Depsidone Synthesis. Part 16.[1,2] Benzophenone–Grisa-3',5'-diene-2',3-dione–Depsidone Interconversion: a New Theory of Depsidone Biosynthesis

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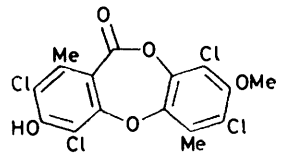
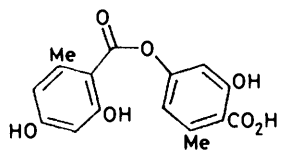
The synthesis of a number of grisa-3',5'-diene-2',3-diones by oxidative coupling of substituted 2,2'-dihydroxy-4-methoxybenzophenones is described. The rearrangement of these grisadienediones to depsidones under basic, acidic, and thermal conditions is described and the mechanisms of these reactions are discussed. It is proposed that depsidone biosynthesis involves the oxidative coupling of benzophenones to grisadienediones which then rearrange to depsidones.

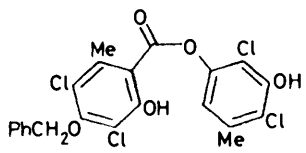
More than twenty years ago the hypothesis[3] was advanced that the biosynthesis of depsidones involved the oxidative coupling of *p*-depsides. Thus the simplest depsidone diploicin (1) would arise from the depside (2). The first synthesis[4] of diploicin (1) which followed shortly after the biosynthetic hypothesis involved the oxidation of the depside (3) and thus purported to be



(1)



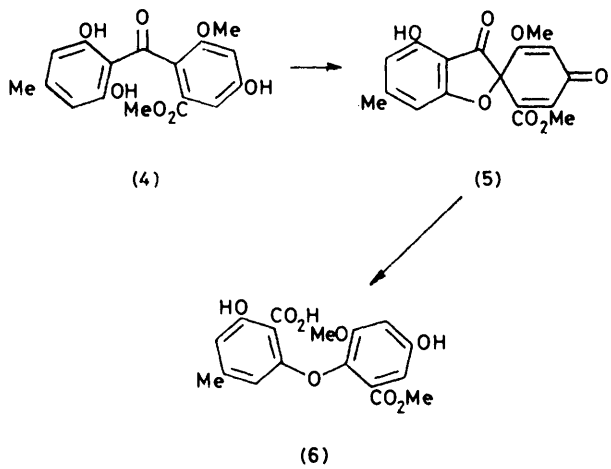
(2)



(3)

biomimetic. Hendrickson *et al.*[5] were suspicious of the generality and efficacy of the seven-membered ring closure of this synthesis and sought to exploit a kinetically more favourable five-membered ring closure such as that involved in the oxidative coupling of substituted 2,4'-dihydroxybenzophenones to grisa-2',5'-diene-3,4'-diones.[6] These compounds, which include dehydrogriseofulvin, were known to undergo hydrolytic cleavage to 2-phenoxybenzoic acids; an example[7] (Scheme 1) is the conversion of sulochrin (4) by oxidative coupling into bisdechlorogeodin (5) and thence, by hydrolysis, into asterric acid (6).

In work[5] connected with the investigation of the structure of the lichen depsidone gangaleoidin[8,9] Hendrickson *et al.*[5] oxidized the benzophenones (7) and (8). The crude products (11) and (12) of these reactions were not adequately characterized but were thought to arise by hydrolysis of the intermediate grisadienediones (9) and (10) (Scheme 2), and on treatment with hot acetic anhydride they yielded the depsidones (13) and (14). Similarly, oxidative coupling of the benzophenone (15) was claimed[5] to yield the grisadienedione (16). However the spectroscopic data reported for this compound [$\nu_{max.}$ ($CHCl_3$) 1 740 and 1 620 cm^{-1}; $\lambda_{max.}$ (EtOH) 272 nm (ε 9 200); δ 2.46 and 2.61 (each 3 H, s, Me)] are incompatible with the grisadienedione (16) but are in keeping with the depsidone (17). We have also used the oxidative coupling of benzophenones in the synthesis of depsidones. Thus we found that treatment of the benzophenones (18)[10] and (22)[11] (Scheme 3) with potassium hexacyanoferrate(III) in aqueous potassium carbonate solution gave directly the depsidones (21) and (24). We reasoned[12] that the initially formed species in these oxidations were the phenoxy-radicals, *e.g.* (19), at the positions *ortho* to the carbonyl group of the unhalogenated A-rings of the benzophenones rather than on the halogenated B-rings which would be expected to be of higher oxidation potential. Homolytic aromatic substitution followed by loss of an electron would then yield the grisadienediones, *e.g.* (20) and (23), presumed to be the

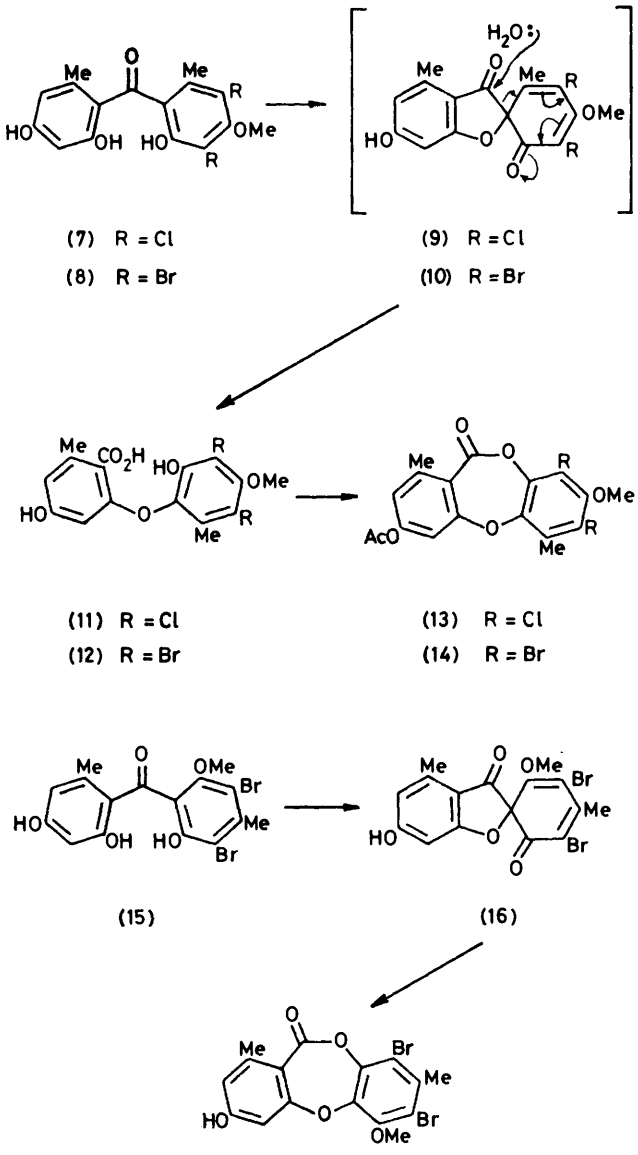


(4) (5) (6)

Scheme 1

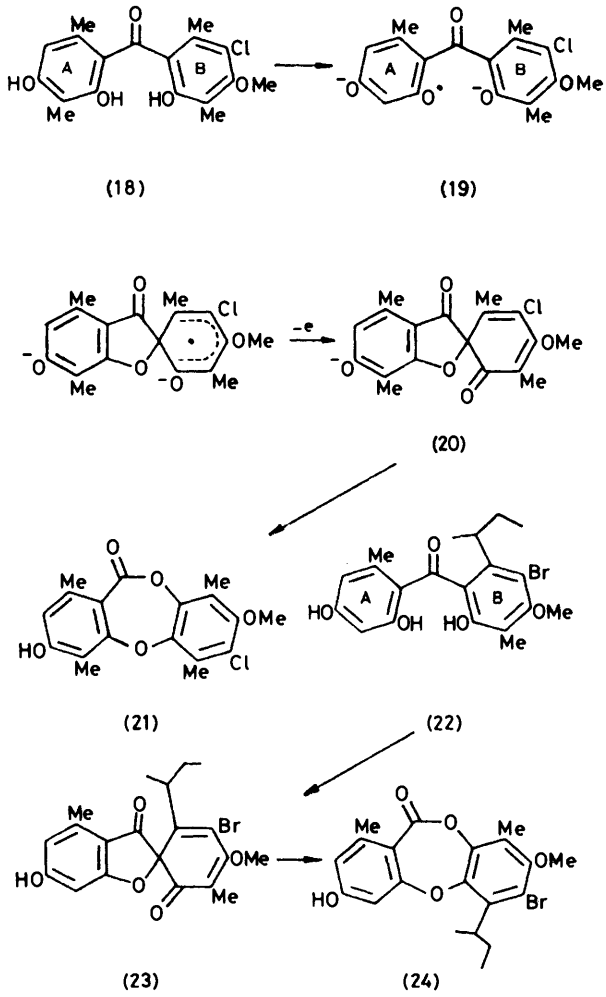
intermediates but not isolated. The mechanism of the conversion of the grisadienediones (20) and (23) into the depsidones (21) and (24) was open to speculation.[10,11] In this paper we present results which throw light on this easy conversion and we propose that the biosynthesis of depsidones follows the same course.

As well as investigating the mechanism of the benzophenone–grisadienedione–depsidone interconversion we sought to synthesize dechlorodiploicin (46).[1] It was therefore necessary to synthesize several new benzophenones by Friedel–Crafts reaction in the presence of trifluoroacetic anhydride between appropriately substituted orsellinic acids and orcinols both protected as their benzyl ethers. The hydroxybenzophenones were then obtained by hydrogenolytic debenzylation. The preparation of the required mononuclear intermediates is now described. Chlorination of methyl orsellinate (25) [8] with one molar equivalent of sulphuryl chloride gave the monochloro-ester (27) [13] which on boiling with aqueous sodium hydroxide underwent hydrolysis and decarboxylation and afforded the chloro-orcinol (29) [13,14] and thence the di-*O*-benzyl compound (30).[14] A similar sequence starting from methyl everninate (26), readily available by selective methylation of methyl orsellinate (25), gave the chloro-ester (28),[15] the phenol (31), and finally the *O*-benzyl compound (32). Treatment of methyl orsellinate (25) with two molar equivalents of sulphuryl chloride gave the dichloro-ester (33) [16] which was best converted into the everninate (35) [16] by complete methylation and selective demethylation of the resultant di-*O*-methyl compound (34) with boron trichloride. Benzylation of this compound then gave the benzyl ether (36) which was readily hydrolysed to the acid (37) [5] on treatment with potassium hydroxide in aqueous dimethyl sulphoxide at *ca.* 90 °C. Similar routes gave the acids (38) [5] and (39).

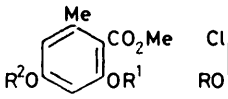


SCHEME 2

When the benzophenone (40) in aqueous potassium carbonate solution was treated rapidly with potassium hexacyanoferrate(III) and the reaction quenched after 30 s, a single grisadienedione was isolated in high yield. This grisadienedione was formulated as the linearly conjugated isomer (43) rather than the cross-conjugated isomer (45) since the chemical shift (δ 6.80) of the low-



SCHEME 3



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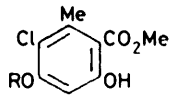
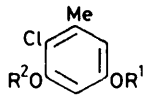
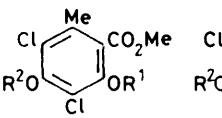
(26) $R^1 = H$, $R^2 = Me$



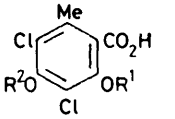
(27) R = H
(28) R = Me



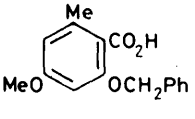
(29) $R^1 = R^2 = H$
(30) $R^1 = R^2 = CH_2Ph$
(31) $R^1 = H$, $R^2 = Me$
(32) $R^1 = CH_2Ph$, $R^2 = Me$



(33) $R^1 = R^2 = H$
(34) $R^1 = R^2 = Me$
(35) $R^1 = H$, $R^2 = Me$
(36) $R^1 = CH_2Ph$, $R^2 = Me$



(37) $R^1 = CH_2Ph$, $R^2 = Me$
(38) $R^1 = R^2 = CH_2Ph$



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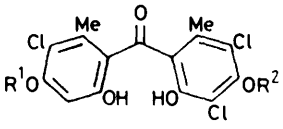
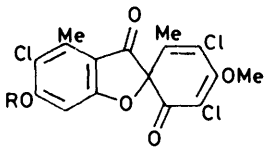
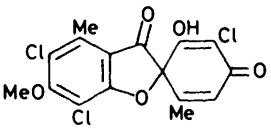


(40) $R^1 = H$, $R^2 = Me$
(41) $R^1 = R^2 = Me$
(42) $R^1 = R^2 = H$



(43) R = H
(44) R = Me



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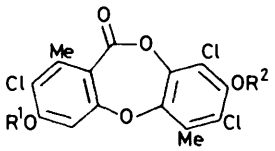
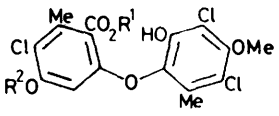
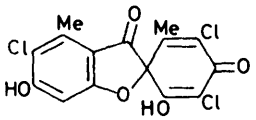


(46) $R^1 = H$, $R^2 = Me$
(47) $R^1 = R^2 = H$
(48) $R^1 = R^2 = Me$



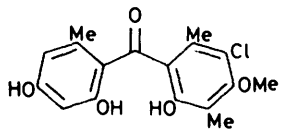
(49) $R^1 = R^2 = H$
(50) $R^1 = Me$, $R^2 = H$
(51) $R^1 = R^2 = Me$



(52)

field one-proton singlet in the n.m.r. spectrum of this product was characteristic of an aromatic proton rather than an olefinic proton. The direction of the oxidative coupling was thus as expected. When this reaction was prolonged for 15 min the products obtained were the grisadienedione (52), or possibly its linearly conjugated tautomer, and the depsidone (46), identical with dechlorodiploicin,[1] in the ratio 1.17 : 1. When exposure of the above product (43) to base was lengthened to 3 h the products isolated were the depsidone (46), the acid (49), and the grisadienedione (52). The results of treating this product mixture with hot acetic anhydride are detailed in the Experimental section. The acid (49) arose by hydrolysis of the depside linkage of the depsidone (46) as shown by exposure of this compound to the same conditions in a separate experiment. The grisadienedione (52) presumably arose from the grisadienedione (43) by basic hydrolysis of the vinylogous ester function. On treatment with sodium methoxide in methanol the grisadienedione (43) gave the diphenyl ether (50). This compound is probably formed by rearrangement of the grisadienedione (43) to the depsidone (46) which then undergoes methanolysis of the depside linkage.

