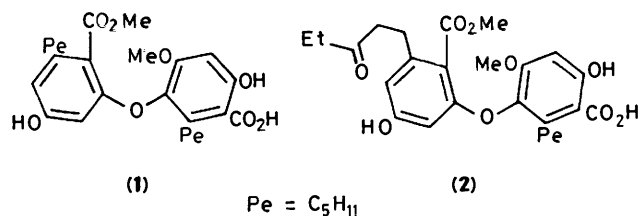


## Depsidone Synthesis. Part 24.<sup>1</sup> The Synthesis of Epiphorellic Acid 2. A Pseudo-depsidone and X-ray Crystal Structure of a Grisadienedione Epoxide

Mark F. Comber, Melvyn V. Sargent,\* Brian W. Skelton, and Allan H. White  
School of Chemistry, The University of Western Australia, Nedlands, Western Australia, 6009

The synthesis of the unusual pseudo-depsidone epiphorellic acid 2 (2) {6-hydroxy-3-[5-hydroxy-2-methoxycarbonyl-3-(3-oxopentylphenoxy)]-4-methoxy-2-pentylbenzoic acid} by a route involving grisadienedione-depsidone rearrangement and subsequent steps is described. The stereospecific epoxidation of grisadienediones, as proved by X-ray crystallography, is discussed.

The pseudo-depsidones are diaryl ethers and they constitute a small group of lichen metabolites which probably arise by catabolism of depsidones<sup>2</sup> or their biogenetic precursors.<sup>3</sup> Recently Garbarino and his co-workers have isolated two new pseudo-depsidones, epiphorellic acids 1 (1) and 2 (2), from the



lichen *Cornicularia epiphorella*.<sup>4</sup> The structure of epiphorellic acid 1 (1) was established by spectroscopic methods and by its relationship with a synthetic compound available from our own work on the synthesis of colensoic acid.<sup>5</sup> The structure of epiphorellic acid 2 (2) relied heavily on <sup>13</sup>C n.m.r. spectroscopy for the location of the ketonic group in the side chain which is present at a position which would not be predicted on the grounds of the acetate-polymalonate biogenetic pathway. Such a 3-oxopentyl side chain is unknown in depsidones and is rare in depsides where the only known examples are the *p*-depsides miriquidic and normiriquidic acids.<sup>6</sup> It was for this reason that we undertook the proof of the structure of epiphorellic acid 2 by unambiguous synthesis.

We adopted, for this purpose, a route based on grisadienedione-depsidone rearrangement which is of considerable generality.<sup>7</sup> In order to construct the requisite benzophenone (15) (see Scheme 1) for oxidative coupling to the grisadienedione (19) we required the ketone (11). This was readily prepared by standard chain extension reactions from the known benzyl alcohol (3),<sup>8</sup> which was first converted into the chloride (4)<sup>7</sup> and thence into the nitrile (5). Hydrolysis of the nitrile (5) supplied the acid (6)<sup>9</sup> and the derived methyl ester (7)<sup>10</sup> on reduction with lithium aluminium hydride, afforded the phenylethanol (8). The derived tosylate (9) then yielded the nitrile (10) which was allowed to undergo a Grignard reaction with ethylmagnesium bromide-diethyl ether in benzene<sup>11</sup> thereby supplying the required ketone (11) in high overall yield.

The benzoic acid (12), required for the Friedel-Crafts synthesis of the benzophenone (14) has been synthesized previously in connection with other work<sup>7</sup> but the method detailed in the Experimental section is more efficient. When the benzoic acid and the ketone were allowed to react at -10 °C in nitromethane in the presence of trifluoroacetic anhydride a high yield of the benzophenone (14) was obtained, which on hydrogenolysis supplied the trihydroxybenzophenone (15). This compound underwent smooth oxidative coupling in basic solution in presence of potassium hexacyanoferrate(III) and yielded the grisadienedione (19). It was evident from the <sup>1</sup>H

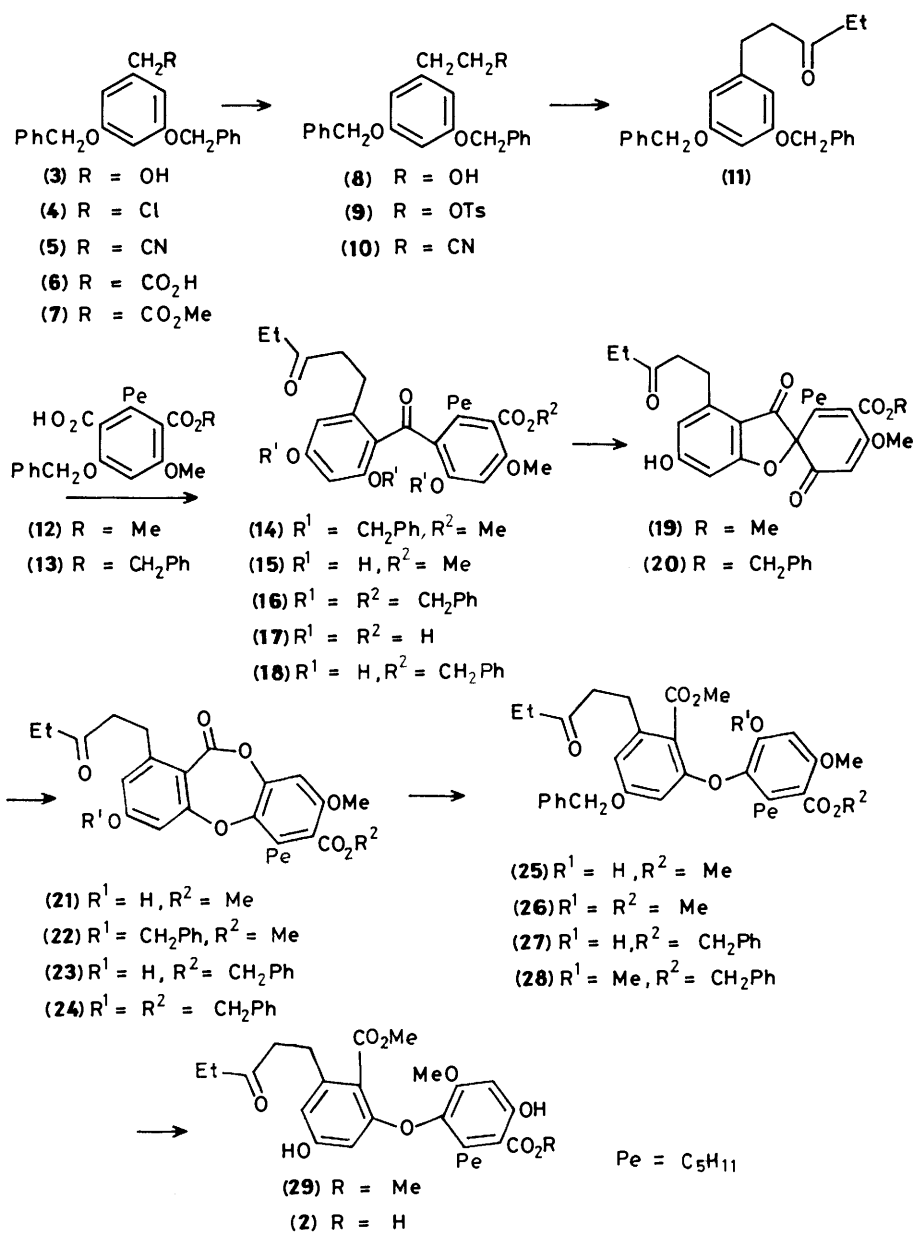
n.m.r. spectrum of the product which exhibited only one signal for an olefinic proton that oxidative coupling had proceeded in the desired direction. The grisadienedione (19) underwent smooth rearrangement to the depsidone (21) in boiling phenetole. Attempts were made to demethylate this compound by heating it at 90 °C with lithium iodide in hexamethylphosphoric triamide. Although the desired reaction occurred, it was attended by much decarboxylation so that the synthetic objective now became methyl epiphorellate 2 (29).

Consequently the depsidone (21) was converted into its benzyl ether (22). This compound, on methanolysis with an excess of sodium methoxide in methanol provided not the expected methyl ester (25) but the 2-acylindanone (30). When 1 mol equiv. of sodium methoxide was used this reaction took the expected course and the methyl ester (25) was obtained. Evidently the methyl ester (25), in presence of an excess of sodium methoxide, undergoes an intramolecular Claisen-type reaction yielding the 2-acylindanone (30). The structure of the latter compound followed readily from spectroscopic and microanalytical data and, in particular, the <sup>1</sup>H n.m.r. spectrum revealed that it was a mixture of keto and enol tautomers.

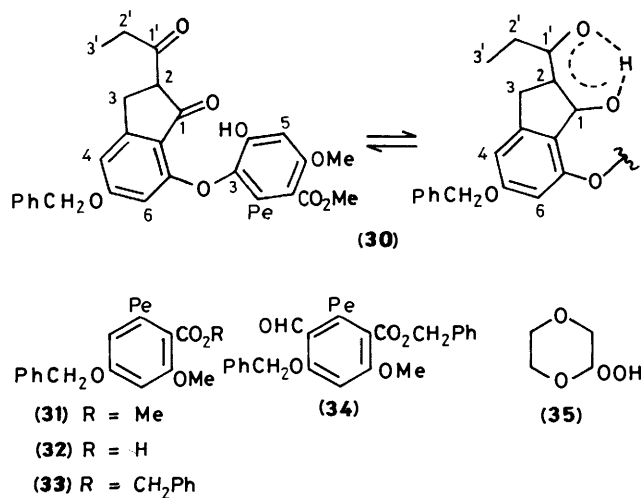
Methylation of the ester (25) gave the methyl ether (26) which on deprotection, first with boron trichloride and then by catalytic hydrogenolysis, yielded methyl epiphorellate 2 (29) the spectroscopic data of which were identical with those recorded in the literature.<sup>4</sup>

In order to synthesize epiphorellic acid 2 (2) it was, therefore, necessary to protect the carboxy group as a benzyl ester. Hydrolysis of the methyl ester (31) gave the benzoic acid (32) which was converted into its benzyl ester (33). This last-mentioned compound underwent Vilsmeier-Haack formylation, and oxidation of the resultant aldehyde (34) supplied the benzoic acid (13). Friedel-Crafts reaction then gave the benzophenone (16) which on catalytic hydrogenolysis gave the trihydroxybenzophenone carboxylic acid (17). Selective benzylation of this compound with benzyl bromide in *N,N*-dimethylformamide in the presence of potassium hydrogen carbonate gave the benzyl ester (18). The remaining steps in the sequence followed closely the ones previously used in the synthesis of methyl epiphorellate 2 (29) and involved the intermediates (20), (23), (24), (27), and (28). Deprotection of compound (28) gave synthetic epiphorellic acid 2 (2) which was identical with the natural product by all the usual criteria, thereby proving the structure of this metabolite.

