

Flavonoid Epoxides. Part 22.¹ Establishment of the Configuration of the Diastereomeric Solvolysis Products of 2-Arylmethylenebenzo[b]furan-3(2H)-one (Aurone) Epoxides

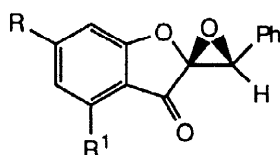
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Received 11 August 1997; accepted 18 December 1997

Abstract: Reaction of aurone epoxides⁴ with a variety of hydroxylic solvents gives rise to a number of diastereomeric solvolysis products. The stereochemistry of these compounds was initially tentatively assigned by comparison of their ¹H nmr spectra with that of the *erythro*-acetal **15a** resulting from acid catalysed methanolysis of the (*Z*)-aurone epoxide **2**. In this paper we establish the configurations of these solvolysis products on a firmer basis, by obtaining the *threo* acetal **15b** by acid catalysed methanolysis of the corresponding (*E*)-aurone epoxide **23**. Both the *erythro*-**15a** and the *threo*-acetal **15b** were independently synthesised by an aldol condensation (using LDA as base) of the acetal **27** with benzaldehyde, and surprisingly a high level of diastereoselectivity was obtained, which was attributed to secondary orbital interactions between the electrophile and the enolate molecule. When bromomagnesium diisopropylamide (BMIDA) was used as the base for this purpose, the product of the self-condensation of **27** was obtained as a single diastereomer along with the *erythro*-acetal **15a** and starting material. © 1998 Elsevier Science Ltd. All rights reserved.

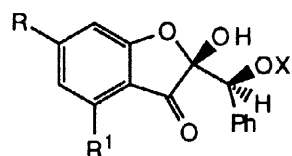
It was reported earlier,³ that the reaction of aurone epoxides⁴ with a variety of hydroxylic solvents afforded a number of diastereomeric solvolysis products. For instance, when the (*Z*)-aurone epoxide **1** was dissolved in aqueous acetone and left standing for 7 days, and the (*Z*)-aurone epoxide **2** was refluxed in the same solvent for 2 hours, hydrolysis products **4** and **6** were obtained. Methanolysis of (*Z*)-aurone epoxides **1**, **2**, and **3** and ethanolysis of the (*Z*)-aurone epoxide **2** furnished the methanolysis products **5**, **7**, **9** and the ethanolysis product **8**. When (*Z*)-aurone epoxide **2** was heated in acetic acid for 1 hour, the acetolysis product **10** was procured. Acetylation of compounds **5**, **7**, **9**, and **10** with an acetic anhydride-pyridine mixture gave in each case two diastereomeric products (**11a, b**), (**12a, b**), (**13a, b**) and (**14a, b**) in ratios of 33:17, 33:17, 28:22, and 33:17.³



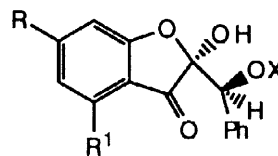
- 1** R = R¹ = H
- 2** R = OMe, R¹ = H
- 3** R = R¹ = OMe

The configurational assignments of these diastereomeric products were tentatively made by a comparison of their ¹H nmr spectra to that of the *erythro*-benzofuranone⁵ **15a**, or to that of its acetate **16a**. Compound **15a** was obtained in 6% yield when a sample of epoxide **2** was dissolved in methanol, treated with a trace of concentrated sulphuric acid and heated gently for 5 minutes, the main product of the reaction was the isomeric α -hydroxy- β -methoxy compound **7** (51%).³ The stereochemistry of **15a** was rationalised as follows: in acid catalysed ring-opening of epoxides, in most cases the C-O bond-breaking progresses to a greater extent than the nucleophile-C bond making process in the transition state and the mechanism is termed 'borderline' S_N2.⁶

In this transition state there is an appreciable amount of carbocation character as indicated by the stereochemical evidence.⁶ In the acid catalysed methanolysis of the epoxide **2** in addition to attack at the β -centre, which is the more favoured reaction path to give **7**, the nucleophile also attacks the

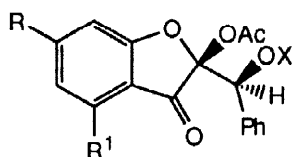


a : $\alpha R, \beta S$ (*erythro*)

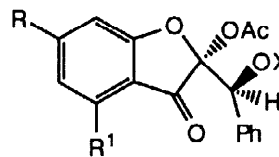


b : $\alpha S, \beta S$ (*threo*)

- 4** **a** or **b**; R = R¹ = X = H
5 **a** or **b**; R = R¹ = H, X = Me
6 **a** or **b**; R = OMe, R¹ = X = H
7 **a** or **b**; R = OMe, R¹ = H, X = Me
8 **a** or **b**; R = OMe, R¹ = H, X = Et
9 **a** or **b**; R = R¹ = OMe, X = Me
10 **a** or **b**; R = OMe, R¹ = H, X = Ac

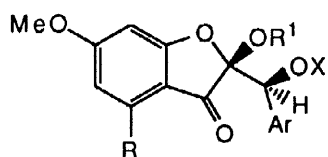


a; $\alpha S, \beta S$ (*erythro*)

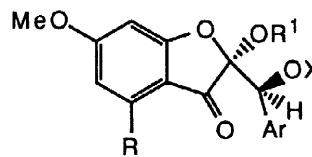


b; $\alpha R, \beta S$ (*threo*)

- 11** **a** or **b**; R = R¹ = H, X = Me
12 **a** or **b**; R = OMe, R¹ = H, X = Me
13 **a** or **b**; R = R¹ = OMe, X = Me
14 **a** or **b**; R = OMe, R¹ = H, X = Ac



a : $\alpha R, \beta S$ (*erythro*)



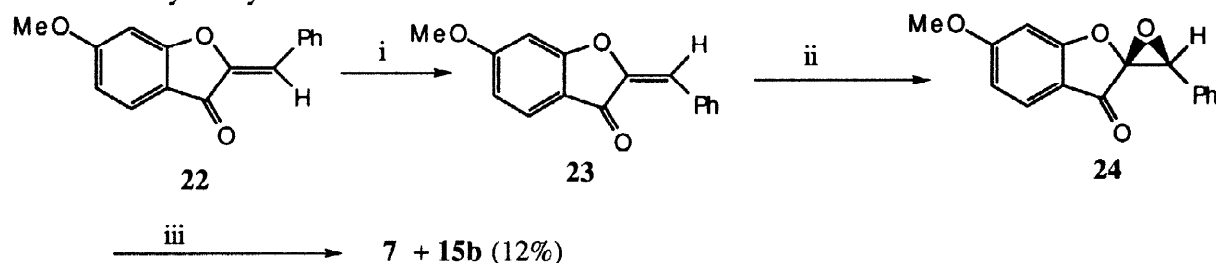
b : $\alpha S, \beta S$ (*threo*)