Brief oxidation (2 min) of the benzophenones (53),[12] (18),[10] and (22) [11] gave the grisadienediones (54), (20), and



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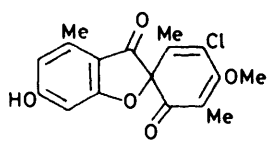

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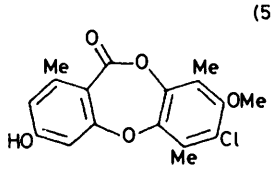
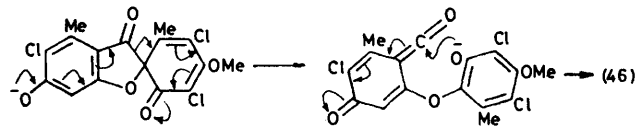


(55)

(23) in high yield. When these compounds were allowed to remain in contact with the basic reaction mixture for 3 h the depsidones (55), (21), and (24) [11] resulted. Hence the grisadienediones must undergo rearrangement to the depsidones. Oxidation of the benzophenones (41) and (42), in contrast, gave only the grisadienediones (44) and (52) even after prolonged exposure to the basic reaction conditions. Hence these grisadienediones do not undergo base-catalysed rearrangement to depsidones. On treatment with the stronger base sodium methoxide in methanol, the grisadienedione (44) underwent β-diketonic cleavage and the diphenyl ether (51) resulted. In view of these results we therefore postulate that ketens are intermediates in the base-catalysed grisadienedione–depsidone rearrangement, *e.g.* (43) to (46) (Scheme 4). The grisadienedione (44) is therefore unable to rearrange to a depsidone under basic conditions because keten formation is blocked. Furthermore the grisadienedione (52) is unable to rearrange to a keten because the ring C

phenolate ion (56) is a poor leaving group. Precedent for the mechanism of this rearrangement is found in the hydrolysis of aryl acetoacetates [17] which occur by an *E1cB* mechanism involving a keten only when the leaving group is sufficiently powerful. A similar mechanism but operating by acid catalysis has been postulated by Barton

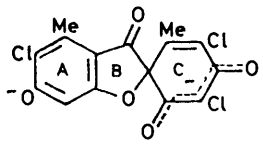


(43)

SCHEME 4

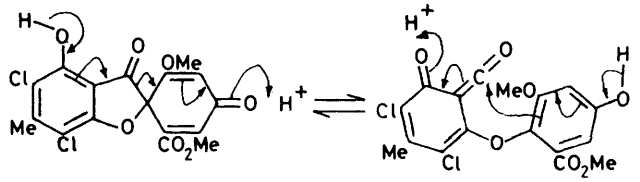
and Scott for the racemization of geodin (57) [18] (Scheme 5). We also found that the grisadienediones (82) (see later) and (20) underwent rearrangement to the depsidones (83) and (21) on treatment with trifluoroacetic acid in dry dichloromethane.

It was observed on m.p. determination that the grisadienedione (43) changed from yellow prisms to colourless needles at 146—155 °C and that these then exhibited the m.p. of the depsidone (46). When this reaction was repeated on a preparative scale by melting the grisadienedione under nitrogen the product indeed proved to



(56)

be the depsidone (46). This thermal rearrangement is a general reaction since compounds (52), (44), (23), and (54) all rearrange to the respective depsidones (47), (48), (24), and (55) on heating in the solid state or in solution in phenetole or diphenyl ether. The grisadienedione thus requires a keto- or a hydroxy-function at the 2′-position for this reaction to occur. A [1,3] or a [1,7] sigmatropic shift is allowed by the rules of conservation of orbital symmetry for these thermal rearrangements,

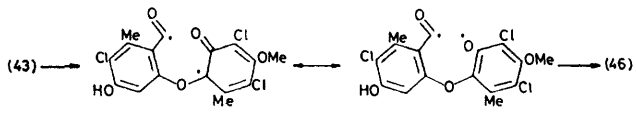


(57)

SCHEME 5

but is probably precluded by unfavourable steric interactions; hence a radical mechanism *e.g.* (43) ⟶ (46) (Scheme 6) is more likely.

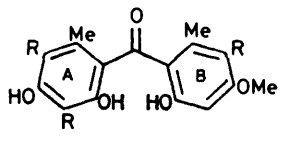
With a view to determining the direction of coupling we investigated the oxidation of the benzophenones (58) and (59). Oxidation of the benzophenone (58) gave only one grisadienedione which was formulated as (60) rather than (62) since the chemical shift (δ 5.46) of the low field one proton singlet in its n.m.r. spectrum was consistent with an olefinic rather than an aromatic



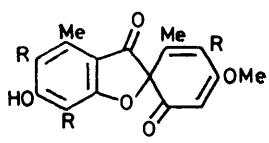
SCHEME 6

proton. On thermolysis this grisadienedione (60) gave the depsidone (63). Further support for the structures of these compounds is the mass spectrum of the depsidone (63) which exhibits peaks ascribed to the ions (65) and (66). The direction of this oxidative coupling can again be rationalized in terms of the oxidation potentials of the phenolate ions *ortho* to the carbonyl group: that on ring A which bears a phenolate ion, a methyl group, and two chlorine atoms presumably being lower than that of ring B which bears a methyl group, a methoxy-group, and one chlorine atom.

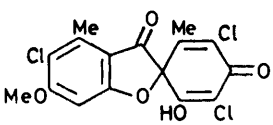
Oxidation of the benzophenone (59) gave the linearly



(58) R = Cl
(59) R = H



(60) R = Cl
(61) R = H



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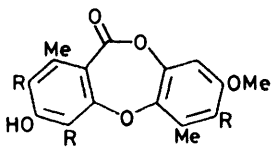
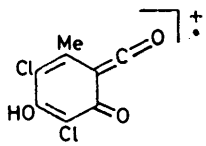
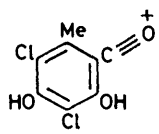


(63) R = Cl
(64) R = H



(65)



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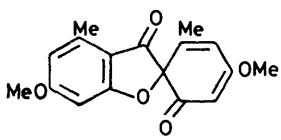

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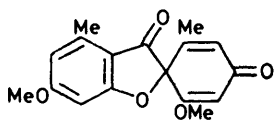
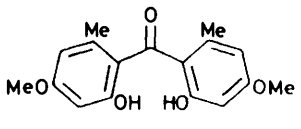


(68)

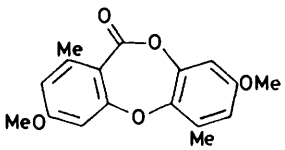
conjugated grisadienedione (61) as expected. This grisadienedione (61) did not rearrange to a depsidone under the basic reaction conditions since the leaving group is not sufficiently powerful. Methylation of this grisadienedione with iodomethane and potassium carbon-

ate in *NN*-dimethylformamide gave the methyl ether (67) different to its known isomer (68).[19] On reduction with zinc dust in acetic acid the grisadienedione (67) gave the benzophenone (69). The grisadienediones (61) and (67) on thermal rearrangement gave the depsidones (64) [9] and (70) respectively.

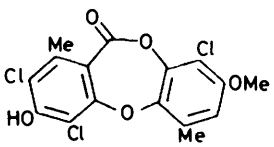
We have previously reported [9] that chlorination of the



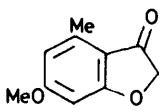
(69)



(70)



(71)

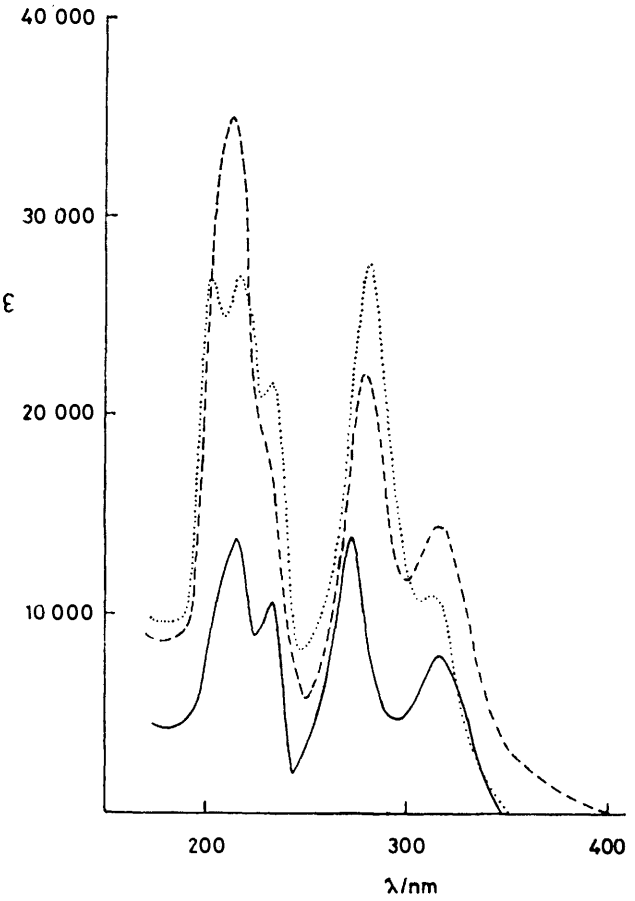


(72)

depsidone (64) gave a trichloro-compound which from its mass spectrum, which exhibited the ions (65) and (66), had two chloro-substituents on the A-ring. This compound is different from compound (63) and therefore must have structure (71). Mahandru and Gilbert [20] have isolated a depsidone, for which they suggest the trivial name fulgidin, from the lichen *Fulgensia fulgida* (Nyl.) Szat., to which they assign the structure (63) on tenuous grounds, since no evidence is provided for the location of the chlorine on ring B. Hence structure (71) is equally tenable. The m.p.s of all three compounds are different, the i.r. spectra ($CHCl_3$) of all three are indistinguishable, and the ^1H n.m.r. spectra of (63) and (71) are indistinguishable but slightly different from that reported for fulgidin. Unfortunately an authentic sample of fulgidin is no longer extant so that its structure remains unresolved.

The i.r. spectra of the grisa-3',5'-diene-2',3-diones are sufficiently similar to those of their grisa-2',5'-diene-3,4'-dione [6] isomers to prevent their differentiation on these grounds. Thus they exhibit a band at 1 710—1 740 cm^{-1} due to the coumaranone carbonyl group. The coumaranone (72) [21] exhibits a carbonyl stretching frequency (CCl_4) at 1 714 cm^{-1}. The carbonyl stretching frequency of the dienone of the grisa-3',5'-diene-2',3-diones falls in the range 1 650—1 690 cm^{-1}. The higher values are due to those compounds with halogens adjacent to the carbonyl group.[22] An examination of the electronic spectra of grisadienediones and related compounds [23] has sometimes been used to differentiate cross-conjugated isomers from their linearly conjugated counterparts. In the Figure is shown the electronic spectra of the grisadienedione isomers (67) and (68) and the β-coumaranone (72). It is seen that the dienone chromophore is completely dominated by the β-coumaranone chromophore. The significant difference between the two dienones is that the linearly conjugated isomer exhibits weak absorption at longer wavelength than its isomer. This is also true for simple cyclohexadienediones.[24]

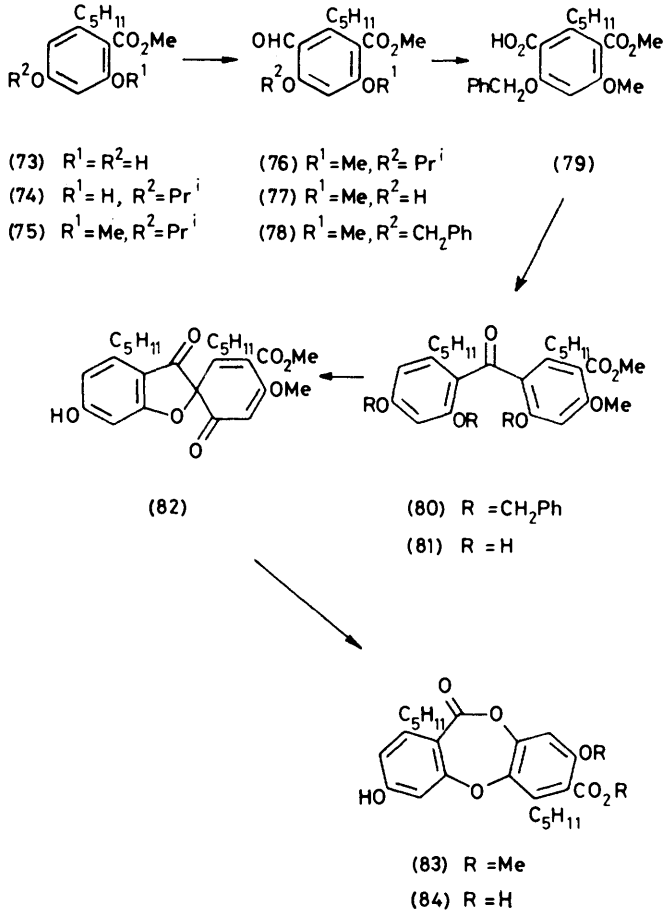
Many of the naturally occurring depsidones retain a carboxy-group at the 7-position. None of the benzophenones yet subjected to oxidative coupling and subsequent rearrangement have yielded depsidones possessing this feature. It was expected that the benzophenone–grisadienedione–depsidone interconversion would occur in the desired way with a carboxylic ester present in such a position. In order to test this we sought to synthesize norcolensoic acid (84), a depsidone which co-occurs with colensoic acid [25] in an unidentified



