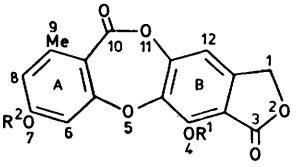
# Depsidone Synthesis. Part 13.[1] The Total Synthesis of Variolaric Acid

By René Jongen, Tony Sala, and Melvyn V. Sargent,* Department of Organic Chemistry, University of Western Australia, Nedlands, Western Australia 6009, Australia

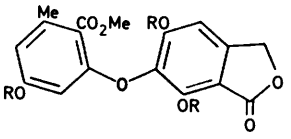
The total synthesis of 4,7-dihydroxy-9-methyl-10*H*-isobenzofuro[5,6-*b*][1,4]benzodioxepin-3,10(1*H*)-dione (variolaric acid) (1), a lichen depsidone, by functionalization of synthetic methyl 3,6-dimethoxy-1,8-dimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-carboxylate (12), is described.

In an earlier paper [2] we established the structure (1) of the biogenetically unusual lichen depsidone variolaric acid [3] by degrading it to the diaryl ether (5) which was synthesized by an Ullmann reaction. We now report the total synthesis of variolaric acid by an unambiguous route which fully confirms our original conclusions.

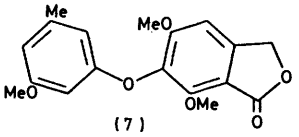
Routes which involved the Ullmann synthesis of diaryl ethers containing the γ-lactone function were not successful. Attempts to obtain the diaryl ether (6) by Ullmann reaction of the bromo-compound (8) [4] and the phenol (10) failed. Similar attempts to obtain the diaryl ether (7) from the bromo-compound (11) and 3-methoxy-5-methylphenol also failed. These failures may be attributed to the instability of the phthalides (10) and (11) under the reaction conditions; the synthesis of these phthalides is recorded in the Experimental section.



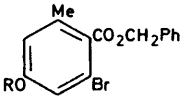
(1) $R^1 = R^2 = H$
(2) $R^1 = R^2 = Me$
(3) $R^1 = H, R^2 = Me$
(4) $R^1 = Me, R^2 = H$



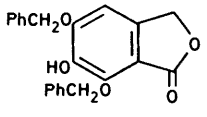
(5) R = Me
(6) $R = CH_2Ph$



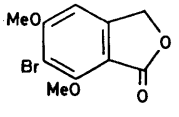
(7)



(8) $R = CH_2Ph$
(9) R = Me

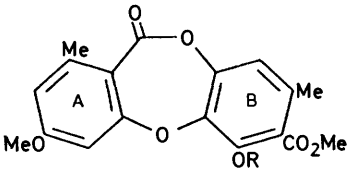


(10)

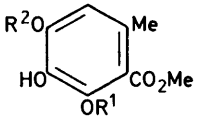


(11)

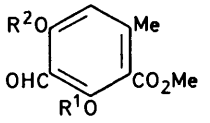
We therefore adopted a route in which the γ-lactone function would be introduced at a later stage of the synthesis by functionalization of the depsidone (12). For the synthesis of this compound the known bromo-compound (9) [5] and the phenol (14) were required. Accordingly, the monobenzylation of methyl haematommate (16) [6] was investigated. Little selectivity was observed in this reaction which gave the monobenzyl ethers (17) and (18), the dibenzyl ether (19), and some starting material. The monobenzyl ethers (17) and (18) were differentiated in the following way. Nuclear Overhauser experiments were carried out on both ethers by saturation of the benzylic ether proton signals in their $^1H$ m.r. spectra and observing the effects on the integrals of the aromatic and formyl proton signals.



