Acid-catalysed Coupling Reactions and Conversions of Isoflavone Epoxides

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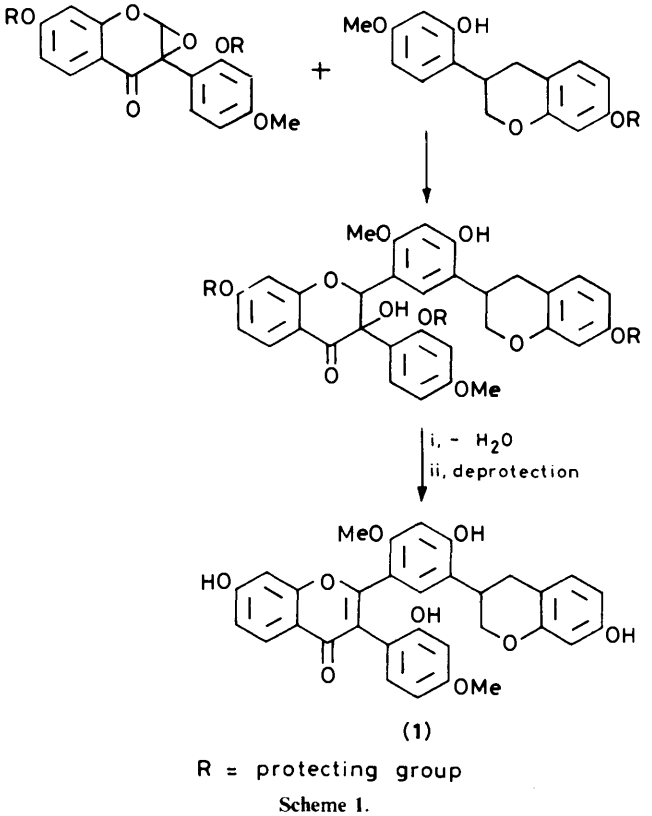
Whereas 4',7-dimethoxy- (**5**) and 4'-methoxy-2',7-ditosyloxy-isoflavone epoxides (**7**) are subject to regioselective acid-mediated methanolysis to yield 2-hydroxy-3-methoxy- and 3-hydroxy-2-methoxy-isoflavanones, the 2'7-dibenzyloxy-4'-methoxy analogue (**6**) is transformed regiospecifically into the 2-hydroxy-3-methoxyisoflavanone (**17**). The course of these coupling reactions is dependent on the B-ring oxygenation pattern.

Epoxide (**5**) reacts with *m*-methoxyphenol at ambient temperature to give a 3-aryl-2-hydroxyisoflavanone (**34**). At 0 °C the latter compound is accompanied by two regioisomeric O–C-coupled analogues (**38**) and (**40**). With phloroglucinol both epoxides (**5**) and (**7**) afford 2,3-diarylbenzofurans [(**27**) and (**29**) respectively] which presumably originate *via* acid-catalysed conversion of intermediate 3-aryl-2-hydroxyisoflavanones (**21**) and (**22**). Differences regarding regioselectivity between the respective nucleophiles (methanol *vs.* phenolic units), and between the phenolic moieties mutually, are rationalised in terms of the effect of nucleophilicity and of steric constraints imposed on the transition states leading to the respective regioisomers.

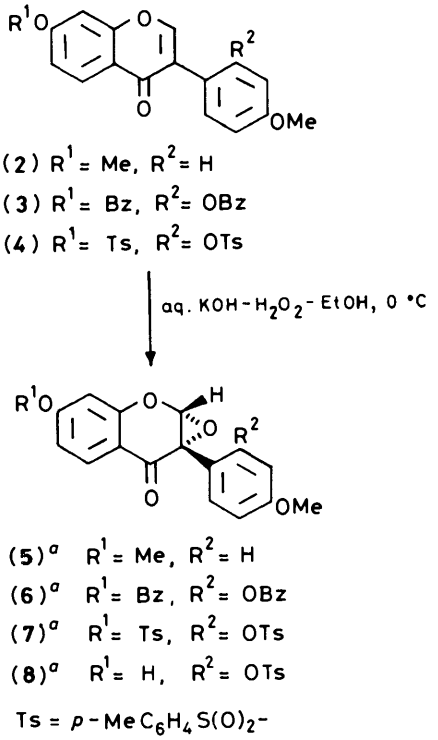
We have recently reported the structural elucidation and synthesis of the first natural bi-isoflavonoid[1,2] from the heartwood of *Dalbergia nitidula* Welw. *ex.* Bak. This compound is accompanied by an analogue with one fully oxidised heterocyclic ring which has been assigned the tentative structure (1) by means of spectroscopic methods.[3] Since this novel metabolite presumably consists of an isoflavan unit linked *via* its B-ring to the 2-vinylic carbon of an isoflavone, the versatile chemistry of α,β-epoxy ketones[4] could, in principle, be utilised in a synthetic sequence to this new class of natural product. (Scheme 1). Such an approach is substantiated by the regiospecific acid-catalysed ethoxylation of the epoxide of 7-methoxyisoflavone[5] at C-2 and the general preference for fragmentation involving cleavage of the C_β–O bond in a variety of flavonoid α,β-epoxy ketones under both acidic and alkaline conditions.[6–14] We now record our detailed results of relevance to the acid-mediated coupling of nucleophilic units to aromatic oxygenated isoflavone 2,3-epoxides.



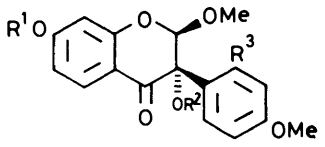
Scheme 1.

Results and Discussion

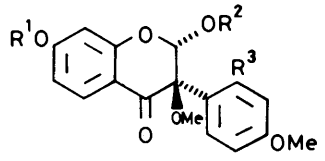
Isoflavones (**2**)—(**4**) reacted with alkaline hydrogen peroxide[15] to give the respective epoxides (**5**)—(**7**) which were sufficiently stable to be purified on silica gel. The basic reaction conditions,



[a] Single enantiomer for each racemate indicated.



(9)[a] R^1 = Me, R^2 = R^3 = H
(10)[a] R^1 = Me, R^2 = Ac, R^3 = H
(11)[a] R^1 = Ts, R^2 = H, R^3 = OTs
(12)[a] R^1 = Ts, R^2 = Ac, R^3 = OTs

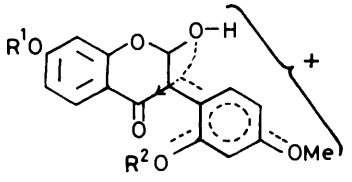


(13)[a] R^1 = Me, R^2 = R^3 = H
(14)[a] R^1 = Me, R^2 = Ac, R^3 = H
(15)[a] R^1 = Ts, R^2 = H, R^3 = OTs
(16)[a] R^1 = Ts, R^2 = Ac, R^3 = OTs
(17)[a] R^1 = Bz, R^2 = H, R^3 = OBz
(18)[a] R^1 = Bz, R^2 = Ac, R^3 = OBz

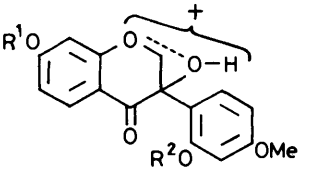
[a] Single enantiomer for each racemate indicated.

however, led to hydrolysis of the 7-tosyloxy function and thus to substantial formation of epoxide (**8**) [(**7**):(**8**) = 1:1]. When treated with methanol and toluene-*p*-sulphonic acid (PTSA) in 2,2,2-trifluoroethanol (TFE) at temperatures ranging from −10 to 25 °C, epoxide (**5**) yielded a 1:1 mixture of single racemates for each of the regioisomeric 3-hydroxy-2-methoxy- (**9**) and 2-hydroxy-3-methoxy-isoflavanone (**13**). Whereas the 2′,7-di-*O*-tosyl epoxide (**7**) under similar conditions also afforded two regioisomers (**11**) and (**15**) (1:3), the 2′-7-di-*O*-benzyl analogue (**6**) reacted in a regiospecific manner to give only the 2-hydroxy-3-methoxyisoflavanone (**17**).