The oxidation of the benzophenone (15) was carried out in aqueous solution with dioxane as co-solvent. It was found that if aged dioxane was used, which contained 0.42% of the hydroperoxide (35),<sup>12</sup> as established by iodometry, the reaction took an unexpected course. The product proved to be the epoxide (36). The spectroscopic properties of this compound were in accord with the assigned structure and in particular the <sup>13</sup>C n.m.r. spectrum revealed the presence of the epoxide carbon

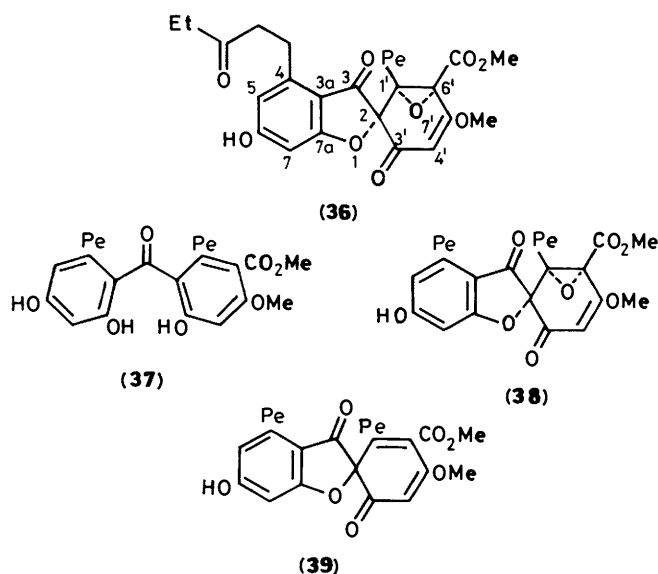


Scheme 1.



atoms at  $\delta$  62.99 and 64.16. On treatment with zinc dust in hot acetic acid it smoothly gave the benzophenone (15).  $\alpha,\beta$ -Epoxy ketones are known to yield alkenes under these conditions<sup>13</sup> and the allylic ether bond of grisadienediones is also susceptible to cleavage under the same conditions.<sup>14</sup> Treatment of the grisadienedione (19) with aqueous potassium carbonate containing aged dioxane also resulted in formation of the epoxide (36) so that Michael addition of hydroperoxide anion is implicated. Griseofulvin also undergoes epoxidation on treatment with alkaline hydrogen peroxide and the reaction is stereospecific.<sup>15</sup> In this case the epoxide ring has been tentatively assigned the  $\alpha$ -orientation, *i.e.*, *trans* to the  $\beta$ -coumaranone carbonyl group, so that epoxidation occurs on the least hindered face of the molecule. We have established a similar stereochemistry for the epoxide (36) by X-ray crystallography.

Treatment of the benzophenone (37) under similar conditions gave the epoxide (38) as expected. Again the grisadienedione (39) was shown to be an intermediate in this reaction.



### Experimental

General directions have been given before.<sup>16</sup> <sup>13</sup>C N.m.r. spectra were recorded at 75.5 MHz on a Bruker AM-300 instrument for solutions in deuteriochloroform, and assignments were assisted by the DEPT technique.

**3,5-Bis(benzyloxy)benzyl Chloride (4).**—A solution of freshly purified thionyl chloride (12.5 ml)<sup>17</sup> in anhydrous dichloromethane was added dropwise at 0 °C to a stirred solution of 3,5-bis(benzyloxy)benzyl alcohol (3) (50.0 g) in dichloromethane (500 ml) and pyridine (12.5 ml). The solution was stirred at room temperature for 3 h and then washed with water and with saturated brine. The crude product crystallized from ether–light petroleum as rods (50.4 g, 95%), m.p. 77–78 °C (lit.,<sup>7</sup> 77–78 °C).

**3,5-Bis(benzyloxy)phenylacetonitrile (5).**—The benzyl chloride (4) (50.4 g) and sodium cyanide (22.0 g) were stirred in *N,N*-dimethylformamide at room temperature for 7 h. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed several times with water and with saturated brine. The crude product crystallized from ether–light petroleum to give prisms (43.4 g, 88%) of the nitrile, m.p. 82–83 °C (Found: C, 80.0; H, 5.95; N, 4.25%;  $M^+$ , 329.  $C_{22}H_{19}NO_2$  requires C, 80.2; H, 5.8; N, 4.25%;  $M$ , 329);  $\delta_H$ (60 MHz,  $CDCl_4$ ) 3.45 (2 H, s,  $CH_2$ ), 4.91 (4 H, s, 2  $\times$   $CH_2Ph$ ), 6.47 (3 H, s, ArH), and 7.30 (10 H, s, Ph).

**3,5-Bis(benzyloxy)phenylacetic Acid (6).**—The foregoing nitrile (5) (43.4 g), methanol (500 ml), and aqueous sodium hydroxide (30%; 150 ml) were heated under reflux for 72 h. The solution was diluted with water, acidified with hydrochloric acid and the crude product isolated by extraction with ethyl acetate. The phenylacetic acid (6) crystallized from chloroform–light petroleum as needles (41.8 g, 91%), m.p. 111–112 °C (lit.,<sup>9</sup> 104–106 °C) (Found: C, 75.85; H, 5.8%;  $M^+$ , 348. Calc. for  $C_{22}H_{20}O_4$ : C, 75.65; H, 5.85%;  $M$ , 348);  $\delta_H$ (80 MHz) 3.57 (2 H, s,  $CH_2$ ), 5.01 (4 H, s,  $CH_2Ph$ ), 5.60 (1 H, br,  $D_2O$  exchangeable OH), 6.55 (3 H, s, ArH), and 7.35 (10 H, m, Ph);  $\nu_{max}$ (KBr) 3 440, 1 694, 1 598, and 1 160  $cm^{-1}$ .

**Methyl 3,5-Bis(benzyloxy)phenylacetate (7).**—Dimethyl sulphate (11.6 ml) was added dropwise with stirring to a solution of the foregoing acid (6) (40.0 g) in anhydrous acetone (400 ml) containing suspended potassium carbonate (16.8 g). After the addition, the mixture was stirred and heated under reflux for 3 h. Work-up gave the ester which crystallized from chloroform–

light petroleum as rods (39.5 g, 95%), m.p. 66–67 °C (lit.,<sup>10</sup> 62 °C) (Found: C, 76.2; H, 6.1%;  $M^+$ , 362. Calc. for  $C_{23}H_{22}O_4$ : C, 75.95; H, 6.25%;  $M$ , 362);  $\delta_H$ (80 MHz) 3.54 (2 H, s,  $CH_2$ ), 3.66 (3 H, s, OMe), 5.00 (4 H, s, 2  $\times$   $CH_2Ph$ ), 6.53 (3 H, s, ArH), and 7.36 (10 H, m, Ph);  $\nu_{max}$ (KBr) 1 727, 1 589, and 1 143  $cm^{-1}$ .

**2-[3,5-Bis(benzyloxy)phenyl]ethanol (8).**—A solution of the ester (7) (45.4 g) in anhydrous ether (250 ml) was added dropwise to a solution of lithium aluminium hydride (6.03 g) in anhydrous ether (600 ml). The solution was stirred and heated under reflux for 2 h, after which it was cooled to 0 °C and treated with saturated aqueous sodium sulphate until coagulation occurred. The salts were filtered off and work-up of the filtrate gave the alcohol (8) which crystallized from chloroform–light petroleum as needles (39.9 g, 95%), m.p. 83–84 °C (Found: C, 79.0; H, 6.65%;  $M^+$  334.  $C_{22}H_{22}O_3$  requires C, 78.6; H, 6.65%;  $M$ , 334);  $\delta_H$ (80 MHz) 1.33 (1 H, b,  $D_2O$  exchangeable OH), 2.79 (2 H, t,  $CH_2CH_2OH$ ), 3.83 (2 H, t,  $CH_2CH_2OH$ ), 5.02 (4 H, s, 2  $\times$   $CH_2Ph$ ), 6.49 (3 H, s, ArH), and 7.37 (10 H, s, Ph);  $\nu_{max}$ (KBr) 3 250, 1 592, 1 156, and 1 492  $cm^{-1}$ .

**2-[3,5-Bis(benzyloxy)phenyl]ethyl Toluene-*p*-sulphonate (9).**—Toluene-*p*-sulphonyl chloride (8.6 g) was added in portions at 0 °C to a stirred solution of the alcohol (8) (10.0 g) and pyridine (4.85 ml) in ethanol-free chloroform (30 ml). The solution was then stirred at 0 °C for 3 h and then ether (100 ml) was added. The solution was washed in turn with water, cold dilute hydrochloric acid, aqueous sodium hydrogen carbonate, water, and finally with saturated brine. The crude product was purified by chromatography over silica gel with 2–60% ether–light petroleum as eluant. The sulphonate (9) (12.5 g, 85%) crystallized from ether–light petroleum as prisms, m.p. 55–56 °C (Found: C, 71.3; H, 5.8; S, 6.55.  $C_{29}H_{28}O_5S$  requires C, 71.25; H, 5.85; S, 6.3%;  $\delta_H$ (80 MHz) 2.38 (3 H, s, Me), 2.88 (2 H, t,  $ArCH_2$ ), 4.22 (2 H, t,  $CH_2O$ ), 4.97 (4 H, s,  $CH_2Ph$ ), 6.33 (2 H, m, 2- and 6-H), 6.48 (1 H, m, 4-H), 7.30 and 7.69 (4 H, AA'BB', tosyl ArH), and 7.37 (10 H, m, Ph).

