Biomimetic Syntheses of Polyketide Aromatics from Reaction of an Orsellinate Anion with Pyrones and a Pyrylium Salt [1]

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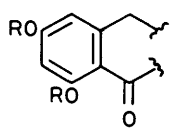
Orsellinate anion (**12**) shows highly regioselective attack on pyrones (**13**), (**22**), and (**30**), and the products were simply converted into derivatives of the polyketides: toralactone (**19**), 6-hydroxymusizin (**26**), and eleutherinol (**32**); although reaction of the anion (**12**) with the pyrylium salt (**33**) is less selective, the major product (**34**) can give derivatives of either alternariol (**36**) or rubrofusarin (**37**) in regiospecific biomimetic reactions.

In the preceding paper [2] we described how a *cis*-enol ether may be used to determine the point of folding of a polyketide chain and may thus be used to give some control over subsequent cyclization reactions. It is possible that this is a mechanism of control used *in vivo* as well as *in vitro* and this would explain why the point of chain folding is the most common position for *O*-methylation in polyketides. However the problems involved in ensuring that the correct oxygen of a poly-β-ketone chain is methylated and that the double bond is in the right position, and has the *cis*-orientation, are formidable. A more reliable method of dictating a *cis*-orientation of two groups is to have them situated *ortho* to one another on a benzene ring, as would be the case in a polyketide intermediate after one aryl ring had been produced. We have therefore investigated the synthesis of molecules containing the partial structure (**1**) which could undergo biomimetic cyclization to produce polyketides. As a starting point for these syntheses we have used the anion of methyl orsellinate dimethyl ether (**2**).[1] Inspection of the structure of polyketides shows that a great many of those that have not undergone extensive modification after aromatisation contain, at the point of chain folding, the partial structure of orsellinic acid (**3**) (see Scheme). Some examples of this are toralactone (**4**), rubrofusarin (**5**), alternariol (**6**), torachrysone (**7**), endocrocin (**8**), averufin (**9**) (the aflatoxin precursor), zearalenon (**10**), and the olivomycins (**11**). It is metabolites of this type which we were aiming to synthesise by our approach.

Results

Treatment of methyl orsellinate dimethyl ether with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C generates the orange-red anion (**12**).[3] Reaction of this anion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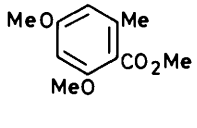
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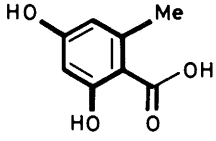
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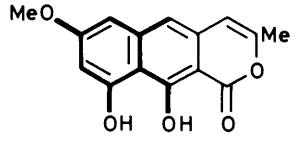
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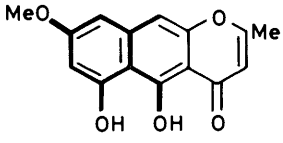
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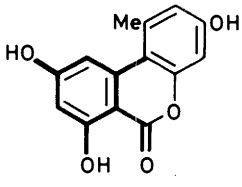
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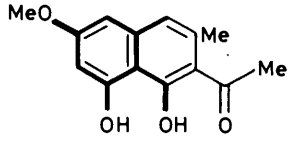
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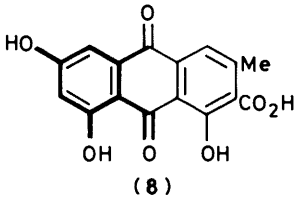
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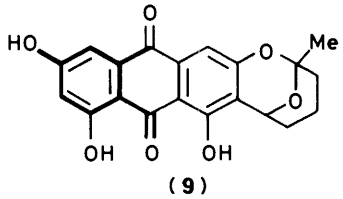
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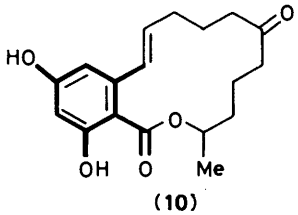
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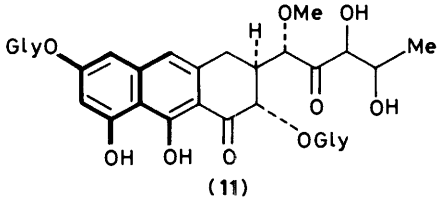
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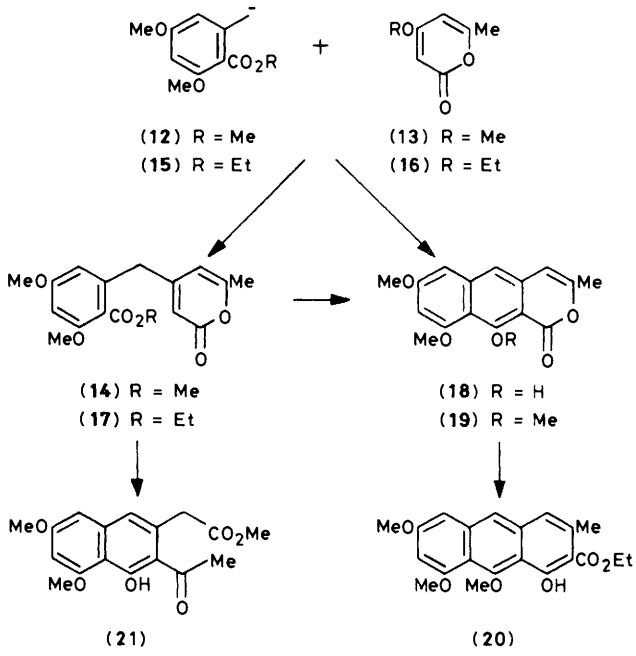
(12) with triacetic lactone methyl ether (13) at −78 °C, followed by quenching while still at −78 °C, gives the 4-benzyl-α-pyrone (14). It was verified that it was the methoxy group at position 4 of the pyrone that had been lost, by using triacetic lactone ethyl ether (16) in place of the methyl ether. The product was the same 4-benzyl-α-pyrone (14) and it was quite clear from the n.m.r. spectrum that the ethoxy group had been lost. In contrast the anion (15) of ethyl orsellinate dimethyl ether with the pyrone (13) gave the 4-benzyl-α-pyrone (17) which retained an ethoxy group. Proof that the product was an α-pyrone and not the isomeric 2-benzyl-γ-pyrone, which would be the product of the expected attack at C-2, came from the spectroscopic data; the only carbonyl absorption in the i.r. spectrum was at 1 735 cm^{-1} (ester and α-pyrone) whereas γ-pyrones absorb at *ca.* 1 670 cm^{-1}. The u.v. spectrum did not show a peak at 240—250 nm characteristic of unconjugated γ-pyrones. The ^{13}C n.m.r. spectrum was as expected for an α-pyrone but showed no signal in the region of δ 180 p.p.m. which is characteristic of the carbonyl of a γ-pyrone.[4] Finally the n.m.r. signals of the pyrone ring protons showed greatly different shifts on addition of $Eu(fod)_3$ as would be predicted for an α-pyrone but not for a γ-pyrone in which the two protons are equidistant from the presumed site of binding, the pyrone carbonyl group.