Differentiation between these isomeric pairs, *e.g.* (**9**) and (**13**), followed from comparison of ^{1}H n.m.r. chemical-shift values of the 2-H singlet displayed by the respective monoacetates [(**14**), δ 7.03; (**10**), δ 6.42; (**16**), δ 6.72; (**12**), δ 6.50]. Close agreement of the chemical shift of 2-H (δ 6.94) in monoacetate (**18**), in comparison with that of (**14**), thus defined the former as the 2-acetoxy-3-methoxy analogue. The results from the acid-mediated methoxylations of epoxides (**5**)—(**7**) are in direct contrast with the regiospecific C-2-ethoxylation of the 2,3-epoxide of 7-methoxyisoflavone by Donnelly *et al.*[5] These differences are, however, explicable in terms of the transition states (**19**) and (**20**) leading to the respective regioisomers. Acid-catalysed cleavage of oxiranes proceeds *via* a borderline



(**19**)



(**20**)

S_N2 mechanism* with the nucleophilic attack occurring preferentially at the carbon best suited to accommodate the developing positive charge.[4] Factors governing stability of an incipient C-3-carbenium ion (**19**) include deactivation by the C-4 carbonyl and activation *via* the 4′- or 2′,4′-oxygenated B-ring, while effects at C-2 in (**20**) are restricted to the resonance contribution by the non-bonding electrons of the heterocyclic oxygen. Isoflavonoid 2,3-epoxides lacking B-ring (4′- or 2′,4′-) oxygenation should, therefore, preferentially react *via* transition state (**20**) to give regiospecific coupling at C-2 (*cf.* the results of Donnelly[5]) while those with 2,4-dioxygenated B-rings [*e.g.* (**6**)] should lead to regiospecific C-3 substitution [transition state (**19**)]. Epoxides (**5**) and (**7**), the transition state [type (**19**)] of the latter relatively destabilised by 2′-*O*-tosylation, clearly represent borderline cases, thus functioning as ambident electrophiles to yield products of regioselective coupling.

The aforementioned criteria for acid-catalysed solvolysis of isoflavone epoxides having been established, the influence of nucleophilic phenolic units on the course of coupling was next examined. Thus, phloroglucinol reacted with epoxides (**5**) and (**7**) in TFE containing PTSA, respectively at 25 and 45 °C, to give the 2,3-diarylbenzofurans (**27**) and (**29**) which were characterised as full methyl ethers (**28**) and (**30**).

Formation of the 2,3-diarylbenzofurans (**27**) and (**29**) may be rationalised according to the sequence depicted in Scheme 2. Initial attack of phloroglucinol presumably leads to the 2-hydroxy-3-arylisoflavanones (**21**) and (**22**). Under acidic conditions compounds (**21**) and (**22**) are in equilibrium with aldehyde (**23**) which may be decarbonylated *via* the geminal diol (**24**) to give enol (**25**). The keto tautomer (**26**) of the latter is then transformed to the benzofurans (**27**) and (**29**) following acid-mediated cyclisation and dehydration.

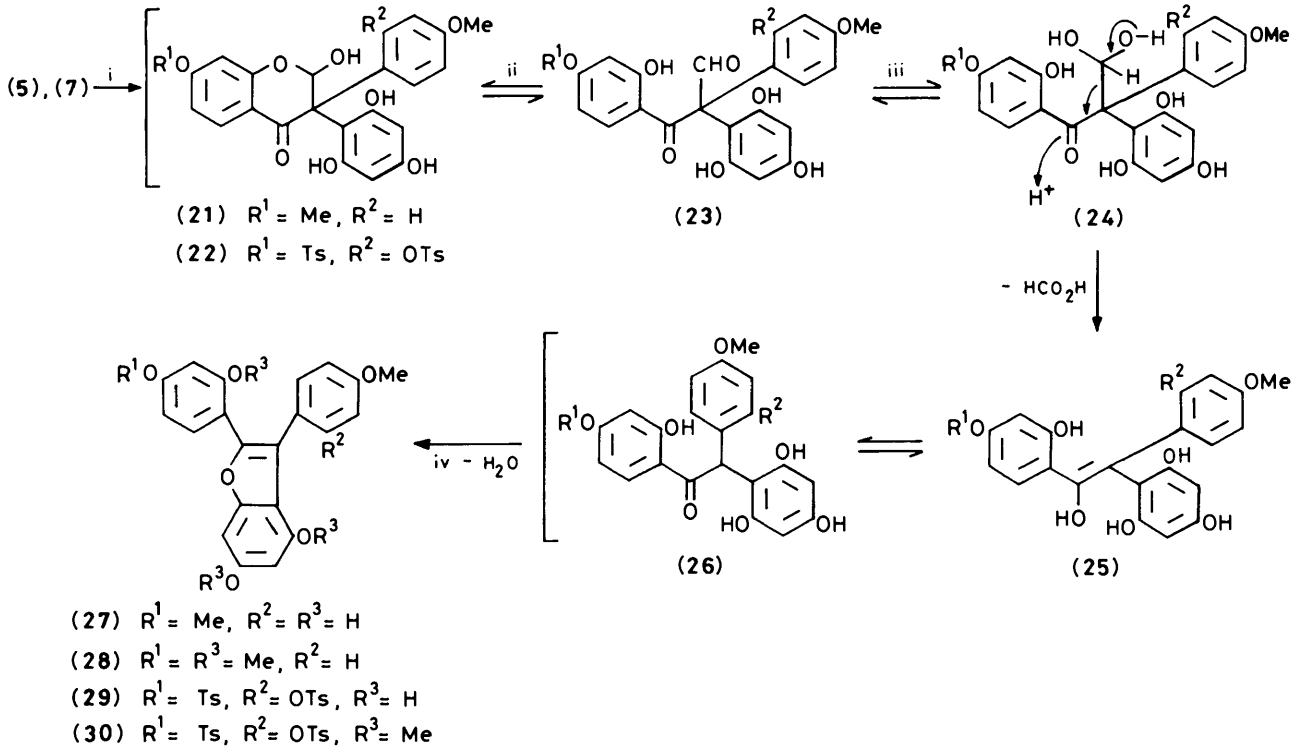
Differentiation between the *O*-methylated benzofurans [(**28**) and (**30**)] and alternative structures of types (**31**), (**32**), and (**33**) followed amongst others from the ^{13}C n.m.r. spectrum of compound (**28**) which indicated the presence of only twenty skeletal carbon atoms.