Electronic spectra of 4',6-dimethoxy-4,6'-dimethylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-2',3(2*H*)-dione (67) (– – – –), 2',6-dimethoxy-4,6'-dimethylspiro[benzofuran-2,1'-cyclohexa-2',5'-diene]-3(2*H*),4'-dione (68) (· · · ·), and 6-methoxy-4-methylbenzofuran-3(2*H*)-one (72) (——)

Australian *Lecanora* species.[26] Hence for the synthesis of the benzophenone (81) (Scheme 7) we required di-*O*-benzylolivetol, which was readily prepared from olivetol,[27] and the acid (79). The acid (79) was prepared from methyl olivetolcarboxylate (73) [25] by the following sequence since both benzyl ethers [28] and free phenols [9] give low yields on formylation with dichloromethyl

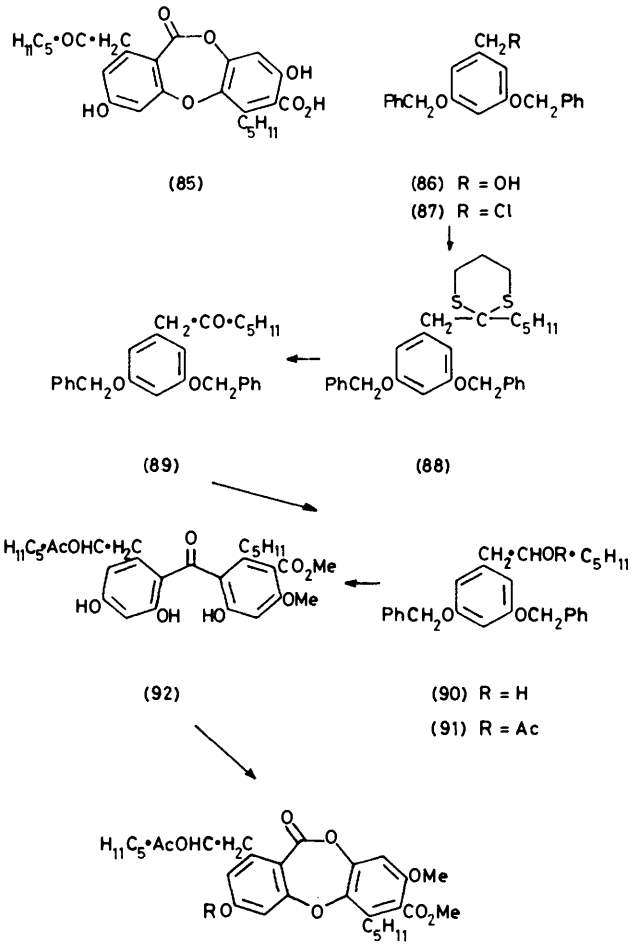
methyl ether. Selective isopropylation [28] of the ester (73) gave the intermediate (74) which on methylation afforded the methyl ester (75). Formylation of this with dichloromethyl methyl ether and tin(IV) chloride gave the aldehyde (76) which was deprotected by treatment with titanium(IV) chloride [28] thus yielding the *o*-



SCHEME 7

hydroxy-aldehyde (77). The derived benzyl ether (78) on oxidation with tetrabutylammonium permanganate [29] in pyridine gave the required acid (79). Friedel–Crafts reaction between the acid (79) and di-*O*-benzylolivetol gave the tri-*O*-benzylbenzophenone (80) which on hydrogenolytic debenzylation gave the required trihydroxybenzophenone (81). Brief oxidation of the benzophenone (81) gave the expected grisadienedione (82) which underwent thermal and acid- or base-catalysed rearrangement to the depsidone (83). Treatment [26] of this depsidone (83) with lithium iodide in hot hexamethylphosphoric triamide under dry nitrogen gave norcolensoic acid (84), identical with an authentic sample.

We attempted to extend this synthesis to that of the more complex depsidone physodic acid (85) [30] (Scheme 8). Hence we required for the construction of the benzophenone (92) the acetate (91) which had already been synthesized by Whalley and his co-workers.[31] The synthesis now described is more convenient. 3,5-Dibenzyloxybenzyl alcohol (86) [32] on boiling in carbon tetrachloride with triphenylphosphine [33] gave the chloride (87). This was used to alkylate 2-lithio-2-pentyl-1,3-dithian [34] and the product (88) was deprotected by treatment with copper(II) chloride and copper(II) oxide in boiling aqueous acetone [35] which yielded the ketone (89). Lithium aluminium hydride reduction of this gave the alcohol (90) which was converted into the acetate (91), which on Friedel–Crafts reaction with the acid (79) and subsequent debenzylation gave the benzophenone (92). Oxidative coupling of this followed by thermolysis of the crude product gave the depsidone (93). Attempts to remove the acetate protecting group from the derived benzyl ether (94) under a wide range of conditions met

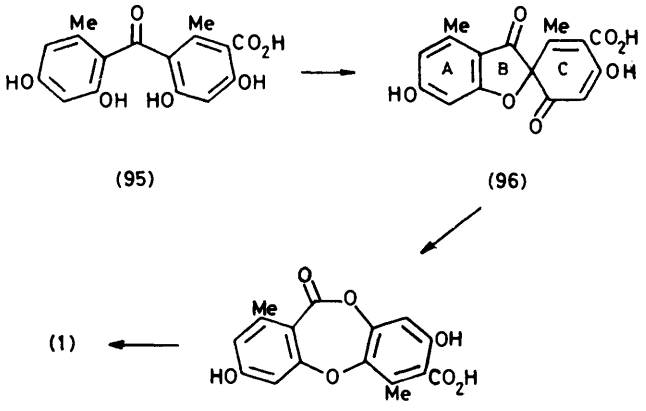


SCHEME 8

with no success. Under mild conditions no reaction occurred but more vigorous conditions lead to cleavage of the depside linkage. The synthesis was not further pursued.

The ready oxidative coupling of benzophenones to grisadienediones and the rearrangement of these to

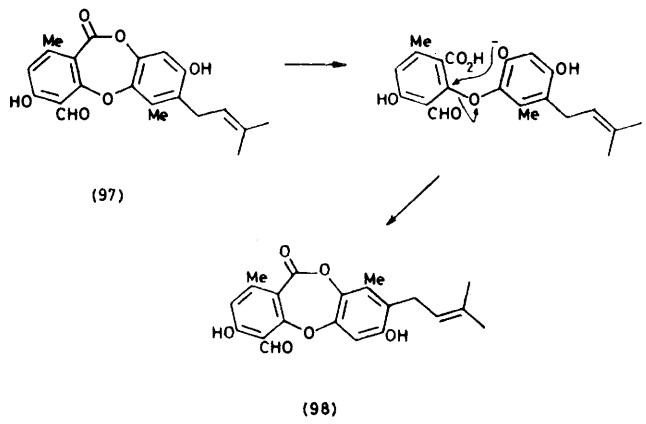
depsidones under acidic or basic conditions suggests that the biosynthesis of depsidones probably follows this course. We have generally used substituted 2,2',4-trihydroxy-4'-methoxybenzophenones in our *in vitro* experiments. The lichen or mould presumably uses benzoylbenzoic acids such as (95) (Scheme 9) which we



(95) (96) (1)

SCHEME 9

envisage is involved in the biosynthesis of diploicin. The rearrangement of the grisadienedione, *e.g.* (96) presumably occurs on an enzyme surface such that the ring-C carbonyl group is protonated or only the ring-A phenol is ionized since it would be expected that ionization of the phenol and the carboxylic acid on ring C would cause this ring to be a poor leaving group. Further transformations of the resultant depsidone such as decarboxylation, chlorination, *O*-methylation, *C*-prenylation, and oxidation of methyl substituents as in the β-orcinol depsidones are unexceptional.

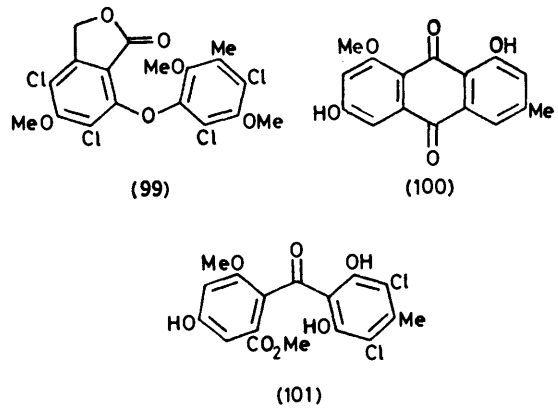


(97) (98)

SCHEME 10

One unusual modification is encountered in the biosynthesis of the depsidones of the fungus *Chaetomium mollicellum* which produces a series of eight depsidones [36] some of which, *e.g.* mollicellin G (97) and mollicellin H (98), appear to be related to each other by lactone opening, Smiles rearrangement, and lactone reclosure. Smiles rearrangements have been reported *in vitro* for derivatives of the depsidone psoromic acid.[37] The depsidone catabolism product canesolide (99) [1] also appears to have arisen from diploicin (1) by lactone cleavage, oxidation, Smiles rearrangement, and *O*-methylation.

If the above hypothesis concerning the biosynthesis of depsidones is accepted then the question arises as to the biosynthetic origin of their benzophenone precursors none of which has been isolated from a lichen. Although benzophenones are doubtlessly important and reactive, and hence short-lived biosynthetic intermediates, their occurrence as secondary metabolites is comparatively rare; only about twenty have been recorded.[38] At least three different pathways are apparent for the biosynthesis of these benzophenones. Those of the higher plants are



(99) (100) (101)

obviously derived from a combination of the shikimate and acetate pathways.[39] The xanthones of the higher plants [40] arise from such benzophenones by oxidative coupling or cyclodehydration (or its equivalent) although benzophenones and xanthones have been rarely found in the same plant.[41]

Fungal benzophenones all arise by the acetate–polymalonate pathway but the details of the process may vary. The benzophenones involved in the biosynthesis of griseofulvin [42] arise directly by folding of a heptaketide. Presumably the same process, followed by cyclodehydration or its equivalent, is involved in the biosynthesis of the lichen xanthones.[43] On the other hand sulochrin (4) arises by the biosynthetic equivalent of a Baeyer–Villiger oxidation of the polyketide anthraquinone questin (100).[44] Similarly geodin (57) is presumably the result of oxidative coupling of the seco-anthraquinone dihydrogeodin (101).[45] A number of fungal xanthones such as the ergochromes,[46] ravenelin,[46] sterigmatocystin,[47] and tajixanthone [48] arise from benzophenones which are also seco-anthraquinones derived by Baeyer–Villiger oxidation. Indeed tajixanthone co-occurs with precursor-like benzophenones.

We now postulate that a fourth mode of benzophenone biosynthesis [49] operates for the depsidone precursors namely the acylation of one unit of an orsellinic acid type by another. Thus *p*-depside and depsidone biosynthesis would diverge at the mononuclear stage.

EXPERIMENTAL

General directions have been given before.[50] Electronic spectra were determined for ethanolic solutions using a Beckman Acta MIV spectrophotometer.

Methyl 5-Chloro-2,4-dihydroxy-6-methylbenzoate (27).—Freshly distilled sulphuryl chloride (21.0 g) in dichloromethane (40 ml) was added dropwise with stirring to a suspension of methyl orsellinate (25) (26.9 g) [8] in dichloromethane (245 ml). After the addition the mixture was heated under reflux for 2.75 h. The solution was diluted with ether and washed with water. The residue was crystallized from ether–light petroleum which gave the chloro-orsellinate (27) as prisms (29.8 g), m.p. 135—137 °C (lit.,[13] 134 °C); δ($CDCl_3$, 60 MHz) 2.54 (3 H, s, Me), 3.91 (3 H, s, OMe), 5.78vbr (1 H, OH), 6.43 (1 H, s, ArH), and 11.23 (1 H, s, OH).

2-Chloro-3,5-dihydroxytoluene (29).—The chloro-orsellinate (27) (25.8 g) and aqueous sodium hydroxide (5%; 1 340 ml) were boiled under reflux under nitrogen for 3.5 h. The cooled solution was acidified and extracted with ethyl acetate. The chloro-orcinol (29) (14.3 g) formed prisms (from benzene), m.p. 136—140 °C (lit.,[14,16] 138—140, 139—141 °C); δ($CDCl_3$, 60 MHz) 2.23 (3 H, s, Me), 6.22 and 6.35 (2 H, AB, *J* 2.5 Hz, ArH), and 7.35br (2 H, OH).

3,5-Dibenzyloxy-2-chlorotoluene (30).—The chloro-orcinol (29) (14.0 g), benzyl bromide (33.2 g), and dry potassium carbonate (49.0 g) were stirred under dry nitrogen in dry *NN*-dimethylformamide (150 ml) for 17 h. The excess of benzyl bromide was removed from the crude product by steam distillation, and the residue was crystallized from light petroleum to form blades (26.2 g) of the orcinol (30), m.p. 76.5—77 °C (lit.,[14] 75.5—76.5 °C) (Found: C, 74.05; H, 5.75; Cl, 10.35%; M^+, 338, 340. Calc. for $C_{21}H_{19}ClO_2$: C, 74.45; H, 5.65; Cl, 10.45%; *M*, 338, 340); δ(CCl_4, 60 MHz) 2.30 (3 H, s, Me), 4.87 and 4.95 (each 2 H, s, CH_2), 6.33 (2 H, s, ArH), and 7.24 (10 H, s, Ph).

Methyl 5-Chloro-2-hydroxy-4-methoxy-6-methylbenzoate (28).—Methyl orsellinate (25) (25.0 g), potassium carbonate (19.0 g), and methyl sulphate (17.3 g) were heated and stirred under reflux in dry acetone (200 ml) for 20 h. The cooled mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The crude product was passed through a column of silica gel with 2.5—5% ethyl acetate–light petroleum as eluant; this gave methyl everninate (26) (23.0 g) as prisms (from dichloromethane–light petroleum), m.p. 147—148 °C (lit.,[51] 148 °C); δ($CDCl_3$, 60 MHz) 2.41 (3 H, s, Me), 3.71 and 3.84 (each 3 H, s, OMe), 6.10 (2 H, s, ArH), and 11.51 (1 H, s, OH). Chlorination of methyl everninate (26) (21.7 g) as above gave the chloro-everninate (28) (18.4 g) as needles (from dichloromethane–light petroleum), m.p. 143—144 °C (lit.,[15] 143—144 °C); δ($CDCl_3$, 60 MHz) 2.58 (3 H, s, Me), 3.83 and 3.89 (each 3 H, s, OMe), 6.31 (1 H, s, ArH) and 11.40br (1 H, OH).