The yield of (14) from a 1 : 1 mixture of the anion (12) and the pyrone (13) was only 40%, and considerable amounts of starting materials were recovered because the product is deprotonated by the anion (12). However the yield could be improved considerably (to 75%) if an excess of lithium di-isopropylamide (up to 1.95 equivalents) was used to generate (12). If the reaction between anion (12) and pyrone (13) is allowed to warm to room temperature before quenching, the 4-benzyl-α-pyrone cyclizes *in situ* to give the naphthopyrone (18)[3] which shows a bright blue fluorescence. This is a methyl ether of the natural product toralactone (4) isolated from pods of the plant *Cassia tora*.[5] Treatment of the purified 4-benzyl-α-pyrone with LDA at −78 °C followed by warming to room temperature also produces the naphthopyrone (18) but the yield is lower than that given by the complete reaction carried out *in situ*. Methylation of (18) with diazomethane over a period of 5 days gave the trimethoxy compound (19) the melting point and spectra of which were the same as reported[5] for the dimethyl ether of toralactone, thus providing positive confirmation of the structure. This is the first reported synthesis of a derivative of this natural product.

After we had completed this work Hauser and Rhee[6] reported a sequence of reactions to convert 2-methoxy-6-methylbenzoic acid into a naphthopyrone very similar to (19). This synthesis involves 11 steps and does not compare well with our two step synthesis. They found that a Reformatsky reaction on their naphthopyrone produced an anthracene. Similarly, reaction of (19) with zinc and ethyl bromoacetate in benzene gave the anthracene (20) in 37% yield. The latter is a protected form of the likely precursor of naturally occurring anthraquinones such as endocrocin (8) and emodin.

In contrast to the cyclization of (14) with LDA, NaOMe–MeOH caused ring-opening of the pyrone followed by cyclization which proceeded mainly through the alternative position (which had been C-5 of the pyrone) to give a naphthylacetate (21). The yield in this reaction was, however, only 21% and so it would be dangerous to draw any conclusion about the regioselectivity of the reaction. The i.r. absorption at 1 745 cm^{-1} due to the unconjugated ester carbonyl indicates that the structure of the product is (21) and not the isomeric 3-acetonyl-2-naphthoate ester which is the other possible product of ring-opening followed by cyclization.

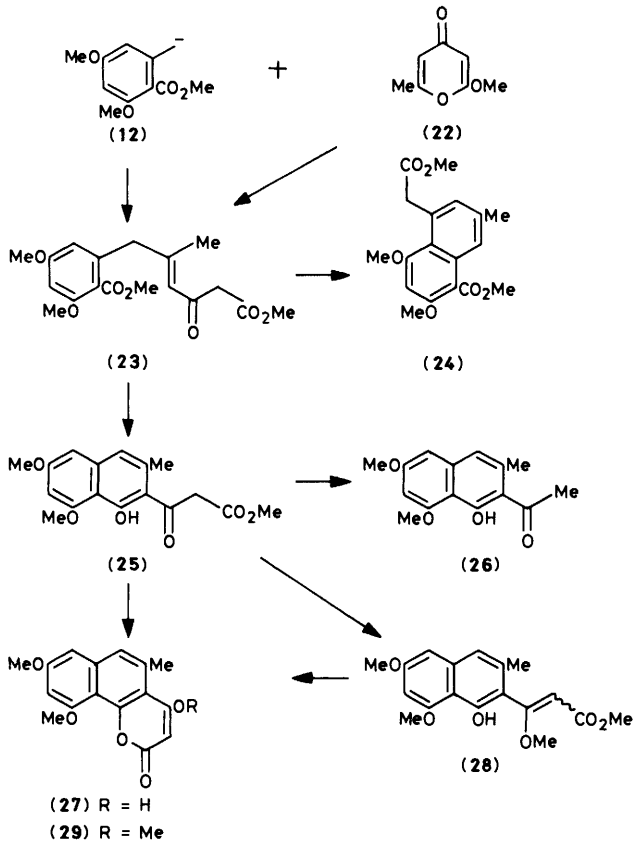
If triacetic lactone is methylated with methyl fluorosulphonate instead of dimethyl sulphate–potassium carbonate the product is not the α-pyrone (13) but the γ-pyrone (22) which has been shown to be the less thermodynamically stable methyl



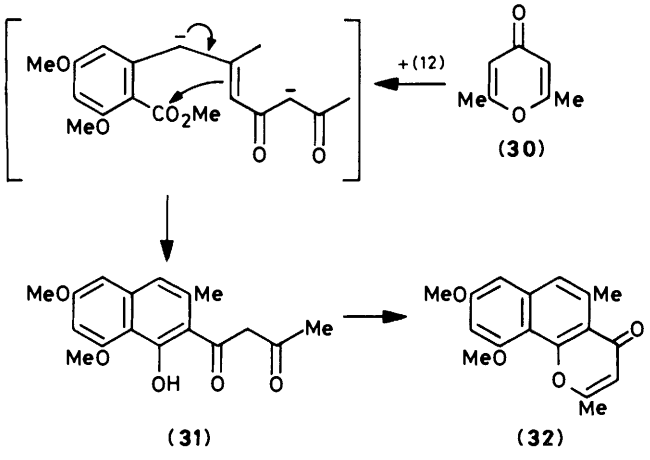
Scheme 1.

ether.[7] Reaction of this pyrone with the anion (12) gave a single product in very good yield. The n.m.r. spectrum showed a mixture of tautomers and/or double-bond isomers none of which could be assigned a precise structure. However subsequent reactions proved that the anion (12) has again attacked by Michael addition this time at C-6 of the pyrone ring. Structure (23) is a likely component of the mixture and the reactions of the mixture were as would be expected for a single compound of that structure. When the mixture was treated with hydrogen chloride in ether a new product m.p. 182—184 °C was formed in high yield, the molecular weight of which from mass spectrometry indicated the elimination of water. U.v. and n.m.r. spectral data indicated that it was a naphthalene and structure (24) was confirmed by the results of double resonance decoupling. Thus the two *meta*-oriented aromatic protons appear as broad singlets (δ 7.38 and 6.91) because allylic coupling to the methyl and methylene protons obscures the coupling between them; on irradiation of the methylene signal (δ 4.08) only the peak at δ 6.91 is sharpened, whereas on irradiation of the methyl signal (δ 2.43) both peaks are sharpened and the one at δ 7.38 appears as a doublet (*J* 2 Hz). If (23) was treated with three equivalents of LDA, and allowed to warm to room temperature, cyclization to the aromatic ester group occurred and the product after work-up was a naphthyl-β-keto ester (25). The product of hydrolysis and decarboxylation of (25) would be a natural product, torachrysone methyl ether (26), which has been found in plant seeds.[8] However, attempted hydrolysis of (25) with NaOH caused very rapid cyclization to the naphthopyrone (27) which resisted further hydrolysis. This cyclization also took place during purification of (25) on silica gel. Methylation of (25) with diazomethane did not protect the phenol but produced an enol ether (28) instead and treatment of this product with NaOH again caused very rapid cyclization to the related naphthopyrone (29). However hydrolysis and decarboxylation of (25) in dilute HCl caused only a small amount of cyclization and the major product was torachrysone methyl ether (26).

