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Novel reaction products from the hypervalent iodine oxidation of hydroxylated stilbenes and isoflavones

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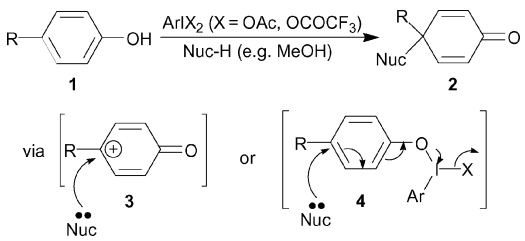
Novel reaction pathways for the hypervalent iodine-mediated oxidation of bioactive phenols containing extended conjugated π-systems are described. Oxidation of 4-hydroxystilbenes in methanol using a hypervalent iodine-based oxidant led to the formal 1,2-addition of methoxy groups across the central stilbene double bond. Treatment of the structurally related 4-hydroxyisoflavone with di(trifluoroacetoxy)iodobenzene leads to the surprising formation of 2,4′-dihydroxybenzil. Potential mechanisms for these new reaction pathways are discussed, and the X-ray crystal structure of 2,4′-dihydroxybenzil is presented. In contrast, oxidation of the corresponding 3-hydroxystilbenes and 3-hydroxyisoflavone led to conventional dienone oxidation products. The antitumour implications of these oxidation processes are briefly highlighted; the novel 4-substituted phenolic oxidation products were found to be inactive in terms of *in vitro* antitumour cellular activity, whereas the 3-substituted phenol products gave novel agents with potent and enhanced antitumour activity in the HCT 116 cancer cell line.

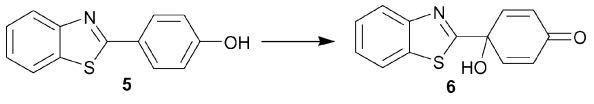
Introduction

The chemical oxidation of simple *para*-substituted phenols **1** to 4,4-disubstituted cyclohexa-2,5-dien-1-ones **2** using a variety of oxidising agents has previously been well-studied.[1] Reagents used to accomplish this transformation include hypervalent iodine oxidants such as diacetoxyiodobenzene (DAIB) and di(trifluoroacetoxy)iodobenzene (DTIB),[2] thallium(III) nitrate,[3] peracetic acid,[4] and electrochemical[5] and photooxidative[6] methods. However, the mechanistic details associated with this simple synthetic transformation remain to be fully elucidated, with the nature of the intermediate (**3** or **4**) dependent on the substituent group R (Scheme 1).



Scheme 1

Our research in this area has focussed on the hypervalent iodine oxidation of bioactive phenols,[7,8] which can give rise to novel products with interesting biological properties, exemplified by the oxidation of 2-(4-hydroxyphenyl)benzothiazole **5** to the experimental antitumour agent (**6**: AW 464) in a single step (Scheme 2).[9]



Scheme 2 *Reagents and conditions*: $PhI(OCOCF_3)_2$, TEMPO, CH_3CN–H_2O (9 : 1).

As part of our studies on the chemistry associated with antitumour phenolic (*E*)-stilbenes[10] and isoflavones,[11] we here report our findings on the unusual hypervalent iodine oxidation pathways undertaken by *para*-substituted phenols of these types, and the resulting novel products. The contrasting conventional oxidation products resulting from the chemical oxidation of the corresponding *meta*-substituted phenols are also presented here. The antitumour activity of these new chemical oxidation products has been studied in two human cancer cell lines.

Results and discussion

Use of fluorous hypervalent iodine oxidant

We have prepared previously a series of 4-hydroxystilbenes (exclusively as (*E*)-isomers) for the purposes of screening for antitumour (apoptosis-inducing) activity and examination of their oxidation chemistry mediated by hypervalent iodine-based reagents.[10] Surprisingly the hydroxylated stilbenes examined (R = H, F, OMe; where R substituents are on the non-hydroxylated ring) were found to be unreactive when treated with the most commonly used hypervalent iodine oxidants DAIB and DTIB in methanol under ambient conditions.

The initial lack of reactivity of 4-hydroxystilbenes was solved through the use of a more reactive "fluorous" oxidant, [bis(trifluoroacetoxy)]tridecafluoro-6-iodohexane **7**.[12] Literature methods for the preparation of this and related fluorous oxidants have previously made use of a 90% solution of hydrogen peroxide in order to prepare the trifluoroperacetic acid[13] required to oxidise commercially available perfluorohexyl iodide to the product. The potentially explosive nature of highly concentrated hydrogen peroxide means that such solutions are no longer available commercially, and methods to concentrate available solutions of lower concentration are hazardous. We therefore devised our own method for the preparation of **7** through the use of commercially available urea–hydrogen peroxide complex (UHP) in place of concentrated hydrogen peroxide solution.

The oxidation of perfluorohexyl iodide using the relatively stable UHP complex in a mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) affords the target oxidant

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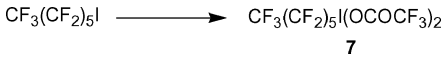


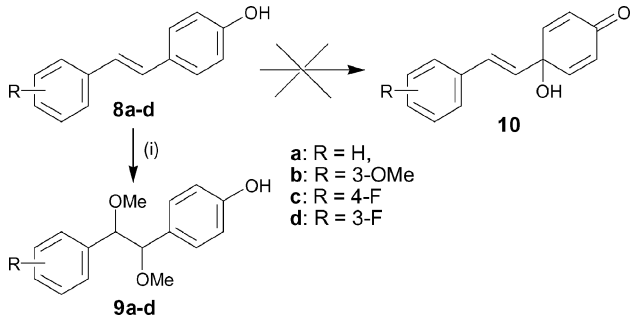
Scheme 3 *Reagents and conditions*: urea–H_2O_2 complex, $(CF_3CO)_2O$, CF_3CO_2H.

