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Use of acyl substituents to favour 2,3-epoxidation of 5,7-dioxygenated flavones with dimethyldioxirane

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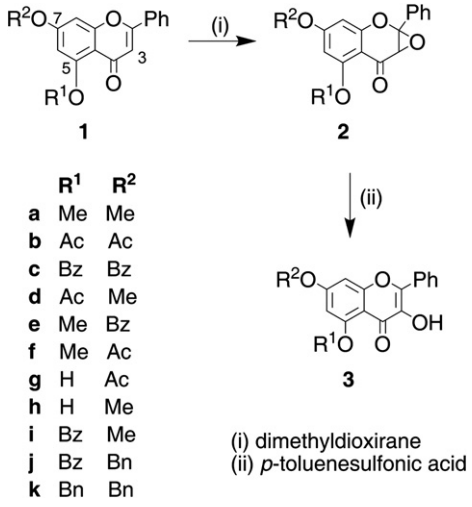
ABSTRACT

The reaction of 5,7-dimethoxyflavone with dimethyldioxirane (DMDO) gives the 2,3-epoxide rapidly at first. However, low levels of ring A hydroxylated by-products are also formed. With increasing proportions of DMDO, demethylation at C-5 becomes apparent and consumption of substrate is not matched by further significant build-up of the epoxide. Deactivation of ring A by the use of acyl groups removes this complication. 5,7-Diacylflavones give excellent yields of epoxides and monoacyl derivatives also react in good yield. Ionization potential maps derived from density functional theory calculations (B3LYP/6-31G*), provide good visual indicators of the relative reactivity of the key nucleophilic loci. The epoxides may be isolated as such, or transformed into flavonols by treatment with *p*-toluenesulfonic acid.

1. Introduction

In the course of work directed towards the synthesis of new isotopically labelled flavones and anthocyanins, we required a high yielding 3-hydroxylation of a protected luteolin. Such a transformation is typically performed by reaction with dimethyldioxirane (DMDO), an efficient oxygen-transfer reagent for methoxy[1–4] and benzyloxy[2,4,5] protected flavones (Scheme 1). Peroxide oxidation of a boron intermediate created from a 3-lithio-flavone provides a useful alternative.[6]

Despite these precedents, all our attempts to employ DMDO for the oxidation of the 5,7-dibenzyloxyflavones under study gave complex mixtures of products. The option involving a boron intermediate also gave limited success. However, given that DMDO is one of the most powerful and convenient oxygen-transfer agents under neutral conditions, we were driven to find out what was complicating the transformation we were trying to achieve, and to determine what changes in functionality were necessary to achieve the desired results. Model studies were conducted on simple chrysin derivatives, commencing with the reaction of 5,7-dimethoxyflavone (**1a**), a compound that has been reported to yield complex mixtures, but no epoxide (**2a**), in this reaction.[7]



Scheme 1. Conversion of flavones (**1**) into 3-hydroxyflavones (**3**) with dimethyldioxirane.

2. Results and discussion

The proposed study required a variety of 5,7-disubstituted chrysin derivatives. The dimethoxy[8,9] (**1a**), diacetoxy[9,10] (**1b**) and dibenzoyloxy[10] (**1c**) compounds are all readily synthesised by published methods, as are the 7-methoxy-5-acetate (**1d**)[11] and the

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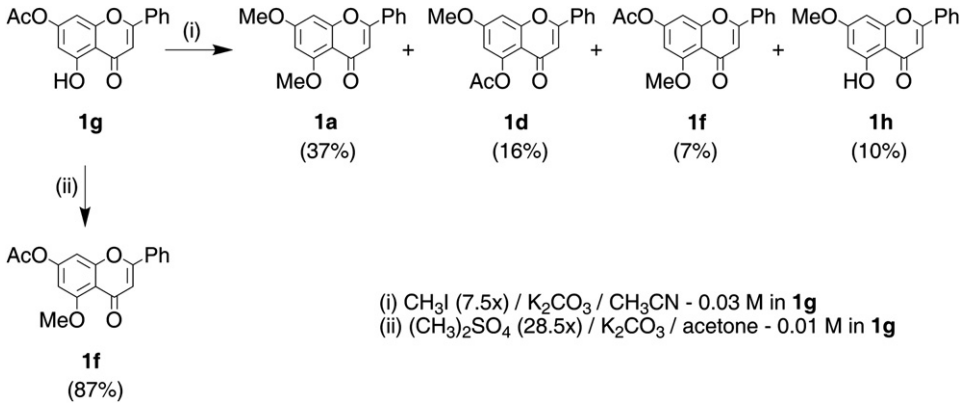
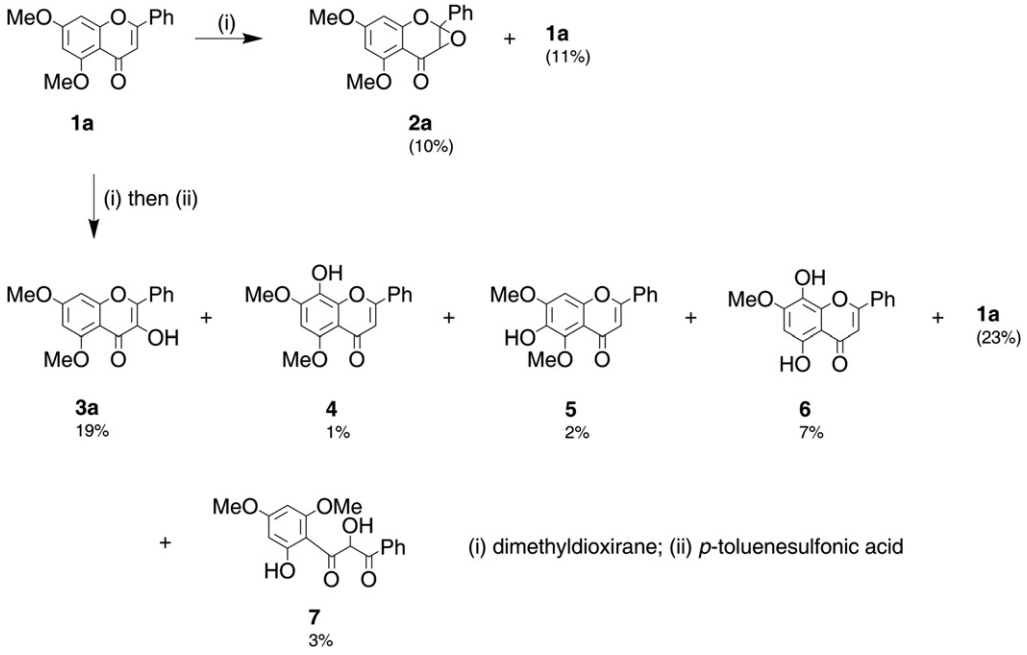
5-methoxy-7-benzoate (**1e**).[12] Initial attempts at formation of the unreported 7-acetoxy-5-methoxyflavone (**1f**) by reaction of 7-acetoxy-5-hydroxyflavone (**1g**) with CH_3I/K_2CO_3 gave poor recovery of the desired compound (Scheme 2). The major components of the reaction mixture were 5,7-dimethoxyflavone (**1a**), 5-acetoxy-7-methoxyflavone (**1d**) and 5-hydroxy-7-methoxyflavone[13] (**1h**). The use of $(CH_3)_2SO_4$ in place of CH_3I gave some improvement, yielding a mixture containing (**1a**), (**1d**) and (**1f**) in a 3:6:5 ratio. Suppression of intermolecular acyl transfer, achieved by carrying out the reaction at much lower substrate concentration, while maintaining a very large excess of the methylating agent, raised isolated yields of **1f** to 87%. Benzoylation of **1h** gave the new compound, 5-benzoyloxy-7-methoxyflavone (**1i**), in 90% yield. A further monoacylated derivative, 5-benzoyl-7-benzyloxyflavone (**1j**), was prepared by selective debenzylation of 5,7-dibenzyloxyflavone (**1k**)[14] with $TiCl_4$ followed by benzoylation.

6-methyl, 6-methoxy and 7-methoxy compounds.[1] Some systems with high levels of ring A substitution were also converted effectively.[2,3] One exception noted in the literature is the 5,7-dimethoxy compound (**1a**) that has been reported to yield an intractable mixture containing no epoxide.[7]

Our initial studies on **1a** (Scheme 3) employed a 3:1 ratio of DMDO to substrate, reacting at 0 °C, followed by a period at room temperature. Unlike the literature report,[7] this did result in a low yield of epoxide **2a** after chromatography on alumina (other by-products were unable to be eluted). Alternatively, when the crude product was treated with *p*-toluenesulfonic acid, and the ensuing mixture was chromatographed on silica, the flavonol **3a** was isolated along with a variety of other products (Scheme 3). Functionalisation of the A-ring was clearly competing with attack at C-3, and some loss of the labile C-5 methoxy grouping was also taking place. Hydroxydione **7** presumably arose through



Scheme 2. Synthesis of 7-acetoxy-5-methoxyflavone (**1f**).

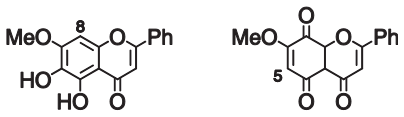


Scheme 3. Reaction of 5,7-dimethoxyflavone (**3a**) with dimethyldioxirane.

Examination of the literature reveals that the DMDO method has been used to transform a number of flavones preferentially into their 3-hydroxy counterparts via the epoxide. These include flavone itself,[1,7] the 5-methoxy[1] and benzyloxy[4] derivatives, and the intervention of water after protonation of the epoxide, and this was demonstrated by reaction of a pure sample of epoxide **2a** with aqueous HCl, which resulted in a higher yield of **7** (60%) along with flavonol **3a** (26%).

