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# Aspects of the Algar-Flynn-Oyamada (AFO) Reaction

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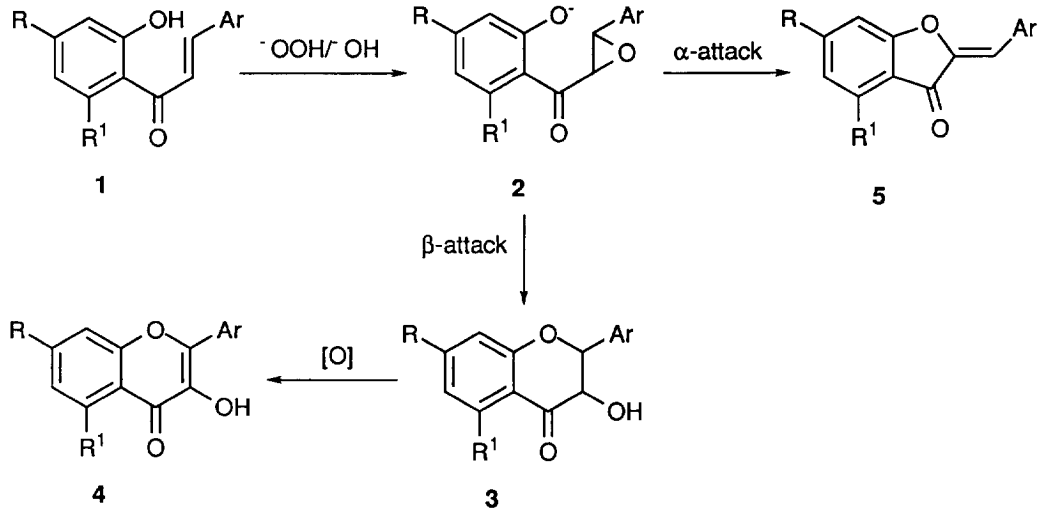
***Abstract:*** The oxidation of 2'-hydroxychalcones **1** with alkaline hydrogen peroxide, commonly known as the Algar, Flynn and Oyamada (AFO) reaction is a convenient method for the synthesis of 2-aryl-3-hydroxy-4H-1-benzopyran-4-ones (flavonols), 2-aryl-2,3-dihydro-3-hydroxy-4H-1-benzopyran-4-ones (2,3-dihydroflavonols), 2-arylidenebenzo[b]furan-3(2H)-ones (aurones) and other flavonoid compounds. Oxidation of substrates bearing a 6'-substituent was initially believed to proceed through an epoxide intermediate, giving aurones or benzofuran-3(2H)-one derivatives as the chief reaction products. This was disputed when it was observed that AFO oxidation of (Z)-2'-hydroxy-α,4',6'-trimethoxychalcone gave the *erythro*-α-methoxybenzofuran-3-one **7** (Scheme 3) instead of the *threo*-isomer, which is expected if an epoxide were an intermediate. Evidence to suggest that an epoxide can be an intermediate in this reaction when 2'-hydroxy-6'-substituted substrates are employed, is described herein. Copyright © 1996 Elsevier Science Ltd

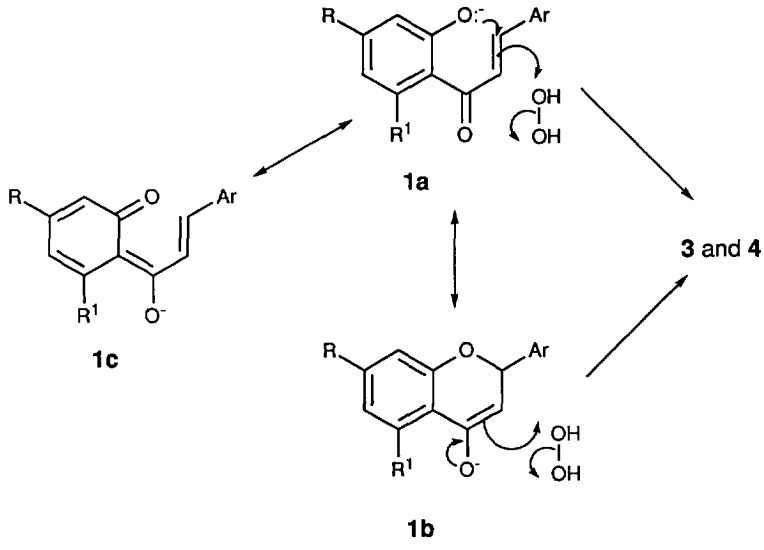
The most frequently used method for the synthesis of 2-aryl-3-hydroxy-4H-1-benzopyran-4-ones (flavonols)(*e.g.* **4** ) is by the alkaline hydrogen peroxide oxidation of 2'-hydroxychalcones (*e.g.***1**, Scheme 1), known as the Algar, Flynn and Oyamada (AFO) reaction.[2] The products found in AFO




**Scheme 1**

reactions are 2-aryl-2,3-dihydro-3-hydroxy-4H-1-benzopyran-4-ones (dihydroflavonols) (*e.g.* **3**), 2-arylidenebenzo[b]furan-3(2H)-ones (aurones) (*e.g.* **5**) (mainly from 2'-hydroxy-6'-substituted chalcones), 2-benzyl-2-hydroxybenzo[b]furan-3(2H)-ones, and 2-arylbenzo[b]furan-3-carboxylic acids.[3] It was originally presumed[4] that epoxides (*e.g.***2**) were intermediates in these reactions, which proceeded by the intramolecular displacement of the oxirane oxygen by the phenoxide at the β-position to give dihydroflavonols, and subsequently flavonols, or at the α-position to give aurones (Scheme 1).

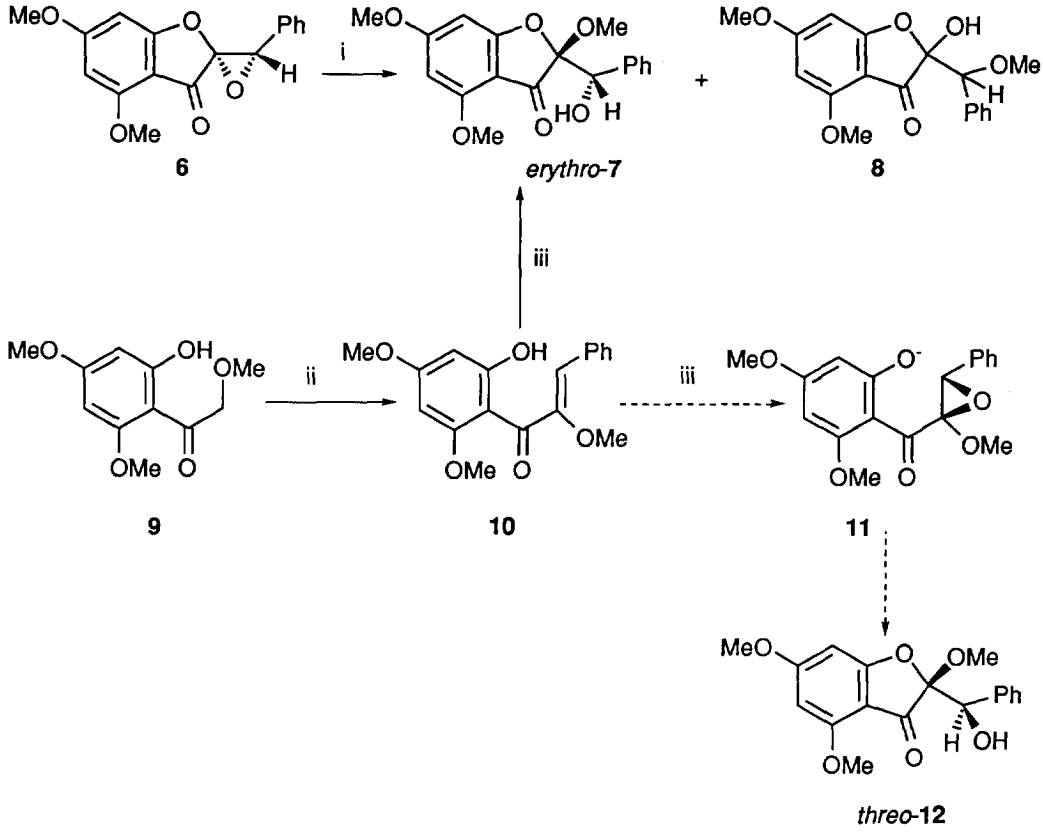
Dean and Podimuang[5] in the course of an investigation into the mechanism of the AFO reaction concluded that epoxides were not intermediates in the formation of dihydroflavonols and flavonols because the strongly alkaline conditions of the reaction convert phenolic chalcones into anions **1a, 1b** (Scheme 2) and, consequently, coulombic repulsion of the hydroperoxide anion as well as internal electronic inactivation towards the addition of hydroperoxide anion, would prevent the formation of epoxides. These authors proposed possible alternative mechanisms as delineated in Scheme 2. However, they argued that inactivation of the chalcone derivative, as depicted in **1b** is prevented in the case of 6'-substituted