7 in a single step through generation of trifluoroperacetic acid *in situ* (Scheme 3). The use of UHP in this instance provides a good alternative to concentrated hydrogen peroxide; the complex is not only more stable and thus preferred from a safety perspective, but in addition avoids the use of water, which here would compromise the solubility of the perfluorinated substrate. However, special care needs to be taken in the order of addition of reagents; the exothermic addition of trifluoroacetic anhydride to a stirred suspension of urea–hydrogen peroxide complex in trifluoroacetic acid should be carried out slowly, keeping the reaction temperature below 0 °C, followed by dropwise addition of the perfluorohexyl iodide to form the required hypervalent oxidant **7**.

Oxidation of 4-hydroxy-(*E*)-stilbenes

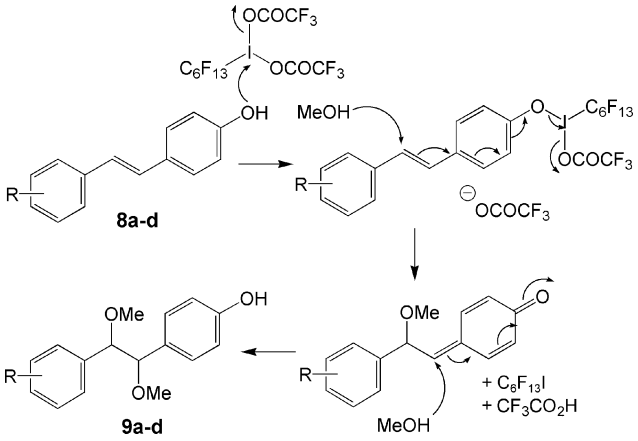
Our reasons for testing the fluorous oxidant **7** for oxidation studies on our 4-hydroxylated stilbenes were two-fold: firstly to provide a more reactive oxidant following the observed lack of reactivity using the more conventional hypervalent iodine oxidants DAIB and DTIB in methanol; and secondly to enable the easy removal of the oxidation reaction by-product tridecafluoro-6-iodohexane by fluorous extraction techniques, according to the principles established by Curran and co-workers.[14] This would avoid the normal chromatographic purification required to remove iodobenzene following conventional hypervalent iodine-mediated oxidation chemistry.

Oxidation of 4-hydroxystilbenes **8a–d** using the fluorous oxidant **7** proved to be experimentally very straightforward, as the perfluorohexyl iodide by-product (bp 140 °C) could be removed simply by evaporation *in vacuo*. However, ^{1}H NMR analysis of the resulting product revealed the rather surprising formal addition of methoxy groups across the central alkene bond to give the novel products **9a–d** (Scheme 4), as opposed to the formation of a hydroxycyclohexa-2,5-dienone **10**, as is the case with other 4-substituted phenols such as 2-(4-hydroxyphenyl)benzothiazole **5**. The 1,2-addition of methoxy groups across a stilbene double bond using hypervalent iodine-based reagents constitutes an unusual synthetic pathway; some literature precedent for the 1,2-addition of oxygen-bearing groups has previously been observed, for example in the formation of a 1,2-diacetate by-product from the manganese triacetate oxidative lactonisation of resveratrol analogues.[15]



Scheme 4 *Reagents and conditions*: (i) $C_6F_{13}I(OCOCF_3)_2$, MeOH.

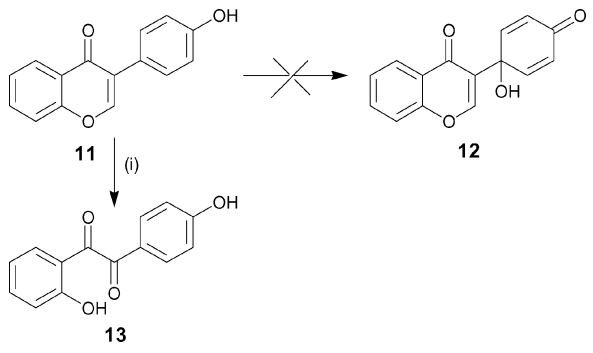
Oxidation of 4-hydroxystilbenes **8a–d** using oxidant **7** gave facile access to diaryl-1,2-dimethoxyethanes **9a–d** in moderate to good yields as mixtures of diastereoisomers (Scheme 4). Separation by column chromatography gave access to pure diastereoisomers as racemic mixtures. A possible mechanism to account for the unusual reaction pathway observed is presented in Scheme 5.



