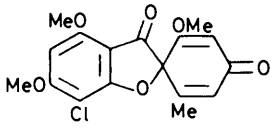
Depsidone Synthesis. Part 21.[1] A New Synthesis of Grisa-2',5'-diene-3,4'-diones †[2]

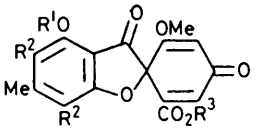
By **Melvyn V. Sargent**, Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia 6009, Australia

Treatment of suitably substituted methyl 2-phenoxybenzoates with titanium(IV) chloride and dry hydrogen chloride afforded grisa-2',5'-diene-3,4'-diones in high yield. The structures of these compounds followed from their thermal stability, their methanolysis to methyl 2-(4-hydroxyphenoxy)benzoates, and their reductive cleavage to 2,4'-dihydroxybenzophenones. Treatment of the benzophenones with base gave xanthones. An attempt to synthesize dehydrogriseofulvin (1) by this method failed.

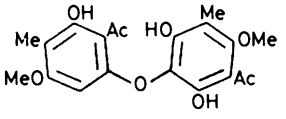
THE grisa-2',5'-diene-3,4'-diones are a small group of polyketide mould metabolites which include dehydrogriseofulvin (1),[3] geodin (2),[4] erdin (3),[4] bidsechlorogeodin (4),[5] and trypacidin (5).[6] Of these the most important is dehydrogriseofulvin (1) which is implicated in the biosynthesis,[7] and is a key intermediate in the chemical synthesis[8,9] of the important antifungal agent griseofulvin. The synthesis of naturally occurring grisa-2',5'-diene-3,4'-diones and their analogues[10] has usually been accomplished by oxidative coupling of benzophenones,[8,11] or by annelation of β-coumaranones.[9] It is now reported that certain grisa-2',5'-diene-3,4'-diones are readily obtained in high yield from *o*-phenoxybenzoic esters by intramolecular *ipso*-acylation.



(1)



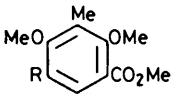
(2) R^1=H, R^2=Cl, R^3=Me
(3) R^1=R^3=H, R^2=Cl
(4) R^1=R^2=H, R^3=Me
(5) R^1=R^3=Me, R^2=H



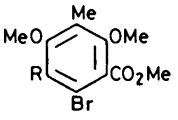
(6)

Whilst engaged in work aimed at the synthesis of the lichen metabolite leprolomin (6),[12] we observed that treatment of the diaryl ether (18) (Scheme 1) with tin(IV) chloride and acetyl chloride in an attempted Friedel–Crafts acylation gave not the expected acetyl compound but a different substance.

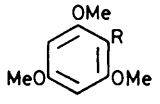
The diaryl ether (18) was readily prepared by Ullmann reaction between the bromo-compound (12) and the phenol (17) under the conditions of Tomita and his co-workers.[13] The starting material for the synthesis of the bromo-compound (12) was 2,4-dimethoxy-3-methylbenzaldehyde,[14] which was converted into the ester (7) by standard methods. Nitration of the ester (7) with copper(II) nitrate trihydrate in acetic anhydride gave the nitro-compound (8), which was catalytically reduced to



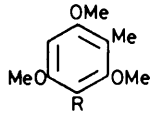
(7) R = H
(8) R = NO_2
(9) R = NH_2
(10) R = Br



(11) R = NH_2
(12) R = H



(13) R = H
(14) R = CHO
(15) R = Me



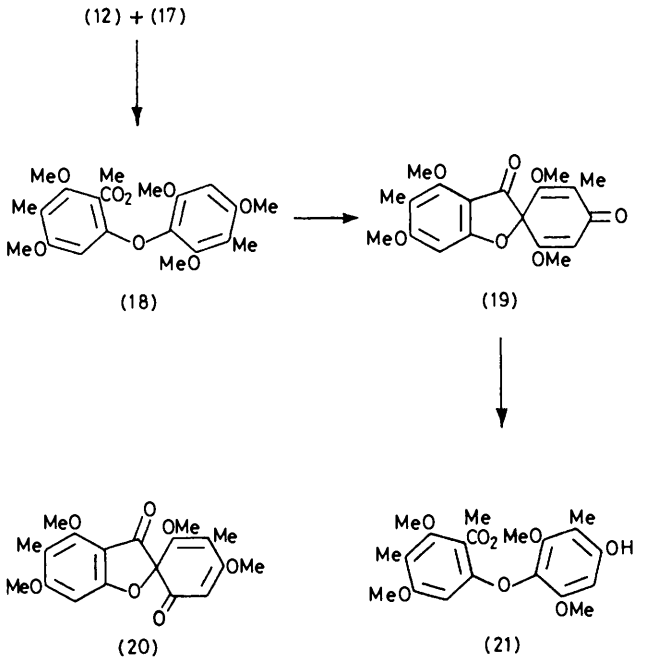
(16) R = CHO
(17) R = OH

the amine (9). Bromination of the amine (9) gave the bromo-amine (11). This compound on deamination then gave the bromo-compound (12), the ^{1}H n.m.r. spectrum of which exhibited the aromatic proton signal as a singlet at δ 6.75. Its isomer (10) was prepared by direct bromination of the ester (7) and as expected the aromatic proton now resonated at much lower field (δ 7.80), thus confirming the structural assignments.

In order to synthesize the phenol (17), the aldehyde (16)[15] was required. Tri-*O*-methylphloroglucinol (13) was therefore subjected to Vilsmeier–Haack formylation and the resulting aldehyde (14)[16] was reduced by the Clemmensen method to the toluene (15),[17] which was then subjected to another Vilsmeier–Haack reaction. Baeyer–Villiger oxidation of the resulting aldehyde (16) and hydrolysis of the intermediate formate then gave the phenol (17).

† Spiro[benzofuran-2,1'-cyclohexa-2',5'-diene]-3,4'-diones.

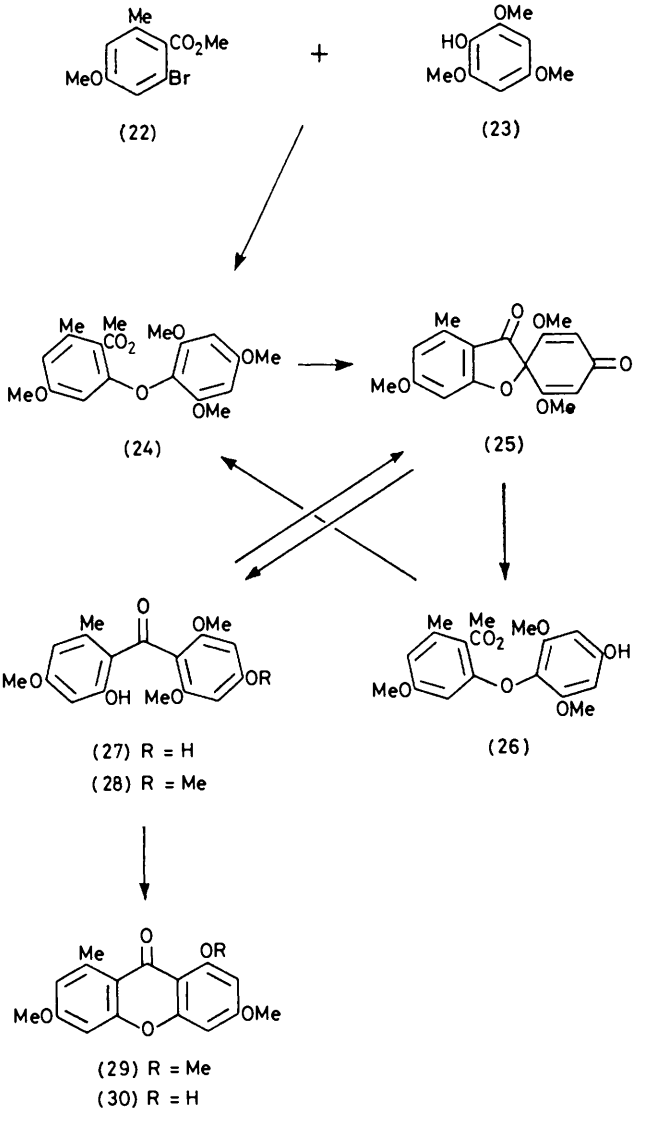
The new product (m.p. 167—168.5 °C) obtained from the diaryl ether (18) could also be prepared by treatment of the ether (18) (Scheme 1) with titanium(IV) chloride in dichloromethane containing dry hydrogen chloride. It had the molecular formula $C_{19}H_{20}O_7$, and the ^1H n.m.r. spectrum exhibited singlets due to a vinylic methyl group at δ 1.94, four methoxy-groups, a vinylic proton



SCHEME 1

at δ 5.68, and an aromatic proton at δ 6.40. The i.r. spectrum exhibited carbonyl stretching bands at 1 720 and 1 664 cm^{-1}. The electronic spectrum was similar to those of both cross-conjugated and linearly conjugated grisadienediones.[18] These data could be rationalized in terms of structure (19) or (20). The former structure was postulated since the compound was thermally stable, whereas linearly conjugated grisadienediones like (20) are known to undergo ready thermal rearrangement to depsidones.[18] In keeping with either of the grisadienedione structures, the compound underwent vinylogous β-diketonic fission on treatment with sodium methoxide in boiling methanol and a phenolic ester formulated as compound (21) resulted.