**3-[3,5-Bis(benzyloxyphenyl)]propionitrile (10).**—A solution of the sulphonate (9) (13.1 g) in dimethyl sulphoxide (DMSO) (30 ml) and 1,2-dimethoxyethane (5.5 ml) was stirred at room temperature with sodium cyanide (2.6 g) for 18 h. Work-up gave the nitrile (10) which crystallized from ether–pentane as needles (8.6 g, 94%), m.p. 55–56 °C (Found: C, 80.45; H, 6.15; N, 4.1%;  $M^+$ , 343.  $C_{23}H_{21}NO_2$  requires C, 80.55; H, 6.55; N, 4.05%;  $M$ , 343);  $\delta_H$ (80 MHz) 2.83 [4 H, m, ( $CH_2$ )<sub>2</sub>], 5.03 (4 H, s,  $CH_2Ph$ ), 6.48 (3 H, m, ArH), and 7.38 (10 H, m, Ph);  $\nu_{max}$ (KBr) 2 240, 1 592, 1 451, and 1 159  $cm^{-1}$ .

**5-[3,5-Bis(benzyloxyphenyl)]pentan-3-one (11).**—The Grignard reagent was prepared from bromoethane (9.8 ml) and magnesium turnings (3.2 g) in benzene (50.5 ml) and ether (15.6 g). This was added dropwise at 0 °C to a stirred solution of the foregoing nitrile (17.8 g) in benzene (25.0 ml). The mixture was stirred for 1 h at room temperature and then poured onto ice and ethyl acetate; an excess of hydrochloric acid (2M) was then added and the mixture stirred for 16 h. The crude product crystallized from light petroleum to give prisms of the ketone (11), (15.7 g, 81%), m.p. 73–74 °C (Found: C, 80.2; H, 7.0%;  $M^+$ , 374.  $C_{25}H_{26}O_3$  requires C, 80.45; H, 7.25%;  $M$ , 374);  $\delta_H$ (80 MHz) 1.05 (3 H, t,  $COCH_2CH_3$ ), 2.39 (2 H, q,  $COCH_2Me$ ), 2.76 (4 H, m,  $CH_2CH_2CO$ ), 5.02 (4 H, s,  $CH_2Ph$ ), 6.46 (3 H, s, ArH), and 7.39 (10 H, br, Ph);  $\nu_{max}$ (film) 1 709, 1 590, and 1 157  $cm^{-1}$ .

**Methyl 4-Benzyloxy-6-hydroxy-2-pentylbenzoate (with Lynette J. Cullen).**—Methyl 2,6-dihydroxy-6-pentylbenzoate (30.0 g),<sup>5</sup> anhydrous potassium carbonate (17.9 g), benzyl bromide (15.0 ml), and acetone (250 ml) were stirred and heated

under reflux for 24 h. The reaction mixture was cooled and poured into ice-cold dilute hydrochloric acid. The crude product, isolated by extraction with ethyl acetate, was chromatographed over a column of silica gel with 2.5% ethyl acetate–light petroleum as eluant. The *benzyl ether* (31.9 g, 77%) crystallized from dichloromethane–light petroleum as prisms, m.p. 44–46 °C (Found: C, 72.85; H, 7.2%;  $M^+$ , 328.  $C_{20}H_{24}O_4$  requires C, 73.15; H, 7.35%;  $M$ , 328);  $\delta_H$ (80 MHz) 0.89 (3 H, t, Me), 0.97–1.77 (6 H, m, 3  $\times$   $CH_2$ ), 2.85 (2 H, t,  $CH_2Ar$ ), 3.91 (3 H, s, OMe), 5.04 (2 H, s,  $CH_2Ph$ ), 6.34 (2 H, br s, 3- and 5-H), 7.38 (5 H, s, Ph), and 11.72 (1 H, s,  $D_2O$  exchangeable OH).

*Methyl 4-Benzyloxy-6-methoxy-2-pentylbenzoate* (**31**) (with *Lynette J. Cullen*).—The foregoing benzyl ether (31.9 g) was methylated with dimethyl sulphate and potassium carbonate in boiling acetone in the usual way. The *ester* (**31**) (29.7 g, 89%) was obtained as an oil (Found:  $M^+$ , 342.183.  $^{12}C_{21}^{1}H_{26}^{16}O_4$  requires  $M$ , 342.193);  $\delta_H$ (80 MHz) 0.87 (3 H, t,  $CH_2CH_3$ ), 1.00–1.81 (6 H, m, 3  $\times$   $CH_2$ ), 2.54 (2 H, t,  $CH_2Ar$ ), 3.76 and 3.86 (each 3 H, s, OMe), 5.05 (2 H, s,  $CH_2Ph$ ), 6.39 (2 H, br s, 3- and 5-H), and 7.34 (5 H, m, Ph).

*Methyl 4-Benzyloxy-3-formyl-6-methoxy-2-pentylbenzoate* (with *Lynette J. Cullen*).—Phosphoryl chloride (31.5 ml) was added dropwise to a stirred solution of the foregoing ester (22.0 g) in anhydrous *N,N*-dimethylformamide (100 ml) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h and then at 70 °C (bath) for 24 h. The cooled solution was poured into an excess of aqueous sodium acetate. The aldehyde, isolated by extraction with ethyl acetate, was crystallized from dichloromethane–light petroleum to yield prisms (19.1 g, 80%), m.p. 82–83 °C (lit.,<sup>7</sup> 83–84 °C) identical with an authentic sample.

*6-Benzyloxy-4-methoxy-3-methoxycarbonyl-2-pentylbenzoic Acid* (**12**) (with *Lynette J. Cullen*).—Sodium chlorite (80% technical; 3.6 g) in water (45 ml) was added dropwise over 15 min to a stirred solution of the foregoing aldehyde (9.0 g) and sulphamic acid (12.6 g) in water (45 ml) and dioxane (90 ml). The solution was stirred for a further 25 min and then poured into water. The crude product was isolated by extraction with ethyl acetate and crystallized from ether–light petroleum whereupon the acid (**12**) (9.1 g, 97%) was obtained as plates, m.p. 88.5–89.5 °C (lit.,<sup>7</sup> 88–89 °C) identical with an authentic sample.

*Methyl 3-[4',6'-Dihydroxy-2'-(3-oxopentyl)benzoyl]-4-hydroxy-6-methoxy-2-pentylbenzoate* (**15**).—Trifluoroacetic anhydride (5.1 ml) was added dropwise to a solution of the benzoic acid (**12**) (5.62 g) in nitromethane (50 ml) at –10 °C and then a solution of the ketone (**11**) (5.44 g) in nitromethane (15 ml) was added in a similar fashion at –10 °C. The solution was stirred at 0 °C for 1.5 h and then diluted with ethyl acetate. The solution was washed in turn with water, aqueous sodium hydrogen carbonate, water, and finally with saturated brine. Removal of the solvent left the benzophenone (**14**) (10.6 g, 98%) as a thick oil. The benzophenone (**14**) (10.6 g) and palladized charcoal (10%, 2.5 g) were stirred under an atmosphere of hydrogen in ethyl acetate (250 ml) containing concentrated hydrochloric acid (4 drops) until absorption ceased. Work-up gave the *benzophenone* (**15**) which crystallized from chloroform–light petroleum as cream prisms (5.4 g, 81%), m.p. 171–172 °C (Found: C, 66.1; H, 6.85%;  $M^+$ , 472.  $C_{26}H_{32}O_8$  requires C, 66.3; H, 7.0%;  $M$ , 472);  $\delta_H$ (80 MHz) 0.76 (3 H, t, Me), 0.95 (3 H, t,  $CH_3CH_2CO$ ), 1.04 (6 H, m, 3  $\times$   $CH_2$ ), 2.27 (2 H, q,  $CH_3CH_2CO$ ), 2.46 (6 H, br, 3  $\times$   $CH_2$ ), 3.82 and 3.85 (each 3 H, s, OMe), 6.22 and 6.33 (2 H, AB,  $J_{3,5}$ , 2.3 Hz, 3'- and 5'-H), 6.41 (1 H, s, 5-H), and 9.50 and 10.10 (each 1 H, br, OH).