When the reaction with DMDO was repeated at lower temperature (−15 °C) for the same overall time, C-5 demethylation became dominant, resulting in the isolation of **6** in 30% yield along with **3a** (13%) and recovered **1a** (10%) after acid treatment. Low levels of 5-hydroxy-7-methoxyflavone (**1h**) were also detected, but the dimethoxyphenols **4** and **5** were not isolated.

Dihydroxyflavone **6** (16%) could also be obtained by reaction of 5-hydroxy-7-methoxyflavone (**1h**) with DMDO (1:2 ratio) if the reaction was halted when approximately half the starting material remained (3 h). This also yielded the positional isomer, 5,6-dihydroxy-7-methoxyflavone **8** (4%). When reaction was conducted at −15 °C for 19 h with a 1:4 ratio of substrate to DMDO, unchanged substrate (29%) was recovered along with **8** (4%). However, 8-hydroxy-5,7-dimethoxyflavone (**6**) was not obtained. In its place the oxidation product, quinone **9**, was isolated in 30% yield. Compound **6** has been reported previously[15] from reaction of **1h** with potassium persulfate. These authors also reported the oxidation of **6** to form **9**. Chu and coworkers[3] have previously made use of the directing influence of a C5 hydroxyl group to direct attack onto C8 and also achieved C5 hydroxylation upon treatment of 6,7,8-trimethoxyflavones with 1 equiv of DMDO.



8 **9**

A series of experiments monitored by HPLC was undertaken on the dimethoxy compound **1a** to explore the effect of varying the DMDO to substrate ratio. Results are illustrated in Fig. 1, which shows levels of unchanged substrate (**1a**), epoxide (**2a**) and the phenolic compounds **4**, **5** and **6** for different DMDO/substrate ratios. Compound **2a** is formed preferentially at lower DMDO levels, with the only other by-products being **4** and **5**, the result of hydroxylation at C-8 or C-6, respectively. With higher proportions of DMDO, C-5 demethylation becomes apparent as the level of **4** decreases and the level of the bis-phenol **6** increases. Accompanying this is the expected fall in the amount of remaining substrate but a dramatic reduction is noted in the relative amount of epoxide being formed along with a considerable increase in the complexity and lack of resolution of the chromatogram. At higher concentrations of DMDO there is clearly some further reaction of the products that were formed at lower concentrations. Furthermore, it does appear that the DMDO reactivity is being diverted by some product species.

Removal of the C-5 methyl group of a 5,7-dimethoxy compound during reaction with DMDO has been noted previously, but in this case the reactant was a flavanone.[16] The authors suggested that the demethylation took place by a radical process and found that reaction in HCl avoided this path by producing a more electrophilic modification of the DMDO reagent. Earlier studies have implicated formation of a radical anion, $\bullet O{-}C(CH_3)_2{-}O{:}^{-}$, from DMDO by electron transfer. This has been initiated by a nitroxide species,[17] a tertiary amine[18] and in cyclic voltammetry studies.[19] A species containing an alkoxy anion may be responsible for the demethylation observed in the reaction with **1a**. The resulting phenoxide species could well be the electron donors to complete the cycle.

It seemed appropriate at this stage to investigate suppressing the reaction in ring A by replacing the alkoxy groupings with acyloxy functions. As a preliminary, some density functional theory (DFT) calculations were carried out.

It has been suggested that alkenes react with dioxirane either as nucleophiles or as electrophiles, depending on the nature of the alkene substituents.[20] However, two recent papers have shown that DMDO reacts in all cases as an electrophile, even when the alkene bears strongly electron-withdrawing groups.[19,21] Both reports propose a spiro transition state that is dominated by the $HOMO_{alkene}/LUMO_{DMDO}$ interaction. DFT calculations (B3LYP/6-311+G(d)) have been conducted[21] for a range of simple alkenes, including one push–pull system, 3-methoxyacrolein, which is somewhat analogous to the flavone systems. Here, an asymmetrical transition state was derived, with a substantially shorter bond to the α-carbon, consistent with attack of an electron deficient reagent at the more electron rich sp^2 centre. The published Gaussian output for this DMDO/3-methoxyacrolein transition state was used as a starting point for DFT calculations on that for reaction of flavone with DMDO. B3LYP calculations were performed using Spartan '08,[22] employing the 6-31G* basis set. The resulting structure, shown in Fig. 2, reveals that bonding to C-3 is considerably more advanced than that to C-2 (r_{2-O}=2.330 Å, r_{3-O}=1.815 Å). This is the reverse order to that calculated for the epoxide product (r_{2-O}=1.404 Å, r_{3-O}=1.457 Å).

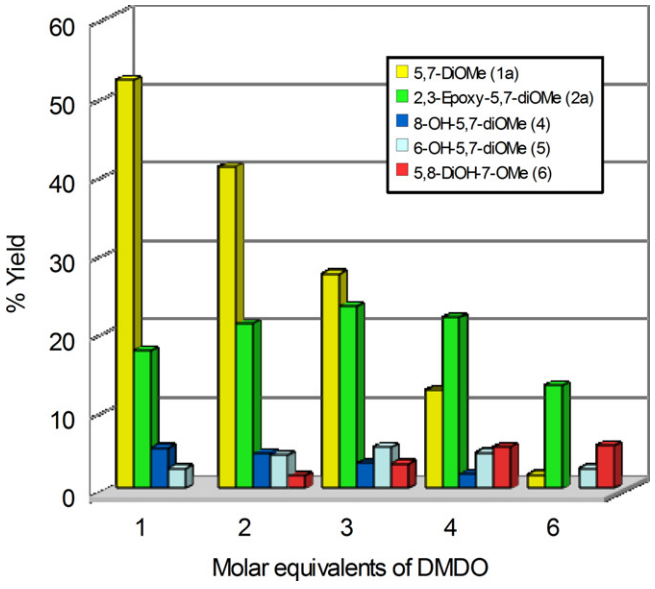


Fig. 1. Product distributions after reaction of varying amounts of dimethyldioxirane with 5,7-dimethoxyflavone (**1a**).

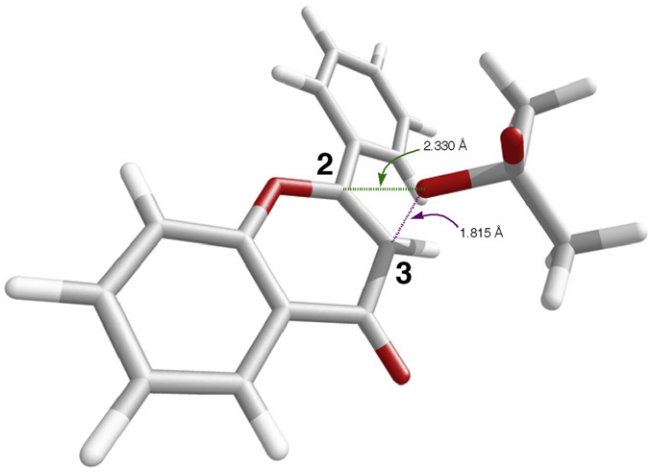


Fig. 2. Calculated transition state (B3LYP/6-31G*) for reaction between flavone and DMDO.

It is noteworthy that with a single methoxyl grouping in ring A, at C5, C6 or C7, the preferred site of attack is at C3.[1] As already discussed, with methoxyl groups at both C5 and C7 (compound **1a**), ring A attack becomes competitive. However, there is quite a delicate balance as introduction of a 4′-methoxyl, as in 4′,5,7-trimethoxyflavone, refocuses oxidation at C3.[4] Given this variability in the site of attack, it was inviting to investigate whether calculated ground state electron distribution could be used to predict the reactivity of these systems. While it is clear that full interpretation of reactivity requires consideration of many factors,[23] a focus on the bond formation to C-3 in the reaction under study seemed warranted by the extreme dissimilarity in the degree of bonding to C-2 and C-3 in the calculated transition state. Local ionization potential maps provide a good visual indicator of sites of potential electrophilic attack.[24] Fig. 3 shows such representations for the dominant conformation of some of the flavones used in this study. The reduced electron availability at all positions as the number of acetate groupings increases is apparent, as is the lack of differentiation at available sites with increased methylation. These studies suggested that diacylation or monoacylation at either C-5 or C-7 should provide sufficient deactivation of ring A to enable efficient C-3 oxidation.

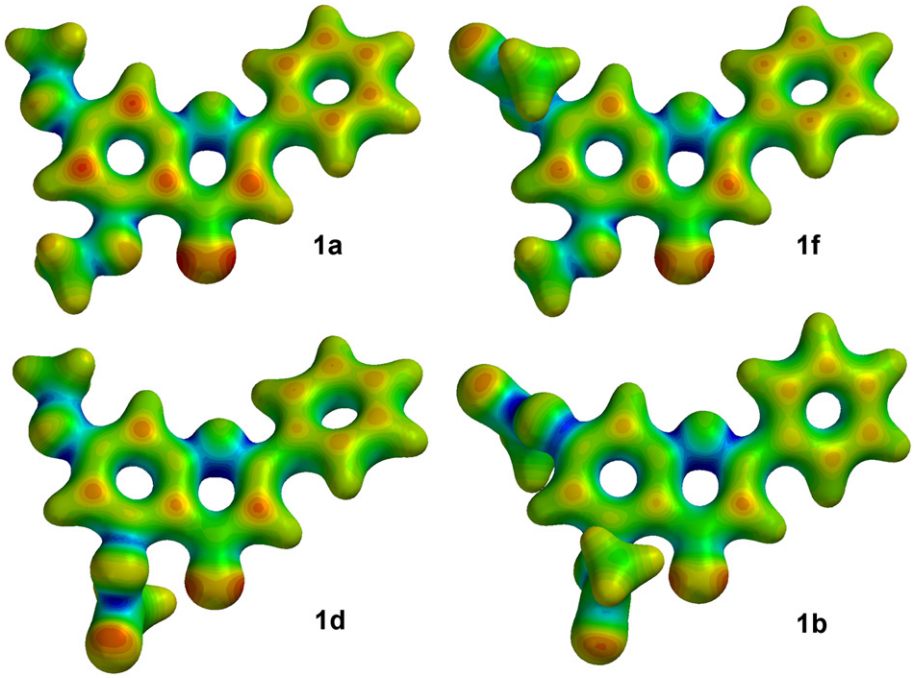


Fig. 3. Ionization potential maps (B3LYP/6-31G*) for some of the flavones used in this study. Red shadings indicate increased electron availability.

