A Diastereoselective Synthesis of the Polyketide Antibiotic Citrinin using Toluate Anion Chemistry

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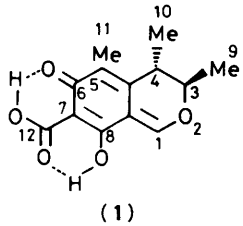
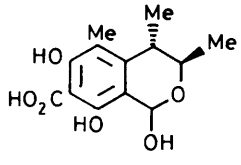
The diastereoselectivity of various synthetic approaches to (±)-*threo*-3-(3,5-dihydroxy-2-methylphenyl)butan-2-ol ('Phenol B') (**4**), based on reactions of benzyl anions with electrophiles, has been investigated. The anion (**9**) derived from ethyl 2,4-dimethoxy-6-ethylbenzoate reacted with acetaldehyde to give mainly an *erythro*-product isolated as the lactone (**12**); acetylation with acetyl chloride to give a ketone, followed by reduction, gave mainly the required *threo*-lactone (**11**). An alternative route was frustrated by decomposition of the benzyl anion derived from 3,4-dihydro-6,8-dimethoxy-3-methyl-1*H*-2-benzopyran-1-one (**17**). Reduction of the carbonyl group of the *threo*-lactone (**11**) to a methyl gave the dimethyl ether of 'Phenol B', which was converted into (±)-citrinin (**1**).

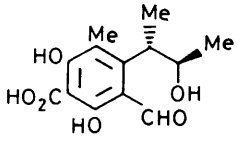
Citrinin (**1**), a yellow, polyketide fungal metabolite was first isolated from *Penicillium citrinum*.[1] Later it was isolated from other fungi of the *Penicillium*[2] and *Aspergillus*[3] species, and also from the leaves of the flowering Australian plant, *Crotalaria crispata*.[4] It exhibits antibacterial activity, being markedly inhibitory to Gram positive bacteria.[2,5] It has not been widely exploited in medicine because of its high toxicity, although it has been recommended for the treatment of skin infections by topical application.[6] The biological action of citrinin is still under study because of its occurrence as a mycotoxin in foodstuffs,[7,8] and also because it has been reported recently as a promising insecticide.[9]



(**1**)



(**2**)



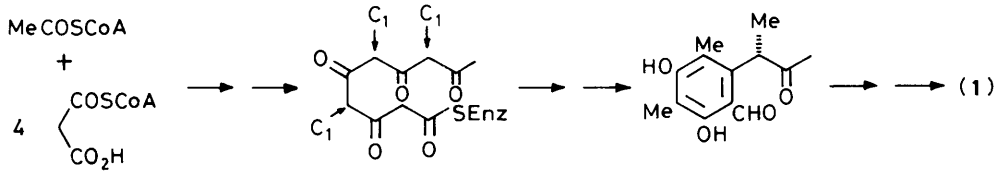
(**3**)

The structure of citrinin (**1**) was proposed by Robertson, Whalley *et al.* on the basis of extensive degradation work by several groups of workers.[10] It will be noted that the *p*-quinomethide structure is an anhydro form of the fully aromatic structure (**2**), itself the cyclic hemiacetal formally derived from the aldehydo acid (**3**). This aldehydo acid is, therefore, a logical initial target of a synthesis of citrinin.

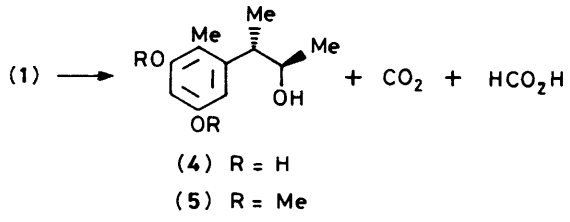
The relative stereochemistry of citrinin was determined by Cram as having the C-9 and C-10 methyl *trans* to each other.[11] Later, two groups of workers contributed to the assignment of the absolute configuration of natural citrinin as that shown in (**1**).[12] An earlier i.r. study (CCl_4 solution) had indicated that the doubly H-bonded structure shown was in equilibrium with another with only one intramolecular H-bond.[13] ^{1}H N.m.r. confirmed that the C-9 and C-10 methyl substituents were *trans* and showed that they were quasi-axial in solution ($CDCl_3$).[14] A more recent *X*-ray investigation of the crystalline state confirmed the *p*-quinomethide structure, with the C(8)–O bond rather longer than the C(6)–O bond.[15] The 9- and 10-methyls were confirmed as *trans* and there were two intramolecular H-bonds as shown.

The alternating oxygenation pattern of citrinin gave rise to speculation that it might be produced biosynthetically from a pentaketide chain formed from five acetate units, with *C*-methylation at three carbon atoms, and early biosynthetic studies were consistent with this hypothesis.[16] More recent experiments with advanced precursors and stable isotopes in Cambridge,[17] Milan,[18] and Tokyo,[19] have supported a biosynthetic pathway shown in outline in Scheme 1.

One of the degradations performed on citrinin in the course of structural determination revealed stereochemical problems which must be taken into account in designing a stereocontrolled synthesis. When citrinin was treated with sulphuric acid it gave carbon dioxide, formic acid, and two isomerides designated phenols A and B (Scheme 2).[1] Phenol A was an optically active dihydric phenol (**4**), and phenol B was proved to be its racemate by resolution of the hydrogen phthalate of its dimethyl ether (**5**).[20] The structure of phenol B was confirmed by synthesis.[21] Phenol A is racemised to phenol B under various acidic conditions, but not by base. Cram[11,22] concluded that this acid-



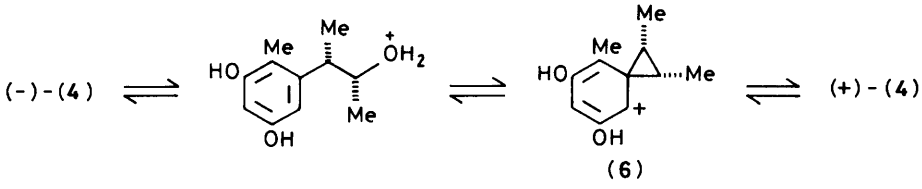
Scheme 1.



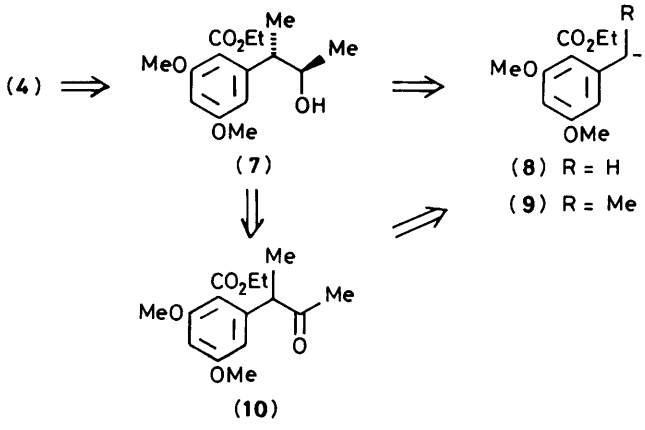
Scheme 2.

conclusions were confirmed by a partial synthesis of (−)-citrinin from phenol A, and (±)-citrinin from phenol B.[23] Modified procedures have been reported for the conversion of phenols A and B into citrinin[24,25] and some analogues.[26]

The synthetic strategy adopted in the present diastereoselective synthesis involves phenol B and is summarised as a retrosynthetic plan in Scheme 4. It exploits benzyl anion chemistry developed in an earlier investigation of the reactions of toluate anions with electrophiles.[27] It was hoped that toluate



Scheme 3.



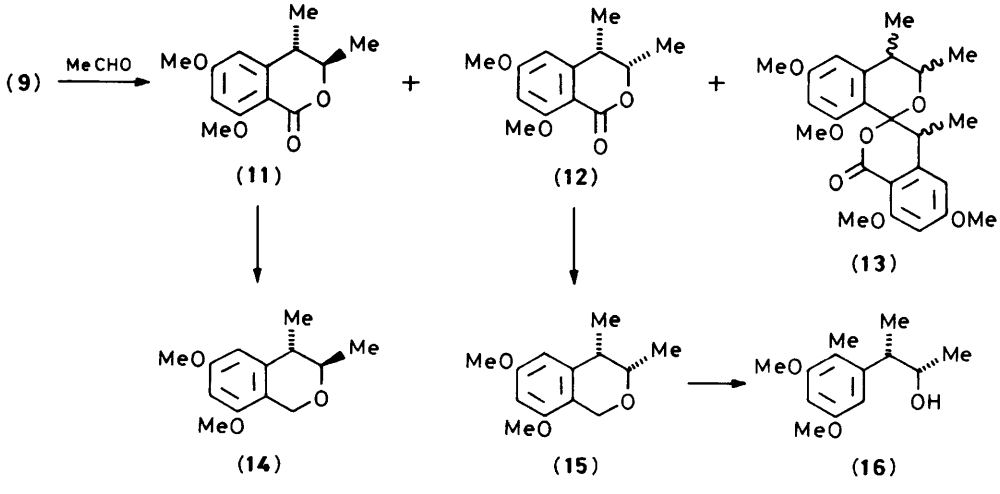
Scheme 4.

catalysed racemisation involves inversion at two adjacent asymmetric centres and he tentatively suggested that it takes place by means of a Wagner–Meerwein rearrangement involving the aryl group as a migrating species *via* the symmetrical phenonium ion (**6**) as indicated in Scheme 3. This result requires that the relative configuration of phenols A and B be *threo* as indicated in (**4**). The absolute configuration indicated for phenol A can be inferred from the *X*-ray results for citrinin. These