*Methyl 2,3-Dihydro-6-hydroxy-4'-methoxy-4-(3-oxopentyl)-2',3-dioxo-6'-pentylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-5'-carboxylate* (**19**).—A solution of potassium hexacyanoferrate(III) (4.17 g) in water (150 ml) was added in one portion to a stirred solution of the benzophenone (**15**) (1.8 g) and potassium carbonate (10.0 g) in water (300 ml) and dioxane (150 ml, freshly distilled from sodium borohydride). The solution was stirred for 10 min and then acidified with dilute hydrochloric acid. The crude product was isolated by extraction with ethyl acetate and purified by radial chromatography with 50% ethyl acetate–light petroleum as eluant. The *grisadienedione* (**19**) (1.31 g, 73%) crystallized from ether–light petroleum as needles, m.p. 127–128 °C (Found: C, 66.15; H, 6.6%;  $M^+$ , 470.  $C_{26}H_{30}O_8$  requires C, 66.35; H, 6.45%;  $M$ , 470);  $\delta_H$ (300 MHz) 0.78 (3 H, t,  $CH_3$ ), 1.02 (3 H, t,  $CH_3CH_2CO$ ), 1.17 (4 H, m, 2  $\times$   $CH_2$ ), 1.78 (4 H, m, 2  $\times$   $CH_2$ ), 2.42 (2 H, q,  $CH_3CH_2CO$ ), 2.65 (2 H, t,  $C_4H_9CH_2$ ), 3.00 (2 H, t,  $COCH_2CH_2$ ), 3.87 and 3.90 (each 3 H, s, OMe), 5.52 (1 H, s, 3'-H), 6.37 and 6.51 (2 H, AB,  $J_{5,7}$ , 1.8 Hz, 5- and 7-H), and 8.78 (1 H, s,  $D_2O$  exchangeable OH);  $\delta_C^*$  7.72 (C- $\epsilon$ ), 13.72 (C- $\epsilon'$ ), 22.00 (C- $\delta'$ ), 26.34 (C- $\alpha$ ), 28.55 (C- $\beta'$ ), 30.25 (C- $\alpha'$ ), 31.71 (C- $\gamma'$ ), 35.86 (C- $\delta$ ), 41.95 (C- $\beta$ ), 52.63 ( $CO_2Me$ ), 57.19 (4'-OMe), 97.21 (C-3'), 97.66 (C-7), 97.74 (spiro C), 107.60 (C-3a), 113.79 (C-5), 127.94 (C-5'), 145.86 (C-4), 150.48 (C-4'), 165.21 (C-6), 166.68 (C-7a), 171.48 (C-8'), 176.50 ( $CO_2Me$ ), 188.60 (CO-2'), 191.11 (CO-3), and 210.88 (CO- $\gamma'$ );  $\nu_{max}$  (KBr) 3 265, 1 736, 1 711, 1 675, 1 610, 1 570, 1 265, 1 155  $cm^{-1}$ ;  $\lambda_{max}$ , 287 and 328 nm (log  $\epsilon$  4.18 and 4.21).

*Methyl 3-Hydroxy-8-methoxy-6-pentyl-1-(3-oxopentyl)-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-7-carboxylate* (**21**).—A solution of the grisadienedione (**19**) (1.0 g) in phenetole (100 ml) was heated under reflux for 10 min. The phenetole was removed by steam distillation and the residue was chromatographed over silica gel with 20% ethyl acetate–light petroleum as eluant. The *depsidone* (**21**) (700 mg, 70%) crystallized from ether–light petroleum as prisms, m.p. 153–154 °C (Found: C, 66.6; H, 6.6.  $C_{26}H_{30}O_8$  requires C, 66.35; H, 6.45%;  $\delta_H$ (300 MHz) 0.89 (3 H, t,  $CH_3$ ), 1.04 (3 H, t,  $CH_3CH_2CO$ ), 1.36 (4 H, m, 2  $\times$   $CH_2$ ), 1.59 (2 H, m,  $CH_2$ ), 2.46 (2 H, q,  $CH_3CH_2CO$ ), 2.70 (2 H, m,  $CH_2$ ), 2.84 and 2.98 (each 2 H, t,  $CH_2$ ), 3.76 and 3.90 (each 3 H, s, OMe), 6.60 and 6.63 (2 H, AB,  $J_{2,4}$ , 2.4 Hz, 2- and 4-H), 6.66 (1 H, s, 9-H), and 7.92 (1 H, s, OH);  $\nu_{max}$  (KBr) 3 140, 1 732, and 1 605  $cm^{-1}$ ;  $\lambda_{max}$ , 268 and 316 nm (log 4.09 and 3.39);  $m/z$  470 ( $M^+$ , 100%), 439 (34), 413 (30), 381 (75), 325 (43), and 221 (17).

*Methyl 3-Benzyloxy-8-methoxy-6-pentyl-1-(3-oxopentyl)-11-oxo-11H-dibenzo[b,e][1,4]dioxepine-7-carboxylate* (**22**).—The *depsidone* (**21**) (700 mg) was benzylated with benzyl bromide and potassium carbonate in *N,N*-dimethylformamide at room temperature. Work-up gave the crude product which was purified by radial chromatography with 30% ethyl acetate–light petroleum as eluant. The *depsidone* (**22**) (780 mg, 94%) crystallized from dichloromethane–light petroleum as prisms, m.p. 107–108 °C (Found: C, 70.4; H, 6.7%;  $M^+$ , 560.  $C_{33}H_{36}O_8$  requires C, 70.7; H, 6.45%;  $M$ , 560);  $\delta_H$ (300 MHz) 0.92 (3 H, t, Me), 1.04 (3 H, t,  $CH_3CH_2CO$ ), 1.39 (4 H, m, 2  $\times$   $CH_2$ ), 1.64 (2 H, m,  $CH_2$ ), 2.42 (2 H, q,  $CH_3CH_2CO$ ), 2.65 (2 H, m,  $CH_2$ ), 2.80 and 3.00 (each 2 H, t,  $CH_2$ ), 3.77 and 3.89 (each 3 H, s, OMe), 5.07 (2 H, s,  $CH_2Ph$ ), 6.64 and 6.75 (2 H, AB,  $J_{3,5}$ , 2.4 Hz, 3- and 5-H), 6.67 (1 H, s, 9-H), and 7.39 (5 H, s, Ph);  $\nu_{max}$  (KBr) 1 725, 1 705, 1 605, 1 560, 1 260, and 1 140  $cm^{-1}$ .

*Methyl 3-[5-Benzyloxy-2-methoxycarbonyl-3-(3-oxopentyl)phenoxy]-4-hydroxy-6-methoxy-2-pentylbenzoate* (**25**).—

\* The benzylic carbon atom of the oxopentyl chain is designated C- $\alpha$ , and that of the pentyl chain is designated C- $\alpha'$ .

Sodium methoxide [from sodium (44 mg) and anhydrous methanol (10 ml)] was added dropwise to a stirred solution of the depsidone (**22**) (900 mg) in anhydrous methanol (200 ml) under dry nitrogen. The solution was stirred at room temperature for 3 h and then a slight excess of dilute hydrochloric acid was added and the bulk of the methanol was removed by evaporation under diminished pressure. The crude product was isolated by extraction with ethyl acetate and purified by radial chromatography with 20% ethyl acetate–light petroleum as eluant to give the *diaryl ether* (**25**) (600 mg, 66%), as a thick oil (Found: C, 69.05; H, 7.1%.  $C_{34}H_{40}O_9$  requires C, 68.9; H, 6.8%);  $\delta_H$ (300 MHz) 0.83 (3 H, t, Me), 1.07 (3 H, t,  $CH_3CH_2CO$ ), 1.22 (4 H, m,  $2 \times CH_2$ ), 1.47 (2 H, br,  $CH_2$ ), 2.42 (2 H, q,  $CH_3CH_2CO$ ), 2.47 (2 H, m,  $CH_2$ ), 2.75 (4 H, m,  $2 \times CH_2$ ), 3.70, 3.90, and 3.97 (each 3 H, s, OMe), 4.92 (2 H, s,  $CH_2Ph$ ), 6.14 and 6.53 (2 H, AB,  $J_{4,6}$  2.3 Hz, 4- and 6-H), 6.44 (1 H, s, 5-H), 7.33 (5 H, m, Ph), and 7.95 (1 H, br s, OH);  $\nu_{max}$ (film) 3 320, 1 715, 1 600, 1 430, and 1 260  $cm^{-1}$ .

*Methyl 3-[5-Benzoyloxy-2,3-dihydro-1-oxo-2-(1'-oxopropyl)-inden-7-yloxy]-4-hydroxy-6-methoxy-2-pentylbenzoate (30)*.—Sodium methoxide [from sodium (1.2 g) and anhydrous methanol (50 ml)] was added dropwise to a stirred solution of the depsidone (**22**) (705 mg) in anhydrous methanol (50 ml) and the solution was stirred at room temperature for 30 min. A slight excess of dilute hydrochloric acid was added and the bulk of the methanol was removed by evaporation under reduced pressure. The crude product was isolated by extraction with ethyl acetate and purified by radial chromatography with 30% ethyl acetate–light petroleum as eluant. The *indanone* (**30**) formed prisms (362 mg, 49%) from dichloromethane–light petroleum, m.p. 121–122 °C (Found: C, 70.5; H, 6.7%;  $M^+$ , 560.  $C_{33}H_{36}O_8$  requires C, 70.7; H, 6.45%;  $M$ , 560);  $\delta_H$ (300 MHz) 60% keto: 40% enol; assignments by spin decoupling; keto tautomer: 0.77 (3 H, m, penty-Me), 1.07 (3 H, t,  $J_{3,2}$  7.0 Hz, 3'-Me), 1.14 (4 H, m,  $2 \times$  penty  $CH_2$ ), 1.42 and 2.39 (each 2 H, m, penty  $CH_2$ ), 2.67 (1 H, dq,  $J_{2,2'}$  19.0 Hz,  $J_{2,3}$  7.0 Hz, 2'-H), 3.17 (1 H, dd,  $J_{3,3}$  16.0,  $J_{3,2}$  7.0 Hz, 3-H), 3.53 (1 H, dq,  $J_{2,2'}$  19.0 Hz,  $J_{2,3}$  7.0 Hz, 2'-H), 3.63 (1 H, dd,  $J_{3,3}$  16.0 Hz,  $J_{3,2}$  4.0 Hz, 3-H), 3.79 and 3.87 (each 3 H, s, OMe), 3.88 (1 H, dd,  $J_{2,3}$  7.0 Hz,  $J_{2,3}$  4.0 Hz, 2-H), 5.01 (2 H, s,  $CH_2Ph$ ), 6.08 (1 H, d,  $J_{6,4}$  1.8 Hz, 6-H), 6.44 (1 H, s, 5-H), 6.67 (1 H, m, 4-H), 7.35 (5 H, m, Ph), and 7.63 (1 H, br, OH); in addition there were signals for the enol tautomer:  $\delta_H$  1.24 (3 H, t,  $J$  7.0 Hz, 3'-Me), 2.36 (2 H, q,  $J$  7.0 Hz, 2'- $CH_2$ ), 3.50 (2 H, s, 3- $CH_2$ ), 4.99 (2 H, s,  $CH_2Ph$ ), 6.16 (1 H, d,  $J_{6,4}$  1.8 Hz, 6-H), 6.67 (1 H, m, 4-H), and 13.50 (1 H, br s, OH);  $\nu_{max}$ (KBr) 1 725, 1 650, 1 600, and 1 460  $cm^{-1}$ ;  $\lambda_{max}$ (MeOH) 279 and 332 nm (log  $\epsilon$  4.15 and 4.14).