In order to provide further evidence for the cross-conjugated structure of the above grisadienedione the diaryl ether (24) was synthesized from the known bromo-compound (22) [19] and the phenol (23) (Scheme 2). Although the synthesis of the phenol (23) has been reported [20] it was more readily obtained by the Baeyer–Villiger oxidation of the aldehyde (14). Treatment of the diaryl ether (24) with titanium(IV) chloride and dry hydrogen chloride then gave the grisadienedione (25). The structure (25) followed from the ^1H n.m.r. spectrum, in which the dienone olefinic protons resonated as a singlet, whereas in the linearly conjugated isomer they would be expected to give rise to an AB system. Methanolysis of the grisadienedione (25) gave the phenolic ester (26), which on methylation afforded the diaryl ether (24). In order to convert the grisadienedione (25) into a known compound it was treated with zinc dust in

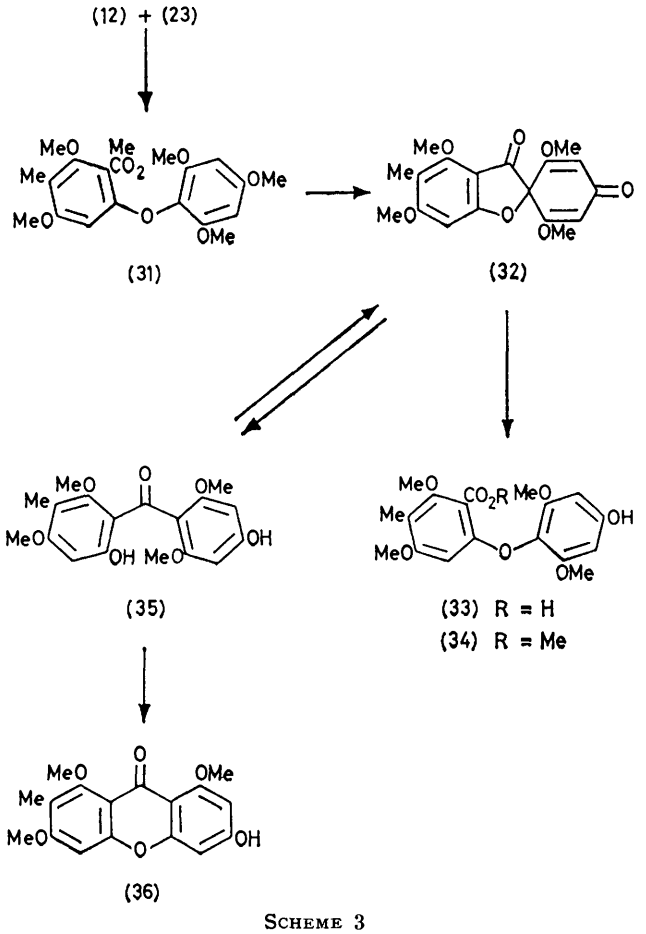


SCHEME 2

acetic acid, which effected reductive cleavage of the allylic ether bond and afforded the dihydroxybenzophenone (27). The structure of this benzophenone was supported by its ^1H n.m.r. spectrum, which exhibited signals for both a free and an intramolecularly hydrogen-bonded hydroxy proton. Oxidative coupling of the benzophenone (27) with alkaline potassium hexacyanoferrate(III) regenerated the grisadienedione (25). Partial methylation of the benzophenone (27) gave the 2-hydroxybenzophenone (28), which as expected exhibited an intramolecularly hydrogen-bonded hydroxy proton signal in its ^1H n.m.r. spectrum. Treatment of this

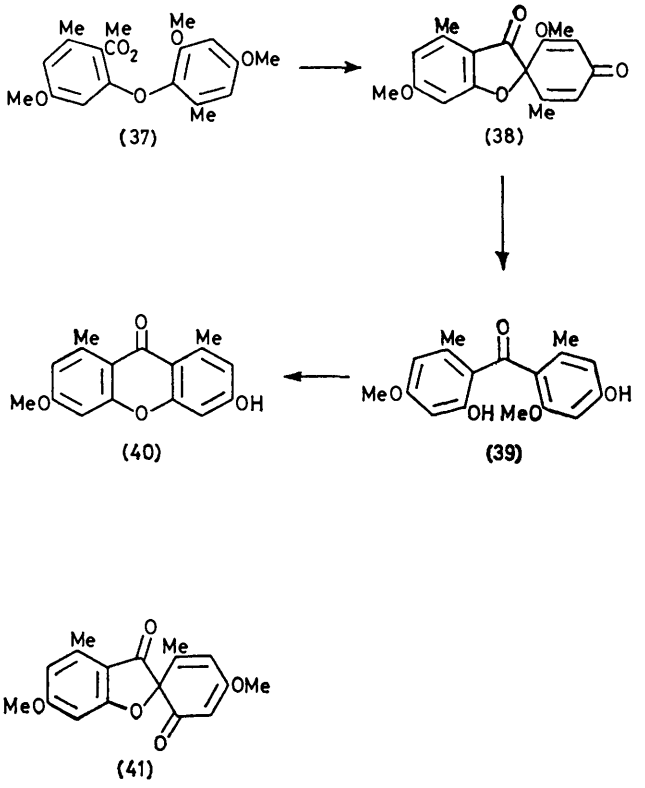
benzophenone (28) with boiling ethanolic potassium hydroxide achieved intramolecular nucleophilic substitution with expulsion of methoxide,[4] thus affording the known *O*-methyl-lichexanthone (29).[21] Partial demethylation of this compound with boron trichloride yielded lichexanthone (30),[21] identical with an authentic specimen.

The diaryl ether (31) (Scheme 3), available by Ullmann reaction between the bromo-compound (12) and the phenol (23), also underwent cyclization on treatment with titanium(IV) chloride and dry hydrogen chloride, and furnished the grisadienedione (32). Hydrolysis of this compound afforded the acid (33) and methanolysis gave the ester (34). Reduction of the grisadienedione (32) gave the benzophenone (35) which could be oxidized back to the grisadienedione (32) with alkaline hexacyanoferrate(III). Prolonged treatment of the benzophenone (35) with boiling aqueous ethanolic potassium hydroxide furnished the xanthone (36).



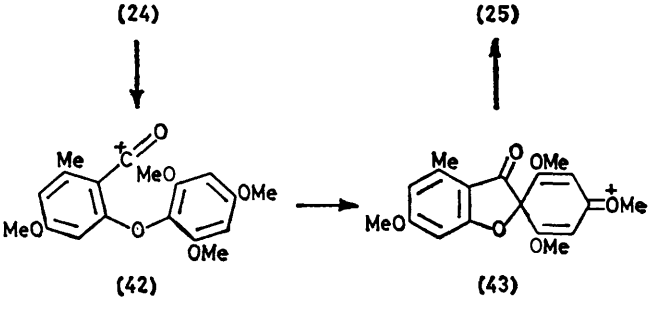
SCHEME 3

In order to synthesize a cross-conjugated grisadienedione for which the linearly conjugated counterpart was known, the diaryl ether (37), which was available from previous work,[22] was treated with titanium(IV) chloride and dry hydrogen chloride (Scheme 4). The product (38) was different from its known isomer (41);[18] it was thermally stable in contrast to compound (41) which undergoes ready thermolysis to a depsidone.[18] Reduction of the grisadienedione (38) gave the benzophenone (39), different from the benzophenone obtained by the reduction of the isomer (41).[18] Ring closure of the benzophenone (39) gave the expected xanthone (40).