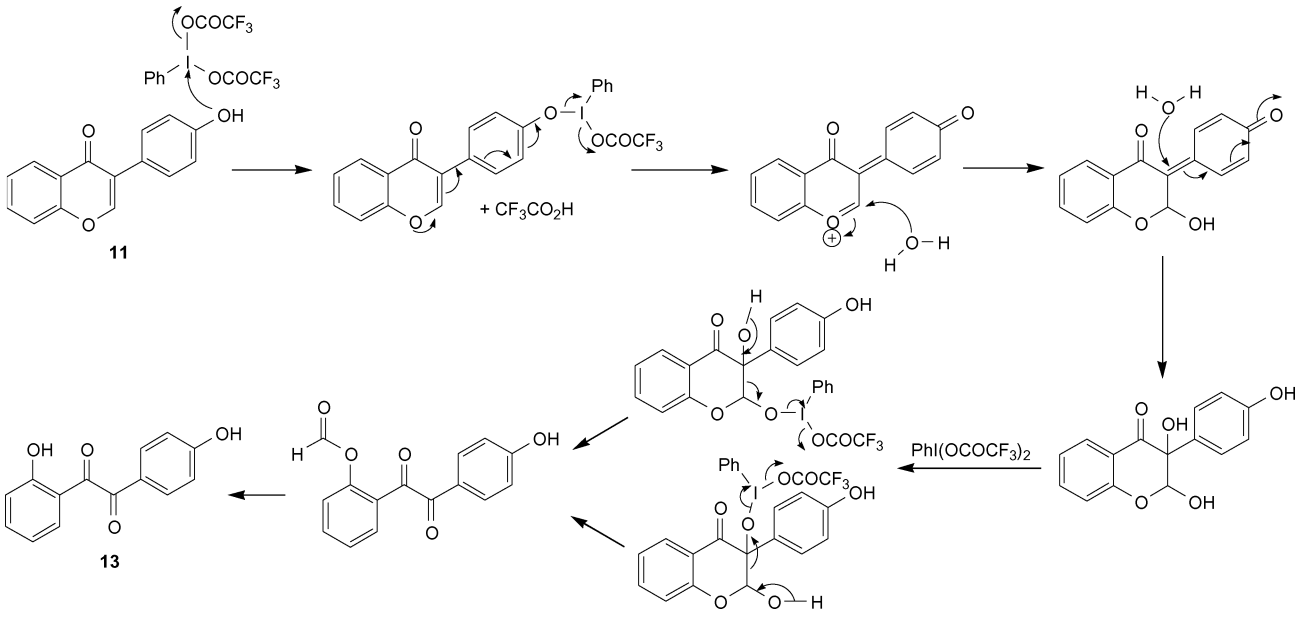
Scheme 5

Oxidation of 4-hydroxyisoflavone

Hydroxylated isoflavonoids of natural origin such as the soya-derived trihydroxylated isoflavone genistein are known to possess a range of biological properties, including anticancer potential.[16] Related chemistry within our group has focussed on the synthesis and application of novel isoflavones and derivatives as potential antitumour agents.[11] Since 4-hydroxyisoflavone **11** is structurally related (as a cyclic variant) to the 4-hydroxystilbenes **8a–d**, we were interested to explore the hypervalent iodine-mediated oxidation chemistry of **11**. However, unlike the 4-hydroxystilbenes, oxidation of 4-hydroxyisoflavone could be achieved under conditions analogous to those used for oxidation of 2-(4-hydroxyphenyl)benzothiazole **5** (DTIB and 2,2,6,6-tetramethylpiperidinyloxy free radical (TEMPO) in acetonitrile–water). Once again, oxidation to the corresponding hydroxycyclohexa-2,5-dienone **12** was not the observed reaction pathway; instead **11** was converted in 46% yield to the 2,4′-dihydroxybenzil **13** (Scheme 6). A possible reaction mechanism to account for the formation of the benzil product is proposed in Scheme 7. It is noteworthy that in the absence of TEMPO, the conversion of **11** to **13** occurs more slowly, and with the formation of significant by-products leading to a lower yield of product **13**. We speculate that TEMPO may in this instance be acting as a "quench" for radical by-products formed during the oxidation process, facilitating workup and isolation of **13** in moderate yield. The role of TEMPO in enhancing the yield of related phenolic oxidation processes has been previously observed.[17] However, the contribution of radical intermediates (not included in the postulated mechanism outlined in Scheme 7), cannot be discounted. The true role of TEMPO, itself a known co-oxidant in the hypervalent iodine oxidation of alcohols,[18] remains the subject of speculation.



Scheme 6 *Reagents and conditions*: (i) $PhI(OCOCF_3)_2$, TEMPO, CH_3CN–H_2O



Scheme 7

An X-ray crystal structure determination for the 2,4′-dihydroxybenzil **13** (Fig. 1[19]) confirms the disparate hydroxylation sites. The 2-hydroxy group forms the expected intramolecular hydrogen bond to the nearby carbonyl oxygen atom with an H · · · O hydrogen bond distance of 1.80 Å.