The next pyrone to be investigated as a polyketide synthon was 2,6-dimethyl-γ-pyrone (30). By analogy with the reaction of anion (12) with γ-pyrone (22) to give (25), (12) reacted with 2,6-



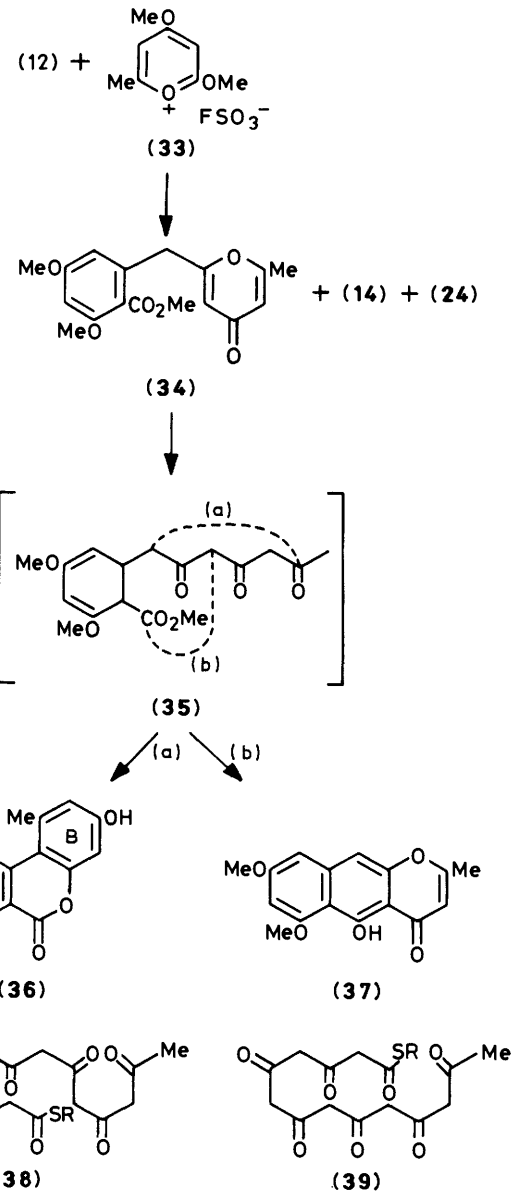
Scheme 2.



Scheme 3.

dimethyl-γ-pyrone (**30**) to give, after cyclization, the naphthyl-β-diketone (**31**) in 79% yield, which further cyclized in trifluoracetic acid solution to give eleutherinol dimethyl ether (**32**) in 90% yield. An alternative synthesis of (**31**) and (**32**) has been mentioned in a review [9] but further details have not been published.

In the reactions described above, the anion (**12**) has shown a strong tendency to attack β to the carbonyl of pyrones. However the third possible methylated derivative of triacetic lactone, the pyrylium salt (**33**) [2] does not have a carbonyl group so the site of attack cannot be predicted. In the event this reaction did not show the selectivity of the previous reactions. The products after treatment with HCl were identified as the



Scheme 4.

previously obtained compounds (**14**) and (**24**) (attack at C-4 and C-6) and the new compound, 2-benzyl-γ-pyrone (**34**). Fortunately the latter product was the major one; it showed all the spectroscopic properties expected for a γ-pyrone, and in addition it formed a hydrochloride salt.

Hydrolysis of the pyrone ring of (**34**) in base should give the triketone (**35**) but this would be expected to cyclize *in situ*. Two cyclizations are possible, (a) or (b) (see Scheme 4), which would lead to derivatives of alternariol (**36**) or rubrofusarin (**37**). When (**34**) was heated with NaOH in aqueous methanol followed by treatment with hydrogen chloride a single product was observed. This was alternariol dimethyl ether (**36**) (83% yield), which on demethylation with hydriodic acid according to the published procedure [10] gave alternariol (**6**).

This short and high-yielding synthesis of the natural product represents a marked improvement over existing syntheses.[10–12]

The alternative cyclization (b) to give the rubrofusarin derivative was not observed in the hydrolysis of (**34**) but could be selected by using a base that does not open the pyrone ring.

Thus treatment of (**34**) with Ph_3CCl gave rubrofusarin monomethyl ether (**37**). The yield (17%) has not been optimized, and it is likely that it could be much higher.

Discussion

The γ-pyrone (**34**) and its ring-opened form (**35**) are protected forms of likely intermediates in the biosynthesis of alternariol and rubrofusarin. Thus the syntheses of (**36**) and (**37**) may be truly biomimetic. In the biosynthesis of alternariol it is known that a single heptaketide chain is involved but it is not known which benzenoid ring is closed first. Our biomimetic approach assumes that ring A is closed first whereas another approach by Harris [11] is based on the assumption that ring B is the first formed. Taken together these two syntheses of alternariol show that, contrary to previous opinion,[11] either biosynthetic pathway is chemically feasible and it will have to be left to biosynthetic studies to settle the matter. There are two possible ways, (**38**) and (**39**), of folding a heptaketide chain to give the rubrofusarin skeleton. Our synthesis follows the pattern in (**38**) and interestingly results in this laboratory have shown that this is also the natural folding pattern employed in the biosynthesis of rubrofusarin by *Fusarium culmorum*.[13] As our results have shown that the preferred cyclization of the triketone chain in (**35**) does not lead to the rubrofusarin skeleton, it is possible that nature selects this cyclization (as we have done) by using a preformed γ-pyrone as in (**34**).

The reactions between the orsellinate derived anion (**12**) and various pyrones and a pyrylium salt have led to several polyketide structures by extremely short routes, and many of the reactions have a surprisingly high degree of regioselectivity, as yet unexplained. Thus both the anion and the pyrones are valuable synthons in the field of polyketide synthesis.

Experimental

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. ^1H N.m.r. spectra were recorded on Varian HAD 100 and Perkin-Elmer R12B and R24A spectrometers, and ^{13}C n.m.r. on a Varian CFT20 spectrometer. All chemical shifts are relative to internal $SiMe_4$. I.r. spectra were recorded on a Perkin-Elmer 157 G spectrometer, and u.v. on a Unicam SP 800B spectrometer. Mass spectra were obtained on AEI, MS9, or MS29 spectrometers. T.l.c. was carried out on commercial plates coated with Merck Kieselgel GF_{254}. P.l.c. was on plates coated with the same silica gel (20 × 20 × 0.1 cm). Tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately before use. The following cooling baths were used: −10 to −15 °C, ice–methanol; −78 °C, solid CO_2–acetone. Unless otherwise indicated, all compounds were pure by t.l.c. and n.m.r.

Lithium Di-isopropylamide (0.5 mmol).—Into a flask containing triphenylmethane (*ca.* 0.5 mg—this acts as an indicator; when on addition of n-butyl-lithium the red colour appears, the solution is quite free of moisture) under an atmosphere of nitrogen was injected di-isopropylamine (0.1 ml, 0.7 mmol), dry THF (2 ml), and n-butyl-lithium (1.7M in hexane; 0.3 ml, 0.51 mmol); the solution was stirred for 15 min before use.