Under conditions similar to those employed for the phloroglucinol coupling, reaction of 4′,7-dimethoxyisoflavone epoxide (**5**) with the less nucleophilic *m*-methoxyphenol also yielded a 3-aryl-2-hydroxyisoflavanone, (**34**). Methylation [CH_3I–K_2CO_3–$(CH_3)_2CO$] of adduct (**34**) gave, in addition to the di-*O*-methyl ether (**35**), the deoxybenzoin (**37**) presumably through base-catalysed decarbonylation of the parent compound (**34**).

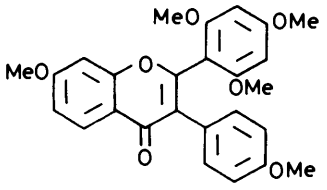
When the coupling reaction was repeated at 0 °C, the C–C-coupled 3-arylflavanone (**34**) was accompanied by two regioisomeric O–C-coupled analogues (**38**) and (**40**) (4:1:1). These were characterised as monoacetates (**39**) and (**41**) which were distinguished by means of ^{1}H n.m.r. chemical-shift differences of the respective C-2 protons [δ 7.28, 7.11, and 6.56 for (**36**), (**39**), and (**41**) respectively].

Results obtained from the coupling of phenolic units to 4′,7-dimethoxyisoflavone epoxide (**5**), *i.e.* preferential formation of C-3-linked products, are at variance with the regioselective acid-catalysed methanolysis of the same substrate. These differences presumably reflect enhanced S_N1 character of the

* Although cleavage of epoxides (**5**)—(**7**) is depicted as a S_N2 process, recent evidence (C. Battistini, P. Crotti, D. Damiani, and F. Macchia, *J. Org. Chem.*, 1979, **44**, 1643; C. Battistini, P. Crotti, and F. Macchia, *ibid.*, 1981, **46**, 434; C. Battistini, P. Crotti, M. Ferretti, and F. Macchia, *ibid.*, 1977, **42**, 4067; C. Battistini, A. Balsamo, G. Berti, P. Crotti, B. Macchia, and F. Macchia, *J. Chem. Soc., Chem. Commun.*, 1974, 712; A. Balsamo, P. Crotti, B. Macchia, and F. Macchia, *Tetrahedron*, 1973, **29**, 199) has shown that aryl groups linked directly to the oxirane ring may alter the steric course of 1,2-adduct formation from almost complete *anti* ring opening to nearly complete *syn* stereoselectivity.



Scheme 2. *Reagents and conditions:* i, phoroglucinol, TFE, PTSA; ii, H^+; iii, H_3O^+; iv, H^+, cyclisation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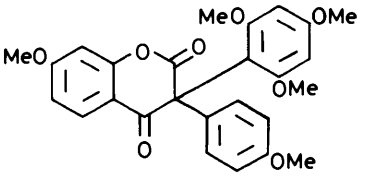
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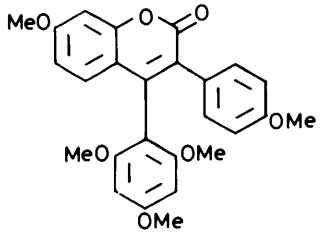
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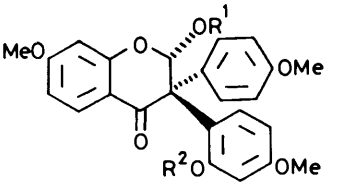
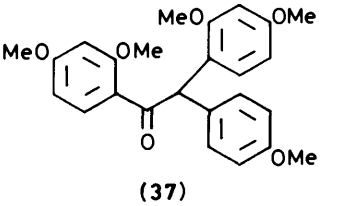
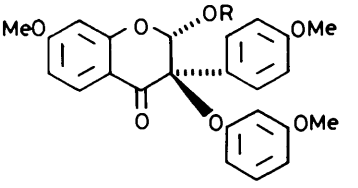
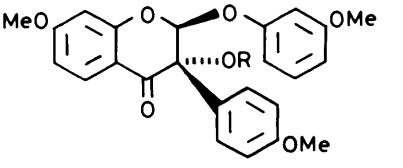

(34)[a] R^1 = R^2 = H
(35)[a] R^1 = R^2 = Me
(36)[a] R^1 = R^2 = Ac


(37)


(38)[a] R = H
(39)[a] R = Ac

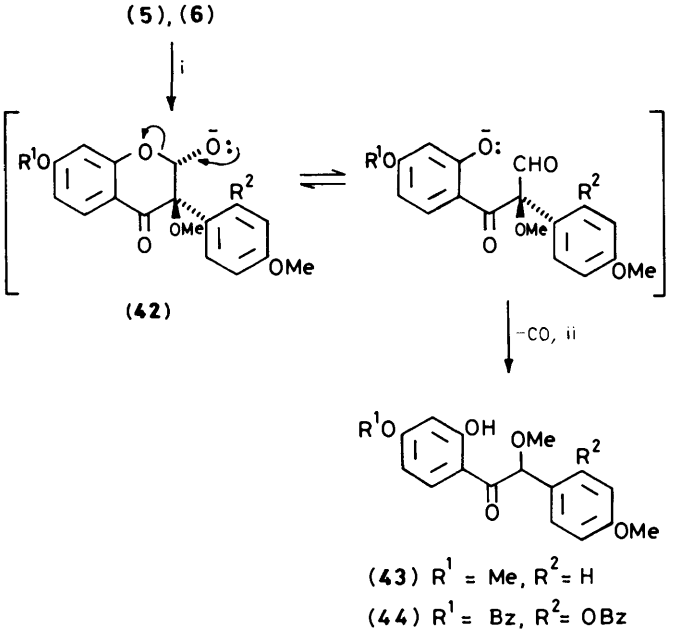

(40)[a] R = H
(41)[a] R = Ac

phenolic coupling in comparison with that of methanol, due to reduced nucleophilicity and increased steric interaction in the former case. Subtle differences in stability of transition states (**19**) and (**20**) in conjunction with steric factors probably favour attack of the phenolic units at C-3 of the oxirane (**5**). The effect of steric interaction on the course of coupling is demonstrated by the results obtained from reaction of *m*-methoxyphenol as nucleophile at 0 °C where products of regioselective *O*-alkylation (**38**) and (**40**) were also obtained. The transition states

[a] Single enantiomer for each racemate indicated.

leading to the latter products clearly exhibit a lower degree of steric strain than those for C–C coupling. Enhanced steric compression in the phloroglucinol adduct (**21**) in comparison with that of the resorcinol analogue (**34**) presumably also facilitates transformation of the former to the 2,3-diarylbenzofuran (**27**).

The direction of oxirane cleavage may often be altered by a change to alkaline reaction conditions. This, taken in conjunction with the observed preferential attack of a hard nucleophile at the less hindered centre,[4] led to extension to base-mediated couplings. However, when the epoxides (**5**) and (**6**) were treated with sodium methoxide in acetonitrile both at −5 and at +25 °C, only the α-methoxydeoxybenzoins (**43**) and (**44**) were obtained (Scheme 3). These products probably arise *via* base-catalysed ring opening of an intermediate C-3 adduct of type (**42**).