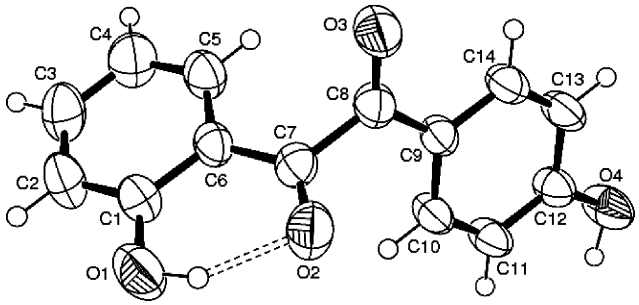


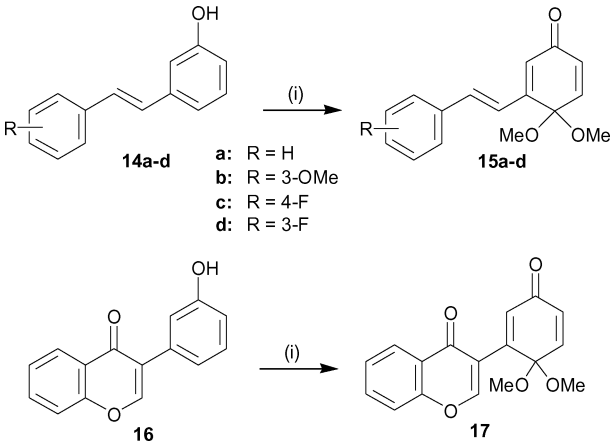
Fig. 1 ORTEP[19] drawing of the 2,4′-dihydroxybenzil molecule **13**. Displacement ellipsoids are drawn at the 50% level.

Oxidation of 3-hydroxy-(*E*)-stilbenes

We have previously reported our studies on the synthesis of novel dienone-based antitumour agents *via* the hypervalent iodine-mediated oxidation of 2-(3-hydroxyphenyl)benzothiazoles.[8] Chemical oxidation of a series of analogous 3-hydroxy-(*E*)-stilbenes **14a–d** (bearing substituents corresponding to the 4-hydroxy series **8a–d**) was achieved simply by treating the phenolic stilbenes with DAIB in methanol at ambient temperature. This simple oxidation process led to the expected substituted 4,4-dimethoxycyclohexa-2,5-dienone oxidation products **15a–d** in moderate yields (45–65%) following column chromatography (Scheme 8).

Oxidation of 3-hydroxyisoflavone

In contrast to the unusual reaction pathway undertaken by 4-hydroxyisoflavone **11**, the corresponding 3-hydroxyisoflavone **16** was found to undergo a conventional course of oxidation when treated with DAIB in methanol to give the isoflavone-substituted dienone **17** in 52% yield (Scheme 8). This expected reaction pathway was analogous to the chemical oxidation of 3-hydroxy-(*E*)-stilbenes.



Scheme 8 *Reagents and conditions*: (i) $PhI(OCOCH_3)_2$, MeOH.

In vitro antitumour activity

Our studies on the generation of novel oxidation products of bioactive phenols have been stimulated by the potential role of metabolic oxidation as a bioactivating event underpinning the biological mechanism of action of antitumour phenols.[9,20] For example, the observation that di- and tri-phenolic tyrphostins decompose in solution to more active protein tyrosine kinase inhibitors,[21] whereas tyrphostins devoid of hydroxyl groups have a rapid onset of cellular activity[22] is suggestive of bioactivation *via* metabolic oxidation.

We have tested the antiproliferative activity of both 4- and 3-hydroxystilbenes **8a–d** and **14a–d** plus their respective oxidation products **9a–d** and **15a–d** to further test the hypothesis that novel phenolic oxidation products can possess enhanced antitumour activity. The hydroxylated stilbenes and their oxidation products were examined in two human cancer cell lines *in vitro* – HCT 116 (colorectal) and MDA MB 468 (breast). The mean GI_{50} results (concentration required to inhibit growth by 50%) are presented in Table 1.

The 4- and 3-hydroxystilbene starting materials display moderate growth inhibitory activity in the two cell lines examined, and are markedly more active in the MDA MB 468 cell line.[10] Oxidation of 4-hydroxystilbenes **8a–d** to the 1,2-dimethoxyethane derivatives has a dramatic dyschemotherapeutic effect, and the resulting oxidation products **9a–d** display essentially no antiproliferative activity. On the other hand, oxidation of

Table 1 Cell growth inhibitory (GI_{50}) activity of substituted (*E*)-hydroxystilbenes and their oxidation products in HCT 116 and MDA MB 468 cell lines (tested in triplicate, mean values presented)

		GI_{50}/μM			GI_{50}/μM	
Phenol	R	HCT 116	MDA MB 468	Oxidation product	HCT 116	MDA MB 468
8a	H	39.6	13.0	**9a**	> 100	>100
8b	3-OMe	37.4	7.2	**9b**	> 100	>100
8c	4-F	21.0	8.1	**9c**	> 100	>100
8d	3-F	40.3	7.7	**9d**	> 100	>100
14a	H	57.4	7.8	**15a**	0.62	2.5
14b	3-OMe	62.0	3.1	**15b**	2.1	3.3
14c	4-F	58.0	4.7	**15c**	1.1	2.2
14d	3-F	44.2	2.1	**15d**	0.46	0.98

the corresponding 3-hydroxystilbenes **14a–d** produces dienone products **15a–d** with greatly enhanced activity in the colon HCT 116 cell line (around 30–100-fold enhancement). However, no significant increase in antiproliferative activity is seen in the MDA MB 468 cell line. Preliminary findings concerning the *in vitro* antitumour activity of hydroxylated isoflavones and their oxidation products are not indicative of enhancement of activity following chemical oxidation (results not shown).