2-*Methoxycarbonyl*-3,5-*dimethoxybenzyl-lithium* (**12**) (0.5 mmol).—Lithium di-isopropylamide solution (0.5 mmol) was cooled to −78 °C and a solution of methyl 2,4-dimethoxy-6-methylbenzoate (**2**) [2] (105 mg, 0.5 *mmol*) in dry THF (1 ml) was injected dropwise; an orange-red colour appeared. The solution was stirred at −78 °C for 30 min before use.

4-(2-*Methoxycarbonyl*-3,5-*dimethoxybenzyl*)-6-*methyl*-2H-*pyran*-2-*one* (**14**).—Into a solution of 2-methoxycarbonyl-3,5-dimethoxybenzyl-lithium (**12**) (0.5 mmol) at −78 °C was injected dropwise a solution of 4-methoxy-6-methyl-2*H*-pyran-2-one (**13**) [14] (70 mg, 0.5 mmol) in dry THF (1 ml). The solution was stirred at −78 °C for 1 h and then concentrated hydrochloric acid (2 ml) was added and the mixture stirred for 10 min while warming to room temperature; water was added (15 ml) and the mixture partially neutralized with sodium carbonate and then extracted with diethyl ether (2 × 10 ml) and ethyl acetate (1 × 10 ml). The organic layers were dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by p.l.c. (2 plates, ethyl acetate–benzene, 1 : 1). Four bands were extracted: R_F 0.6, methyl 2,4-dimethoxy-6-methylbenzoate (**2**) (27 mg, 26%): R_F 0.25, 4-methoxy-6-methyl-2*H*-pyran-2-one (**13**) (28 mg, 40%): R_F 0.35, 4-*benzylpyrone* (**14**) (63 mg, 40%) as a pale yellow oil (Found: M^+, 318.1105. $C_{17}H_{18}O_6$ requires *M*, 318.1102); $\delta_H(CDCl_3)$ 6.40 (1 H, d, *J* 2 Hz), 6.26 (1 H, d, *J* 2 Hz), 5.91 (1 H, br s), 5.86 (1 H, br s), 3.84 (3 H, s), 3.83 (3 H, s), 3.81 (3 H, s), 3.67 (2 H, br s), and 2.18 (3 H, s); $\nu_{max.}$ (CCl_4) 2 970w, 1 735s, and 1 605 cm^{-1}; $\lambda_{max.}$ (MeOH) 247sh and 288 nm; *m/z* 318, 287, 286, 244, and 231; $\delta_C(CDCl_3)$ 168.0 (CO_2Me), 163.0 (C-6), 161.9 (C-2), 161.6 (C-5′), 158.9 (C-4), 157.6 (C-3′), 136.9 (C-1′), 116.8 (C-2′), 110.6 (C-3), 107.1 (C-6′), 105.2 (C-5), 97.7 (C-4′), 56.2 (OMe), 55.6 (OMe), 52.2 (CO_2Me), 39.0 (CH_2), and 19.9 (CH_3). If 1.95 equivalents of lithium di-isopropylamide were used the yield of (**14**) could be improved to 75%.

The fourth band, R_F 0.5, yielded an oil (16 mg) which was dissolved in dry diethyl ether (5 ml), the solution saturated with hydrogen chloride gas and left overnight; on evaporation of this solution crystalline material was obtained, *methyl* 2,4-*dimethoxy*-5,7-*dimethyl*-1-*naphthoate* (15 mg, 11%), m.p. 116—118 °C (from acetone–hexane) (Found: C, 70.3; H, 7.4. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%); $\delta(CCl_4)$ 7.14 (1 H, br s), 6.79 (1 H, br s), 6.32 (1 H, s), 3.88 (6 H, s), 3.85 (3 H, s), 2.72 (3 H, s), and 2.39 (3 H, s); $\nu_{max.}$ (CCl_4) 2 940, 1 730, 1 605, 1 585, and 1 460 cm^{-1}; $\lambda_{max.}$ (MeOH) 240, 295, 306, 324, and 333 nm; *m/z* 274 (M^+) and 243.

When this experiment was repeated using 4-ethoxy-6-methyl-2*H*-pyran-2-one (**16**) [15] (77 mg, 0.5 mmol), instead of the 4-methoxy-6-methyl-2*H*-pyran-2-one (**13**), the product was identical with the above 4-benzylpyran-2-one (**14**) (40 mg, 25%).

4-(2-*Ethoxycarbonyl*-3,5-*dimethoxybenzyl*)-6-*methyl*-2H-*pyran*-2-*one* (**17**).—The synthesis of the methyl ester of the benzylpyrone was followed using ethyl 2,4-dimethoxy-6-methylbenzoate (**15**) (112 mg, 0.5 mmol) instead of the corresponding methyl ester. The yield of the *benzyl-α-pyrone* (**17**) was 41 mg (25%) as a colourless oil (Found: M^+, 332.1250. $C_{18}H_{20}O_6$ requires *M*, 332.1260); $\delta(CDCl_3)$ 6.39 (1 H, d, *J* 2 Hz), 6.24 (1 H, d, *J* 2 Hz), 5.89 (1 H, br s), 5.86 (1 H, br s), 4.29 (2 H, q, *J* 7 Hz), 3.81 (3 H, s), 3.78 (3 H, s), 3.66 (2 H, s), 2.16 (3 H, s), and 1.30 (3 H, t, *J* 7 Hz); $\nu_{max.}$ (CCl_4) 2 940w, 1 735, 1 605, 1 270, and 1 205 cm^{-1}; $\lambda_{max.}$ (EtOH) 247 and 288 nm; *m/z* 332 (M^+), 287, 245, 244, 231, and 217.

Methyl 3-*Acetyl*-4-*hydroxy*-5,7-*dimethoxy*-2-*naphthylacetate* (**21**).—4-(2-Methoxycarbonyl-3,5-dimethoxybenzyl)-6-methyl-2*H*-pyran-2-one (**14**) (56 mg, 0.18 mmol) was dissolved in a solution of sodium methoxide in methanol (1.45M; 5 ml) and stood at room temperature for 2.5 h (by this time t.l.c. showed no starting material remained). The solution was poured into 2% sulphuric acid (25 ml) and extracted with diethyl ether (3 × 10 ml). The ethereal layers were dried over magnesium sulphate and evaporated under reduced pressure. The residue was purified by p.l.c. (diethyl ether) and yielded the following: R_F 0.7, naphthopyrone (**18**) (see later) (1.5 mg, 3%); R_F 0.6, the *naphthylacetate* (**21**) (12 mg, 21%), m.p. 120—125 °C (Found: M^+, 318.1132. $C_{17}H_{18}O_6$ requires *M*, 318.1104);