SCHEME 4

It is suggested that the above conversions of *o*-phenoxybenzoic esters into cross-conjugated grisadienediones are intramolecular *ipso*-benzoylations. The *o*-phenoxybenzoic esters would readily give an acylium ion, *e.g.* (42) (Scheme 5), presumably complexed with the

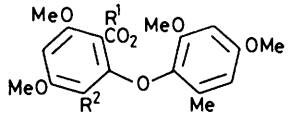


SCHEME 5

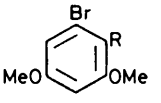
Lewis acid, by an $A_{Ac}1$ type mechanism because of the steric acceleration and stabilization of the positive charge provided by the adjacent electron donating substituents. *ipso*-Substitution of the highly activated orcinol or phloroglucinol moiety would then yield a

Wheland intermediate, *e.g.* (43), which could then undergo S_N2 attack by chloride at the least hindered methoxy-group thus yielding the cross-conjugated dienone. Intermolecular *ipso*-nitration and halogenation of phenols and their derivatives are well documented.[23] Intramolecular *ipso*-acylations, however, are comparatively rare, the only previously described examples being in the indole series.[24]

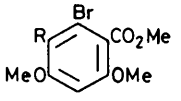
It was of interest to apply the new method of grisa-2',5'-diene-3,4'-dione synthesis to the case of dehydrogriseofulvin (1). The diaryl ether (44) was therefore



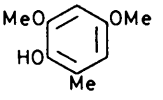
(44) R^1 = Me, R^2 = Cl
(45) R^1 = Me R^2 = H
(46) R^1 = R^2 = H



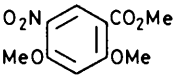
(47) R = H
(48) R = CHO
(49) R = Cl



(50) R = H
(51) R = Cl
(52) R = NO_2



(53)



(54)

required. Vilsmeier–Haack formylation of 3,5-dimethoxybromobenzene (47) [25] gave almost exclusively the aldehyde (48), the structure of which followed from its ^{1}H n.m.r. spectrum. Oxidation of this aldehyde with sodium chlorite [26] in aqueous dioxan and methylation of the acidic products gave the bromo-ester (50) and the bromochloro-ester (51). The former ester was also readily prepared by permanganate oxidation of the aldehyde (48) to the acid and subsequent methylation. The structure of the bromo-chloro-ester (51) was proved by hydrolysis and decarboxylation of the resultant acid, which gave the bromo-chloro-compound (49). Compound (49) also resulted from chlorination of 3,5-dimethoxybromobenzene (47), and its unsymmetrical substitution pattern was immediately apparent from its ^{1}H n.m.r. spectrum.

An attempted Ullmann reaction between the bromochloro-ester (51) and the phenol (53) [27] gave none of the required diaryl ether (44). Nitration of the bromo-ester (50) gave exclusively the nitro-compound (52). Again an attempted Ullmann reaction of compound (52) with the phenol (53) gave no diaryl ether but only the known debromo-compound (54),[28] thereby proving the structure of the starting material (52).

Ullmann reaction of the bromo-ester (50) with the phenol (53), however, gave the diaryl ether (45). On treatment with titanium(IV) chloride and dry hydrogen chloride the acid (46) resulted. Presumably alkyl–oxygen cleavage, rather than acyl–oxygen cleavage, occurred in this case since the methoxy-group adjacent to the ester is unable to provide sufficient steric compression.

EXPERIMENTAL

General directions have been given before.[29] Electronic spectra were determined using a Beckmann Acta MIV spectrophotometer.

Methyl 2,4-Dimethoxy-3-methylbenzoate (7).—(*a*) Potassium permanganate (265 g) in water (3 l) was added dropwise with stirring to a solution of 2,4-dimethoxy-3-methylbenzaldehyde [14] (85.0 g) in acetone (1.5 l) over 3 h. The mixture was stirred for a further 14 h and then clarified by the passage of sulphur dioxide. The usual work-up gave 2,4-dimethoxy-3-methylbenzoic acid (40.9 g), a small sample of which gave needles (from methanol), m.p. 144—145 °C (lit.,[30] 146—147°). Methylation with methyl sulphate and potassium carbonate in acetone under reflux during 1 h gave the ester (7) (42.7 g), b.p. 152—154 °C at 8 mmHg. A sample formed *plates* (from light petroleum), m.p. 36—37 °C (Found: C, 62.75; H, 6.8. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7%).

(*b*) The foregoing aldehyde (98.0 g) was converted into the oxime (104.3 g) by heating under reflux in methanol (410 ml) and water (180 ml) with hydroxylamine hydrochloride (48.0 g) and hydrated sodium acetate (95 g). A sample formed *needles* (from dichloromethane–light petroleum), m.p. 113—114 °C (Found: C, 61.6; H, 6.65; N, 7.15. $C_{10}H_{13}NO_3$ requires C, 61.55; H, 6.7; N, 7.15%). The crude oxime (103.3 g) was heated under reflux with acetic anhydride (400 ml) for 1.5 h. The solution was poured into hot water (4 l) and after a time the crude nitrile (100.8 g) was separated by filtration. A sample formed needles of *2,4-dimethoxy-3-methylbenzonitrile* (from light petroleum), m.p. 46—47 °C (Found: C, 68.1; H, 6.3; N, 7.85. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%). The nitrile (100 g) was heated under reflux in methanol (700 ml) and water (300 ml) with potassium hydroxide (110 g) for 7 days. The usual work-up gave the acid (95.7 g) which was converted into the ester (7) as before

Methyl 2,4-Dimethoxy-3-methyl-5-nitrobenzoate (8).—(*a*) Copper(II) nitrate trihydrate (15.25 g) was added in portions over 1 h to a stirred solution of the ester (7) (10.5 g) in acetic anhydride (60 ml), so that the reaction temperature did not exceed 50 °C. The reaction exhibited an induction period of *ca.* 15 min before any temperature increase was observed. The mixture was stirred for a further hour after the addition and it was then poured into ice and water. The crude product was separated by filtration, washed with water, dried *in vacuo*, and then chromatographed over silica gel with 2.5—15% ethyl acetate–light petroleum as eluant. Early fractions afforded *methyl 2-hydroxy-4-methoxy-3-methyl-5-nitrobenzoate* (0.3 g) as needles (from dichloromethane–light petroleum), m.p. 109—110 °C (Found: C, 49.6; H, 4.75; N, 5.7%; M^+, 241. $C_{10}H_{11}NO_6$ requires C, 49.8; H, 4.6; N, 5.8%; *M*, 241); δ ($CDCl_3$; 60 MHz) 2.28 (3 H, s, Me), 3.91 and 3.99 (each 3 H, s, OMe), 8.31 (1 H, s, ArH), and 11.44 (1 H, s, OH). Further elution gave the *nitro-compound* (8) (7.1 g), which formed pale yellow prisms (from dichloromethane–light petroleum), m.p. 79—80 °C

(Found: C, 51.85; H, 5.3; N, 5.45%; M^+, 255. $C_{11}H_{13}NO_6$ requires C, 51.75; H, 5.15; N, 5.5%; *M*, 255); δ ($CDCl_3$; 60 MHz) 2.26 (3 H, s, Me), 3.80 (3 H, s, OMe), 3.86 (6 H, s, 2 × OMe), and 8.08 (1 H, s, ArH).

(*b*) The ester (7) (20.0 g) in acetic anhydride (40 ml) was added dropwise with stirring over 1.5 h to copper(II) nitrate trihydrate (13.2 g) in acetic anhydride (80 ml) so that the reaction temperature did not exceed 40 °C. The mixture was then stirred at room temperature for 21 h and then worked up as before. The crude product was crystallized from light petroleum–dichloromethane (charcoal) and then from cyclohexane thus affording the nitro-compound (8) (14.6 g).