Conclusions

In conclusion, we have demonstrated in this report that hypervalent iodine-mediated oxidation of bioactive phenols such as simple hydroxylated stilbenes and isoflavones can lead to novel and interesting reaction pathways and products. Further studies in this area will help to clarify the rules governing reaction pathways for phenolic compounds with extended conjugated π-electron systems using hypervalent iodine-based oxidants, and should shed light on the mechanistic details underpinning this interesting and novel chemistry. We have further tested our hypothesis that phenolic oxidation can lead to novel products with enhanced antitumour activity. In this case the non-conventional oxidation products **9a–d** from 4-hydroxystilbenes were inactive in the models examined; whereas the conventional hypervalent iodine-mediated 3-hydroxystilbene oxidation products **15a–d** displayed potent (low to submicromolar) activity in the colon-derived HCT 116 cell line. Further studies concerning the antitumour potential of dienone products **15a–d** will be reported in due course.

Experimental

Commercial reagents and solvents were used as received, unless otherwise specified. Melting points were recorded on a Gallenkamp melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer in solvents as specified, with tetramethylsilane as internal standard. Low resolution mass spectra were recorded on a Micromass Platform (AP^+, ES^+). High resolution mass spectrometry (HRMS) was carried out by the services provided by the School of Chemistry, University of Nottingham and EPSRC National Mass Spectrometry Service Centre, Swansea, UK. Silica gel TLC was performed on 60F–254 pre-coated sheets (Merck). Elemental analyses were carried out by the microanalysis service, School of Chemistry, University of Nottingham. X-Ray diffraction data were collected on an Enraf-Nonius CAD4 diffractometer (Mo–Kα irradiation at 293 K). The structure was solved by direct methods and refined by full-matrix least squares.

[Bis(trifluoroacetoxy)]tridecafluoro-6-iodohexane (7)

Trifluoroacetic anhydride (4.2 mL, 30 mmol) was added very slowly to a stirred suspension of urea–hydrogen peroxide complex (2.82 g, 30 mmol) in TFA (60 mL) at −5 °C, maintaining the temperature of the solution below 0 °C throughout the addition (**Caution**: the reaction is exothermic and potentially explosive). Stirring was continued at this temperature for 30 min. Perfluorohexyl iodide (6.48 mL, 30 mmol) was then added dropwise, with continuous stirring. The reaction mixture was left to stir at 0 °C for 2 h, then allowed to reach room temperature and left overnight. The excess TFA was removed *in vacuo* to give **7**[12] (28.2 mmol, 94%) as a white solid, mp 67 °C (decomposition); δ_F (CD_3OD) −77.8 (6F, m, 2 × $OCOCF_3$), −81.3 (2F, m, CF_2I), −82.8 (3F, m, CF_3), −117.0 (2F, m, CF_2), −123.1 (2F, m, CF_2), −124.11 (2F, m, CF_2), −127.7 (2F, m, CF_2); IR ν/cm^{-1} 1744 (C=O). *m*/*z* 673 ($M^+ + 1$).

General method for the oxidation of substituted 4-hydroxy-(*E*)-stilbenes

The substituted 4-hydroxy-(*E*)-stilbene **8a–d** (3.0 mmol) was dissolved in methanol. [Bis(trifluoroacetoxy)]tridecafluoro-6-iodohexane **7** was added as one portion at room temperature, and the mixture was left to stir for 10 min. The solution was concentrated *in vacuo*, to give the oxidation product as a mixture of diastereoisomers. Purification by flash column chromatography (hexane–EtOAc 80 : 20) afforded pure diastereoisomers as crystalline white solid products.

1-(4-Hydroxyphenyl)-1,2-dimethoxy-2-phenylethane (9a).

Fraction 1. Yield 34%; mp 144–146 °C; δ_H ($CDCl_3$) 7.27 (3H, m, ArH), 7.17 (2H, m, ArH), 7.04 (2H, d, *J* 8.5 Hz, ArH), 6.75 (2H, d, *J* 8.5 Hz, ArH), 4.98 (1H, s, ArOH), 4.31 (1H, d, *J* 5.5 Hz, ArCHOMe), 4.26 (1H, d, *J* 5.5 Hz, ArCHOMe), 3.16 (3H, s, OCH_3), 3.14 (3H, s, OCH_3). δ_C (CD_3OD) δ 158.5 (COH), 139.9 (ArC), 130.6 (ArCH), 130.3 (ArC), 129.5 (ArCH), 129.3 (ArCH), 129.1 (ArCH), 116.1 (ArCH), 89.5 (CHOMe), 89.0 (CHOMe), 57.5 (OCH_3), 57.2 (OCH_3). IR ν/cm^{-1} 3274 (OH), 2964 (CH), 2834 (CH), 1267, 1117, 1091; *m*/*z* (EI) 259 ($M^+ + 1$), 227 ($M^+ - OMe$). Anal. ($C_{16}H_{18}O_3$) %C: calcd 74.40, found 74.06; %H: calcd 7.02, found 6.80.

Fraction 2. Yield 29%; mp 165–167 °C; δ_H ($CDCl_3$) 7.30 (3H, m, ArH), 7.18 (2H, m, ArH), 7.09 (2H, d, *J* 8.5 Hz, ArH), 6.77 (2H, d, *J* 8.5 Hz, ArH), 5.37 (1H, s, ArOH), 4.28 (1H, d, *J* 7.7 Hz, ArCHOMe), 4.26 (1H, d, *J* 7.7 Hz, ArCHOMe), 3.25 (3H, s, OCH_3), 3.23 (3H, s, OCH_3); IR ν/cm^{-1} 3397 (OH), 2898 (CH), 2847 (CH), 1284, 1125, 1054; *m*/*z* (EI) 259 ($M^+ + 1$), 227 ($M^+ - OMe$). Accurate *m*/*z* (ES−) found: 257.1170; $C_{16}H_{18}O_3$ requires 257.1178.