*Methyl 3-[5-Benzoyloxy-2-methoxycarbonyl-3-(3-oxopentyl)-phenoxy]-4,6-dimethoxy-2-pentylbenzoate (26)*.—A solution of the diaryl ether (**25**) (600 mg) and iodomethane (0.1 ml) in anhydrous *N,N*-dimethylformamide (30 ml) was stirred at room temperature with potassium carbonate (150 mg) for 5 h. The crude product was purified by radial chromatography with 10% ethyl acetate–light petroleum as eluant to give the *diaryl ether* (**26**) (505 mg, 82%) as a thick oil (Found: C, 69.45; H, 6.7%;  $M^+$ , 606.  $C_{35}H_{42}O_9$  requires C, 69.3; H, 6.7%;  $M$ , 606);  $\delta_H$ (300 MHz) 0.81 (3 H, t, Me), 1.06 (3 H, t,  $CH_3CH_2CO$ ), 1.23 (4 H, m,  $2 \times CH_2$ ), 1.43 (2 H, m,  $CH_2$ ), 2.44 (4 H, m,  $2 \times CH_2$ ), 2.78 and 2.87 (each 2 H, t,  $CH_2$ ), 3.71, 3.88, 3.881, and 3.886 (each 3 H, s, OMe), 4.90 (2 H, s,  $CH_2Ph$ ), 5.91 and 6.45 (2 H, AB,  $J_{4,6}$  2.3 Hz, 6- and 4-H), 6.39 (1 H, s, 5-H), and 7.30–7.35 (5 H, m, Ph);  $\nu_{max}$ (film) 1 710, 1 595, 1 425, and 1 260  $cm^{-1}$ .

*Methyl 6-Hydroxy-3-[5-hydroxy-2-methoxycarbonyl-3-(3-oxopentyl)phenoxy]-4-methoxy-2-pentylbenzoate (Methyl Epiphorellate 2) (29)*.—A solution of boron trichloride (630 mg)

in dichloromethane (5 ml) was added dropwise at  $-10^\circ C$  to a stirred solution of the diaryl ether (**26**) (162 mg) in dichloromethane (10 ml) and the solution was stirred at  $-10^\circ C$  for 0.5 h. Work-up gave a crude product which was dissolved in ethyl acetate (10 ml) containing concentrated hydrochloric acid (1 drop) and stirred under hydrogen with palladized charcoal (10%; 20 mg) until absorption ceased. Work-up gave the *epiphorellate* (**29**) which crystallized from chloroform–light petroleum as prisms (120 mg, 88%), m.p. 109–110 °C (lit.,<sup>4</sup> 108–109 °C) (Found: C, 64.45; H, 6.7.  $C_{27}H_{34}O_9$  requires C, 64.55; H, 6.8%);  $\delta_H$ (300 MHz) 0.84 (3 H, t, Me), 1.04 (3 H, t,  $CH_3CH_2CO$ ), 1.27 (6 H, m,  $3 \times CH_2$ ), 2.42 (2 H, q,  $CH_3CH_2CO$ ), 2.77 (6 H, m,  $3 \times CH_2$ ), 3.72, 3.89, and 3.93 (each 3 H, s, OMe), 5.78 and 6.27 (2 H, AB,  $J_{4,6}$  2.2 Hz, 6- and 4-H), 6.05 (1 H, s, 5-OH), 6.42 (1 H, s, 5-H), and 11.71 (1 H, s, 6-OH);  $\delta_C$  7.74 (C- $\epsilon$ ), 14.07 (C- $\epsilon'$ ), 22.42 (C- $\delta'$ ), 27.97 (C- $\alpha$ ), 28.44 (C- $\beta'$ ), 30.44 (C- $\alpha'$ ), 32.19 (C- $\gamma'$ ), 36.07 (C- $\delta$ ), 43.67 (C- $\beta$ ), 52.11 (2- $CCO_2Me$ ), 52.16 (1- $CCO_2Me$ ), 55.90 (4-OMe), 98.88 (5-CH), 98.89 (6-CH), 104.39 (1- $CCO_2Me$ ), 109.41 (4-CH), 115.13 (2- $CCO_2Me$ ), 133.95 (2-C $CH_2$ ), 139.87 (3-CO), 142.06 (3-C- $CH_2$ ), 157.69 (5-C-OH), 157.79 (4-COMe), 157.84 (6-COH), 162.57 (1-CO), 168.45 (2- $CO_2Me$ ), 171.63 (1- $CO_2Me$ ), and 211.30 ( $\gamma$ -CO);  $\nu_{max}$ (KBr) 3 440, 3 220, 2 860, 1 730, 1 685, 1 660, 1 610, 1 440, 1 380, 1 325, 1 270, 1 240, 1 210, 1 150, 1 090, 1 050, 950, and 840  $cm^{-1}$ ;  $\lambda_{max}$  257, 286, and 309 nm (log  $\epsilon$  4.50, 4.03, 3.48, and 3.48);  $m/z$  502 ( $M^+$ , 78%); 470 (49), and 395 (58).

*4-Benzyl-6-methoxy-2-pentylbenzoic Acid (32)*.—A solution of the ester (**31**) (15.0 g) and potassium hydroxide (25.5 g) in dimethyl sulphoxide (300 ml) and water (40 ml) was stirred at 100 °C (bath) for 16 h. The solution was cooled and diluted with water and acidified with dilute hydrochloric acid. The crude product was isolated by extraction with ethyl acetate and then crystallized from dichloromethane–light petroleum to afford prisms (11.5 g, 80%) of the *acid* (**32**), m.p. 66–67 °C (Found: C, 73.3; H, 7.6%;  $M^+$ , 328.  $C_{20}H_{24}O_4$  requires C, 73.15; H, 7.35%;  $M$ , 328);  $\delta_H$ (80 MHz) 0.88 (3 H, t,  $CH_2CH_3$ ), 1.30 (6 H, m,  $3 \times CH_2$ ), 2.79 (2 H, t,  $CH_2Ar$ ), 3.84 (3 H, s, OMe), 5.08 (2 H, s,  $CH_2Ph$ ), 6.43 and 6.48 (2 H, AB,  $J_{3,5}$  2.2 Hz, 3- and 5-H), and 7.39 (5 H, s, Ph) and 9.50 (1 H, br, OH);  $\nu_{max}$ (KBr) 3 160, 1 680, 1 595, 1 440, 1 320, and 1 155  $cm^{-1}$ .

*Benzyl 4-Benzoyloxy-6-methoxy-2-pentylbenzoate (33)*.—Benzoylation of the acid (**32**) (11.4 g) with benzyl bromide and potassium carbonate in boiling acetone gave the *ester* (**33**) (12.0 g, 83%) as an oil (Found: C, 77.65; H, 7.25%;  $M^+$ , 418.  $C_{27}H_{30}O_4$  requires C, 77.5; H, 7.2%;  $M$ , 418);  $\delta_H$ (80 MHz) 0.83 (3 H, t,  $CH_2CH_3$ ), 1.23 (6 H, m,  $3 \times CH_2$ ), 2.49 (2 H, t,  $CH_2Ar$ ), 3.73 (3 H, s, OMe), 5.03 (2 H, s,  $OCH_2Ph$ ), 5.32 (2 H, s,  $CO_2CH_2Ph$ ), 6.38 (2 H, s, ArH), and 7.36 (10 H, br,  $2 \times Ph$ );  $\nu_{max}$ (film) 1 720, 1 600, 1 580, 1 450, 1 150, and 1 090  $cm^{-1}$ .

*Benzyl 4-Benzoyloxy-3-formyl-6-methoxy-2-pentylbenzoate (34)*.—Formylation of the benzyl ester (**33**) (16.0 g) with phosphoryl chloride (18.7 ml) and *N,N*-dimethylformamide by a method similar to that described previously gave the *aldehyde* (**34**) (17.1 g, 100%) as a gum pure enough for the next step. A sample crystallized from dichloromethane–light petroleum as clusters of prisms, m.p. 83–84 °C (Found: C, 75.45; H, 6.85%;  $M^+$ , 355.  $C_{28}H_{30}O_5$  requires C, 75.3; H, 6.8%;  $M$ , 355);  $\delta_H$ (80 MHz) 0.84 (3 H, t,  $CH_2CH_3$ ), 1.30 (6 H, m,  $3 \times CH_2$ ), 2.83 (2 H, t,  $CH_2Ar$ ), 3.78 (3 H, s, OMe), 5.16 (2 H, s,  $OCH_2Ph$ ), 5.33 (3 H, s,  $CO_2CH_2Ph$ ), 6.39 (1 H, s, ArH), 7.37 (10 H, m,  $2 \times Ph$ ), and 10.54 (1 H, s, CHO);  $\nu_{max}$ (KBr) 1 715, 1 670, 1 575, 1 255, and 1 150  $cm^{-1}$ .

**6-Benzyloxy-3-benzyloxycarbonyl-4-methoxy-2-pentylbenzoic Acid (13).**—The aldehyde (34) was oxidized in a similar manner to that described for the preparation of compound (11). The acid (13) (84%) crystallized from dichloromethane–light petroleum as needles, m.p. 118–119 °C (Found: C, 73.0; H, 6.65.  $C_{28}H_{30}O_6$  requires C, 72.7; H, 6.55%);  $\delta_H$  (80 MHz) 0.80 (3 H, t, Me), 1.20 (6 H, m, 3  $\times$  CH<sub>2</sub>), 2.62 (2 H, t, CH<sub>2</sub>Ar), 3.74 (3 H, s, OMe), 5.16 (2 H, s, OCH<sub>2</sub>Ph), 5.33 (2 H, s, CO<sub>2</sub>CH<sub>2</sub>Ph), 6.37 (1 H, s, ArH), 7.36 (10 H, m, 2  $\times$  Ph), and 8.05 (1 H, br s, OH);  $\nu_{max}$  (KBr) 1724, 1690, 1590, 1195, and 1070 cm<sup>-1</sup>;  $\lambda_{max}$  (MeOH) 286 nm (log  $\epsilon$  3.57).