**Scheme 2**

chalcones, because this substituent sterically inhibits the carbonyl group from attaining coplanarity with the phenolic ring, and epoxide formation is therefore possible. Consequently, they retained the postulated intermediacy of chalcone epoxides in the case of the formation of aurones and benzofuran-3(2H)-one derivatives from 6'-substituted-2'-hydroxychalcones, at 0°C to ambient temperatures.

This conclusion was subsequently questioned,[6,7] when Brady *et al.*[6] found that acid catalysed methanolysis of the aurone epoxide **6** (Scheme 3) gave the *erythro*[8]-α-methoxy derivative **7** (as the minor product) which was also obtained in 80% yield by the alkaline hydrogen peroxide oxidation of 2'-hydroxy-α,4',6'-trimethoxychalcone **10**.[7] The major product of the former reaction was the α–hydroxy-β-methoxy compound **8**, present in solution as a mixture of ring-chain tautomers.[9] The *erythro*-configuration of the benzofuranone **7** was assigned[6] on the basis of the known stereochemistry of the aurone epoxide **6** and on the mode of opening ($S_N2$ 'borderline') of the oxirane ring.[6,10] The Z-configuration of the chalcone **10** was assigned on the basis of the operation of "overlap control"[11] in such reactions. This agrees with the observation by Fischer and Arlt[12] that chalcones produced in such condensation reactions always had the configuration in which the carbonyl and the β-aryl groups were in a *trans* orientation to each other. Subsequently, Volsteedt *et al.* [13] presented experimental evidence for the *trans*-configuration of α,2',4,4',6'-pentamethoxychalcone, prepared from α,2,4,6-tetramethoxyacetophenone on condensation with anisaldehyde under basic conditions.

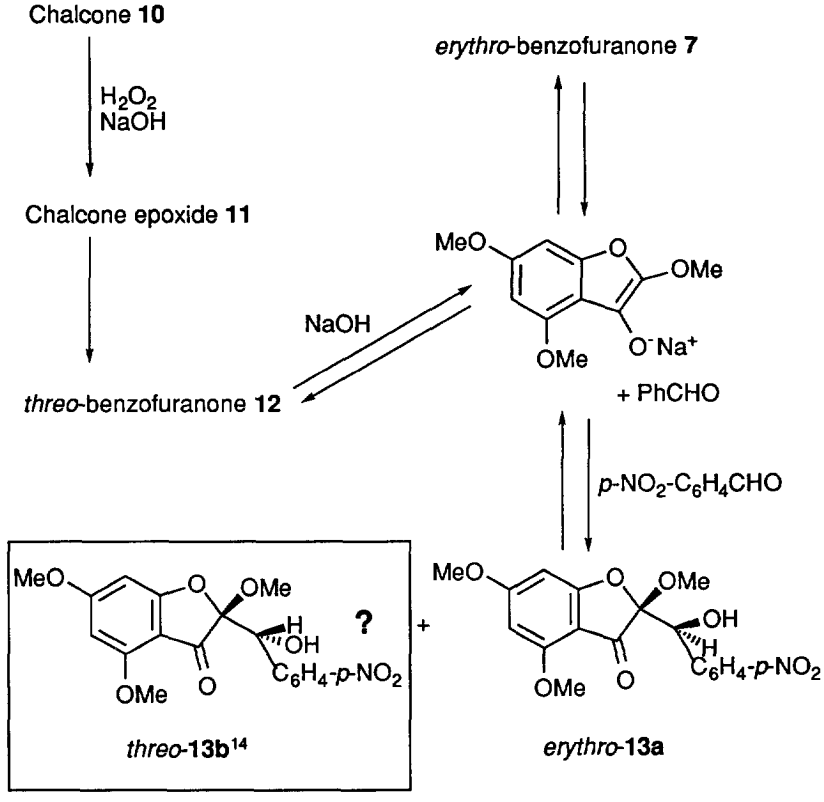



**Scheme 3** *Reagents:* i, MeOH, $H_2SO_4$; ii, PhCHO, $NaOH_{(aq.)}$; iii, $H_2O_2$, $NaOH_{(aq.)}$

From the work of Zimmerman and co-workers[11] it may be predicted that any epoxide intermediate, if formed in the AFO oxidation of chalcone **10** would also have the carbonyl and the β-phenyl groups *trans* to each other, as in epoxide **11**. Attack by the phenoxide at the α–position of the epoxide ring in **11** would be expected to occur with inversion of configuration to give the *threo*-benzofuranone **12**. However, the product obtained in this AFO reaction was identical to that obtained by acid catalysed methanolysis of the aurone epoxide **6** which had been assigned the *erythro*-configuration.[6,7] This result suggested that an epoxide was not an intermediate in the oxidation of **10** to **7**. However, before reaching a final conclusion on this, further evidence was required for the configuration of the putative chalcone epoxide intermediate **11**; and the possibility of equilibration occuring between the isomeric compounds **7** and **12** through a retrograde aldol reaction had also to be excluded. Since the mechanistic course of the AFO formation of aurones remained uncertain at this juncture, further investigation of the reaction mechanism was required. The work described in this paper was undertaken to throw further light on this reaction.

The possibility of a retrograde aldol reaction occurring after this reaction had taken place, was investigated by a crossover experiment involving the alkaline hydrogen peroxide oxidation of chalcone **10** in the presence of 4-nitrobenzaldehyde. The reaction gave a product mixture, and while various attempts to

separate it were without success, the $^1$H NMR spectrum of the crude product indicated that it was a mixture of the *erythro*-benzofuranone **7** and the *erythro*-nitrobenzofuranone **13a**[14] (Scheme 4) in a ratio of *ca.* 1 : 1.5. The structure of **13a** was confirmed by an independent synthesis and the

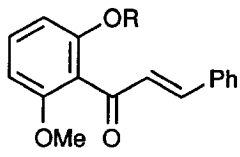


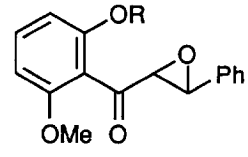

**Scheme 4**

stereochemistry was assigned on the basis of a comparison of its $^1$H NMR spectrum with those of some key assignment compounds (*vide infra*). This result indicated that a retrograde aldol reaction had occurred in the reaction, either on a hydrated chalcone, resulting from conjugate addition of hydroxide ion to chalcone **10**, on benzofuranone **12** or its isomer **7**. Support for the latter was obtained when a mixture of *erythro*-compound **7**, *erythro*-**13a** and *threo*-nitrobenzofuranone **13b** was obtained when benzofuranone **7** was treated with alkali in the presence of 4-nitrobenzaldehyde under the same conditions as the AFO reaction, but with the absence of hydrogen peroxide. Therefore these results imply that epoxide **11** may be an intermediate in the AFO reaction, which could cyclise into the *threo*-benzofuranone **12** and this could subsequently isomerise into the *erythro*-isomer **7** (Scheme 4).