Reaction of 5,7-diacetoxyflavone (**1b**) with DMDO yielded the new epoxide (**2b**) in 98% yield. Treatment of this epoxide with *p*-toluenesulfonic acid then gave the previously unreported 3-hydroxyflavone (**3b**). Analogous results were obtained for the dibenzoate (**1c**), which yielded epoxide (**2c**) and 3-hydroxyflavone (**3c**), again both new compounds. In each case it is noteworthy that there was complete transformation of the starting material, in addition to selective reaction at C-3. Any thought that the presence or absence of starting material at the end of reactions carried out under similar conditions might be a reflection of faster reaction rates for the acyloxy compounds was dispelled by carrying out a competitive reaction on equimolar amounts of the dimethoxy (**1a**) and diacetoxy (**1b**) compounds. The ^{1}H NMR spectrum of the reaction mixture showed that **1a** had reacted to the extent of approximately 30% and the dominant product was epoxide **2a**. There was no evidence of reaction of the diacetoxy compound. Thus, while the acyl groups slow down reaction at all positions, they completely suppress ring A functionalisation, yet still allow a workable reaction rate at C-3.

It was now of interest to explore cases with lesser electron withdrawal in ring A. Four monoacyl methoxyflavones, the acetates **1d** and **1f** and the benzoates **1e** and **1i**, were reacted under similar conditions with a fourfold excess of DMDO. The ensuing crude epoxides were transformed directly into the corresponding flavonols in overall yields ranging from 66 to 78%. ^{1}H NMR spectra of crude reaction mixtures revealed no sign of ring A oxidation, and in three cases showed no remaining starting material. The exception was 5-acetoxy-7-methoxyflavone (**1d**), which yielded 8% of unchanged starting material. The 5-benzoyl-7-benzyloxy compound **1j** was similarly transformed in 73% yield.

3. Conclusions

Contrary to a previous literature report,[7] 5,7-dimethoxyflavone (**1a**) does react quickly with DMDO to form the epoxide (**2a**) along with two ring A hydroxylation products, **4** and **5**. However, minor by-products appear to become implicated in a process that rapidly consumes the reagent and diverts the transformation of the reactant to produce multiple by-products including those resulting from demethylation at C-5. Isolation of clean samples of **2a** requires stopping the reaction early before these processes gain domination. A better approach to samples of flavonol (**3a**) is to use the published boron mediated strategy.[6] However, the model studies reported here have demonstrated that efficient and selective introduction of an oxygen atom to C-3 of an oxygenated flavone can be achieved by reaction with DMDO if the flavone has an appropriate electron-withdrawing group at either C-5 or C-7, and we have successfully applied this methodology to synthetic studies that are currently in process with luteolin derivatives. We have also shown that

molecular modelling techniques that are available on a standard personal computer can provide some insight into which combinations of groups will achieve the desired results. Studies reported here made use of the less computer intensive 6-31+G* basis set. Parallel calculations using the 6-311+G** basis set gave very similar results, hence the additional computer time is not warranted. These observations on a previously unpredictable reaction, open up a new avenue of approaches to more complex flavonols. This work has enabled the synthesis of several new 2,3-epoxyflavones and flavonols and also details the first synthesis of the previously undescribed 7-acetoxy-5-methoxyflavone (**1f**).

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian 500 MHz VNMRS (500/125 MHz), Varian 400-MR (400/100 MHz) or Varian Inova-300 (300/75 MHz) spectrometers. The residual proton signal of the solvent was used as an internal reference for ^{1}H spectra (δ 7.26) and the solvent carbon signal for ^{13}C spectra (δ 77.1). Coupling constants are reported in hertz. Standard 2D correlation experiments were used to assign peaks. Infrared (IR) spectra were recorded as thin films, KBr disks or Nujol mulls (NaCl disks) on a Perkin–Elmer spectrum 100 FTIR spectrophotometer. High Resolution Mass Spectra were recorded on a Bruker Microtof-Q spectrometer. Microanalyses were performed by the Campbell Microanalytical Laboratory, Chemistry Department, University of Otago. Melting points were recorded on a Reichert hot bench. Column chromatography was performed using Kieselgel 60 (230–400 mesh) silica gel or Spence H alumina. Preparative TLC was performed on glass plates pre-coated with silica gel 60 F_{254} to a layer thickness of 0.5 mm. HPLC analysis was carried out using an Agilent HP1100, controlled with EziChrom Elite, at 20 °C on a C18 column (Phenomenex Prodigy ODS(3) 5 μm, 100 Å, 250×3 mm) with a 2×4 mm C18 guard column. The mobile phase was acetonitrile in water: t_0=40%, $t_{12.5}$=70%, t_{15}=100%, t_{16}=40%, t_{20}=40%. The flow rate was 0.5 mL/min, with an injection volume of 5 μL.

DMDO was prepared as previously described[25] and the acetone solution was dried at −15 °C over 4 Å molecular sieves.

4.2. Molecular modelling

All calculations were carried out with Spartan '08.[22] For the flavone reactants (**1**), conformational searching was conducted at the AM1 level allowing the default rotational steps about all rotatable bonds. The structures obtained were submitted for equilibrium geometry DFT calculations, which employed the B3LYP[26,27] exchange-correlation functionals, together with the 6-31G* basis set.[28] The ensuing structures were characterized by infra-red frequency calculations in order to verify that true minima had been attained for compounds (no imaginary frequencies) or that a transition state had been reached (one imaginary frequency). Ionization potential surfaces were obtained by projecting the ionization property on to a density surface with a fixed isovalue of 0.09 $e \cdot a_0^{-3}$ and property range of 10–20 eV.

4.3. Preparation of new monoacyl chrysin derivatives

*4.3.1. 7-Acetoxy-5-methoxyflavone (**1f**).* Dimethyl sulfate (5 mL, 53 mmol) was added dropwise to a stirred mixture of 7-acetoxy-5-hydroxyflavone (**1g**)[9] (0.547 g, 1.84 mmol) and K_2CO_3 (1.544 g, 11.17 mmol) in AR acetone (150 mL). The mixture was heated under reflux with vigorous stirring for 7.5 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was chromatographed on silica (51 g) eluting with a CH_2Cl_2/EtOAc gradient. Elution with EtOAc gave **1f** (0.498 g, 87%) as a white solid; mp 163–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.34 (s, 3H, C**H**$_3$CO), 3.97 (s, 3H, OC**H**$_3$), 6.58 (d, 1H, J=2.0 Hz, H-6), 6.71 (s, 1H, H-3), 6.98 (d, 1H, J=2.0 Hz, H-8), 7.49–7.54 (m, 3H, H-3′, 4′, 5′), 7.85 (ddm, J=8.0, 1.5 Hz, 2H, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.3 (q, **C**H$_3$COO), 56.7 (q, OCH_3), 101.1 (d, C-6), 103.3 (d, C-8), 109.2 (d, C-3), 112.6 (s, C-4a), 126.1 (2×d, C-2′, 6′), 129.0 (2×d, C-3′, 5′), 131.3 (s, C-1′), 131.5 (d, C-4′), 154.6 (s, C-7), 158.7 (s, C-8a), 160.8 (s, C-5), 161.3 (s, C-2), 168.5 (s, CH$_3$**C**O), 177.6 (s, C4); IR (KBr) ν_{max} 3096, 3054, 2981, 2946, 2855, 1767, 1653, 1607, 1580, 1496, 1477, 1466, 1422, 1370, 1337, 1310, 1288, 1261, 1198, 1135, 1094, 1078, 1030, 1006, 981, 956, 892, 854, 843, 818, 780, 769, 696, 676, 624, 607 cm^{-1}; HRMS (+ve ESI) m/z 333.0727 $[M+Na]^+$ (calcd for $C_{18}H_{14}NaO_5$ 333.0733). Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.7; H, 4.6. Found: C, 69.4; H, 4.4%.

*4.3.2. 5-Benzoyloxy-7-methoxyflavone (**1i**).* A solution of 5-hydroxy-7-methoxyflavone (**1h**)[13] (0.513 g, 1.91 mmol) in pyridine (12 mL) was heated with benzoyl chloride (2 mL, 17 mmol) at 65 °C for 8 h. The solvents were removed under vacuum at 60 °C, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3×70 mL). The combined CH_2Cl_2 extracts were washed with HCl (2 M, 50 mL) then saturated $NaHCO_3$ (50 mL). Drying (Na_2SO_4) and evaporation of the solvent was followed by chromatography on silica (30 g). Elution with a CH_2Cl_2/Et_2O gradient yielded a fraction (5% Et_2O/CH_2Cl_2), which was recrystallised from rectified spirit to yield **1i** (0.537 g, 90%); mp 168–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.93 (s, 3H, OC**H**$_3$), 6.56 (s, 1H, H-3), 6.75 (d, J=2.5 Hz, 1H, H-6), 6.93 (d, J=2.5 Hz, 1H, H-8), 7.50 (ddm, J=8.0, 8.0 Hz, 2H, H-3′, 5′), 7.50 (m, 1H, H-4′), 7.51 (ddm, J=8.0, 8.0 Hz, 2H, H-3″, 5″), 7.62 (dddd, J=7.5, 7.5, 1.5, 1.5 Hz, 1H, H-4″), 7.85 (ddm, J=7.5, 1.5 Hz, 2H, H-2′, 6′), 8.26 (ddm, J=8.0, 1.5 Hz, 2H, H-2″, 6″); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.0 (q, O**C**H$_3$), 99.2 (d, C-8), 108.5 (d, C-3), 108.5 (d, C-6), 111.4 (s, C-4a), 126.1 (2×d, C-2′, 6′), 128.5 (2×d, C-3″, 5″), 129.0 (d, C-3′, 5′), 129.8 (s, C-1″), 130.4 (2×d, C-2″, 6″), 131.4 (d, C-4′), 131.5 (s, C-1′), 133.3 (d, C-4″), 150.8 (s, C-5), 158.9 (s, C-8a), 161.9 (s, C-2), 163.5 (s, C-7), 165.4 (s, Ph–**C**OO), 176.4 (s, C-4); IR (KBr) ν_{max} 3056, 3014, 2941, 2839,1740, 1652, 1610, 1492, 1450, 1430, 1378, 1350, 1261, 1207, 1174, 1153, 1056, 1023, 955, 905, 886, 830, 818, 774, 764, 696, 665, 640 cm^{-1}; HRMS (+ve ESI) m/z 395.0865 $[M+Na]^+$ (calcd for $C_{23}H_{16}NaO_5$ 395.0890). Anal. Calcd for $C_{23}H_{16}O_5$: C, 74.2; H, 4.3. Found: C, 74.3; H, 4.4%.