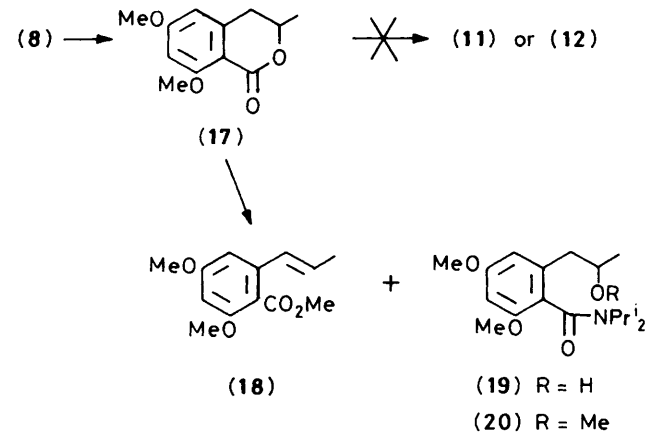
anion (**8**) might be converted into (**7**) by successive addition of MeI and MeCHO (in either order) (strategy A), or by methylation and acetylation (again in either order) to give (**10**), followed by reduction (strategy B). Having served its function as an anion stabilising group, the CO_2R group of (**7**) would be reduced to provide the aryl methyl substituent of phenol B (**4**). The efficiency of the approach depends critically on the stereoselectivity of the reactions which generate the second chiral centre in (**7**). The chance of devising a reaction which is stereoselective in the desired sense is good, given the diversity of routes available for converting (**8**) into (**7**).

Our first choice was strategy A, and we adopted the tactic in which the anion (**8**) is methylated to form an ethyl group which is then deprotonated to form (**9**), followed by reaction with acetaldehyde. An efficient procedure for the methylation was already available.[27] Formation of the anion (**9**) using LDA as base proved troublesome but satisfactory conditions were devised on the basis of control experiments involving work-up with deuterium oxide: 80% of the starting material could be recovered in which 71% of the molecules carried a deuterium atom. On reaction with acetaldehyde the anion (**9**) gave a mixture of diastereoisomeric lactones (**11**) and (**12**) in good yield (64—70%), with one of the diastereoisomers being present in large excess (4:1). A minor by-product (**13**) was also isolated.

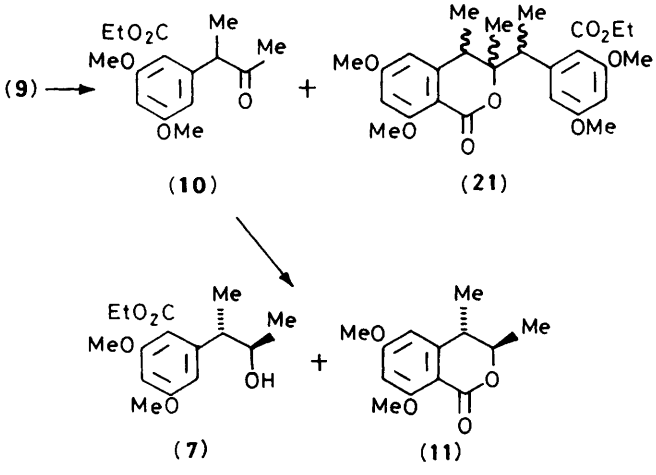
We were not able to make any firm assignment of the relative configurations of the two isomers using the Karplus equation.[28]



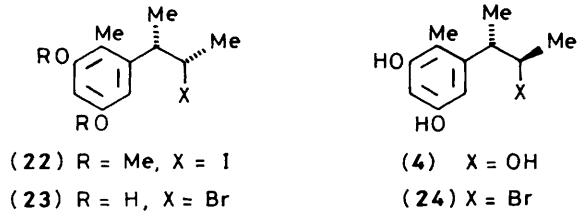
Scheme 5.



Scheme 6.



Scheme 7.



The observed values for the coupling constant between 3-H and 4-H were 2.9 Hz for the major isomer, and 6.5 Hz for the minor isomer. It might be expected that the desired *threo* isomer in its preferred conformation would have the two hydrogens approximately antiperiplanar, and therefore that it would show the larger coupling constant. However, it should be noted that in citrinin (**1**) which has a similar *threo*-stereochemistry, the coupling constant between 3-H and 4-H is close to zero, presumably because steric crowding in the molecule causes the heterocyclic ring to be twisted.[14]

In view of the resulting uncertainty concerning the conformation of the lactone rings of (**11**) and (**12**), we resorted to chemical correlation, in which the ester group is reduced to a methyl group, to give a derivative of phenol A or its *erythro* diastereoisomer. Comparison with the degradation product obtained from natural sources would, therefore, provide a basis for stereochemical assignment. The major lactone diastereoisomer was reduced to an isochroman, (**14**) or (**15**), by treatment with di-isobutylaluminium hydride (DIBAL). The ^{1}H n.m.r. resonance for 4-H of this compound appeared as a double quartet at δ 2.55 (*J* 2 and 7 Hz) very similar to that of the starting lactone. The benzyl ether residue was further reduced, by hydrogenolysis using a palladium–charcoal catalyst, to give a methyl group. The product was then compared with the dimethyl ether of phenol A produced by degradation of citrinin. Both the t.l.c. properties and the n.m.r. spectrum of the synthetic material were different from those of the degradation product. Since the phenol A derivative is known to have the *threo*-stereochemistry, we can conclude that the synthetic material is (**16**), which has the *erythro*-stereochemistry. Therefore, the major product of the reaction of (**9**) with acetaldehyde must be the *erythro*-lactone (**12**), rather than the desired *threo*-lactone (**11**).

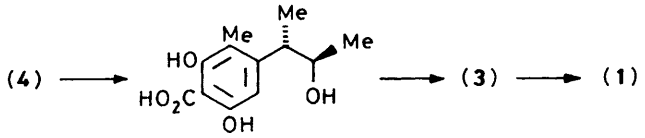
We next explored the alternative tactic in implementing strategy A of Scheme 4. This involved reversing the order of the two steps as indicated in Scheme 6, so that the anion (**8**) is allowed to react with acetaldehyde to give a lactone (**17**) which might then be converted into a benzyl anion and methylated. In exploratory work it was found that the desired anion did not form satisfactorily from (**17**) using di-isopropylamide as base. A mixture of products was obtained, which included the alkene (**18**), and amides (**19**) and (**20**), produced by nucleophilic attack of di-isopropylamide on the carbonyl group of the lactone. Presumably this nucleophilic attack is facilitated with the lactone because its carbonyl group is held coplanar with the benzene ring, and is therefore less susceptible to steric hindrance from the adjacent *ortho* substituents. The n.m.r. spectra of (**19**) and (**20**) were unexpectedly complex, presumably because of the existence of rotational isomers which interconvert relatively slowly at room temperature.

Our third, and ultimately successful approach, based on strategy B of Scheme 4, was to acetylate the anion (**9**) to produce the ketone (**10**), which might then be reduced to (**7**). The acetylation proved to be more troublesome than the reaction with acetaldehyde, as indicated in Scheme 7, because of competing formation of diastereoisomeric products (**21**), in which two molecules of anion have reacted with one of the acylating agent, acetyl chloride. Subsequently it was found that this side reaction could be suppressed by using high dilution and very low temperatures. Under these conditions the desired ketone (**10**) could be obtained in 50% yield. Other acetylating agents were tried, without success.

The advantage of this approach is that the reduction of the ketone group would be expected[29] to give the *threo*-isomer and this expectation was borne out in practice. Reduction with sodium borohydride gave a mixture of the lactone (**11**) and the hydroxy ester (**7**). The latter could be converted into the former by treatment of the crude mixture with sodium hydride, to give an overall high yield of the lactone. Only one stereoisomer was present (less than 2% of the minor isomer), and this was shown to be the *threo*-isomer (**11**) by conversion into the dimethyl ether of the racemate of phenol A (**4**) (alias phenol B), in subsequent steps of the synthesis. These involved, as before, successive reduction of the carbonyl group to a methylene (DIBAL) and then a methyl (hydrogenolysis). The n.m.r. and t.l.c. properties of the racemic product were identical with those of the optically active dimethyl ether (**5**) of phenol A.

The next task was to demethylate the methoxy groups of (**5**) which proved to be troublesome. In exploratory experiments with the *erythro*-diastereoisomer (**16**), treatment with iodotrimethylsilane resulted in the production of (**22**), in which the hydroxy group is replaced by an iodo group without cleavage of the methyl ether residues. Boron tribromide proved to be more effective giving a diphenol (**23**), although once again the alcoholic hydroxy was replaced by halogen. The same reaction on the *threo*-diasteroisomer gave a mixture of the desired racemic phenolic alcohol (**4**), and the corresponding bromo

derivative (**24**). The latter could be hydrolysed to (**4**) on treatment with aqueous base; alternatively, and more efficiently, the crude demethylation products could be treated with aqueous base to give a good yield of racemic (**4**) directly.



(**25**)

Scheme 8.