Earlier work in this laboratory[15] presented evidence to show that an epoxide could be an intermediate in the AFO oxidation of 2'-hydroxy-6'-methoxychalcone **14c** into 4-methoxyaurone **5** (R = H, R$^1$ = OMe and Ar = Ph). The latter was the main product when 2'-tosyloxychalcone epoxide **15a** was treated with alkali at room

temperature. Adams and Main[16] succeeded in preparing the unprotected 2'-hydroxy-6'-methoxychalcone epoxide **15c** by epoxidising the tetrahydropyranyl chalcone derivative **14b** and

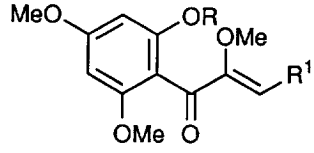



**14** **a**, R = Ts **15**
**b**, R = THP
**c**, R = H

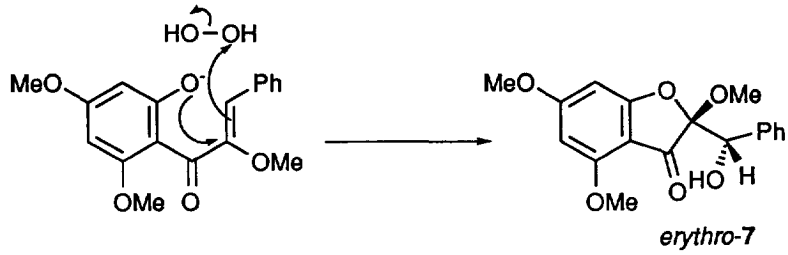
subsequently removing the protecting group under mild acid conditions. Treatment of this epoxide **15c** at various pHs with buffers in aqueous acetonitrile solutions at room temperature led in the majority of experiments to the products resulting from α- and β-cyclisation in ratios of 5-6 : 1. The α-cyclisation products were the corresponding aurone, hydrated aurone, and the benzofuranone resulting from the retrograde aldol reaction of the latter. The β-cyclisation product was 5-methoxyflavonol. Again this result is evidence that an epoxide is an intermediate in the alkaline hydrogen peroxide oxidation of 2'-hydroxy-6'-substituted-chalcones.

It was stated earlier that on the basis of overlap control the putative chalcone epoxide intermediate **11** (Scheme 3) would have the β-phenyl and the carbonyl groups *trans* to each other. In order to obtain further evidence for formation and configuration of this compound, attempts were made to oxidise 2'-tosyloxychalcone **16a** under AFO conditions, but they were without success.[6] This result suggests that an



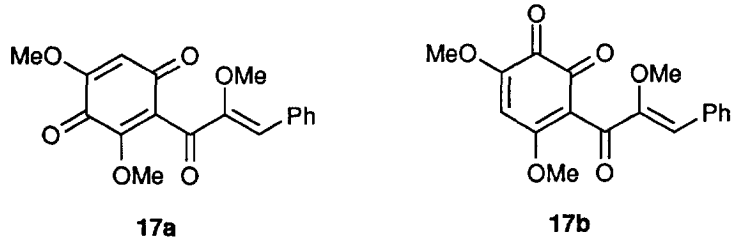

**16a**, R = Ts, $R^1$ = Ph
**18**, R = H, $R^1$ = $C_6H_4$-*p*-$NO_2$

epoxide is not an intermediate in the AFO oxidation of chalcone **10** into benzofuranone **7** and as a consequence it led to a plausible alternative mechanism, not involving an epoxide intermediate, analogous to the one postulated by Dean and Podimuang for flavonol formation in the AFO reaction which had been given in the earlier communication[6] (see Scheme 5). Further attempts to obtain the epoxide of chalcone **16a** using a variety of other oxidising reagents including sodium hypochlorite and 3-chloroperbenzoic acid were




**Scheme 5**

without success. When the unprotected chalcone **10** was treated with 3-chloroperbenzoic acid, the only product obtained was an orange compound, the elemental and spectroscopic analyses of which were consistent with the quinoid structure **17a** or **17b**, but with the aid of a nuclear Overhauser enhancement (nOe) experiment, it was shown that this compound had the structure **17a** (Fig. 1).




**17a** **17b**

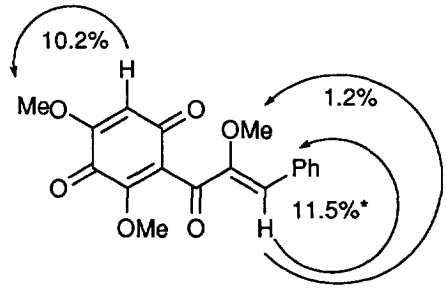
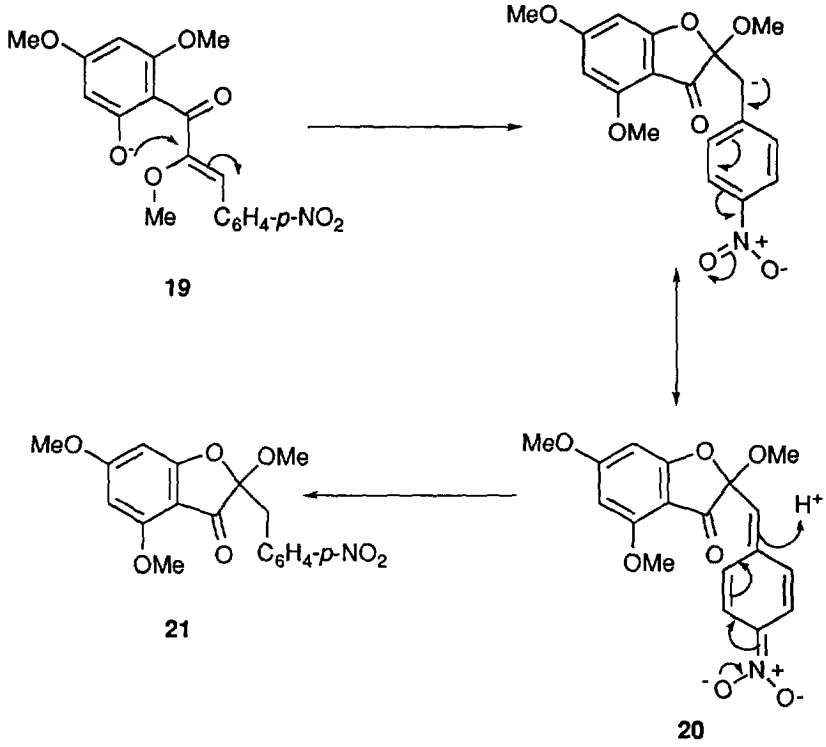



**Fig.1** nOe connectivity diagram. * Irradiation of the signal for the β-proton led to this enhancement in the signal for the 2'-, 6'-H of the β-phenyl group.