δ(CCl_4) 9.38 (1 H, s), 6.82 (1 H, s), 6.48 (1 H, d, *J* 2 Hz), 6.28 (1 H, d, *J* 2 Hz), 3.99 (3 H, s), 3.82 (3 H, s), 3.73 (2 H, s), 3.63 (3 H, s), and 2.53 (3 H, s); $\nu_{max.}$ (CCl_4) 3 400br, 1 745, 1 685, 1 630, and 1 370 cm^{-1}; $\lambda_{max.}$ (MeOH) 234, 256sh, 261, 317sh, and 347 nm; (MeOH + 1 drop NaOH) 233, 255sh, 263, 274sh, 347, and 394 nm; *m/z* 318 (M^+), 303, 287, 276, 275, 257, 257, and 244. This compound gave a positive Gibb's test.[16]

10-*Hydroxy*-7,9-*dimethoxy*-3-*methyl*-1H-*naphtho*[2,3-c]-*pyran*-1-*one* (**18**) (*Toralactone Monomethyl Ether B*).—A solution of lithium di-isopropylamide (0.39 mmol) was injected dropwise into a solution of 4-(2-methoxycarbonyl-3,5-dimethoxybenzyl)-6-methyl-2*H*-pyran-2-one (**14**) (57 mg, 0.18 mmol) in dry THF (1 ml) under an atmosphere of nitrogen, cooled to −15 °C. The solution was stirred for 30 min, and then concentrated hydrochloric acid (1 ml) was added. After 5 min the mixture was partially neutralized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (4 × 10 ml). The combined organic layers were washed with saturated brine, dried over magnesium sulphate, and evaporated to dryness under reduced pressure. The residue was purified by p.l.c. (diethyl ether, R_F 0.7) and yielded the naphthopyrone (**18**) [3] (10 mg, 20%). Also recovered was starting material (15 mg, 26%). When this experiment was repeated with lithium di-isopropylamide (0.26 mmol) and 4-(2-ethoxycarbonyl-3,5-dimethoxybenzyl)-6-methyl-2*H*-pyran-2-one (17) (41 mg, 0.125 mmol) the product was the same naphthopyrone (**18**) (4 mg, 11%).

7,9,10-*Trimethoxy*-3-*methyl*-1H-*naphtho*[2,3-c]*pyran*-1-*one* (**19**) (*Toralactone Dimethyl Ether*).—Diazomethane generated from 50% aqueous potassium hydroxide (2 ml) and *N*-nitrosomethylurea (0.5 g, 4.85 mmol) with diethyl ether (5 ml) was distilled directly into a suspension of 10-hydroxy-7,9-dimethoxy-3-methyl-1*H*-naphtho[2,3-*c*]pyran-1-one (**18**) (46 mg, 0.16 mmol) in dry diethyl ether (50 ml). After 5 days at room temperature, in the dark, with occasional shaking, t.l.c. indicated almost complete reaction. The solution was evaporated to dryness under reduced pressure and the residue purified by p.l.c. (diethyl ether, R_F 0.6) to yield colourless crystals of the methyl ether (48 mg, 99%), m.p. 181—184 °C (from MeOH) (lit.,[5] 181 °C) (Found: C, 68.2; H, 5.4. Calc. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37%). The spectra of this compound were identical with those reported for the dimethyl ether of toralactone:[5] δ($CDCl_3$) 7.22 (1 H, s), 6.63 (1 H, d, *J* 2 Hz), 6.46 (1 H, d, *J* 2 Hz), 6.12 (1 H, br s), 3.99 (3 H, s), 3.98 (3 H, s), 3.92 (3 H, s), and 2.22 (3 H, s); $\nu_{max.}$ ($CHCl_3$) 1 725, 1 675, 1 620, 1 570, and 1 350 cm^{-1}; $\lambda_{max.}$ (EtOH) 271 (log $\varepsilon_{max.}$ 4.75), 281 (4.78), 294 (4.55), 380 (3.72), and 262sh nm; *m/z* 300 (M^+) and 271. The pyrone (**18**) could also be methylated to produce (**19**) using Me_2SO_4–K_2CO_3 in acetone.

Ethyl 1-*Hydroxy*-6,8,9-*trimethoxy*-3-*methylanthracene*-2-*carboxylate* (**20**).—Into a vigorously stirred solution of 7,9,10-trimethoxy-3-methyl-1*H*-naphtho[2,3-*c*]pyran-1-one (33 mg, 0.11 mmol) in dry benzene (5 ml), heated under reflux with freshly sandpapered zinc foil cut into small pieces (100 mg, 1.53 mmol), was dripped, over a period of 45 min, a solution of ethyl bromoacetate (0.1 ml, 0.90 mmol) in dry benzene (5 ml). After a further 2 h diethyl ether (15 ml) was added and the mixture was washed successively with 1M-sulphuric acid (10 ml), 0.5M-sulphuric acid (10 ml) (to dissolve the excess zinc), 5% aqueous sodium hydrogen carbonate (5 ml), and saturated brine. The organic layer was then dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by p.l.c. (dichloromethane–diethyl ether, 10:1, R_F 0.45) to give orange crystals of the *anthracenecarboxylate* exhibiting a green fluorescence (15 mg, 37%), m.p. 152—154 °C (from hexane) (Found: M^+, 370.1416. $C_{21}H_{22}O_6$ requires M^+, 370.1416); δ($CDCl_3$) 11.45 (1 H, s), 7.75 (1 H, s), 7.09 (1 H, br s), 6.71 (1 H, d, *J* 2 Hz), 6.44 (1 H, d, *J* 2 Hz), 4.47 (2 H, q, *J* 7 Hz), 4.02 (3 H, s), 4.00 (3 H, s), 3.93 (3 H, s), 2.50 (3 H, d, *J* 1 Hz), and 1.45 (3 H, t, *J* 7 Hz); $\nu_{max.}$ (CCl_4) 1 725w, 1 620, and 1 165 cm^{-1}; $\lambda_{max.}$ (EtOH) 235, 271, 290sh, 383, 400, and 420; (EtOH + NaOH) 269 and 392 nm; *m/z* 370 (M^+) and 324.

2-*Methoxy*-6-*methyl*-4H-*pyran*-4-*one* [7] (**22**).—Methyl fluorosulphonate (10 ml) was distilled from anhydrous potassium carbonate by vacuum transfer directly onto 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 g, 7.94 mmol) and the mixture stirred for 2 h at room temperature. The methyl fluorosulphonate was then removed by vacuum transfer (and could be re-used). A solution of the residue in 10% aqueous sodium hydroxide was nearly saturated with sodium chloride, and then extracted with ethyl acetate (6 × 15 ml). The organic layers were washed with saturated brine, dried over magnesium sulphate, and evaporated to dryness under reduced pressure to give the methyl ether (0.72 g, 64%), m.p. 91—94 °C [from light petroleum (b.p. 40—60 °C)] (lit.,[16] 92.5—94 °C); δ($CDCl_3$) 5.90 (1 H, m), 5.38 (1 H, d, *J* 2 Hz), 3.93 (3 H, s), and 2.24 (3 H, s); i.r., u.v., and mass spectra were as reported.[7]

Methyl 6-(2-*Methoxycarbonyl*-3,5-*dimethoxyphenyl*)-5-*methyl*-3-*oxohex*-4-*enoate* (**23**) (*and Tautomers*).—Into a solution of 2-methoxycarbonyl-3,5-dimethoxybenzyl-lithium (**12**) (0.5 mmol) at −78 °C was injected a solution of 2-methoxy-6-methyl-4*H*-pyran-4-one (**22**) (70 mg, 0.5 mmol) in dry THF (1 ml). The solution was stirred at −78 °C for 3 h and then poured into 2% sulphuric acid (20 ml) and extracted with diethyl ether (3 × 10 ml). The ethereal layers were dried over magnesium sulphate and evaporated to dryness under reduced pressure to give an oil (163 mg, 93%). T.l.c. of the oil indicated one, very nearly pure, product (diethyl ether, R_F 0.6). The n.m.r. spectrum indicated a complex mixture of tautomers; $\nu_{max.}$ (CCl_4) 1 730, 1 690w, 1 600, 1 165, and 1 105 cm^{-1}; $\lambda_{max.}$ (MeOH) 243 and 281sh; (MeOH + 1 drop NaOH) 238 and 284 nm; *m/z* 350 (M^+), 332, 277, and 276.