The remaining steps to produce citrinin from (±)-(**4**) required carboxylation, formylation, and cyclisation. This was achieved by the variation of Gores method (Scheme 8).[25] First the phenol B was carboxylated with CO_2 to give the acid (**25**). This was then formylated, using ethyl orthoformate, to give an aldehyde (**3**), which cyclised *in situ* to the required quinomethide structure (**1**). The product was spectroscopically identical with (−)-citrinin from natural sources. Thus a stereoselective synthesis of (±)-citrinin in eight steps from the ethyl orsellinate anion (**8**) has been achieved. The retrosynthetic plan illustrated in Scheme 4 could provide the basis of a totally enantioselective route, if suitable enantioselectivity can be achieved in the conversion of (**8**) into (**7**), and racemisation can be avoided in subsequent steps.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer; unless otherwise stated, all samples were dissolved in carbon tetrachloride and all reported peaks were strong. U.v. spectra were taken on a Unicam SP1800 or SP8000 spectrophotometer on solutions in 95% ethanol unless otherwise stated. ^{1}H N.m.r. spectra were recorded using a Varian EM360A, EM390, CFT20, HAD100, or XL100, or a Bruker WH400 instrument; unless otherwise stated, samples were dissolved in deuteriochloroform with tetramethylsilane as internal standard. ^{2}H N.m.r. spectrometry was performed on a WH400 instrument. Mass spectra were obtained using an AEI MS300 spectrometer.

Column chromatography on silica gel was performed using Merck Kieselgel 60. Qualitative thin layer chromatography (t.l.c.) was carried out on commercially prepared plates coated with Merck Kieselgel GF_{254}. Preparative layer chromatography (p.l.c.) was performed on plates (20 cm × 20 cm × 0.1 cm) coated with the same material.

Tetrahydrofuran (THF) was dried by distillation from $LiAlH_4$ immediately before use. Dry acetone was prepared by distillation from anhydrous potassium carbonate.

Oil-free sodium hydride was prepared from the commercially available material by washing several times with light petroleum (b.p. 60—80 °C), decanting the washings and finally drying in a stream of nitrogen gas. Di-isopropylamine was distilled from sodium hydroxide, then calcium hydride and stored under nitrogen.

In the standard work-up procedure, the reaction mixture was poured into an excess of dilute sulphuric acid and extracted twice with diethyl ether and twice with ethyl acetate. The organic layers were washed with saturated aqueous sodium hydrogen carbonate followed by saturated brine, dried over Na_2SO_4 (or $MgSO_4$) and evaporated to dryness under reduced pressure.

Lithium Di-isopropylamide (0.5 *mmol*).—Into a flask containing triphenylmethane (0.5 mg) 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.

Deuteriation of Ethyl 2-Ethyl-4,6-dimethoxybenzoate.[27]—Lithium di-isopropylamide (0.37 mmol) in dry THF (1 ml) under argon was cooled to −78 °C and the 2-ethylbenzoate (60 mg, 0.25 mmol) in dry THF (1 ml) was added dropwise to the stirred solution. A deep red colour, attributed to anion (**9**), developed. The solution was kept for 1 min at −15 °C and then for 30 min at −78 °C. D_2O (1 ml) in dry THF (1 ml) was then added dropwise, whereupon the mixture became colourless. It was stirred while being warmed to room temperature over 30 min. After standard work-up, an oil was obtained which was puried by p.l.c. [diethyl ether–light petroleum (b.p. 60—80 °C), 1:1] to give one main band, R_F 0.5, which yielded starting material (48 mg, 80%) showing 71% monodeuteriation in the aromatic methylene group by n.m.r. and mass spectroscopy (Found: $M^+ + 1$, 239.1273. $C_{13}H_{17}DO_4$ requires $M + 1$, 239.1284); n.m.r. as for undeuteriated material but with the intensity of the peaks at δ_H 1.19 (t, *J* 7 Hz, CH_2CH_3) and 2.58 (q, *J* 7 Hz, CH_2CH_3) reduced, and an additional peak at δ_H 1.18 (d, *J* 7 Hz, $CHDCH_3$); *m/z* 239 ($M^+ + 1$, 55%), 238 (M^+, 25), 194 ($M + 1 -$ OEt, 100), 193 ($M + 1 -$ EtOH and $M -$ OEt, 50), 192 ($M -$ EtOH, 50), and 191 (20).

(±)-threo- and (±)-erythro-3,4-*Dihydro*-6,8-*dimethoxy*-3,4-*dimethyl*-1*H*-2-*benzopyran*-1-*one* (**11**) *and* (**12**).—A solution of lithium di-isopropylamide (0.70 mmol) in dry THF and under argon in the side-arm of the flask was cooled to −78 °C. Ethyl 2-ethyl-4,6-dimethoxybenzoate[27] (109 mg, 0.46 mmol) in dry THF (1 ml) was added dropwise to give the usual deep red colour attributed to the anion (**9**). After 40 min at −78 °C, the mixture was poured gradually during 10 min into a solution of acetaldehyde (0.13 ml, 101 mg, 2.3 mmol) in THF (0.5 ml) contained in the main body of the flask also at −78 °C. The colour of each added portion of anion was discharged rapidly. The mixture was stirred while warming to room temperature over 2 h and then ethanol (2 ml) was added. Standard work-up gave a yellow oil which was purified by p.l.c. [diethyl ether, 4 elutions; ethyl acetate–light petroleum (b.p. 60—80 °C), 1:1, 3 elutions] to give four bands.

The first R_F 0.5, yielded (±)-3,4-*dihydro*-6,6′,8,8′-*tetramethoxy*-3,4,4′-*trimethylspiro*[1H-2-*benzopyran*-1,3′-(3H-2-*benzopyran*)]-1′(4′H)-*one* (**13**) (12 mg, 12%) as prisms, m.p. 201—203 °C (from acetone) (Found: C, 67.0; H, 6.7. $C_{24}H_{28}O_7$ requires C, 67.28; H, 6.59%); $\nu_{max.}$ ($CHCl_3$) 2 855w and 2 840w (CH of OMe), 1 710 (C=O), 1605 (Ar), and 1585 cm^{-1} (Ar); $\lambda_{max.}$ 222sh, 266, and 297 nm; δ_H (400 MHz) 1.03 (3 H, d, *J* 6.8 Hz, $CHCH_3$), 1.12 (3 H, d, *J* 6.9 Hz, $CHCH_3$), 1.13 (3 H, d, *J* 6.8 Hz, $CHCH_3$), 2.50 [1 H, dq, *J* 2.9 and 6.9 Hz, $CH(CH_3CH)$], 3.76, 3.80, 3.87, and 3.94 (4 × 3 H, s, $ArOCH_3$), 4.34 [1 H, dq, *J* 2.9 and 6.8 Hz, $OCH(CH_3CH]$, 4.50 (1 H, q, *J* 6.8 Hz, $CHCH_3$), and 6.25, 6.34, 6.41, and 6.44 (4 × 1 H, d, *J* 2.0 Hz, Ar*H*) (Found: M^+, 428.1833. $C_{24}H_{28}O_7$ requires *M*, 428.1835); *m/z* 428 (M^+, 5%), 384 ($M -$ MeCHO, 5), 383 (5), 353 (10), and 219 (15).

The second band, R_F 0.65, contained a mixture of products which were separated by further p.l.c. eluting firstly with [diethyl ether–light petroleum (b.p. 60—80 °C), 1:1, 1 elution and 2:1, 2 elutions, and then with diethyl ether–light petroleum (b.p. 60—80 °C)–ethyl acetate, 10:2:1, 4 elutions] to give two isomeric lactones. The lower R_F band gave the *threo*-isomer (**11**) (13 mg, 12%), as prisms, m.p. 125—126 °C (from ethyl acetate–hexane) (lit.,[1] 122—124 °C probably in optically active form) (Found: C, 65.9; H, 6.8. Calc. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%); $\nu_{max.}$ 2 840w (CH of OMe), 1 730 (C=O), 1 605 (Ar), and 1 585 cm^{-1} (Ar); $\lambda_{max.}$ 262 and 295 nm; δ_H (80 MHz) 1.32 (3 H, d, *J* 6.8

Hz, $CHCH_3$), 1.38 (3 H, d, *J* 6.5 Hz, $CHCH_3$), 2.75 (1 H, m, *J* 6.8 Hz, $CH(CH_3CH)$, 3.86 (3 H, s, $ArOCH_3$), 3.91 (3 H, s, $ArOCH_3$), 4.29 (1 H, m, *J* 6.8 Hz, $OCH(CH_3)CH$), and 6.39 (2 H, br s, Ar*H*) (Found: M^+, 236.1047. Calc. for $C_{13}H_{16}O_4$: *M*, 236.1048); *m/z* 236 (M^+, 100%), 193 (20), 192 (*M* − MeCHO, 55), 191 (45), and 190 (30). The higher R_F isomer, later identified as the *erythro*-lactone (**12**) (11 mg), was isolated as an oil, pure by t.l.c. (Found: M^+, 236.1045. $C_{13}H_{16}O_4$ requires *M*, 236.1048); $\nu_{max.}$ 2840w (CH of OMe), 1725 (C=O), 1610 (Ar), and 1585 cm^{-1} (Ar); $\lambda_{max.}$ 261 and 296 nm; δ_H (80 MHz) 1.20 (3 H, d, *J* 7.2 Hz, $CHCH_3$), 1.36 (3 H, d, *J* 6.5 Hz, $CHCH_3$), 2.76 [1 H, dq, *J* 2.7 and 7.2 Hz, $CH(CH_3)CH$], 3.85 (3 H, s, $ArOCH_3$), 3.90 (3 H, s, $ArOCH_3$), 4.57 [1 H, dq, *J* 2.7 and 6.5 Hz, $OCH(CH_3)CH$], 6.29 (1 H, d, *J* 2.2 Hz, Ar*H*), and 6.38 (1 H, d, *J* 2.2 Hz, Ar*H*); *m/z* 236 (M^+, 100%), 193 (20), 192 (*M* − MeCHO, 60), 191 (40), and 190 (30).