Methyl 5-Amino-2,4-dimethoxy-3-methylbenzoate (9).—The nitro-compound (8) (20.3 g) in ethyl acetate (200 ml) was shaken with 10% palladized charcoal (2.0 g) under 4 atm of hydrogen until absorption ceased. The usual work up gave the *amine* (9) (19.6 g) as an oil, a sample of which had b.p. 160—165 °C (bath) at 0.4 mmHg (Found: C, 59.2; H, 6.7; N, 6.05%; M^+, 225. $C_{11}H_{15}NO_4$ requires C, 58.65; H, 6.7; N, 6.2%; *M*, 225); δ ($CDCl_3$; 60 MHz) 2.18 (3 H, s, Me), 3.45br (2 H, s, NH_2), 3.68 (6 H, s, 2 × OMe), 3.79 (3 H, s, OMe), and 6.95 (1 H, s, ArH).

Methyl 6-Bromo-2,4-dimethoxy-3-methylbenzoate (12).—Bromine (15.7 g) in carbon tetrachloride (50 ml) was added rapidly to a stirred solution of the amine (9) (19.6 g) in dichloromethane at −78 °C. After a further 15 min at −78 °C the solution was poured into an excess of aqueous potassium carbonate and extracted with ether. The extract was washed with brine and dried. The crude oily product (11) in dioxan (300 ml), water (200 ml), and concentrated hydrochloric acid (50 ml) was cooled to 0 °C and treated with stirring with a solution of sodium nitrite (6.6 g) in a little water, added dropwise, so that the reaction temperature was below 5 °C. Urea (1 g) was added after a further 15 min and then cold 50% phosphinous acid (230 ml) was added dropwise over 1 h with ice-cooling. The mixture was stirred for a further 2 h at 0 °C and then set aside for 20 h at 0 °C. The mixture was extracted with ether and the extract was washed in turn with dilute ammonia solution, water, dilute hydrochloric acid, and brine. Steam distillation gave the product (12) (16.7 g) as an *oil*, a sample of which had b.p. 135 °C (bath) at 0.01 mmHg (Found: C, 46.05; H, 4.5; Br, 27.5%; M^+, 288/290. $C_{11}H_{13}BrO_4$ requires C, 45.7; H, 4.55; Br, 27.65%; *M*, 288/290); δ ($CDCl_3$; 60 MHz) 2.07 (3 H, s, Me), 3.73, 3.78, and 3.88 (each 3 H, s, OMe), and 6.75 (1 H, s, ArH).

Methyl 5-Bromo-2,4-dimethoxy-3-methylbenzoate (10).—Bromine (3.82 g) in carbon tetrachloride (25 ml) was added dropwise over 10 min to a stirred solution of the ester (7) (5.03 g) in carbon tetrachloride (10 ml). After 16 h the solution was worked up in the usual way. The n.m.r. spectrum of the crude product indicated that some demethylation had occurred. Methylation of this material with methyl sulphate and potassium carbonate in boiling acetone gave the *bromo-compound* (10) (6.0 g), which formed needles (from cold light petroleum), m.p. 28—29.5 °C (Found: C, 45.55; H, 4.6; Br, 27.5. $C_{11}H_{13}BrO_4$ requires C, 45.7; H, 4.55; Br, 27.65%); δ (CCl_4; 60 MHz) 2.33 (3 H, s, Me), 3.78, 3.80, and 3.74 (each 3 H, s, OMe), and 7.80 (1 H, s, ArH).

2,4,6-Trimethoxybenzaldehyde (14).—Phosphoryl chloride (20 ml) was added dropwise over 15 min to a stirred solution of 1,3,5-trimethoxybenzene (13) (33.7 g) in *N,N*-dimethylformamide (100 ml) at 0 °C. The solution was then stirred at room temperature for 1.5 h and then poured into ice and water. Next day the product was separated by filtration, washed with water, and dried. The aldehyde (14) (36.9 g) formed stout prisms (from dichloromethane–light petroleum), m.p. 118.5—120 °C (lit.,[16] 118 °C); δ ($CDCl_3$; 60 MHz) 3.80 (9 H, s, 3 × OMe), 5.99 (2 H, s, ArH), and 10.19 (1 H, s, CHO).

2,4,6-Trimethoxyphenol (23).—A solution of *m*-chloroperbenzoic acid (9.1 g, 90%) in dichloromethane (100 ml) was added at 0 °C to a stirred solution of the aldehyde (14) (5.0 g) in dichloromethane (30 ml) over 0.5 h. The solution was then stirred at room temperature for 1.5 h, diluted with ethyl acetate, and extracted exhaustively with saturated aqueous sodium hydrogen carbonate. The crude formate was hydrolysed at 0 °C under nitrogen during 1 h with aqueous methanolic 10% potassium hydroxide. Acidification and isolation with ether gave the phenol (23) (2.9 g), m.p. 63—64 °C (lit.,[20] 64 °C) [from light petroleum (charcoal)]; δ ($CDCl_3$; 60 MHz) 3.70 (3 H, s, OMe), 3.80 (6 H, s, 2 × OMe), 4.98br (1 H, OH), and 6.09 (2 H, s, ArH).

2,4,6-Trimethoxy-3-methylbenzaldehyde (16).—The aldehyde (14) (30.0 g), zinc amalgam [from zinc dust (150 g)], glacial acetic acid (270 ml), water (220 ml), and concentrated hydrochloric acid (220 ml) were stirred and heated under reflux for 2 h. The mixture was filtered through Celite, diluted with ice and water, and then extracted with light petroleum. The extract was washed in turn with water, saturated aqueous sodium hydrogen carbonate, and saturated brine and then steam distilled. This gave 2,4,6-trimethoxytoluene (15)[17] (21.3 g) as an oil, δ (CCl_4; 60 MHz) 1.85 (3 H, s, Me), 3.58 (3 H, s, OMe), 3.60 (6 H, s, 2 × OMe), and 5.80 (2 H, s, ArH). Formylation of this material as described above gave the aldehyde (16) (18.0 g) as needles (from light petroleum), m.p. 85—86 °C (lit.,[15] 84 °C); δ ($CDCl_3$; 60 MHz) 2.01 (3 H, s, Me), 3.71 (3 H, s, OMe), 3.82 (6 H, s, 2 × OMe), 6.12 (1 H, s, ArH), and 10.16 (1 H, s, CHO).

2,4,6-Trimethoxy-3-methylphenol (17).—Baeyer–Villiger oxidation of the aldehyde (16) (10.0 g) with *m*-chloroperbenzoic acid (17.0 g) and hydrolysis of the crude formate as described above gave the crude product which on chromatography over silica gel with 2.5—10% ethyl acetate–light petroleum as eluant gave the *phenol* (17) (5.9 g) as an oil (Found: M^+, 198.0876. $^{12}C_{10}{}^1H_{14}{}^{16}O_4$ requires *M*, 198.0892); δ ($CDCl_3$; 60 MHz) 2.08 (3 H, s, Me), 3.71, 3.78, and 3.80 (each 3 H, s, OMe), 5.11 (1 H, s, OH), and 6.21 (1 H, s, ArH).

General Procedure for Ullmann Reactions.—The phenol (20 mmol), the bromo-compound (20 mmol), and dry finely divided potassium carbonate (3.5 g) were stirred in dry pyridine (20 ml) under dry nitrogen and the bath temperature was raised gradually to 130 °C. Copper(II) oxide (1.5 g) was added and the mixture was stirred under nitrogen at 140 °C (bath) for 15 h. The cooled mixture was diluted with ether and the suspension was filtered through Celite. The solution was then washed in turn with cold dilute hydrochloric acid, cold 10% potassium hydroxide solution, water, and finally saturated brine. The crude product was then chromatographed over silica gel with ethyl acetate–light petroleum as eluant.

Methyl 2,4-Dimethoxy-6-(2,4,6-trimethoxy-3-methylphenoxy)-3-methylbenzoate (18).—Prepared in 65% yield by Ullmann reaction between methyl 6-bromo-2,4-dimethoxy-3-methylbenzoate (12) and 2,4,6-trimethoxy-3-methylphenol (17), this formed *prisms* (from dichloromethane–

light petroleum), m.p. 147—148 °C (Found: C, 61.95; H, 6.5%; M^+, 406. $C_{21}H_{26}O_8$ requires C, 62.05; H, 6.45%; M, 406); δ ($CDCl_3$) 90 MHz) 2.04 and 2.08 (each 3 H, s, Me), 3.56, 3.76, 3.77, 3.80, 3.83, and 3.90 (each 3 H, s, OMe), and 5.85 and 6.33 (each 1 H, s, ArH).