**3-[4',6'-Dihydroxy-2'-(3-oxopentyl)benzoyl]-4-hydroxy-6-methoxy-2-pentylbenzoic Acid (17).**—This compound was prepared in 96% overall yield in a similar manner to the ester (15) from the ketone (11) and the benzoic acid (13). It formed hygroscopic needles from chloroform–light petroleum, m.p. 150–158 °C (Found: C, 65.55; H, 6.95.  $C_{25}H_{30}O_8$  requires C, 65.5; H, 6.6%);  $\delta_H$  (300 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 0.80 (3 H, t, Me), 0.91 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.11 (4 H, m, 2  $\times$  CH<sub>2</sub>), 1.45 (2 H, m, CH<sub>2</sub>), 2.32 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 2.60 (6 H, m, 3  $\times$  CH<sub>2</sub>), 3.81 (3 H, s, OMe), 6.30 (2 H, br s, 3'- and 5'-H), 6.50 (1 H, s, 5-H), 10.00 (3 H, br, 3  $\times$  OH), and 12.00 (1 H, br, OH);  $\nu_{max}$  (KBr) 1710, 1590, 1450, 1310, and 830 cm<sup>-1</sup>.

**Benzyl 3-[4',6'-Dihydroxy-2'-(3-oxopentyl)benzoyl]-4-hydroxy-6-methoxy-2-pentylbenzoate (18).**—A solution of the foregoing acid (17) (1.60 g) and benzyl bromide (600 mg) were stirred with potassium hydrogen carbonate (350 mg) in anhydrous *N,N*-dimethylformamide at room temperature for 14 h. The solution was poured into water and the crude product isolated by extraction with ethyl acetate and then purified by radial chromatography with 60% ethyl acetate–light petroleum as eluant. The ester (18) (1.0 g, 53%) was obtained as prisms, m.p. 114–116 °C (Found: C, 69.75; H, 6.7.  $C_{32}H_{36}O_8$  requires C, 70.05; H, 6.6%)  $\delta_H$  (300 MHz) 0.72 (3 H, t, Me), 0.80 (2 H, q, CH<sub>2</sub>), 0.91 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.01 (2 H, q, CH<sub>2</sub>), 1.17 and 2.17 (each 2 H, m, CH<sub>2</sub>), 2.21 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 2.47 (4 H, m, 2  $\times$  CH<sub>2</sub>), 3.79 (3 H, s, OMe), 5.30 (2 H, AB, *J* 12.0 Hz, CH<sub>2</sub>Ph), 6.23 and 6.33 (2 H, AB, *J*<sub>3',5'</sub> 2.4 Hz, 3'- and 5'-H), 6.40 (1 H, s, 5-H), 7.30–7.42 (5 H, m, Ph), 8.32 (1 H, br s, 4'-OH), 9.50 and 10.48 (each 1 H, s, 4- and 6'-OH);  $\nu_{max}$  (KBr) 1745, 1640, 1495, and 1280 cm<sup>-1</sup>.

**Benzyl 2,3-Dihydro-6-hydroxy-4'-methoxy-2',3-dioxo-4-(3-oxopentyl)-6'-pentylspiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-5'-carboxylate (20).**—This compound was obtained by oxidative coupling of the benzophenone (18) in a manner similar to that described for the preparation of compound (19). The crude product was purified by radial chromatography with 50% ethyl acetate–light petroleum as eluant. The griseodienedione (20) was obtained as a gum (52%) which was homogeneous on t.l.c.; *m/z* 546 (*M*<sup>+</sup>, 2%), 237 (1), 221 (2), and 91 (100);  $\delta_H$  (300 MHz) 0.72 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.02 (3 H, t, Me), 1.05 (4 H, m, 2  $\times$  CH<sub>2</sub>), 1.20 (2 H, m, CH<sub>2</sub>), 1.78 and 2.23 (each 1 H, m, CH<sub>2</sub>Bu), 2.44 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 2.65 and 3.01 (each 2 H, m, CH<sub>2</sub>), 3.85 (3 H, s, OMe), 5.30 and 5.34 (2 H, AB, *J* 12.0 Hz, CH<sub>2</sub>Ph), 5.52 (1 H, s, 3'-H), 6.37 and 6.47 (2 H, AB, *J*<sub>5,7</sub> 2.0 Hz, 5- and 7-H), and 7.35 (5 H, m, Ph).

**Benzyl 3-Hydroxy-8-methoxy-6-pentyl-11-oxo-1-(3-oxopentyl)-11H-dibenzo[b,e][1,4]dioxepine-7-carboxylate (23).**—This compound was obtained in a similar manner to compound (21). The depsidone (83%) crystallized from dichloromethane–light petroleum as prisms, m.p. 86–88 °C, homogenous on t.l.c.; *m/z* 546 (*M*<sup>+</sup>, 3%) and 91 (100);  $\delta_H$  (300 MHz) 0.85 (3 H, t, Me), 1.03 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.23 (4 H, m, 2  $\times$  CH<sub>2</sub>), 1.49 (2 H, m, CH<sub>2</sub>), 2.44 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 2.62 (2 H, m, CH<sub>2</sub>), 2.82 and

2.98 (each 2 H, t, CH<sub>2</sub>), 3.75 (3 H, s, OMe), 5.34 (2 H, s, CH<sub>2</sub>Ph), 6.55 and 6.61 (2 H, AB, *J*<sub>2,4</sub> 2.4 Hz, 2- and 4-H), 6.65 (1 H, s, 9-H), and 7.35–7.44 (5 H, m, Ph);  $\nu_{max}$  (KBr) 1720, 1680, 1595, 1575, 1460, 1260, and 1140 cm<sup>-1</sup>.

**Benzyl 3-Benzyloxy-8-methoxy-6-pentyl-11-oxo-1-(3-oxopentyl)-11H-dibenzo[b,e][1,4]dioxepine-7-carboxylate (24).**—Benzoylation of the foregoing compound (23) gave the depsidone (24) as a gum (80%) which was homogeneous on t.l.c.; *m/z* 636 (*M*<sup>+</sup>, 0.5%) and 91 (100);  $\delta_H$  (300 MHz) 0.87 (3 H, t, Me), 1.04 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.24 (4 H, m, 2  $\times$  CH<sub>2</sub>), 1.50 (2 H, m, CH<sub>2</sub>), 2.41 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 2.59 (2 H, m, CH<sub>2</sub>), 2.79 and 3.01 (each 2 H, brt, CH<sub>2</sub>), 3.76 (3 H, s, OMe), 5.06 (2 H, s, ArOCH<sub>2</sub>Ph), 5.34 (2 H, s, CO<sub>2</sub>CH<sub>2</sub>Ph), 6.61 and 6.73 (2 H, AB, *J*<sub>2,4</sub> 2.5 Hz, 2- and 4-H), 6.66 (1 H, s, 9-H), and 7.38 (10 H, m, 2  $\times$  Ph);  $\nu_{max}$  (KBr) 1720, 1600, 1565, 1455, 1420, 1340, 1260, 1210, and 1140 cm<sup>-1</sup>.

**Benzyl 3-[5-Benzyloxy-2-methoxycarbonyl-3-(3-oxopentyl)-phenoxy]-4-hydroxy-6-methoxy-2-pentylbenzoate (27).**—Methanalysis of the foregoing depsidone (24) by a method similar to that described for the preparation of compound (25) gave the diaryl ether (27) as a gum (73%) (Found: C, 71.6; H, 6.9%; *M*<sup>+</sup>, 668.  $C_{40}H_{42}O_9$  requires C, 71.85; H, 6.65%; *M*, 668)  $\delta_H$  (300 MHz) 0.78 (3 H, t, Me), 1.06 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.39 (2 H, br, CH<sub>2</sub>), 1.63 (6 H, br, 3  $\times$  CH<sub>2</sub>), 2.38 (2 H, m, CH<sub>2</sub>), 2.42 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 3.77 and 3.96 (each 3 H, s, OMe), 4.90 (2 H, s, OCH<sub>2</sub>Ph), 5.36 (2 H, s, CO<sub>2</sub>CH<sub>2</sub>Ph), 6.43 (1 H, s, 5-H), 6.52 and 6.12 (2 H, AB, *J*<sub>4,6</sub> 2.3 Hz, 6- and 4-H), 6.43 (1 H, s, 5-H), and 7.27–7.48 (10 H, m, 2  $\times$  Ph);  $\nu_{max}$  (film) 1720, 1605, 1435, 1260, and 1145 cm<sup>-1</sup>.

**Benzyl 3-[5-Benzyloxy-2-methoxycarbonyl-3-(3-oxopentyl)-phenoxy]-4,6-dimethoxy-2-pentylbenzoate (28).**—Methylation of the foregoing diaryl ether (27) gave the product (95%) as a gum which was homogeneous on t.l.c.; *m/z* 682 (*M*<sup>+</sup>, 1%) and 91 (100);  $\delta_H$  (300 MHz) 0.76 (3 H, t, Me), 1.05 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.31, 1.59, and 2.38 (each 2 H, m, CH<sub>2</sub>), 2.41 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 2.78 and 2.84 (each 2 H, m, CH<sub>2</sub>), 3.71, 3.83, and 3.86 (each 3 H, s, OMe), 4.88 (2 H, s, OCH<sub>2</sub>Ph), 5.34 (2 H, s, CO<sub>2</sub>CH<sub>2</sub>Ph), 5.89 and 6.43 (2 H, AB, *J*<sub>4,6</sub> 2.3 Hz, 6- and 4-H), 6.38 (1 H, s, 5-H), and 7.26–7.46 (10 H, m, 2  $\times$  Ph).