The third band from the original p.l.c., R_F 0.7, yielded more of the *erythro*-lactone (**12**) (45 mg), pure by t.l.c. and identical with that isolated as above, giving a total yield of (56 mg, 52%).

The fourth p.l.c. band, R_F 0.9, gave starting material (26 mg, 24%).

(−)-threo-3-(3,5-*Dihydroxy*-2-*methylphenyl*)*butan*-2-*ol* ('*Phenol A*') (**4**).—Crude material obtained by degradation of (−)-citrinin (**1**) with alkali [1] was purified by recrystallisation to give (−)-phenol A (**4**), as prisms, m.p. 126—128 °C (from $CHCl_3$) (lit.,[1] 128—130 °C) (Found: M^+, 196.1098. Calc. for $C_{11}H_{16}O_3$: *M*, 196.1100); $\lambda_{max.}$ 220sh and 282 nm; δ_H (80 MHz; CH_3COCD_3), 1.11 (3 H, d, *J* 6 Hz, $CHCH_3$), 1.13 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.10 (3 H, s, $ArCH_3$), 3.04 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.85 [1 H, m, *J* 3 and 6 Hz, $HOCH(CH_3)CH$], 6.26 (1 H, d, *J* 2 Hz, Ar*H*), 6.35 (1 H, d, *J* 2 Hz, Ar*H*), 7.6 (1 H, br s, OH), and 7.8 (1 H, br s, OH); δ_H (80 MHz; CH_3CN) 1.12 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.13 (3 H, d, *J* 6 Hz, $CHCH_3$), 2.07, (3 H, s, $ArCH_3$), 2.98 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.76 (1 H, m, $HOCHCH_3$), 6.17 (1 H, d, *J* 2 Hz, Ar*H*), and 6.32 (1 H, d, *J* 2 Hz, Ar*H*); *m/z* 196 (M^+, 15%, 152 (*M* − MeCHO, 100, and 151 (30).

(−)-threo-3-(3,5-*Dimethoxy*-2-*methylphenyl*)*butan*-2-*ol* (**5**).—(−)-*threo*-3-(3,5-Dihydroxy-2-methylphenyl)butan-2-ol (**4**) (10 mg, 0.05 mmol) was dissolved with stirring in dry acetone (3 ml) in the presence of anhydrous potassium carbonate (25 mg, 0.18 mmol). Dimethyl sulphate (0.012 ml, 16 mg, 0.13 mmol) was added, and the mixture heated at reflux with stirring and under nitrogen for 15 h. The residual potassium carbonate was filtered off and the filtrate added to concentrated ammonia solution (*d*, 0.880; 4 ml) and stirred for 2 h. After addition of water (2 ml), the mixture was acidified to pH 2 and extracted with diethyl ether (2 × 10 ml) and ethyl acetate (10 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (10 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give an oil. After p.l.c. [diethyl ether–light petroleum (b.p. 60—80 °C), 1:1, 2 elutions], one main band, R_F 0.4, was obtained which gave the (−)-dimethoxy alcohol (**5**) [1] (8 mg, 70%) as an oil (Found: M^+, 224.1414. Calc. for $C_{13}H_{20}O_3$: *M*, 224.1412); $\nu_{max.}$ 3590m (OH), 2840m (CH of OMe), 1610 (Ar), and 1595 cm^{-1} (Ar); $\lambda_{max.}$ 224 and 280 nm; δ_H (80 MHz) 1.17 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.26 (3 H, d, *J* 6 Hz, $CHCH_3$), 2.14 (3 H, s, $ArCH_3$), 3.05 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.80 (6 H, s, $ArOCH_3$), 3.87 [1 H, m, partly obscured, $HOCH(CH_3)CH$], 6.36 (1 H, d, *J* 2 Hz, Ar*H*), and 6.43 p.p.m. (1 H, d, *J* 2 Hz, Ar*H*); *m/z* 224 (M^+, 35%), 180 (*M* − MeCHO, 100), 179 (*M* − MeCHOH, 50), and 165 (40).

(±)-erythro-3,4-*Dihydro*-6,8-*dimethoxy*-3,4-*dimethyl*-1H-2-*benzopyran* (**15**).—To (±)-*erythro*-3,4-dihydro-6,8-dimethoxy-3,4-dimethyl-1*H*-2-benzopyran-1-one (**12**) (100 mg, 0.42 mmol) in dry toluene (5 ml) under argon at room temperature was added slowly with stirring di-isobutylaluminium hydride (1.53M in toluene; 0.79 ml, 1.21 mmol). The mixture was stirred for 4 h at room temperature before the addition of hydrochloric acid (2M; 4 ml). After dilution with water (4 ml), a toluene layer was separated. More hydrochloric acid (2M; 4 ml) was added to the aqueous layer and the latter was extracted with diethyl ether (2 × 10 ml) and ethyl acetate (10 ml). The combined organic layers were washed with hydrochloric acid (1M; 3 × 10 ml), aqueous sodium hydrogen carbonate (5%; 10 ml), and saturated brine (10 ml), and then dried (Na_2SO_4). Evaporation to dryness under reduced pressure gave a yellow oil which was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 2:1] to give one main band, R_F 0.8, from which was obtained the *dihydroxybenzopyran* (**15**) (47 mg, 50%) as crystals, m.p. 69—71 °C (from hexane) (Found: C, 70.2; H, 8.1. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.16%); $\nu_{max.}$ 2835m (CH of OMe), 1610 (Ar), 1600 (Ar), and 1490 cm^{-1} (Ar); $\lambda_{max.}$ 221sh and 276 nm; δ_H (80 MHz) 1.17 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.25 (3 H, d, *J* 6 Hz, m $CHCH_3$), 2.55 [1 H, dq, *J* 2 and 7 Hz, $ArCH(CH_3)CH$], 3.76 (3 H, s, $ArOCH_3$), 3.78 (3 H, s, $ArOCH_3$, total integral 4 H), 4.56 (1 H, d, *J* 15.5 Hz, $ArCH_AH_BO$), 4.85 (1 H, d, *J* 15.5 Hz, $ArCH_AH_BO$), and 6.27 (2 H, s, Ar*H*); (Found: M^+, 222.1248. $C_{13}H_{18}O_3$ requires *M*, 222.1256); *m/z* 222 (M^+, 50%), 221 (*M* − H, 20), and 178 (*M* − MeCHO, 100).

(±)-erythro-3-(3,5-*Dimethoxy*-2-*methylphenyl*)*butan*-2-*ol* (**16**).—(±)-*erythro*-3,4-dihydro-6,8-dimethoxy-3,4-dimethyl-1*H*-2-benzopyran (**15**) (25 mg, 0.11 mmol) in methanol (3 ml) and glacial acetic acid (3 ml) was hydrogenated for 24 h at room temperature over 10% palladium-charcoal catalyst (25 mg). The mixture was then filtered through Celite, and evaporated to dryness under reduced pressure to give an oil. After p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:2] two main bands were obtained.

The first, R_F 0.5, yielded the (±)-alcohol (**16**) [21] (16 mg, 63%) as an oil which was pure by t.l.c. (Found: M^+, 224.1404. Calc. for $C_{13}H_{20}O_3$: *M*, 224.1412); $\nu_{max.}$ 3 640w and 3 600w (OH), 2 840w (CH of OMe), 1 610 (Ar), and 1 595 cm^{-1} (Ar); $\lambda_{max.}$ 223sh and 279 nm; δ_H (80 MHz) 1.11 (3 H, d, *J* 6.5 Hz, $CHCH_3$), 1.27 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.12 (3 H, s, $ArCH_3$), 3.04 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.78 (3 H, s, $ArOCH_3$), 3.80 (3 H, s, $ArOCH_3$), 3.87 [1 H, m, *J* 6.5 Hz, $HOCH(CH_3)CH$], and 6.35 (2 H, s, Ar*H*); *m/z* 224 (M^+, 40%), 180 (*M* − MeCHO, 100), 179 (*M* − MeCHOH, 45), and 165 (30).

The second band, R_F 0.75, gave starting material (**15**) (4 mg, 16%).

Action of Lithium Di-isopropylamide followed by Methyl Iodide on Dihydrobenzopyranone (**17**).—Lithium di-isopropylamide (0.68 mmol) in THF under argon was prepared in the usual way, and cooled to −78 °C. 3,4-Dihydro-6,8-dimethoxy-3-methyl-1*H*-2-benzopyran-1-one (**17**) [27] (100 mg, 0.45 mmol) in dry THF (1.5 ml) was added dropwise to give a light orange solution. This was stirred for 30 min at −78 °C, after which methyl iodide (0.05 ml, 114 mg, 0.80 mmol) was added dropwise and the mixture stirred for 2 min before more methyl iodide (0.05 ml, 114 mg, 0.80 mmol) was added. The mixture was stirred for a further 1 h at −78 °C and then whilst the mixture warmed to room temperature over 4 h. Ethanol (5 ml) was added to the resultant light yellow solution which was then stirred overnight before it was subjected to standard work-up to give a light brown oil. P.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:2, 2 elutions] gave three bands containing characterisable products.