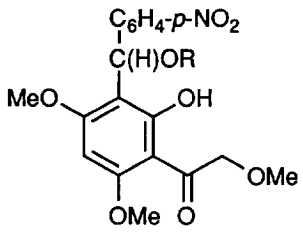
A number of attempts at the independent synthesis of 2-(hydroxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one were made. One such method was to prepare chalcone **18**, and carry out an AFO reaction on this chalcone. However, the base catalysed condensation of 2-hydroxy-α,4,6-trimethoxyacetophenone **9** (Scheme 3), with 4-nitrobenzaldehyde yielded not the desired chalcone **18** but rather the corresponding benzofuranone **21** (84% yield) as the only product. Chalcone **18** may well have been an intermediate in this reaction, and a possible mechanism is given in Scheme 6. It is postulated that phenolate **19** (resulting from deprotonation of the 2'-OH group in chalcone **18**) cyclises into the benzofuranone anion **20** (in a manner analogous to that delineated in Scheme 5) and protonation of this intermediate gives compound **21**. Cyclisation at the α-carbon, which is a favoured 5-*Exo-Trig*[17] process is considered to take precedence over cyclisation at the β-carbon, which would be a favourable 6-*Endo-Trig* [17] process, on the basis that the conformation of the anionic species **19** is likely to be s-*cis* (in the s-*trans* conformation there is expected to be

unfavourable dipole-dipole interaction between the carbonyl group and the α-methoxyl group) and examination of scale models has shown that if **19** possesses such a conformation in the transition state, the α-position will be attacked more readily than the β-position due to the closer proximity of the 2'-$O^-$ to the former position rather than to the latter.




**Scheme 6**

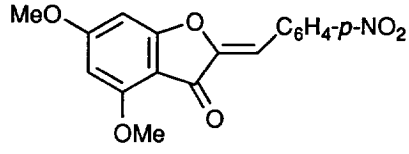
When the condensation was attempted by means of acid catalysis (dry hydrogen chloride in ethanol), acid catalysed Friedel-Crafts acylation was the dominant reaction, affording 2-hydroxy-3-(α-hydroxy-4-nitrophenylmethyl)-α,4,6-trimethoxyacetophenone **22a** and 2-hydroxy-3-(α-ethoxy-4-nitrophenylmethyl)-α,4,6-trimethoxyacetophenone **23a** or the corresponding 5-(α-hydroxy-4-nitrophenylmethyl) **22b** and 5-(α-ethoxy-4-nitrophenylmethyl) **23b** isomers, respectively. (The microanalytical and spectroscopic data obtained for these compounds were consistent with structures **22a** and **22b** or with their corresponding 5-substituted isomers, but the spectroscopic data employed was unable to distinguish whether these compounds existed as the 3-substituted isomer or the 5-substituted isomer.)




**22a** R = H **22b**

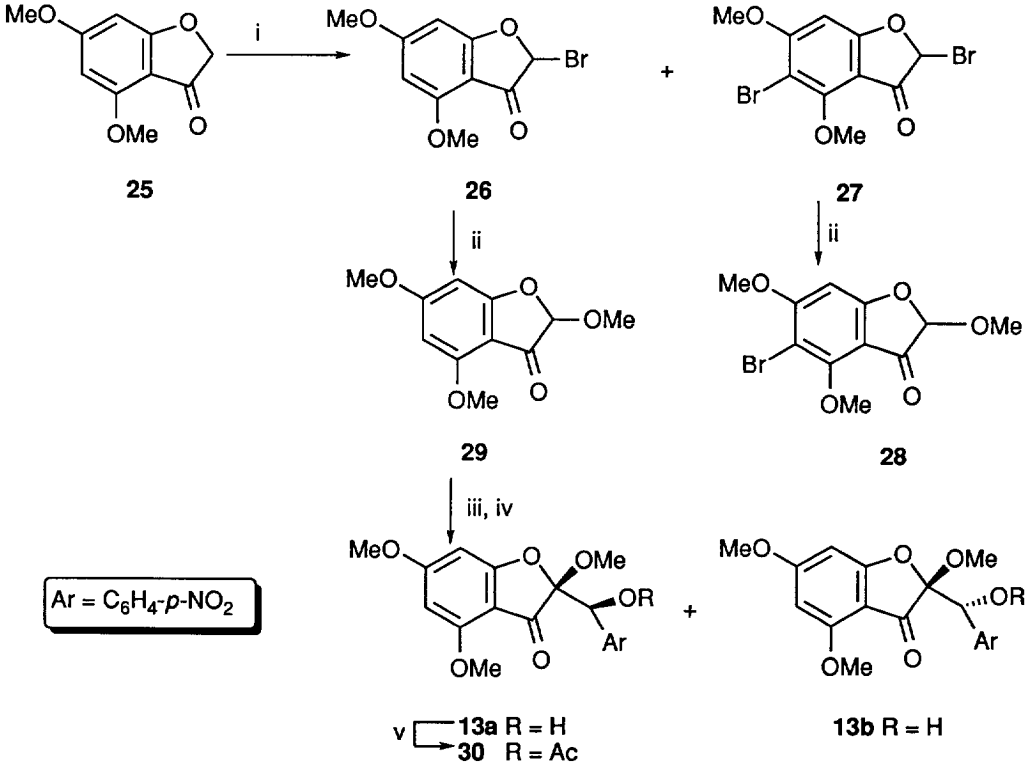
**23a** R = Et **23b**

Another approach to the synthesis of **13** was to prepare the epoxide of nitroaurone **24** and subject it to acid catalysed methanolysis. However, all attempts to epoxidise the nitroaurone were without success.




**24**

Finally the successful synthesis of the diastereomers **13a** and **13b** is outlined in Scheme 7.

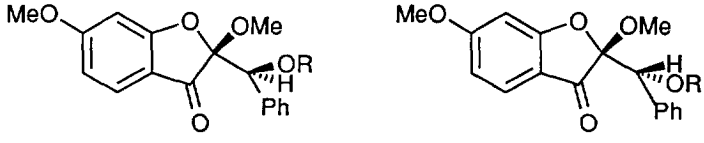



**25** **26** **27** **29** **28**

**Scheme 7** *Reagents and conditions:* i $Br_2$ (1.0 equiv.), dioxane-$Et_2O$ (1 : 1), 0°C; ii MeOH, r.t.; iii LDA (1.2 equiv.), THF, -78°C, 30 min; iv 4-$NO_2C_6H_4CHO$, THF, -78°C, 45 min; v $Ac_2O$, pyridine, r.t.

Bromination of 4,6-dimethoxybenzofuranone **25** with bromine in dioxane-ether afforded a mixture of two bromo compounds **26** and **27** in 62 and 24% yields, respectively. Compound **27** was used in a model methanolysis study, and furnished the acetal **28** in 65% yield. Similar treatment of compound **26** gave the acetal **29** in 24% yield. The key step in this synthesis was an aldol condensation of the acetal **29** with 4-nitrobenzaldehyde using lithium diisopropylamide (LDA) at -78°C affording the nitrobenzofuranone isomers **13a** and **13b** in 33 and 13% yields (d.e. 20%),[22] respectively, with acetylation of the former isomer affording the acetoxy derivative **30**. Table 1 contains the $^1$H NMR data for compounds **13a, 13b** and **30**, and also the $^1$H NMR data for the key assignment compounds which were *erythro*- and *threo*-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **31a**[18] and **31b** plus their respective acetoxy derivatives **32a**[18] and **32b**. (Note, the synthesis of **31b** and **32b** will be given in a subsequent publication by us). The stereochemical assignment for isomers **13a** and **13b** was made on the following basis: The isomer with the most downfield shift for 5-H, 7-H, β-H and 6-OMe, but possessing the most upfield shift for the α-OMe was assigned the *erythro*-configuration **13a** in accord with the δ-values observed for compounds **31a** and **31b**. Confirmation of this assignment was obtained when it was noticed that the acetate derivative of