**6-Hydroxy-3-[5-hydroxy-2-methoxycarbonyl-3-(3-oxopentyl)-phenoxy]-4-methoxy-2-pentylbenzoic Acid (Epiphorellic Acid 2).**—Deprotection of the foregoing compound (28) (166.5 mg) by a method similar to that described for the preparation of methyl epiphorellate 2 (29) gave a crude product which was purified by radial chromatography with ethyl acetate–light petroleum–acetic acid (160:39:1) as eluant. The epiphorellic acid (2) (83 mg, 70%) crystallized from dichloromethane–light petroleum as prisms, m.p. 150–152 °C (lit.,<sup>4</sup> 146–148 °C) (Found: C, 63.65; H, 6.6.  $C_{26}H_{32}O_9$  requires C, 63.9; H, 6.6%);  $\delta_H$  (300 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 0.83 (3 H, t, Me), 1.00 (3 H, t, CH<sub>3</sub>CH<sub>2</sub>CO), 1.10 (2 H, m, CH<sub>2</sub>), 1.31 (4 H, m, 2  $\times$  CH<sub>2</sub>), 1.47 (2 H, m, CH<sub>2</sub>), 2.47 (2 H, q, CH<sub>3</sub>CH<sub>2</sub>CO), 2.77 (4 H, m, 2  $\times$  CH<sub>2</sub>), 2.94 (2 H, m, CH<sub>2</sub>), 3.80 and 3.85 (each 3 H, s, OMe), 5.79 and 6.38 (2 H, AB, *J*<sub>4,6</sub> 2.2 Hz, 6- and 4-H), and 6.55 (1 H, s, 5-H);  $\delta_C$  (CD<sub>3</sub>CO) 8.03 (C-ε), 14.35 (C-ε'), 23.09 (C-δ'), 28.47 (C-α), 28.77 (C-β'), 31.36 (C-α'), 32.92 (C-γ'), 36.03 (C-δ), 44.04 (C-β), 52.09 (CO<sub>2</sub>Me), 56.39 (4-OMe), 99.09 (5-CH), 99.66 (6-CH), 105.22 (1-CCO<sub>2</sub>H), 109.55 (4-CH), 115.45 (2-CCO<sub>2</sub>Me), 134.65 (2-CCH<sub>2</sub>), 140.93 (3-CO), 143.01 (3-CCH<sub>2</sub>), 158.33 (4-COMe), 158.63 (5-COH), 159.99 (6-COH), 163.90 (1-CO), 168.74 (CO<sub>2</sub>Me), 173.50 (CO<sub>2</sub>H), and 209.69 (CO-γ);  $\nu_{max}$  (KBr) 3360, 2960, 2860, 1740, 1700, 1655, 1625, 1485, 1450, 1435, 1415, 1370, 1280, 1240, 1215, 1150, 1100, 1030, 830, and 740 cm<sup>-1</sup>; *m/z* (70 eV) 444 (*M*<sup>+</sup>, 45%), 413 (8), 381 (20), 355 (57), 337 (10),

285 (54), 271 (11), 193 (35), 192 (47), 163 (25), 138 (34), and 137 (100). This material was identical with an authentic sample of the natural product (h.p.l.c., t.l.c. in three different solvent systems, and mixed m.p.).

**Methyl 2,3-Dihydro-6-hydroxy-5'-methoxy-4-(3-oxopentyl)-3,3'-dioxo-1' $\beta$ -pentylspiro[benzofuran-2,2'-oxabicyclo[4.1.0]hept-5-ene]-6' $\beta$ -carboxylate (36).**—(a) The oxidation experiment was repeated using dioxane which contained 0.42% hydroperoxide and the crude product was purified by radial chromatography with 50% ethyl acetate–light petroleum as eluant. The epoxide (36) (60%) was obtained as stout rods (from ether–light petroleum), m.p. 198–199 °C (Found: C, 63.85; H, 6.5%;  $M^+$ , 486.  $C_{26}H_{30}O_9$  requires C, 64.2; H, 6.2%;  $M$ , 486);  $\delta_H$  (300 MHz) 0.78 (3 H, t, Me), 1.02 (3 H, t,  $CH_3CH_2CO$ ), 1.11 (2 H, m,  $CH_2$ ), 1.20–1.68 (6 H, m,  $3 \times CH_2$ ), 2.43 (2 H, q,  $CH_3CH_2CO$ ), 2.71 (2 H, t,  $CH_2$ ), 3.06 (2 H, m,  $CH_2$ ), 3.91 (6 H, s,  $2 \times OMe$ ), 5.51 (1 H, s, olefinic H), 6.44 and 6.57 (each 1 H, brs, 5- and 7-H), and 8.74 (1 H, br, OH);  $\delta_C$  7.66 (C- $\epsilon$ ), 13.67 (C- $\epsilon'$ ), 21.65 (C- $\delta$ ), 22.00 (C- $\alpha$ ), 24.16 (C- $\beta$ ), 26.21 (C- $\alpha'$ ), 31.76 (C- $\gamma$ ), 35.89 (C- $\delta$ ), 41.86 (C- $\beta$ ), 53.16 ( $CO_2Me$ ), 58.14 (5'- $OMe$ ), 62.99 (C-1'), 64.16 (C-6'), 94.89 (C-spiro), 97.56 (C-4'), 100.27 (C-7); 109.43 (C-3a), 113.64 (C-5), 145.16 (C-4), 164.30 (C-6), 166.76 (C-7a), 173.77 (C-5'), 176.58 ( $CO_2Me$ ), 185.49 ( $CO_3$ ), 189.90 ( $CO_3'$ ), and 211.31 ( $CO_3$ );  $\nu_{max}$  ( $KBr$ ) 1 748, 1 710, and 1 670  $cm^{-1}$ ;  $\lambda_{max}$  (MeOH) 231, 276, and 319 nm ( $\log \epsilon$  4.06, 4.26, and 3.97).

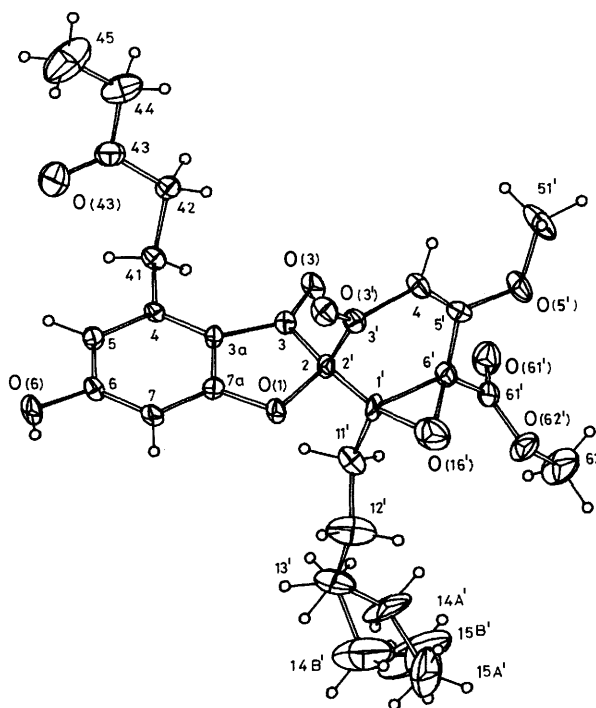
(b) A solution of the grisadienedione (19) (100 mg) and potassium carbonate (560 mg) were stirred in water (20 ml) and the aged dioxane (8 ml) for 15 min. Work-up gave the epoxide (80 mg, 78%) (36), m.p. and m.m.p. 198–199 °C.

**Reduction of the Epoxide (36) with Zinc and Acetic Acid.**—A solution of the epoxide (36) (400 mg) in acetic acid (20 ml) was heated on a steam-bath with zinc dust (2.0 g) for 2 h. The solution was cooled, filtered and then poured into water. The product was isolated by extraction with ethyl acetate in the usual way. The benzophenone (15) (358 mg, 92%) crystallized from chloroform–light petroleum as prisms, m.p. and mixed m.p. 171–172 °C.

**Methyl 2,3-Dihydro-6-hydroxy-5'-methoxy-3-oxo-1' $\beta$ ,4-dipentylspiro(benzofuran-2,2'-oxabicyclo[4.1.0]hept-5-ene)-6' $\beta$ -carboxylate (38).**—(a) Potassium hexacyanoferrate(III) (500 mg) in water (18 ml) was added at once to a stirred solution of the benzophenone (37) (200 mg)<sup>7</sup> and potassium carbonate (1.16 g) in water (36 ml) and the aged dioxane (18 ml) and the solution was stirred for 20 min. Work-up gave the epoxide (38) (170 mg, 86%) as prisms, m.p. 207–209 °C (Found: C, 66.0; H, 6.9%;  $M^+$ , 472.  $C_{26}H_{32}O_8$  requires C, 66.1; H, 6.85%;  $M$ , 472);  $\delta_H$  (300 MHz) 0.77 and 0.88 (each 3 H, t, Me), 1.12 and 1.29 (each 4 H, m,  $2 \times CH_2$ ), 1.37–1.71 (4 H, m,  $2 \times CH_2$ ), 1.94 (2 H, br,  $CH_2$ ), 2.77 (2 H, m,  $CH_2$ ), 3.913 and 3.908 (each 3 H, s,  $OMe$ ), 5.52 (1 H, s, olefinic H), 6.36 and 6.55 (2 H, AB,  $J_{5,7}$  1.8 Hz, 5- and 7-H), and 8.37 (1 H, s, OH);  $\delta_C$  13.70 and 13.99 (each  $CH_3$ ), 22.00 and 22.48 (each  $CH_2CH_2$ ), 24.18, 28.73, 29.64, 31.50, 31.62, and 31.89 (each  $CH_2$ ), 51.17 ( $CO_2Me$ ), 58.18 ( $OMe$ ), 63.06 and 64.29 (C-1' and -6'), 94.93 (spiro C), 97.27 (C-4'), 100.41 (C-7), 109.54 (C-3a), 113.07 (C-5), 147.69 (C-4), 164.42 and 166.56 (C-7a and -6), 174.10 (C-5'), 176.37 ( $CO_2Me$ ), 186.15 ( $CO_3$ ), and 189.87 ( $CO_3'$ ).

