (log ε) = 216.2 (4.322), 269.6 nm (3.959).
IR (neat): ν_{max} = 3200 (C=*C–H*), 1760 (C=O), 1630 cm^{-1} (C=C).
^{1}H NMR: δ = 1.26 (t, 3H, *J* = 7.1 Hz, CO$_2$CH$_2$CH_3), 1.68 (m, 4H, H-3″, H-4″), 2.31 (t, 2H, *J* = 7.5 Hz, H-5″), 2.44 (t, 2H, *J* = 7.4 Hz, H-2″), 3.78 (s, 3H, OCH$_3$), 3.79 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 4.03 (s, 2H, H-8), 4.13 (q, 2H, *J* = 7.1 Hz, CO$_2$CH_2CH$_3$), 6.21 (d, 1H, *J* = 2.2 Hz, H-5), 6.34 (d, 1H, *J* = 2.2 Hz, H-3), 6.84 and 7.11 (d, 4H, *J* = 8.7 Hz, H-2′, H-3′).
MS (CI): *m/z* (%) = 476 (M$^+$ + NH$_4$, 8), 459 (M$^+$ + H, 36), 337 (6), 317 (4), 311 (5), 304 (12), 303 (68), 287 (56), 285 (20), 279 (10), 271 (8), 197 (11), 192 (23), 181 (40), 176 (53), 174 (67), 173 (100), 159 (57), 155 (90), 145 (47), 136 (36), 121 (38), 115 (7), 102 (7), 46 (13), 45 (30).
HRMS: obsd (MH$^+$) 458.4953. Calcd for $C_{25}H_{30}O_8$, 458.4947.

2,4-Dimethoxy-6-[5-(methoxycarbonyl)pentanoyloxy]phenyl 4-Methoxybenzyl Ketone **(8b)**: colourless oil; yield: 1.14 g (62%).
UV: λ_{max} (log ε) = 206.5 (4.373), 267.2 nm (3.907).
IR (neat): ν_{max} = 2951 (C=*C–H*), 1763 (C=O), 1736 (C=O), 1613 cm^{-1} (C=C).
^{1}H NMR: δ = 1.46–1.83 (m, 4H, H-3″, H-4″), 2.32 (t, 2H, *J* = 7.4 Hz, H-5″), 2.45 (t, 2H, *J* = 7.3 Hz, *H*-2″), 3.61 (s, 3H, CO$_2$CH_3), 3.71 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.00 (s, 2H, H-8), 6.20 (d, 1H, *J* = 2.2 Hz, H-5), 6.33 (d, 1H, *J* = 2.2 Hz, H-3), 6.84 and 7.11 (d, 4H, *J* = 8.7 Hz, H-2′, H-3′).
MS (CI): *m/z* (%) = 462 (M$^+$ + NH$_4$, 11), 445 (M$^+$ + H, 41), 414 (3), 385 (6), 329 (52), 301 (72), 295 (8), 165 (11), 164 (5), 159 (60), 155 (90), 121 (38), 102 (7), 46 (12), 45 (15).
HRMS: obsd 444.5248. Calcd for $C_{24}H_{28}O_8$, 444.5248.

2,4-Dimethoxy-6-[8-(methoxycarbonyl)octanoyloxy]phenyl 4-Methoxybenzyl Ketone **(8c)**: colourless oil; yield: 1.81 g (62%).
UV: λ_{max} (log ε) = 203.5 (4.357), 269.1 nm (3.781).
IR (neat): ν_{max} = 2937 (Ar C–H), 1731 (C=O), 1613 cm^{-1} (=C–H Ar).
^{1}H NMR: δ = 1.32–1.36 (m, 6H, H-4″, H-5″, H-6″), 1.62–1.64 (m, 4H, H-3″, H-7″), 2.28 (t, 2H, *J* = 7.6 Hz, H-8″), 2.41 (t, 2H, *J* = 7.8 Hz, H-2″), 3.67 (s, 3H, CO$_2$CH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.04 (s, 2H, H-8), 6.21 (d, 1H, *J* = 2.2 Hz, H-5), 6.34 (s, 1H, *J* = 2.2 Hz, H-3), 6.82 and 7.10 (d, 4H, *J* = 8.7 Hz, H-2′, H-3′).
MS (CI): *m/z* (%) = 487 (M$^+$ + H, 100), 455 (23), 423 (4), 365 (11), 303 (92), 220 (29), 181 (71), 155 (12), 121 (5).
MS (EI): *m/z* (%) = 365 (15), 303 (4), 181 (100), 152 (4), 121 (16).
HRMS: obsd (MH$^+$) 487.2332. Calcd for $C_{27}H_{35}O_8$, 487.2332.

2-[8-(Butoxycarbonyl)octanoyloxy]-4,6-dimethoxyphenyl 4-Methoxybenzyl Ketone **(8d)**: colourless oil; yield: 1.68 g (84%).
UV: λ_{max} (log ε) = 204.0 (4.313), 285.6 (3.920), 324.2 nm (3.547).
IR (neat): ν_{max} = 2936 (C=*C–H*), 1729 (C=O), 1612 cm^{-1} (C=C-Ar).
^{1}H NMR: δ = 0.93 [t, 3H, *J* = 7.4 Hz, CO$_2$(CH$_2$)$_3$CH_3], 1.32–1.42 [m, 8H, H-4″, H-5″, H-6″, CO$_2$(CH$_2$)$_2$CH_2CH$_2$CH$_3$], 1.59–1.64 (m, 6H, H-3″, H-7″, CO$_2$CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 2.29 (t, 2H, *J* = 7.6 Hz, H-8″), 2.41 (t, 2H, *J* = 7.8 Hz, H-2″), 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.04 (s, 2H, H-8), 4.07 (t, 2H, *J* = 6.7 Hz,

Table 1. ^{13}C NMR of C-2 Substituted Deoxybenzoins in $CDCl_3$[a]