(12) R = Me
(13) R = H



(14) $R^1 = Me, R^2 = CH_2Ph$
(15) $R^1 = R^2 = CH_2Ph$



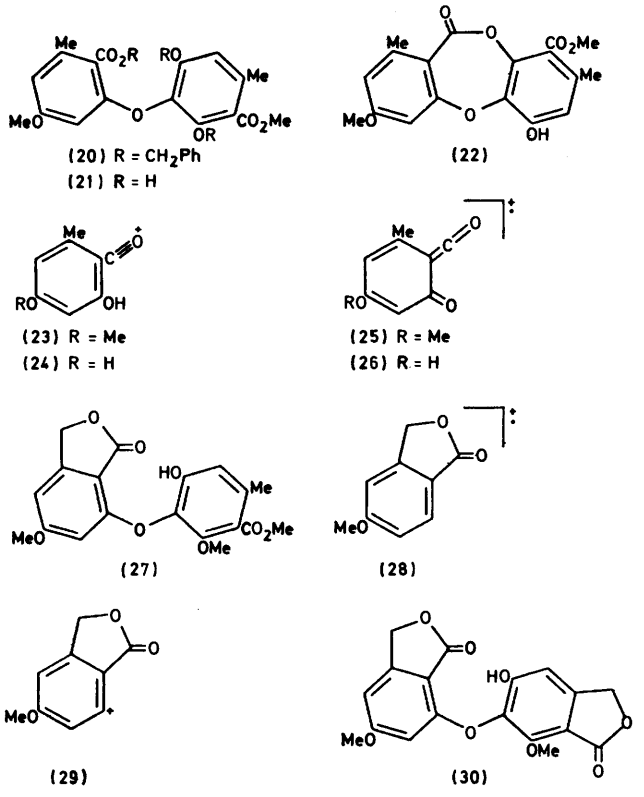
(16) $R^1 = R^2 = H$
(17) $R^1 = H, R^2 = CH_2Ph$
(18) $R^1 = CH_2Ph, R^2 = H$
(19) $R^1 = R^2 = CH_2Ph$

The integral of the aromatic proton signal for the ether (17) experienced a 21% enhancement and no effect was observed for the integral of the formyl proton signal, thus confirming the position of the benzyl group. In contrast no enhancement was found for the integral of the aromatic proton signal of compound (18), but an enhancement of 12% was observed for the integral of the formyl proton signal.

Since the mixture of products from the monobenzylation of methyl haematommate was not easily separated the dibenzyl ether (19) was prepared. This compound was subjected to Baeyer–Villiger oxidation [7] and mild hydrolysis of the resultant formate gave the phenol (15). Ullmann reaction between the bromo-compound (9) and the phenol (15) then gave the diaryl ether (20) in 75% yield. Hydrogenolytic debenzylation gave the dihydroxycarboxylic acid (21). Lactonization of compound (21) was achieved with hot acetic anhydride and the resultant depsidone acetates were subjected to mild hydrolysis. This gave a mixture of the depsidones (13) and (22) in the ratio 1 : 2. Trifluoroacetic anhydride, however, gave directly the same depsidones in a 3 : 2 ratio. The structures of these compounds followed from their elementary analyses and spectroscopic properties. The $^1H$ n.m.r. spectrum of compound (13) showed an intramolecularly hydrogen-bonded proton signal at δ 11.79 whereas the spectrum of its isomer (22) showed a free hydroxy proton signal at 9.18. The

i.r. spectrum ($CHCl_3$) of compound (13) exhibited carbonyl stretching frequencies at 1 744 (depsidone) and 1 664 (intramolecularly hydrogen-bonded ester) $cm^{-1}$. In contrast the depsidone (22) showed carbonyl stretching frequencies at 1 743 (depsidone) and 1 734 (free ester) $cm^{-1}$.