- 15** **a** or **b**; R = H, R¹ = Me, X = H, Ar = Ph
16 **a** or **b**; R = H, R¹ = Me, X = Ac, Ar = Ph
17 **a** only; R = H, R¹ = Et, X = H, Ar = Ph
18 **a** only; R = OMe, R¹ = Me, X = H, Ar = Ph
19 **a** only; R = OMe, R¹ = H, X = Ac, Ar = Ph
20 **a** or **b**; R = OMe, R¹ = Me, X = H, Ar = C₆H₄-*p*-NO₂
21 **a** only; R = OMe, R¹ = Me, X = Ac, Ar = C₆H₄-*p*-NO₂

epoxide ring at the α -position to give the α -methoxy- β -hydroxy product **15a**. An S_N1 mechanism was ruled out on the basis that it would involve the generation of a carbocation adjacent to the carbonyl group and therefore attack by nucleophile at the α -position must involve inversion of configuration at this centre giving the *erythro*-isomer **15a**. However, to establish the stereochemical configuration of the solvolysis products **4-10**

on a firmer basis, it was necessary to compare the ^1H nmr spectra of these diastereomeric products, to that of the *threo*- α -methoxy- β -hydroxy isomer **15b** in addition to the *erythro*-isomer **15a**. We report now the synthesis of compound **15b**, and that of its acetate derivative, with concomitant assignment of the stereochemical configuration of these compounds on a firmer basis.

The synthesis of **15b** is delineated in Scheme 1. The (*E*)-aurone **23** was obtained in 38% yield (the remainder being starting material) by u.v. irradiation of its geometrical isomer in accordance with the procedure used by Brady *et al.*⁷

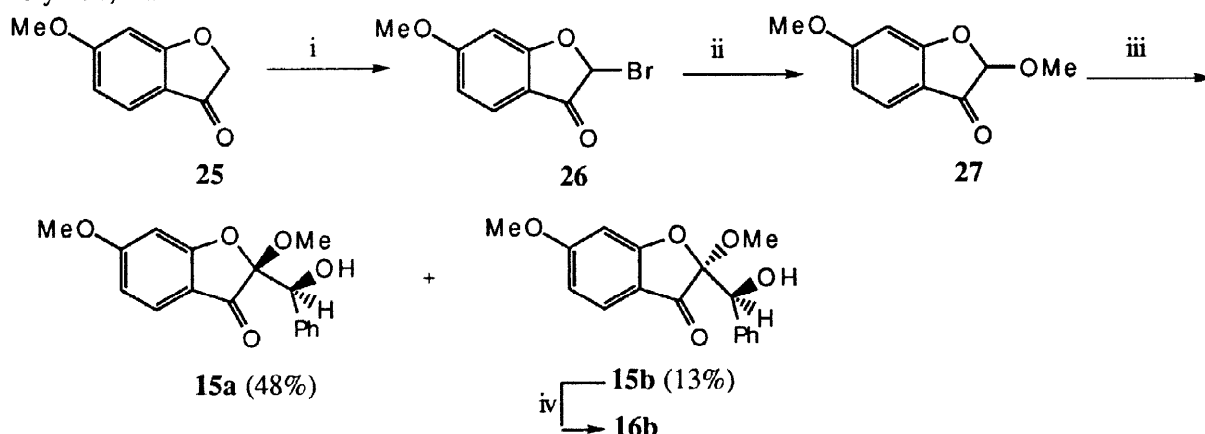


Scheme 1 Reagents and conditions: i, hv, C_6H_6 (dry), 63h, 38%; ii, mCPBA (80%⁸, 1.4 eq.), C_6H_6 (dry), reflux, 3.25h, 33%, or DMD (2.2 eq.), MeAc, CHCl_3 , r.t., 34h, quant.; iii, MeOH, H_2SO_4 conc. (cat.), 100°C , 10 min

Epoxidation of (*E*)-aurone **23** was performed using mCPBA in anhydrous benzene⁹ affording the epoxide **24** in a moderate yield of 33%, the reaction only went with 61% conversion giving a mixture of (*E*)-aurone **23** (18%) and (*Z*)-aurone **22** (21%), respectively. A far better yield of epoxide **24** (quantitative) was obtained using dimethyldioxirane (DMD) as a solution in acetone.¹⁰

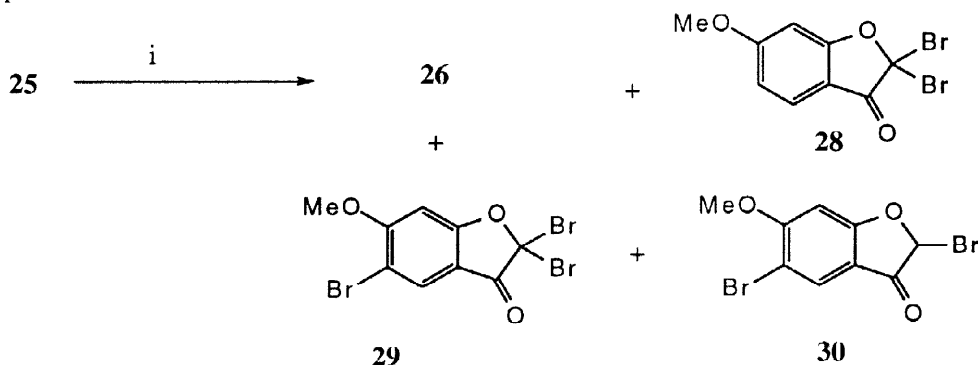
Acid catalysed methanolysis of (*E*)-aurone epoxide **24** furnished the hemiacetal benzofuranone **7** and the desired acetal **15b** in a ratio of 79 : 21 as determined by ^1H nmr analysis. An earlier attempt at obtaining the acetal was unsuccessful and instead of obtaining **15b**, 2,6-dimethoxybenzofuranone **27** (Scheme 2) was procured in 5% yield along with the hemi-acetal **7** in 67% yield. It was presumed that **27** was the product of a *retro*-aldol reaction on acetal **15b**, due to overexposure of this compound to alkali during the work-up; much reduced exposure time of the acetal **15b** to base, led to its successful isolation.

An independent synthesis of the acetal diastereomers **15a** and **15b**, and of the acetate derivative of **15b**, namely **16b**, was then conducted. This is delineated in Scheme 2.