Compound	8a	8b	8c	8d	8e	8f	19
C1	116.0	116.0	116.8	116.8	116.7	116.7	122.7
C2	149.2	149.0	149.6	149.6	149.6	149.6	149.0
C3	96.5	96.5	96.4	95.3	96.3	96.3	109.5
C4	162.2	162.3	162.1	162.1	162.1	162.1	163.5
C5	100.2	100.2	100.1	100.2	100.2	100.2	111.5
C6	158.8	158.8	158.7	158.7	158.7	158.7	132.3
C1'	126.8	126.8	126.8	126.8	127.2	126.8	126.7
C2'	130.8	130.8	130.8	130.8	130.7	130.7	130.1
C3'	113.7	113.7	113.7	113.7	113.7	113.7	114.0
C4'	158.4	158.4	158.5	158.3	158.3	158.3	158.5
C1"	171.6	171.6	171.9	171.9	171.9	171.9	171.7
C2"	33.9	33.9	33.9	34.3	33.9	34.3	33.82
C3"	23.9	24.0	24.9	28.9	28.8	29.0	24.25
C4"	23.9	24.0	24.8	24.9	24.8	24.9	24.28
C5"	33.7	33.7	24.6	24.4	24.8	24.4	33.65
C6"	–	–	24.8	24.9	24.8	24.4	130.4
C7"	–	–	24.9	28.9	24.8	24.9	–
C8"	–	–	28.9	34.0	28.8	28.9	–
C9"	–	–	–	–	33.9	33.1	–
C7	199.8	201.2	199.8	199.8	199.7	199.7	195.9
C8	49.7	49.7	49.7	49.7	49.7	49.7	46.60
OMe	55.2	55.3	55.2	55.2	55.1	55.1	55.1
OMe	55.6	55.7	55.6	55.6	55.5	55.5	55.7
OMe	55.9	55.9	55.9	55.8	55.8	5.8	–
Ester							
CH_3	14.2	51.3	51.5	13.7	51.4	13.7	51.50
C=O	173.4	176.3	179.2	173.9	177.9	173.9	173.8
CH_2	60.3			19.1		19.1	
				30.7		30.7	
				64.1		64.1	

[a] Where the multiplicities are the same and the chemical shifts are close, assignments could be interchanged.

$CO_2CH_2(CH_2)_2CH_3$), 6.20 (d, 1H, J = 2.2 Hz, H-5), 6.33 (s, 1H, J = 2.2 Hz, H-3), 6.81 and 7.10 (d, 4H, J = 8.7 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 510 ($M^+ - H_2O$, 18), 407 (3), 311 (7), 284 (9), 227 (8), 101 (100), 152 (14), 135 (20), 97 (11), 83 (18), 69 (17), 55 (40).
MS (CI): *m/z* (%) = 546 ($M^+ + NH_4$, 10), 529 ($M^+ + H$, 25), 511 (100), 303 (52), 285 (21), 262 (90), 245 (41), 181 (20), 155 (12).
HRMS: obsd ($M^+ + NH_4$) 560.3240. Calcd for $C_{31}H_{46}NO_8$, 560.3740.
HRMS: obsd (MH^+) 529.2800. Calcd for $C_{30}H_{41}O_8$, 529.3700.

2,4-Dimethoxy-6-[9-(methoxycarbonyl)nonanoyloxy]phenyl 4-Methoxybenzyl Ketone **(8e)**: colourless oil; yield: 1.34 g (68%).
UV: λ_{max} (log ε) = 203.7 (4.273), 283.2 nm (3.736).
IR (neat): ν_{max} = 2933 (C=*C–H*), 2855 (C–H), 1737 (C=O), 1615 cm^{-1} (C=C).
^1H NMR ($CDCl_3$): δ = 1.13–1.62 (m, 8H, H-4″, H-5″, H-6″, H-7″), 1.60–1.63 (m, 4H, H-3″, H-8″), 2.30 (t, 2H, J = 7.6 Hz, H-9″), 2.33 (t, 2H, J = 7.6 Hz, H-2″), 3.65 (s, 3H, CO_2CH_3), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.03 (s, 2H, H-8), 6.21 (d, 1H, J = 2.2 Hz, H-5), 6.34 (s, 1H, J = 2.2 Hz, H-3), 6.81 and 7.10 (d, 4H, J = 8.7 Hz, H-2′, H-3′).
MS (CI): *m/z* (%) = 560 ($M^+ + NH_4$, 25), 543 ($M^+ + H$, 70), 421 (10), 303 (100), 259 (8), 101 (44).
HRMS: obsd (MH^+) 501.2488. Calcd for $C_{28}H_{38}O_8$, 501.2488.

2-[9-(Butoxycarbonyl)nonanoyloxy]-4,6-dimethoxyphenyl 4-Methoxybenzyl Ketone **(8f)**: colourless oil; yield: 1.33 g (65%).
UV: λ_{max} (log ε) = 204.4 (4.378), 283.2 nm (3.892).
IR (neat): ν_{max} = 2934 (C=*C–H*), 2857 (C–H), 1725 (C=O), 1614 cm^{-1} (C=C).
^1H NMR; δ = 0.93 [t, 3H, J = 7.4 Hz, $CO_2(CH_2)_3CH_3$], 1.26–1.31 [m, 10H, H-4″, H-5″, H-6″, H-7″, $CO_2(CH_2)_2CH_2CH_3$], 1.34–1.63 (m, 6H, H-3″, H-8″, $CO_2CH_2CH_2CH_2CH_3$), 2.29 (t, 2H, J = 7.6 Hz, H-9″), 2.40 (t, 2H, J = 7.6 Hz, H-2″), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.03 (s, 2H, H-8), 5.25 [t, 2H, J = 6.7 Hz, $CO_2CH_2(CH_2)_2CH_3$], 6.21 (d, 1H, J = 2.2 Hz, H-5), 6.34 (s, 1H, J = 2.2 Hz, H-3), 6.81 and 7.10 (d, 4H, J = 8.7 Hz, H-2′, H-3′).
MS (CI): *m/z* (%) = 560 ($M^+ + NH_4$, 25), 543 ($M^+ + H$, 70), 421 (10), 303 (100), 259 (8), 101 (44).
HRMS: obsd ($M^+ + NH_4$) 560.3240. Calcd for $C_{31}H_{46}NO_8$, 560.3740.
HRMS: obsd (MH^+) 544.6680. Calcd for $C_{31}H_{44}O_8$, 544.6618.