1-(4-Hydroxyphenyl)-1,2-dimethoxy-2-(3-methoxyphenyl)ethane (9b).

Fraction 1. Yield 19%; mp 85 °C; δ_H ($CDCl_3$) 7.22 (1H, t, *J* 8.0 Hz, ArH), 7.08 (2H, d, *J* 8.5 Hz, ArH), 6.86 (5H, m, ArH), 6.59 (1H, s, ArOH), 4.39 (1H, d, *J* 5.5 Hz, ArCHOMe), 4.31 (1H, d, *J* 5.5 Hz, ArCHOMe), 3.75 (3H, s, $ArOCH_3$), 3.20 (3H, s, OCH_3), 3.18 (3H, s, OCH_3); IR ν/cm^{-1} 3347 (OH), 2944 (CH), 2826 (CH), 1272, 1226, 1161, 1091; *m*/*z* (EI) 288 ($M^+ + 1$). Anal. ($C_{17}H_{20}O_4$) %C: calcd 70.81, found 70.45; %H: calc 6.99, found 6.96.

Fraction 2. Yield 28%; mp 160 °C; δ_H ($CDCl_3$) 7.10 (1H, t, *J* 8.2 Hz, ArH), 6.93 (2H, d, *J* 8.5 Hz, ArH), 6.71 (5H, m, ArH), 5.19 (1H, s, ArOH), 4.27 (2H, s, 2 × ArCHOMe), 3.72 (3H, s, $ArOCH_3$), 3.29 (3H, s, OCH_3), 3.27 (3H, s, OCH_3); IR ν/cm^{-1} 3277 (OH), 2990 (CH), 2872 (CH), 1281, 1214, 1083, 1050; *m*/*z* (EI) 288 ($M^+ + 1$). Accurate *m*/*z* (ES−) found: 287.1302; $C_{17}H_{20}O_4$ requires 287.1284.

1-(4-Hydroxyphenyl)-1,2-dimethoxy-2-(4-fluorophenyl)ethane (9c).

Fraction 1. Yield 31%; mp 139–140 °C; δ_H ($CDCl_3$) 7.15 (2H, m, ArH), 7.02 (4H, m, ArH), 6.75 (2H, d, *J* 8.5 Hz, ArH), 5.69 (1H, s, ArOH), 4.34 (1H, d, *J* 5.3 Hz, ArCHOMe), 4.29 (1H, d, *J* 5.3 Hz, ArCHOMe), 3.19 (3H, s, OCH_3), 3.17 (3H, s, OCH_3); IR ν/cm^{-1} 3359 (OH), 2940 (CH), 2828 (CH), 1337 (C–F), 1218, 1104, 1013; *m*/*z* (EI) 277 ($M^+ + 1$). Anal. ($C_{16}H_{17}FO_3$) %C: calcd 69.55, found 69.53; %H: calc 6.20, found 6.31.

Fraction 2. Yield 28%; mp 166 °C; δ_H ($CDCl_3$) 7.01 (3H, m, ArH), 6.86 (3H, m, ArH), 6.70 (2H, d, *J* 8.6 Hz, ArH), 5.28 (1H, s, ArOH), 4.32 (1H, d, *J* 7.7 Hz, ArCHOMe), 4.26 (1H, d, *J* 7.7 Hz, ArCHOMe), 3.27 (3H, s, OCH_3), 3.26 (3H, s, OCH_3); IR ν/cm^{-1} 3271 (OH), 2901 (CH), 2872 (CH), 1358 (C–F), 1231, 1083, 1062; *m*/*z* (EI) 277 ($M^+ + 1$). Accurate *m*/*z* (ES−) found: 275.1073; $C_{16}H_{17}FO_3$ requires 275.1084.

1-(-Hydroxyphenyl)-1,2-dimethoxy-2-(3-fluorophenyl)ethane (9d).

Fraction 1. Yield 31%; mp 122–123 °C; δ_H ($CDCl_3$) 7.27 (1H, m, ArH), 7.04 (2H, d, *J* 8.5 Hz, ArH), 6.92 (3H, m, ArH), 6.76 (2H, d, *J* 8.5 Hz, ArH), 4.74 (1H, s, ArOH), 4.29 (1H, d, *J* 5.5 Hz, ArCHOMe), 4.25 (1H, d, *J* 5.5 Hz, ArCHOMe), 3.19 (3H, s, OCH_3), 3.16 (3H, s, OCH_3); IR ν/cm^{-1} 3381 (OH), 2935 (CH), 2886 (CH), 1332 (C–F), 1251, 1097; *m*/*z* (EI) 277 ($M^+ + 1$). Anal. ($C_{16}H_{17}FO_3$) %C: calcd 69.55, found 69.71; %H: calcd 6.20, found 6.40.

Fraction 2. Yield 34%; mp 178 °C; δ_H ($CDCl_3$) 7.14 (1H, m, ArH), 6.90 (2H, d, *J* 8.5 Hz, ArH), 6.79 (3H, m, ArH), 6.67 (2H, d, *J* 8.5 Hz, ArH), 4.73 (1H, s, ArOH), 4.30 (1H, d, *J* 5.2 Hz, ArCHOMe), 4.25 (1H, d, *J* 5.2 Hz, ArCHOMe), 3.29 (3H, s, OCH_3), 3.26 (3H, s, OCH_3); IR ν/cm^{-1} 3254 (OH), 2938 (CH), 2794 (CH), 1358 (C–F), 1276, 1215, 1117; *m*/*z* (EI) 277 ($M^+ + 1$). Accurate *m*/*z* (ES−) found: 275.1108; $C_{16}H_{17}FO_3$ requires 275.1084.