**The Key Assignment Compounds**




**31a** R = H **31b**

**32a** R = Ac **32b**

**Table 1.** $^1$H NMR δ-values for Compounds **13a, 13b , 30** and the Key Assignment Compounds.

| Proton | 13a[a] | 13b[a] | 30[b] | 31a[b] | 31b[b] | 32a[b] | 32b[b] |
|---|---|---|---|---|---|---|---|
| 3', 5'-H | 8.18 (dd)[c] | 8.38 (d)[d] | 8.22 (d)[d] | | | | |
| 2', 6'-H | 7.70 (dd)[c] | 7.59 (d)[d] | 7.65 (d)[d] | | | | |
| β-Ph | | | | 7.40 (m)[e] | 7.27 (m)[e] | 7.36 (m)[e] | 7.35 (m)[e] |
| 4-H | | | | 7.50 (d)[f] | 7.35 (d)[f] | 7.56 (d)[f] | 7.40 (d)[f] |
| 5-H | 6.08 (d)[g] | 5.99 (d)[g] | 6.07 (d)[g] | 6.58 (dd)[f] | 6.48 (dd)[f] | 6.65 (dd)[f] | 6.53 (dd)[f] |
| 7-H | 6.23 (d)[g] | 6.16 (d)[g] | 6.23 (d)[g] | 6.53 (d)[f] | 6.42 (d)[f] | 6.59 (d)[f] | 6.49 (d)[f] |
| 4-OMe | 3.91 | 3.86 | 3.95 | | | | |
| 6-OMe | 3.89 | 3.84 | 3.93 | 3.88 | 3.83 | 3.92 | 3.87 |
| β–H | 5.06 | 5.03 | 6.06 | 5.08 (d) | 5.01 | 6.06 | 6.15 |
| α–OMe | 3.15 | 3.25 | 3.21 | 3.26 | 3.33 | 3.21 | 3.29 |
| β-OR | R = H[h] | R = H[h] | 1.93 R = Ac | 2.58 (d) R = H | 3.25 R = H | 1.86 R = Ac | 2.12 R = Ac |

[a]Spectra recorded in $CDCl_3$-$CD_3CN$ with TMS as internal standard; [b]Spectra recorded in $CDCl_3$ with TMS as internal standard; [c]*ortho*-coupling J=9.0 Hz, 2', 6'-H—β-H coupling 1.0 Hz; [d]*ortho*-coupling J≈9.0 Hz; [e]the mean value is given; [f]*ortho*-coupling J=8-9 Hz and *m*eta-coupling J=2-2.5 Hz; [g]*meta*-coupling J≈1.8 Hz; [h] δ-value not specified due to probable peak overlap.

**13a**, i.e. compound **30**, possessed exactly the same chemical shift for the α-OMe protons and the β-proton as that of the key assignment acetoxy compound **32a**, with almost the same chemical shift for the 6-OMe protons as that of compound **32a**.

In conclusion, the work presented in this paper presents evidence to show that epoxides can still be intermediates in the AFO reaction (at ambient temperature or lower) of 6'-substituted 2'-hydroxychalcones.

## EXPERIMENTAL

*General.*—Melting points were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. $^1$H NMR spectra were obtained using a Varian HR 60 A, Jeol JNM-PMX-60, a Bruker AM200 and a Jeol JNM-GX 270 FT spectrometer. $^{13}$C NMR were recorded on a Jeol JNM-GX 270 FT (67.80 MHz) and a Bruker AMX500 (126 MHz) spectrometer and such spectra were assigned using DEPT editing or by analogy with spectra obtained using such an editing technique. The nOe experiment was performed on the Bruker AMX500 spectrometer. Tetramethylsilane was used as the internal standard in all NMR's recorded on the Varian HR 60A, Jeol JNM-PMX-60 and the Jeol JNM-GX 270 FT spectrometer, and chemical shifts are reported as $\delta_H$(ppm) or $\delta_C$(ppm) from this standard. *J*-values are given in Hz. Infra-red spectra were recorded on a Beckman IR 5 spectrometer, a Perkin-Elmer 1710, a Perkin-Elmer 1740 Infra-red F.T. spectrometer, and a Mattison Galaxy Series F.T. I.R. 3000. Mass spectra were determined on a VG Analytical 70H and a Finnegan-Mat INCOS 50 mass spectrometer using electron impact and chemical ionization techniques. Elemental analyses were performed by the microanalytical department in the chemistry department at University College Dublin. Separations by column chromatography were performed using Merck Kieselgel 60 (70-230 mesh ASTM). Merck precoated Kieselgel 60$F_{254}$ was used for TLC and Merck Kieselgel $PF_{254+336}$ for Preparative Layer Chromatography (PLC). All solvents were purified and dried by standard techniques.

*Treatment of 2'-hydroxy-α,4',6'-trimethoxychalcone* **10** *with 4-nitrobenzaldehyde and alkaline hydrogen peroxide.*—A mixture of 10% aqueous sodium hydroxide (3.6 cm$^3$) and 30% hydrogen peroxide (0.36 cm$^3$) was added to a solution of 2'-hydroxy-α,4',6'-trimethoxychalcone[19] (0.1 g, 0.32 mmol) and 4-nitrobenzaldehyde (50 mg, 0.33 mmol) in methanol at 0°C. The mixture was kept at this temperature for 12 h and was then diluted with an equal volume of water. The resulting precipitate was collected, washed with water and dried. The precipitate (80 mg) resisted attempts to separate it into its individual components. An analysis of the $^1$H NMR spectrum of the precipitate indicated that it contained both (αR,βS ; αS,βR)-2-(hydroxyphenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **7** and its homologue (αR,βS ; αS,βR)-2-(hydroxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **13a** in the ratio 1 : 1.5. $\delta_H$ (60 MHz; $(CD_3)_2SO$) 2.99 (2 x 3H, s, α-OMe), 3.81 (2 x 3H, s, 6-OMe), 3.89 (2 x 3H, s, 4-OMe), 4.80 (2 x 1H, m, β–H), 5.70 (2 x 1H, m, β-OH), 6.15 (2 x 1H, m, 5-H), 6.37 (2 x 1H, m, 7-H), 7.35 (5H, m, $C_6H_5$) and 7.93 (4H, m, 4-$NO_2C_6H_4$).

*Treatment of* (αR,βS ; αS,βR)-2-(*hydroxyphenylmethyl*)-2,4,6-*trimethoxybenzo*[b]*furan*-3(2H)-*one* **7** *with* 4-*nitrobenzaldehyde in the presence of aqueous alkali*.—A mixture of (αR,βS ; αS,βR)-2-(hydroxyphenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **7** (74 mg, 0.23 mmol), 4-nitrobenzaldehyde (58 mg, 0.39 mmol) and methanol (10 $cm^3$) was stirred under nitrogen at 0°C. 10% aqueous sodium hydroxide (2.4 $cm^3$) was added slowly to the mixture and stirring was continued at the same temperature for 30 min. The temperature was increased to room temperature and stirred for a further 6 h. Water (13 $cm^3$) was added and the reaction mixture extracted with dichloromethane (2 x 14 $cm^3$), dried ($CaSO_4$) and evaporation to dryness afforded a white solid, which was purified by PLC on silica gel developed with chloroform-petroleum spirits (b.p. 60-80°C)-acetone (5 : 4 : 1) to give three bands, listed in order of increasing polarity.

Band 1 gave (αR,βS ; αS,βR)-2-(hydroxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **13a** (11 mg, 13%) as colourless needles, m.p. 186-188°C (from EtOH). (See the independent synthesis below for spectroscopic and analytical data).