4-Methoxybenzyl 4-Methoxy-2-[5-(methoxycarbonyl)pentanoyloxy]phenyl Ketone (19):
To a stirred solution of deoxybenzoin **18**[6] (1.0 g, 3.68 mmol) in anhyd pyridine (10 mL) was added **4b** (0.786 g, 4.40 mmol). The mixture was left for 3 d at r.t. after which the solvent was removed at the pump. The residue was taken into $CHCl_3$ (50 mL), washed with water (2 ×

Table 2. ^{13}C NMR of C-2 Substituted Isoflavones[a]

Compound Solvent[b]	**2a** C	**10a** A	**10b** A	**10c** A	**10d** A	**10e** A	**10f** A	**14** B	**15a** A	**15b** A	**16** B	**17b** C	**20** A
C2	159.2	162.8	162.8	163.5	163.6	163.6	163.5	160.2	162.4	162.3	162.5	163.3	158.7
C3	123.9	125.3	125.3	125.5	125.4	125.5	125.6	124.9	123.7	123.7	125.0	123.8	125.1
C4	182.7	173.3	173.7	174.2	173.9	174.3	174.0	175.7	181.5	181.4	182.8	182.7	176.7
C5	165.7	161.2	161.2	161.5	161.1	161.2	161.2	164.3	166.6	166.5	164.0	165.8	127.6
C6	99.8	95.8	95.6	95.7	95.8	95.6	95.7	95.8	97.9	97.9	99.6	99.8	165.2
C7	168.5	163.7	163.8	163.8	163.7	163.7	163.7	164.3	165.4	165.4	164.0	168.4	164.1
C8	94.5	92.3	92.3	92.8	94.5	92.3	92.3	92.3	92.1	92.1	93.4	94.5	99.8
C8a	158.4	158.9	159.0	158.9	158.9	158.9	158.9	159.0	157.6	157.6	158.2	158.4	157.6
C4a	105.0	108.8	108.8	108.7	108.8	108.8	108.8	108.0	105.1	105.1	108.4	105.0	117.3
C1'	122.7	124.0	124.0	123.1	123.8	123.9	123.9	123.7	121.6	121.6	124.1	122.6	123.0
C2'	132.8	131.7	131.7	131.7	131.7	131.7	131.7	131.4	131.5	131.5	132.7	132.8	131.5
C3'	116.3	113.6	113.6	113.6	113.6	113.6	113.6	113.5	114.2	114.1	115.4	116.3	113.9
C4'	163.3	159.5	159.5	159.6	159.5	159.6	159.6	159.6	159.4	159.4	159.4	159.2	159.1
C1"	32.8	31.7	31.7	31.9	31.9	32.0	32.0	31.4	32.0	29.7	33.2	32.7	32.04
C2"	25.3	24.4	24.9	27.2	27.2	29.0	29.0	24.0	24.7	24.3	25.5	25.2	24.36
C3"	27.7	26.7	26.8	26.4	26.4	27.3	27.3	26.4	26.8	26.8	27.9	27.6	25.86
C4"	34.2	33.9	33.5	24.8	24.8	24.9	24.9	33.2	33.8	32.0	34.7	34.0	35.56
C5"	–	–	–	26.4	26.4	24.9	24.9	–	–	–	–	–	–
C6"	–	–	–	28.7	28.7	27.3	27.3	–	–	–	–	–	–
C7"	–	–	–	33.9	34.2	28.9	28.9	–	–	–	–	–	–
C8"	–	–	–	–	–	34.0	35.4	–	–	–	–	–	–
OMe	–	55.2	55.3	55.1	55.2	55.2	55.2	54.6	55.5	55.3	56.3	–	55.26
OMe	–	55.7	55.7	55.6	55.6	55.7	55.8	55.3	55.8	55.8	56.9	–	55.78
OMe	–	56.2	56.2	56.1	56.1	56.2	56.2	55.4	–	–	–	–	–
CH_3	–	14.2	51.6	51.4	13.7	51.6	13.7	–	14.2	51.6	–	–	51.6
C=O	177.1	176.3	176.3	176.3	176.4	176.3	176.3	177.1	173.2	176.3	177.0	175.4	173.7
CH_2		60.3			19.1		19.2		60.4				
					30.6		30.7						
					64.1		64.1						

[a] Where the multiplicities are the same and chemical shifts are close, assignments could be interchanged.
[b] Solvents: A. $CDCl_3$; B. $CDCl_3/CD_3OD$ 1:1; C. CD_3OD

10 mL), dried ($MgSO_4$), filtered and the solvent evaporated. The residue was further pumped down in high vacuum to remove any last traces of pyridine. Purification was effected by flash chromatography (silica gel, Et_2O/hexane 1:1 up to 6:4) which gave starting material **18** (0.39 g, 39%) and then product **19** (0.94 g, 61%) as an oil which solidified to a pale yellow solid mp 68 °C on standing overnight at 0 °C.
UV: λ_{max} (log ε) = 269 (4.319), 220 nm (4.477).
IR: ν_{max} = 3020, 1732, 1682, 1610 cm^{-1}.
^1H NMR: δ = 1.68, 1.70 (m, 4H, H-3″, H-4″), 2.30 (t, 2H, *J* = 7.4 Hz, H-5″), 2.58 (t, 2H, *J* = 7.3 Hz, H-2″), 3.61 (s, 3H, COOCH_3), 3.76 (s, 3H, ArOCH_3), 3.81 (s, 3H, ArOCH_3), 4.02 (s, 2H, H-8), 6.59 (d, 1H, *J* = 2.2 Hz, H-3), 6.71 (dd, 1H, J_1 = 8, J_2 = 2 Hz, H-5), 6.82 (d, 2H, *J* = 8 Hz, H-3′), 7.07 (d, 2H, *J* = 8 Hz, H-2′), 7.84 (d, 1H, *J* = 8 Hz, H-6).
MS (CI): *m/z* (%) = 432 ($M^+ + NH_4$, 98), 416 (12), 415 (23), 383 (10), 290 (70), 282 (31), 274 (26), 273 (100), 259 (17), 257 (43), 178 (57), 177 (28), 168 (13), 162 (45), 160 (24).
HRMS: obsd ($M^+ + NH_4$) 432.20220. Calcd for $C_{23}H_{30}NO_7$, 432.20223.