2,4′-Dihydroxybenzil (13). A solution of DTIB (0.65 g, 1.50 mmol) in acetonitrile (5 mL) was added slowly to a stirred suspension of TEMPO (0.031 g, 0.20 mmol) and 3-(4-hydroxyphenyl)-4*H*-1-benzopyranone **11** (0.238 g, 1.00 mmol) in a 1 : 1 mixture of acetonitrile and water (40 mL). The solution volume was immediately reduced *in vacuo* to approximately 20 mL, then water (50 mL) and ethyl acetate (50 mL) were added. The organic phase was separated and washed with saturated aqueous potassium carbonate (50 mL). The aqueous layer was then neutralised using 1 M HCl and extracted using 20% MeOH–CH_2Cl_2 (2 × 200 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised from methanol to give 2,4′-dihydroxybenzil (0.167 g, 46%) as a yellow solid, mp 160–163 °C; δ_H ($CDCl_3$) 11.44 (1H, s, ArOH), 7.92 (1H, d, *J* 10.0 Hz, ArH, 7.52 (2H, m, ArH), 7.14 (1H, m, ArH), 6.93 (3H, m, ArH), 5.75 (1H, br s, ArOH); δ_C ($CDCl_3$) 200.0 (C=O), 191.2 (C=O), 163.8 (ArC), 162.5 (ArC), 138.5 (ArCH), 133.5 (ArCH), 133.0 (ArCH), 126.3 (ArC), 120.1 (ArCH), 119.1 (ArCH), 117.1 (ArC), 116.4 (ArCH); IR ν/cm^{-1} 3369 (OH), 1629 (C=O), 1599, 1575, 1514, 1485, 1452; *m*/*z* (EI) 242 (M^+). Accurate *m*/*z* (ES−) found: 242.0571; $C_{14}H_{10}O_4$ requires 242.0579.

Crystal data. Compound **13**. $C_{14}H_{10}O_4$, M = 242.22, monoclinic, a = 17.771(5) Å, b = 10.833(2) Å, c = 15.115(4) Å, β = 124.564(18)°, U = 2396.3(10) Å^3, T = 293(2) K, space group $C2/c$, Z = 8, μ(MoKα) = 0.71073 mm^{-1}, 4305 reflections measured, 1456 unique (R_{int} = 0.0610) which were used in all calculations. The final $R1$ and $wR2$ were 0.0435 and 0.1113 (for $I > 2\sigma(I)$), and 0.0700 and 0.1268 (for all data).

CCDC reference number 279000. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b510240e.

General method for the oxidation of substituted 3-hydroxy-(*E*)-stilbenes

The substituted 3-hydroxy-(*E*)-stilbene **14a–d** (1 mmol) was dissolved in methanol. Diacetoxyiodobenzene (3 mmol) was added as one portion at room temperature, and the mixture was left to stir for 10 min. The solvent was then removed *in vacuo* and the residue purified by flash chromatography ($CHCl_3$) to afford the product **15a–d** as a pale yellow to orange oil.

4,4-Dimethoxy-3-styrylcyclohexa-2,5-dien-1-one (15a). Orange oil. Yield 65%. ^{1}H NMR ($CDCl_3$) δ 7.60 (1H, d, *J* 16.0 Hz, CH=CH), 7.54 (2H, m, ArH), 7.35 (3H, m, ArH), 6.88 (1H, d, *J* 16.0 Hz, CH=CH), 6.71 (1H, d, *J* 10.0 Hz, H-2), 6.54 (1H, d, *J* 1.6 Hz, H-3), 6.50 (1H, dd, *J* 10.0, 1.6 Hz, H-1), 3.23 (6H, s, 2 × OMe); ^{13}C NMR (CD_3OD) δ 185.5 (C=O), 151.8, 144.2, 137.7, 136.2, 132.4, 129.3 (×2), 128.8, 128.3, 127.5 (×2), 122.8, 96.3 ($C^q(OCH_3)_2$), 51.3 (2 × OCH_3); IR ν/cm^{-1} 1668 (C=O), 1584 (aromatic C=C), 1291 (C–O), 1107 (C–O), 967 (*trans* C=C). Accurate *m*/*z* (ES−) found 256.1106; $C_{16}H_{16}O_3$ requires 256.1099. Anal. ($C_{16}H_{16}O_3$) %C: calcd 74.98, found 75.35; %H: calcd 6.29, found 6.36.