Band 2 furnished (αR,βR ; αS,βS)-2-(hydroxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **13b** (17 mg, 20%) as colourless prisms, m.p. 212-214°C (from MeOH). (See the independent synthesis below for spectroscopic and analytical data).

Band 3 afforded (αR,βS ; αS,βR)-2-(hydroxyphenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **7** (15 mg, 20%) as needles, m.p. 200-202°C (from EtOH) (lit.,[7b] m.p. 201-203°C).

*Bromination of* 4,6-*dimethoxybenzo*[b]*furan*-3(2H)-*one* **25** *with bromine*.—A mixture of 4,6-dimethoxybenzo[b]furan-3(2H)-one[20] **25** (960 mg, 4.9 mmol), dioxane (15 $cm^3$) and diethyl ether (15 $cm^3$) was treated with a solution of bromine (0.25 $cm^3$, 4.85 mmol) in diethyl ether/dioxane [(30 $cm^3$)(1 : 1)] over 2.25 h at 0°C. Water (90 $cm^3$) was added and it was extracted with chloroform (100 $cm^3$). The organic layer was dried ($CaSO_4$) and evaporation to dryness afforded a yellow oil, which was chromatographed on silica gel with n-hexane-ethyl acetate (1 : 1) to furnish two bands. The lower band gave 2-bromo-4,6-dimethoxybenzo[b]furan-3(2H)-one **26** (0.82g, 62% ) as a solid, m.p. 143-145°C (from EtOH) (Found: C, 43.24; H, 3.35; Br, 29.50. $C_{10}H_9BrO_4 \cdot {}^1/_8H_2O$ requires C, 43.62; H, 3.39; Br, 29.02%); $\nu_{max}$(KBr)/$cm^{-1}$ 1721(C=O) and 1631; $\delta_H$(60 MHz; $CDCl_3$) 3.92 (3H, s, 6-OMe), 3.95 (3H, s, 4-OMe), 6.12 (1H, d, *J* 2.2, 5-H), 6.24 (1H, d, *J* 2.2, 7-H) and 6.47 (1H, s, 2-H); $\delta_C$(67.80 MHz; $CDCl_3$) 56.28 (6-$OCH_3$), 56.33 (4-$OCH_3$), 77.44 (2-C), 90.00 (5-C), 94.37 (7-C), 102.88 (9-C), 160.00 (4-C), 170.61 (6-C), 173.64 (8-C) and 190.00 (3-C); m/z (E.I.) 274 ($M^+$ +2, 36%), 272 ($M^+$, 33), 193 ($M^+$ - $^{79}Br$, 100), 165 ($M^+$ - $C^{79}BrO$, 11), 164 ($M^+$ - $C^{79}BrHO$, 10), 163 ($M^+$ - $CH_2{}^{79}BrO$, 32), 137 ($M^+$ - $C_2{}^{79}BrO_2$, 20), 136 ($M^+$ - $C_2{}^{79}BrHO_2$, 3) and 106 ($C_7H_6O^+$, 33).

The upper band afforded 2,5-dibromo-4,6-dimethoxybenzo[b]furan-3(2H)-one **27** (0.41g, 24%) as a brown solid, m.p. 158-161°C $\nu_{max}$(KBr)/$cm^{-1}$ 1723 (C=O) and 1615; $\delta_H$(60 MHz; $CDCl_3$) 4.04 (6H, s, 4- and 6-OMe), 6.20 (1H, s, 7-H) and 6.52 (1H, s, 2-H); $\delta_C$(67.80 MHz; $CDCl_3$) 56.63 (6-$OCH_3$), 57.25 (4-$OCH_3$), 77.26 (2-C), 86.07 (5-C), 90.78 (7-C), 102.75 (9-C), 159.49 (8-C), 165.98 (4-C), 168.18 (6-C) and 189.70 (3-C); m/z (E.I.) 354 ($M^+$ +4, 29%), 352 ($M^+$ +2, 59), 350 ($M^+$, 29), 273 ($M^+$ +2 - $^{79}Br$, 75), 271 (75), 243 (8), 164 (100) and 149 ($C_8H_5O_3^+$, 12) (Found $M^+$ +4, 353.8723. $C_{10}H_8{}^{81}Br_2O_4$ requires M+4, 353.8748).

*5-Bromo-2,4,6-trimethoxybenzo*[b]*furan*-3(2H)-*one* **28**.—A mixture of 2,5-dibromo-4,6-dimethoxybenzo[b]furan-3(2H)-one **27** (165 mg, 0.47 mmol) and methanol (10 $cm^3$) was stirred at room temperature for 8 days. Evaporation of the solvent furnished a brown solid which crystallised in needles of 5-Bromo-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **28** (92 mg, 65%) from ethanol, m.p. 159-161°C (Found: C, 43.37; H, 4.09; Br, 25.83. $C_{11}H_{11}BrO_5$ requires C, 43.71; H, 3.67; Br, 26.13%); $\nu_{max}$(KBr)/$cm^{-1}$ 1713 (C=O) and 1614; $\delta_H$(60 MHz; $CDCl_3$) 3.64 (3H, s, 2-OMe), 3.96 (3H, s, 6-OMe), 4.00 (3H, s, 4-OMe), 5.32 (1H, s, 2-H) and 6.08 (1H, s, 7-H); $\delta_C$(67.80 MHz; $CDCl_3$) 56.45 (2-$OCH_3$), 57.04 (6-$OCH_3$), 57.09 (4-$OCH_3$), 85.40 (5-C), 89.56 (7-C), 103.78 (2-C), 104.34 (9-C), 159.18 (8-C), 165.87 (4-C), 169.32 (6-C) and 190.48 (3-C); m/z (E.I.) 304 ($M^+$ +2, 58%), 302 ($M^+$, 63), 289 (3), 287 (3), 274 (60), 272 (69), 261 (35), 259 (39), 243 (100), 214 (60), 184 (60) and 105 ($C_7H_5O^+$, 13).

2,4,6-*Trimethoxybenzo*[b]*furan*-3(2H)-*one* **29**.—A mixture of 2-bromo-4,6-dimethoxybenzo[b]furan-3(2H)-one **26** (730 mg, 2.67 mmol) and methanol (25 $cm^3$) was stirred at room temperature for 78 h. Water (40 $cm^3$) was added and this mixture was extracted with diethyl ether (40 $cm^3$), dried ($K_2CO_3$) and evaporated to dryness under reduced pressure to afford an orange oil. Purification by silica gel column chromatography with n-hexane-EtOAc (1 : 1) yielded 2,4,6-trimethoxybenzo[b]furan-3(2H)-one **29** (144 mg, 24%) as a gum (Varma *et al.* [21] also reported this compound as being a gum) $\nu_{max}$(NaCl)/$cm^{-1}$ 1714 (C=O) and 1620; $\delta_H$(60 MHz; $CDCl_3$) 3.56 (3H, s, 2-OMe), 3.86 (3H, s, 6-OMe), 3.89 (3H, s, 4-OMe), 5.22 (1H, s, 2-H), 6.00 (1H, d, *J* 2.2, 5-H) and 6.12 (1H, d, *J* 2.2, 7-H); $\delta_C$(67.80 MHz; $CDCl_3$) 56.11 (6-$OCH_3$), 56.16 (4-$OCH_3$), 56.44 (2-$OCH_3$), 89.12 (7-C), 93.12 (5-C), 103.28 (9-C), 103.40 (2-C), 159.56 (4-C), 170.77 (6-C), 174.39 (8-C) and 190.73 (3-C); m/z (E.I.) 224 ($M^+$, 22%), 209 ($M^+$-Me, 15), 194 ($M^+$-$CH_2O$, 90), 181 ($M^+$-Me -CO, 90), 164 ($M^+$-$C_2H_4O_2$, 43), 136 ($C_8H_8O_2^+$, 7) and 106 ($C_7H_6O^+$, 100) (Found $M^+$, 224.0657. Calc. for $C_{11}H_{12}O_5$ M, 224.0685).