Isoflavones 10a–f; General Procedure:
To a stirred solution of C-2 substituted deoxybenzoin **8** (0.40 mmol) in anhyd DMF (10 mL) under argon was added successively freshly distilled Et_3N (1.60 mmol) and freshly distilled TMSCl (0.80 mmol). After heating for ca. 48 h at 160 °C (oil bath temperature) until all of the starting material had been consumed as indicated by TLC, the mixture was allowed to cool to r.t., concentrated under reduced pressure and the residue diluted with EtOAc (50 mL). The EtOAc solution was washed with water (2 × 10 mL), dried (anhyd $MgSO_4$), filtered and concentrated to give an orange oil. Purification by flash chromatography (gradient elution Et_2O/hexane 4:1 to 100% Et_2O) gave the desired isoflavone.

2-[4-(Ethoxycarbonyl)butyl]-4′,5,7-trimethoxyisoflavone **(10a)**: white solid; yield: 113 mg (72%); mp 86–89 °C.
UV: λ_{max} (log ε) = 205.9 (4.647), 245.0 nm (4.477).
IR: ν_{max} = 2937 (C–H), 2840 (OCH_3 str), 1728 (C=O ring), 1639 cm^{-1} (C=O ester).
^1H NMR: δ = 1.24 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.59–1.72 (m, 4H, H-2″, H-3″), 2.25 (t, 2H, *J* = 7.2 Hz, H-4″), 2.51 (t, 2H, *J* = 7.7 Hz, H-1″), 3.83 (s, 3H, OCH_3), 3.89 (s, 6H, 2 × OCH_3), 4.10 (q, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 6.33 (d, 1H, *J* = 2.3 Hz, H-6), 6.44 (d, 1H, *J* = 2.3 Hz, H-8), 6.92 and 7.14 (d, 4H, *J* = 8.8 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 440 (M^+, 57), 439 (14), 411 (10), 395 (8), 339 (28), 311 (50), 218 (22), 188 (24), 181 (35), 121 (38), 102 (28), 41 (54).
HRMS: obsd 440.1835. Calcd for $C_{25}H_{28}O_7$, 440.1835.
Anal. $C_{25}H_{28}O_7$ calcd C, 68.17; H, 6.41. Found C, 68.19; H, 6.33.

4′,5,7-Trimethoxy-2-[4-(methoxycarbonyl)butyl]isoflavone **(10b)**: white solid; yield: 118 mg (69%); mp 74–75 °C.
UV: λ_{max} (log ε) = 204.9 (4.671), 247.0 nm (4.478).

IR: ν_{max} = 3020 (C–H), 2841 (OCH_3 str), 1732 (C=O ring), 1613 (C=O ester), 1216 cm^{-1} (C–O).
^1H NMR: δ = 1.60–1.70 (m, 4H, H-2″ H-3″), 2.26 (t, 2H, *J* = 7.3 Hz, H-4″), 2.51 (t, 2H, *J* = 7.4 Hz, H-1″), 3.65 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 6H, 2 × OCH_3), 6.33 (d, 1H, *J* = 2.3 Hz, H-6), 6.44 (d, 1H, *J* = 2.3 Hz, H-8), 6.93 and 7.14 (d, 4H, *J* = 8.7 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 426 (M^+, 57), 412 (8), 395 (10), 311 (12), 218 (22), 181 (100), 135 (25), 121 (59).
HRMS: obsd 426.1679. Calcd for $C_{24}H_{26}O_7$, 426.1679.
Anal. $C_{24}H_{26}O_7$ calcd C, 67.68; H, 6.57. Found C, 67.72; H, 6.61.

4′,5,7-Trimethoxy-2-[7-(methoxycarbonyl)heptyl]isoflavone **(10c)**:
white solid; yield: 167 mg (87%); mp 99–100 °C.
UV: λ_{max} (log ε) = 201.6 (4.669), 252.2 nm (3.532).
IR: ν_{max} = 2938 (C=*C–H*), 1732 (C=O ring), 1613 cm^{-1} (C=O ester).
^1H NMR: δ = 1.21–1.33 (m, 6H, H-3″, H-4″, H-5″), 1.56–1.65 (m, 4H, H-2″, H-6″), 2.28 (t, 2H, *J* = 7.6 Hz, H-7″), 2.48 (t, 2H, *J* = 7.9 Hz, H-1″), 3.65 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.33 (d, 1H, *J* = 2.3 Hz, H-6), 6.45 (d, 1H, *J* = 2.3 Hz, H-8), 6.93 and 7.15 (d, 4H, *J* = 8.7 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 468 (M^+, 100), 467 (31), 439 (27), 438 (9), 437 (22), 366 (5), 340 (22), 339 (59), 309 (30), 218 (25), 181 (50), 145 (45), 137 (38), 121 (34), 102 (15), 41 (47).
MS (CI): *m/z* (%) = 469 (M^+ + H, 100), 468 (M^+, 3), 303 (72), 155 (30), 52 (60).
HRMS: obsd 468.2148. Calcd for $C_{27}H_{32}O_7$, 468.2148.