*4.3.3. 5-Benzoyloxy-7-benzyloxyflavone (**1j**).* A solution of $TiCl_4$ (1 M in CH_2Cl_2, 0.31 mL, 0.31 mmol) was added dropwise to a solution of 5,7-dibenzyloxyflavone (**1k**)[5] (0.220 g, 0.476 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was carefully added to a stirred solution of saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the volatiles were removed in vacuo to afford crude 7-benzyloxy-5-hydroxyflavone (0.170 g, 98%) as an orange solid, which was used without further purification. Benzoyl chloride (0.5 mL) was then added to a solution of this flavone (0.17 g, 0.51 mmol) in anhydrous pyridine (3 mL) at 0 °C and the reaction mixture was stirred at 60 °C for 5 h then at room temperature for 48 h. The reaction mixture was quenched with methanol and the volatiles were removed in vacuo. The residue was diluted with CH_2Cl_2 (20 mL) and the organic phase was washed with dil HCl (1 M, 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and volatiles were removed in vacuo. The crude product was purified by column chromatography on silica gel (20 g, CH_2Cl_2 elution) to afford **1j** (0.180 g, 79%) as a white solid; mp 137–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.20 (s, 2H, PhC**H**$_2$O), 6.60 (s, 1H, H-3), 6.85 (d, J=2.5 Hz, 1H, H-6), 7.02 (d, J=2.5 Hz, 1H, H-8), 7.43 (m, 5H, H-2‴, 6‴), 7.52 (m, 3H, H-3′, 4′, 5′), 7.52 (dd, J=8.5, 8.5 Hz, 2H, H-3″, 5″), 7.64 (dd, J=8.5, 8.5 Hz, 1H, H-4″), 7.85 (dd,

J=1.0, 7.5 Hz, 2H, H-2′, 6′), 8.26 (dd, J=1.5, 8.5 Hz, 2H, H-2″, 6″); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 70.9 (t, Ph**C**H_2O), 100.2 (d, C-8), 108.6 (d, C-3), 109.2 (d, C-6), 111.7 (s, C-4a), 126.2 (2×d, C-2′, 6′), 127.7 (2×d, C-2‴, 6‴), 128.6 (2×d, C-3″, 5″), 128.6 (d, C-4″), 128.9 (2×d, C-3‴, 5‴), 129.1 (3×d, C-3′, 4′, 5′), 129.9 (s, C-1″), 130.5 (2×d, C-2″, 6″), 131.5 (s, C-1′), 133.4 (d, C-4″), 135.5 (s, C-1‴), 150.9 (s, C-5), 158.9 (s, C-8a), 162.1 (s, C-2), 162.7 (s, C-7), 165.4 (s, Ph**C**OO), 176.5 (s, C-4); IR (thin film) ν_{max} 3062, 1740, 1645, 1493, 1450, 1375, 1351, 1262, 1159, 1093, 1058, 1028, 696 cm^{-1}; HRMS (+ve ESI) m/z 449.1365 [M+H]$^+$ (calcd for $C_{29}H_{21}O_5$ [M+H]$^+$ 449.1384).

4.4. Dimethyldioxirane treatment of flavones

A solution of DMDO in acetone (~0.1 M, volume, amount) was added to a stirred solution of the flavone (mass, amount) in dry CH_2Cl_2 (volume) over powdered molecular (4 Å) sieves (mass) at the prescribed temperature. The reaction mixture was maintained at this temperature for the stated time, then, in some cases, allowed to warm to room temperature and stirred for a further stated time. The mixture was filtered through a layer of anhydrous Na_2SO_4 on a layer of Celite® and the volatiles were removed in vacuo at room temperature.

*4.4.1. Reaction with 5,7-dimethoxyflavone (**1a**).*

*4.4.1.1. Preparation of epoxide **2a**.* (a) DMDO solution (20 mL, ~2 mmol), **1a** (0.188 g, 0.666 mmol), 4 Å sieves (0.500 g), CH_2Cl_2 (5 mL), 0 °C (3 h). The crude product was purified by chromatography on alumina (10 g). Elution with CH_2Cl_2 gave 4,6-dimethoxy-1a-phenyl-1a*H*-oxireno[2,3-*b*]chromen-7(7a*H*)-one (**2a**) (0.019 g, 10%) as a yellow solid. Elution with EtOAc gave unchanged **1a** (0.021 g, 11%). The bulk of the product resisted elution with isopropyl alcohol. Epoxide **2a**, a yellow solid had mp 115–118 °C; ^{1}H NMR[†](500 MHz, $CDCl_3$) δ_H 3.82 (s, 1H, H-3), 3.84 (s, 3H, 7-OC**H**$_3$), 3.89 (s, 3H, 5-OC**H**$_3$), 6.22 (d, J=2.0 Hz, 1H, H-8), 6.26 (d, J=2.0 Hz, 1H, H-6), 7.43–7.47 (m, 3H, H-3′, 4′, 5′), 7.59 (m, 2H, H-2′, 6′); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 55.8 (q, 7-O**C**H$_3$), 56.4 (q, 5-O**C**H$_3$), 65.4 (d, C-3), 84.7 (s, C-2), 94.1 (d, C-6), 94.9 (d, C-8), 104.7 (s, C-4a), 126.0 (2×d, C-2′, 6′), 128.8 (2×d, C-3′, 5′), 129.9 (d, C-4′), 133.0 (s, C-1′), 159.6 (s, C-8a), 162.0 (s, C-5), 166.1 (s, C-7), 186.5 (s, C-4); IR (KBr) ν_{max} 3115, 3044, 3004, 2983, 2846, 1681, 1600, 1557, 1496, 1471, 1423, 1352, 1327, 1285, 1231, 1186, 1161, 1118, 1083, 1034, 1014, 1002, 957, 928, 914, 863, 829, 799, 761, 720, 695, 673, 644, 627, 597, 575, 562, 529, 500, 464, 434 cm^{-1}; HRMS (+ve ESI) m/z 321.0747 [M+Na]$^+$ (calcd for $C_{17}H_{14}NaO_5$ 321.0733). An identical reaction mixture was used to form the 3-hydroxy compound (**3a**) (vide infra).

(b) DMDO solution (20 mL, ~2 mmol), **1a** (0.145 g, 0.514 mmol), 4 Å sieves (0.500 g), CH_2Cl_2 (5 mL), −15 °C (19 h). This mixture was used to form the 3-hydroxy compound (**3a**) (vide infra).

*4.4.1.2. Analysis of effects of changing the DMDO: **1a** ratio.* A stock solution of 5,7-dimethoxyflavone (**1a**)[8,9] (0.100 g, 0.354 mmol) and benzophenone (0.065 g 0.357 mmol) in dry CH_2Cl_2 (5 mL) was prepared. In each experiment, DMDO in acetone (~0.1 M) was added to a stirred mixture of the stock solution (500 μL, 0.0357 mmol of **1a**) and powdered molecular (4 Å) sieves (0.050 g) containing sufficient acetone to make up a total reaction volume of 2.5 mL at 0 °C. Reaction systems were prepared containing 1, 2, 3, 4 and 6 M equiv of DMDO. Each reaction mixture was stirred at 0 °C for 4 h when an aliquot (500 μL) was removed and filtered through a layer of anhydrous Na_2SO_4 on Celite®. The reaction mixtures were stirred at room temperature for a further 20 h and resampled as before. Each filtrate was evaporated and the residue was taken up into methanol (2 mL) for HPLC analysis. Levels of components were monitored by their absorptions at 280 nm. Compounds monitored are listed along with retention times (s) and relative response factors at this wavelength: 6-hydroxy-5,7-dimethoxyflavone (**5**) (5.21, 3.27); 8-hydroxy-5,7-dimethoxyflavone (**4**) (7.05, 1.59); epoxide (**2a**) (9.59, 2.50); reactant (**1a**) (10.08, 3.17); 5,8-dihydroxy-7-methoxyflavone (**6**) (10.62, 2.42); benzophenone (14.61, 1).