Scheme 3. *Reagents and conditions:* i, $^-$OMe; ii, H_3O^+

Experimental

T.l.c. was performed on DC-Plastikfolin Kieselgel 60 PF_{254} (0.25 mm) and the plates were sprayed with H_2SO_4–HCHO (40:1 v/v) after development. Preparative plates (p.l.c.) [Kieselgel PF_{254} (1.0 mm)] were air-dried and used without prior activation. Methylations were performed with methyl iodide and anhydrous K_2CO_3 in dry acetone at 60 °C, whilst acetylations were carried out with acetic anhydride–anhydrous pyridine. ^1H And ^{13}C n.m.r. spectra were recorded, unless specified to the contrary, on a Bruker WP-80 spectrometer for solutions in $CDCl_3$ at 30 °C with $SiMe_4$ as internal standard. Mass spectral data were recorded on a Varian CH-5 instrument, and i.r. spectra for solutions in chloroform. M.p.s were determined with a Reichert hot-stage apparatus and are uncorrected. Analyses (C & H) were performed by Analytische Laboratorien, Fritz-Pregl-Strasse 24, 5270 Gummersbach 1 Elbach, W. Germany.

Synthesis of Isoflavonoids.—*4′,7-Dimethoxyisoflavone* (**2**). 2-Hydroxy-4-methoxyacetophenone (3.0 g) was dissolved in a mixture of ethanol (50 ml) and 60% KOH (75 ml) and the mixture was stirred at room temperature for 30 min. 4-Methoxybenzaldehyde (3.5 g) was added and the mixture was stirred overnight, then acidified (3M-HCl), and extracted with ethyl acetate (3 × 100 ml). Evaporation of the solvent, followed by crystallisation from ethanol, gave 2′-hydroxy-4,4′-dimethoxychalcone (3.0 g) as yellow needles, m.p. 116 °C (lit.,[16] 114 °C).

The chalcone (2.5 g) was dissolved in absolute methanol–dry dioxane (200 ml; 1:1 v/v), thallium(III) nitrate (3 g) was added, and the mixture was stirred at room temperature for 4 days. After addition of 3M-HCl (80 ml) the mixture was refluxed for 5 h and cooled to room temperature. The isoflavone (**2**) (2.3 g) crystallised from the reaction mixture as cream coloured needles, m.p. 164 °C (lit.,[17] 160 °C).

2′,7-Dibenzyloxy-4′-methoxyisoflavone (**3**). Under conditions similar to those described above, base-catalysed condensation of 4-benzyloxy-2-hydroxyacetophenone (3.0 g) and 2-benzyloxy-4-methoxybenzaldehyde (4.0 g) yielded 2,4′-dibenzyloxy-2′-hydroxy-4-methoxychalcone (3.0 g) as yellow needles, m.p. 154 °C (from EtOH).

The chalcone (3.0 g) was then transformed by means of the $Tl(NO_3)_3$–HCl method[18,19] to the isoflavone (**3**) (2.1 g) which crystallised from the reaction mixture as needles, m.p. 133 °C; δ_H 8.19 (d, *J* 8.8 Hz, 5-H), 7.84 (s, 2-H), 7.50—7.20 (m, 2 × OCH_2Ph), 7.25 (d, *J* 9.0 Hz, 6′-H), 7.00 (dd, *J* 2.5 and 8.8 Hz, 6-H), 6.86 (d, *J* 2.5 Hz, 8-H), 6.56 (d, *J* 2.5 Hz, 3′-H), 6.52 (dd, *J* 2.5 and 9.0 Hz, 5′-H), 5.08 and 5.00 (each s, 2 × OCH_2Ph), and 3.73 (s, 4′-OMe); *m/z* 464 (M^+, 12%), 373 (23.0), 282 (4.0), 238 (3.5), 227 (3.6), 119 (6.5), and 91 (100).

4′-Methoxy-2′,7-ditosyloxyisoflavone (**4**). Catalytic debenzylation [H_2, 10% Pd–C (300 mg); 2 h] of the dibenzyloxyisoflavone (**3**) (1.5 g), followed by p.l.c. in hexane–benzene–acetone (4:4:1 v/v), afforded the dihydroxy analogue[20] (R_F 0.32) (350 mg) as light-brown needles, m.p. 191—195 °C (from MeOH); δ_H([$^2H_6$]acetone) 8.28 (s, 2-H), 8.13 (d, *J* 8.5 Hz, 5-H), 7.22 (d, *J* 9.0 Hz, 6′-H), 7.05 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.98 (d, *J* 2.5 Hz, 8-H), 6.50 (dd, *J* 2.5 and 9.0 Hz, 5′-H), 6.50 (d, *J* 2.5 Hz, 3′-H), and 3.78 (s, 4′-OMe); *m/z* 284 (M^+, 100%), 267 (34), 148 (60), and 137 (24).

Treatment of the 2′,7-dihydroxyisoflavone (300 mg) with toluene-*p*-sulphonyl chloride (500 mg) in dry pyridine (5 ml) for 8 h at room temperature, followed by p.l.c. in hexane–benzene–acetone (4:4:2 v/v), gave the ditosyl derivative (**4**) (R_F 0.49) (420 mg) as *needles*, m.p. 161 °C [from EtOH–C_6H_6 (19:1 v/v)] (Found: C, 61.0; H, 4.3. $C_{30}H_{24}O_9S_2$ requires C, 60.8; H, 4.1%); δ_H (300 MHz; $CDCl_3$) 8.04 (d, *J* 9.0 Hz, 5-H), 7.80 [d, *J* 8.5 Hz, 2-,6-H (Ts)], 7.74 (s, 2-H), 7.42 [d, *J* 8.5 Hz, 2-,6-H (Ts)], 7.39 [d, *J* 8.5 Hz, 3-,5-H (Ts)], 7.29 (d, *J* 8.3 Hz, 6′-H), 7.23 (d, *J* 2.3 Hz, 8-H), 6.99 (dd, *J* 2.3 and 8.5 Hz, 6-H), 6.93—6.86 [m, 3′-,5′-H and 3-,5-H (Ts)], 3.84 (s, 4′-OMe), and 2.48 and 2.14 (each s, 2 × Me); *m/z* 592 (M^+, 11%), 438 (17), 437 (16), 422 (26), 421 (100), 282 (20, 267 (12), 155 (12), 151 (9), 119 (30), and 91 (80).

Synthesis of Isoflavone Epoxides.—*4′,7-Dimethoxyisoflavone epoxide* (**5**). A solution of the isoflavone (**2**) (1.5 g) in a mixture of 80% (aq.) EtOH (75 ml) and dioxane (45 ml) was treated with a mixture of 30% H_2O_2 (15 ml) and 15% (aq.) KOH (30 ml) for 45 min at 0 °C. The mixture was acidified with ice-cold M-HCl, carefully neutralised ($NaHCO_3$), and extracted with ethyl acetate (3 × 50 ml). Evaporation of the dried (Na_2SO_4) solution, followed by p.l.c. in hexane–benzene–acetone (5:4:1 v/v), afforded the epoxide (**5**) (R_F 0.46) (980 mg) as *needles*, m.p. 164 °C [from EtOH–acetone (19:1 v/v)] (Found: C, 68.5; H, 4.7. $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7%); δ_H 7.94 (d, *J* 8.5 Hz, 5-H), 7.38 (d, *J* 8.8 Hz, 2′-,6′-H), 6.91 (d, *J* 8.8 Hz, 3′-,5′-H), 6.72 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.50 (d, *J* 2.5 Hz, 8-H), 5.47 (s, 2-H), and 3.84 and 3.78 (each s, 2 × OMe); *m/z* 298 (M^+, 5.8%), 282 (7.2), 270 (39.0), 269 (100), 255 (7.6), 241 (5.4), 211 (5.7), 151 (16), 148 (5.5), 135 (47.0), 132 (5.8), 128 (10.0), and 107 (5.3).