Methylation of the depsidone (13) gave compound (12) which was subjected to photobromination.[1] The resultant mixture was boiled with aqueous dioxan in order to hydrolyse the benzyl bromides and the products were




then separated by chromatography. In addition to some starting material three other components were isolated. The major component proved to be di-*O*-methylvariolaric acid (2). The $^1H$ n.m.r. spectrum (90 MHz, $CD_3SOCD_3$) of this compound exhibited a broad 3 H singlet at δ 2.42 ($W_{\frac{1}{2}}$ 2.0 Hz, 9-Me), two sharp singlets at 3.85 and 4.16 (each OMe), a 2 H doublet at 5.29 (lactone $CH_2$), a 2 H multiplet at 6.78—6.93 (6- and 8-H), and a broad 1 H singlet at 7.34 ($W_{\frac{1}{2}}$ 2.0 Hz, 12-H). Irradiation at δ 2.42 resolved the aromatic multiplet into an AB system ($J$ 2.5 Hz), while irradiation at 5.29 caused sharpening ($W_{\frac{1}{2}}$ 0.7 Hz) of the 12-H signal. The mass spectrum exhibited a molecular ion (base peak) and peaks at *m/e* 165 (30%) and 164 (20) attributed to the ions (23) and (25). The elemental compositions of these ions were confirmed by high resolution measurements. The i.r. spectrum ($CHCl_3$) exhibited carbonyl stretching frequencies at 1 765 (phthalide) and 1 752 (depsidone) $cm^{-1}$. A more polar component was identified as the phthalide (27). The $^1H$ n.m.r. spectrum of this product exhibited a signal for the phthalide methylene protons at δ 5.29 and one for a high field aromatic proton at 6.09 characteristic of the H-inside conformation of a tri-*ortho*-substituted diaryl ether.[8] The i.r. spectrum ($CHCl_3$) of compound (27) had carbonyl stretching frequencies at 1 745 (phthalide) and 1 733 (ester) $cm^{-1}$. The mass spectrum, in keeping with the assigned structure, exhibited a molecular ion peak (45%), an $M$ — MeOH ion peak (base), and peaks at *m/e* 164 (38) and 163 (10) attributed to the ions (28) and (29). The elemental compositions of these ions were confirmed by high resolution measurements. Compound (27) must be formed by bromination of the methyl group on the ring A of compound (12) and subsequent hydrolysis with concomitant cleavage of the depside linkage. The most polar product of the above reaction was the dilactone (30), which must be formed by bromination occurring on the methyl groups of both rings A and B of compound (12) and subsequent hydrolysis. Its structure again followed from spectroscopic data (see Experimental section).

Treatment of di-*O*-methylvariolaric acid (2) with anhydrous lithium iodide in hot hexamethylphosphoric triamide effected demethylation at the 4-position and gave compound (3). The structure of this product followed from its high resolution mass spectrum which exhibited the ion (23). Prolonged treatment of di-*O*-methylvariolaric acid (2) with boron tribromide under scrupulously anhydrous conditions gave the mono-*O*-methylvariolaric acid (4), isomeric with compound (3). The high resolution mass spectrum of compound (4), as expected, exhibited the ions (24) and (26). When this compound was treated with lithium iodide in hot hexamethylphosphoric triamide demethylation occurred and variolaric acid (1), identical with the natural product, was obtained.

## EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Light petroleum was a fraction of b.p. 58—65°. All organic extracts were dried over anhydrous sodium sulphate. Silica gel was B.D.H. 60—120 mesh, and crude products were preadsorbed from dichloromethane prior to chromatography. P.l.c. plates (20 × 20 × 0.1 cm) were coated with Merck Kieselgel $GF_{254}$. Lithium iodide dihydrate was dried for 36 h at 100° and 0.01 mmHg. $^1H$ N.m.r. spectra were determined at 60 MHz using a Hitachi–Perkin-Elmer R-24B, at 80 MHz using a Brüker WP-80, or at 90 MHz using a Brüker HX-90 instrument. Solutions for nuclear Overhauser experiments were degassed. Mass spectra were recorded with a Varian MAT CH-7 (low resolution) or a Varian MAT 311 (high resolution) instrument at 70 eV. I.r. spectra were determined with a Perkin-Elmer 282 spectrophotometer.