Methyl 4-Methoxy-2-(2,4,6-trimethoxyphenoxy)-6-methylbenzoate (24).—Prepared in 59% yield by Ullmann reaction between methyl 2-bromo-4-methoxy-6-methylbenzoate (22) [19] and 2,4,6,-trimethoxyphenol (23), this formed *blades* (from dichloromethane–light petroleum), m.p. 125—126 °C (Found: C, 62.85; H, 6.25%; M^+, 362. $C_{19}H_{22}O_7$ requires C, 63.0; H, 6.1%; M, 362); δ ($CDCl_3$; 90 MHz) 2.34 (3 H, s, Me), 3.64 (3 H, s, OMe), 3.73 (6 H, s, 2 × OMe), 3.78 and 3.89 (each 3 H, s, OMe), 5.96 and 6.33 (2 H, AB, J 2.5 Hz, 3- and 5-H), and 6.18 (2 H, s, 3′- and 5′-H).

Methyl 2,4-Dimethoxy-6-(2,4,6-trimethoxyphenoxy)-3-methylbenzoate (31).—Prepared in 56% yield by Ullmann reaction between methyl 6-bromo-2,4-dimethoxy-3-methylbenzoate (12) and 2,4,6-trimethoxyphenol (23), this was isolated by crystallization of the crude product from dichloromethane–light petroleum (charcoal); it formed *needles*, m.p. 117—118 °C (Found: C, 61.55; H, 6.25%; M^+, 392. $C_{20}H_{24}O_8$ requires C, 61.2; H, 6.25%; M, 392); δ ($CDCl_3$; 90 MHz) 2.04 (3 H, s, Me), 3.59 (3 H, s, OMe), 3.76 (6 H, s, 2 × OMe), 3.79, 3.80, and 3.88 (each 3 H, s, OMe), 5.94 (1 H, s, 5-H), and 6.19 (2 H, s, 3′- and 5′-H).

General Procedure for Intramolecular Acylation.—Dry hydrogen chloride was passed into dry dichloromethane (10 ml) at 0 °C until the solution was saturated. Titanium(IV) chloride (1 ml) in dry dichloromethane (5 ml) was then added with stirring followed dropwise by the substrate (1 mmol) in dry dichloromethane (5 ml). The solution was then stirred at room temperature until the starting material could no longer be detected by t.l.c. The solution was diluted with ethyl acetate and washed in turn with saturated aqueous sodium hydrogen carbonate, water, and saturated brine. The crude product was then crystallized.

2′,4,6,6′-Tetramethoxy-3′,5-dimethylspiro[benzofuran-2,1′-cyclohexa-2′,5′-diene]-3(2H),4′-dione (19).—Prepared in 85% yield (2 h reaction time) from methyl 2,4-dimethoxy-6-(2,4,6-trimethoxy-3-methylphenoxy)-3-methylbenzoate (18), this formed rosettes of *needles* (from dichloromethane–light petroleum), m.p. 167—168.5 °C (Found: C, 63.4; H, 5.55%; M^+, 360. $C_{19}H_{20}O_7$ requires C, 63.35; H, 5.6%; M, 360); δ ($CDCl_3$; 90 MHz) 1.94 (3 H, s, 3′-Me), 2.05 (3 H, s, 5-Me), 3.64, 3.72, 3.93, and 4.04 (each 3 H, s, OMe), 5.68 (1 H, s, 5′-H), and 6.40 (1 H, s, 7-H); $\nu_{max.}$ ($CHCl_3$) 1 720 (C=O), 1 664 (C=O), 1 614 (C=C), and 1 590 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 206, 219, 235, 287, and 329 nm (ε 28 000, 29 700, 23 100, 27 200, and 6 800).

Methyl 6-(4-Hydroxy-2,6-dimethoxy-3-methylphenoxy)-2,4-dimethoxy-3-methylbenzoate (21).—The foregoing grisadienedione (19) (500 mg) was heated under reflux with methanolic sodium methoxide [from methanol (50 ml) and sodium (0.1 g)] under dry nitrogen for 1 h. The usual work up gave the *phenol* (21) (510 mg) as rods (from methanol), m.p. 101—102 °C (Found: C, 61.1; H, 6.0%; M^+, 392. $C_{20}H_{24}O_8$ requires C, 61.2; H, 6.15%; M, 392); δ ($CDCl_3$; 60 MHz) 1.99 and 2.11 (each 3 H, s, Me), 3.55, 3.60, 3.68, 3.70, and 3.80 (each 3 H, s, OMe), 4.97 (1 H, br, OH), and 5.71 and 6.11 (each 1 H, s, ArH).

2′,6,6′-Trimethoxy-4-methylspiro[benzofuran-2,1′-cyclohexa-2′,5′-diene]-3(2H),4′-dione (25).—(*a*) Prepared in 90% yield (12 h reaction time) from methyl 4-methoxy-2-(2,4,6-trimethoxyphenoxy)-6-methylbenzoate (24), this formed pale yellow *needles* (from dichloromethane–light petroleum), m.p. 273—274 °C (Found: C, 64.5; H, 5.2%; M^+, 316. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.1%; M, 316); δ ($CDCl_3$; 60 MHz), 2.49 (3 H, s, Me), 3.57 (6 H, s, 2′- and 6′-OMe), 3.82 (3 H, s, 6-OMe), 5.52 (2 H, s, 3′- and 5′-H), and 6.32 (2 H, s, 5- and 7-H); $\nu_{max.}$ ($CHCl_3$) 1 716 (C=O), 1 664 (C=O), 1 621 (C=C), 1 610 (C=C), and 1 592 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 236, 278, and 313 nm (ε 26 400, 27 400, and 11 900).

(*b*) 2,4′-Dihydroxy-2′,4,6′-trimethoxy-6-methylbenzophenone (27) (75 mg) and potassium carbonate (0.6 g) were stirred in dioxan (5 ml) and water (20 ml) and treated rapidly with potassium hexacyanoferrate(III) (150 mg) in water (15 ml). The solution was stirred for 0.5 h, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water and saturated brine. The crude product crystallised from dichloromethane–light petroleum as pale yellow needles of the grisadienedione (25) (47 mg), m.p. and mixed m.p. 273—274 °C.

Methyl 2-(4-Hydroxy-2,6-dimethoxyphenoxy)-4-methoxy-6-methylbenzoate (26).—Methanolysis of the grisadienedione (25) (200 mg) as described for compound (19) gave the *ester* (26) (86%) as plates (from dichloromethane–light petroleum), m.p. 170—171 °C (Found: C, 61.85; H, 5.85%; M^+, 348. $C_{18}H_{20}O_7$ requires C, 62.05; H, 5.8%; M, 348); δ ($CDCl_3$; 90 MHz) 2.33 (3 H, s, Me), 3.60 (6 H, s, 2 × OMe), 3.65 and 3.69 (each 3 H, s, OMe), 5.97 and 6.33 (2 H, AB, J 2.5 Hz, 3- and 5-H), and 6.08 (2 H, s, 3′ and 5′-H). On methylation with iodomethane and potassium carbonate in *N,N*-dimethylformamide at room temperature, this substance gave methyl 4-methoxy-2-(2,4,6-trimethoxyphenoxy)-6-methylbenzoate (24) (91%) as blades (from dichloromethane–light petroleum), m.p. and mixed m.p. 125—126 °C.

2,4′-Dihydroxy-2′,4,6′-trimethoxy-6-methylbenzophenone (27).—The grisadienedione (25) (750 mg) and zinc dust (4.0 g) were stirred in glacial acetic acid (50 ml) for 1 h. The usual work up gave the *benzophenone* (27) (620 mg) as yellow rods (from dichloromethane–light petroleum), m.p. 192—193 °C (Found: C, 64.05; H, 5.5%; M^+, 318. $C_{17}H_{18}O_8$ requires C, 64.15; H, 5.7%; M, 318); δ ($CDCl_3$; 80 MHz) 1.92 (3 H, s, Me), 3.68 (6 H, s, 2 × OMe), 3.82 (3 H, s, OMe), 5.61 (1 H, br, D_2O-exchangeable OH), 6.06 (2 H, s, 3′- and 5′-H) 6.18 and 6.35 (2 H, AB, J 2.6 Hz, 3- and 5-H), and 13.61 (1 H, s, D_2O-exchangeable OH).