The first R_F 0.1 to 0.2, gave an oil identified as 2-(2-*hydroxypropyl*)-N,N-*di*-isopropyl-4,6-*dimethoxybenzamide* (**19**) (53 mg, 36% crude) which produced two spots on t.l.c. and an n.m.r.

spectrum suggesting a mixture. Further attempts at separation by p.l.c. (ethyl acetate–toluene, 1:1) gave two fractions. The first, R_F 0.3, gave the product (38 mg, 26%) as prisms, m.p. 119—121 °C (from ethyl acetate–hexane) (Found: C, 66.6; H, 9.1; N, 4.3. $C_{18}H_{29}NO_4$ requires C, 66.85; H, 9.04; N, 4.33%); $\nu_{max.}$ 3 500—3 200w (OH, H-bonded), 2 840w (CH of OMe), 1 610 (Ar, $CONR_2$), and 1 380m and 1 370m cm^{-1} ($CHMe_2$); $\lambda_{max.}$ 209 and 280 nm; δ_H (400 MHz) 1.02 and 1.6 (2 × 3 H, d, *J* 6.8 Hz, $CHCH_3$), 1.26 (3 H, d, *J* 5.9 Hz, $CHCH_3$), 1.54 and 1.57 (2 × 3 H, d, *J* 6.9 Hz, $CHCH_3$), 2.42 (1 H, dd, *J* 9.8 and 13.7 Hz, $ArCH_AH_BCHOH$), 2.69 (1 H, dd, *J* 3.9 and 13.7 Hz, $ArCH_AH_BCHOH$), 3.49 [2 H, m, *J* 6.9 Hz, $CHCH_3$), 3.69 (1 H, m, $CH(OH)CH_3$], 3.75 and 3.79 (2 × 3 H, s, $ArOCH_3$), and 6.29 and 6.36 (2 × 1 H, d, *J* 2 Hz, Ar*H*); *m/z* 323 (M^+, 5%), 308 (M − Me, 5), 292 (M − OMe, 15), 279 (M − MeCHO, 30), 264 (75), 248 (20), 236 (40), 223 (M − $NPri_2$, 60), 205 (65), 195 (10), and 179 (80). Despite the accurate microanalysis and repeated separation by p.l.c., into one main band and a minor lower one which appeared well resolved, this fraction was always a mixture containing mainly material of R_F 0.3, but also a little material of R_F 0.2, as evidenced by t.l.c. and n.m.r. This suggested that the two materials were isomeric and interconverting on silica. The lower R_F material predominated in a small second fraction (3 mg, 2%) isolated as an oil by extracting the band of R_F 0.2, repeatedly in several p.l.c. runs. Although this could not be obtained free from higher R_F material, as shown by t.l.c. and n.m.r., the major peaks in the n.m.r. spectrum showed differences from those of the fraction containing mainly the latter (Found: M^+, 323.2105. $C_{18}H_{29}NO_4$ requires M, 323.2097); $\nu_{max.}$ and $\lambda_{max.}$ major peaks as for higher R_F material; δ_H (80 MHz), 1.03, 1.12, and 1.21 (3 × 3 H, d, *J* 6.8 Hz, $CHCH_3$), 1.55 (6 H, d, *J* 6.8 Hz, $CHCH_3$), 2.51 (1 H, dd, *J* 6.8 and 13.7 Hz, $ArCH_AH_BCHOH$), 2.78 (1 H, dd, *J* 3.9 and 13.7 Hz, $ArCH_AH_BCHOH$), 3.49 (2 H, m, *J* 6.8 Hz, $CHCH_3$), 3.66 (1 H, m, $CHCH_3$), 3.76 and 3.80 (2 × 3 H, s, $ArOCH_3$), and 6.32 and 6.37 (2 × 1 H, d, *J* 2.1; 0 Hz, Ar*H*); *m/z* peaks as for higher R_F material.

The second band from the original p.l.c. R_F 0.35, yielded N,N-*di-isopropyl*-2,4-*dimethoxy*-6-(2-*methoxypropyl*)*benzamide* (**20**) (23 mg, 15%) as needles, m.p. 113—115 °C (from acetone–hexane) (Found: M^+, 337.2266. $C_{19}H_{31}NO_4$ requires M, 337.2253); $\nu_{max.}$ (2 840m (CH of OMe), 1 635 ($CONR_2$), 1 610 (Ar), and 1 380m and 1 370m cm^{-1} ($CHMe_2$); $\lambda_{max.}$ 208 and 283 nm; δ_H (400 MHz) 1.03, 1.06, 1.09, and 1.15 (total intensity 9 H, 4 × d, *J* 6.8 ,6.8, 6.8, and 5.9 Hz, respectively, $CHCH_3$), 1.53 and 1.5 (total intensity 6 H, 2 × d, *J* 6.8 Hz, $CHCH_3$), 2.40 and 2.53 (total intensity 1 H, 2 × dd, *J* 7.8 and 13.7, and *J* 4.9 and 13.7 Hz respectively, $ArCH_AH_BCHO$), 2.67 and 2.95 (total intensity 1 H, 2 × dd, *J* 7.8 and 13.7, and *J* 4.9 and 13.7 Hz respectively, $ArCH_ACH_BCHO$), 3.25 and 3.35 (total intensity 3 H, 2 × s, $ROCH_3$), 3.45 [1 H, m, $CH_2CH(OMe)CH_3$], 3.65 (2 H, m, *J* 6.8 Hz, $CHCH_3$), 3.74 and 3.79 (total intensity 6 H, 2 × s, $ArOCH_3$), 6.29 (1 H, d, *J* 2.0 Hz, Ar*H*), and 6.39 and 6.45 (total intensity 1 H, 2 × d, *J* 2.0 Hz, Ar*H*); *m/z* 337 (M^+, 10%), 322 (M − Me, 50), 306 (M − OMe, 25), 264 (55), 237 (M − $NPri_2$, 70), 205 (100), and 179 (55).

The third band from the original p.l.c., R_F 0.75, was subjected to further p.l.c. in the same solvent system to give methyl 2,4-dimethoxy-6-prop-1-enylbenzoate[30] (**18**) (10 mg, 9%) as an oil which was pure by t.l.c. (Found: M^+, 236.1050. Calc. for $C_{13}H_{16}O_4$: M, 236.1049); $\nu_{max.}$($CHCl_3$), 2 860m and 2 840m (CH of OMe), 1 725 (C=O), 1 655w (C=C), 1 605 (Ar), 1 585 (Ar), and 965w cm^{-1}; $\lambda_{max.}$ 217sh, 253, and 290sh nm; δ_H (400 MHz) 1.85 (3 H, dd, *J* 1.7 and 6.3 Hz, $CHCHCH_3$), 3.79, 3.81, and 3.88 (3 × 3 H, s, OCH_3), 6.20 (1 H, dq, *J* 6.3 and 15.6 Hz, $CHCHCH_3$), 6.33 (1 H, d, *J* 2.0 Hz, ArH), 6.37 (part of: 1 H, dd, *J* 1.7 and 15.6 Hz, $ArCHCHCH_3$), and 6.57 (1 H, d, *J* 2.0 Hz, Ar*H*); *m/z* 2 136 (M^+, 5%), 221 (M − Me, 50), 205 (M − OMe, 100), and 177 (25).

Ethyl (±)-2,4-*Dimethoxy*-6-(1-*methyl*-2-*oxopropyl*)*benzoate* (**10**).—(*a*) Lithium di-isopropylamide (0.75 mmol) in dry THF (1 ml) under argon was prepared in the usual way in the side-arm of a flask and cooled to −15 °C. Ethyl 2-ethyl-4,6-dimethoxybenzoate (119 mg, 0.50 mmol) in dry THF (1 ml) was added, whereupon the deep red colour attributed to anion (**9**) appeared immediately. After 1 min at −15 °C, the mixture was cooled to −78 °C and stirred for a further 20 min. Meanwhile in the main body of the flask, a solution of acetyl chloride (0.071 ml, 78 mg, 1.0 mmol) in THF (1 ml) had been prepared at −78 °C and the anion solution was added gradually to this over 20 min while maintaining the same temperature. Each portion of anion solution lost its colour rapidly after addition and a light yellow solution resulted after the mixture had been stirred for 2 h at −78 °C, diluted with ethanol (5 ml), and warmed to room temperature. After standard work-up, a yellow oil was obtained which was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1 : 1] to give four main bands.