*Methyl 2,4-Diacetoxy-3-(diacetoxymethyl)-6-methylbenzoate.*—Methyl haematommate (16)[6] (30.0 g) was heated (steam-bath) with acetic anhydride (250 ml) and perchloric acid (70%; 1 ml) for 5 h. The solution was poured into water and the usual work-up gave the *tetra-acetate* (52.6 g). A sample formed prisms (from ether–light petroleum), m.p. 130—131° (Found: C, 54.85; H, 5.1. $C_{18}H_{20}O_{10}$ requires

C, 54.55; H, 5.1%); δ(90 MHz; $CCl_4$) 2.04 (6 H, s, 2 × COMe), 2.32 and 2.35 (each 3 H, s, COMe), 2.41 (3 H, s, Me), 3.86 (3 H, s, OMe), 6.93 (1 H, s, ArH), and 7.97 (1 H, s, CH).

*1,3-Dihydro-5,7-dihydroxy-1-oxo-6-isobenzofurancarbaldehyde*.—The foregoing tetra-acetate (35.0 g) was brominated in portions. Each (5.0 g) in carbon tetrachloride (450 ml) was boiled under reflux over a 250 W tungsten lamp, and then *N*-bromosuccinimide (2.3 g) and t-butyl peroxide (3 drops) were added. The mixture was heated under reflux for 17 h and then worked up as usual. The combined crude products were heated under reflux with dioxan (700 ml) and water (450 ml) for 25 h. The crude product was chromatographed over silica gel with 10—50% ethyl acetate–light petroleum as eluant. Early fractions gave methyl haematommate (16) (7.3 g) which was followed by the *phthalide* (8.0 g) which formed plates (from acetone–light petroleum), m.p. 200° (decomp.) (Found: C, 55.95; H, 3.3%; $M^+$, 194. $C_9H_6O_5$ requires C, 55.7; H, 3.1%; *M*, 194); δ(90 MHz; $CD_3SOCD_3$) 5.21 (2 H, s, $CH_2$), 6.60 (1 H, s, ArH), and 10.30 (1 H, s, CHO).

*5,7-Dibenzyloxy-1,3-dihydro-1-oxo-6-isobenzofurancarbaldehyde*.—The foregoing phthalide (5.4 g), benzyl bromide (105 g), and potassium hydrogencarbonate (36 g) were stirred at room temperature under dry nitrogen in *NN*-dimethylformamide (240 ml) for 1.5 h. The usual work-up gave the crude product, and the excess of benzyl bromide was removed in steam. The *phthalide* formed plates (6.0 g) (from dichloromethane–light petroleum), m.p. 151—152° (Found: C, 73.65; H, 4.65%; $M^+$, 374. $C_{23}H_{18}O_5$ requires C, 73.8; H, 4.85%; *M*, 374); δ(90 MHz; $CDCl_3$) 5.15 and 5.19 (each 2 H, s, PhC$H_2$), 5.46 (2 H, s, $CH_2$), 6.74 (1 H, s, ArH), 7.38 (10 H, m, 2 × Ph), and 10.37 (1 H, s, CHO).

*6-Hydroxy-5,7-dibenzyloxyisobenzofuran-1(3H)-one* (10).—A solution of the foregoing aldehyde (6.2 g) in dry dichloromethane (250 ml) was added dropwise over 0.5 h to a stirred solution of *m*-chloroperbenzoic acid (85%, 5.9 g) in dry dichloromethane (350 ml) at room temperature. After a further 4 h work-up gave the crude formate which was stirred at 10 °C in dioxan (150 ml), under nitrogen, during the dropwise addition of aqueous potassium hydroxide (10%, 115 ml) over 0.5 h. The usual work-up gave the *phenol* (10) (5.95 g) as prisms (from dichloromethane–light petroleum), m.p. 137—138° (Found: C, 72.5; H, 4.95%; $M^+$, 362. $C_{22}H_{18}O_5$ requires C, 72.9; H, 5.0%; *M*, 362); δ(90 MHz; $CDCl_3$) 5.01 and 5.12 (each 2 H, s, PhC$H_2$), 5.39 (2 H, s, $CH_2$), 5.91br (1 H, OH), 6.12 (1 H, s, ArH), and 7.34 (10 H, m, 2 × Ph).