2-Hydroxy-2′,4,4′,6′-tetramethoxy-6-methylbenzophenone (28).—The benzophenone (27) (584 mg), potassium carbonate (255 mg), and dimethyl sulphate (235 mg) were stirred and heated under reflux in acetone (25 ml) for 23 h. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The crude product was chromatographed over silica gel with 5—15% ethyl acetate–light petroleum as eluant. The *benzophenone* (28) (518 mg) formed plates (from dichloromethane–light petroleum), m.p. 161—162 °C (Found: C, 65.0; H, 6.05%; M^+, 332. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.05%; M, 332); δ ($CDCl_3$; 90 MHz) 1.90 (3 H, s, Me), 3.71 (6 H, s, 2 × OMe), 3.80 and 3.84 (each 3 H, s, OMe), 6.13 (2 H, s, 3′- and 5′-H), 6.14 and 6.33 (2 H, AB, J 2.5 Hz, 3- and 5-H), and 13.67 (1 H, s, D_2O-exchangeable OH).

1,3,6-Trimethoxy-8-methylxanthen-9-one (29).—The benzophenone (28) (446 mg) and ethanolic 1% potassium hydroxide (50 ml) were heated under reflux for 2 h. The solution was poured into water and extracted with ethyl acetate. The crude product formed plates (from methanol) of the xanthone (29) (373 mg), m.p. 156—157 °C (lit.,[21] 156 °C); δ

($CDCl_3$; 90 MHz) 2.85 (3 H, s, *W*/2 1.9 Hz, Me), 3.82, 3.84, and 3.94 (each 3 H, s, OMe), 6.26 and 6.33 (2 H, AB, *J* 2.5 Hz, 2- and 4-H), and 6.57 (2 H, s, *W*/2 2.0 Hz, 5- and 7-H); irradiation at δ 2.85 sharpened the singlet at δ 6.57.

1-*Hydroxy*-3,6-*dimethoxy*-8-*methylxanthen*-9-*one* (30).—A slow stream of boron trichloride was passed into a stirred solution of the xanthone (29) (350 mg) in dichloromethane (40 ml) at 0 °C for 3 min. The solution was stirred at 0 °C for 1 h and at room temperature for 2 h. The usual work-up gave lichexanthone (30) (247 mg) as pale yellow needles (from chloroform–methanol), m.p. and mixed m.p. 194—195 °C (lit.,[21] 187 °C); δ ($CDCl_3$; 90 MHz) 2.82 (3 H, s, *W*/2 2.0 Hz, Me), 3.85 and 3.87 (each 3 H, s, OMe), 6.28 (2 H, s, 2- and 4-H), 6.34 (2 H, s, *W*/2 1.9 Hz, 5- and 7-H), and 13.35 (1 H, s, D_2O-exchangeable, OH); irradiation at δ 2.82 sharpened the singlet at δ 6.34.

2′,4,6,6′-*Tetramethoxy*-5-*methylspiro*[*benzofuran*-2,1′-*cyclohexa*-2′,5′-*diene*]-3(2H),4′-*dione* (32).—(*a*) Prepared in 78% yield (65 h reaction time) from methyl 2,4-dimethoxy-6-(2,4,6-trimethoxyphenoxy)-3-methylbenzoate (31), this formed *plates* (from dichloromethane–light petroleum), m.p. 265—267 °C (Found: C, 62.2; H, 5.2%; M^+, 346. $C_{18}H_{18}O_7$ requires C, 62.4; H, 5.25%; *M*, 346); δ ($CDCl_3$; 60 MHz) 2.00 (3 H, s, Me), 3.55 (6 H, s, 2′- and 6′-OMe), 3.82 and 3.92 (each 3 H, s, OMe), 5.50 (2 H, s, 3′- and 5′-H), and 6.24 (1 H, s, 7-H); $\nu_{max.}$ ($CHCl_3$) 1 720 (C=O), 1 664 (C=O), 1 618 (C=C), and 1 590 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 218, 236, 285, and 326 nm (ε 35 800, 35 750, 38 600, and 10 400).

(*b*) Oxidative coupling of 4′,6-dihydroxy-2,2′,4,6′-tetramethoxy-3-methylbenzophenone (35) as described for compound (27) gave the grisadienedione (32) (74%) as plates (from dichloromethane–light petroleum), m.p. and mixed m.p. 265—267 °C.

6-(4-*Hydroxy*-2,6-*dimethoxyphenoxy*)-2,4-*dimethoxy*-3-*methylbenzoic Acid* (33).—The grisadienedione (32) (433 mg), potassium hydroxide (1.0 g), dimethyl sulphoxide (15 ml), and water (2 ml) were stirred under nitrogen on a steam-bath for 3 h. The usual work-up gave the *acid* (33) (357 mg) as prisms (from ethyl acetate), m.p. 183—184 °C (Found: C, 59.4; H, 5.65%; M^+, 364. $C_{18}H_{20}O_8$ requires C, 59.35; H, 5.55%; *M*, 364); δ ($CDCl_3$; 80 MHz) 2.07 (3 H, s, Me), 3.64 (3 H, s, OMe), 3.79 (6 H, s, 2 × OMe), 3.87 (3 H, s, OMe), 6.04 (1 H, s, 5-H), and 6.18 (2 H, s, 3′- and 5′-H).

Methyl 6-(4-*Hydroxy*-2,6-*dimethoxyphenoxy*)-2,4-*dimethoxy*-3-*methylbenzoate* (34).—Methanolysis of the grisadienedione (32), as described for compound (19), gave the *ester* (34) (84%) as needles (from dichloromethane–light petroleum), m.p. 137—138 °C (Found: C, 60.35; H, 5.8%; M^+, 378. $C_{19}H_{22}O_8$ requires C, 60.3; H, 5.85%; *M*, 378); δ ($CDCl_3$; 60 MHz) 1.99 (3 H, s, Me), 3.55 (9 H, s, 3 × OMe), 3.73 and 3.81 (each 3 H, s, OMe), 5.60 (1 H, br, OH), 5.85 (1 H, s, 5-H), and 6.00 (2 H, s, 3′- and 5′-H).

4′,6-*Dihydroxy*-2,2′,4,6′-*tetramethoxy*-3-*methylbenzophenone* (35).—Reduction of the grisadienedione (32) as described for compound (25) gave the *benzophenone* (35) (85%) as yellow plates (from methanol), m.p. 239—241 °C (Found: C, 61.85; H, 5.85%; M^+, 348. $C_{18}H_{20}O_7$ requires C, 62.05; H, 5.8%; *M*, 348); δ ($CDCl_3$–CD_3SOCD_3; 60 MHz) 1.91 (3 H, s, Me), 3.16 (3 H, s, OMe), 3.61 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 6.02 (2 H, s, 3′- and 5′-H), and 6.18 (1 H, s, 5-H).

6-*Hydroxy*-1,3,8-*trimethoxy*-2-*methylxanthen*-9-*one* (36).—The benzophenone (35) (319 mg) and potassium hydroxide (0.5 g) were heated under reflux in ethanol (20 ml) and water (10 ml) for 23 h. The usual work up gave the *xanthone* (36) (220 mg) as prisms (from chloroform–methanol), m.p. 296—300° (decomp., block preheated to 280 °C) (Found: C, 64.35; H, 5.25%; M^+, 316. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.1%; *M*, 316); δ (CD_3SOCD_3; 60 MHz) 2.01 (3 H, s, Me), 3.63, 3.72, and 3.81 (each 3 H, s, OMe), 6.19 (2 H, s, 5- and 7-H), and 6.63 (1 H, s, 4-H).