The first, R_F 0.15, yielded an oil (60 mg, 51%) which appeared as a mixture by n.mr. and t.l.c. and was separated by further p.l.c. (diethyl ether, 5 elutions) to give two bands. First, R_F 0.5, was a lower R_F isomer of *ethyl* (±)-2-[1-(3,4-*dihydro*-6,8-*dimethoxy*-3,4-*dimethyl*-1-*oxo*-1H-2-*benzopyran*-3-*yl*)*ethyl*]-4,6-*dimethoxybenzoate* (**21**) (42 mg, 36%) isolated as prisms, m.p. 135—137 °C (from ethyl acetate–hexane) (Found: C, 65.9; H, 7.1. $C_{26}H_{32}O_8$ requires C, 66.09; H, 6.83%); $\nu_{max.}$ 2 960m and 2 940m (both CH), 2 840m (CH of OMe), 1 725 (C=O), 1 605 (Ar), 1 590sh (Ar), and 1 460m cm^{-1} (CH_2/CH_3); $\lambda_{max.}$ 218sh, 261, and 290sh nm; δ_H (400 MHz) 0.99 (3 H, s, CCH_3), 1.26 (3 H, d, *J* 6.8 Hz, $CHCH_3$), 1.28 (3 H, t, *J* 6.8 Hz, CH_2CH_3), 1.40 (3 H, d, *J* 6.8 Hz, $CHCH_3$), 3.18 and 3.28 (2 × 1 H, q, *J* 6.8 Hz, $CHCH_3$), 3.77, 3.86, 3.88, and 3.91 (4 × 3 H, s, $ArOCH_3$), 4.23 (2 H, q, *J* 6.8 Hz, OCH_2CH_3), and 6.35, 6.39, 6.41, and 7.03 (4 × 1 H, d, *J* 2.0 Hz, Ar*H*) (Found: M^+, 472.2115. $C_{26}H_{32}O_8$ requires M, 472.2097); *m/z* 472 (M^+, 5%), 427 (M − OEt, 15), and 235 (M − $C_{13}H_{17}O_4$, 100). Also isolated from this second p.l.c., R_F 0.55, was a higher R_F isomer of *ethyl* (±)-2-[1-(3,4-*dihydro*-6,8-*dimethoxy*-3,4-*dimethyl*-1-*oxo*-1H-2-*benzopyran*-3-*yl*)*ethyl*]-4,6-*dimethoxybenzoate* (**21**) (9 mg, 8%) as an oil (Found: M^+, 472.2095. $C_{26}H_{23}O_8$ requires M, 472.2097); $\nu_{max.}$ 2 960m and 2 940m (both CH), 2 840m (CH of OMe), 1 725 (C=O), 1 605 (Ar), 1 590sh (Ar), and 1 460 cm^{-1} (CH_2/CH_3); $\lambda_{max.}$ 217sh, 265, and 290 nm; δ_H (400 MHz) 1.21 and 1.30 (2 × 3 H, d, *J* 6.8 Hz, $CHCH_3$), 1.33 (3 H, t, *J* 6.8 Hz, CH_2CH_3), 1.45 (3 H, s, CCH_3), 2.85 and 3.19 (2 × 1 H, q, *J* 6.8 Hz, $CHCH_3$), 3.80, 3.82, 3.84, and 3.91 (4 × 3 H, s, $ArOCH_3$), 4.34 (2 H, q, *J* 6.8 Hz, OCH_2CH_3), 6.26 (1 H, d, *J* 2.0 Hz, Ar*H*), 6.37 (2 H, Br s, Ar*H*), and 6.60 (1 H, d, *J* 2.0 Hz, Ar*H*); *m/z* 472 (M^+, 10%), 427 (M − OEt, 30), and 235 (M − $C_{13}H_{17}O_4$, 100). This material also contained a trace of the lower R_F isomer (see above) according to n.m.r. and t.l.c.

The second band from the original p.l.c., R_F 0.6, gave an oil (26 mg) which was purified by further p.l.c. [diethyl ether–light petroleum (b.p. 60—80 °C), 1:2, 4 elutions, R_F 0.5] to give *ethyl* (±)-2,4-*dimethoxy*-6-(1-*methyl*-2-*oxopropyl*)*benzoate* (**10**) (13 mg, 9%) as prisms, m.p. 58—59 °C (from hexane) (Found: C, 64.5; H, 7.3. $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19%); $\nu_{max.}$ 2 840w (CH of OMe), 1 730sh (C=O), 1 720 (C=O), 1 610 (Ar), and 1 590 cm^{-1} (Ar); $\lambda_{max.}$ 242sh and 283 nm; δ_H (80 MHz) 1.32 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.36 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.05 (3 H, s, $COCH_3$), 3.74 (1 H, qw, *J* 7 Hz, $CHCH_3$), 3.76 and 3.80 (2 × 3 H, s, $ArOCH_3$), 4.37 (2 H, m q, *J* 7 Hz, OCH_2CH_3), 6.20 (1 H, d, *J* 3 Hz, Ar*H*), and 6.36 (1 H, d, *J* 2 Hz, Ar*H*); (Found: M^+, 280.1295. $C_{15}H_{20}O_5$ requires M, 280.1311); *m/z* 280 (M^+, 40%), 238 (M − CH_2CO, 100), 235 (M − OEt, 55), 234 (M − EtOH, 30), 193 (50), 192 (85), and 191 (60).

The third band from the original p.l.c., R_F 0.75, gave starting material (29 mg, 17%).

(b) In a further experiment, the anion (**9**) (0.50 mmol) was generated as above, but from lithium di-isopropylamide (0.75 mmol) in dry THF (30 ml) in a standard round-bottomed flask. The anion solution, at −78 °C, was transferred dropwise *via* a double-ended needle into another flask containing acetyl chloride (0.142 ml, 156 mg, 2.0 mmol) in dry THF under argon at −130 °C. Each drop instantly lost its colour and when addition was complete (20 min) a light yellow solution resulted. This was stirred for 1 h at −130 °C before it was diluted with ethanol (5 ml) and allowed to warm to room temperature. After standard work-up, a yellow oil was obtained which was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C); 1 : 2, 1 elution and 1 : 1, 1 elution] to give three main bands.

The first, R_F 0.15, gave ethyl (±)-2-[1-(3,4-dihydro-6,8-dimethoxy-3,4-dimethyl-1-oxo-1*H*-2-benzopyran-3-yl)ethyl]-4,6-dimethoxybenzoate (**21**) (14 mg, 12%) as an oil containing a mixture of the previously isolated diastereoisomers by n.m.r. and t.l.c.

The second band, R_F 0.65, yielded the oxo ester (**10**) (60 mg, 43%), pure by t.l.c. and n.m.r. and identical with the previously obtained material.

The third p.l.c. band, R_F 0.75, gave starting material (27 mg, 23%).

(±)-threo-3,4-*Dihydro*-6,8-*dimethoxy*-3,4-*dimethyl*-1H-2-*benzopyran*-1-*one* (**11**).—(*a*) To ethyl (±)-2,4-dimethoxy-6-(1-methyl-2-oxopropyl)benzoate (**10**) (50 mg, 0.18 mmol) in methanol (5 ml) was added sodium borohydride (34 mg, 0.90 mmol) and the mixture was stirred for 80 min at room temperature. After standard work-up, an oil was obtained which was purified by p.l.c. (diethyl ether) to give two main bands.

The first, R_F 0.2, yielded the *threo*-lactone (**11**) (16 mg, 38%) as prisms identical with the material obtained as described above. T.l.c. [diethyl ether–ethyl acetate–light petroleum (b.p. 60—80 °C), 10:1.1, 4 elutions], prior to recrystallisation, showed a trace amount only of the *erythro*-isomer (**12**) which was not detectable by ^{1}H n.m.r. (80 MHz).

The second band, R_F 0.45, gave ethyl (±)-*threo*-2-(2-hydroxy-1-methylpropyl)-4,6-dimethoxybenzoate (**7**) (27 mg, 54%) as an oil (Found: M^+, 282.1455. $C_{15}H_{22}O_5$ requires M, 282.1467); $\nu_{max.}$ 3 600 (OH), 3 510—3 410w (H bonded OH), 2 840w (CH of OMe), 1 730 (C=O), 1 610 (Ar), and 1 590sh cm^{-1} (Ar); $\lambda_{max.}$ (245sh and 289 nm; δ_H (80 MHz), 1.21 (6 H, d, *J* 6 Hz, CHCH_3), 1.35 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.67 [1 H, m, *J* 7 Hz, ArC*H*(CH$_3$)CH], 3.79 (6 H, s, ArOCH_3m total intensity 7 H), 4.35 (2 H, q, *J* 7 Hz, OCH_2CH_3), and 6.33 and 6.45 (2 × 1 H, d, *J* 2 Hz, Ar*H*); *m/z* 282 (M^+, 10%), 238 (M − MeCHO, 75), 237 (M − OEt, 20), 193 (55), 192 (100), and 191 (60). This material was shown to be almost entirely the *threo*-diasteroisomer (**7**), with only a slight trace of the *erythro*-diasteroisomer, by its conversion as follows to the *threo*-lactone (**11**) [with only a trace of the *cis*-lactone (**12**)].

The hydroxy ester (22 mg, 0.08 mmol) was added to sodium hydride (oil free; 18 mg, 0.75 mmol) in dry THF (1 ml) at room temperature and stirred for 1 h. After standard work-up, the *threo*-lactone (**11**) (15 mg, 81%) was obtained as prisms, identical with previous material. The crude material showed a very slight trace of *cis*-lactone (**12**) by t.l.c. (diethyl ether, 5 elutions), but not enough was present to show in the n.mr. spectrum (80 MHz).

(*b*) Method (*a*) was followed except that the quantities used were: oxo ester (**10**) (363 mg, 1.30 mmol), methanol (20 ml), and sodium borohydride (256 mg, 6.47 mmol). The reaction mixture was stirred for 1 h at room temperature after which the solvent was removed under reduced pressure with gentle heating (water-bath) and the residue diluted with water (10 ml). The mixture was extracted with ethyl acetate (4 × 10 ml), and the extract afforded a white solid which on recrystallisation gave the *threo*-lactone (**11**) (260 mg) as prisms, m.p. 124—126 °C (from ethyl acetate–hexane), identical with material obtained previously. The recrystallisation mother-liquors were concentrated and subjected to p.l.c. (diethyl ether, 5 elutions) to give two bands. The first, R_F 0.5, gave more of *threo*-lactone (**11**) (3 mg) (total yield 263 mg, 86%). The second band, R_F 0.55, gave *cis*-lactone (**12**) (7 mg, 2%) as an oil which was identical with material obtained previously.