*Methyl 3-Bromo-2,4-dimethoxy-6-methylbenzoate*.—This was prepared by an adaptation of the method of Sargent *et al.*[9] Bromine (78.0 g) in acetic acid (200 ml) was added to a warm solution of methyl dihydro-orsellinate (50.0 g) in acetic acid (250 ml) at such a rate that the temperature was 40—45 °C. The mixture was then stirred for 24 h at room temperature, and then poured into water. The crude product (68.2 g) was separated by filtration, washed with water, and dried *in vacuo*. It was then methylated in the usual way with methyl sulphate and potassium carbonate in dry acetone. This gave an oil which was distilled under diminished pressure and the fraction, b.p. 118—122° at 0.1 mmHg, was crystallized from light petroleum giving prisms (46.3 g) of the product, m.p. 65—66° (lit.,[9] 66—67°).

*Bromination of Methyl 3-Bromo-2,4-dimethoxy-6-methylbenzoate*.—A solution of the ester (4.64 g) in carbon tetrachloride (90 ml) was boiled under reflux over a 150 W tungsten lamp whilst bromine (2.30 g) in carbon tetrachloride (50 ml) was added dropwise over 0.5 h. The solution was then heated under reflux for 1 h, cooled, diluted with ethyl acetate, and worked up in the usual way. The crude product was chromatographed over silica gel with 0—5% ethyl acetate–light petroleum as eluant. This gave first *methyl 3-bromo-6-(dibromomethyl)-2,4-dimethoxybenzoate* (1.34 g) as needles (from methanol), m.p. 98—99° (Found: C, 29.6; H, 2.6; Br, 58.6. $C_{11}H_{11}Br_3O_4$ requires C, 29.55; H, 2.5; Br, 53.55%); δ(60 MHz; $CCl_4$) 3.83, 3.89, and 3.95 (each 3 H, s, OMe), 6.81 (1 H, s, ArH), and 7.21 (1 H, s, CH). Further elution afforded the starting material (0.84 g) which was followed by *methyl 3-bromo-6-(bromomethyl)-2,4-dimethoxybenzoate* (3.50 g) as needles (from dichloromethane–light petroleum), m.p. 89—90° (Found: C, 35.9; H, 3.35; Br, 43.35%, $M^+$, 366, 368, 370. $C_{11}H_{12}Br_2O_4$ requires C, 35.9; H, 3.3; Br, 43.4%; *M*, 366, 368, 370); δ(60 MHz; $CCl_4$) 3.81 (3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 4.41 (2 H, s, $CH_2$), and 6.60 (1 H, s, ArH).

*6-Bromo-5,7-dimethoxyisobenzofuran-1(3H)-one* (11).—(a) A solution of methyl 3-bromo-6-(bromomethyl)-2,4-dimethoxybenzoate (300 mg) in aqueous dioxan (azeotropic mixture; 30 ml) was heated under reflux for 8 h. The usual work-up gave the phthalide (11) (180 mg) as needles (from methanol), m.p. 206—207° (lit.,[10] 207—209°) (Found: C, 44.1; H, 3.4; Br, 29.25%; $M^+$, 272, 274. Calc. for $C_{10}H_9BrO_4$: C, 44.0; H, 3.3; Br, 29.25%; *M*, 272, 274); δ(90 MHz; $CDCl_3$–$CD_3SOCD_3$) 3.97 and 4.00 (each 3 H, s, OMe), 5.28 (2 H, d, *J* 1.0 Hz, 3-H), and 7.12 (1 H, t, *J* 1.0 Hz, 4-H). Irradiation at δ 5.28 sharpened the aromatic proton signal.

(b) Similar treatment of the mixture (25.0 g) of bromocompounds obtained from the bromination of methyl 3-bromo-2,4-dimethoxy-6-methylbenzoate gave a crude product (18.5 g) which was crystallized from methanol and yielded the phthalide (11) (11.3 g), m.p. 206—207°.