(αR,βS ; αS,βR)-**13a** and (αR,βR ; αS,βS)-2-(*Hydroxy-4-nitrophenylmethyl*)-2,4,6-*trimethoxybenzo*[b]*furan*-3(2H)-*one* **13b**.—n-Butyllithium (2.5 mol $dm^{-3}$ in n-hexane, 0.19 $cm^3$) was added to a stirred solution of diisopropylamine (0.07 $cm^3$, 0.48 mmol) in dry tetrahydrofuran (12 $cm^3$) at -78°C under nitrogen. Stirring was continued for 15 min before a solution of 2,4,6-trimethoxybenzo[b]furan-3(2H)-one **29** (90 mg, 0.4 mmol) in dry tetrahydrofuran (20 $cm^3$), cooled to -78°C, was added and stirring was continued at the same temperature for 30 min. 4-Nitrobenzaldehyde (61 mg, 0.48 mmol) in dry tetrahydrofuran (10 $cm^3$) was added and the mixture was stirred for a further 45 min. The reaction was quenched by adding the mixture to 10% aqueous ammonium chloride (50 $cm^3$) and it was extracted with diethyl ether (35 $cm^3$). The organic layer was washed with brine (2 x 50 $cm^3$), dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a white solid (150 mg). The solid was purified by PLC on silica gel developed with chloroform-petroleum spirits (b.p. 60-80°C)-acetone to give two bands. The lower band afforded a white solid (50 mg, 33%) which recrystallised from ethanol as colourless needles of (αR,βS ; αS,βR)-2-(hydroxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **13a**, m.p. 186-189°C (Found: C, 56.01; H, 4.73; N, 3.16. $C_{18}H_{17}NO_8 \cdot {}^1/_2H_2O$ requires C, 56.24; H, 4.72; N, 3.65%); $\nu_{max}$(KBr)/$cm^{-1}$ 3371 (O-H), 1687 (C=O) and 1611; $\delta_H$(270 MHz; $CD_3CN$-$CDCl_3$) 3.15 (3H, s, 2-OMe), 3.89 (3H, s, 6-OMe), 3.91 (3H, s, 4-OMe), 5.06 (1H, s,

-C*H*(OH)-4-$NO_2$-$C_6H_4$), 6.08 (1H, d, *J* 1.8, 5-H), 6.23 (1H, d, *J* 1.8, 7-H), 7.70 (2H, dd, *J* 9 and 1, 2', 6'-H) and 8.18 (2H, d, *J* 9, 3', 5'-H); $\delta_C$(67.80 MHz; $CD_3CN$-$CDCl_3$) 51.25 (2-$OCH_3$), 55.58 (6-$OCH_3$), 55.77 (4-$OCH_3$), 72.84 (-*C*H(OH)-4-$NO_2$-$C_6H_4$), 88.61 (7-C), 92.42 (5-C), 104.29 (9-C), 107.72 (2-C), 122.02 (3', 5'-C), 128.84 (2', 6'-C), 146.13 (1'-C), 147.14 (4'-C), 158.21 (4-C), 170.44 (6-C), 174.03 (8-C) and 191.74 (3-C); m/z (C.I.) 376 ($M^+$+1, 100%), 358 ($M^+$+1-$H_2O$, 5), 344 ($M^+$+1-MeOH, 9), 224 ($C_{11}H_{12}O_5^+$, 87), 209 ($C_{10}H_9O_5^+$, 34) and 152 ($C_7H_6NO_3^+$, 36).

The higher band furnished a white solid (19 mg, 13%) which recrystallised from ethanol as prisms of (αR,βR ; αS,βS)-2-(hydroxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **13b**, m.p. 211-214°C (Found: C, 53.63; H, 4.28; N, 3.35. $C_{18}H_{17}NO_8 \cdot 4/3H_2O$ requires C, 54.13; H, 4.47; N, 3.51%); $\nu_{max}$(KBr)/$cm^{-1}$ 3488 (O-H), 1698 (C=O) and 1620; $\delta_H$(270 MHz; $CD_3CN$-$CDCl_3$) 3.25 (3H, s, 2-OMe), 3.84 (3H, s, 6-OMe), 3.86 (3H, s, 4-OMe), 5.03 (1H, s, -C*H*(OH)-4-$NO_2$-$C_6H_4$), 5.99 (1H, d, *J* 1.8, 5-H), 6.16 (1H, d, *J* 1.8, 7-H), 7.59 (2H, dd, *J* 9 and 1, 2', 6'-H) and 8.38 (2H, d, *J* 9, 3', 5'-H). A $^1H$ NMR spectrum of compound **13b** previously run in $CDCl_3$ showed an additional doublet (*J 5.8* ) at 2.80 ppm which was ascribed to the β-OH group; a spin decoupling experiment revealed that it was coupled with the β–proton which appeared as a doublet (*J 5.8* ) at 5.21 ppm; m/z (C.I.) 376 ($M^+$+1, 12%), 344 ($M^+$+1-MeOH, 3), 224 ($C_{11}H_{12}O_5^+$, 23), 209 ($C_{10}H_9O_5^+$, 16) and 151 ($C_7H_5NO_3^+$, 100).

(αR,βS ; αS,βR)-2-(*Acetoxy-4-nitrophenylmethyl*)-2,4,6-*trimethoxybenzo*[b]*furan*-3(2H)-*one* **30**.—(αR,βS ; αS,βR)-2-(hydroxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **13a** (21 mg, 0.056 mmol), acetic anhydride (4 $cm^3$) and dry pyridine (0.1 $cm^3$, 1.23 mmol) were stirred at room temperature for 49 h. The mixture was diluted with water (15 $cm^3$) and left standing at room temperature for 36 h. This was followed by extraction with chloroform (20 $cm^3$), drying ($MgSO_4$) and evaporation to dryness under reduced pressure to give a pale yellow oil, which when triturated with EtOH-water it afforded colourless needles of (αR,βS ; αS,βR)-2-(acetoxy-4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **30** (14 mg, 60%), m.p. 190-192°C (Found: C, 56.12; H, 4.54; N, 3.15. $C_{20}H_{19}NO_9 \cdot 1/2H_2O$ requires C, 56.32; H, 4.73; N, 3.29%); $\nu_{max}$(KBr)/$cm^{-1}$ 1745 (C=O, acetate), 1709 (C=O, ring system) and 1623; $\delta_H$(270 MHz; $CDCl_3$) 1.93 (3H, s, OCOMe), 3.21 (3H, s, 2-OMe), 3.93 (3H, s, 6-OMe), 3.95 (3H, s, 4-OMe), 6.06 (1H, s, -C*H*(OAc)-4-$NO_2$-$C_6H_4$), 6.07 (1H, d, *J* 1.9, 5-H), 6.23 (1H, d, *J* 1.9, 7-H), 7.65 (2H, d, *J* 8.6, 2', 6'-H) and 8.22 (2H, d, *J* 8.6, 3', 5'-H); $\delta_C$(67.80 MHz; $CDCl_3$) 20.67 (CO*C*$H_3$), 52.26 (2-$OCH_3$), 56.23 (6-$OCH_3$), 56.26 (4-$OCH_3$), 74.49 (-*C*H(OH)-4-$NO_2$-$C_6H_4$), 88.87 (7-C), 93.31 (5-C), 104.41 (9-C), 106.87 (2-C), 123.08 (3', 5'-C), 129.38 (2', 6'-C), 142.23 (1'-C), 147.99 (4'-C), 158.95 (4-C), 168.54 (O*C*O$CH_3$), 171.10 (6-C), 174.25 (8-C), and 190.94 (3-C); m/z (E.I.) 417 ($M^+$, 0.5%), 358 ($M^+$ - $C_2H_3O_2$, 0.5), 224 ($C_{11}H_{12}O_5^+$, 33), 223 ($M^+$ - $C_9H_8NO_4$, 100), 209 ($C_{11}H_{12}O_5^+$ -Me, 21), 195 ($C_9H_9NO_4^+$, 2) , 181 ($C_{11}H_{12}O_5^+$ -Me -CO, 11), 137 ($C_8H_9O_2^+$, 4) and 106 ($C_7H_6O^+$, 6).