2′,7-Dibenzyloxy-4′-methoxyisoflavone epoxide (**6**). Similar treatment of the isoflavone (**3**) (550 mg) with alkaline hydrogen peroxide, followed by identical work-up and purification

procedures as the above, yielded epoxide (**6**) (R_F 0.46) (400 mg) as *needles*, m.p. 126 °C (from EtOH–acetone) (Found: C, 74.9; H, 4.9. $C_{30}H_{24}O_6$ requires C, 74.5; H, 5.0%); δ_H 7.94 (d, *J* 8.5 Hz, 5-H), 7.40—7.15 (m, 2 × OCH_2Ph), 7.28 (d, *J* 8.8 Hz, 6′-H), 6.78 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.63—6.47 (m, 3′-,5′- and 8-H), 5.44 (s, 2-H), 5.09 and 5.00 (each s, 2 × OCH_2Ph), and 3.77 (s, 4′-OMe); *m/z* 480 (M^+, 13%), 452 (39), 451 (100), 362 (14), 361 (38), 345 (10), 151 (3), and 91 (20).

4′-*Methoxy*-2′,7-*ditosyloxyisoflavone epoxide* (**7**). Under conditions similar to the above, the ditosyloxyisoflavone (**4**) (360 mg) afforded two fractions, R_F 0.57 and 0.33, after p.l.c. separation in hexane–benzene–acetone (4:4:2 v/v). The R_F 0.57 fraction gave the *ditosyloxyisoflavone epoxide* (**7**) (100 mg) as an amorphous solid (Found: C, 58.9; H, 4.2. $C_{30}H_{24}O_{10}S_2$ requires C, 59.2; H, 4.0%); δ_H 7.81 (d, *J* 8.5 Hz, 5-H), 7.77 [d, *J* 8.5 Hz, 2,-6-H (Ts)], 7.59 [d, *J* 8.5 Hz, 2-,6-H (Ts)], 7.34 [d, *J* 8.5 Hz, 3-,5-H (Ts)], 7.34 (d, *J* 8.5 Hz, 6′-H), 7.09 [d, *J* 8.5 Hz, 3-,5-H) (Ts)], 6.86 (dd, *J* 2.5 and 8.5 Hz, 5′-H), 6.86 (d, *J* 2.5 Hz, 3′- or 8-H), 6.75 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.67 (d, *J* 2.5 Hz, 8- or 3′-H), 5.56 (s, 2-H), 3.75 (s, 4′-OMe), and 2.47 and 2.31 [each s, 2 × Me (Ts)]; *m/z* 608 (M^+, 1.5%), 579 (11), 426 (12), 425 (44), 421 (11), 305 (13), 289 (10), 271 (11), 270 (18), 155 (19), 151 (15), 139 (24), 119 (6), and 91 (100).

The R_F 0.33 fraction afforded 7-hydroxy-4′-methoxy-2′-tosyloxyisoflavone epoxide (**8**) (130 mg) as an amorphous solid, δ_H([$^2H_6$]acetone) 7.70 (d, *J* 8.5 Hz, 5-H), 7.61 [d, *J* 8.5 Hz, 2-,6-H (Ts)], 7.34 (d, *J* 8.5 Hz, 6′-H), 7.27 [d, *J* 8.5 Hz, 3-,5-H (Ts)], 6.94 (dd, *J* 2.5 and 8.5 Hz, 5′-H), 6.70 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.66 (d, *J* 2.5 Hz, 3′-H), 6.52 (d, *J* 2.5 Hz, 8-H), 5.56 (s, 2-H), 3.75 (s, 4′-OMe), and 2.38 [s, Me (Ts)]; *m/z* 454 (M^+, 4.9%), 425 (8.1), 305 (13), 299 (10), 289 (15), 272 (23), 271 (100), 267 (6.4), 243 (7.3), 227 (7.0), 200 (7.8), 155 (11), 151 (16), 139 (24), 137 (14), 92 (14), and 91 (55).

Acid-catalysed Methanolysis of Epoxides (**5**)—(**7**).—4′,7-Dimethoxyisoflavone epoxide (**5**) (50 mg) was dissolved in TFE–methanol (10:1 v/v; 5 ml) containing PTSA (5 mg), and the mixture was stirred at room temperature for 1 h. Following neutralisation ($NaHCO_3$) and extraction with ethyl acetate (3 × 30 ml), p.l.c. in hexane–benzene–acetone (5:4:1 v/v; × 2) gave a fraction (40 mg) at R_F 0.13 which consisted of the 3-hydroxy-2,4′,7-trimethoxy- and 2-hydroxy-3,4′,7-trimethoxyisoflavanone (**9**) and (**13**) respectively. Acetylation of this mixture and subsequent p.l.c. separation in hexane–benzene–acetone (5:4:1 v/v) gave two bands, at R_F 0.48 and 0.35.

The R_F 0.48 fraction afforded 3-*acetoxy*-2,4′,7-*trimethoxyisoflavanone* (**10**) (17 mg) as an amorphous solid (Found: C, 64.4; H, 5.3. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%); δ_H 8.00 (d, *J* 8.5 Hz, 5-H), 7.44 (d, *J* 8.8 Hz, 2′-,6′-H), 6.94 (d, *J* 8.8 Hz, 3′-,5′-H), 6.72 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.51 (d, *J* 2.5 Hz, 8-H), 6.42 (s, 2-H), 3.87, 3.83, and 3.16 (each s, 3 × OMe), and 1.83 (s, 3-OAc); *m/z* 372 (M^+, 4.2%), 330 (7.3), 313 (1.7), 222 (72), 181 (13), 180 (100), 151 (39), and 135 (22).

The R_F 0.35 band gave 2-*acetoxy*-3,4′,7-*trimethoxyisoflavanone* (**14**) (13 mg) as an amorphous solid (Found: C, 64.2; H, 5.4%); δ_H 7.91 (d, *J* 8.5 Hz, 5-H), 7.47 (d, *J* 8.8 Hz, 2′-,6′-H), 7.03 (s, 2-H), 6.91 (d, *J* 8.8 Hz, 3′-,5′-H), 6.66 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.38 (d, *J* 2.5 Hz, 8-H), 3.81, 3.80, and 3.20 (each s, 3 × OMe), and 2.11 (s, 2-OAc); *m/z* 372 (M^+, 3.3%), 330 (6.0), 313 (4.1), 223 (11), 222 (80), 181 (14), 180 (100), 151 (37), and 135 (20).

2′,7-Dibenzyloxy-4′-methoxyisoflavone epoxide (**6**) (50 mg) was treated as above with PTSA (10 mg) in TFE–methanol for 1.5 h. Identical work-up and purification procedures afforded 2′,7-*dibenzyloxy*-2-*hydroxy*-3,4′-*dimethoxyisoflavanone* (**17**) (R_F 0.22) (43 mg) as an amorphous solid (Found: C, 72.5; H, 5.6. $C_{31}H_{28}O_7$ requires C, 72.6; H, 5.5%); δ_H 7.72 (d, *J* 8.5 Hz, 5-H), 7.50—7.02 (m, 2 × OCH_2Ph), 7.28 (d, *J* 8.8 Hz, 6′-H), 6.72—6.44 (m, 3′-,5′- and 6-,8-H), 5.69 (d, *J* 12.3 Hz, 2-H), 5.06 and 4.88 (each s, 2 × OCH_2Ph), 4.25 (d, *J* 12.3 Hz, 2-OH), and 3.78 and 3.38 (each s, 2 × OMe); *m/z* 512 (M^+, 14%), 483 (3.7), 466 (5.6), 452 (5.8), 421 (19), 361 (11), 314 (13), 285 (8.6), 258 (17), 257 (100), 228 (11), 227 (44), 195 (23), 121 (14), and 91 (15).