2-[7-(Butoxycarbonyl)heptyl]-4′,5,7-trimethoxyisoflavone **(10d)**:
white solid; yield: 139 mg (68%); mp 65–66 °C.
UV: λ_{max} (log ε) = 210.2 (4.706), 251.6 nm (4.603).
IR: ν_{max} 2935 (C=*C–H*), 1732 (C=O ring), 1613 cm^{-1} (C=O ester).
^1H NMR: δ = 0.86 [t, 3H, *J* = 4.8 Hz, $CO_2(CH_2)_3CH_3$], 1.10–1.20 (m, 6H, H-3″, H-4″, H-5″), 1.56–1.72 (m, 8H, H-2″, H-6″, $CO_2CH_2CH_2CH_2CH_3$), 2.20 (t, 2H, *J* = 7.6 Hz, H-7″), 2.38 (t, 2H, *J* = 7.9 Hz, H-1″), 3.83 (s, 3H, OCH_3), 3.89 (s, 6H, 2 × OCH_3), 3.99 [t, 2H, *J* = 6.7 Hz, $CO_2CH_2(CH_2)_2CH_3$], 6.27 (d, 1H, *J* = 2.3 Hz, H-6), 6.38 (d, 1H, *J* = 2.3 Hz, H-8), 6.88 and 7.08 (d, 4H, *J* = 8.8 Hz, H-2′, H-3′).
MS (CI): *m/z* (%) = 511 (M^+ + H, 90), 483 (37), 391 (11), 244 (8), 219 (10).
HRMS: obsd (MH^+) 511.2696. Calcd for $C_{30}H_{39}O_7$, 511.2696.

4′,5,7-Trimethoxy-2-[8-(methoxycarbonyl)octyl]isoflavone **(10e)**:
white solid; yield: 153 mg (77%); mp 103–104 °C.
UV: λ_{max} (log ε) = 204.7 (4.706), 246.9 nm (4.582).
IR: ν_{max} = 2935 (C=*C–H*), 1732 (C=O ring), 1613 cm–^{1} (C=O ester).
^1H NMR: δ = 1.22–1.26 (m, 8H, H-3″, H-4″, H-5″, H-6″), 1.57–1.65 (m, 4H, H-2″, H-7″), 2.28 (t, 2H, *J* = 7.6 Hz, H-8″), 2.47 (t, 2H, *J* = 7.9 Hz, H-1″), 3.66 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.33 (d, 1H, *J* = 2.3 Hz, H-6), 6.45 (d, 1H, *J* = 2.3 Hz, H-8), 6.2 and 7.14 (d, 4H, *J* = 8.8 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 482 (M^+, 100), 481 (16), 453 (18), 451 (15), 339 (50), 337 (25), 309 (30), 218 (25), 181 (50), 145 (35), 127 (38), 121 (34), 102 (17), 41 (68).
HRMS: obsd 482.2304. Calcd for $C_{28}H_{34}O_7$, 482.2304.
Anal. $C_{28}H_{34}O_7$ calcd C, 69.69; H, 7.10. Found: C, 69.35; H, 7.42.

2-[8-(Butoxycarbonyl)octyl]-4′,5,7-trimethoxyisoflavone **(10f)**:
white solid; yield: 153 mg (72%); mp 69–72 °C.
UV: λ_{max} (log ε) = 212.3 (4.702), 254.3 nm (4.594).
IR: ν_{max} = 2935 (C–H-Ar), 1732 (C=O ester), 1613 cm^{-1} (C=O ring).
^1H NMR: δ = 0.95 [t, 3H, *J* = 4.8 Hz, $CO_2(CH_2)_3CH_3$], 1.24–1.40 (m, 8H, H-3″, H-4″, H-5″, H-6″), 1.57–1.65 (m, 8H, H-2″, H-7″, $CO_2CH_2CH_2CH_2CH_3$), 2.27 (t, 2H, *J* = 7.6 Hz, H-8″), 2.47 (t, 2H, *J* = 7.9 Hz, H-1″), 3.83 (s, 3H, OCH_3), 3.89 (s, 6H, 2 × OCH_3), 4.06 [t, 2H, *J* = 6.7 Hz, $CO_2CH_2(CH_2)_2CH_3$], 6.33 (d, 1H, *J* = 2.3 Hz, H-6), 6.44 (d, 1H, *J* = 2.3 Hz, H-8), 6.92 and 7.14 (d, 4H, *J* = 8.8 Hz, H-2′, H-3′).
MS (CI): *m/z* (%) = 525 (M^+ + H, 100), 495 (10), 425 (8), 391 (1), 286 (16).
HRMS: obsd (MH^+) 525.2850. Calcd for $C_{31}H_{41}O_7$, 525.2850.

Preparation of Diketone 13:
To a solution of deoxybenzoin **8a** (100 mg, 0.23 mmol), in anhyd THF (1 mL) under a positive pressure of argon was added ethyl (trimethylsilyl)acetate (106 μL, 0.32 mmol) followed by 1.0 M TBAF in anhyd THF (21 μL, 0.021 mmol) and the reaction stirred at r.t. for 24 h. All volatile material was removed under high vacuum (2.00 Torr) to give a brown gum. Purification by flash chromatography (Et_2O/hexane 2:1 graduating to 100% Et_2O) afforded pure diketone **13** as a colourless oil; yield: 80 mg (72%).
UV: λ_{max} (log ε) = 209 (4.293), 265 nm (4.040).
IR: ν_{max} = 3620 (O–H), 2989 (Ar-H), 1746 (C=O), 1705 (C=O), 1690 cm^{-1} (C=O).
^1H NMR: δ = 1.23 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.54 (m, 4H, $CH_2CH_2CH_2CH_2CO_2Et$), 2.22 (t, 2H, *J* = 6.8 Hz, CH_2CO_2Et), 2.50 (t, 2H, *J* = 6.7 Hz, $COCH_2$), 3.80 (s, 6H, 2 × OCH_3), 3.83 (s, 3H, OCH_3), 4.09 (q, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 5.78 [s, 1H, COC*H*(Ar)], 5.90 (d, 1H, *J* = 2.4 Hz, H-5), 6.08 (d, 1H, *J* = 2.4 Hz, H-3), 6.91 and 7.15 (d, 4H, *J* = 8.2 Hz, H-2′, H-3′), 13.65 (s, 1H, O*H*).
^{13}C NMR: δ = 14.2 ($CO_2CH_2CH_3$), 23.0, 24.2 [$CH_2(CH_2)_2CH_2CO_2Et$], 34.0 [$CH_2(CH_2)_2CH_2CO_2Et$], 41.3 [$CH_2(CH_2)_2CH_2CO_2Et$], 55.2, 55.6, 55.8 (3 × OCH_3), 60.3 ($CO_2CH_2CH_3$), 70.31 (COC*H*CO), 91.1 (C-3), 94.0 (C-5), 105.5 (C-1), 114.1 (C-3′,C-5′), 125.5 (C-1′), 131.2 (C-2′, C-6′), 159.3 (C-4′), 161.7 (C-6), 166.4 (C-2), 168.1 (C-4), 173.4 (CO_2Et), 198.9 (*C*O-CHAr), 204.9 (ArCH*C*OCH_2).