Methyl 5-*Methoxycarbonyl*-6,8-*dimethoxy*-3-*methyl*-1-*naphthylacetate* (**24**).—(*a*) Methyl 6-(2-methoxycarbonyl-3,5-dimethoxyphenyl)-5-methyl-3-oxohex-4-enoate (**23**) (93 mg, 0.27 mmol) was dissolved in diethyl ether (10 ml) and the solution was saturated with hydrogen chloride gas and allowed to stand overnight at room temperature; it was then evaporated to dryness under reduced pressure. The residue was purified by p.l.c. (diethyl ether, R_F 0.4) and yielded the 1-*naphthylacetate* (**24**) (61 mg, 69%) as colourless crystals, m.p. 182—184 °C (from aqueous methanol) (Found: M^+, 332.1251. $C_{18}H_{20}O_6$ requires *M*, 332.1260); δ($CDCl_3$) 7.38 (1 H, br s) 6.91 (1 H, br s), 6.50 (1 H, s), 4.08 (2 H, s), 3.99 (3 H, s), 3.92 (3 H, s), 3.88 (3 H, s), 3.67 (3 H, s), and 2.43 (3 H, s); $\nu_{max.}$ ($CHCl_3$) 1 720, 1 605, 1 585, and 1 350 cm^{-1}; $\lambda_{max.}$ (EtOH) 242, 297, 307, 321, and 332 nm; *m/z* 332 (M^+), 301, 274, and 273.

(*b*) Methyl 6-(2-methoxycarbonyl-3,5-dimethoxyphenyl)-5-methyl-3-oxohex-4-enoate (**23**) (33 mg, 0.09 mmol) was dissolved in trifluoracetic acid and allowed to stand for 20 min, it was then evaporated to dryness under reduced pressure. P.l.c. (diethyl ether) of the residue yielded the above 1-naphthylacetate (**24**) (R_F 0.4; 19 mg, 61%) and *methyl* 6,8-*dimethoxy*-3-*methyl*-1-*naphthylacetate* (R_F 0.7; 9 mg, 35%) as a yellow oil (Found: M^+, 274.1182. $C_{16}H_{18}O_4$ requires *M*, 274.1205); δ(CCl_4) 7.26 (1 H, br s), 6.75 (1 H, br s), 6.53 (1 H, d, *J* 2 Hz), 6.29 (1 H, d, *J* 2 Hz), 3.97 (2 H, s), 3.84 (3 H, s), 3.82 (3 H, s), 3.59 (3 H, s), and 2.43 (3 H, s); $\nu_{max.}$ ($CHCl_3$) 1 730, 1 630, 1 160, and 1 120 cm^{-1}; $\lambda_{max.}$ (EtOH) 239, 275sh, 285, 295, 318, and 331 nm; *m/z* 274 (M^+) and 215.

Methyl 3-(1-*Hydroxy*-6,8-*dimethoxy*-3-*methyl*-2-*naphthyl*)-3-*oxopropanoate* (**25**).—(*a*) A solution of methyl 6-(2-methoxycarbonyl-3,5-dimethoxyphenyl)-5-methyl-3-oxohex-4-enoate (**23**) (61 mg, 0.17 mmol) in dry THF (1 ml) under an atmosphere of nitrogen was cooled to −15 °C and a solution of lithium di-isopropylamide (0.35 mmol) was injected. The solution was stirred and allowed to warm to room temperature and more lithium di-isopropylamide (0.17 mmol) was injected dropwise. The mixture was stirred for a further 20 min and then poured into 2% sulphuric acid (15 ml) and extracted with diethyl ether (3 × 10 ml). The combined ethereal extracts were washed with saturated brine then dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue showed virtually a single spot on t.l.c. (CH_2Cl_2–diethyl ether, 9:1, R_F 0.45). Purification on p.l.c. gave the β-*keto ester* (**25**) (39 mg, 70%), m.p. 105 °C (decomp.); δ(CCl_4) 9.42 (1 H, s), 6.85 (1 H, br s), 6.46 (1 H, d, *J* 2 Hz), 6.28 (1 H, d, *J* 2 Hz), 4.01 (3 H, s), 3.93 (2 H, s), 3.85 (3 H, s), 3.68 (3 H, s), and 2.38 (3 H, s); $\nu_{max.}$ (CCl_4) 3 390br, 1 745, 1 690w, 1 630, and 1 365 cm^{-1}; $\lambda_{max.}$ (MeOH) 234, 259, 264, 310, and 344 nm; *m/z* 318 (M^+), 286, and 245. This compound gave a positive Gibb's test.[16]

(*b*) Into a solution of 2-methoxycarbonyl-3,5-dimethoxybenzyl-lithium (**12**) (1.5 mmol) at −78 °C was injected a solution of 2-methoxy-6-methyl-4*H*-pyran-4-one (**22**) (210 mg, 1.5 mmol) in dry THF (3 ml). The mixture was stirred for 3 h and then a solution of lithium di-isopropylamide (1.5 mmol) was injected and the mixture allowed to warm to room temperature (15 min). More lithium di-isopropylamide solution (1.5 mmol) was injected dropwise and the mixture stirred for a further 20 min before being poured into 2% sulphuric acid (40 ml) and extracted with diethyl ether (3 × 20 ml). The ethereal layers were dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue (528 mg) was shown by t.l.c. and n.m.r. to be the nearly pure β-keto-ester (**25**) identical with the above compound. Purification by column chromatography (SiO_2, CH_2Cl_2) however produced the pure compound in a yield of only 113 mg (24%), the remaining material appearing to have cyclized on the silica gel to give the pyrone (**27**) described in the next experiment.