Acetylation of the 2-hydroxyisoflavanone (**17**) (43 mg) yielded 2-acetoxy-2′,7-dibenzyloxy-3,4′-dimethoxyisoflavanone (**18**) (40 mg) as an amorphous solid, δ_H 7.75 (d, *J* 8.5 Hz, 5-H), 7.45—7.15 (m, 2 × OCH_2Ph), 7.25 (d, *J* 8.8 Hz, 6′-H), 6.94 (s, 2-H), 6.72—6.38 (m, 3′-,5′- and 6-,8-H), 5.03 and 4.97 (each s, 2 × OCH_2Ph), 3.75 and 3.31 (each s, 2 × OMe), and 1.98 (s, 2-OAc); *m/z* 554 (M^+, 2.8%), 328 (47), 255 (7.6), 237 (5.4), 195 (69), 178 (7.0), 163 (11), 151 (5.1), and 91 (100).

4′-Methoxy-2′,7-ditosyloxyisoflavone epoxide (**7**) (40 mg) in TFE–methanol containing PTSA (10 mg) was stirred at 35 °C for 3 h. Work-up as above, followed by p.l.c. separation in hexane–benzene–acetone (4:4:2 v/v), gave a mixture of the 3-hydroxy-2,4′-dimethoxy- and 2-hydroxy-3,4′-dimethoxy-2′,7-ditosyloxyisoflavanone (**11**) and (**15**) respectively at R_F 0.35 (31 mg). Acetylation of this mixture and subsequent p.l.c. separation in hexane–benzene–acetone (5:4:1 v/v) afforded two bands, at R_F 0.51 and 0.42.

The R_F 0.51 fraction yielded 3-*acetoxy*-2,4′-*dimethoxy*-2′,7-*ditosyloxyisoflavanone* (**12**) (7 mg) as an amorphous solid (Found: C, 58.4; H, 4.7. $C_{33}H_{30}O_{12}S_2$ requires C, 58.1; H, 4.5%); δ_H 7.89 [d, *J* 8.3 Hz, 2-,6-H (Ts)], 7.80 [d, *J* 8.5 Hz, 2-,6-H (Ts)], 7.70 (d, *J* 9.0 Hz, 5-H), 7.44 (d, *J* 9.0 Hz, 6′-H), 7.36 [d, *J* 8.5 Hz, 3-,5-H (Ts)], 7.31 [d, *J* 8.3 Hz, 3-,5-H (Ts)], 7.06 (d, *J* 2.5 Hz, 3′-H), 6.80 (dd, *J* 2.5 and 9.0 Hz, 5′-H), 6.78 (dd, *J* 2.5 and 9.0 Hz, 6-H), 6.64 (d, *J* 2.5 Hz, 8-H), 6.50 (s, 2 H), 3.78 and 3.09 (each s, 2 × OMe), and 2.48 [s, 2 × Me (Ts)] and 1.92 (s, 3-OAc); *m/z* 682 (M^+, 2.3%), 640 (8.3), 485 (11), 425 (16), 421 (8.3), 392 (38), 351 (12), 350 (55), 291 (13), 270 (9.0), 196 (13), 195 (96), 193 (10), 178 (8.4), 167 (7.8), 163 (30), 155 (29), 151 (22), 135 (10), and 91 (100).

The R_F 0.42 band gave 2-*acetoxy*-3,4′-*dimethoxy*-2′,7-*ditosyloxyisoflavanone* (**16**) (22 mg) as an amorphous solid (Found: C, 58.5; H, 4.5. $C_{33}H_{30}O_{12}S_2$ requires C, 58.1; H, 4.5%); δ_H 7.83 [d *J* 8.5 Hz, 2-,6-H (Ts)], 7.72 [d, *J* 8.0 Hz, 2-,6-H (Ts)], 7.61 (d, *J* 8.5 Hz, 5-H), 7.31 [d, *J* 8.5 Hz, 3-,5-H (Ts)], 7.27 [d, *J* 8.0 Hz, 3-,5-H (Ts)], 7.23 (d, *J* 8.8 Hz, 6′-H), 7.14 (d, *J* 2.5 Hz, 3′-H), 6.77 (dd, *J* 2.5 and 8.8 Hz, 5′-H), 6.73 (dd, *J* 2.5 and 8.5 Hz, 6-H), 6.72 (s, 2-H), 6.52 (d, *J* 2.5 Hz, 8-H), 3.81 and 3.20 (each s, 2 × OMe), 2.47 and 2.41 [each s, 2 × Me (Ts)], and 2.00 (s, 2-OAc); *m/z* 682 (M^+, 0%), 640 (10), 485 (12), 425 (15), 392 (43), 351 (20), 350 (81), 321 (9.4), 291 (18), 270 (12), 196 (19), 195 (100), 193 (11), 178 (23), 167 (10), 163 (38), 155 (32), 151 (31), 137 (11), 135 (10), and 91 (100).

Acid-mediated Coupling of Epoxides (**5**) *and* (**7**) *with Phenolic Nucleophiles*.—A solution of 4′,7-dimethoxyisoflavone epoxide (**5**) (50 mg) and phloroglucinol (50 mg) in TFE (5 ml) was treated with PTSA (5 mg) at room temperature for 30 min. The mixture was neutralised (aq. $NaHCO_3$) and extracted with ethyl acetate (3 × 5 ml). Evaporation of the extract, followed by p.l.c. of the residue in benzene–acetone (8:2 v/v), gave 4,6-dihydroxy-2-(2′-hydroxy-4′-methoxyphenyl)-3-(4″-methoxyphenyl)-benzofuran (**27**) (R_F 0.39) (34 mg) as an amorphous solid; δ_H 7.39 (d, *J* 8.8 Hz, 2″-,6″-H), 7.02 (d, *J* 8.8 Hz, 3″-,5″-H), 6.95 (d, *J* 8.8 Hz, 6′-H), 6.95—6.72 (br s, OH), 6.63 (d, *J* 2.1 Hz, 3′-H), 6.48 (d, *J* 2.5 Hz, 7-H), 6.31 (dd, *J* 2.1 and 8.8 Hz, 5′-H), 6.25 (d, *J* 2.5 Hz, 5-H), 5.31—5.00 (br s, OH), and 3.84 and 3.77 (each s, 2 × OMe).