2-[4-(Ethoxycarbonyl)butyl]-4′,5,7-trimethoxyisoflavone (10a):
To a solution of diketone **13** (100 mg, 0.24 mmol) in anhyd CH_2Cl_2 (10 mL) under argon was added 4-toluenesulfonic acid (60 mg, 0.33 mmol) with stirring. After 3 h the mixture was diluted with water (15 mL), extracted with EtOAc (3 × 20 mL) and the combined organic phases dried (anhyd $MgSO_4$), then concentrated in vacuo to afford 72 mg (72%) of product identical in all respects with isoflavone **10a**.

2-[4-(Ethoxycarbonyl)butyl]-5-hydroxy-4′,7-dimethoxyisoflavone (15a):
To a solution of isoflavone **10a** (324 mg, 0.77 mmol) in anhyd CH_2Cl_2 (3 mL) at –20 °C under a positive pressure of argon was added 1.0 M BBr_3 in CH_2Cl_2 (770 μL, 0.77 mmol) and the mixture allowed to warm slowly to r.t. while monitoring by reversed phase HPLC. Once the reaction was complete by HPLC (ca. 3 h), water (2 mL) was added and the product extracted with EtOAc (4 × 5 mL). The combined organic phases were dried (anhyd $MgSO_4$) then concentrated under reduced pressure to afford an oily brown solid which was purified by crystallisation from Et_2O to provide **15a** as a white solid; yield: 269 mg (87%); mp 58–60 °C.
UV: λ_{max} (log ε) = 204.3 (4.643), 257.3 nm (4.583).
UV (MeOH + $AlCl_3$): λ_{max} = 206.9, 266.4, 310.2, 367.0 nm.
IR: ν_{max} = 3360 (br. OH), 2950 (C=*C–H*), 1728 (C=O ester), 1639 cm^{-1} (C=O ring).
^1H NMR: δ = 1.24 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.63–1.81 (m, 4H, H-2″, H-3″), 2.25 (t, 2H, *J* = 7.4 Hz, H-4″), 2.57 (t, 2H, *J* = 7.3 Hz, H-1″), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.11 (q, 2H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 6.34 (d, 1H, *J* = 2.3 Hz, H-6), 6.38 (d, 1H, *J* = 2.3 Hz, H-8), 6.99 and 7.18 (d, 4H, *J* = 8.6 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 426 (M^+, 36), 325 (100), 181 (5), 167 (13), 118 (23), 91 (50).
MS (CI): *m/z* (%) = 427 (M^+ + H, 100).
HRMS: obsd 426.1679. Calcd for $C_{24}H_{26}O_7$, 426.1679.

5-Hydroxy-4′,7-dimethoxy-2-[4-(methoxycarbonyl)butyl]isoflavone (15b):
Isoflavone **10b** (149 mg, 0.36 mmol) in CH_2Cl_2 (1 mL) was treated with 1.0 M BBr_3 in CH_2Cl_2 (360 μL, 0.36 mmol) as above to provide after crystallisation from Et_2O **15b**; yield: 126 mg (88%); mp 62–64 °C.
UV: λ_{max} (log ε) = 203.8 (4.675), 256.9 nm (4.586).
UV (MeOH + $AlCl_3$): λ_{max} = 206.9, 266.4, 310.2, 367.0 nm.
IR: ν_{max} = 3360 (br. OH), 3157 (C–H Ar), 1732 (C=O ester), 1656 cm^{-1} (C=O ring).
^{1}H NMR: δ = 1.60–1.63 (m, 2H, H-3″), 1.63–1.70 (m, 2H, H-2″), 2.27 (t, 2H, *J* = 7.1 Hz, H-4″), 2.53 (t, 2H, *J* = 7.7 Hz, H-1″), 3.65 (s, 3H, CO_2CH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.33 (d, 1H, *J* = 2.3 Hz, H-6), 6.38 (d, 1H, *J* = 2.3 Hz, H-8), 6.99 and 7.18 (d, 4H, *J* = 8.8 Hz, H-2′), 12.85 (s, 1H, OH).
MS (EI): *m/z* (%) = 412 (M^+, 36), 381 (5), 339 (10), 325 (100), 311 (8), 181 (16), 167 (16), 115 (16).
MS (CI): *m/z* (%) = 413 (M^+ + H, 100).
HRMS: obsd 412.1522. Calcd for $C_{23}H_{24}O_7$, 412.1522.

2-(4-Carboxybutyl)-4′,5,7-trimethoxyisoflavone (14):
A solution of isoflavone **10a** (80 mg, 0.18 mmol) dissolved in 50% aq Na_2CO_3/EtOH (1:1, 2 mL) was heated at reflux until the starting isoflavone was completely consumed as indicated by reversed phase HPLC. The EtOH was removed in vacuo, then the residue was diluted in water (1 mL) and extracted with EtOAc (3 × 2 mL). The combined EtOAc phases were extracted with sat. aq $NaHCO_3$ (5 × 2 mL). The combined aq $NaHCO_3$ phases were cooled to 0 °C, then acidified using concd HCl (pH 1), and extracted with EtOAc (10 × 5 mL). The combined EtOAc phases were dried (anhyd $MgSO_4$), filtered and concentrated under reduced pressure to afford the isoflavone acid **14** as a white solid; yield: 62 mg (81%); mp 159–161 °C.
UV: λ_{max} (log ε) = 201.7 (4.775), 246.1 nm (4.791).
IR: ν_{max} = 3387 (O–H), 2948 (C=*C–H*), 1732 cm–^{1} (C=O ester).
^{1}H NMR ($CDCl_3$/CD_3OD 1:1): δ = 1.36–1.64 (m, 2H, H-3″), 1.69–1.78 (m, 2H, H-2″), 2.25 (t, 2H, *J* = 7.2 Hz, H-4″), 2.57 (t, 2H, *J* = 7.6 Hz, H-1″), 3.83 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.41 (d, 1H, *J* = 2.3 Hz, H-6), 6.57 (d, 1H, *J* = 2.3 Hz, H-8), 6.97 and 7.16 (d, 4H, *J* = 8.8 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 426 (M^+, 37), 412 (100), 418 (17), 383 (7), 366 (12), 353 (4), 339 (36), 325 (66), 311 (19), 218 (23), 181 (42), 162 (14), 145 (21), 121 (20).
MS (CI): *m/z* (%) = 427 (MH^+, 35), 413 (100), 399 (22).
HRMS: obsd 412.3520. Calcd for $C_{23}H_{24}O_7$, 412.3520.