*4.4.2. Reaction with 5,7-diacetoxyflavone (**1b**).* DMDO solution (40 mL, ~4 mmol), 5,7-diacetoxyflavone (**1b**)[9,10] (0.500 g, 1.48 mmol), CH_2Cl_2 (8 mL), 4 Å sieves (0.500 g), 0 °C (3 h), room temperature (72 h). 4,6-Bis(acetoxy)-1a-phenyl-1a*H*-oxireno [2,3-*b*]chromen-7(7a*H*)-one (**2b**) (0.510 g, 98%) was obtained as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.31 (s, 3H, C**H**$_3$COO), 2.39 (s, 3H, C**H**$_3$COO), 3.78 (s, 1H, H-3), 6.73 (d, J=2.0 Hz, 1H, H-6), 6.96 (d, J=2.0 Hz, 1H, H-8), 7.48 (m, 3H, H-3′, 4′, 5′), 7.58 (m, 2H, H-2′, 6′); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.0 (q, **C**H$_3$COO), 21.3 (q, **C**H$_3$COO), 64.7 (d, C-3), 85.1 (s, C-2), 109.6 (d, C-8), 111.0 (s, C-4a), 112.8 (d, C-6), 126.1 (2×d, C-2′, 6′), 129.0 (2×d, C-3′, 5′), 130.3 (d, C-4′), 132.4 (s, C-1′), 151.3 (s, C-5), 156.0 (s, C-7), 157.9 (s, C-8a), 167.9 (s, CH$_3$**C**OO), 169.3 (s, CH$_3$**C**OO), 186.2 (s, C-4); IR (thin film) ν_{max} 3071, 1777, 1687, 1622, 1579, 1436, 1368, 1289, 1187, 1131, 1067, 1026, 905, 697 cm^{-1}; HRMS (+ve ESI) m/z 377.0681 [M+Na]$^+$ (calcd for $C_{19}H_{14}NaO_7$ 377.0632).

*4.4.3. Reaction with 5,7-dimethoxyflavone (**1a**)/5,7-diacetoxyflavone (**1b**).* DMDO solution (1 mL, ~0.1 mmol), (**1a**) (0.014 g, 0.050 mmol), (**1b**) (0.017 g, 0.050 mmol), CH_2Cl_2 (250 μL), 4 Å sieves (0.025 g), 0 °C (3 h). ^{1}H NMR showed that approximately 30% of the **1a** had been converted into epoxide **2a** but epoxide **2b** was not detected. Minor peaks in the δ 12–14 region were noted.

*4.4.4. Reaction with 5,7-dibenzoyloxyflavone (**1c**).* DMDO solution (40 mL, ~4 mmol), 5,7-dibenzoyloxyflavone (**1c**)[10] (0.150 g, 0.324 mmol), CH_2Cl_2 (8 mL), 4 Å sieves (0.500 g), 0 °C (3 h), room temperature (72 h). Recrystallisation from ethanol gave 4,6-bis (benzoyloxy)-1a-phenyl-1a*H*-oxireno[2,3-*b*]chromen-7(7a*H*)-one (**2c**) (0.140 g, 95%) as a white solid; mp 102–104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.79 (s, 1H, H-3), 7.04 (d, J=2.5 Hz, 1H, H-6), 7.16 (d, J=2.5 Hz, 1H, H-8), 7.55 (m, 3H, H-3′, 4′, 5′), 7.55 (ddm, J=8.5, 8.5 Hz, 2H, H-3″, 5″), 7.55 (ddm, J=7.5, 7.5 Hz, 2H, H-3‴, 5‴), 7.61 (m, 2H, H-2′, 6′), 7.66 (ddm, J=8.5, 8.5 Hz, 1H, H-4″), 7.66 (ddm, J=7.5, 7.5 Hz, 1H, H-4‴), 8.19 (dd, J=1.0, 7.5 Hz, 2H, H-2‴, 6‴), 8.23 (dd, J=1.5, 8.5 Hz, 2H, H-2″, 6″); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 64.7 (d, C-3), 85.1 (s, C-2), 109.8 (d, C-8), 111.3 (s, C-4a), 113.1 (d, C-6), 126.0 (2×d, C-2′, 6′), 128.8 (2×d, C-3″, 5″), 128.8 (2×d, C-3‴, 6‴), 128.9 (2×d, C-3′, 5′), 129.0 (2×d, C-3‴, 5‴), 130.2 (d, C-4′), 130.5 (2×d, C-2″, 6″), 130.6 (2×d, C-1″, 1‴), 132.4 (s, C-1′), 133.8 (d, C-4‴), 134.3 (d, C-4″), 151.6 (s, C-5), 156.3 (s, C-7), 157.9 (s, C-8a), 163.8 (s, Ph**C**OO), 164.9 (s, Ph**C**OO), 186.1 (s, C-4); IR (thin film) ν_{max} 1747, 1688, 1620, 1451, 1433, 1244, 1178, 1134, 1082, 1069, 1050, 1025, 890, 704 cm^{-1}; HRMS (+ve ESI) m/z 501.0911 [M+Na]$^+$ (calcd for $C_{29}H_{18}NaO_7$ 501.0945).

*4.4.5. Reaction with 5-acetoxy-7-methoxyflavone (**1d**).* DMDO solution (20 mL, ~2 mmol), 5-acetoxy-7-methoxyflavone (**1d**)[11] (0.305 g, 0.982 mmol), CH_2Cl_2 (5 mL), 4 Å sieves (0.500 g), 0 °C (3 h), room temperature (24 h). The crude epoxide had ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.38 (s, 3H), 3.72 (s, 1H), 3.85 (s, 3H), 6.44 (d, J=2.0 Hz, 1H), 6.55 (d, J=2.0 Hz, 1H), 7.44–7.47 (m, 3H), 7.56–7.59 (m, 2H)—unchanged **1d** (ca. 10%) was also present. This mixture was used to form the 3-hydroxy compound (**3d**) (vide infra).

*4.4.6. Reaction with 7-benzoyloxy-5-methoxyflavone (**1e**).* DMDO solution (20 mL, ~2 mmol), 7-benzoyloxy-5-methoxyflavone (**1e**)[12] (0.302 g, 0.811 mmol), CH_2Cl_2 (5 mL), 4 Å sieves (0.500 g),

[†] For convenience, NMR data for epoxides 2a, 2b and 2c are listed with flavone compound numbering

0 °C (3 h), room temperature (24 h). The crude epoxide, which had ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.89 (s, 1H), 3.95 (s, 3H), 6.62 (d, J=2.0 Hz, 1H), 6.73 (d, J=2.0 Hz, 1H), 7.45–7.48 (m, 3H), 7.53 (ddm, J=8.0, 8.0 Hz, 2H), 7.57–7.61 (m, 2H), 7.66 (ddm, J=8.0, 8.0 Hz, 1H), 8.18 (ddm, J=1.5, 8.0 Hz, 2H), was converted directly to the 3-hydroxy compound (**3e**) (vide infra).

*4.4.7. Reaction with 7-acetoxy-5-methoxyflavone (**1f**).* DMDO solution (20 mL, ~2 mmol), 7-acetoxy-5-methoxyflavone (**1f**) (0.305 g, 0.982 mmol), CH_2Cl_2 (5 mL), 4 Å sieves (0.500 g), 0 °C (3 h), room temperature (24 h). The crude epoxide, which had ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.31 (s, 3H), 3.86 (s, 1H), 3.91 (s, 3H), 6.47 (d, J=2.0 Hz, 1H), 6.59 (d, J=2.0 Hz, 1H), 7.44–7.47 (m, 3H), 7.55–7.60 (m, 2H), was converted directly to the 3-hydroxy compound (**3f**) (vide infra).

*4.4.8. Reaction with 5-hydroxy-7-methoxyflavone (**1h**).* (a) DMDO solution (20 mL, ~2 mmol), 5-hydroxy-7-methoxyflavone (**1h**)[13] (0.268 g, 0.999 mmol), 4 Å sieves (0.500 g), CH_2Cl_2 (5 mL), 0 °C (4 h). The mixture was separated by chromatography on silica (25 g). Elution with CH_2Cl_2/EtOAc; 49:1 gave unchanged **1h** (0.137 g, 51%). Elution with CH_2Cl_2/EtOAc; 9:1 gave 5,8-dihydroxy-7-methoxyflavone (**6**) (0.040 g, 16%). Elution with CH_2Cl_2/EtOAc; 7:3 gave 5,6-dihydroxy-7-methoxyflavone (**8**) (0.010 g, 4%). Compound **6** had mp 234–236 °C (from EtOAc) (lit.[15] 234–235 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.98 (s, 3H, OC**H**$_3$), 5.22 (br s, 1H, 8-O**H**), 6.45 (s, 1H, H-6), 6.65 (s, 1H, H-3), 7.52 (m, 2H, H-3′, 5′), 7.53 (m, 1H, H-4′), 7.94 (ddm, J=8.0, 1.5 Hz, 2H, H-2′, 6′), 12.29 (s, 1H, 5-O**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.6 (q, O**C**H$_3$), 95.2 (d, C-6), 105.1 (s, C-4a), 105.4 (d, C-3), 126.1 (s, C-8), 126.5 (2×d, C-2′, 6′), 129.2 (2×d, C-3′, 5′), 131.5 (s, C-1′), 132.0 (d, C-4′), 143.4 (s, C-8a), 152.2 (s, C-7), 154.4 (s, C-5), 164.1 (s, C-2), 183.0 (s, C-4); IR (KBr) ν_{max} 3421, 3198, 3011, 2939, 2846, 1660, 1616, 1578, 1560, 1521, 1495, 1453, 1439, 1418, 1350, 1328, 1293, 1268, 1251, 1219, 1170, 1160, 1121, 1034, 1013, 936, 849, 821, 780, 752, 715, 682, 662, 602, 564, 502, 473 cm^{-1}; HRMS (−ve ESI) m/z 283.0619 $[M-H]^+$ (calcd for $C_{16}H_{11}O_5$ 283.0612). Compound **8** had mp 215–217 °C (from CH_2Cl_2/petroleum spirit) (lit.[29] 235–238 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.00 (s, 3H, C**H**$_3$O), 5.38 (br s, 1H, 6-O**H**), 6.61 (s, 1H, H-8), 6.68 (s, 1H, H-3), 7.51 (m, 2H, H-3′, 5′), 7.53 (m, 1H, H-4′), 7.88 (ddm, J=8.0, 1.5 Hz, 2H, H-2′, 6′), 12.48 (br s, 1H, 5-O**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.6 (q, **C**H$_3$O), 90.6 (d, C-8), 105.6 (d, C-3), 106.2 (s, C-4a), 126.4 (2×d, C-2′, 6′), 129.2 (2×d, C-3′, 5′), 129.7 (s, C-6), 131.6 (s, C-1′), 131.9 (d, C-4′), 145.7 (s, C-8a), 150.8 (s, C-5), 153.0 (s, C-7), 164.2 (s, C-2), 182.7 (s, C-4); IR (KBr) ν_{max} 3444, 3072, 3023, 2942, 2843, 1668, 1612, 1587, 1563, 1503, 1474, 1458, 1415, 1365, 1311, 1287, 1244, 1206, 1175, 1159, 1107, 1090, 1037, 1024, 982, 908, 856, 808, 779, 765, 727, 693, 661, 649, 598, 567, 519 cm^{-1}; HRMS (−ve ESI) m/z 283.0613 $[M-H]^+$ (calcd for $C_{16}H_{11}O_5$ 283.0612).