*6-Bromo-3-hydroxy-5,7-dimethoxyisobenzofuran-1(3H)-one*.—Methyl 3-bromo-6-(dibromomethyl)-2,4-dimethoxybenzoate (500 mg) was heated under reflux in aqueous dioxan (azeotropic mixture; 30 ml) for 88 h. The usual work-up gave the *pseudo-acid* (298 mg) as prisms (from ethyl acetate–light petroleum), m.p. 165—166° (Found: C, 41.1; H, 3.25%; $M^+$, 288, 290. $C_{10}H_9BrO_5$ requires C, 41.55; H, 3.15%; *M*, 288, 290); δ(60 MHz; $CDCl_3$) 3.95 and 4.05 (each 3 H, s, OMe), 6.40 (1 H, s, 3-H), and 6.79 (1 H, s, 4-H).

*Benzylation of Methyl Haematommate* (16).—(a) Methyl haematommate (16) (1.000 g), potassium carbonate (1.260 g), and benzyl bromide (770 mg) were stirred together in dry *NN*-dimethylformamide (10 ml) under dry nitrogen for 24 h. The crude product, obtained as usual, was chromatographed over silica gel with 1.5% ethyl acetate–light petroleum as eluant. This gave first the starting material (250 mg) followed by *methyl 2-benzyloxy-3-formyl-4-hydroxy-6-methylbenzoate* (18) (550 mg) as rods (from dichloromethane–light petroleum), m.p. 111.5—112.5° (Found: C, 68.05; H, 5.4. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.4%); δ(90 MHz; $CDCl_3$) 2.35 (3 H, s, Me), 3.87 (3 H, s, OMe), 5.06 (2 H, s, $CH_2$), 6.59 (1 H, s, ArH), 7.36 (5 H, s, Ph), 9.99 (1 H, s, CHO), and 11.78 (1 H, s, OH); $\nu_{max.}$ ($CCl_4$) 1 738 (ester CO) and 1 643 (bonded aldehyde CO) $cm^{-1}$. Further elution afforded *methyl 4-benzyloxy-3-formyl-2-hydroxy-6-methylbenzoate* (17) (320 mg) as needles

(from ether–light petroleum), m.p. 89—91° (Found: C, 67.75; H, 5.3. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.4%), δ(90 MHz; $CDCl_3$) 2.36 (3 H, s, Me), 3.90 (3 H, s, OMe), 5.14 (2 H, s, $CH_2$), 6.32 (1 H, s, ArH), 7.39 (5 H, s, Ph), and 12.54 (1 H, s, OH); $\nu_{max.}$ ($CCl_4$) 1 733 (ester CO) and 1 646 (bonded aldehyde CO) $cm^{-1}$. Further elution afforded *methyl* 2,4-*bisbenzyloxy*-3-*formyl*-6-*methylbenzoate* (19) (298 mg) as plates (from ether–light petroleum), m.p. 78.5—79°, or prisms (from dichloromethane–light petroleum), m.p. 87—88° (Found: C, 78.8; H, 5.55%; $M^+$, 390. $C_{24}H_{22}O_5$ requires C, 78.85; H, 5.7%; *M*, 390); δ(60 MHz; $CDCl_3$) 2.31 (3 H, s, Me), 3.67 (3 H, s, OMe), 4.95 and 5.05 (each 2 H, s, $CH_2$), 6.52 (1 H, s, ArH), 7.29 (10 H, m, 2 × Ph), and 10.91 (1 H, s, CHO).

(b) Methyl haematommate (16) (35.0 g) and potassium carbonate (90.0 g) in dry *NN*-dimethylformamide (350 ml) were stirred under dry nitrogen whilst benzyl bromide (58.2 g) in *NN*-dimethylformamide (50 ml) was added dropwise over 0.5 h. The mixture was stirred for a further 30 h and then worked up in the usual way. The excess of benzyl bromide was removed from the crude product by steam distillation and the residue was crystallized from dichloromethane–light petroleum which gave the aldehyde (19) (62.1 g), m.p. 87—88°.