2-Chloro-5-hydroxy-3-methoxytoluene (31) —The chloro-everninate (28) (7.4 g), sodium hydroxide (18.5 g), and water (370 ml) were boiled under reflux under nitrogen for 4 h. Acidification and isolation with ethyl acetate gave the crude product which was boiled and stirred under reflux under dry nitrogen with 2,2′-bipyridyl (0.6 g) and copper(I) oxide (0.2 g) in dry bis-(2-methoxyethyl) ether (50 ml) for 2 h. The cooled mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The *orcinol* (31) (3.5 g) formed needles (from dichloromethane–light petroleum), m.p. 104—104.5 °C (Found: C, 55.7; H, 5.1; Cl, 20.45%; M^+, 172, 174. $C_8H_9ClO_2$ requires C, 55.65; H, 5.25; Cl, 20.55%; *M*, 172, 174); δ(CCl_4, 60 MHz) 2.21 (3 H, s, Me), 3.70 (3 H, s, OMe), 4.72br (1 H, D_2O exchangeable OH), and 6.10 (2 H, s, ArH).

5-Benzyloxy-2-chloro-3-methoxytoluene (32).—Benzylation of the orcinol (31) as before gave the benzyl ether as a thick oil; δ(CCl_4, 60 MHz) 2.23 (3 H, s, Me), 3.65 (3 H, s, OMe), 4.82 (2 H, s, CH_2), 6.22 (2 H, s, ArH), and 7.20 (5 H, s, Ph); *m/e* 264 and 262 (M^+).

Methyl 3,5-Dichloro-2,4-dihydroxy-6-methylbenzoate (33).—Freshly distilled sulphuryl chloride (32.0 g) in dichloromethane (50 ml) was added dropwise with stirring to methyl orsellinate (25) (20.0 g) in dichloromethane (500 ml). The mixture was then heated under reflux for 7 h and most of the dichloromethane was evaporated off. The residue, in ethyl acetate, was washed with water. The crude product crystallized from dichloromethane–light petroleum as prisms (23.2 g) of the dichloro-orsellinate (33), m.p. 118—119 °C (lit.,[16] 118—119 °C); δ($CDCl_3$—CD_3SOCD_3, 60 MHz) 2.51 (3 H, s, Me) and 3.90 (3 H, s, OMe).

Methyl 3,5-Dichloro-2-hydroxy-4-methoxy-6-methylbenzoate (35).—The dichloro-orsellinate (33) (22.9 g) was converted into the di-*O*-methyl ether (34) by methylation with methyl sulphate and potassium carbonate in acetone in the usual way. The crude product (24.5 g) in dichloromethane (500 ml) was stirred at 0 °C whilst boron trichloride (47.6 g) in dichloromethane (300 ml) was added dropwise over 1 h. The solution was then stirred at room temperature for 2.5 h. The usual work-up gave the dichloroeverninate (35) (22.3 g) as needles (from dichloromethane–light petroleum), m.p. 80—82 °C (lit.,[16] 79—81 °C); δ(CCl_4, 60 MHz) 2.46 (3 H, s, Me), 3.80 and 3.87 (each 3 H, s, OMe), and 11.40br (1 H, OH).

2-Benzyloxy-3,5-dichloro-4-methoxy-6-methylbenzoic Acid (37).—The dichloroeverninate (35) (22.2 g) was benzylated as before, and the crude benzyl ether (36), potassium hydroxide (30.0 g), dimethyl sulphoxide (700 ml), and water (190 ml) were stirred and heated on a steam-bath for 3.5 h. The usual work-up gave the acid (37) (26.0 g), which crystallized from dichloromethane–light petroleum as fine needles, m.p. 151—153 °C, or as stout rods, m.p. 166—169 °C (lit.,[5] 166—168 °C); δ($CDCl_3$–CD_3SOCD_3, 60 MHz) 2.40 (3 H, s, Me), 3.91 (3 H, s, OMe), 5.03 (2 H, s, CH_2), 7.30 (5 H, m, Ph), and 9.67 (1 H, s, OH).

2,4-Dibenzyloxy-3,5-dichloro-6-methylbenzoic Acid (38).—Benzylation of the dichloro-orsellinate (33) (17.6 g) as above gave the di-*O*-benzyl ether which was hydrolysed (4 h) with potassium hydroxide (30 g), water (40 ml), and dimethyl sulphoxide (400 ml), as before. The acid (38) (22.3 g) formed needles (from chloroform–methanol), m.p. 186—188 °C (lit.,[5] 185—187 °C).

2-Benzyloxy-4-methoxy-6-methylbenzoic Acid (39).—Methyl everninate (26) (13.3 g), benzyl bromide (9.0 ml), and potassium carbonate (19.0 g) were stirred and boiled under reflux in acetone (300 ml) for 20 h. The salts were separated by filtration and washed with acetone and the solvent was removed under reduced pressure. The excess of benzyl bromide was removed in steam. This gave methyl 2-benzyloxy-4-methoxy-6-methylbenzoate as an oil; δ(CCl_4, 60 MHz) 2.18 (3 H, s, Me), 3.57 and 3.69 (each 3 H, s, OMe), 4.87 (2 H, s, CH_2), 6.11 (2 H, s, ArH), and 7.17 (5 H, s, Ph). This ester, potassium hydroxide (20.0 g), water (25 ml), and dimethyl sulphoxide (200 ml) were stirred together on a steam-bath for 6 h. Work-up in the usual way gave the *acid* (39) as needles (17.1 g) (from dichloromethane–light petroleum), m.p. 99—100 °C (Found: C, 70.55; H, 6.0%;

M^+, 272. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%; M, 272); δ(CCl_4, 60 MHz) 2.32 (3 H, s, Me), 3.58 (3 H, s, OMe), 4.90 (2 H, s, CH_2), 6.10 (2 H, s, ArH), 7.09 (5 H, m, Ph), and 12.10 (1 H, s, OH).

General Method for Preparation of Benzophenones.—Trifluoroacetic anhydride (15 ml) in 1,2-dichloroethane (20 ml) was added in a thin stream at 0 °C with stirring to the orsellinic acid (10 mmol) in 1,2-dichloroethane (40 ml). Then at room temperature the orcinol (10 mmol) in 1,2-dichloroethane (40 ml) was added dropwise over 15 min. The solution was stirred at room temperature for 1 h and then heated under reflux for 5 h. The solution was cooled and diluted with ether and washed in turn with water, dilute ammonium hydroxide solution, water and finally with saturated brine. The *O*-benzylbenzophenone was then purified by chromatography over silica gel with ethyl acetate–light petroleum as eluant. The *O*-benzylbenzophenone (5.0 g) was stirred under hydrogen with 10% palladium–charcoal (0.5 g) in ethyl acetate (200 ml), containing concentrated hydrochloric acid (5 drops), until absorption ceased. Work-up then gave the benzophenones in >90% yield.

3,5,5′-*Trichloro*-2,2′,4′-*trihydroxy*-4-*methoxy*-6,6′-*dimethylbenzophenone* (40).—Friedel–Crafts reaction between 3,5-dibenzyloxy-2-chlorotoluene (30) and 2-benzyloxy-3,5-dichloro-4-methoxy-6-methylbenzoic acid (37) gave 2,2′,4′-*tribenzyloxy*-3,5,5′-*trichloro*-4-*methoxy*-6,6′-*dimethylbenzophenone* (42%) as stout prisms (from chloroform–methanol), m.p. 142—143.5 °C (Found: C, 67.1; H, 4.7; Cl, 16.35%; M^+, 660, 662, 664. $C_{37}H_{31}Cl_3O_5$ requires C, 67.15; H, 4.7; Cl, 16.05%; M, 660, 662, 664); δ($CDCl_3$, 90 MHz) 2.06 and 2.24 (each 3 H, s, Me), 3.87 (3 H, s, OMe), 4.34 (2 H, $W_{\frac{1}{2}}$ 12.0 Hz, CH_2), 4.70 and 5.16 (each 2 H, s, CH_2), 6.45 (1 H, s, ArH), and 6.76—7.46 (15 H, m, 3 × Ph). Hydrogenolysis gave the *benzophenone* (40) as yellow prisms (from dichloromethane–light petroleum), m.p. 168.5—169.5 °C (Found: C, 49.2; H, 3.3; Cl, 27.3%; M^+, 390, 392, 394. $C_{16}H_{13}Cl_3O_5$ requires C, 49.05; H, 3.35; Cl, 27.15%; M, 390, 392, 394); δ($CDCl_3$, 90 MHz) 2.01 and 2.15 (each 3 H, s, Me), 3.93 (3 H, s, OMe), 6.40vbr (2 H, OH), 6.59 (1 H, s, ArH), and 12.22vbr (1 H, OH).

5-*Chloro*-2,2′,4′-*trihydroxy*-4-*methoxy*-3,3′,6,6′-*tetramethylbenzophenone* (18).—This method is an improvement on that of Sargent *et al.*[10] Trifluoroacetic anhydride (30 ml) in dichloromethane (50 ml) was added dropwise with stirring at 0 °C to a solution of 1,3-dibenzyloxy-2,5-dimethylbenzene (16.25 g) and 2-benzyloxy-5-chloro-4-methoxy-3,6-dimethylbenzoic acid (6.5 g) in dichloromethane (200 ml) over 15 min. The cooling-bath was removed and the mixture was stirred at room temperature for 5.5 h and then worked up as above. The crude product was chromatographed over silica gel with 0—10% ethyl acetate–light petroleum as eluant. 2,2′,4′-Tribenzyloxy-5-chloro-4-methoxy-3,3′,6,6′-tetramethylbenzophenone (5.0 g, 40%) was obtained as plates (from chloroform–methanol), m.p. 143—144 °C (lit.,[10] 143—144 °C). Hydrogenolysis gave the benzophenone (18) as pale yellow prisms (from chloroform), m.p. 176—177 °C (lit.,[10] 176—177 °C).

3,5,5′-*Trichloro*-2,2′-*dihydroxy*-4,4′-*dimethoxy*-6,6′-*dimethylbenzophenone* (41).—Friedel–Crafts reaction between 5-benzyloxy-2-chloro-3-methoxytoluene (32) and 2-benzyloxy-3,5-dichloro-4-methoxy-6-methylbenzoic acid (37) gave 2,2′-*dibenzyloxy*-3,5,5′-*trichloro*-4,4′-*dimethoxy*-6,6′-*dimethylbenzophenone* (28%) as needles (from dichloromethane–light petroleum), m.p. 164—166 °C (Found: C, 63.45; H, 4.7; Cl, 18.35%; M^+, 584, 586, 588. $C_{31}H_{27}Cl_3O_5$ requires C, 63.55; H, 4.65; Cl, 18.15%; M, 584, 586, 588); δ($CDCl_3$, 90 MHz) 2.05 and 2.24 (each 3 H, s, Me), 3.87 and 3.88 (each 3 H, s, OMe), 4.46 (2 H, $W_{\frac{1}{2}}$ 12.0 Hz, CH_2), 4.80 (2 H, s, CH_2), 6.42 (1 H, s, ArH), and 6.82—7.37 (10 H, m, 2 × Ph). Hydrogenolysis gave the *benzophenone* (41) as yellow prisms (from dichloromethane–light petroleum), m.p. 137—138 °C (Found: C, 50.4; H, 4.0; Cl, 26.15%; M^+, 404, 406, 408. $C_{17}H_{15}Cl_3O_5$ requires C, 50.35; H, 3.75; Cl, 26.2%; M, 404, 406, 408); δ($CDCl_3$, 60 MHz) 2.00 and 2.16 (each 3 H, s, Me), 3.92 (6 H, s, 2 × OMe), 6.38 (1 H, s, OH), 6.46 (1 H, s, ArH), and 12.49 (1 H, s, OH).

3,5,5′-*Trichloro*-2,2′,4,4′-*tetrahydroxy*-6,6′-*dimethylbenzophenone* (42).—Friedel–Crafts reaction between 3,5-dibenzyloxy-2-chlorotoluene (30) and 2,4-dibenzyloxy-3,5-dichloro-6-methylbenzoic acid (38) gave 2,2′,4,4′-tetrabenzyloxy-3,5,5′-trichloro-6,6′-dimethylbenzophenone (33%) as a viscous oil; δ($CDCl_3$, 60 MHz) 2.03 and 2.21 (3 H, s, Me), 4.31br (2 H, s, CH_2), 4.60, 4.90, and 5.04 (each 2 H, s, CH_2), 6.32 (1 H, s, ArH), and 6.52—7.60 (20 H, m, 4 × Ph). Hydrogenolysis gave the *benzophenone* (42) as pale yellow prisms (from dichloromethane–light petroleum), m.p. 201—203 °C (Found: C, 48.1; H, 3.2; Cl, 28.3%; M^+, 376, 378, 380. $C_{15}H_{11}Cl_3O_5$ requires C, 47.7; H, 2.95; Cl, 28.15%; M, 376, 378, 380); δ($CDCl_3$–CD_3COCD_3, 60 MHz) 2.06 and 2.10 (each 3 H, s, Me) and 6.48 (1 H, s, ArH).