(b) DMDO solution (20 mL, ~2 mmol), 5-hydroxy-7-dimethoxyflavone (**1h**) (0.136 g, 0.507 mmol), 4 Å sieves (0.500 g), CH_2Cl_2 (5 mL), −15 °C (19 h). The mixture was separated by chromatography on silica (18 g). Elution with CH_2Cl_2/EtOAc; 49:1 gave unchanged **1h** (0.040 g, 29%). Elution with CH_2Cl_2/EtOAc; 9:1 gave 5,6-dihydroxy-7-methoxyflavone (**8**) (0.006 g, 4%). Elution with EtOAc gave 7-methoxy-2-phenyl-4*H*-1-benzopyran-4,5,8-trione (**9**) (0.043 g, 30%). Compound **9** had mp 250–252 °C (from EtOAc) (lit.[15] 245–247 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.89 (s, 3H, OC**H**$_3$), 6.06 (s, 1H, H-6), 7.03 (s, 1H, H-3), 7.55 (d, J=8.0 Hz, 2H, H-2′, 6′), 7.55 (dd, J=8.0, 8.0 Hz, 1H, H-4′), 7.85 (dd, J=8.0, 8.0 Hz, 2H, H-3′, 5′) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 56.9 (q, O**C**H$_3$), 109.3 (d, C-6), 115.9 (d, C-3), 117.0 (s, C-4a), 126.4 (2×d, C-3′, 5′), 129.5 (2×d, C-2′, 6′), 129.6 (s, C-1′), 132.6 (d, C-4′), 155.6 (s, C-8a), 157.1 (s, C-7), 162.5 (s, C-2), 175.1 (s, C-8), 175.3 (s, C-4), 182.5 (s, C-5) ppm; IR (KBr) ν_{max} 3084, 2942, 2845, 1699, 1676, 1667, 1640, 1613, 1574, 1495, 1448, 1411, 1361, 1283, 1239, 1122, 1072, 1035, 1007, 979, 932, 889, 867, 856, 808, 773, 688, 666, 646, 533, 508, 464, 408 cm^{-1}; HRMS (+ve ESI) m/z 305.0451 $[M+Na]^+$ (calcd for $C_{16}H_{10}NaO_5$ 305.0420).

*4.4.9. Reaction with 5-benzoyloxy-7-methoxyflavone (**1i**).* DMDO solution (20 mL, ~2 mmol), 5-benzoyloxy-7-methoxyflavone (**1i**) (0.306 g, 0.822 mmol), CH_2Cl_2 (5 mL), 4 Å sieves (0.500 g), 0 °C (3 h), room temperature (24 h). The crude epoxide, which had ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.16 (s, 3H), 3.70 (s, 1H), 3.88 (s, 3H), 6.59 (d, J=2.0 Hz, 1H), 6.61 (d, J=2.0 Hz, 1H), 7.44–7.49 (m, 3H), 7.52 (ddm, J=8.0, 8.0 Hz, 2H), 7.57–7.61 (m, 2H), 7.64 (ddm, J=8.0, 8.0 Hz, 1H), 8.21 (ddm, J=1.5, 8.0 Hz, 2H), was converted directly to the 3-hydroxy compound (**3i**) (vide infra).

*4.4.10. Reaction with 5-benzoyloxy-7-benzyloxyflavone (**1j**).* DMDO solution (20 mL, ~2 mmol), 5-benzoyloxy-7-benzyloxyflavone (**1j**) (0.030 g, 0.067 mmol), CH_2Cl_2 (5 mL), 4 Å sieves (0.500 g), 0 °C (3 h), room temperature (24 h). The crude epoxide was converted directly to the 3-hydroxy compound (**3j**) (vide infra).

4.5. Synthesis of 3-hydroxyflavones

A solution of the flavonyl epoxide (mass, amount) and *p*-toluenesulfonic acid monohydrate (0.010 g) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 18 h before the volatiles were removed in vacuo at room temperature (method A), or the solution was washed with saturated $NaHCO_3$ (5 mL), dried (Na_2SO_4) and evaporated in vacuo at room temperature (method B).

*4.5.1. 5,7-Dimethoxy-3-hydroxyflavone (**3a**).* (a) Crude epoxide **2a** (prepared as for Section 4.4.1.1 (a)) gave a mixture which was separated by chromatography on silica gel (25 g). Elution with CH_2Cl_2/EtOAc; 17:3 gave a mixture which, on preparative TLC (CH_2Cl_2), yielded 2-hydroxy-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-phenylpropane-1,3-dione (**7**) (0.015 g, 3%). Further elution with CH_2Cl_2/EtOAc; 17:3 gave 5,8-dihydroxy-7-methoxyflavone (**6**) (0.025 g, 7%). Elution with CH_2Cl_2/EtOAc; 4:1 gave compound **3a** (0.092 g, 19%). Elution with CH_2Cl_2/EtOAc; 3:7 gave a mixture from which 6-hydroxy-5,7-dimethoxyflavone (**5**) (0.010 g, 2%) was isolated by preparative TLC (CH_2Cl_2/EtOAc; 1:4). This was followed by unchanged **1a** (0.110 g, 23%). Elution with EtOAc gave a mixture, which gave 8-hydroxy-5,7-dimethoxyflavone (**4**) (0.005 g, 1%) on preparative TLC (CH_2Cl_2/EtOAc; 1:4×2). Compound **3a** had mp 172–173 °C (lit.[6] 172–174 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.92 (s, 3H, 5-OC**H**$_3$), 3.98 (s, 3H, 7-OC**H**$_3$), 6.35 (d, J=2.0 Hz, 1H, H-8), 6.56 (d, J=2.0 Hz, 1H, H-6), 7.42 (br s, 1H, O**H**), 7.51 (ddm, J=7.5, 7.5 Hz, 2H, H-3′, 5′), 7.59 (ddm, J=7.5, 7.5 Hz, 1H, H-4′), 8.20 (dm, J=7.5 Hz, 2H, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 55.9 (q, 5-O**C**H$_3$), 56.5 (q, 7-O**C**H$_3$), 92.5 (d, C-6), 95.9 (d, C-8), 106.4 (s, C-4a), 127.3 (2×d, C-2′, 6′), 128.6 (2×d, C-3′, 5′), 129.7 (d, C-4′), 131.2 (s, C-1′), 138.4 (s, C-3), 141.9 (s, C-2), 159.2 (s, C-8a), 160.7 (s, C-7), 164.6 (s, C-5), 172.2 (s, C-4); IR (KBr) ν_{max} 3318, 3014, 2954, 2842, 1610, 1574, 1562, 1492, 1466, 1455, 1435, 1407, 1370, 1258, 1229, 1215, 1158, 1136, 1079, 1051, 1031, 1004, 965, 929, 877, 819, 803, 770, 733, 701, 647, 623, 601, 541, 462, 429 cm^{-1}; HRMS (+ve ESI) m/z 299.0905/321.0720 $[M+H]^+$/$[M+Na]^+$ (calcd for $C_{17}H_{15}O_5$/$C_{17}H_{14}NaO_5$ 299.0914/321.0733). Compound **4** had ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.94 (s, 3H, 5-OC**H**$_3$), 4.02 (s, 3H, 7-OC**H**$_3$), 5.39 (br s, 1H, O**H**), 6.46 (s, 1H, H-6), 6.66 (s, 1H, H-3), 7.48 (m, 3H, H-4′), 7.91 (m, 2H, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.5 (q, 7-O**C**H$_3$), 57.0 (q, 5-O**C**H$_3$), 92.5 (d, C-6), 108.4 (d, C-3), 109.2 (s, C-4a), 126.2 (2×d, C-2′, 6′), 128.0 (s, C-8), 129.1 (2×d, C-3′, 5′), 131.4 (d, C-4′), 131.6 (s, C-1′), 146.1 (s, C-8a), 150.0 (s, C-7), 153.3 (s, C-5), 160.9 (s, C-2), 178.1 (s, C-4); IR (KBr) ν_{max} 3482, 3205, 2930, 2848, 1640, 1610, 1580, 1510, 1495, 1450, 1438, 1399, 1341, 1303, 1247, 1208, 1125, 1109, 1042, 998, 956, 932, 857, 808, 767, 686, 671, 658, 548, 489 cm^{-1}; HRMS (+ve ESI) m/z