Scheme 2 Reagents and conditions: i, Br_2 (0.99 eq.), dioxane/ Et_2O (1:1), 1.5h, 0°C , 97%; ii, MeOH, r.t., 48h, 25%; iii, LDA (1.2 eq.), THF, -78°C , 30 min, then PhCHO (1.0 eq.) was added, -78°C , 35 min; iv, Ac_2O , pyridine, r.t., 48h, 94%

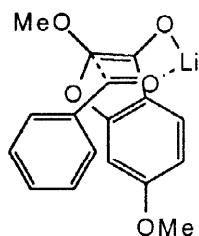
Bromination of benzofuranone **25** using the procedure used earlier in this laboratory¹¹ gave the desired 2-bromo compound **26** in poor yield along with by-products (Scheme 3) and unidentified decomposition products. When bromine (1.0 eq.) was added very slowly over 2h to the substrate **25** in diethyl ether at -10°C and this was followed by warming to room temperature, the *gem*-dibromo compound **28** was obtained as the sole reaction product.



Scheme 3 Reagents and conditions: i, Br_2 (1.0 eq.), Et_2O , 0°C , 40 min

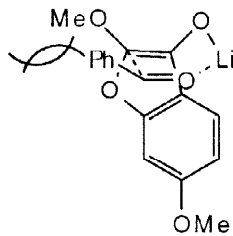
However, when a 1:1 mixture of dioxane:diethyl ether was used as the reaction solvent, the mono-bromo compound **26** was obtained almost quantitatively.

The key step in this synthesis was the aldol condensation to afford the diastereomers **15a** and **15b** in a ratio of 86 : 24 in favour of the *erythro*-isomer **15a**. This may be rationalised by evoking a 6-membered chelate model in a boat conformation (Fig. 1) and attack of the enolate on the *Si*-face of the aldehyde, Transition State A (Fig. 1). Examination of molecular models shows that there is the possibility of π -stacking or edge to face stacking^{12a} between the phenyl group of the aldehyde and the benzene moiety of the enolate molecule, thus favouring attack from the *Si*-face of the electrophile. *Re*-face attack, Transition State B (Fig. 1), is unfavoured as it is devoid of such a stabilising influence and there is a non-bonded interaction between the 2-methoxyl of the enolate and the phenyl group of the electrophile. Further precedence for the above transition state model comes from the work of Pridgen *et al.*^{12b} who carried out aldol reactions with chiral haloacetyl oxazolidinones and aromatic aldehydes giving predominantly *anti* aldol products which suggested that the reaction proceeded through a boat-like transition state. As a consequence these workers



Transition State A, favoured.

Note, the aldehyde proton has been omitted, as in T.S. B, for the sake of clarity and the phenyl ring of the aldehyde is skewed with respect to the benzofuranone phenyl ring for the same reason.



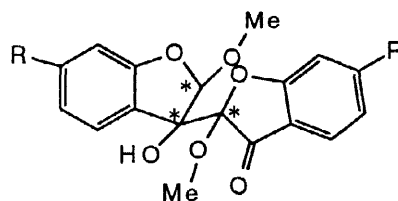
Transition State B, disfavoured.

Fig. 1. Proposed transition states accounting for the diastereoselectivity in the formation of **15a**.

hypothesised that secondary orbital interactions of the arene ring with either the oxazolidinone carbonyl or the α -halogen, had an influence on the product stereochemistry.

During the course of this work it was reported by Liotta and coworkers¹³ that the ratio of *threo* (*anti*):*erythro* (*syn*) diastereomer could be greatly improved in the aldol reaction by using magnesium (II) cations: it was of interest for us to see if we could reverse the selectivity in our system by using their methodology. In accordance with the literature,¹³ $\text{MgBr}_2 \cdot \text{OEt}_2$ was added to the lithium enolate soon after complete formation and a ^1H nmr spectrum of the crude reaction product showed an *erythro* : *threo* ratio of 56 : 44, with the quantity of *threo* isomer greatly increased, but with the diastereoselectivity greatly reduced. This result is hard to rationalise, but it could be explained by the following hypothesis, that this reaction proceeded by a different transition state to that described earlier; one in which attack of the electrophile by the enolate from the *Si*-face wasn't favoured to such an extent over attack on the *Re*-face in the absence of magnesium (II) cation.

When the same condensation reaction was repeated using bromomagnesium diisopropylamide (BMDA) as the base, two compounds were formed along with starting material: these were *erythro*-(2-hydroxyphenylmethyl)-2,6-dimethoxybenzofuran-3(2H)-one **15a** and a single diastereomer of 2-(3-hydroxy-2,6-dimethoxy-2,3-dihydrobenzofuran-3-yl)-2,6-dimethoxybenzofuran-3(2H)-one **32**. The ratio of **15a** : **32** : **27** was found by ^1H nmr to be 3 : 3 : 2.



(31) R = H

(32) R = OMe

This was quite an interesting result in that only one diastereomer out of a possible four was obtained for the dimeric compound **32**, and it would appear that formation of the magnesium enolate of **27** occurred much slower than formation of the corresponding lithium enolate, thus explaining the occurrence of self-condensation¹⁴ and the recovery of starting material. The formation of the *erythro*-isomer **15a** to the seemingly total exclusion of its *threo*-isomer **15b** may be rationalised if a transition state model like that given in Fig. 1 for the lithium enolate case is evoked. What also is worth observing, is that the parent dimer **31**, had earlier been synthesised by Antus *et al.*¹⁵ when they treated 2-methoxy-2-(4-methoxybenzoyl)benzofuran-3(2H)-one with 0.1M sodium methoxide at 25°C to afford *via* a *retro*-Claisen condensation/aldol reaction sequence, a mixture of 2-methoxybenzofuran-3(2H)-one, methyl 4-methoxybenzoate and a mixture of two diastereomers of **31** which were assigned the (2*R*,2'*S*,3'*R*) and (2*S*,2'*S*,3'*R*) configurations, respectively. The compound to which they have assigned the (2*R*,2'*S*,3'*R*) relative stereochemistry¹⁶ has an ^1H nmr spectrum similar to that of dimer **32**. We also tentatively assigned this same relative stereochemistry to **32**, on the basis of what is considered to be the most favourable mode of attack of the enolate upon the ketone as depicted in Fig. 2. However, at the moment in the absence of stereochemical proof for this structure, this remains speculation.

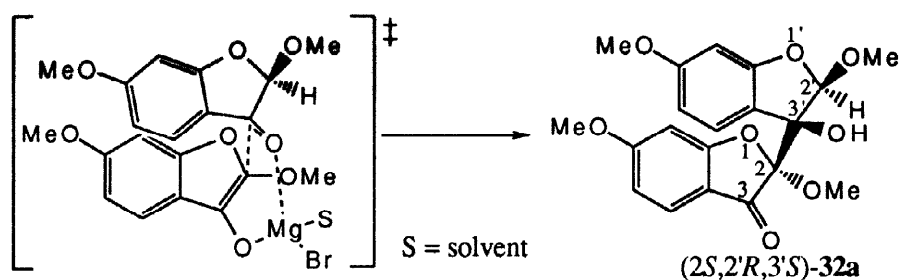


Fig. 2. Possible transition state leading to (2*S*,2'*R*,3'*S*)-**32a**. Again, π - π stacking is considered to have a strong role in determining the T.S. structure.