3,5,5′-*Trichloro*-2,2′,4-*trihydroxy*-4′-*methoxy*-6,6′-*dimethylbenzophenone* (58).—Friedel–Crafts reaction between 5-benzyloxy-2-chloro-3-methoxytoluene (32) and 2,4-dibenzyloxy-3,5-dichloro-6-methylbenzoic acid (38) gave 2,2′,4-*tribenzyloxy*-3,5,5′-*trichloro*-4′-*methoxy*-6,6′-*dimethylbenzophenone* (42%) as translucent plates (from chloroform–methanol), m.p. 155—156 °C (Found: C, 67.35; H, 4.9; Cl, 16.5. $C_{37}H_{31}Cl_3O_5$ requires C, 67.15; H, 4.7; Cl, 16.05%); δ($CDCl_3$, 60 MHz) 2.02 and 2.21 (each 3 H, s, Me), 3.81 (3 H, s, OMe), 4.40br (2 H, s, CH_2), 4.71 and 4.90 (each 2 H, s, CH_2), 6.30 (1 H, s, ArH), and 6.70—7.60 (15 H, m, 3 × Ph). Hydrogenolysis gave the *benzophenone* (58) as yellow prisms (from dichloromethane–light petroleum), m.p. 174—175.5 °C (Found: C, 49.2; H, 3.45; Cl, 27.35%; M^+, 390, 392, 394. $C_{16}H_{13}Cl_3O_5$ requires C, 49.05; H, 3.35; Cl, 27.15%; M, 390, 392, 394); δ($CDCl_3$, 90 MHz) 1.98 and 2.07 (each 3 H, s, Me), 3.94 (3 H, s, OMe), and 6.49 (1 H, s, ArH).

2,2′,4′-*Trihydroxy*-4-*methoxy*-6,6′-*dimethylbenzophenone* (59).—Friedel–Crafts reaction between 3,5-dibenzyloxytoluene[52] and 2-benzyloxy-4-methoxy-6-methylbenzoic acid (39) gave 2,2′,4′-tribenzyloxy-4-methoxy-6,6′-dimethylbenzophenone (95%) as a viscous oil, *m/e* 558 (M^+). Hydrogenolysis gave the *benzophenone* (59) as prisms (from dichloromethane–light petroleum), m.p. 158—160 °C (Found: C, 66.4; H, 5.7%; M^+, 288. $C_{16}H_{16}O_5$ requires C, 66.65; H, 5.6%; M, 288), δ($CDCl_3$–CD_3SOCD_3, 90 MHz) 1.91 and 2.00 (each 3 H, s, Me), 3.77 (3 H, s, OMe), and 6.24 (4 H, m, ArH).

Oxidative Coupling of 3,5,5′-*Trichloro*-2,2′,4′-*trihydroxy*-4-*methoxy*-6,6′-*dimethylbenzophenone* (40).—(*a*) Potassium hexacyanoferrate(III) (100 mg) in water (6.25 ml) was added in one portion to a stirred solution of the benzophenone (40) (50 mg) and potassium carbonate (375 mg) in water (12.5 ml). After 30 s the solution was poured into the calculated amount of dilute hydrochloric acid and extracted with ethyl acetate. This gave 3′,5,5′-*trichloro*-6-*hydroxy*-4′-*methoxy*-4,6′-*dimethylspiro*[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-

2′,3(2H)-*dione* (43) (43 mg) as brilliant yellow prisms (from ether–cyclohexane), which changed into colourless needles at 146—155 °C, m.p. 268—270 °C (Found: M^+, 387.965 1. $^{12}C_{16}{}^{1}H_{11}{}^{35}Cl_3{}^{16}O_5$ requires M, 387.967 2); δ($CDCl_3$–CD_3COCD_3, 60 MHz) 1.88 and 2.50 (each 3 H, s, 6′- and 4-Me), 4.20 (3 H, s, OMe), and 6.80 (1 H, s, ArH); $\lambda_{max.}$ 206, 220, 283, 335, and 380 nm (ε 31 600, 30 600, 10 900, 7 000, and 2 200); $\nu_{max.}$ (CCl_4) 1 732 (C=O), 1 696 (C=O), and 1 605 (C=C) cm^{-1}.

(*b*) A solution of potassium hexacyanoferrate(III) (7.0 g) in water (437.5 ml) was added dropwise to a stirred solution of the benzophenone (40) (3.5 g) and potassium carbonate (26.25 g) in water (875 ml). The solution was stirred for a total of 3 h, acidified, and extracted with ethyl acetate. The extract was extracted several times with saturated aqueous sodium hydrogencarbonate and these extracts were also acidified and extracted with ethyl acetate. The hydrogencarbonate-insoluble material was passed through a column of silica gel with 15—30% ethyl acetate–light petroleum as eluant. This gave 2,7,9-*trichloro*-3-*hydroxy*-8-*methoxy*-1,6-*dimethyldibenzo*[b,e][1,4]*dioxepin*-11-*one* (*dechlorodiploicin*) (46) (860 mg) as needles (from chloroform–methanol), m.p. and mixed m.p. 272.5—274 °C, identical (mass and n.m.r. spectra and R_F values in three solvent systems) with a sample of the natural material [1] (Found: C, 49.55; H, 3.15; Cl, 27.25. $C_{16}H_{11}Cl_3O_5$ requires C, 49.3; H, 2.85; Cl, 27.3%). A portion (200 mg) of the hydrogencarbonate-soluble material was subjected to preparative t.l.c. [benzene–dioxan–acetic acid (120 : 10 : 1 v/v)] which gave from a fast band 3-*chloro*-6-(3,5-*dichloro*-2-*hydroxy*-4-*methoxy*-6-*methylphenoxy*)-4-*hydroxy*-2-*methylbenzoic acid* (49) (31.1 mg) as needles (from aqueous methanol), m.p. 165—190 °C (Found: C, 46.8; H, 3.35%; M^+, 406, 408, 410. $C_{16}H_{13}Cl_3O_6$ requires C, 47.15; H, 3.2%; M, 406, 408, 410); δ($CDCl_3$, 90 MHz) 2.27 and 2.50 (3 H, s, Me), 3.90 (3 H, s, OMe), 4.32br (3 H, OH), and 6.18 (1 H, s, ArH). The slower band gave 3′,5,5′-*trichloro*-2′,6-*dihydroxy*-4,6′-*dimethylspiro*[*benzofuran*-2,1′-*cyclohexa*-2′,5′-*diene*]-3(2H),4′-*dione* (52) (157 mg) as prisms (from acetone–benzene), m.p. 192—195 °C with resolidification to needles at 220 °C and m.p. 275—277 °C (Found: M^+, 373.953 8. $^{12}C_{15}{}^{1}H_9{}^{35}Cl_3{}^{16}O_5$ requires M, 373.951 5); δ(CD_3SOCD_3, 90 MHz) 1.71 (3 H, s, 6′-Me), 2.45 (3 H, s, 4-Me), and 6.61 (1 H, s, ArH); $\lambda_{max.}$ 223, 240, 285, and 330 nm (ε 23 600, 19 200, 21 600, and 10 600); $\nu_{max.}$ ($CHCl_3$) 1 728 (C=O), 1 681 (C=O), 1 652, and 1 608 (C=C) cm^{-1}. The remaining hydrogencarbonate-soluble material was heated on a steam-bath with acetic anhydride (100 ml) for 12 h and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel with 2.5—30% ethyl acetate–light petroleum as eluant. This gave first 3-*acetoxy*-2,7,9-*trichloro*-8-*methoxy*-1,6-*dimethyldibenzo*[b,e][1,4]*dioxepin*-11-*one* (207 mg) as needles (from dichloromethane–light petroleum), m.p. 180.5—182 °C (Found: C, 49.9; H, 2.9; Cl, 24.6%; M^+, 430, 432, 434. $C_{18}H_{13}Cl_3O_6$ requires C, 50.1; H, 3.05; Cl, 24.65%; M, 430, 432, 434); δ($CDCl_3$, 90 MHz) 2.37 (3 H, s, MeCO), 2.48 and 2.57 (each 3 H, s, Me), 3.86 (3 H, s, OMe), and 7.01 (1 H, s, ArH); $\nu_{max.}$ (CCl_4) 1 791 (acetate C=O) and 1 770 (depsidone C=O) cm^{-1}. On treatment with aqueous pyridine at 90 °C this gave dechlorodiploicin (46), m.p. and mixed m.p. 272.5—274 °C. Further elution gave 3,8-*diacetoxy*-2,7,9-*trichloro*-1,6-*dimethyldibenzo*[b,e][1,4]-*dioxepin*-11-*one* (474 mg) as needles (from dichloromethane–light petroleum), m.p. 219—222 °C (Found: C, 49.7; H, 2.7; Cl, 23.15%; M^+, 458, 460, 462. $C_{19}H_{13}Cl_3O_7$ requires C, 49.65; H, 2.85; Cl, 23.15%; M, 458, 460, 462); δ($CDCl_3$, 90 MHz) 2.36 and 2.38 (each 3 H, s, MeCO), 2.49 and 2.56 (each 3 H, s, Me), and 7.02 (1 H, s, ArH); $\nu_{max.}$ (CCl_4) 1 795 (acetate C=O) and 1 770 (depsidone C=O) cm^{-1}. On hydrolysis with aqueous pyridine at 90 °C this gave 2,7,9-*trichloro*-3,8-*dihydroxy*-1,6-*dimethyldibenzo*[b,e][1,4]*dioxepin*-11-*one* (47) as needles (from chloroform–carbon tetrachloride), m.p. 275—277 °C (Found: M^+, 373.959 2. $^{12}C_{15}{}^{1}H_9{}^{35}Cl_3{}^{16}O_5$ requires M, 373.951 5); δ($CDCl_3$–CD_3SOCD_3–CD_3COCD_3, 60 MHz) 2.46 and 2.50 (each 3 H, s, Me) and 6.76 (1 H, s, ArH). Further elution gave 6-*acetoxy*-3′,5,5′-*trichloro*-2′-*hydroxy*-4,6′-*dimethylspiro*[*benzofuran*-2,1′-*cyclohexa*-2′,5′-*diene*]-3(2H),4′-*dione* (896 mg) as pale yellow prisms (from methanol), m.p. 193—198 °C (Found: C, 48.75; H, 2.6; Cl, 25.2%; M^+, 416, 418, 420. $C_{17}H_{11}Cl_3O_6$ requires C, 48.9; H, 2.65; Cl, 25.45%; M, 416, 418, 420); δ($CDCl_3$, 90 MHz) 1.91 (3 H, s, 6′-Me), 2.41 (3 H, s, MeCO), 2.66 (3 H, s, 4-Me), 4.16vbr (1 H, OH), and 7.01 (1 H, s, ArH); $\lambda_{max.}$ 225.5, 268, and 333 nm (ε 35 400, 23 900, and 6 700); ν_{max} (CCl_4) 1 792 (C=O), 1 740 (C=O), 1 692 (C=O), 1 661, and 1 618 (C=C) cm^{-1}. Further elution gave material (938 mg) which was treated with hot wet pyridine as before, and the crude product was chromatographed over silica gel with 15% ethyl acetate–light petroleum. This gave 3,5-*dichloro*-2,4-*dihydroxy*-6-*methylphenyl* 4-*chloro*-5-*hydroxy*-3-*methylphenyl ether* (429 mg) as prisms (from dichloromethane–light petroleum), m.p. 86 °C with resolidification to platelets at *ca.* 120 °C, and m.p. 188—190 °C (Found: C, 46.65; H, 3.70. $C_{14}H_{11}Cl_3O_4{\cdot}\frac{1}{2}H_2O$ requires C, 46.9; H, 3.35%; Found: M^+, 348, 350, 352. $C_{14}H_{11}Cl_3O_4$ requires M, 348, 350, 352), δ($CDCl_3$, 90 MHz) 2.14 (3 H, s, Me), 2.31 (3 H, s, $W_{\frac{1}{2}}$ 1.9 Hz, 6-Me), and 6.34 (2 H, s, $W_{\frac{1}{2}}$ 2.0 Hz, ArH).

(*c*) Oxidation of the benzophenone (40) (50 mg) as under (*b*), but for 15 min gave the grisadienedione (52) and the depsidone (46) in the ratio 1.17 : 1 (n.m.r.)

Treatment of the Depsidone (46) *with Aqueous Potassium Carbonate.*—The depsidone (46) (50 mg) and potassium carbonate (375 mg) were stirred in water (15 ml) for 3.25 h. The solution was acidified and extracted with ethyl acetate. The crude product contained the acid (49) and the depsidone (46) in the ratio 2.2 : 1 (n.m.r.).

Methanolysis of 3′,5,5′-*Trichloro*-6-*hydroxy*-4′-*methoxy*-4,6′-*dimethylspiro*[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-2′,3(2H)-*dione* (43).—The grisadienedione (43) (40 mg) was stirred at room temperature for 2 h with sodium methoxide [from sodium (40 mg)] in dry methanol (10 ml) when more sodium (50 mg) was added and stirring was continued for a further 2 h. The usual work-up gave a crude product which was subjected to preparative t.l.c. (15% ethyl acetate–light petroleum) which gave methyl 3-chloro-6-(3,5-dichloro-2-hydroxy-4-methoxy-6-methylphenoxy)-4-hydroxy-2-methylbenzoate (50) (20 mg) as prisms (from dichloromethane–light petroleum), m.p. 175—176.5 °C (lit.,[1] 175—176.5 °C), identical (mass and n.m.r. spectra) with a sample prepared previously.[1]

Oxidative Coupling of 5-*Chloro*-2,2′,4′-*trihydroxy*-4-*methoxy*-3,6,6′-*trimethylbenzophenone* (53).—(*a*) Potassium hexacyanoferrate(III) (0.4 g) in water (20 ml) was added in one portion to a stirred solution of the benzophenone (53) [12] (200 mg) and potassium carbonate (1.4 g) in water (20 ml). After 2 min, acidification with the calculated volume of dilute hydrochloric acid and extraction with ethyl acetate gave 5′-*chloro*-6-*hydroxy*-4′-*methoxy*-3′,4,6′-*trimethylspiro*-[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-2′,3(2H)-*dione* (54)

(180 mg) as yellow prisms (from acetone–benzene) which changed to colourless needles *ca.* 170 °C with m.p. 296—298 °C (decomp.) (Found: C, 61.0; H, 4.8; Cl, 10.6. $C_{17}H_{15}ClO_5$ requires C, 61.0; H, 4.5; Cl, 10.6%); δ($CDCl_3$–CD_3COCD_3, 60 MHz) 1.81 (6 H, s, 3'- and 6'-Me), 2.38 (3 H, s, 4-Me), 3.89 (3 H, s, OMe), 6.34 and 6.43 (2 H, AB, *J* 2.5 Hz, ArH); $\lambda_{max.}$ 206, 283, and 316 nm (ε 33 300, 13 100, and 7 900), and $\lambda_{infl.}$ 380 nm (ε 1 300); $\nu_{max.}$ ($CHCl_3$) 1 717 (C=O), 1 661 (C=O), 1 615 (C=C), and 1 590 (C=C) cm^{-1}.