(b) Treatment of the grisadienedione (39)<sup>7</sup> with aqueous potassium carbonate and aged dioxane during 20 min as described for the conversion of compound (19) into compound (36) gave the epoxide (38), m.p. and m.m.p. 207–209 °C.

**Structure Determination.**—A unique data set was measured at  $\sim 295$  K to  $2\theta_{max} = 40^\circ$  using an Enraf-Nonius CAD-4



**Figure 1.** A single molecule of compound (36). 20% Thermal ellipsoids and labelling are shown for the non-hydrogen atoms; hydrogen atoms have arbitrary radii of 0.1 Å. Note that C(64,5) are disordered over components A,B.

diffractometer in conventional  $2\theta/\theta$  scan mode (monochromatic  $Mo-K_{\alpha}$  radiation,  $\lambda$  0.710 69 Å). 2 824 Independent reflections were measured, 1 462 with  $I > 3\sigma(I)$  being considered 'observed' and used in the full matrix least-squares refinement after solution of the structure by direct methods. Anisotropic thermal parameters were refined for all non-hydrogen atoms; ( $x$ ,  $y$ ,  $z$ ,  $U_{iso}$ )<sub>H</sub> were included constrained at estimated values. Conventional residuals on  $|F|$  at convergence,  $R$ ,  $R'$  were 0.074, 0.073, statistical weights derivative of  $\sigma^2(I) = \sigma^2(I_{diff}) + 0.005 \sigma^4(I_{diff})$  being used. Neutral atom complex scattering factors were employed;<sup>18</sup> computation used the XTAL 2.4 program system<sup>19</sup> implemented by S. R. Hall. Pertinent results are given in the Figure and Table. Thermal and hydrogen atom parameters, non-hydrogen atom geometries, and other structural parameters are available from the Cambridge Crystallographic Data Centre on request.\*

**Crystal data.**  $C_{26}H_{30}O_9$ ,  $M = 486.5$ , Triclinic, space group  $P\bar{1}(C_i^1, No. 2)$ ,  $a = 15.427(6)$ ,  $b = 10.986(4)$ ,  $c = 8.100(4)$  Å,  $\alpha = 105.57(4)$ ,  $\beta = 93.50(4)$ ,  $\gamma = 108.25(3)^\circ$ ,  $U = 1 240(1)$  Å<sup>3</sup>.  $D_c(Z = 2) = 1.30$  g  $cm^{-3}$ .  $F(000) = 516$ .  $\mu_{Mo} = 0.6$   $cm^{-1}$ , specimen: 0.33  $\times$  0.22  $\times$  0.04 mm (no absorption correction).

**Abnormal features.** The precision of the determination is adversely affected by the use of a poorly diffracting specimen of less than optimum size, with high thermal motion at the peripheral substituents, and disorder in the hydrocarbon chain. H(6) was located in a difference map.

**Structural Commentary.**—The results of the structure determination, albeit not of high precision, in consequence of the difficulties noted above, are consistent with the above stoichiometry and connectivity and are definitive of the stereochemistry.

\* For details, see 'Instructions for Authors (1989)', *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

Table. Non-hydrogen atom co-ordinates

Atom	x	y	z
O(1)	0.358 6(4)	0.226 8(6)	0.186 3(6)
C(2)	0.363 0(7)	0.247 0(10)	0.372 3(10)
C(3)	0.447 0(6)	0.212 2(8)	0.426 3(11)
O(3)	0.463 5(4)	0.202 7(6)	0.570 8(7)
C(3a)	0.494 3(7)	0.196 5(9)	0.276 6(10)
C(4)	0.573 0(7)	0.169 6(8)	0.249 2(9)
C(41)	0.633 4(6)	0.150 5(9)	0.388 8(10)
C(42)	0.691 3(7)	0.282 7(10)	0.520 3(11)
C(43)	0.775 2(9)	0.359 0(13)	0.465 0(15)
O(43)	0.797 2(6)	0.315 7(11)	0.329 2(13)
C(44)	0.829 6(9)	0.493 1(14)	0.579 1(18)
C(45)	0.904 0(11)	0.577 0(16)	0.512 0(25)
C(5)	0.598 8(6)	0.159 0(9)	0.085 2(10)
C(6)	0.542 4(7)	0.174 7(9)	-0.045 2(10)
O(6)	0.574 2(4)	0.162 7(6)	-0.198 4(6)
C(7)	0.462 0(7)	0.197 8(9)	-0.022 0(10)
C(7a)	0.438 2(7)	0.207 6(9)	0.144 2(10)
C(1')	0.281 1(7)	0.149 6(12)	0.402 1(12)
C(11')	0.248 9(8)	0.000 2(11)	0.306 4(13)
C(12')	0.175 1(11)	-0.050 5(18)	0.158 9(20)
C(13')	0.141 6(13)	-0.204 2(18)	0.083 2(20)
C(14A')	0.070 8(30)	-0.263 6(46)	0.138 2(82)
C(14B')	0.041 9(60)	-0.280 6(84)	-0.009 0(72)
C(15A')	-0.031 5(50)	-0.273 9(94)	0.051 8(106)
C(15B')	-0.000 8(60)	-0.320 7(95)	0.098 8(133)
O(16')	0.200 2(6)	0.197 0(8)	0.412 9(9)
C(3')	0.380 7(7)	0.394 7(11)	0.458 4(11)
O(3')	0.414 0(5)	0.479 4(7)	0.388 8(7)
C(4')	0.362 7(7)	0.431 0(10)	0.637 6(11)
C(5')	0.303 4(7)	0.336 2(10)	0.690 1(11)
O(5')	0.277 6(5)	0.350 3(7)	0.848 8(8)
C(51')	0.323 9(9)	0.478 1(12)	0.976 8(12)
C(6')	0.252 6(7)	0.200 0(11)	0.580 7(11)
C(61')	0.198 5(10)	0.094 9(11)	0.657 1(13)
O(61')	0.240 6(6)	0.061 4(8)	0.757 5(10)
O(62')	0.112 9(6)	0.051 7(8)	0.611 7(9)
C(62')	0.065 7(9)	-0.056 8(14)	0.678 7(17)

Crystallizing in a centrosymmetric space group, the crystals are racemic; one molecule comprises the asymmetric unit of the structure. At the given level of precision, bond lengths and angles lie about the expected norms for the relevant fragments, and are deposited with the other structural parameters; of more interest are the relative disparities of the component fragments. As might be expected the phenyl ring is planar ( $\chi^2$  3.7); atom deviations of the five-membered ring (and associates) are respec-

tively for O(1), C(2), C, O(3), C(3',1'): -0.06, 0.10, 0.00, -0.07, 1.49, -1.03 Å, showing no gross deviation from planarity of the five-membered ring. Within the six-membered non-aromatic ring, the fragments CCOC and CCCO(Me)C define tolerable planes, but with a dihedral angle of 22.7° between them due to torsion about C(3')-C(4'). Relative to the CCCO(Me)C plane, ( $\chi^2$  1.5), non-defining atom deviations are C(2'), O(3'), O(16'), C(61'): 0.58, -0.34, -1.15, 0.22 Å; torsion angles around the ring, commencing at the C(2')-C(3') bond are 41, -24, -2, 13, 4, -29°.

### Acknowledgements

We thank Dr. J. A. Elix for making the comparison between the synthetic and authentic samples of epiphorellic acid 2.

### References

- Part 23, T. Sala, M. V. Sargent, B. W. Skelton, and A. H. White, *Aust. J. Chem.*, 1982, **35**, 1065.
- J. A. Elix, A. A. Whitton, and M. V. Sargent, *Fortschr. Chem. Org. Naturst.*, 1984, **45**, 104.
- J. A. Elix, U. A. Jenie, and J. L. Parker, *Aust. J. Chem.*, 1987, **40**, 1451.
- P. Fiedler, V. Gambaro, J. A. Garbarino, and W. Quilhot, *Phytochemistry*, 1986, **25**, 461.
- P. Djura and M. V. Sargent, *Aust. J. Chem.*, 1976, **29**, 1069.
- J. A. Elix and V. K. Jayanthi, *Aust. J. Chem.*, 1986, **39**, 791.
- T. Sala and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1981, 855.
- E. Reimann, *Chem. Ber.*, 1969, **102**, 2881.
- H. Gerlach, *Helv. Chim. Acta*, 1977, **60**, 3039.
- N. Kitagiri, J. Nakano, and T. Kato, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2710.
- P. Cannone, G. Foscolos, and G. Lemay, *Tetrahedron Lett.*, 1980, **21**, 155.
- G. O. Schenk, H.-D. Becker, K.-H. Schulte-Elte, and C. H. Krauch, *Chem. Ber.*, 1963, **96**, 509.
- H. Heusser, G. Saucy, R. Anliker, and O. Jeger, *Helv. Chim. Acta*, 1952, **35**, 2090; C. Djerassi, G. W. Krakower, A. J. Lemin, L. H. Lin, J. S. Mills, and R. Villotti, *J. Am. Chem. Soc.*, 1958, **80**, 6284.
- M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1982, 403.
- H. Newman, *J. Org. Chem.*, 1970, **35**, 3990.
- M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2553.
- W. Rigby, *Chem. Ind.*, 1969, 1508.
- J. A. Ibers and W. C. Hamilton, 'International Tables for X-ray Crystallography,' The Kynoch Press, Birmingham, 1974, vol. 4.
- S. R. Hall and J. M. Stewart (eds.), 'XTAL User's Manual, Version 2.4,' Universities of Western Australia and Maryland, 1988.

Received 24th May 1988; Paper 8/02071J