*Methyl* 2,4-*Bisbenzyloxy*-3-*hydroxy*-6-*methylbenzoate* (15).—The aldehyde (19) (25.0 g) was oxidized with *m*-chloroperbenzoic acid (90%, 26.0 g) over 4.5 h as before. Hydrolysis of the formate gave the *phenol* (15) (24.0 g) as needles (from dichloromethane–light petroleum), m.p. 119.5—120.5° (Found: C, 72.9; H, 5.55%; $M^+$, 378. $C_{23}H_{22}O_5$ requires C, 73.0; H, 5.85%; *M*, 378); δ(60 MHz; $CDCl_3$) 2.20 (3 H, s, Me), 3.74 (3 H, s, OMe), 5.06 (4 H, s, 2 × $CH_2$), 6.48 (1 H, s, ArH), and 7.31 (10 H, m, 2 × Ph).

*Methyl* 3-(2-*Benzyloxycarbonyl*-5-*methoxy*-3-*methylphenoxy*)-2,4-*bisbenzyloxy*-6-*methylbenzoate* (20).—The bromo-compound (9) (5.4 g), the phenol (15) (6.2 g), and dry finely ground potassium carbonate (10.0 g) were stirred and heated in dry pyridine (30 ml) to 130 °C (bath) under dry nitrogen. Copper(II) oxide (2.0 g) was then added and the mixture was stirred and heated at 150 °C (bath) for 18 h. The mixture was cooled, diluted with ethyl acetate, and the suspension was filtered through Kieselguhr. The filtrate was washed in turn with dilute hydrochloric acid, dilute sodium hydroxide, and finally with saturated brine. The crude products from two such reactions were combined and chromatographed over silica gel with 0—25% ethyl acetate–light petroleum as eluant. This gave the *diaryl ether* (20) (15.2 g) as an oil (Found: $M^+$, 632.239 7. $^{12}C_{39}{}^{1}H_{36}{}^{16}O_8$ requires *M*, 632.240 9); δ(90 MHz; $CDCl_3$) 2.29 and 2.35 (each 3 H, s, Me), 3.61 and 3.74 (each 3 H, s, OMe), 4.99, 5.02, and 5.33 (each 2 H, s, $CH_2$), 5.98 and 6.38 (each 1 H, m, 6′- and 4′-H), 6.59 (1 H, m, 5-H), 7.23 (10 H, s, 2 × Ph), and 7.25 (5 H, s, Ph). Irradiation at δ 2.29 sharpened the 5-H signal, whilst irradiation at 2.35 resolved the 6′- and 4′-H multiplets into an AB system (*J* 2.5 Hz).

2-(2,6-*Dihydroxy*-3-*methoxycarbonyl*-4-*methylphenoxy*)-4-*methoxy*-6-*methylbenzoic Acid* (21).—The diaryl ether (20) (13.2 g) and 10% palladized charcoal (3.0 g) were stirred under hydrogen in ethyl acetate (600 ml), containing concentrated hydrochloric acid (10 drops), until absorption ceased. Work-up in the usual way furnished the *acid* (21) (7.6 g) as prisms (from chloroform–methanol), m.p. 227—229° (Found: C, 58.25; H, 5.2. $C_{18}H_{18}O_8 \cdot \frac{1}{2}H_2O$ requires C, 58.55; H, 5.2%); δ(90 MHz; $CD_3COCD_3$–$CD_3SOCD_3$) 2.41 and 2 45 (each 3 H, s, Me), 3.70 and 3.93 (each 3 H, s, OMe), 6.22 and 6.56 (2 H, AB, *J* 2.3 Hz, 3- and 5-H), and 6.40 (1 H, s, 5′-H). Irradiation at δ 2.45 sharpened the 5-H signal, *m/e* 362 ($M^+$).