321.0719 $[M+Na]^+$ (calcd for $C_{17}H_{14}NaO_5$ 321.0733). Compound **5** had mp 204–206 °C (lit.[30] 206–207 °C); ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.02 (s, 6H, 5 and 7-OC**H**$_3$), 5.90 (br s, 1H, O**H**), 6.69 (s, 1H, H-8), 6.85 (s, 1H, H-3), 7.50 (m, 1H, H-4′), 7.51 (m, 2H, H-3′, 5′), 7.87 (ddm, J=8.0, 1.5 Hz, 2H, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.6 (q, 7-O**C**H$_3$), 62.7 (q, 5-O**C**H$_3$), 96.4 (d, C-3), 108.3 (d, C-8), 112.5 (s, C-4a), 126.1 (2×d, C-2′, 6′), 129.1 (2×d, C-3′, 5′), 131.4 (d, C-4′), 131.7 (s, C-1′), 136.8 (s, C-6), 144.1 (s, C-7), 152.2 (s, C-8a), 152.4 (s, C-5), 161.5 (s, C-2), 177.2 (s, C-4); IR (KBr) ν_{max} 3414, 3110, 3000, 2982, 2924, 1687, 16,359, 1602, 1497, 1469, 1454, 1436, 1425, 1361, 1332, 1304, 1279, 1264, 1221, 1201, 1157, 1089, 1041, 1029, 994, 948, 908, 883, 843, 815, 768, 728, 706, 687, 618, 562, 510, 485 cm^{-1}; HRMS (+ve ESI) m/z 321.0733 $[M+Na]^+$ (calcd for $C_{17}H_{14}NaO_5$ 321.0733). Compound **7**, a yellow solid, had mp 139–141 °C (from rectified spirit); ^1H NMR (500 MHz, $CDCl_3$) δ_H 3.24 (s, 3H, 6′-OC**H**$_3$), 3.81 (s, 3H, 4′-OC**H**$_3$), 4.72 (d, J=6.5 Hz, 1H, 2-O**H**), 5.79 (d, J=2.0 Hz, 1H, H-5′), 6.12 (d, J=2.0 Hz, 1H, H-3′), 6.14 (d, J=6.5 Hz, 1H, H-2), 7.53 (ddm, J=8.0, 7.5 Hz, 2H, H-3″, 5″), 7.62 (dddd, J=7.5, 7.5, 1, 1 Hz, 1H, H-4″), 8.11 (ddm, J=8, 1.5 Hz, 2H, H-2″, 6″), 13.05 (s, 1H, H-2′-O**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 55.3 (q, 6′-O**C**H$_3$), 55.9 (q, 4′-O**C**H$_3$), 76.6 (d, C-2), 91.3 (d, C-5′), 94.2 (d, C-3′), 103.8 (s, C-1′), 128.9 (2×d, C-3″, 5″), 129.1 (2×d, C-2″, 6″), 133.6 (d, C-4″), 135.4 (s, C-1″), 162.1 (s, C-6′), 167.6 (s, C-2′), 167.7 (s, C-4′), 194.2 (s, C-3), 198.2 (s, C-1); IR (KBr) ν_{max} 3414, 3068, 3007, 2976, 2946, 2854, 1687, 1628, 1605, 1580, 1466, 1449, 1436, 1423, 1391, 1331, 1304, 1279, 1221, 1205, 1182, 1157, 1112, 1089, 1002, 992, 956, 938, 840, 814, 789, 706, 675, 618, 571, 534, 448, 433 cm^{-1}; HRMS (+ve ESI) m/z 339.0850 $[M+Na]^+$ (calcd for $C_{17}H_{16}NaO_6$ 339.0839). Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.6; H, 5.1. Found: C, 64.4; H, 5.1%.

(b) Crude epoxide **2a** (prepared in Section 4.4.1.1 (b)) gave a mixture, which was separated by chromatography on silica gel (18 g). Elution with CH_2Cl_2/EtOAc; 17:3 gave **1h** (0.002 g, 1%), **7** (0.002 g, 1%) followed by **6** (0.028 g, 30%). Elution with CH_2Cl_2/EtOAc; 4:1 gave **3a** (0.020 g, 13%). Elution with CH_2Cl_2/EtOAc; 3:7 gave **1a** (0.014 g, 10%).

*4.5.2. 5,7-Diacetoxy-3-hydroxyflavone (**3b**).* Epoxide **2b** (0.510 g, 1.44 mmol) (method A) gave **3b** (0.450 g, 88%) as a yellow solid after recrystallisation from rectified spirit; mp 109–111 °C; ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.36 (s, 3H, C**H**$_3$COO), 2.47 (s, 3H, C**H**$_3$COO), 6.87 (d, J=2.0 Hz, 1H, H-6), 7.06 (s, 1H, O**H**), 7.38 (d, J=2.0 Hz, 1H, H-8), 7.47 (dm, J=7.5 Hz, 1H, H-4′), 7.52 (dm, J=7.5 Hz, 2H, H-3′, 5′), 8.19 (dd, J=1.5, 7.5 Hz, 2H, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.1 (q, **C**H$_3$COO), 21.3 (q, **C**H$_3$COO), 109.1 (d, C-8), 112.2 (s, C-4a), 113.1 (d, C-6), 127.7 (2×d, C-2′, 6′), 128.7 (2×d, C-3′, 5′), 130.6 (s, C-1′), 130.7 (d, C-4′), 138.7 (s, C-3), 144.4 (s, C-2), 149.9 (s, C-5), 154.1 (s, C-7), 156.7 (s, C-8a), 168.1 (s, CH$_3$**C**OO), 169.5 (s, CH$_3$**C**OO), 171.5 (s, C-4); IR (Nujol) ν_{max} 3310, 1772, 1629, 1614, 1410, 1226, 1214, 1186, 1148, 1123, 1073, 1022, 774, 693 cm^{-1}; HRMS (+ve ESI) m/z 355.0807 $[M+H]^+$ (calcd for $C_{19}H_{15}O_7$ 355.0812).Anal. Calcd for $C_{19}H_{14}O_7$: C, 64.4; H, 4.0. Found: C, 64.2; H, 4.0%.

*4.5.3. 5,7-Dibenzoyloxy-3-hydroxyflavone (**3c**).* Epoxide **2c** (0.060 g, 0.125 mmol) (method A) gave **3c** (0.055 g, 89%) as a yellow solid after recrystallisation from rectified spirit; mp 212–213 °C; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.03 (br s, 1H, O**H**), 7.16 (d, J=2.0 Hz, 1H, H-6), 7.48 (dd, J=7.0, 7.0 Hz, 1H, H-4′), 7.53 (dd, J=7.0, 7.0 Hz, 2H, H-3′, 5′), 7.56 (m, 2H, H-3″, 5″), 7.58 (d, J=2.0 Hz, 1H, H-8), 7.58 (m, 2H, H-3‴, 5‴), 7.67 (dd, J=7.5, 7.5 Hz, 1H, H-4‴), 7.69 (dd, J=7.5, 7.5 Hz, 1H, H-4″), 8.21 (d, J=7.0 Hz, 2H, H-2′, 6′), 8.22 (d, J=7.5 Hz, 2H, H-2″, 6″), 8.30 (d, J=7.5 Hz, 1H, H-2‴, 6‴); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 109.4 (d, C-8), 112.5 (s, C-4a), 113.6 (d, C-6), 127.7 (2×d, C-2′, 6′), 128.6 (s, C-1″), 128.7 (2×d, C-3′, 5′), 128.8 (d, C-3″, 5″), 128.9 (2×d, C-3‴, 5‴), 129.4 (s, C-1‴), 130.4 (d, C-4′), 130.5 (2×d, C-2″, 6″), 130.5 (d, C-2‴, 6‴), 130.6 (s, C-1′), 133.9 (d, C-4‴), 134.4 (d, C-4″), 138.8 (s, C-3), 144.4 (s, C-2), 150.2 (s, C-5), 154.5 (s, C-7), 156.8 (s, C-8a), 164.0 (s, Ph**C**″OO), 165.1 (s, Ph**C**‴OO), 171.5 (s, C-4); IR (thin film) ν_{max} 3305, 2924, 1739, 1616, 1451, 1241, 1149, 1054, 1021, 701, 688 cm^{-1}; HRMS (+ve ESI) m/z 479.1114 $[M+H]^+$ (calcd for $C_{29}H_{19}O_7$ 479.1125). Anal. Calcd for $C_{29}H_{18}O_7$: C, 72.8; H, 3.8. Found: C, 72.8; H, 3.9%.

*4.5.4. 3-Hydroxy-5-acetoxy-7-methoxyflavone (**3d**).* Crude epoxide derived from **1d** (0.305 g, 0.982 mmol), containing unchanged **1d** (ca. 10%) (method B) gave **3d** (0.180 g) after recrystallisation from chloroform. Chromatography of the mother liquors on silica gel (10 g, $CHCl_3$ elution) gave an additional portion of **3d** (0.033 g, overall yield 66%) along with unchanged starting material (**1d**) (0.025 g, 8%). Compound **3d**, yellow crystals, decomposed 170–180 °C and had ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.46 (s, 3H, C**H**$_3$COO), 3.92 (s, 3H, OC**H**$_3$), 6.64 (d, J=2.0 Hz, 1H, H-6), 6.87 (d, J=2.0 Hz, 1H, H-8), 7.44 (ddm, J=7.5, 7.5 Hz, 1H, H-4′), 7.51 (ddm, J=7.5, 7.5 Hz, 2H, H-3′, 5′), 8.17 (dm, J=7.5 Hz, 2H, H-2′, 6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.1 (q, **C**H$_3$COO), 56.0 (q, O**C**H$_3$), 98.4 (d, C-8), 108.4 (d, C-6), 108.5 (s, C-4a), 127.4 (2×d, C-2′, 6′), 128.6 (2×d, C-3′, 5′), 130.0 (d, C-4′), 130.8 (s, C-1′), 138.2 (s, C-3), 143.4 (s, C-2), 150.1 (s, C-8a), 158.0 (s, C-5), 163.7 (s, C-7), 169.6 (s, CH$_3$**C**OO), 171.3 (s, C-4); IR (KBr) ν_{max} 3301, 2975, 2846, 1769, 1623, 1603, 1573, 1559, 1497, 1454, 1417, 1374, 1288, 1259, 1229, 1207, 1160, 1120, 1088, 1070, 1040, 1010, 970, 892, 877, 839, 828, 772, 734, 722, 701, 693, 628, 620, 604, 591, 573, 552, 538, 488, 457, 419; HRMS (+ve ESI) m/z 349.0690 $[M+Na]^+$ (calcd for $C_{18}H_{14}NaO_6$ 349.0683). Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.3; H, 4.3. Found: C, 66.3; H, 4.3%.