2-(4-Carboxybutyl)-4′,5,7,-trimethoxyisoflavone (14):
A solution of isoflavone **10b** (80 mg, 0.19 mmol) dissolved in 5% aq Na_2CO_3/EtOH (1:1, 2 mL) was heated at reflux, until complete by HPLC. Workup was performed as for the previous procedure to give 57 mg (73%) of the previously identified isoflavone **14**.

2-(4-Carboxybutyl)-5-hydroxy-4′,7-dimethoxyisoflavone (16):
A solution of either isoflavone **15a** or **15b** (70 mg, 0.16 mmol) in 5% aq Na_2CO_3/EtOH (1:1, 1 mL) was heated at reflux temperature until the reaction was complete by HPLC. The EtOH was removed in vacuo and the residue acidified to pH 1 at 0 °C by addition of concd HCl, then saturated with NH_4Cl and extracted repeatedly with EtOAc and $CHCl_3$. The combined organic phases were dried (anhyd $MgSO_4$), filtered and concentrated to provide a pale green solid which was purified by recrystallisation from EtOAc to afford from **15a** 35 mg (55%), and from **15b** 40 mg (60%) of the isoflavone acid **16** as a white solid.
UV: λ_{max} (log ε) = 206.5 (4.782), 256.1 nm (4.781).
IR: ν_{max} = 3054 (O–H), 2989 (C=*C–H*), 1732 (C=O ester), 1615 cm^{-1} (C=O ring).
^{1}H NMR ($CDCl_3$/CD_3OD 1:1): δ = 1.60–1.80 (m, 4H, H-3″ H-2″), 2.14 (t, 2H, *J* = 7.2 Hz, H-4″), 2.57 (t, 2H, *J* = 7.6 Hz, H-1″), 3.86 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.28 (d, 1H, *J* = 2.3 Hz, H-6), 6.44 (d, 1H, *J* = 2.3 Hz, H-8), 6.99 and 7.18 (d, 4H, *J* = 8.8 Hz, H-2′, H-3′).
HRMS: obsd 398.1366. Calcd for $C_{22}H_{22}O_7$, 398.1366.

2-(4-Carboxybutyl)-4′,5,7-trihydroxyisoflavone (2a):
To a solution of isoflavone **10a** (324 mg, 0.77 mmol) in anhyd CH_2Cl_2 (3 mL) at –20 °C under a positive pressure of argon was added 1.0 M BBr_3 in CH_2Cl_2 (6.40 mL, 6.40 mmol) and the mixture allowed to warm slowly to r.t. while monitoring by reversed phase HPLC. Once the reaction was complete by HPLC (ca. 8 h) the mixture was concentrated under reduced pressure to afford an oily brown solid which was purified using a reversed phase column (gradient elution 50% MeOH/H_2O to 100% MeOH) to afford **2a**; yield: 214 mg (75%); mp 230–232 °C.
UV: λ_{max} (log ε) = 203.4 (4.782), 256.8 nm (4.745).
UV (MeOH + $AlCl_3$): λ_{max} = 206.9, 266.4, 310.2, 367.0 nm.
IR: ν_{max} = 3360 (br. OH), 3020 (C=*C–H*), 1735 (C=O ring), 1615 cm^{-1} (C=O).
^{1}H NMR (CD_3OD): δ = 1.52–1.56 (m, 2H, H-3″), 1.67–1.71 (m, 2H, H-2″) 2.21 (t, 2H, *J* = 7.2 Hz, H-4″), 2.54 (t, 2H, *J* = 7.6 Hz, H-1″), 6.16 (d, 1H, *J* = 2.3 Hz, H-6), 6.30 (d, 1H, *J* = 2.3 Hz, H-8), 6.85 and 7.05 (d, 4H, *J* = 8.6 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 370 (M^+, 30), 352 (8), 311 (9), 297 (83), 153 (100).
MS (CI): *m/z* (%) = 371 (M^+ + H, 53), 353 (22), 271 (11).
HRMS: obsd 370.3800. Calcd for $C_{20}H_{18}O_7$, 370.3800.
Anal. $C_{20}H_{18}O_7$ calcd C, 64.87; H, 4.90. Found C, 64.87; H, 4.89.

4′,5,7-Trihydroxy-2-[4-(methoxycarboxy)butyl]isoflavone (17b):
To a solution of isoflavone **10b** (190 mg, 0.446 mmol) in anhyd CH_2Cl_2 (2 mL) at –78 °C under a positive pressure of argon was added 1.0 M BBr_3 in CH_2Cl_2 (3.6 mL, 3.6 mmol) precooled to –78 °C. The mixture was kept at –78 °C for 4 h, then at –20 °C for a further 4 h, before being allowed to warm slowly to r.t. overnight. Once the reaction was complete by HPLC the reaction was stopped by adding anhyd MeOH whilst cooling at 0 °C. The solvents were evaporated under reduced pressure to afford a brown solid which was purified using reversed phase flash chromatography (gradient elution 50% MeOH/H_2O to 100% MeOH) to afford **17b**; yield: 170 mg (100%); mp 142–143 °C.
^{1}H NMR (CD_3OD): δ = 1.52–1.56 (m, 2H, H-3″), 1.67–1.71 (m, 2H, H-2″) 2.21 (t, 2H, *J* = 7.2 Hz, H-4″), 2.54 (t, 2H, *J* = 7.6 Hz, H-1″), 3.60 (s, 3H, OCH_3), 6.16 (d, 1H, *J* = 2.3 Hz, H-6), 6.30 (d, 1H, *J* = 2.3 Hz, H-8), 6.85 and 7.05 (d, 4H, *J* = 8.6 Hz, H-2′, H-3′).
MS (EI): *m/z* (%) = 370 (M^+, 30), 352 (8), 311 (9), 297 (83), 153 (100).
MS (ES+): *m/z* (%) = 408 (20), 407 (M^+ + Na, 100), 386 (20), 385 (M^+ + H, 83).
MS: (ES-): *m/z* (%) = 429 (20), 384 (20), 383 (M^+ – H, 100).
HRMS: obsd 385.1287. Calcd for $C_{21}H_{21}O_7$, 385.1287.