(*b*) The benzophenone (53) (100 mg) was oxidized as under (*a*) except that the solution was stirred for 3 h. This gave 7-chloro-3-hydroxy-8-methoxy-1,6,9-trimethyldibenzo-[*b*,*e*][1,4]dioxepin-11-one (55) (91 mg) as prisms (from methanol), m.p. 297—299 °C (decomp.) [lit.,[12] 270 °C (decomp.)], identical (mass and n.m.r. spectra) with a sample synthesized previously.[12]

Oxidative Coupling of 5-Chloro-2,2'4'-trihydroxy-4-methoxy-3,3'6,6'-tetramethylbenzophenone (18).—(*a*) This benzophenone (18) was oxidized in the same manner as the benzophenone (53) [method (a)] and gave *5'-chloro-6-hydroxy-4'-methoxy-3',4,6',7-tetramethylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-2',3(2H)-dione* (20) (89%) as yellow prisms (from ether–cyclohexane) which changed into colourless needles at *ca.* 150 °C, and again into prisms at *ca.* 200 °C, m.p. 290—291 °C (Found: M^+, 348.075 2. $^{12}C_{18}{}^{1}H_{17}{}^{35}Cl^{16}O_5$ requires *M*, 348.076 4); δ($CDCl_3$–CD_3COCD_3, 60 MHz) 1.81 (6 H, s, 3'- and 6'-Me), 2.12 and 2.31 (each 3 H, s, ArMe), 3.87 (3 H, s, OMe), and 6.30 (1 H, s, ArH); $\lambda_{max.}$ 218.5 and 293 nm (ε 25 000 and 15 400) and $\lambda_{infl.}$ 380 nm (ε 1 400); $\nu_{max.}$ ($CHCl_3$) 1 710 (C=O), 1 668 (C=O), 1 632 (C=C), and 1 599 (C=C) cm^{-1}.

(*b*) The benzophenone (18) was oxidized in the same manner as the benzophenone (53) [method (*b*)]. Integration of the n.m.r. spectrum of the product indicated that it contained the grisadienedione (20) (40%) and the depsidone (21) [10] (60%).

Oxidative Coupling of 5-Bromo-2,2',4'-trihydroxy-4-methoxy-3,6'-dimethyl-6-s-butylbenzophenone (22).—This benzophenone (22) [11] was oxidized in the same manner as the benzophenone (53) [method (*a*)] and gave *5'-bromo-6-hydroxy-4'-methoxy-3',4-dimethyl-6'-s-butylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-2',3(2H)-dione* (23) (87%) as yellow needles (from ether–cyclohexane), m.p. 134—136 °C (Found: C, 56.95; H, 5.2; Br, 18.6%; M^+, 420, 422. $C_{20}H_{21}BrO_5$ requires C, 57.0; H, 5.0; Br, 18.95%; *M*, 420, 422); δ($CDCl_3$, 80 MHz) 0.86 (3 H, t, 4''-Me), 1.22 (3 H, d, 1''-Me), 1.66br (2 H, quintet, diastereotopic CH_2), 1.90 (3 H, s, 3'-Me), 2.38 (3 H, s, 4-Me), 3.00 (1 H, m, CH), 4.05 (3 H, s, OMe), 6.38 and 6.56 (each 1 H, apparent s, ArH); $\lambda_{max.}$ 204, 282.5, and 317 nm (ε 28 800, 11 200, and 7 000), and $\lambda_{infl.}$ 385 nm (ε 1 050); $\nu_{max.}$ (CCl_4) 1 722 (C=O), 1 652 (C=O), and 1 629 (C=C) cm^{-1}.

Oxidative Coupling of 3,5,5'-Trichloro-2,2'-dihydroxy-4,4'-dimethoxy-6,6'-dimethylbenzophenone (41).—Potassium hexacyanoferrate(III) (1.0 g) in water (60 ml) was added dropwise to a stirred solution of the benzophenone (41) (0.5 g) and potassium carbonate (3.75 g) in water (125 ml). The mixture was stirred for 1 h and then worked up. This gave *3',5,5'-trichloro-4',6-dimethoxy-4,6'-dimethylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-2',3(2H)-dione* (44) (0.3 g) as yellow rods [from dichloromethane–light petroleum (charcoal)], m.p. 174—195 °C with resolidification to colourless needles, m.p. 228—231 °C (Found: C, 50.55; H, 3.2; Cl, 26.45%; M^+, 402, 404, 406. $C_{17}H_{13}Cl_3O_5$ requires C, 50.6; H, 3.25; Cl, 26.35%; *M*, 402, 404, 406); δ($CDCl_3$, 60 MHz) 1.88 and 2.52 (each 3 H, s, 6'- and 4-Me), 3.99 and 4.22 (each 3 H, s, OMe), and 6.13 (1 H, s, ArH); $\lambda_{max.}$ 223, 280.5, and 332 nm (ε 25 700, 18 100, and 10 400), and $\lambda_{infl.}$ 385 nm (ε 2 000); $\nu_{max.}$ (CCl_4) 1 730 (C=O), 1 690 (C=O), and 1 613 (C=C) cm^{-1}.

Oxidative Coupling of 3,5,5'-Trichloro-2,2',4,4'-tetrahydroxy-6,6'-dimethylbenzophenone (42).—Potassium hexacyanoferrate(III) (200 mg) in water (12.5 ml) was added dropwise to a stirred solution of the benzophenone (42) (100 mg) and potassium carbonate (750 mg) in water (25 ml). After the addition the solution was stirred for a further 5 min and worked up as above. This gave the grisadienedione (52) (85 mg) as prisms (from acetone–benzene), m.p. 192—195 °C with resolidification to needles at 220 °C and m.p. 275—277 °C. The same product was obtained when the reaction mixture was stirred for 0.5 h after the addition of the potassium hexacyanoferrate(III).

Methanolysis of 3',5,5'-Trichloro-4',6-dimethoxy-4,6'-dimethylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-2',3(2H)-dione (44).—The grisadienedione (44) (50 mg) was methanolysed as above. This gave *methyl 3-chloro-6-(3,5-dichloro-2-hydroxy-4-methoxy-6-methylphenoxy)-4-methoxy-2-methylbenzoate* (51) (76%) as prisms [from dichloromethane–light petroleum (charcoal)], m.p. 111—112 °C (Found: C, 49.75; H, 3.95; Cl, 24.25%; M^+, 434, 436, 438. $C_{18}H_{17}Cl_3O_6$ requires C, 49.4; H, 3.9; Cl, 24.3%; *M*, 434, 436, 438); δ($CDCl_3$, 60 MHz) 2.28 and 2.38 (each 3 H, s, Me), 3.68, 3.80, and 3.95 (each 3 H, s, OMe), and 5.98 (1 H, s, ArH).

Acid-catalysed Rearrangement of Methyl 2,3-Dihydro-6-hydroxy-4'-methoxy-2',3-dioxo-4,6'-dipentylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-5'-carboxylate (82).—The grisadienedione (82) (102 mg) and trifluoroacetic acid (0.5 ml) were stirred in dry dichloromethane (30 ml) at room temperature for 2 h. The solution was diluted with ethyl acetate and washed in turn with water, aqueous sodium hydrogencarbonate, water, and finally saturated brine. The crude product was subjected to preparative t.l.c. (5—15% ethyl acetate–light petroleum). This gave the depsidone (83) (49.7 mg) as a gum, identical to that prepared later.

Acid-catalysed Rearrangement of 5'-Chloro-6-hydroxy-4'-methoxy-3',4,6',7-tetramethylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-2',3(2H)-dione (20).—The grisadienedione (20) (17 mg) and trifluoroacetic acid (0.2 ml) were stirred in dry dichloromethane (10 ml) for 15 min. Work-up as above gave 7-chloro-3-hydroxy-8-methoxy-1,4,6,9-tetramethyldibenzo[*b*,*e*][1,4]dioxepin-11-one (21) (10 mg) as prisms (from methanol), m.p. 287—288 °C (lit.,[10] 287—288 °C) identical (mass and n.m.r. spectra) with an authentic sample.

General Method for Thermolysis of Grisadienediones.—The grisadienedione under dry nitrogen was heated alone, with the aid of a Wood's metal bath at the stated bath temperature, or heated under reflux in phenetole or diphenyl ether for the stated time. The solvent was removed by steam distillation.

Thermolysis of 3',5,5'-Trichloro-6-hydroxy-4'-methoxy-4,6'-dimethylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-2',3(2H)-dione (43).—This grisadienedione (43) (33 mg) (190 °C for 5 min) gave a melt which was crystallized from chloroform–methanol and furnished dechlorodiploicin (46) (20 mg), m.p. and mixed m.p. 272.5—274 °C, identical (mass and n.m.r. spectra) with the sample prepared previously.

Thermolysis of 3',5,5'-Trichloro-2',6-dihydroxy-4,6'-dimethylspiro[benzofuran-2,1'-cyclohexa-2',5'-diene]-3(2H),4'-

dione (52).—This grisadienedione (52) (58 mg) [diphenyl ether (15 ml), 45 min] gave a crude product which was subjected to preparative t.l.c. (30% ethyl acetate–light petroleum) and furnished 2,7,9-trichloro-3,8-dihydroxy-1,6-dimethyldibenzo[*b,e*][1,4]dioxepin-11-one (47) (25 mg), m.p. and mixed m.p. 275—277 °C. The derived di-*O*-methyl ether (48), prepared in the usual way, had m.p. and mixed m.p. 230—231.5 °C (lit.,[1] 230—231.5 °C).

Thermolysis of 3'5,5'-*Trichloro*-4',6-*dimethoxy*-4,6'-*dimethylspiro*[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (44).—This grisadienedione (44) (42 mg) (250 °C for 5 min) gave a melt which was crystallized from dichloromethane–light petroleum (charcoal) and furnished 2,7,9-trichloro-3,8-dimethoxy-1,6-dimethyldibenzo[*b,e*][1,4]dioxepin-11-one (dechloro-*O*-methyldiploicin) (48) (31 mg) as needles, m.p. and mixed m.p. 230—231.5 °C (lit.,[1] 230—231.5 °C), identical (mass and n.m.r. spectra and R_F values in three solvent systems) with the natural product.[1]

Thermolysis of 5'-*Bromo*-6-*hydroxy*-4'-*methoxy*-3',4-*dimethyl*-6'-*s*-*butylspiro*[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (23).—This grisadienedione (23) (100 mg) [diphenyl ether (5 ml), 5 min] gave a crude product which was subjected to preparative t.l.c. (10% ethyl acetate–light petroleum) and furnished 7-bromo-3-hydroxy-8-methoxy-1,9-dimethyl-6-s-butyldibenzo[*b,e*][1,4]dioxepin-11-one (24) (95 mg) as prisms (from ether–light petroleum), m.p. 171—171.2 °C (lit.,[11] 161—163 °C) identical (mass and n.m.r. spectra) with the sample synthesized previously.[11]

Thermolysis of 5'-*Chloro*-6-*hydroxy*-4'-*methoxy*-3',4,6'-*trimethylspiro*[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (54).—This grisadienedione (54) (20 mg) (220 °C for 5 min) gave 7-chloro-3-hydroxy-8-methoxy-1,6,9-trimethyldibenzo[*b,e*][1,4]dioxepin-11-one (55) (15 mg) as prisms (from methanol), m.p. and mixed m.p. 297—299 °C (decomp.), identical (mass and n.m.r. spectra) with the sample obtained above.

Oxidative Coupling of 3,5,5'-*Trichloro*-2,2',4-*trihydroxy*-4'-*methoxy*-6,6'-*dimethylbenzophenone* (58).—Potassium hexacyanoferrate(III) (100 mg) in water (6.25 ml) was added in one portion to a stirred solution of the benzophenone (58) (50 mg) and potassium carbonate (375 mg) in water (12.5 ml). After 2 min the solution was acidified with the calculated volume of dilute hydrochloric acid and extracted with ethyl acetate. This gave 5,5',7-*trichloro*-6-*hydroxy*-4'-*methoxy*-4,6'-*dimethylspiro*[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (60) (45 mg) as pale yellow prisms (from acetone–cyclohexane), m.p. 138—142 °C with resolidification to needles which changed to lustrous prisms at 195—200 °C, and m.p. 259.5—261.5 °C (Found: M^+, 387.968 1. $^{12}C_{16}{}^{1}H_{11}{}^{35}Cl_3{}^{16}O_5$ requires *M*, 387.967 2); δ($CDCl_3$, 60 MHz) 1.88 and 2.61 (each 3 H, s, 6'- and 4-Me), 3.97 (3 H, s, OMe), and 5.43 (1 H, s, 3'-H); $\lambda_{max.}$ 224, 290, 333, and 380 nm (ε 26 500, 12 400, 6 400, and 1 200); $\nu_{max.}$ ($CHCl_3$) 1 728 (C=O), 1 669 (C=O), 1 630 (C=C), and 1 604 (C=C) cm^{-1}.