Reduction of the (±)-threo-*Lactone* (**11**).—(a) *With di-iso-butylaluminium hydride.* To (±)-*threo*-3,4-dihydro-6,8-dimethoxy-3,4-dimethyl-1*H*-2-benzopyran-1-one (**11**) (34 mg, 0.14 mmol) in dry toluene (5 ml) under argon at room temperature was added slowly with stirring di-isobutylaluminium hydride (1.53M in toluene; 0.28 ml, 0.43 mmol), and the mixture was stirred for 9 h. Hydrochloric acid (2M; 10 ml) was then added, and the mixture was diluted with water (5 ml). The toluene layer was separated and the aqueous layer extracted with diethyl ether (2 × 10 ml) and the ethyl acetate (2 × 10 ml). The combined organic layers were washed with hydrochloric acid (1M; 10 ml), aqueous sodium hydrogen carbonate (5%, 10 ml), and saturated aqueous sodium chloride (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow oil. P.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:2; R_F 0.7] gave (±)-*threo*-3,4-dihydro-6,8-dimethoxy-3,4-dimethyl-1*H*-2-benzopyran (**14**) (23 mg, 72%) as an oil, pure by t.l.c., b.p. 80—85 °C/0.1 mmHg, which crystallised as prisms, m.p. 48—50 °C (from hexane) (Found: C, 70.05; H, 8.1. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.16%); $\nu_{max.}$ 2 840m (CH of OMe), 1 610 (Ar), and 1 495 cm^{-1} (Ar); $\lambda_{max.}$ 224 and 278 nm; δ_H (80 MHz) 1.24 (3 H, d, *J* 7 Hz, CHCH_3), 1.32 (3 H, d, *J* 6.5 Hz, CHCH_3), 2.59 [1 H, m, *J* 7 Hz, ArC*H*(CH$_3$)CH], 3.43 [1 H, m, *J* 6.5 Hz, OC*H*(CH$_3$)CH], 3.76 (3 H, s, ArOCH_3), 3.78 (3 H, s, ArOCH_3), 4.50 (1 H, d, *J* 15 Hz, ArCH_AH$_B$O), 4.83 (1 H, d, *J* 15 Hz, ArCH$_A$$H_B$O), 6.27 (1 H, d, *J* 2 Hz, Ar*H*), and 6.39 (1 H, d, *J* 2 Hz) (Found: M^+, 222.1262. $C_{13}H_{18}O_3$ requires M, 222.1256); *m/z* 222 (M^+, 45%), 221 (M − HJ, 25), and 178 (M − MeCHO, 100).

(b) *With lithium aluminium hydride.* To the (±)-*erythro*-lactone (**11**) (90 mg, 0.38 mmol) in dry THF (15 ml) was added slowly lithium aluminium hydride (116 mg, 3.05 mmol). The mixture was heated at reflux for 4.5 h and then left overnight at room temperature. It was then cooled to 0 °C and ice-cold water (3 ml) added. Sulphuric acid (50%; 5 ml) was now added at 0 °C, followed by saturated aqueous ammonium chloride (5 ml). The mixture was extracted with diethyl ether (2 × 10 ml) and ethyl acetate (2 × 15 ml) and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (10 ml) and saturated brine (10 ml) dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow oil. This was purified by bulb-to-bulb distillation to give the (±)-*threo*-dihydrobenzopyran (**14**) (61 mg, 72%) as an oil, b.p. 80—85 °C/0.1 mmHg, which was pure by t.l.c.

(±)-threo-3-(3,5-*Dimethoxy*-2-*methylphenyl*)*butan*-2-*ol* (**5**).—(±)-*threo*-3,4-Dihydro-6,8-dimethoxy-3,4-dimethyl-1*H*-2-benzopyran (**14**) (110 mg, 0.50 mmol) in methanol (8 ml) and glacial acetic acid (4 ml) was hydrogenated for 26 h at room temperature over 10% palladium–charcoal catalyst (110 mg). The mixture was filtered through Celite and the filtrate evaporated to dryness under reduced pressure to give an oil which was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:2; R_F 0.4] to give the (±)-alcohol (**5**)[20,21] (96 mg, 86%) as an oil which was pure by t.l.c. (Found: M^+, 224.1406. Calc. for $C_{13}H_{20}O_3$: M, 224.1412); $\nu_{max.}$ 3 590m (OH), 2 840m (CH of OMe), 1 610 (Ar), and 1 595 cm^{-1} (Ar); $\lambda_{max.}$ 220sh and

279 nm; δ_H (80 MHz) 1.17 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.25 (3 H, d, *J* 6 Hz, $CHCH_3$), 2.14 (3 H, s, $ArCH_3$), 3.05 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.79 (6 H, s, $ArOCH_3$), 3.87 [1 H, partly obscured, $HOCH(CH_3)CH$], 6.35 (1 H, d, *J* 2 Hz, Ar*H*), and 6.42 (1 H, d, *J* 2 Hz, Ar*H*); *m/z* 224 (M^+, 40%), 180 (*M* − MeCHO, 100), 179 (*M* − MeCHOH, 50), and 165 (30).

Treatment of the (±)-erythro-*Dimethoxy Alcohol* (**16**) *with Iodotrimethylsilane.*—To (±)-*erythro*-3-(3,5-dimethoxy-2-methylphenyl)butan-2-ol (**16**) (10 mg, 0.045 mmol) in dry chloroform under argon was added iodotrimethylsilane (0.025 ml, 36 mg, 0.18 mmol). The solution was stirred for 16 h at room temperature, after which t.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:1] showed that little change had occurred. Consequently, the solution was stirred for 11 h at 50 °C, cooled to room temperature, diluted with methanol (10 ml), and stirred for 15 min at room temperature. The solution was evaporated to dryness under reduced pressure to give an oil, which was dissolved in diethyl ether–ethyl acetate (1:1, 10 ml), and the solution washed with aqueous sodium bisulphite and saturated brine, dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give an oil. After p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:4, 2 elutions; R_F 0.75], (±)-2-(3,5-*dimethoxy*-2-*methylphenyl*)-3-*iodobutane* (**22**) (5 mg, 34%) was obtained as an oil which was pure by t.l.c. (Found: M^+, 334.0442. $C_{13}H_{19}IO_2$ requires *M*, 334.0430); $\nu_{max.}$ 2 840w (CH of OMe), 1 610 (Ar), and 1 590 cm^{-1} (Ar); $\lambda_{max.}$ 281 nm; δ_H (80 MHz) 1.39 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.79 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.10 (3 H s, $ArCH_3$), 3.07 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.77 (6 H, s, $ArOCH_3$), 4.24 [1 H, m, *J* 7 Hz, $ICH(CH_3)CH$], and 6.31 (2 H, s, Ar*H*); *m/z* 334 (M^+, 80%), 207 (*M* − I, 10), and 152 (70).

Treatment of the (±)-*Dimethoxy Alcohol* (**16**) *with Boron Tribromide.*—To (±)-*erythro*-3-(3,5-dimethoxy-2-methylphenyl)-butan-2-ol (**16**) (12 mg, 0.05 mmol) in dry dichloromethane (2 ml) under argon at −78 °C, was added with stirring boron tribromide (0.1 ml, 262 mg, 1.05 mmol). The mixture was stirred while it warmed slowly to room temperature, and then at that temperature for a total of 16 h. Diethyl ether (10 ml) was then added cautiously, followed by water (10 ml). The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 10 ml) and ethyl acetate (10 ml). The combined organic layers were washed with saturated brine (10 ml), dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give a yellow oil. Purification of this by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:11, R_F 0.5], gave (±)-2-*bromo*-3-(3,5-*dihydroxy*-2-*methylphenyl*)*butane* (**23**) (9 mg, 65%) as an oil which was pure by t.l.c. and apparently a single diastereoisomer by n.m.r. (Found: M^+, 258.0270. $C_{11}H_{15}BrO_2$ requires *M*, 258.2566), $\nu_{max.}$ 3 615 (OH), 3 600—3 100m (H bonded OH), 1 620 (Ar), 1 600 (Ar), and 1 500w cm^{-1} (Ar); $\lambda_{max.}$ 284 nm; δ_H (80 MHz) 1.38 and 1.57 (2 × 3 H, d, *J* 7 Hz, $CHCH_3$), 2.13 (3 H, s, $ArCH_3$), 3.22 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 4.20 [1 H, m, *J* 7 Hz, $BrCH(CH_3)CH$], and 6.24 (2 H, s, Ar*H*); *m/z* 260 and 258 (M^+, 10%), 179 (*M* − Br, 100), and 151 (55).

Treatment of the (±)-*Dimethoxy Alcohol* (**5**) *with Boron Tribromide.*—(*a*) To (±)-*threo*-3-(3,5-dimethoxy-2-methylphenyl)-butan-2-ol (**5**) (10 mg, 0.045 mmol) in dry dichloromethane (4 ml) under argon at −78 °C, was added with stirring boron tribromide (0.045 ml, 111 mg, 0.47 mmol). The mixture was stirred while it warmed slowly to room temperature and at that temperature, for a total of 16 h. It was then cooled to 0 °C before addition of diethyl ether (5 ml) and saturated aqueous sodium hydrogen carbonate (10 ml). The organic layer was separated and then the aqueous layer was extracted with diethyl ether (2 × 10 ml), acidified to pH 3, and further extracted with ethyl acetate (2 × 10 ml). The combined organic extracts were washed with saturated brine (10 ml), dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give a yellow oil. This was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C); 1:2, 2 elutions and 1:1, 1 elution] to give two main bands.