*4.5.5. 7-Benzoyloxy-3-hydroxy-5-methoxyflavone (**3e**).* Crude epoxide derived from **1e** (0.302 g, 0.811 mmol) (method B) gave **3e** (0.202 g, 64%), a white solid, after recrystallisation from isopropyl alcohol; mp 184–185 °C; ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.04 (s, 3H, OC**H**$_3$), 6.70 (d, J=2.0 Hz, 1H, H-6), 7.14 (d, J=2.0 Hz, 1H, H-8), 7.38 (br s, 1H, O**H**), 7.45 (ddm, J=7.5, 7.5 Hz, 1H, H-4′), 7.52 (ddm, J=7.5, 7.5 Hz, 2H, H-3′, 5′), 7.56 (ddm, J=7.5, 7.5 Hz, 2H, H-3″, 5″), 7.68 (ddm, J=7.5, 7.5 Hz, 1H, H-4″), 8.15 (dm, J=7.5 Hz, 4H, H-2′, 6′, 2″, 6″); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.8 (q, O**C**H$_3$), 100.3 (d, C-6), 103.5 (d, C-8), 109.5 (s, C-4a), 127.4 (2×d, C-2′, 6′), 128.6 (2×d, C-3′, 5′), 128.8 (s, C-1″), 128.8 (d, C-3″, 5″), 130.0 (d, C-4′), 130.3 (d, C-2″, 6″), 130.8 (s, C-1′), 134.2 (d, C-4″), 138.7 (s, C-3), 142.8 (s, C-2), 155.3 (s, C-7), 157.7 (s, C-8a), 160.6 (s, C-5), 164.3 (s, Ph**C**OO), 172.3 (s, C-4); IR (KBr) ν_{max} 3455, 3059, 2942, 1743, 1615, 1484, 1465, 1450, 1437, 1402, 1363, 1322, 1245, 1220, 1202, 1148, 1076. 1061, 1026, 1008, 979, 877, 811, 803, 763, 706, 689, 622, 599, 550 cm^{-1}; HRMS (+ve ESI) m/z 389.1004/411.0825 $[M+H]^+/[M+Na]^+$ (calcd for $C_{23}H_{17}O_6$/$C_{23}H_{16}NaO_6$ 389.1020/411.0839). Anal. Calcd for $C_{23}H_{16}O_6$: C, 71.1; H, 4.2. Found: C, 71.0; H, 4.1%.

*4.5.6. 3-Hydroxy-7-acetoxy-5-methoxyflavone (**3f**).* Crude epoxide derived from (**1f**) (0.305 g, 0.982 mmol) (method B) gave **3f** (0.201 g) as pale yellow crystals, after recrystallisation from isopropyl alcohol. Chromatography of the mother liquors on silica gel (10 g, $CHCl_3$ elution) gave a further portion (0.029 g, overall yield 72%); mp 165–167 °C; ^1H NMR (500 MHz, $CDCl_3$) δ_H 2.35 (s, 3H, C**H**$_3$COO), 4.00 (s, 3H, OC**H**$_3$), 6.55 (d, 1H, J=2.0 Hz, H-6), 7.00 (d, J=2.0 Hz, 1H, H-8), 8.20 (dm, J=7.5 Hz, 2H, H-2′, 6′), 7.51 (ddm, J=7.5, 7.5 Hz, 2H, H-3′, 5′), 7.45 (ddm, J=7.5, 7.5 Hz, 1H, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 21.3 (q, **C**H$_3$CO), 56.7 (q, O**C**H$_3$), 100.2 (d, C-6), 103.3 (d, C-8), 109.5 (s, C-4a), 127.4 (2×d, C-2′, 6′), 128.6 (2×d, C-3′, 5′), 130.0 (d, C-4′), 130.8 (s, C-1′), 138.7 (s, C-3), 142.8 (s, C-2), 155.0 (s, C-7), 157.6 (s, C-8a), 160.6 (s, C-5), 168.4 (s, CH$_3$**C**OO), 172.3 (s, C-4); IR (KBr) ν_{max} 3195, 2944, 1760, 1649, 1626, 1574, 1481, 1460, 1442, 1405, 1366, 1225, 1146, 1130, 1099, 1075, 1033, 1005, 983, 899, 878, 825, 771, 707, 689 cm^{-1}; HRMS (+ve ESI) m/z 349.0673

$[M+Na]^+$ (calcd for $C_{18}H_{14}NaO_6$ 349.0683). Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.3; H, 4.3. Found: C, 66.5; H, 4.3%.

*4.5.7. 5-Benzoyloxy-3-hydroxy-7-methoxyflavone (**3i**).* Crude epoxide derived from **1i** (0.306 g, 0.822 mmol) (method B) gave **3i** (0.249 g, 78%), as pale yellow crystals, after recrystallisation from isopropyl alcohol; mp 169–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.95 (s, 3H, OC**H**$_3$), 6.78 (d, J=2.5 Hz, 1H, H-6), 6.92 (d, J=2.5 Hz, 1H, H-8), 7.02 (br s, 1H, H-O**H**), 7.37 (br t, J=7.5 Hz, 1H, H-4′), 7.44 (br t, J=7.5 Hz, 2H, H-3′, 5′), 7.55 (br t, J=8 Hz, 2H, H-3″, 5″), 7.60 (br t, J=8 Hz, 1H, H-4″), 8.18 (br d, J=8.0 Hz, 2H, H-2′, 6′), 8.26 (br d, J=8.0 Hz, 2H, H-2″, 6″); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 56.1 (q, O**C**H$_3$), 98.6 (d, C-8), 108.7 (d, C-6), 108.7 (s, C-4a), 127.5 (2×d, C-2′, 6′), 128.6 (2×d, C-3′, 5′), 128.8 (2×d, C-3″, 5″), 129.5 (s, C-1′), 130.0 (d, C-4′), 130.4 (2×d, C-2″, 6″), 130.9 (s, C-1″), 133.7 (d, C-4″), 138.3 (s, C-3), 143.4 (s, C-2), 150.4 (s, C-5), 158.1 (s, C-8a), 163.8 (s, C-7), 165.3 (s, Ph**C**OO), 171.3 (s, C-4); IR (KBr) ν_{max} 3313, 3061, 2974, 2938, 2840, 1742, 1627, 1574, 1497, 1451, 1431, 1412, 1374, 1316, 1294, 1260, 1222, 1197, 1159, 1093, 1071, 1049, 1034, 1020, 949, 877, 837, 767, 702, 630 cm^{-1}; HRMS (+ve ESI) m/z 411.080 $[M+Na]^+$ (calcd for $C_{23}H_{16}NaO_6$ 411.0839). Anal. Calcd for $C_{23}H_{16}O_6$: C, 71.1; H, 4.2. Found: C, 71.2; H, 4.2%.

*4.5.8. 5-Benzoyloxy-7-benzyloxy-3-hydroxyflavone (**3j**).* Crude epoxide derived from **1j** (0.030 g, 0.067 mmol) (method A) gave an oil, which on chromatography on silica gel (10 g, CH_2Cl_2 elution) gave **3j** (0.023 g, 73%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.21 (s, 2H, PhC**H**$_2$O), 6.87 (d, J=2.5 Hz, 1H, H-6), 7.02 (d, J=2.5 Hz, 1H, H-8), 7.02 (s, 1H, 3-O**H**), 7.40 (dm, J=7.0 Hz, 1H, H-4‴), 7.45 (dm, J=7.0 Hz, 4H, H-2‴, 3‴, 5‴, 6‴), 7.47 (dm, J=7.5 Hz, 1H, H-4′), 7.52 (dd, J=7.5, 7.5 Hz, 2H, H-3′, 5′), 7.56 (dd, J=7.5, 7.5 Hz, 2H, H-3″, 5″), 7.67 (dd, J=7.5, 7.5 Hz, 1H, H-4″), 8.18 (d, J=7.5 Hz, 2H, H-2′, 6′), 8.29 (d, J=7.5 Hz, 2H, H-2″, 6″); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 70.9 (t, Ph**C**H$_2$O), 99.6 (d, C-8), 108.9 (s, C-4a), 109.2 (d, C-6), 127.5 (2×d, C-2′, 6′), 127.7 (2×d, C-2‴, 6‴), 128.7 (3×d, C-3′, 4′, 5′), 128.8 (d, C-3‴, 5‴), 128.9 (d, C-3″, 5″), 129.6 (s, C-1′), 130.1 (d, C-4‴), 130.5 (2×d, C-2″, C-6″), 130.9 (s, C-1″), 133.7 (d, C-4″), 135.4 (s, C-1‴), 138.4 (s, C-3), 143.5 (s, C-2), 150.5 (s, C-5), 158.1 (s, C-8a), 162.9 (s, C-7), 165.3 (s, Ph**C**OO), 171.4 (s, C-4); IR (thin film) ν_{max} 3304, 2926, 1742, 1627, 1495, 1451, 1413, 1261, 1165, 1092, 1027, 702 cm^{-1}; HRMS (+ve ESI) m/z 465.1323 $[M+H]^+$ (calcd for $C_{29}H_{21}O_6$ 465.1333).

4.6. 2-Hydroxy-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-phenylpropane-1,3-dione (7)

A solution of epoxide **2a** (0.050 g, 0.168 mmol) in AR acetone (3 mL) was stirred with dil HCl (2 M, 1 mL) at room temperature for 18 h. The solvents were removed in vacuo at room temperature and the resulting material was chromatographed on silica (5 g). Elution with $CHCl_3$ gave hydroxydione **7** (0.032 g, 60%) followed by flavonol **3a** (0.013 g, 26%).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.11.076. ^{1}H and ^{13}C NMR data ($CDCl_3$) for the flavones starting materials used in this study. These data include MOL files and InChiKeys of the most important compounds described in this article.

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