2′,6-*Dimethyoxy*-4,6′-*dimethylspiro*[*benzofuran*-2,1′-*cyclohexa*-2′,5′-*diene*]-3(2H),4′-*dione* (38).—Prepared in 65% yield (reaction time 40 h) from methyl 4-methoxy-2-(2,4-dimethoxy-6-methylphenoxy)-6-methylbenzoate (37),[22] this formed *needles* (from dichloromethane–light petroleum), m.p. 190—192 °C (Found: C, 68.35; H, 5.45%; M^+, 300. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.35%; *M*, 300); δ ($CDCl_3$; 90 MHz) 1.77 (3 H, d, $J_{5',6'\text{-Me}}$ 1.5 Hz, 6′-Me), 2.54 (3 H, s, *W*/2 2.0 Hz, 4-Me), 3.64 (3 H, s, 2′-OMe), 3.91 (3 H, s, 6-OMe), 5.67 (1 H, d, $J_{5',6'\text{-Me}}$ 1.5 Hz, 5′-H), 6.19 (1 H, m, *W*/2 3.5 Hz, 3′-H), and 6.50 (2 H, m, *W*/2 3.1 Hz, 5- and 7-H) (irradiation at δ 1.77 caused collapse of the 3′-H signal to a doublet, and irradiation at δ 2.54 caused the 5- and 7-H signals to collapse to a narrow AB system); $\nu_{max.}$ ($CHCl_3$) 1 712 (C=O), 1 669 (C=O), 1 617 (C=C), and 1 590 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 203, 217, 233, 281, and 315 nm (ε 26 600, 26 900, 21 500, 27 500, and 18 800).

2,4′-*Dihydroxy*-2′,4-*dimethoxy*-6,6′-*dimethylbenzophenone* (39).—Reduction of the grisadienedione (38) as described for compound (25) gave the *benzophenone* (39) (83%) as pale yellow prisms (from dichloromethane–light petroleum), m.p. 176—177 °C (Found: C, 67.75; H, 6.1%; M^+, 302. $C_{17}H_{18}O_5$ requires C, 67.55; H, 6.0%; *M*, 302); δ ($CDCl_3$; 80 MHz) 1.82 and 2.05 (each 3 H, s, Me), 3.70 and 3.82 (each 3 H, s, OMe), 5.12 (1 H, s, OH), 6.18 and 6.32 (2 H, AB, *J* 3.1 Hz, ArH), 6.27 (2 H, s, ArH), and 13.70 (1 H, s, OH).

3-*Hydroxy*-6-*methoxy*-1,8-*dimethylxanthen*-9-*one* (40).—Treatment of the benzophenone (39) with aqueous ethanolic potassium hydroxide for 54 h, as described for compound (35), gave the *xanthone* (40) (45%) as needles [from methanol (charcoal)], m.p. 235—237 °C (Found: C, 70.55; H, 6.1%; M^+, 270. $C_{16}H_{14}O_4$ requires C, 70.6; H, 5.9%; *M*, 270); δ ($CDCl_3$–CD_3SOCD_3; 80 MHz) 2.79 and 2.80 (each 3 H, s, Me), 3.88 (3 H, s, OMe), and 6.60 (4 H, narrow m, ArH).

2-*Bromo*-4,6-*dimethoxybenzaldehyde* (48).—Phosphoryl chloride (10 ml) was added dropwise at 0 °C to a stirred solution of 1-bromo-3,5-dimethoxybenzene (47) [25] (9.1 g) in *N*,*N*-dimethylformamide (40 ml). The solution was then stirred for 0.5 h at room temperature and heated on a steam-bath for 4 h. The mixture was then poured into ice and water. Next day, the crude product (8.8 g) was separated by filtration, washed with water, and dried *in vacuo*. A sample formed *needles*, m.p. 89—90 °C [from dichloromethane–light petroleum (charcoal)] (Found: C, 43.8; H, 3.7; Br, 32.55%; M^+, 244/246. $C_9H_9BrO_3$ requires C, 44.1; H, 3.7; Br, 32.6%; *M*, 244/246); δ ($CDCl_3$; 90 MHz) 3.86 and 3.89 (each 3 H, s, OMe), 6.42 and 6.77 (2 H, AB, $J_{3,5}$ 2.1 Hz, 5- and 3-H), and 10.30 (1 H, s, CHO).

Oxidation of 2-*Bromo*-4,6-*dimethoxybenzaldehyde* (48).—(*a*) A solution of the foregoing crude aldehyde (48) (8.8 g) and sulphamic acid (8.9 g) in dioxan (180 ml) and water (85 ml) was stirred at room temperature and treated dropwise over 10 min with sodium chlorite (80% technical; 10.2 g) in a little water. After a further 40 min the solution was diluted with water and extracted with ethyl acetate. The crude acids, isolated with sodium hydrogen carbonate in the usual way, were esterified with iodomethane and potas-

sium carbonate in *N,N*-dimethylformamide at room temperature. The crude esters were chromatographed over silica gel with 2.5—20% ethyl acetate–light petroleum as eluant. Early fractions gave *methyl 4-bromo-2,6-dimethoxybenzoate* (106 mg) as laths (from dichloromethane–light petroleum), m.p. 94—95 °C (Found: C, 43.7; H, 4.1; Br, 29.05%; M^+, 274/276. $C_{10}H_{11}BrO_4$ requires C, 43.65; H, 4.05; Br, 29.05%; *M*, 274/276); δ ($CDCl_3$; 90 MHz) 3.80 (6 H, s, 2 × OMe), 3.88 (3 H, s, OMe), and 6.71 (2 H, s, ArH). Further elution gave *methyl 6-bromo-2,4-dimethoxybenzoate* (50) (3.3 g) as needles (from dichloromethane–light petroleum), m.p. 43—44 °C (Found: C, 43.55; H, 4.1; Br, 29.0%; M^+, 274/276. $C_{10}H_{11}BrO_4$ requires C, 43.65; H, 4.05; Br, 29.05%; *M*, 274/276); δ ($CDCl_3$; 90 MHz) 3.78 (6 H, s, 2 × OMe), 3.89 (3 H, s, OMe), and 6.40 and 6.60 (2 H, AB, $J_{3.5}$ 2.1 Hz, 5- and 3-H). Further elution gave *methyl 2-bromo-3-chloro-4,6-dimethoxybenzoate* (51) (3.9 g) as needles (from dichloromethane–light petroleum), m.p. 126—127 °C (Found: C, 38.5; H, 3.3%; M^+, 308/310/312. $C_{10}H_{10}BrClO_4$ requires C, 38.8; H, 3.25%; *M*, 308/310/312); δ ($CDCl_3$; 90 MHz) 3.84 (3 H, s, OMe), 3.92 (6 H, s, 2 × OMe), and 6.48 (1 H, s, ArH).

(*b*) Oxidation of the aldehyde (48) with potassium permanganate in boiling acetone in the usual way and methylation of the crude acid gave the ester (50) (78%).

2-Chloro-3,5-dimethoxybromobenzene (49).—(*a*) Chlorine (360 mg) in carbon tetrachloride (10 ml) was added to 1-bromo-3,5-dimethoxybenzene (47) (1.12 g) in carbon tetrachloride (10 ml) and the mixture was stirred at room temperature for 15 min. The crude product was chromatographed over silica gel with light petroleum as eluant, which gave the *chloro-compound* (49) (0.9 g) as needles (from light petroleum), m.p. 67—68 °C (Found: C, 38.2; H, 3.15%; M^+, 250/252/254. $C_8H_8BrClO_2$ requires C, 38.2; H, 3.2%; *M*, 250/252/254); δ ($CDCl_3$; 60 MHz) 3.70 and 3.79 (each 3 H, s, OMe), and 6.33 and 6.64 (2 H, AB, *J* 2.5 Hz, 4- and 6-H).

(*b*) Methyl 2-bromo-3-chloro-4,6-dimethoxybenzoate (51) (1.00 g) was heated for 2 h on a steam-bath with potassium hydroxide (2.0 g), water (3 ml), and dimethyl sulphoxide (15 ml). The usual work-up gave the derived *acid* (650 mg) as needles (from ethyl acetate), m.p. 221—222 °C (Found: C, 36.45; H, 2.9%; M^+, 294/296/298. $C_9H_8BrClO_4$ requires C, 36.55; H, 2.75%, *M*, 294/296/298). The acid (642 mg) and copper chromite (150 mg) were heated under reflux in quinoline (10 ml) under dry nitrogen for 20 min. The crude product was extracted with boiling light petroleum and the solution was boiled with charcoal. Preparative t.l.c. of the oily product (243 mg) gave the chloro-compound (49) (105 mg), m.p. and mixed m.p. 67—68 °C (from light petroleum).