The configuration of the aurone epoxide solvolysis products **4–10** and of their acetate derivatives **11–14** listed in the Table were earlier tentatively assigned by Brady *et al.*³ on the basis of a comparison of their ^1H nmr spectra with those of the *erythro*-isomer **15a** and its acetate derivative **16a**. They are now more firmly established by comparison of the same spectra with those of both the *erythro*-isomer **15a** and the *threo*-isomer **15b** and of their respective acetates **16a** and **16b** (see Table). Examination of the ^1H nmr δ values for the key diastereomeric pairs, namely **15a**, **15b** and **16a**, **16b** show some interesting trends. The 4, 5, 7-H and 6-OMe signals for the *erythro*-isomers in each case, appear further downfield than the corresponding δ values in the *threo*-isomers (see Table). Also the difference in the chemical shifts between corresponding signals are quite close to each other, the difference in the δ values for the above protons between **15a** and **15b** is 0.14, 0.08, 0.11 and 0.02 ppm. In the case of the acetoxy diastereomers **16a** and **16b** the difference in δ values was found to be 0.16, 0.13, 0.10 and 0.03 ppm. This trend is the same for the corresponding protons in each diastereomeric pair given in the Table. It is also worth noting that the same trend exists for the β -Ph signals in all the diastereomeric pairs given in the Table, as observed for the key isomeric pairs **15a**, **15b** and **16a**, **16b**. The β -substituent in the case of the key acetoxy isomers **16a** and **16b** shows a reversal to the above trend, the *threo*-isomer in this case possesses the more downfield chemical shift, and the difference is a sizeable 0.26 ppm. This trend together with the significant chemical shift difference, continues for all diastereomeric pairs having β -acetoxy substituents listed in the Table, with the exception of **20a** and **20b** where the peaks failed to be located due to probable peak overlap. Of minor significance is the observation of the same trend for the α -substituents¹⁷ as that for the β -substituents in both key diastereomeric pairs. This trend in δ values for the α -substituents continues for nearly all the diastereomeric pairs listed in the Table. The configuration of the diastereomeric pair (**20a,b**) which was synthesised by an aldol condensation reaction, and of the acetate **21a**, have already been assigned on this basis.¹⁸

Clearly from the above discussion there exists some type of anisotropic effect which accounts for the difference in δ -values for corresponding protons in the *erythro* (**a**) - and *threo* (**b**)-isomers. Examination of scale models at various conformations failed to afford an insight into the origin of such anisotropic effects, and it was impossible to assign a favoured conformation to any of the diastereomers listed in the Table.

EXPERIMENTAL

General.—Melting points were determined on a Reichert-Jung Thermovar apparatus and are uncorrected. ^1H NMR spectra were obtained using a Jeol JNM-PMX-60, and a Jeol JNM-GX 270 FT spectrometer. ^{13}C NMR were recorded on a Jeol JNM-GX 270 FT (67.80 MHz) spectrometer and such spectra were assigned using DEPT editing or by analogy with spectra obtained using such an editing technique, and in

Table: ^1H nmr^a signals for some aurone epoxide solvoysis products, derivatives and similar compounds

Compound	β -Ph ^b	4-H ^c	5-H ^c	7-H ^c	6-OMe	β -H	α -Substituent	β -Substituent
5a ^d	7.50m					4.60	OH 4.95	OMe 3.16
5b ^d	7.20m					4.62	OH 4.95	OMe 3.44
7a	7.48m	7.56	6.64dd	6.57d	3.87	4.57	OH 5.00	OMe 3.16
7b	7.23m	7.32	6.47dd	6.35d	3.77	4.60	OH 5.00	OMe 3.42
9a ^e	7.40m		6.13d	6.27d	f	4.40	OH 7.61	OMe 2.98
9b ^e	7.24m		6.02d	6.20d	f	4.45	OH 7.72	OMe 3.17
10a ^d	7.45m				3.89	6.04	OAc 1.92	OAc 1.92
10b ^d	7.28m				3.83	6.11	OAc 2.17	OAc 2.17
11a ^d	7.55m	7.65dd				4.62	OMe 3.10	OMe 3.10
11b ^d	7.23m	7.40dd				4.58	OAc 2.13	OMe 3.34
12a	7.50m	7.65d	6.70dd	6.55d	3.90	4.63	OAc 1.98	OMe 3.16
12b	7.15m	7.22d	6.38dd	6.28d	3.75	4.50	OAc 2.09	OMe 3.33
13a	7.54m		6.15d	6.25d	f	4.67	OAc 1.96	OMe 3.17
13b			5.95d	6.15d	f	4.65	OAc 2.12	OMe 3.41
14a	7.41m	7.59d	6.65dd	6.54d	3.84	6.10	OAc 1.97	OAc 1.86
14b	7.25m	7.39d	6.55dd	6.45d	3.82	6.19	OAc 2.09	OAc 2.12
15a	7.40m	7.49d	6.56dd	6.53d	3.85	5.08ds	OMe 3.23	OH 2.61ds
15b	7.27m	7.35d	6.48dd	6.42d	3.83	5.01	OMe 3.33	OH 3.25h
16a	7.40	7.56d	6.66	6.59d	3.90	6.08	OMe 3.19	OAc 1.86
16b	7.35m	7.40d	6.53dd	6.49d	3.87	6.15	OMe 3.29	OAc 2.12
20a ⁱ	j		6.08dk	6.23dk	f	5.06	OMe 3.15	OH ⁱ
20b ⁱ	j		5.99dk	6.16dk	f	5.03	OMe 3.25	OH ⁱ
21a	j		6.07k	6.23dk	f	6.06	OMe 3.21	OAc 1.93

^a In δ values relative to TMS in CDCl_3 unless otherwise stated. ^b When multiplets, the mean values are given. ^c Doublets (d); *ortho*-coupling, J 8–9 Hz; *meta*-coupling, J 2–2.5 Hz; *Para*-coupling, J ca 1 Hz. ^d A-Ring protons not fully resolved. ^e $(\text{CD}_3)_2\text{SO}$ as solvent. ^f The signals for the 4- and 6-OMe groups were not distinguished: for 9a both at 3.84, for 9b both at 3.74, for 13a at 3.99 and 3.90; for 13b both at 3.84; for 20a 3.89 and 3.91; for 20b 3.84 and 3.86; and for 21a 3.93 and 3.95. ^g (d) ca. 5 Hz. ^h This was a tentative assignment. ⁱ Recorded in CDCl_3 - CD_3CN with TMS as internal standard. ^j 20a 8.18 (3',5'-H)d, *ortho*-coupling J = 9 Hz, 7.70 (2',6'-H)dd, *ortho*-coupling J = 9 Hz, 2',6'-H- β -H coupling 1 Hz; 20b 8.38 (3',5'-H)d, *ortho*-coupling J = ca. 9 Hz, 7.59 (2',6'-H)d, *ortho*-coupling J = ca. 9 Hz; 21a 8.22 (3',5'-H)d, *ortho*-coupling J = ca. 9 Hz, 7.65 (2',6'-H)d, J = ca. 9 Hz. ^k *meta*-coupling J = ca. 1.8 Hz. ^l δ value not specified due to probable peak overlap.