Methylation (MeI) of the phenolic benzofuran (**27**) (34 mg) followed by p.l.c. in hexane–benzene–acetone (5:4:1 v/v) afforded the full *methyl ether* (**28**) (R_F 0.54) (21 mg) as an amorphous solid (Found: C, 71.4; H, 5.5. $C_{25}H_{24}O_6$ requires C, 71.4; H, 5.8%); δ_H (300 MHz; $CDCl_3$; 19 °C) 7.29 (d, *J* 9.0 Hz, 2″-,

6″-H), 7.24 (d, *J* 8.5 Hz, 6′-H), 6.81 (d, *J* 9.0 Hz, Hz, 3″-,5″-H), 6.70 (d, *J* 2.0 Hz, 7-H), 6.46 (dd, *J* 2.4 and 8.5 Hz, 5′-H), 6.41 (d, *J* 2.4 Hz, 3′-H), 6.32 (*J* 2.0 Hz, 5-H), and 3.87, 3.82 (×2), 3.74 and 3.49 (each s, 5 × OMe); δ_C 162.5 (s, C-4″), 159.7 (s, C-2′), 159.4 (s, C-4′), 159.1 (s, C-7a), 157.5 (s, C-6), 155.6 (s, C-4), 148.1 (s, C-2), 133.1 (d, C-6′), 131.3 (d, C-2″, -6″), 127.2 (s, C-1″), 118.8 (s, C-1′), 144.1 (s, C-3a), 113.1 (d, C-3″, -5″), 112.5 (s, C-3), 105.0 (d, C-5′), 99.4 (d, C-3′), 94.7 (d, C-7), 88.8 (d, C-5), and 55.9, 55.3, and 55.0 (each q, 5 × OMe); *m/z* 420 (M^+, 100%), 405 (23), 390 (1.4), 375 (2.4), 331 (2.4), 255 (0.9), 210 (14), 195 (2.3), 187 (2.6), 165 (5.4), 152 (1.4), 151 (2.4), 150 (1.5), 137 (1.5), 135 (2.1), 122 (1.8), and 121 (2.9).

A solution of 4′-methoxy-2′,7-ditosyloxyisoflavone epoxide (**7**) (50 mg) and phloroglucinol (100 mg) in TFE (5 ml) was stirred with PTSA (10 mg) at 45 °C for 3 h. Work-up as above and p.l.c. in hexane–chloroform–methanol (2:7:1 v/v) afforded a band at R_F 0.44, which was methylated (MeI) and the product purified by means of p.l.c. in hexane–benzene–acetone (5:4:1 v/v). *4,6-Dimethoxy-2-(2′-methoxy-4′-tosyloxyphenyl)-3-(4″-methoxy-2″-tosyloxyphenyl)benzofuran* (**30**) (R_F 0.22) (12 mg) was obtained as an amorphous solid (Found: C, 62.9; H, 4.8. $C_{38}H_{34}O_{11}S_2$ requires C, 62.5; H, 4.7%); δ_H (300 MHz; $CDCl_3$; 19 °C) 7.70 [d, *J* 8.5 Hz, 2-,6-H (Ts)], 7.36 [d, *J* 8.5 Hz, 3-,5-H (Ts)], 7.23 (d, *J* 8.5 Hz, 6′- or 6″-H), 7.21 [d, *J* 8.3 Hz, 2-,6-H (Ts)], 6.97 (d, *J* 8.5 Hz, 6″- or 6′-H), 6.87 (d, *J* 2.5 Hz, 3′- or 3″-H), 6.80 (dd, *J* 2.5 and 8.5 Hz, 5′- or 5″-H), 6.69 [d, *J* 8.3 Hz, 3-,5-H (Ts)], 6.58 (d, *J* 1.9 Hz, 7-H), 6.52 (d, *J* 2.3 Hz, 3″- or 3′-H), 6.45 (dd, *J* 2.3 and 8.5 Hz, 5″- or 5′-H), 6.11 (d, *J* 1.9 Hz, 5-H), 3.86 (×2), 3.59 and 3.49 (each s, 4 × OMe), and 2.45 and 2.18 [each s, 2 × Me (Ts)]; *m/z* 730 (M^+, 57%), 576 (43), 575 (47), 421 (22), 405 (47), 303 (13), 291 (11), 287 (40), 243 (13), 181 (11), 158 (11), 155 (35), 137 (17), and 91 (100).

Treatment of 4′,7-dimethoxyisoflavone epoxide (**5**) (75 mg) with *m*-methoxyphenol (150 mg) under conditions identical to those for the phloroglucinol coupling, followed by p.l.c. in benzene–acetone (95:5 v/v), gave a single fraction, at R_F 0.10 (27 mg). Methylation (MeI) of a portion of this band (13.5 mg) and subsequent p.l.c. separation in hexane–benzene–acetone (5:4:4 v/v) afforded two fractions, R_F 0.31 (3 mg) and 0.24 (9 mg).

The R_F 0.31 band gave *2,2′,4′,7-tetramethoxy-3-(4″-methoxyphenyl)isoflavanone* (**35**) (3 mg) as an amorphous solid (Found: C, 69.3; H, 5.6. $C_{26}H_{26}O_7$ requires C, 69.3; H, 5.8%); δ_H (80 MHz; $CDCl_3$; 80 °C) 7.89 (d, *J* 8.8 Hz, 5-H), 7.55 (d, *J* 9.0 Hz, 2″-,6″-H), 6.77 (d, *J* 9.0 Hz, 3″-,5″-H), 6.58 (d, *J* 8.5 Hz, 6′-H), 6.53 (dd, *J* 2.5 and 8.8 Hz, 6-H), 6.50—6.31 (m, 3′- and 8-H), 6.30 (dd, *J* 2.5 and 8.5 Hz, 5′-H), 6.03 (s, 2-H), and 3.78, 3.75 (×2), 3.66 and 3.50 (each s, 5 × OMe); *m/z* 450 (M^+, 99%), 390 (14), 375 (21), 314 (13), 301 (26), 300 (100), 285 (22), 257 (23), 181 (8.7), 165 (10), 151 (11), 135 (8.0), 122 (10), and 121 (63).

The R_F 0.24 band (9 mg) gave *2,2′,4,4′-tetramethoxy-α-(4″-methoxyphenyl)deoxybenzoin* (**37**) as an amorphous solid (Found: C, 70.9; H, 6.2. $C_{25}H_{26}O_6$ requires C, 71.1; H, 6.2%); δ_H (80 MHz; $CDCl_3$; 80 °C) 7.72 (d, *J* 8.5 Hz, 6-H), 7.14 (d, *J* 8.8 Hz, 2″-,6″H), 6.88 (d, *J* 9.0 Hz, 6′-H), 6.75 (d, *J* 8.8 Hz, 3″-,5″-H), 6.50—6.25 (m, 3-,3′-,5- and 5′-H), 6.20 (s, α-H), and 3.75, 3.72, 3.70 (×2), and 3.66 (each s, 5 × OMe); *m/z* 422 (M^+, 1.2%), 271 (9.5), 258 (18), 257 (99), 166 (20), 165 (100), 122 (12), and 121 (54).

Acetylation of the remaining portion (13.5 mg) of the R_F 0.10 fraction, afforded 2,2′-diacetoxy-4′,7-dimethoxy-3-(4″-methoxyphenyl)isoflavanone (**36**) as an amorphous solid (8 mg); δ_H 7.89 (d, *J* 8.8 Hz, 5-H), 7.59 (d, *J* 8.8 Hz, 2″-,6″-H), 7.28 (s, *2-H*), *6.80* (*d*, *J* 8.8 Hz, 3″-,5″-H), 6.69—6.34 (m, 3′-,5′-,6-,6′- and 8-H), 3.78, 3.76, and 3.70 (each s, 3 × OMe), and 2.25 and 1.97 (each s, 2 × OAc); *m/z* 506 (M^+, 2.1%), 464 (6.8), 447 (2.5), 370 (3.9), 356 (39), 328 (11), 315 (20), 314 (100), 272 (32), 243 (21), 151 (38), and 121 (29).