The first, R_F 0.25, yielded (±)-*threo*-(3,5-dihydroxy-2-methylphenyl)butan-2-ol ('phenol B') (**4**) (4 mg, 46%) as prisms, m.p. 167—170 °C (from $CHCl_3$) (lit.,[1] 169—170 °C) (Found: M^+, 196.1101. Calc. for $C_{11}H_{16}O_3$: *M*, 196.1100); $\nu_{max.}$ (Nujol) 3 500—2 600m (OH), 1 600 (Ar), and 1 510m cm^{-1} (Ar); $\lambda_{max.}$ 220sh and 280 nm; δ_H (60 MHz; CD_3COCD_3), 1.11 (3 H, d, *J* 6 Hz, $CHCH_3$), 1.14 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.10 (3 H, s, $ArCH_3$), 3.04 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.85 [1 H, m, *J* 3 and 6 Hz, $HOCH(CH_3)CH$], 6.26 (1 H, d, *J* 2 Hz, Ar*H*), 6.35 (1 H, d, *J* 2 Hz, Ar*H*), and 7.8 (2 H, br s, OH); δ_H (80 MHz; CD_3CN), 1.12 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.13 (3 H, d, *J* 6 Hz, $CHCH_3$), 2.078 (3 H, s, $ArCH_3$), 2.98 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.74 [1 H, m, *J* 6 Hz, $HOCH(CH_3)CH$], 6.18 (1 H, d, *J* 2 Hz, Ar*H*), and 6.32 (1 H, d, *J* 2 Hz, Ar*H*); *m/z* 196 (*M*, 10%), 178 (*M* − H_2O, 15), and 152 (*M* − MeCHO, 30).

The second band, R_F 0.7, gave (**24**), a diastereoisomer of (**23**) described above (6 mg, 52%) as an oil (Found: M^+, 260.0249. $C_{11}H_{15}BrO_2$ requires *M*, 260.0235); $\nu_{max.}$ 3 610 (OH), 3 600—3 100m (H bonded OH), 1 620m (Ar), 1 600m (Ar), and 1 495m cm^{-1} (Ar); $\lambda_{max.}$ 284 nm; δ_H (80 MHz) 1.31 and 1.64 (2 × 3 H, d, *J* 7 Hz, $CHCH_3$), 2.15 (3 H, s, $ArCH_3$), 3.45 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 4.28 [1 H, m, *J* 7 Hz, $BrCH(CH_3)CH$], and 6.23 and 6.34 (2 × 1 H, d, *J* 2 Hz, Ar*H*); *m/z* 260 and 258 (M^+, 20%), 179 (*M* − Br, 20), and 151 (100).

(*b*) In a further experiment, a similar method was used except that the following quantities were used: (±)-*threo*-dimethoxy alcohol (**5**) (400 mg, 1.79 mmol) in dry dichloromethane (15 ml) and boron tribromide (3.44 ml, 9.01 g, 36 mmol) in dry dichloromethane (3 ml). After proceeding as far as cooling at 0 °C and adding diethyl ether (15 ml), the work-up was modified by the addition of water (5 ml) followed by aqueous sodium hydroxide (5%; 15 ml). The mixture was stirred while it warmed to room temperature over 12 h; the aqueous layer was then separated and the organic layer extracted with aqueous sodium hydroxide (10%; 3 × 20 ml). The combined aqueous extracts were washed with diethyl ether (20 ml) and then acidified to pH 1. This acidified aqueous solution was then extracted with ethyl acetate (4 × 50 ml), and the combined organic layers were washed with saturated brine (50 ml), dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give a yellow oil. This was purified by p.l.c. [ethyl acetate–light petroleum (b.p. 60—80 °C], 1:1, R_F 0.2) to give the (±)-phenol (**4**) ('phenol B') (278 mg, 79%) which was identical with the material isolated as described in (*a*).

(±)-threo-2,6-*Dihydroxy*-4-(2-*hydroxy*-1-*methylpropyl*)-3-*methylbenzoic Acid* (**25**).—(±)-*threo*-3-(3,5-Dihydroxy-2-methylphenyl)butan-2-ol (**4**) (180 mg, 0.92 mmol), dry potassium hydrogen carbonate (720 mg), and glycerol (3 ml) were stirred together at 150 °C for 7 h under an atmosphere of dry carbon dioxide. After the mixture had cooled to room temperature, water (10 ml) and diethyl ether (10 ml) were added and the aqueous layer was separated and then washed with diethyl ether (10 ml). The aqueous layer was acidified and extracted with ethyl acetate (4 × 10 ml) and then the combined extracts were washed with saturated brine (10 ml), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give the acid (**25**) (165 mg, 75%) as prisms, m.p. 145—149 °C (decomp.; from acetone–toluene) [lit.,[23b] m.p. 175—176 °C (decomp.)] (Found: M^+, 240.0985. Calc. for $C_{12}H_{16}O_5$: *M*, 240.0998); $\nu_{max.}$ (Nujol) 3 360m (OH), 3 300—2 500m (H

bonded OH), 1 680 (C=O), 1 635 (Ar), and 1 590m cm^{-1} (Ar); $\lambda_{max.}$ 216, 252, and 316 nm; δ_H (90 MHz; CD_3COCD_3) 1.15 (3 H, d, *J* 6 Hz, $CHCH_3$), 1.6 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.15 (3 H, s, $ArCH$), 3.10 [1 H, m, *J* 7 Hz, $ArCH(CH_3)CH$], 3.90 [1 H, m, *J* 6 Hz, $HOCH(CH_3)CH$], 5.5 (br s, OH and H_2O), and 6.50 (1 H, s, ArH); *m/z* 240 (M^+, 20%), 222 ($M - H_2O$, 10), 196 ($M - CO_2$, 30), and 178 ($M - CO_2$ and H_2O, 100). The material was used in the next experiment without further purification.

(±)-threo-4,6-*Dihydro*-8-*hydroxy*-3,4,5-*trimethyl*-6-*oxo*-3H-2-*benzopyran*-7-*carboxylic Acid* (*Citrinin*) (**1**).—Hydrogen chloride gas was bubbled gently through a solution of (±)-*threo*-2,6-dihydroxy-4-(2-hydroxy-1-methylpropyl)-3-methylbenzoic acid (**25**) (60 mg, 0.25 mmol) in ethyl orthoformate (2 ml) at 0 °C for 20 min, during which time the solution became red. Water (5 ml) and ethyl acetate (5 ml) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 5 ml) and the combined organic layers were then extracted with saturated aqueous sodium hydrogen carbonate (4 × 10 ml). The combined aqueous layers were acidified with concentrated hydrochloric acid and extracted with ethyl acetate (4 × 10 ml). The combined organic extracts were washed with saturated brine (10 ml), dried (Na_2SO_4), and evaporated to dryness under reduced pressure to give yellow–brown crystals. These were recrystallised to give (±)-citrinin (**1**) (24 mg, 38%) as prisms, m.p. 171—175 °C (decomp.; from $CHCl_3$–hexane) [lit.,[23] 175 °C (decomp.) from methanol] (Found: M^+, 250.0854. Calc. for $C_{13}H_{14}O_5$: *M*, 250.0841); $\nu_{max.}$ (2 960m, 2 940m, 2 880w, and 2 860w (all CH), 1 680 (C=O), 1 640 (C=C), 1 485 (CH), 1 380m (CH), 1 310m (C–O), 1 180m (=C–O–C), 1 135m (C–O–C), and 970m cm^{-1} (OH) [lit.,[13] for (−)-citrinin, 3 200, 2 935, 2 870, 1 685, 1 640, 1 600, 1 480, 1 380, 1 310, 1 180, 1 130, and 950 cm^{-1}]; $\lambda_{max.}$ 252 and 319 nm [lit.,[23] for (−)-citrinin, 250 and 331 nm; (−)-citrinin, 252 and 321 nm]; δ_H (80 MHz) 1.23 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.34 (3 H, d, *J* 6.5 Hz, $CHCH_3$), 2.02 (3 H, s, CCH_3), 2.98 [1 H, q, *J* 7 Hz, $CH(CH_3)CH$], 4.75 [1 H, q, *J* 6.5 Hz, $OCH(CH_3)CH$], 8.21 (1 H, s, C=C*H*O), 15.09 (1 H, br s, OH), and 15.81 (1 H, br s, OH) [lit.,[14] for (−)-citrinin, (60 MHz) 1.25 (3 H, d, *J* 6.5 Hz), 1.38 (3 H, d, *J* 6.5 Hz), 2.03 (3 H, s), 3.04 (1 H, q, *J* 6.5 Hz), 4.84 (1 H, q, *J* 6.5 Hz), 8.3 (1 H, s), 13.7 (1 H, s), and 15.2 p.p.m. (1 H, s); contemporary spectrum of (−)-citrinin, 1.23 (3 H, d, *J* 7.3 Hz), 1.35 (3 H, d, *J* 6.8 Hz), 2.02 (3 H, s), 2.99 (1 H, q, *J* 7.3 Hz), 4.78 (1 H, q, *J* 6.8 Hz), 8.24 (1 H, s), 15.09 (1 H, s), and 15.86 p.p.m. (1 H, s)]; *m/z* 250 (M^+, 70%), 232 ($M - H_2O$, 10), 217 (15), 206 ($M - CO_2$, 30), and 179 (100).

Acknowledgements

We thank the S.E.R.C. for financial support.

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Received 29*th November* 1985; *Paper* 5/2093