some cases assignment was made by recourse to published chemical shift correlation tables.¹⁹ Tetramethylsilane was used as the internal standard in all NMR spectra recorded on the Jeol JNM-PMX-60 and the Jeol JNM-GX 270 FT spectrometer, and chemical shifts are reported as δ_{H} (ppm) or δ_{C} (ppm) from this standard. *J*-values are given in Hz. Infra-red spectra were recorded on a Perkin-Elmer 1710, a Perkin-Elmer 1740 Infra-red F.T. and a Mattison Galaxy Series F.T. I.R. 3000 spectrometer. 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 (Art. 7734). Merck precoated Kieselgel 60F₂₅₄ was used for TLC and Merck Kieselgel PF₂₅₄₊₃₃₆ for Preparative Layer Chromatography (PLC). All solvents were purified and dried by standard techniques.

(α S, β S; α R, β R)-2,6-Dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15b**

A mixture of (*E*)-2-benzylidene-6-methoxybenzo[b]furan-3(2H)-one epoxide **24** (0.03 g, 0.11 mmol) and methanol (10 mL) was treated with concentrated sulphuric acid (3 drops) and heated on a steam bath for 10 min. The reaction mixture was allowed to cool to room temperature. It was then diluted with water (23 mL), extracted with diethyl ether (2 x 30 mL), dried (MgSO₄) and evaporated to dryness to furnish an oil²⁰ (0.029 g). This oil was dissolved in chloroform (20 mL) and extracted with aqueous sodium hydroxide (10%; 20 mL), washed with saturated aqueous sodium chloride, dried (MgSO₄) and upon evaporation to dryness under reduced pressure, gave (α S, β S; α R, β R)-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15b** as a white solid (0.004 g, 12%), which crystallised from ethanol-water as colourless cubes, m.p. 113.5–115.5°C; δ_{H} (270 MHz; CDCl₃) 3.15 [s(br), -C(OH)HPh, 1H], 3.34 (s, 2-OMe, 3H), 3.84 (s, 6-OMe, 3H), 5.01 [s, -C(OH)HPh, 1H], 6.42 (d, *J* 2.0 Hz, 7-H, 1H), 6.47 (dd, *J* 8.6, 2.0 Hz, 5-H, 1H), 7.18 (m, 3', 4', 5'-H, 3H), 7.36 (d, *J* 8.6 Hz, 4-H, 1H) and 7.37 (m, 2', 6'-H, 2H) (see below for full characterisation). The alkaline extract containing (α R, β S; α S β R)-**7 a**³ and (α S, β S; α R, β R)-2-hydroxy-6-methoxy-3-(methoxyphenylmethyl)benzo[b]furan-3(2H)-one **7b**³ was discarded in the case of this experiment.

Bromination of 6-methoxybenzo[b]furan-3(2H)-one **25**

Experiment a:

6-Methoxybenzo[b]furan-3(2H)-one **25**²¹ (1.0 g, 6.1 mmol) in anhydrous diethyl ether (30 mL) at 0°C was treated with bromine (0.3 mL, 6.1 mmol) over a period of 40 min under an atmosphere of nitrogen. The mixture was diluted with water (30 mL), treated with activated decolourising charcoal and dried (CaSO₄). Evaporation of the solvent to dryness yielded a red oil (1.24 g) which was purified by PLC on silica gel developed with benzene—n-hexane (7 : 3) to afford four bands listed in order of increasing polarity.

Band 1:

Gave 2-bromo-6-methoxybenzo[b]furan-3(2H)-one **26** (0.24 g, 20%) as a red solid, m.p. 85–90°C [lit.¹¹ m.p. 95°C (decomp)]; δ_{H} (60 MHz; CDCl₃) 3.90 (s, 6-OMe, 3H), 6.46 (s, 2-H, 1H), 6.58 (d, *J* 2.0 Hz, 7-H, 1H), 6.76 (dd, *J* 8.7, 2.0 Hz, 5-H, 1H) and 7.64 (d, *J* 8.6 Hz, 4-H, 1H).

Band 2:

Afforded 2,5-dibromo-6-methoxybenzo[b]furan-3(2H)-one **30** (0.085 g, 7%) as a yellow solid, m.p. 158–161°C (lit.²² m.p. 160°C); δ_{H} (60 MHz; CDCl₃) 4.00 (s, 6-OMe, 3H), 6.48 (s, 2-H, 1H), 6.63 (s, 7-H, 1H) and 7.88 (s, 4-H, 1H); δ_{C} (67.80 MHz; CDCl₃) 57.17 (6-OMe), 76.54 (2-C), 96.66 (7-C), 108.18 (5-C), 111.82 (9-C), 129.26 (4-C), 164.24 (6-C), 171.82 (8-C) and 191.52 (3-C).

Band 3:

Gave 2,2-dibromo-6-methoxybenzo[b]furan-3(2H)-one as a solid **28** (0.16 g, 13%) which crystallised as needles from diethyl ether, m.p. 134–135°C; $\nu_{\max}(\text{KBr})$ 1728 and 1620 cm^{-1} ; δ_{H} (60 MHz; CDCl_3) 3.92 (s, 6-OMe, 3H), 6.60 (d, J 2.4 Hz, 7-H, 1H), 6.78 (dd, J 8.5, 2.4 Hz, 5-H) and 7.64 (d, J 8.5 Hz, 4-H, 1H); δ_{C} (67.80 MHz; CDCl_3); 56.39 (6-OMe), 79.06 (2-C), 96.93 (7-C), 106.83 (9-C), 113.92 (5-C), 127.86 (4-C), 169.05 (8-C), 169.71 (6-C) and 186.81 (3-C); m/z (E.I.) 324 ($\text{M}^+ + 4$, 3), 322 ($\text{M}^+ + 2$, 6), 320 (M^+ , 3), 243 ($\text{M}^+ + 2 - ^{79}\text{Br}/\text{M}^+ + 4 - ^{81}\text{Br}$, 81), 241 ($\text{M}^+ - ^{79}\text{Br}/\text{M}^+ + 2 - ^{81}\text{Br}$, 100), 215 ($\text{M}^+ + 2 - \text{CO}^{79}\text{Br}$, 17), 213 ($\text{M}^+ - \text{CO}^{79}\text{Br}$, 18), 106 ($\text{C}_7\text{H}_6\text{O}^+$, 56), 91 ($\text{C}_7\text{H}_6\text{O}^+ - \text{CH}_3$, 7) and 75 ($\text{C}_7\text{H}_6\text{O}^+ - \text{CH}_3\text{O}$, 18%). Found: C, 33.72; H, 1.88; Br, 50.20; $\text{C}_9\text{H}_6\text{Br}_2\text{O}_3$ requires: C, 33.57; H, 1.88; Br, 49.64%.