4,4-Dimethoxy-3-[2-(3-methoxyphenyl)vinyl]cyclohexa-2,5-dien-1-one (15b). Yellow oil. Yield 45%. ^{1}H NMR ($CDCl_3$) δ 7.59 (1H, d, *J* 16.35 Hz, CH=CH), 7.28 (1H, t, *J* 8.0 Hz, ArH), 7.18 (1H, d, *J* 7.7 Hz, ArH), 7.08 (1H, m, ArH), 6.95 (1H, m, ArH), 6.88 (1H, d, *J* 16.35 Hz, CH=CH), 6.73 (1H, d, *J* 10.2 Hz, H-2), 6.56 (1H, d, *J* 1.95 Hz, H-3), 6.51 (1H, dd, *J* 10.2, 1.9 Hz, H-1), 3.86 (3H, s, OMe), 3.26 (6H, s, 2 × OMe); ^{13}C NMR (CD_3OD) δ 185.4 (C=O), 159.8, 151.7, 144.1, 137.6, 137.4, 132.3, 129.7, 127.6, 123.0, 120.1, 115.2, 112.3, 96.3 ($C^q(OCH_3)_2$), 55.2 (OCH_3), 51.2 (2 × OCH_3); IR ν/cm^{-1} 1664 (C=O), 1575 (C=C), 1215 (C–O), 1108 (C–O), 973 (*trans* C=C). Accurate *m*/*z* (ES−) found 286.1209; $C_{17}H_{18}O_4$ requires 286.1205.

4,4-Dimethoxy-3-[2-(4-fluorophenyl)vinyl]cyclohexa-2,5-dien-1-one (15c). Orange oil. Yield 54%. ^{1}H NMR ($CDCl_3$) δ 7.56 (1H, d, *J* 16.0 Hz, CH=CH), 7.53 (2H, m, ArH), 7.10 (2H, t, *J* 8.1 Hz, ArH), 6.78 (1H, d, *J* 17.0 Hz, CH=CH), 6.71 (1H, d, *J* 10.0 Hz, H-2), 6.52 (1H, d, *J* 2.0 Hz, H-3), 6.50 (1H, dd, *J* 10.0, 2.0 Hz, H-1), 3.23 (6H, s, 2 × OMe); ^{13}C NMR (CD_3OD) δ 185.9 (C=O), 162.0 (1C, d, *J* 239.3 Hz), 152.1, 144.5, 136.9, 132.8, 129.7 (2C, d, *J* 8.2 Hz), 127.9, 116.4 (2C, d, *J* 21.8 Hz), 96.7 ($C^q(OCH_3)_2$), 51.7 (2 × OCH_3); IR ν/cm^{-1} 1666 (C=O), 1582 (aromatic C=C), 1215 (C–O), 978 (*trans* C=C). Accurate *m*/*z* (ES−) found 274.1009; $C_{16}H_{15}FO_3$ requires 274.1005.

4,4-Dimethoxy-3-[2-(3-fluorophenyl)vinyl]cyclohexa-2,5-dien-1-one (15d). Orange oil. Yield 54%. ^{1}H NMR ($CDCl_3$) δ 7.55 (1H, d, *J* 16.3 Hz, CH=CH), 7.35 (3H, m, ArH), 7.06 (1H, m, ArH), 6.86 (1H, d, *J* 16.3 Hz, CH=CH), 6.74 (1H, d, *J* 10.2 Hz, H-2), 6.54 (1H, d, *J* 1.8 Hz, H-3), 6.50 (1H, dd, *J* 10.2, 1.8 Hz, H-1), 3.26 (6H, s, 2 × OMe); ^{13}C NMR (CD_3OD) δ 185.4 (C=O), 165.0 (1C, d, *J* 246.1 Hz), 151.4, 144.1, 138.7 (1C, d, *J* 8.0 Hz), 136.4 (1C, d, *J* 2.7 Hz), 132.4, 130.3 (1C, d, *J* 8.3 Hz), 128.1, 124.1, 123.5 (1C, d, *J* 2.7 Hz), 116.2 (1C, d, *J* 21.4 Hz), 113.8 (1C, d, *J* 21.9 Hz), 96.4 ($C^q(OCH_3)_2$), 51.3 (2 × OCH_3); IR ν/cm^{-1} 1664 (C=O), 1582 (aromatic C=C), 1106 (C–O), 979 (*trans* C=C). Accurate *m*/*z* (ES−) found 274.1008; $C_{16}H_{15}FO_3$ requires 274.1005.

3-(6,6-Dimethoxy-3-oxocyclohexa-1,4-dienyl-4*H*-1-benzopyran-4-one (17). A solution of bis(trifluoroacetoxy)iodobenzene (0.13 g, 0.30 mmol) in methanol (1 mL) was added dropwise to a solution of 3-hydroxyisoflavone **16** (0.05 g, 0.21 mmol) in methanol (10 mL). The solution was then concentrated *in*

vacuo and the residue partitioned between dichloromethane (20 mL) and saturated aqueous potassium carbonate (20 mL). The separated organic layer was washed with water (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (15 : 85 hexane–ethyl acetate) to give the dienone product **17** (0.031 g, 52%) as a pale yellow solid, mp 167–170 °C; δ_H ($CDCl_3$) 9.00 (1H, s, H-2), 8.29 (1H, dd, *J* 8.0, 1.6 Hz, ArH), 7.71 (2H, m, ArH and C=CH), 7.49 (2H, m, ArH), 6.73 (1H, d, *J* 10.0 Hz, HC=CH), 6.54 (1H, dd, *J* 10.0, 2.0 Hz, HC=CH), 3.27 (6H, s, OCH_3); IR ν/cm^{-1} 1728 (C=O), 1672 (C=O), 1647, 1617, 1565, 1266; *m*/*z* (EI) 298 (M^+). Anal. ($C_{17}H_{14}O_5$) %C: calcd 68.45, found 68.12; %H: calcd 4.73, found 5.10.

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