4-*Hydroxy*-8,10-*dimethoxy*-5-*methyl*-2H-*naphtho*[1,2-b]-*pyran*-2-*one* (**27**).—Methyl 3-(1-hydroxy-6,8-dimethoxy-3-methyl-2-naphthyl)-3-oxopropanoate (**25**) (52 mg, 0.16 mmol) was dissolved in 2% aqueous sodium hydroxide (2 ml) and allowed to stand for 1 min; it was then acidified with 3M-hydrochloric acid. The mixture was left for 15 min to complete precipitation, then the mother liquor was decanted off and the residue washed with water and dried *in vacuo* to give the *naphthopyrone* (47 mg, 100%), m.p. 282 °C (decomp.) (Found: M^+, 286.0844. $C_{16}H_{14}O_5$ requires *M*, 286.0841); [$(CD_3)_2SO$] 7.18 (1 H, br s), 6.79 (1 H, d, *J* 2 Hz), 6.63 (1 H, d, *J* 2 Hz), 5.61 (1 H, s), 3.85 (3 H, s), 3.81 (3 H, s), and 2.63 (3 H, s); $\nu_{max.}$ (Nujol) 3 150br, 1 695, 1 665, 1 625, 1 590, 1 290, 1 265, and 1 205 cm^{-1}; $\lambda_{max.}$ (MeOH) 232, 254, 273, 284, 314, 326, 352, and 359 nm; (MeOH + 1 drop NaOH) 231, 254, 276, 289, 335, and 349 nm; *m/z* 286 (M^+) and 216.

Methyl 3-(1-*Hydroxy*-6,8-*dimethoxy*-3-*methyl*-2-*naphthyl*)-3-*methoxypropenoate* (**28**).—Diazomethane generated from *N*-nitrosomethylurea (0.5 g, 4.85 mmol), 50% aqueous potassium hydroxide (2 ml), and diethyl ether (5 ml) was distilled directly onto methyl 3-(1-hydroxy-6,8-dimethoxy-3 methyl-2-naphthyl)-3-oxopropanoate (**25**) (55 mg, 0.17 mmol) in dry diethyl ether (30 ml). The solution was left for 4 days and then evaporated to dryness under reduced pressure. This residue was purified by p.l.c. ($CHCl_3$–MeOH, 98:2) to give the *methyl ether* as an oil (30 mg, 52%); δ(CCl_4) 8.86 (1 H, s), 6.85 (1 H, br s), 6.46 (1 H, d, *J* 2 Hz), 6.18 (1 H, d, *J* 2 Hz), 5.31 (1 H, s), 3.86 (3 H, s), 3.78 (3 H, s), 3.72 (3 H, s), 3.46 (3 H, s), and 2.21 (3 H, br s); $\nu_{max.}$ (CCl_4) 3 420, 2 940, 1 725, 1 630, and 1 365 cm^{-1}; $\lambda_{max.}$ (EtOH) 233, 266sh, 306, 322, and 335; *m/z* 332 (M^+), 314, 200, 286, and 272. This compound gave a positive Gibb's test.[16]

4,8,10-*Trimethoxy*-5-*methyl*-2H-*naphtho*[1,2-b]*pyran*-2-*one* (**29**).—To a solution of methyl 3-(1-hydroxy-6,8-dimethoxy-3-methyl-2-naphthyl)-3-methoxypropenoate (**28**) (22 mg, 0.07 mmol) in methanol (2 ml) was added 1% aqueous NaOH (4 ml); precipitation started immediately. After 15 min the mixture was cooled in ice and filtered. The residue was washed with methanol–water (1:1) and dried *in vacuo* to yield the *naphthopyrone* (17.5 mg, 88%) as needles exhibiting a blue fluorescence, m.p. 216—220 °C (Found: M^+, 300.1004. $C_{17}H_{16}O_5$ requires *M*, 300.0998); δ($CDCl_3$) 7.21 (1 H, d, *J* 2 Hz), 6.54 (1 H, d, *J* 2 Hz), 5.70 (1 H, s), 4.02 (3 H, s), 3.95 (3 H, s), 3.92 (3 H, s), and 2.68 (3 H, s); $\nu_{max.}$ ($CHCl_3$) 2 930w, 1 705, 1 630, 1 610, 1 600, and 1 450 cm^{-1}; $\lambda_{max.}$ (MeOH) 232, 271, 281, 313, 355, and 367 nm; *m/z* 300 (M^+) and 272.

2-*Acetyl*-1-*hydroxy*-6,8-*dimethoxy*-3-*methylnaphthalene* (**26**).—To a solution of methyl 3-(1-hydroxy-6,8-dimethoxy-3-methyl-2-naphthyl)-3-oxopropanoate (**25**) (35 mg, 0.11 mmol) in 95% ethanol (3.2 ml) was added 6M-hydrochloric acid (1.3 ml) and the solution heated at reflux for 45 min. It was then cooled, diluted with water (5 ml) and the mixture treated with saturated aqueous sodium hydrogen carbonate until just alkaline; it was then extracted with diethyl ether (3 × 10 ml). The combined ethereal extracts were dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was dissolved in carbon tetrachloride and filtered, and the filtrate was evaporated to dryness under reduced pressure to yield the crystalline ketone (20 mg, 70%), m.p. 82—94 °C. After three recrystallizations from ether–hexane the compound had m.p. 94—98 °C (lit.,[17] 98—99 °C) (Found: C, 68.7; H, 6.4%; M^+, 260.1052. Calc. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2%; *M*, 260.1049). Spectral data were as reported.[17]

1-(1-*Hydroxy*-6,8-*dimethoxy*-3-*methyl*-2-*naphthyl*)*butane*-1,3-*dione* (**31**).—To a solution of 2-methoxycarbonyl-3,5-dimethoxybenzyl-lithium (**12**) (0.5 mmol) was injected dropwise a solution of 2,6-dimethyl-4*H*-pyran-4-one (**30**) (62 mg, 0.5 mmol) in dry THF (1 ml) and the mixture stirred at −78 °C for 40 min. Lithium di-isopropylamide solution (0.5 mmol) was added and the mixture was allowed to warm to 0 °C. Further lithium di-isopropylamide was added dropwise and stirring continued at 0 °C for 20 min. The mixture was poured into 2% sulphuric acid (20 ml) and extracted with diethyl ether (3 × 10 ml). The ethereal layers were dried over magnesium sulphate and evaporated to dryness under reduced pressure. T.l.c. showed the residue consisted largely of a single yellow spot (R_F 0.6, diethyl ether–dichloromethane, 1:1) which showed a green fluorescence and a red colour with ferric chloride. This was purified by p.l.c. to yield the butanedione as a yellow oil (120 mg, 79%). N.m.r. showed a mixture of two tautomers, the major one being an enol form; δ($CDCl_3$) 9.54 (1 H, s), 6.97 (1 H, br s), 6.58 (1 H, d, *J* 2 Hz), 6.39 (1 H, d, *J* 2 Hz), 5.89 (1 H, s), 3.97 (3 H, s), 3.87 (3 H, s), 2.40 (3 H, s), and 2.14 (3 H, s); $\lambda_{max.}$ (EtOH) 228, 264, and 367; (EtOH + NaOH) 234, 273, 297, and 335sh nm.