Band 4:

Afforded 2,2,5-tribromo-6-methoxybenzo[b]furan-3(2H)-one **29** as a yellow solid (0.036 g, 3%) which crystallised from ethanol as needles, m.p. 160–162°C (lit.²² m.p. 164°C).

Experiment b:

6-Methoxybenzo[b]furan-3(2H)-one **25** (0.6 g, 3.7 mmol) in diethyl ether (35 mL) at -10°C was treated with a solution of bromine (0.19 mL, 3.7 mmol) in diethyl ether/chloroform (50 : 50) (25 mL) over 2 h. The mixture was stirred at 0°C for a further 30 min., diluted with water (60 mL), treated with activated decolourising charcoal and dried (CaSO_4). Evaporation of the solvent under reduced pressure furnished a pale yellow solid, which crystallised from diethyl ether as needles of 2,2-dibromo-6-methoxybenzo[b]furan-3(2H)-one **28** (0.6 g, 50%), m.p. 134–135°C.

Experiment c:

A mixture of 6-methoxybenzo[b]furan-3(2H)-one **25** (4.63 g, 0.028 mol), dioxane (25 mL) and diethyl ether (25 mL) was treated with a solution of bromine (4.46 g, 27.7 mmol) in diethyl ether/dioxane (50 : 50) (40 mL) over a period of 1 h at 0°C . Stirring was continued at the same temperature for 30 min. It was filtered, water (25 mL) was added, followed by chloroform (25 mL), the organic layer was dried (CaSO_4) and the solvent evaporated to give 2-bromo-6-methoxybenzo[b]furan-3(2H)-one **26** (6.64 g, 97%) as a brown solid. This solid was dried under vacuum (*ca.* 0.1 mmHg for 5 h), m.p. 85–90°C [lit.¹¹ m.p. 95°C (decomp.)]; $\nu_{\max}(\text{KBr})$ 1723 and 1617 cm^{-1} ; δ_{H} (60 MHz; CDCl_3) 3.91 (s, 6-OMe, 3H), 6.48 (s, 2-H, 1H), 6.59 (d, J 2.0 Hz, 7-H, 1H), 6.75 (dd, J 8.7 and 2.0 Hz, 5-H, 1H) and 7.66 (d, J 8.6 Hz, 4-H, 1H); δ_{C} (67.80 MHz; CDCl_3) 56.19 (6-OMe), 76.84 (2-C), 96.90 (7-C), 110.71 (9-C), 113.08 (5-C), 126.59 (4-C), 169.0 (8-C), 172.95 (6-C) and 192.38 (3-C); m/z (E.I.) 244 ($\text{M}^+ + 2$, 23), 242 (M^+ , 23), 163 ($\text{M}^+ - ^{79}\text{Br}$, 100), 135 ($\text{M}^+ - \text{C}^{79}\text{BrO}$, 51), 134 ($\text{M}^+ - \text{C}^{79}\text{BrHO}$, 20), 107 ($\text{C}_7\text{H}_7\text{O}^+$, 7.5) and 106 ($\text{C}_7\text{H}_6\text{O}^+$, 37%); Found C, 44.07; H, 2.96; Br, 32.74; M^+ , 241.9559. Calc. for $\text{C}_9\text{H}_7\text{BrO}_3$ C, 44.47; H, 2.90; Br, 32.87%. M^+ , 241.9578.

2,6-Dimethoxybenzo[b]furan-3(2H)-one 27

A mixture of 2-bromo-6-methoxybenzo[b]furan-3(2H)-one **26** (3.25 g, 13.37 mmol) and methanol (45 mL) was stirred at room temperature for 48 h at which stage an orange precipitate appeared. This was filtered, washed with cold ethanol—petroleum spirits (b.p. 60–80°C) (50 : 50) and recrystallised from ethanol to give needles of 2,6-dimethoxybenzo[b]furan-3(2H)-one **27** (0.645 g, 25%), m.p. 113–115°C (lit.¹⁵ m.p. 116–117°C); $\nu_{\max}(\text{KBr})$ 1723 and 1621 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 3.63 (s, 2-OMe, 3H), 3.90 (s, 6-OMe, 3H), 5.30 (s, 2-H, 1H), 6.50 (d, J 2.1 Hz, 7-H, 1H), 6.65 (dd, J 8.6, 2.1 Hz, 5-H, 1H), 7.57 (d, J 8.6 Hz, 4-H, 1H); δ_{C} (67.80 MHz; CDCl_3) 55.99 (2-OMe), 56.91 (6-OMe), 96.38 (7-C), 103.31 (2-C), 111.80 (5-C), 113.00 (9-C), 126.12 (4-C),

169.16 (8-C), 174.17 (6-C) and 193.48 (3-C); m/z (E.I.) 194 (M^+ , 19), 166 ($M^+ - CO$, 1.3), 164 ($M^+ - CH_2O$, 93), 151 ($M^+ - CO - CH_3$, 61), 135 ($C_8H_7O_2^+$, 29), 134 ($C_8H_6O_2^+$, 100), 107 ($C_7H_7O^+$, 15%) and 106 ($C_7H_6O^+$, 86%); Found C, 62.02; H, 5.26; Calc. for $C_{10}H_{10}O_4$ C, 61.84; H, 5.20%.

($\alpha R, \beta S; \alpha S, \beta R$)-**15a** and ($\alpha S, \beta S; \alpha R, \beta R$)-2,6-Dimethoxy-2-(hydroxyphenylmethyl)-benzo[b]furan-3(2H)-one **15b**

Experiment a:

n-Butyllithium (2.5 M in *n*-hexane; 0.75 mL) was added to a stirred solution of diisopropylamine (0.26 mL, 1.8 mmol) in anhydrous tetrahydrofuran (14 mL) at -78°C under nitrogen. Stirring was continued for 15 min. A solution of 2,6-dimethoxybenzo[b]furan-3(2H)-one **27** (0.3 g, 1.55 mmol) in anhydrous tetrahydrofuran (20 mL) — previously cooled to -78°C — was added slowly and stirring was continued at the same temperature for a further 30 min. Benzaldehyde (0.16 mL, 1.55 mmol) in anhydrous tetrahydrofuran (8 mL) cooled to -78°C was added and stirred for 35 min. The mixture was added to aqueous ammonium chloride (10%; 60 mL) and it was extracted with diethyl ether (60 mL). It was washed with saturated aqueous sodium chloride (2 x 45 mL), dried ($CaSO_4$) and evaporated to dryness to yield a yellow solid (0.6 g). The solid was purified by column chromatography (eluant: benzene—ethyl acetate; 3 : 2) on silica gel. Two bands were recovered and are given in order of increasing polarity.