2-(4-Carboxybutyl)-4′,5,7-trihydroxyisoflavone (2a):
10% aq NaOH (5 mL) was added to a solution of the isoflavone **17b** (50 mg, 0.13 mmol) in EtOH (5 mL) and the mixture stirred at r.t. for 24 h. The EtOH was removed under reduced pressure, the residue dissolved in water, cooled to 0 °C and acidified to pH 1 with 50% HCl (8 mL). The aqueous mixture was extracted with EtOAc (3 × 5 mL), dried (anhyd $MgSO_4$), filtered and concentrated to provide **2a** as an off-white powder; yield: 49 mg (100%).

4′,7-Dimethoxy-2-[4-(methoxycarbonyl)butyl]isoflavone (20):
Deoxybenzoin ester **19** (0.265 g, 0.64 mmol) was dissolved in anhyd DMF (16 mL) and Et_3N (350 μL) and TMSCl (162 μL) was added to the stirred solution. The mixture was heated for 24 h under reflux after which the solvent was removed, first on a rotary evaporator and then at 50 °C under high vacuum. The crude product (0.263 g) was placed on a silica column and eluted with Et_2O/light petroleum 8:2. This gave starting material (0.043 g, 7%) and then product **20** as a white solid; yield: 0.154 g (61%); mp 78 °C.

UV: λ_{max} (log ε) = 211 (4.689), 265 nm (4.652).
IR: ν_{max} = 30239 (C–H), 1733 (C=O ester), 1626 cm^{-1} (C=O ring).
^{1}H NMR: δ = 1.62 (m, 2H, H-3″), 1.68 (m, 2H, H-2″), 2.24 (t, 2H, *J* = 5.7 Hz, H-4″), 2.52 (t, 2H, *J* = 6.14 Hz, H-1″), 3.62 (s, 3H, CO_2CH_3), 3.82 (s, 3H, $ArOCH_3$), 3.88 (s, 3H, $ArOCH_3$), 6.82 (d, 1H, *J* = 1.8 Hz, H-8), 6.89 (m, 3H, H-6, H-3′), 7.14 (d, 2H, *J* = 6.6 Hz, H-2′), 8.09 (d, 1H, *J* = 9.1 Hz, H-5).
MS (EI): *m/z* (%) = 396 (13), 323 (10), 310 (10), 309 (30), 295 (15).
HRMS: obsd 396.1573. Calcd for $C_{23}H_{24}O_6$, 396.15729.

*We thank the Welsh Office for financial support for this work, Signorina M Chiari Danti for the syntheses of **19** and **20**, and Mr S R Szadja for the preparation of **17b** and its conversion to **2a**.*

(1) Armstrong, B. E.; Doll, R. *Inst. J. Cancer* **1975**, *15*, 617.
(2) Watanabe, S. *Eur. J. Cancer* **1993**, *29A*, 2305.
(3) Kato, I.; Tominga, S.; Kuroishi, T. *Jpn. J. Cancer Res.* **1987**, *78*, 349.
(4) Adlercruetz, H. *Front. Gastrointest. Res.* **1988**, *14*, 165.
(5) Adlercruetz, H.; Musey, P. I.; Fotsis, T.; Bannwart, C.; Wahala, K.; Makela, T.; Brunow, G.; Hase,T. *Clin. Chem. Acta.* **1986**, *158*, 147.
(6) Baker, W.; Chadderton, J.; Harbourne, J. B.; Ollis, W. D. *J. Chem. Soc.* **1953**, 1852.
(7) Whalley, W. B. *J. Chem. Soc.* **1953**, 1059.
(8) Gakhodize, A. M. *J. Appl. Chem.* **1950**, *23*, 589.
(9) Spoerri, P. E.; DuBois, A. S. *Org. React.* ***1949***, *5*, 387.
(10) de Boer, T. J.; Backer, H. J. *Org. Synth. Coll. Vol. 4* **1963**, 250.
(11) Saitoh, M.; Fujisaki, S.; Ishii, Y.; Nishiguchi, T. *Tetrahedron Lett.* **1996**, *37*, 6733.
(12) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346.
(13) Stork, G.; Hudrlick, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462.
(14) House, H. O.; Czuba, L. J.; Gail, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(15) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.
(16) Moersch, G. W.; Morrow, D. F.; Neuklis, W. A. *J. Med. Chem.* **1967**, *10*, 154.
(17) Bokhan, S. A. N. N.; Whalley, W. B. *J. Chem. Soc.* **1963**, 5322.
(18) Freidlin, G. N.; Chukur, A. P.; Dzarokhova, L. J. *Zh. Org. Khim.* **1965**, *1*, 1367.
(19) Yoshida, M. *J. Agric. Chem. Soc. Jpn.* **1937**, *13*, 120.
(20) Noller, C. R.; Adams, R. *J. Am. Chem. Soc.* **1926**, *48*, 1074.
(21) Pennington, F. C.; Celmer, W. D.; McLarmore, W. M.; Bogert, V. V.; Solomons, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 109.
(22) Morgan, G. T.; Walton, E. *J. Chem. Soc.* **1936**, 902.
(23) Bishop, W. S. *Org. Synth.* ***1945***, *25*, 71.