8,10-*Dimethoxy*-2,5-*dimethyl*-4H-*naphtho*[1,2-b]*pyran*-4-*one* (**32**) (*Eleutherinol Dimethyl Ether*).—1-(1-Hydroxy-6,8-dimethoxy-3-methyl-2-naphthyl)butane-1,3-dione (**31**) (75 mg, 0.25 mmol) was dissolved in trifluoracetic acid (5 ml). The solution immediately went red and was allowed to stand at room temperature for 30 min by which time it had turned to an orange-yellow. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (15 ml) and washed with saturated aqueous sodium hydrogen carbonate

(2 × 8 ml). The washings were re-extracted with ethyl acetate (1 × 10 ml) and the combined organic layers were dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was pure by t.l.c. and n.m.r. (63 mg, 89%), m.p. 185—187 °C (lit.,[18] 186 °C (Found: C, 71.65; H, 5.80. Calc. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67%); δCDCl$_3$) 7.08 (1 H, br s), 6.51 (1 H, d, *J* 2 Hz), 6.43 (1 H, d, *J* 2 Hz), 6.13 (1 H, br s), 3.90 (3 H, s), 3.88 (3 H, s), 2.84 (3 H, s), and 2.34 (3 H, s); $\nu_{max.}$ ($CHCl_3$) 1 655, 1 615, 1 605, 1 390, and 1 365 cm^{-1}; $\lambda_{max.}$ (EtOH) 235, 268, 342sh, and 353 nm; 284 (M^+).

2-(2-*Methoxycarbonyl*-3,5-*dimethoxybenzyl*)-6-*methyl*-4H-*pyran*-4-*one* (**34**).—2-Methoxycarbonyl-3,5-dimethoxybenzyllithium (12) (1 mmol) was generated in a flask fitted with a side-arm. A tube containing 2,4-dimethoxy-6-methylpyrylium fluorosulphonate[2] (**33**) (254 mg, 1 mmol) positioned in the side-arm was pushed into the benzyl-lithium solution at −78 °C by the action of a magnet on a magnetic stirring bead below the tube. The mixture was stirred at −78 °C for 2.5 h and then a solution of lithium di-isopropylamide (1 mmol) was injected in and the mixture stirred for a further 30 min before the addition of concentrated hydrochloric acid (4 ml). The mixture was allowed to warm to room temperature and after it had been allowed to stand overnight it was diluted with water (20 ml) and the mixture partially neutralized with sodium carbonate; it was then extracted with ethyl acetate (3 × 10 ml). The combined ethyl acetate extracts were washed with water and then saturated brine, dried over magnesium sulphate, and evaporated to dryness under reduced pressure. The residue was purified by p.l.c. (ethyl acetate, R_F 0.2) and yielded the γ-*pyrone* (111 mg, 35%). After treatment of a solution of the γ-pyrone in ethyl acetate with activated charcoal, evaporation of the filtrate under reduced pressure and trituration of the residual oil with light petroleum (b.p. 60—80 °C), gave crystals, m.p. 122—125 °C (Found: C, 63.95; H, 5.85. $C_{17}H_{18}O_6$ requires C, 64.14; H, 5.70%); δ_H($CDCl_3$) 6.40 (1 H, d, *J* 2 Hz), 6.32 (1 H, d, *J* 2 Hz), 5.99 (2 H, m), 3.82 (11 H, m), and 2.20 (3 H, s); $\nu_{max.}$ ($CHCl_3$) 1 720, 1 665, 1 605, and 1 160 cm^{-1}; $\lambda_{max.}$ (MeOH) 242 and 284 nm; *m*/*z* 318 (M^+), 287, 259, 179, and 151; δ_C($CDCl_3$) 180.0 (C-4), 167.8 (CO_2Me), 166.6 and 165.6 (C-2 and C-6), 161.9 (C-5′), 159.1 (C-3′), 135.4 (C-1′), 116.5 (C-2′), 114.0 (C-3 and C-5), 107.2 (C-6′), 97.9 (C-4′), 56.3 (OMe), 55.6 (OMe), 52.2 (CO_2Me), 37.7 (CH_2), 19.8 (Me).

Treatment of a solution of the γ-pyrone in ethyl acetate–ether with hydrogen chloride gas followed by trituration gave crystals of the hydrochloride, m.p. *ca.* 70 °C with evolution of gas then 124.5—125.5 °C.

3-*Hydroxy*-7,9-*dimethoxy*-1-*methyl*-6H-*dibenzo*[b,d]*pyran*-6-*one* (**36**) (*Alternariol Dimethyl Ether*).—2-(2-Methoxycarbonyl-3,5-dimethoxybenzyl)-6-methyl-4*H*-pyran-4-one (**34**) (68 mg, 0.21 mmol) was dissolved in methanol (8 ml) and 10% aqueous sodium hydroxide (4 ml) was added. The solution was heated at reflux for 1 h. Most of the methanol was evaporated under reduced pressure 1M-hydrochloric acid (12 ml) was added, and the mixture extracted with ethyl acetate (3 × 10 ml). The organic layers were washed with saturated brine, then hydrogen chloride gas was bubbled in for 2 min and the solution left overnight. Water (30 ml) was added and the mixture almost neutralized with sodium carbonate and shaken. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 10 ml). The combined organic layers were washed with saturated brine, dried over magnesium sulphate, and evaporated to dryness under reduced pressure to give the dibenzopyrone (51 mg, 83%), pure by t.l.c. and n.m.r., m.p. 292 °C (decomp.) (from EtOH) (lit.,[10] 292—294 °C) (Found M^+, 286.0838. Calc. for $C_{16}H_{14}O_5$: *M*, 286.0842). All spectra were as reported.[10]

5-*Hydroxy*-6,8-*dimethoxy*-2-*methyl*-4H-*naphtho*[2,3-b]-*pyran*-4-*one* (**37**) (*Rubrofusarin Monomethyl Ether B*).—A solution of triphenylmethane (150 mg, 0.61 mmol) in dry THF (1.5 ml) was cooled to 0 °C and n-butyl-lithium (1.7M in hexane; 0.32 ml, 0.54 mmol) was injected in and the solution stirred for 15 min; it was then cooled to −15 °C and injected dropwise into a solution of 2-(2-methoxycarbonyl-3,5-dimethoxybenzyl)-6-methyl-4*H*-pyran-4-one (**34**) (70 mg, 0.22 mmol) in dry THF (5 ml) cooled to −15 °C. The solution was stirred for 1 h and then concentrated hydrochloric acid (2 ml) was added and the mixture stirred at room temperature for 10 min. Water (20 ml) was added, the mixture was almost neutralised with sodium carbonate and extracted with ethyl acetate (3 × 10 ml). The organic layers were washed with saturated brine, dried over magnesium sulphate, and evaporated to dryness under reduced pressure. The residue was purified by p.l.c. (CH_2Cl_2–ether, 9:1, R_F 0.5) to yield the naphthopyrone (11 mg, 17%), m.p. 210—214 °C (lit.,[19] 213 °C) (Found: C, 66.9; H, 5.2. Calc. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93%); δ($CDCl_3$) 14.88 (1 H, s), 6.92 (1 H, s), 6.55 (1 H, d, *J* 2 Hz), 6.37 (1 H, d, *J* 2 Hz), 5.97 (1 H, s), 3.99 (3 H, s), 3.91 (3 H, s), and 2.35 (3 H, s); the u.v. and i.r. spectra were as reported;[19] *m*/*z* 286 (M^+), 268, 257, 240, and 239.

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