Thermolysis of 5,5',7-*Trichloro*-6-*hydroxy*-4'-*methoxy*-4,6'-*dimethylspiro*[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (60).—This grisadienedione (60) (100 mg) [phenetole (10 ml, 10 min)] gave a crude product which was subjected to preparative t.l.c. (30% ethyl acetate–light petroleum). The faster band furnished 2,4,7-*trichloro*-3-*hydroxy*-8-*methoxy*-1,6-*dimethyldibenzo*[b,e][1,4]*dioxepin*-11-*one* (63) (55 mg) as needles (from dichloromethane–light petroleum) which changed to stout prisms at 190—200 °C, m.p. 260—260.5 °C (Found: C, 49.45; H, 3.2; Cl, 27.2. $C_{16}H_{11}Cl_3O_5$ requires C, 49.3; H, 2.85; Cl, 27.3%); δ($CDCl_3$, 80 MHz) 2.52 and 2.63 (each 3 H, s, Me), 3.86 (3 H, s, OMe), and 6.71 (1 H, s, ArH), *m/e* 392 (15%), 391 (11), 390 (38), 389 (10), 388 (40), 375 (14), 373 (13), 357 (16), 356 (15), 355 (70), 354 (21), 353 (100), 347 (11), 345 (11), 327 (15), 325 (20), 221 (5), 220 (6), 219 (5), 218 (5), 174 (13), 172 (16), 170 (43), 155 (16), 137 (13), and 111 (18); $\nu_{max.}$ ($CHCl_3$) 1 749 (C=O) cm^{-1}.

Oxidative Coupling of 2,2',4'-*Trihydroxy*-4-*methoxy*-6,6'-*dimethylbenzophenone* (59).—(*a*) Potassium hexacyanoferrate(III) (1.0 g) in water (100 ml) was added in one portion to a stirred solution of the benzophenone (59) (0.5 g) and potassium carbonate (3.5 g) in water (100 ml). Work-up after 5 min in the usual way gave a crude product which was crystallized from ethyl acetate–light petroleum (charcoal) and gave 6-*hydroxy*-4'-*methoxy*-4,6'-*dimethylspiro*-[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (61) (0.2 g) as pale yellow blades, m.p. 170—173 °C (Found: C, 67.2; H, 5.0%; M^+, 286. $C_{16}H_{14}O_5$ requires C, 67.15; H, 4.95%; *M*, 286); δ($CDCl_3$, 80 MHz) 1.81 (3 H, d, $J_{6'\text{-Me},5'}$ 1.3 Hz, 6'-Me), 2.39 (3 H, s, 4-Me), 3.88 (3 H, s, OMe), 5.49 (1 H, d, $J_{3',5'}$ 2.1 Hz, 3'-H), 6.13 (1 H, apparent t, 5'-H), 6.19 and 6.45 (2 H, broadened AB, *J* 2.0 Hz, ArH), and 8.65 (1 H, s, D_2O exchangeable OH); irradiation at δ 1.81 caused the collapse of the triplet at δ 6.13 to a doublet, $J_{3',5'}$ 2.1 Hz; $\lambda_{max.}$ 215, 287, and 318 nm (ε 40 600, 20 200, and 13 900) and $\lambda_{infl.}$ 235 nm (ε 14 200); $\nu_{max.}$ ($CHCl_3$) 1 712 (C=O), 1 669 (C=O), and 1 618 (C=C) cm^{-1}.

(*b*) Oxidation of the benzophenone (59) as above and work-up after 23 h gave the same products.

Methylation of 6-*Hydroxy*-4'-*methoxy*-4,6'-*dimethylspiro*-[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (61).—The grisadienedione (61) (310 mg), potassium carbonate (300 mg), and iodomethane (2 ml) were stirred together at room temperature in dry *NN*-dimethylformamide (10 ml) under dry nitrogen for 2 h. The usual work-up gave 4',6-*dimethoxy*-4,6'-*dimethylspiro*[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (67) as prisms (250 mg) (from dichloromethane–light petroleum), with no definite m.p. and slow conversion into depsidone above 180 °C (Found: C, 67.95; H, 5.4%; M^+, 300. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.35%; *M*, 300); δ($CDCl_3$, 80 MHz) 1.79 (3 H, d, $J_{6'\text{-Me},5'}$ 1.3 Hz, 6'-Me), 2.47 (3 H, s, 4-Me), 3.82 and 3.89 (each 3 H, s, OMe), 5.42 (1 H, d, $J_{3',5'}$ 2.1 Hz, 3'-H), 6.13 (1 H, apparent t, $W_{\frac{1}{2}}$ 5.0 Hz, 5'-H), and 6.44 and 6.59 (2 H, broadened AB, *J* 2.1 Hz, ArH); irradiation at δ 1.79 caused the collapse of the triplet at δ 6.13 to a doublet, $J_{3',5'}$ 2.1 Hz; $\lambda_{max.}$ 213, 279, and 317 nm (ε 34 900, 22 000, and 14 400), and $\lambda_{infl.}$ 230 nm (ε 17 900); $\nu_{max.}$ ($CHCl_3$) 1 738w (C=O), 1 710 (C=O), 1 669 (C=O), 1 645 (C=C), and 1 620 (C=C) cm^{-1}.

Reduction of 4',6-*Dimethoxy*-4,6'-*dimethylspiro*[*benzofuran*-2,1'-*cyclohexa*-3',5'-*diene*]-2',3(2H)-*dione* (67). The grisadienedione (67) (180 mg) in glacial acetic acid (10 ml) was stirred with zinc dust (1.0 g) for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate and filtered through Kieselguhr. The filtrate was washed successively with water, aqueous sodium hydrogencarbonate, water, and finally with saturated brine. The crude product crystallized from dichloromethane–light petroleum as yellow prisms (170 mg) of 2,2'-*dihydroxy*-4,4'-*dimethoxy*-6,6'-*dimethylbenzophenone* (69), m.p. 159—160 °C (Found: C, 67.5; 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) 1.92 (6 H, s, 2 × Me), 3.82 (6 H, s, 2 × OMe), 6.27 and 6.37 (4 H, AB, *J* 2.5 Hz, ArH), and 9.73 (2 H, s, OH).

Thermolysis of 6-*Hydroxy*-4′-*methoxy*-4,6′-*dimethylspiro*-[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-2′,3(2H)-*dione* (61).—This grisadienedione (61) (70 mg) [phenetole (10 ml), 10 min] gave a crude product which crystallized from chloroform–light petroleum as needles (45 mg) of 3-hydroxy-8-methoxy-1,6-dimethyldibenzo[*b*,*e*][1,4]dioxepin-11-one (64), m.p. 198—201 °C (lit.,[9] 198—199 °C); δ($CDCl_3$, 80 MHz) 2.41 and 2.47 (each 3 H, s, Me), 3.73 (3 H, s, OMe), 5.81br (1 H, OH), and 6.57 (4 H, s, $W_{\frac{1}{2}}$ 5.0 Hz, ArH).

Thermolysis of 4′,6-*Dimethoxy*-4,6′-*dimethylspiro*[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-2′,3(2H)-*dione* (67).—This grisadienedione (67) (100 mg) [phenetole (10 ml), 10 min] gave a crude product which was subjected to preparative t.l.c. (20% ethyl acetate–light petroleum). 3,8-*Dimethoxy*-1,6-*dimethyldibenzo*[b,e][1,4]*dioxepin*-11-*one* (70) (68 mg) formed prisms (from dichloromethane–light petroleum), m.p. 94—95 °C (Found: C, 67.8; H, 5.4%; M^+, 300. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.35%; *M*, 300); δ(CCl_4, 90 MHz) 2.38 and 2.43 (each 3 H, s, Me), 3.67 and 3.78 (each 3 H, s, OMe), 6.40 and 6.49 (2 H, AB, *J* 2.9 Hz, ArH), and 6.49 (2 H, s, $W_{\frac{1}{2}}$ 2.9 Hz, ArH).

Chlorination of 3-*Hydroxy*-8-*methoxy*-1,6-*dimethyldibenzo*-[b,e][1,4]*dioxepin*-11-*one* (64).—Chlorination of the depsidone (64) by the method of Sargent and co-workers [9] gave 2,4,9-trichloro-3-hydroxy-8-methoxy-1,6-dimethyldibenzo-[*b*,*e*][1,4]dioxepin-11-one (71) as needles (from chloroform–cyclohexane), m.p. 237—239 °C (lit.,[9] 238—240 °C); δ($CDCl_3$, 80 MHz) 2.52 and 2.63 (each 3 H, s, Me), 3.86 (3 H, s, OMe) and 6.70 (1 H, s, ArH); *m/e* 392 (14%), 390 (42), 388 (38), 375 (13), 373 (13), 357 (18), 356 (24), 355 (70), 354 (33), 353 (100), 347 (10), 339 (11), 327 (16), 325 (26), 319 (16), 221 (6), 220 (5), 219 (9), 218 (7), 211 (14), 170 (32), and 136 (16); $\nu_{max.}$ ($CHCl_3$) 1 748 (C=O) cm^{-1}.

3,5-*Dibenzyloxy*-1-*pentylbenzene*.—Olivetol [27] (19.3 g), potassium carbonate (60 g), *NN*-dimethylformamide (150 ml), and benzyl bromide (28 ml) were stirred together under dry nitrogen at room temperature for 18 h. The usual work-up gave the *product* (37.8 g) as a thick oil, homogeneous on t.l.c. (Found: M^+, 360.207 1. $^{12}C_{25}{}^{1}H_{28}{}^{16}O_2$ requires *M*, 360.208 9); δ(CCl_4, 60 MHz) 0.84 (3 H, deformed t, Me), 1.36br (6 H, 3 × CH_2), 2.42 (2 H, deformed t, CH_2), 4.81 (4 H, s, 2 × CH_2), 6.13 (3 H, s, ArH), and 7.11 (10 H, s, 2 × Ph).

Methyl 2-*Hydroxy*-4-*isopropyloxy*-6-*pentylbenzoate* (74).—Methyl 2,4-dihydroxy-6-pentylbenzoate (73) [25] (23.8 g), 2-bromopropane (12.3 g), potassium carbonate (13.8 g) and dry *NN*-dimethylformamide (75 ml) were stirred together under dry nitrogen at 80 °C (bath) for 24 h. The mixture was poured into water and extracted with ethyl acetate. The crude product was chromatographed over silica gel with 0—2.5% ethyl acetate–light petroleum as eluant. The *product* (74) (15.7 g) was obtained as an oil, homogeneous on t.l.c. (Found: M^+, 280.167 3. $^{12}C_{16}{}^{1}H_{24}{}^{16}O_4$ requires *M*, 280.167 4); δ(CCl_4, 60 MHz) 0.89 (3 H, deformed t, Me), 1.31 (12 H, d, superimposed on br CH_2, 2 × Me and 3 × CH_2), 2.75 (2 H, deformed t, CH_2), 3.80 (3 H, s, OMe), 4.42 (1 H, septet, CH), 6.01 (2 H, s, ArH), and 11.39 (1 H, s, OH).

Methyl 4-*Isopropyloxy*-2-*methoxy*-6-*pentylbenzoate* (75).—The phenol (74) (15.1 g), potassium carbonate (15 g), methyl sulphate (7 ml), and acetone (100 ml) were stirred and heated under dry nitrogen for 20 h. The usual work-up gave the product (75) as an *oil* (15.7 g) homogeneous on t.l.c. (Found: M^+, 294.182 5. $^{12}C_{16}{}^{1}H_{26}{}^{16}O_4$ requires *M*, 294.183 1); δ(CCl_4, 60 MHz) 0.90 (3 H, deformed t, Me), 1.30 (12 H, d, superimposed on br CH_2, 2 × Me and 3 × CH_2), 2.46 (2 H, deformed t, CH_2), 3.70 (6 H, s, 2 × OMe), 4.45 (1 H, septet, CH), and 6.08 (2 H, s, ArH).

Methyl 3-*Formyl*-4-*hydroxy*-6-*methoxy*-2-*pentylbenzoate* (77).—Tin(IV) chloride (10 ml) in dry dichloromethane (20 ml) was added dropwise at 0 °C over 15 min to a stirred solution of the substrate (75) (12.0 g) and dichloromethyl methyl ether (10 ml) in dry dichloromethane (100 ml). The mixture was stirred at 0 °C for 4 h and then worked-up in the usual way. The crude product (76) in dry dichloromethane (150 ml) was stirred at 0 °C and treated dropwise with titanium(IV) chloride (15.5 g). The mixture was stirred at 0 °C for 3 h and then poured onto ice. The crude product was filtered through a column of silica gel with 5% ethyl acetate–light petroleum as eluant. The *aldehyde* (77) (7.3 g) formed needles (from light petroleum), m.p. 76—77 °C (Found: C, 64.1; H, 7.3%; M^+, 280. $C_{15}H_{20}O_5$ requires C, 64.25; H, 7.2%; *M*, 280); δ(CCl_4, 60 MHz) 0.90 (3 H, deformed t, Me), 1.40br (6 H, 3 × CH_2), 2.69 (2 H, deformed t, CH_2), 3.73 and 3.78 (each 3 H, s, OMe), 6.10 (1 H, s, ArH), 9.91 (1 H, s, CHO), and 12.44 (1 H, s, OH).

Methyl 4-*Benzyloxy*-3-*formyl*-6-*methoxy*-2-*pentylbenzoate* (78).—The substrate (77) (8.3 g), benzyl bromide (5 ml), potassium carbonate (10 g), and dry *NN*-dimethylformamide (50 ml) were stirred together under dry nitrogen at room temperature for 18 h. The usual work-up gave the *aldehyde* (78) (10.3 g) as prisms (from methanol), m.p. 83—84 °C (Found: C, 71.0; H, 6.95; M^+, 370. $C_{22}H_{26}O_5$ requires C, 71.35; H, 7.05%; *M*, 370); δ(CCl_4, 60 MHz) 0.90 (3 H, deformed t, Me), 1.40br (6 H, 3 × CH_2), 2.71 (2 H, deformed t, CH_2), 3.68 and 3.75 (each 3 H, s, OMe), 5.01 (2 H, s, CH_2), 6.22 (1 H, s, ArH), 7.26 (5 H, s, Ph), and 10.46 (1 H, s, CHO).