*Treatment of* 2'-*hydroxy*-α,4',6'-*trimethoxychalcone* **10** *with* 3-*chloroperbenzoic acid.*—A solution of 2'-hydroxy-α,4',6'-trimethoxychalcone[19] **10** (1.0g, 3.2 mmol) and 3-chloroperbenzoic acid (2.5g, 14.5 mmol) in dry carbon tetrachloride (150 $cm^3$) was allowed to stand at room temperature for 24 h. The mixture was diluted with chloroform, and the chloroform solution was washed with 5% aqueous sodium bicarbonate and with

water, before being dried over magnesium sulphate. On removal of the solvent under reduced pressure an orange oil was obtained which on crystallisation from methanol gave orange prisms of 2,6-dimethoxy-3-(α-methoxycinnamoyl)-1,4-benzoquinone **17a** (780 mg, 75%), m.p. 158°C (Found: C, 65.50; H, 4.80. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.91%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1638 (C=O); $\delta_H$(200 MHz; $CDCl_3$) 3.86 (3H, s, 4-OMe), 3.89 (3H, s, 6-OMe), 3.97 (3H, s, α-OMe), 5.88 (1H, s, 3-H), 6.71 (1H, s, β-H), 7.38 (3H, s br, 3'-, 4'-, 5'-H) and 7.78 (2H, s br, 2'-, 6'-H); $\delta_C$(126 MHz; $CDCl_3$) 189.7, 185.9, 177.3 (C=O), 157.4, 154.1, 152.7, 132.9 (4-, 6-, 1-, 1'-C), 130.5 (2'-, 6'-C), 129.9 (4'-C), 128.9 (3-C), 128.7 (3'-, 5'-C), 122.7 (α–OMe), 107.0 (β-C), 60.6, 59.3, 56.7 (α-, 4-, 6-OMe).

2-(4-*Nitrophenylmethyl*-2,4,6-*trimethoxybenzo*[b]*furan*-3(2H)-*one* **21**.—To a mixture of 2-hydroxy-α,4,6-trimethoxyacetophenone **9**[23] (1.0 g, 4.42 mmol) and 4-nitrobenzaldehyde (700 mg, 4.63 mmol) in ethanol (30 $cm^3$) was added 10% aqueous potassium hydroxide (20 $cm^3$) and the resulting solution was stirred for 3 h. The reaction mixture was then acidified at 0°C with dilute hydrochloric acid. The resulting precipitate was collected and on recrystallisation from methanol gave yellow cubes of 2-(4-nitrophenylmethyl)-2,4,6-trimethoxybenzo[b]furan-3(2H)-one **21** (1.2 g, 84%), m.p. 167°C (Found: C, 60.58; H, 4.60; N, 3.80. $C_{18}H_{17}NO_7$ requires C, 60.16; H, 4.77; N, 3.90%); $\nu_{max}$(KBr)/$cm^{-1}$ 1710 (C=O); $\delta_H$(60 MHz; $CDCl_3$) 3.31 (5H, s, 2-OMe and $C_6H_5CH_2$), 3.94 (6H, s, 4- and 6-OMe), 6.07 (1H, d, *J* 2, 5-H), 6.20 (1H, d, *J* 2, 7-H), 7.54 (2H, d, *J* 9, 2' and 6'-H) and 8.18 (2H, d, *J* 9, 3' and 5'-H).

*Treatment of* 2-*hydroxy*-α,4,6-*trimethoxyacetophenone* **9** *with dry hydrogen chloride in ethanol*.—A solution of 2-hydroxy-α,4,6-trimethoxyacetophenone **9** (1.0 g, 4.42 mmol) and 4-nitrobenzaldehyde (1.0 g, 6.62 mmol) in ethanol (50 $cm^3$) was saturated with dry hydrogen chloride gas. The resulting solution was allowed to stand for 24 h at room temperature. The solvent was removed under reduced pressure and the residual oil obtained was separated by PLC [chloroform-petroleum spirits (60-80°C)(1 : 1)] to give two main bands. The upper band was extracted with chloroform and the residual oil obtained on removal of the solvent was triturated with methanol to give needles of 2-hydroxy-3-(α-ethoxy-4-nitrophenylmethyl)-α,4,6-trimethoxyacetophenone[24a] **22a** (477 mg, 27%), m.p. 138°C (Found: C, 59.55; H, 5.45; N, 3.20. $C_{20}H_{23}NO_8$ requires C, 59.25; H, 5.72; N, 3.46%); $\nu_{max}$(KBr)/$cm^{-1}$ 2950 (O-H) and 1625 (C=O); $\delta_H$(60 MHz; $CDCl_3$) 1.30 (3H, t, *J* 6.6, $CH_3CH_2$), 3.57 (3H, s, α–OMe), 3.62 (2H, q, *J* 6.6, $CH_3CH_2$), 3.87 (3H, s, 4-OMe), 4.03 (3H, s, 6-OMe), 4.69 (2H, s, $MeOCH_2$), 6.13 (1H, s, 5-H), 6.29 (1H, s, benzylic-H), 7.70 (2H, d, *J* 9, 2' and 6'-H), 8.34 (2H, d, *J* 9, 3' and 5'-H) and 14.07 (1H, s, 2-OH).

Similar treatment of the lower band gave cubes of 2-hydroxy-3-(α-hydroxy-4-nitrophenylmethyl)-α,4,6-trimethoxyacetophenone[24b] **23a** (120 mg, 7%), m.p. 187°C (Found: C, 56.84; H, 4.89; N, 3.51. $C_{18}H_{19}NO_8$ requires C, 57.29; H, 5.08; N, 3.71%); $\nu_{max}$(KBr)/$cm^{-1}$ 3425 (O-H) and 1610 (C=O); $\delta_H$(60 MHz; $CDCl_3$) 3.57 (3H, s, α-OMe), 4.01 (3H, s, 4-OMe), 4.03 (3H, s, 6-OMe), 4.34 (1H, d, *J* 11.7, benzylic-OH), 4.67 (2H, s, $MeOCH_2$), 6.13 (1H, s, 5-H), 6.38 (1H, d, *J* 11.7, benzylic-H), 7.63 (2H, d, *J* 9, 2' and 6'-H), 8.24 (2H, d, *J* 9, 3' and 5'-H) and 14.23 (1H, s, 2-OH).

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*Note* : A very recent report by Schlenoff *et al.* presents evidence contradicting the hypothesis of Dean and Podimuang,[5] and they assert that an epoxide is an intermediate in the AFO oxidation of 2'-hydroxy chalcones to flavonols: Gao, F.; Johnson, K.F.; Schlenoff, J.B. *J. Chem. Soc., Perkin Trans.* 2 **1996**, 269.

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