Band 1:

Gave ($\alpha R, \beta S; \alpha S, \beta R$)-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15a** as a solid (0.223 g, 48%) which crystallised from ethanol—ethyl acetate (50 : 50) as colourless needles, m.p. $173\text{--}175^\circ\text{C}$ (lit.³ m.p. $171\text{--}172^\circ\text{C}$); ν_{\max} (KBr) 3435, 1693 and 1604 cm^{-1} ; δ_H (60 MHz; $CDCl_3$) 2.58 (d, J 4.6 Hz, β -OH, 1H), 3.26 (s, 2-OMe, 3H), 3.88 (s, 6-OMe, 3H), 5.09 (d, J 4.6 Hz, β -H, 1H), 6.53 (d, J 2.2 Hz, 7-H, 1H), 6.58 (dd, J 8.6, 2.2 Hz, 5-H, 1H), 7.31 (m, 3', 4', 5'-H, 3H), 7.49 (m, 2', 6'-H, 2H) and 7.50 (d, J 8.6 Hz, 4-H, 1H); δ_C (67.80 MHz; $CDCl_3$) 52.47 (2-OMe), 55.96 (6-OMe), 75.39 [$-C(H)OHPh$], 95.87 (7-C), 108.79 (2-C), 111.60 (5-C), 114.55 (9-C), 125.37 (4-C), 127.87 (2', 6'-C), 127.92 (4'-C), 128.41 (3', 5'-C), 137.44 (1'-C), 169.11 (8-C), 174.55 (6-C) and 196.36 (3-C); m/z 301 (C.I.) ($M^+ + 1$, 100), 283 ($M^+ + 1 - H_2O$, 43), 269 ($M^+ + 1 - MeOH$, 8), 195 ($M^+ + 1 - C_7H_6O$, 63), 194 ($M^+ + 1 - C_7H_7O$, 37), 179 ($C_{10}H_{10}O_4^+ - CH_3$, 8) and 107 ($C_7H_7O^+$, 50%); Found C, 68.16; H, 5.41; Calc. for $C_{17}H_{16}O_5$ C, 67.98; H, 5.38%.

Band 2:

Gave ($\alpha S, \beta S; \alpha R, \beta R$)-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15b** as a solid (0.061 g, 13%) which was recrystallised from methanol—ethyl acetate (50 : 50) with a trace of *n*-hexane to give cubes, m.p. $113\text{--}115^\circ\text{C}$; ν_{\max} (KBr) 3467, 1694 and 1608 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 3.25 [s(br), $-C(H)OHPh^*$, 1H], 3.33 (s, 2-OMe, 3H), 3.83 (s, 6-OMe, 3H), 5.01 [s, $-C(OH)HPh$, 1H], 6.42 (d, J 2.0 Hz, 7-H, 1H), 6.48 (dd, J 8.6, 2.0 Hz, 5-H, 1H), 7.17 (m, 3', 4', 5'-H, 3H), 7.35 (d, J 8.6 Hz, 4-H, 1H) and 7.36 (m, 2', 6'-H, 2H). (*This assignment is tentative.); δ_C (67.80 MHz; $CDCl_3$) 52.72 (2-OCH₃), 55.95 (6-OCH₃), 75.42 [$-C(H)OHPh$], 95.65 (7-C), 108.65 (2-C), 111.69 (5-C), 114.19 (9-C), 125.33 (4-C), 127.76 (2', 6', 4'-C), 128.35 (3', 5'-C), 135.46 (1'-C), 169.13 (8-C), 173.95 (6-C) and 195.26 (3-C); m/z (C.I.) 301 ($M^+ + 1$, 47), 283 ($M^+ + 1 - H_2O$, 44), 269 ($M^+ + 1 - MeOH$, 7), 195 ($M^+ - C_7H_6O$, 100), 194 ($M^+ + 1 - C_7H_7O$, 51), 179 ($C_{10}H_{10}O_4^+ - CH_3$, 16) and 107 ($C_7H_7O^+$, 99%). Found C, 67.76; H, 5.36; $C_{17}H_{16}O_5$ requires C, 67.98; H, 5.38%.

Experiment b:

This experiment was carried out in much the same manner as for experiment a, with one major difference, the reaction mixture was treated with magnesium dibromoetherate (0.5 g, 1.55 mmol) in anhydrous tetrahydrofuran

(20 mL) after the addition of 2,6-dimethoxybenzo[b]furan-3(2H)-one **27** (0.3 g) and the mixture was stirred at -78°C for 10 min. Benzaldehyde (0.16 mL) was then added and stirring was continued at the same temperature for 1 h. The work-up was the same as before. The crude solid was purified to give two bands, which were identified as ($\alpha R, \beta S; \alpha S, \beta R$)-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15a** (0.16 g, 33%), m.p. $173\text{--}174^{\circ}\text{C}$ (lit.³ m.p. $171\text{--}172^{\circ}\text{C}$) and ($\alpha S, \beta S; \alpha R, \beta R$)-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15b** (0.116 g, 25%), m.p. $113\text{--}115^{\circ}\text{C}$.

Reaction of 2,6-dimethoxybenzo[b]furan-3(2H)-one with in situ generated bromomagnesium diisopropylamide (BMDA)

Diisopropylamine (0.26 mL, 1.8 mmol) was added to a mixture of magnesium dibromoetherate (0.6 g, 2.33 mmol) and anhydrous tetrahydrofuran (18 mL). *n*-Butyllithium (2.5 M in *n*-hexane; 0.75 mL) was added and it was left stirring at -78°C for 15 min. 2,6-Dimethoxybenzo[b]furan-3(2H)-one **27** (0.3 g, 1.55 mmol) in anhydrous tetrahydrofuran (20 mL) previously cooled to -78°C , was added in two portions and it was left stirring at -78°C for 30 min. A precooled solution of benzaldehyde (0.16 mL) in anhydrous tetrahydrofuran (8 mL) was added and the reaction mixture stirred for a further 30 min. The work-up was similar to that of experiment a. Purification of the crude product was by column chromatography (eluant: chloroform—ethyl acetate; 9 : 1) on silica gel. Three bands were obtained and are given in order of increasing polarity.