6-*Benzyloxy*-4-*methoxy*-3-*methoxycarbonyl*-2-*pentylbenzoic Acid* (79).—Tetrabutylammonium permanganate [29] (8.3 g) in pyridine (100 ml) was added dropwise with stirring over 2 h to a solution of the aldehyde (78) (10.0 g) in pyridine (50 ml) under dry nitrogen. The mixture was stirred for 5 h and then poured into an excess of ice-cold dilute hydrochloric acid. The usual work-up gave a crude product which was filtered through a column of silica gel with 5—20% ethyl acetate–light petroleum as eluant. The *acid* (79) (7.5 g) formed plates (from dichloromethane–light petroleum), m.p. 88—89 °C (Found: C, 68.25; H, 6.65%; M^+, 386. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.8%; *M*, 386); δ($CDCl_3$, 90 MHz) 0.85 (3 H, deformed t, Me), 1.43br (6 H, 3 × CH_2), 2.63 (2 H, deformed t, CH_2), 3.71 and 3.86 (each 3 H, s, OMe), 5.12 (2 H, s, CH_2), 6.35 (1 H, s, ArH), 7.32 (5 H, m, Ph), and 10.48br (1 H, OH).

Methyl 3-(2,4-*Dihydroxy*-6-*pentylbenzoyl*)-4-*hydroxy*-6-*methoxy*-2-*pentylbenzoate* (81).—Trifluoroacetic anhydride (25 ml) in dry dichloromethane (50 ml) was added in a thin stream at 0 °C to a stirred solution of the acid (79) (5.0 g) in dry dichloromethane (100 ml). Di-*O*-benzylolivetol (18.5 g) in dry dichloromethane (100 ml) was then added dropwise at 0 °C over 15 min. The mixture was stirred at room temperature for 2 h and then worked up as usual. Chromatography gave the tri-*O*-benzylbenzophenone (80) which on hydrogenation gave the title *benzophenone* (81) (3.65 g) as aggregates of pale yellow prisms (from ether–light petroleum), m.p. 140—141 °C (Found: C, 68.1; H, 7.4. $C_{26}H_{34}O_7$ requires C, 68.1; H, 7.45%); δ($CDCl_3$, 90 MHz) 0.77 (6 H, deformed t, 2 × Me), 1.17br (12 H, 6 × CH_2), 2.19 (4 H, deformed t, 2 × CH_2), 3.82 and 3.86 (each 3 H, s, OMe), 6.20 and 6.29 (2 H, AB, *J* 2.5 Hz, ArH), 6.42 (1 H, s,

ArH), 6.48br (1 H, D_2O exchangeable OH), and 9.40br and 10.07br (each 1 H, D_2O exchangeable OH).

Oxidative Coupling of Methyl 3-(2,4-*Dihydroxy*-6-*pentylbenzoyl*)-4-*hydroxy*-6-*methoxy*-2-*pentylbenzoate* (81).—(*a*) Potassium hexacyanoferrate(III) (562 mg) in water (20 ml) was added in one portion to a stirred solution of the benzophenone (81) (228 mg) and potassium carbonate (1.32 g) in water (40 ml) and dioxan (20 ml). After 10 min the usual work-up gave *methyl* 2,3-*dihydro*-6-*hydroxy*-4′-*methoxy*-2′,3-*dioxo*-4,6′-*dipentylspiro*[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-5′-*carboxylate* (82) (197 mg) as very pale yellow needles (from ether–light petroleum), m.p. 128—130 °C (Found: C, 68.35; H, 7.15%; M^+, 456. $C_{26}H_{32}O_7$ requires C, 68.4; H, 7.05%; *M*, 456); δ($CDCl_3$, 90 MHz) 0.77 and 0.86 (each 3 H, deformed t, Me), 1.29br (12 H, 6 × CH_2), 1.94vbr (2 H, 6′-CH_2), 2.70 (2 H, deformed t, 4-CH_2), 3.86 and 3.89 (each 3 H, s, OMe), 5.53 (1 H, s, 3′-H), 6.29 and 6.44 (2 H, br AB, *J* 2.0 Hz, ArH), and 8.86vbr (1 H, D_2O exchangeable OH); $\lambda_{max.}$ 215, 288, and 315 nm (ε 37 200, 21 000, and 15 200) and $\lambda_{infl.}$ 375 nm (ε 1 500); $\nu_{max.}$ (CCl_4) 1 742 (C=O), 1 720 (C=O), 1 652 (C=O), and 1 624 (C=C) cm^{-1}.

(*b*) Repetition of experiment (*a*) with stirring for 2 h gave a mixture of the grisadienedione (82) and the depsidone (83) in the ratio 63 : 37 (n.m.r.).

Thermolysis of Methyl 2,3-*Dihydro*-6-*hydroxy*-4′-*methoxy*-2′,3-*dioxo*-4,6′-*dipentylspiro*[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-5′-*carboxylate* (82).—This grisadienedione (82) (660 mg) [phenetole (50 ml), 10 min] gave a crude product which was subjected to preparative t.l.c. (5—10% ethyl acetate–light petroleum) and furnished *methyl* 3-*hydroxy*-8-*methoxy*-1,6-*dipentyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (83) (511 mg) as a gum, homogeneous on t.l.c. (Found: M^+, 456.212 2. $^{12}C_{26}{}^1H_{32}{}^{16}O_7$ requires *M*, 456.214 8), δ($CDCl_3$, 90 MHz) 0.85 and 0.88 (each 3 H, deformed t, Me), 1.43br (12 H, 6 × CH_2), 2.69 and 2.76 (each 2 H, deformed t, CH_2), 3.74 and 3.90 (each 3 H, s, OMe), 6.58 (2 H, s, $W_{\frac{1}{2}}$ 3.1 Hz, 2,4-H), 6.63 (1 H, s, 9-H), and 7.29vbr (1 H, OH).

3,5-*Dibenzyloxybenzyl Chloride* (87).—3,5-Dibenzyloxybenzyl alcohol (86) [32] (50.0 g) and triphenylphosphine (42.0 g) were boiled under reflux in dry carbon tetrachloride (1 l) for 60 h. The reaction mixture was then filtered and the residue was washed with hot light petroleum. Removal of the solvent under reduced pressure gave the crude product which was chromatographed over silica gel with 2.5% ethyl acetate–light petroleum as eluant. The *benzyl chloride* (87) crystallized from ether–light petroleum as rods (46.4 g), m.p. 77—78 °C (Found: C, 74.45; H, 5.4; Cl, 10.25%; M^+, 338, 340. $C_{21}H_{19}ClO_2$ requires C, 74.4; H, 5.65; Cl, 10.5%; *M*, 338, 340); δ(CCl_4, 60 MHz) 4.37 (2 H, s, CH_2), 4.90 (4 H, s, CH_2), 6.53 (3 H, s, ArH), and 7.63 (10 H, s, Ph).

2-(3,5-*Dibenzyloxybenzyl*)-2-*pentyl*-1,3-*dithian* (88).—A solution of (2-pentyl-1,3-dithian-2-yl)lithium [34] [from 2-pentyl-1,3-dithian (20 g) and butyl-lithium (1.13M in pentane; 100 ml)] in anhydrous tetrahydrofuran (300 ml) was treated with 3,5-dibenzyloxybenzyl chloride (33.8 g) (87) in one portion at −78 °C under dry nitrogen. The resulting mixture was stirred at −78 °C for 2 h, at −50 °C for 0.5 h, and then left to stand at 0 °C for 16 h. Work-up in the usual way gave the crude product which was chromatographed over neutral alumina (activity III) with 0—5% chloroform–light petroleum as eluant to give the *dithian* (88) (20.4 g) as a colourless oil homogeneous on t.l.c. (Found: M^+, 492.214 8. $^{12}C_{30}{}^1H_{36}{}^{16}O_4{}^{32}S_2$ requires *M*, 492.215 7); δ($CDCl_3$, 90 MHz) 0.90 (3 H, deformed t, Me), 1.12—2.18 (10 H, m, 5 × CH_2), 2.80 (4 H, deformed t, SCH_2), 3.13 (2 H, s, $ArCH_2$), 5.00 (4 H, s, OCH_2), 6.55 (3 H, s, ArH), and 7.35 (10 H, m, Ph).

1-(3,5-*Dibenzyloxyphenyl*)*heptan*-2-*one* (89).—Copper(II) chloride dihydrate (2.5 g) and copper(II) oxide (2.5 g) were added in one portion to a stirred solution of the dithian (88) (5 g) in acetone–water (99 : 1 v/v; 250 ml). The mixture was heated under reflux for 1 h then filtered through Celite. The filtrate was diluted with ethyl acetate and worked up as usual to give the ketone (89) (4.1 g) as a viscous oil [31] homogeneous on t.l.c. (Found: M^+, 402.218 9. Calc. for $^{12}C_{27}{}^1H_{30}{}^{16}O_3$: *M*, 402.219 5); δ($CDCl_3$, 90 MHz) 0.87 (3 H, deformed t, Me), 1.09—1.81 (6 H, m, 3 × CH_2), 2.39 (2 H, t, *J* 7.2 Hz, $COCH_2$), 3.56 (2 H, s, $ArCH_2$), 4.99 (4 H, s, OCH_2), 6.40—6.60 (3 H, AX_2, J_{AX} 2.0 Hz, 3 × ArH), and 7.36 (10 H, m, Ph).

1-(3,5-*Dibenzyloxyphenyl*)*heptan*-2-*ol* (90).—A solution of the ketone (89) (5.25 g) in dry ether (50 ml) was added dropwise over 10 min to a rapidly stirred solution of lithium aluminium hydride (1.0 g) in dry ether (50 ml). The mixture was heated under reflux for 5 h and then quenched with saturated aqueous sodium sulphate. The usual work-up gave the pure (t.l.c.) alcohol (90) (5.2 g) as an oil [31] (Found: M^+, 404.234 8. Calc. for $^{12}C_{27}{}^1H_{32}{}^{16}O_3$: *M*, 404.235 1); δ($CDCl_3$, 90 MHz) 0.89 (3 H, deformed t, Me), 1.07—1.62 (8 H, m, 4 × CH_2), 1.75br (1 H, D_2O exchangeable OH), 2.39—2.83 (2 H, AB part of ABX, J_{AB} 13.5 Hz, $ArCH_2$), 3.73 (1 H, m, CH), 4.96 (4 H, s, OCH_2), 6.46 (3 H, s, ArH), and 7.33 (10 H, m, Ph).

1-(3,5-*Dibenzyloxytolyl*)*hexyl Acetate* (91).—The alcohol (90) was acetylated in the usual way (acetic anhydride–pyridine) to give the acetate (91) in quantitative yield as an oil,[31] homogeneous on t.l.c. (Found: M^+, 446.245 0. Calc. for $^{12}C_{29}{}^1H_{34}{}^{16}O_4$: *M*, 446.245 7); δ($CDCl_3$, 90 MHz) 0.87 (3 H, deformed t, Me), 1.03—1.73 (8 H, m, 4 × CH_2), 1.96 (3 H, s, COMe), 2.54—2.95 (2 H, AB part of ABX, J_{AB} 13.5 Hz, $ArCH_2$), 4.99 (4 H, s, OCH_2), 5.07 (1 H, m, CH), 6.46 (3 H, s, ArH), and 7.36 (10 H, m, Ph).

Methyl 3-[6-(2-*Acetoxyheptyl*)-2,4-*dihydroxybenzoyl*]-4-*hydroxy*-6-*methoxy*-2-*pentylbenzoate* (92).—Friedel–Crafts reaction between 1-(3,5-dibenzyloxytolyl)hexyl acetate (91) and 6-benzyloxy-3-methoxycarbonyl-4-methoxy-2-pentylbenzoic acid (79) for 100 h at room temperature gave, after chromatography over Sephadex LH-20 with methanol as eluant, methyl 3-[6-(2-acetoxyheptyl)-2,4-dibenzyloxybenzoyl]-4-benzyloxy-6-methoxy-2-pentylbenzoate (54%) as an oil; δ(CCl_4, 60 MHz), 0.58—1.80 (20 H, m, aliphatic H), 1.81 (3 H, s, COMe), 2.08—2.85 (4 H, m, $ArCH_2$), 3.58 and 3.70 (each 3 H, s, OMe), 4.56br (5 H, 2 × OCH_2 and CH), 4.89 (2 H, s, OCH_2), 5.97 (1 H, s, ArH), 6.19br (2 H, ArH), 6.56—7.39 (10 H, m, 2 × Ph), and 7.20 (5 H, s, Ph). Hydrogenolysis of the tribenzyloxy-compound above gave the *benzophenone* (92) as a yellow gum, homogeneous on t.l.c. (Found: M^+, 544.266 2. $^{12}C_{30}{}^1H_{40}{}^{16}O_9$ requires *M*, 544.267 2); δ($CDCl_3$, 80 MHz) 0.62—1.81 (20 H, m, aliphatic H), 1.92 (3 H, s, COMe), 2.01—2.81 (4 H, m, $ArCH_2$), 3.86 (6 H, s, OMe), 4.84 (1 H, m, CH), 6.26br (2 H, ArH), and 6.42 (1 H, s, ArH).

Methyl 1-(2-*Acetoxyheptyl*)-3-*hydroxy*-8-*methoxy*-6-*pentyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (93).—A solution of potassium hexacyanoferrate(III) (12 g) in water (300 ml) was added in one portion to a stirred solution of the benzophenone (92) (3 g) and potassium carbonate (21 g) in water (300 ml) and dioxan (300 ml). The solution was stirred for 10 min then acidified with dilute hydrochloric acid and worked up as usual. This gave the crude grisadienedione

which was heated under reflux in phenetole (130 ml) for 10 min. The solvent was removed by steam distillation and the crude product obtained was chromatographed over silica gel with 5—15% ethyl acetate–light petroleum as eluant to give the *depsidone* (93) (1.6 g) as an oil, homogeneous on t.l.c. (Found: M^+, 542.252 8. $^{12}C_{30}{}^{1}H_{38}{}^{16}O_9$ requires M, 542.251 6); δ(CCl_4, 60 MHz) 0.62—1.79 (20 H, m, aliphatic H), 1.85 (3 H, s, COMe), 2.32—3.34 (4 H, m, $ArCH_2$), 3.66 and 3.75 (each 3 H, s, OMe), 5.07 (1 H, m, CH), 6.32br (2 H, ArH), 6.44 (1 H, s, ArH), and 7.42br (1 H, OH).

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