A solution of 4′,7-dimethoxyisoflavone epoxide (**5**) (500 mg), *m*-methoxyphenyl (800 mg), and PTSA (10 mg) in TFE (20 ml) was stirred at 0 °C for 45 min. The mixture was neutralised (aq. $NaHCO_3$) and extracted with ethyl acetate (3 × 10 ml). Evaporation of the dried (Na_2SO_4) solution, followed by p.l.c. in benzene–acetone (95:5 v/v), gave two fractions, at R_F 0.33 (130 mg) and 0.08 (230 mg). Acetylation of the R_F 0.08 band (230 mg) afforded the 2-acetoxy-3-arylisoflavanone (**36**) (140 mg), identical with that previously described. Acetylation of the R_F 0.33 fraction (60 mg) and subsequent p.l.c. separation in hexane–benzene–acetone (5:4:1 v/v) afforded two bands, at R_F 0.42 (18 mg) and 0.33 (18 mg).

The R_F 0.42 band gave *3-acetoxy-4′,7-dimethoxy-2-(3″-methoxyphenoxy)isoflavanone* (**41**) (18 mg) as an amorphous solid (Found: C, 67.0 H, 5.6. $C_{26}H_{24}O_8$ requires C, 67.2; H, 5.2%); δ_H 7.78 (d, *J* 8.5 Hz, 5-H), 7.48 (d, *J* 8.8 Hz, 2′-,6′-H), 6.86 (d, *J* 8.8 Hz, 3′-,5′-H), 6.56 (s, 2-H), 7.03—6.22 (m, 2″-,4″-,5″-,6-,6″- and 8-H), 3.86, 3.81, and 3.61 (each s, 3 × OMe), and 1.89 (s, 3-OAc); *m/z* 464 (M^+, 1.8%), 341 (32), 300 (15), 299 (75), 282 (20), 281 (14), 271 (9.2), 254 (5.3), 243 (6.4), 163 (29), 151 (12), 135 (100), 132 (19), and 124 (4.8).

The R_F 0.33 band afforded *2-acetoxy-4′,7-dimethoxy-3-(3″-methoxyphenoxy)isoflavanone* (**39**) (18 mg) as an amorphous solid (Found: C, 66.9; H, 5.4. $C_{26}H_{24}O_8$ requires C, 67.2; H, 5.2%); δ_H 7.91 (d, *J* 8.8 Hz, 5-H), 7.42 (d, *J* 8.8 Hz, 2′-,6′-H), 7.11 (s, 2-H), 6.80 (d, *J* 8.8 Hz, 3′-,5′-H), 6.61 (dd, *J* 2.5 and 8.8 Hz, 6-H), 7.06—6.22 (m, 2″-,4″-,5″-,6″- and 8-H), 3.81, 3.75, and 3.63 (each s, 3 × OMe), and 2.09 (s, 2-OAc); *m/z* 464 (M^+, 1.8%), 341 (34), 300 (17), 299 (71), 281 (12), 271 (7.9), 243 (6.3), 163 (26), 151 (18), 149 (7.7), 135 (100), 132 (9.8), and 124 (5.8).

Base-catalysed Conversions of Epoxides (**5**) *and* (**6**).—4′,7-Dimethoxyisoflavone epoxide (**5**) (50 mg), sodium methoxide (50 mg), and 18-crown-6 (5 mg) were dissolved in anhydrous acetonitrile (5 ml) and the mixture was stirred at room temperature for 2 h. Following addition of water (5 ml) and 3M-HCl (0.5 ml), the mixture was extracted with ethyl acetate (3 × 5 ml) and the extract was neutralised with aq. $NaHCO_3$. Evaporation of the solvent, and subsequent p.l.c. separation of the residue in hexane–benzene–acetone (5:4:1 v/v), afforded 2-hydroxy-α,4,4′-trimethoxydeoxybenzoin (**43**) (R_F 0.50) (23 mg) as an amorphous solid; δ_H 10.00 (s, 2-OH), 7.81 (d, *J* 9.5 Hz, 6-H), 7.38 (d, *J* 8.8 Hz, 2′-,6′-H), 6.88 (d, *J*, 8.8 Hz, 3′-,5′-H), 6.34 (d, *J* 2.0 Hz, 3-H), 6.33 (dd, *J* 2.0 and 9.5 Hz, 5-H), 5.41 (s, α-H), and 3.78, 3.77, and 3.41 (each s, 3 × OMe); *m/z* 302 (M^+, 2.1%), 153 (12), 152 (43), 151 (100), 136 (33), 135 (37), and 108 (24).

Similar treatment of 2′,7-dibenzyloxy-4′-methoxyisoflavone epoxide (**6**) (50 mg) at room temperature for 8 h, and p.l.c. separation of the product in hexane–benzene–acetone (5:4:1 v/v), gave a single band, at R_F 0.38. Further p.l.c. purification in ethylene dichloride afforded 2′,4-dibenzyloxy-2-hydroxy-α,4′-dimethoxydeoxybenzoin (**44**) (R_F 0.20) (10 mg) as an amorphous solid; δ_H 10.03 (s, 2-OH), 7.72 (d, *J* 9.0 Hz, 6-H), 7.60—7.25 (m, 2 × OCH_2Ph), 7.47—7.25 (d, *J* 8.0 Hz, 6′-H), 6.55 (d, *J* 2.3 Hz, 3′-H), 6.50 (dd, *J* 2.3 and 8.0 Hz, 5′-H), 6.45 (d, *J* 2.3 Hz, 3-H), 6.27 (dd, *J* 2.3 and 9.0 Hz, 5-H), 6.02 (s, α-H), 5.13 and 5.03 (each s, 2 × OCH_2Ph), and 3.75 and 3.38 (each s, 2 × OMe); *m/z* 484 (M^+, 0%), 361 (10), 257 (87), 227 (5.0), 151 (6.7), 147 (5.5), 137 (1.1), 124 (13), 121 (32), 108 (14), 103 (8.3), and 91 (100).

Synthesis of 4-Phenyl-7-methoxy-3-(4-methoxyphenyl)-coumarin.—A mixture of 2-hydroxy-4-methoxybenzophenone (800 mg) and *p*-methoxyphenylacetyl chloride (2.5 g) in dry acetone (75 ml) was stirred with anhydrous K_2CO_3 (10 g) at 60 °C for 5 h. After filtration and evaporation of the solvent, the residue was heated in 2% methanolic aq. NaOH (100 ml) for 15 min. The mixture was neutralised with M-HCl and extracted with ethyl acetate (3 × 50 ml). Evaporation of the solvent and crystallisation of the residue from methanol gave the coumarin

(300 mg) as needles, m.p. 209 °C; $\nu_{max.}(CHCl_3)$ 1 720 cm^{-1} (δ-lactone); δ_H 7.38—7.19 (m, Ph), 7.13 (d, *J* 8.8 Hz, 5-H), 7.03 (d, *J* 8.8 Hz, 2′-,6′-H), 6.91 (d, *J* 2.5 Hz, 8-H), 6.73 (dd, *J* 2.5 and 8.8 Hz, 6-H), 6.69 (d, *J* 8.8 Hz, 3′-,5′-H), and 3.86 and 3.72 (each s, 2 × OMe); *m/z* 358 (M^+, 100%), 357 (15), 330 (22), 316 (12), 315 (55), 271 (5.1), 215 (7.8), 179 (6.9), 165 (12), 135 (7.7), 113 (5.1), and 101 (5.6).

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