Band 1:

Afforded 2-(3-hydroxy-2,6-dimethoxy-2,3-dihydrobenzofuran-3-yl)-2,6-dimethoxybenzo[b]furan-3(2H)-one **32** (0.157 g, 26%) which crystallised as cubes from petroleum spirits (b.p. $60\text{--}80^{\circ}\text{C}$)—ethyl acetate (4 : 1), m.p. $146\text{--}149^{\circ}\text{C}$; ν_{max} (KBr) 3477, 1747, 1719 and 1613 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 3.22 (s, 2'-OMe, 3H), 3.49 (s, 3'-H, 1H), 3.71 (s, 2-OMe, 3H), 3.79 (s, 6'-OMe, 3H), 3.92 (s, 6-OMe 3H), 6.18 (s, 2'-H, 1H), 6.42 (d, J 2.2 Hz, 7'-H, 1H), 6.54 (dd, J 8.4, 2.2 Hz, 5'-H, 1H), 6.63 (m, 5-H, 7-H, 2H), 7.49 (d, J 8.4 Hz, 4'-H, 1H) and 7.55 (d, J 9.0 Hz, 4-H, 1H); δ_{C} (67.80 MHz; CDCl_3) 52.47 (2-OMe), 55.47 (6-OMe), 56.00 (6'-OMe), 57.50 (2'-OMe), 75.39 (3'-C), 82.11 (9'-C), 95.87 (7-C), 96.11 (2'-C), 105.11 (7'-C), 107.78 (5'-C), 108.53 (2-C), 111.58 (5-C), 114.73 (9-C), 125.33 (4'-C), 126.77 (4-C), 159.89 (8'-C), 162.43 (6'-C), 169.17 (8-C), 174.66 (6-C) and 196.36 (3-C); m/z 388 (M^+ , 1), 371 ($\text{M}^+ - \text{OH}$, 3), 194 ($\text{C}_{10}\text{H}_{10}\text{O}_4^+$, 74), 179 (100), 164 (66), 151 (58), 134 (68) and 106 (68%); Found C, 61.68; H, 4.90; $\text{C}_{20}\text{H}_{20}\text{O}_8$ requires C, 61.84; H, 5.20%.

Band 2:

Afforded 2,6-dimethoxybenzo[b]furan-3(2H)-one **27** (0.045 g, 15%) which crystallised as needles from ethanol—petroleum spirits (b.p. $60\text{--}80^{\circ}\text{C}$) (50 : 50) m.p. $113\text{--}115^{\circ}\text{C}$ (lit.¹⁵ m.p. $116\text{--}117^{\circ}\text{C}$).

Band 3:

Gave ($\alpha R, \beta S; \alpha S, \beta R$)-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15a** (0.13 g, 28%) which crystallised as needles from ethanol—ethyl acetate (50 : 50), m.p. $173\text{--}175^{\circ}\text{C}$. (lit.³ m.p. $171\text{--}172^{\circ}\text{C}$).

($\alpha S, \beta S; \alpha R, \beta R$)-2-(Acetoxyphenylmethyl)-2,6-dimethoxybenzo[b]furan-3(2H)-one **16b**

A mixture of ($\alpha S, \beta S; \alpha R, \beta R$)-2,6-dimethoxy-2-(hydroxyphenylmethyl)benzo[b]furan-3(2H)-one **15b** ($0.0165\text{ g}, 5.49 \times 10^{-5}\text{ mol}$), acetic anhydride (3 mL) and anhydrous pyridine (0.04 mL, 0.49 mmol) was stirred at room temperature for 23 h. The mixture was poured into ice—water (50 mL) and left standing at 4°C for 48 h. The precipitate was filtered, washed with water and dried under vacuum (@ 1 Torr) over $\text{CaCl}_2/\text{CaSO}_4$ for 3 days. The filtrate was extracted with chloroform (2 x 50 mL), dried (MgSO_4) and evaporated to dryness to afford a white solid, which was pooled with the precipitate above. The combined solids crystallised as needles of ($\alpha S, \beta S; \alpha R, \beta R$)-2-(acetoxyphenylmethyl)-2,6-dimethoxybenzo[b]furan-3(2H)-one **16b** (0.018 g, 94%) m.p.

180–182°C; ν_{\max} (KBr) 1739, 1714 and 1609 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.12 (s, CO_2Me , 3H), 3.29 (s, 2-OMe, 3H), 3.87 (s, 6-OMe, 3H), 6.15 [s, $-\text{C}(\text{OAc})\text{HPh}$, 1H], 6.49 (d, J 2.0 Hz, 7-H, 1H), 6.53 (dd, J 8.5, 2.0 Hz, 5-H, 1H), 7.32 (m, 3', 4', 5'-H, 3H), 7.38 (m, 2', 6'-H, 2H) and 7.40 (d, J 8.5 Hz, 4-H, 1H); δ_{C} (67.80 MHz; $\text{CD}_3\text{CN}/\text{CDCl}_3$) 20.93 (CO_2Me), 52.58 (2-OMe), 56.28 (6-OMe), 75.39 [$\text{CH}(\text{OAc})\text{Ph}$], 96.30 (7-C), 107.45 (2-C), 111.91 (5-C), 114.16 (9-C), 125.85 (4-C), 128.19 (2', 6'-C), 128.27 (4'-C), 128.84 (3', 5'-C), 133.76 (1'-C), 169.41 (OCOMe), 169.58 (8-C), 173.86 (6-C) and 193.86 (3-C); m/z 342 (M^+ , 0.5), 283 ($\text{M}^+ - \text{OAc}$, 12), 251 ($\text{M}^+ - \text{OAc} - \text{MeOH}$, 13), 236 ($\text{M}^+ - \text{OAc} - \text{MeOH} - \text{CH}_3$, 53), 194 ($\text{C}_{10}\text{H}_{10}\text{O}_4^+$, 100), 179 ($\text{C}_{10}\text{H}_{10}\text{O}_4^+ - \text{CH}_3$, 88) and 151 ($\text{C}_{10}\text{H}_{10}\text{O}_4^+ - \text{CH}_3 - \text{CO}$, 10%); Found C, 65.53; H, 5.51; $\text{C}_{19}\text{H}_{18}\text{O}_6 \cdot \frac{1}{4} \text{H}_2\text{O}$ requires C, 65.78; H, 5.39% $\text{M}^+ - \text{C}_2\text{H}_3\text{O}_2$, 283.0997. $\text{C}_{19}\text{H}_{18}\text{O}_6$ requires $\text{M} - \text{C}_2\text{H}_3\text{O}_2$, 283.0970.

ACKNOWLEDGEMENTS

A.J.B would like to thank EOLAS (the Irish Science and Technology Research Agency) for financial support and Prof. D.M.X. Donnelly (University College Dublin) for helpful advice and assistance during the course of this work.

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