Methyl 2-Bromo-4,6-dimethoxy-3-nitrobenzoate (52).—Copper(II) nitrate trihydrate (2.2 g) was added in portions over 0.5 h to a stirred solution of methyl 2-bromo-3,5-dimethoxybenzoate (50) (2.0 g) in acetic anhydride (10 ml). After stirring for a further 2 h, the mixture was poured into ice and water and the crude product was separated by filtration and dried *in vacuo*. It crystallized from dichloromethane–light petroleum (charcoal) as pale yellow *prisms* (1.5 g), m.p. 153—154 °C (Found: C, 37.65; H, 3.1; Br, 25.0; N, 4.2. $C_{10}H_{19}BrNO_6$ requires C, 37.5; H, 3.15; Br, 24.95; N, 4.4%); δ ($CDCl_3$; 90 MHz) 3.89 (3 H, s, OMe), 3.92 (6 H, s, 2 × OMe), and 6.53 (1 H, s, ArH).

Attempted Ullmann Reaction between Methyl 2-Bromo-4,6-dimethoxy-3-nitrobenzoate (50) *and 2,4-Dimethoxy-6-methylphenol* (53).—Carried out by the general method (6.5 h reaction time), this gave a crude product which on crystallization from dichloromethane–light petroleum (charcoal) afforded methyl 2,4-dimethoxy-5-nitrobenzoate (54) (53%) as very pale yellow blades, m.p. 147—148 °C (lit.,[28] 147 °C); δ ($CDCl_3$; 60 MHz) 3.82, 3.93, and 3.95 (each 3 H, s, OMe), 6.43 (1 H, s, 3-H), and 8.58 (1 H, s, 6-H).

Methyl 4,6-Dimethoxy-2-(2,4-dimethoxy-6-methylphenoxy)-benzoate (45).—Prepared in 41% yield from methyl 2-bromo-4,6-dimethoxybenzoate (50) and 2,4-dimethoxy-6-methylphenol (53),[27] this formed hexagonal plates (from dichloromethane–light petroleum), m.p. 128—129° (Found: C, 62.85; H, 6.15%; M^+, 362. $C_{19}H_{22}O_7$ requires C, 63.0; H, 6.1%; *M*, 362); δ ($CDCl_3$; 90 MHz) 2.14 (3 H, s, Me), 3.63, 3.72, 3.78, 3.81, and 3.89 (each 3 H, s, OMe), 5.64 and 6.10 (2 H, AB, *J* 2.3 Hz, 3- and 5-H), and 6.33 and 6.39 (2 H, AB, *J* 2.5 Hz, 3′- and 5′-H) (irradiation at δ 2.14 sharpened the lower-field AB system).

4,6-Dimethoxy-2-(2,4-dimethoxy-6-methylphenoxy)benzoic Acid (46).—Treatment of methyl 4,6-dimethoxy-2-(2,4-dimethoxy-6-methylphenoxy)benzoate (45) with titanium(IV) chloride and hydrogen chloride by the general method gave the *acid* (46) (88%) as needles (from dichloromethane–light petroleum), m.p. 197—199 °C (Found: C, 61.9; H, 6.05%; M^+, 348. $C_{18}H_{20}O_7$ requires C, 62.05; H, 5.8%; *M*, 348); δ ($CDCl_3$; 90 MHz) 2.20 (3 H, s, Me), 3.67, 3.73, 3.80, and 3.89 (each 3 H, s, OMe), 5.71 and 6.16 (2 H, AB, *J* 2.3 Hz, 3- and 5-H), and 6.37 (2 H, s, 3′- and 5′-H).

I thank the Australian Research Grants Committee for financial support.

[1/787 *Received*, 18*th May*, 1981]

REFERENCES

[1] Part 20, P. M. McEwen and M. V. Sargent, *J. Chem. Soc., Perkin Trans. I*, 1981, 883.
[2] Preliminary communication, M. V. Sargent, *J. Chem. Soc., Chem. Commun.*, 1980, 285.
[3] W. J. McMaster, A. I. Scott, and S. Trippett, *J. Chem. Soc.*, 1960, 4628.
[4] D. H. R. Barton and A. I. Scott, *J. Chem. Soc.*, 1958, 1767.
[5] S. Natori and H. Nishika, *Chem. Pharm. Bull.*, 1962, **10**, 117; C. E. Stickings and A. Mahmoodian, *Biochem. J.*, 1964, **92**, 1718.
[6] W. B. Turner, *J. Chem. Soc.*, 1965, 6658; J. Balan, A. Kjaer, S. Kovac, and R. H. Shapiro, *Acta Chem. Scand.*, 1965, **19**, 528.
[7] C. M. Harris, J. S. Roberson, and T. M. Harris, *J. Am. Chem. Soc.*, 1976, **98**, 5380.
[8] A. C. Day, J. Nabney, and A. I. Scott, *J. Chem. Soc.*, 1961, 4067; D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, 1963, **19**, 1.
[9] M. Gerecke, E. Kyburg, C. v. Planta, and A. Brossi, *Helv. Chim. Acta*, 1962, **45**, 2241 and earlier papers; S. Danishefsky and F. J. Walker, *J. Am. Chem. Soc.*, 1979, **101**, 7018.
[10] J. F. Grove, *Fortschr. Chem. Org. Naturst.*, 1964, **22**, 203.
[11] A. I. Scott, *Proc. Chem. Soc.*, 1958, 195; R. F. Curtis, C. H. Hassall, D. W. Jones, and T. W. Williams, *J. Chem. Soc.*, 1960, 4838; R. F. Curtis, C. H. Hassall, and D. W. Jones, *J. Chem. Soc.*, 1965, 6960.
[12] J. A. Elix, U. Engkaninan, A. J. Jones, C. L. Raston, M. V. Sargent, and A. H. White, *Aust. J. Chem.*, 1978, **31**, 2057.
[13] M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.*, 1965, **13**, 1341.
[14] J. P. Lambooy, *J. Am. Chem. Soc.*, 1956, **78**, 771.
[15] G. Lloyd and W. B. Whalley, *J. Chem. Soc.*, 1956, 3209.
[16] J. Kenyon and R. F. Mason, *J. Chem. Soc.*, 1952, 4964.
[17] K. Freudenberg and M. Harder, *Liebigs Ann. Chem.*, 1927, **451**, 213.
[18] T. Sala and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1981, 855.

[19] M. V. Sargent, P. Vogel, and J. A. Elix, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1986.
[20] J. M. Harkin and J. R. Obst, *Tappi*, 1974, **57**, 118.
[21] Y. Asahina and H. Nogami, *Bull. Chem. Soc. Jpn.*, 1942, **17**, 202.
[22] T. Sala, M. V. Sargent, and J. A. Elix, *J. Chem. Soc., Perkin Trans. 1*, 1981, 849.
[23] R. B. Moodie and K. Schofield, *Acc. Chem. Res.*, 1976, **9**, 287; S. R. Hartshorn, *Chem. Soc. Rev.*, 1974, **3**, 167.
[24] A. H. Jackson, B. Naidoo, A. E. Smith, A. S. Bailey, and M. H. Vandrevala, *J. Chem. Soc., Chem. Commun.*, 1978, 779.
[25] N. B. Dean and W. B. Whalley, *J. Chem. Soc.*, 1954, 4638; R. A. Benkeser, R. A. Hickner, D. I. Hoke, and O. H. Thomas, *J. Am. Chem. Soc.*, 1958, **80**, 5289.
[26] B. O. Lindgren and T. Nilsson, *Acta Chem. Scand.*, 1973, **27**, 888.
[27] I. M. Godfrey, M. V. Sargent, and J. A. Elix, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1353.
[28] E. Späth, K. Klager, and C. Schlosser, *Ber.*, 1931, **64**, 2203.
[29] R. Jongen, T. Sala, and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2588.
[30] R. C. Shah and M. C. Laiwalla, *J. Chem. Soc.*, 1938, 1828.