*Ring Closure of the Acid* (21).—(a) *With acetic anhydride.* The acid (21) (200 mg) in acetic anhydride (10 ml) was heated on a steam-bath for 1.5 h and the solvent was then removed under reduced pressure. The residue, in pyridine (1 ml) and water (5 ml) was then heated on a steam-bath for 20 h. The mixture was diluted with ethyl acetate and washed in turn with dilute hydrochloric acid, water, and saturated brine. The crude product was then separated by p.l.c. (10% ethyl acetate–benzene) and yielded methyl 6-hydroxy-3-methoxy-1,8-dimethyl-11-oxo-11*H*-dibenzo-[*b*,*e*][1,4]dioxepin-7-carboxylate (13) (30 mg) and methyl 6-hydroxy-3-methoxy-1,8-dimethyl-11-oxo-11*H*-dibenzo-[*b*,*e*][1,4]dioxepin-9-carboxylate (22) (60 mg) which had $^1H$ n.m.r. spectra identical to those described in (b).

(b) *With trifluoroacetic anhydride.* The acid (21) (6.4 g), dry toluene (180 ml), and trifluoroacetic anhydride (25.0 g) were stirred at room temperature for 4 h. The solvents were removed under reduced pressure and the residue was chromatographed over silica gel with 2.5—10% ethyl acetate–benzene as eluant. This gave first *methyl* 6-*hydroxy*-3-*methoxy*-1,8-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e]-[1,4]*dioxepin*-7-*carboxylate* (13) (3.1 g) as needles (from dichloromethane–methanol), m.p. 221—223°, with slight sweating from 215° (Found: C, 62.85; H, 4.55. $C_{18}H_{16}O_7$ requires C, 62.8; H, 4.7%); δ(90 MHz; $CDCl_3$) 2.47 (6 H, s, 2 × Me), 3.82 and 3.96 (each 3 H, s, OMe), 6.56 and 6.78 (each 1 H, ABq, *J* 3.0 Hz, ArH), 6.62 (1 H, s, 9-H), and 11.79 (1 H, s, OH). Irradiation at δ 2.47 sharpened all the aromatic proton signals. For the i.r. spectrum see the Discussion section, *m/e* 345 (13%, $M^+ + 1$), 344 (56, $M^+$), 313 (36), 312 (100), 285 (23), 284 (83), 257 (13), 256 (8), 245 (18), 229 (18), 228 (29), 165 (13), and 164 (4). Further elution afforded *methyl* 6-*hydroxy*-3-*methoxy*-1,8-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-9-*carboxylate* (22) (2.01 g) as prisms (from dichloromethane–light petroleum), m.p. 175—178° (Found: C, 62.55; H, 4.6. $C_{18}H_{16}O_7$ requires C, 62.8; H, 4.7%); δ(90 MHz; $CD_3COCD_3$) 2.23 and 2.44 (each 3 H, s, Me), 3.85 and 3.86 (each 3 H, s, OMe), 6.67 and 7.00 (each 1 H, ABq, *J* 2.4 Hz, ArH), 6.78 (1 H, s, 7-H), and 9.10 (1 H, s, OH). Irradiation at δ 2.23 sharpened the 7-H proton signal. For the i.r. spectrum see the Discussion section, *m/e* 345 (21%, $M^+ + 1$), 344 (88, $M^+$), 313 (25), 312 (100), 285 (23), 284 (83), 268 (13), 256 (13), 229 (25), 228 (42), 213 (25), 165 (21), and 164 (6).

*Methyl* 3,6-*Dimethoxy*-1,8-*dimethyl*-11-*oxo*-11H-*dibenzo*-[b,e][1,4]*dioxepin*-7-*carboxylate* (12).—The depsidone (13) (3.0 g), potassium carbonate (5.0 g), and iodomethane (5.0 g) in dry *NN*-dimethylformamide (250 ml) were stirred at room temperature for 24 h. The usual work-up gave the *depsidone* (12) (2.5 g) as needles (from chloroform–methanol), m.p. 156—159° (Found: C, 63.8; H, 5.1%; $M^+$, 358. $C_{19}H_{18}O_7$ requires C, 63.6; H, 5.05%; *M*, 358); δ(90 MHz; $CDCl_3$) 2.27 and 2.49 (each 3 H, s, Me), 3.81 and 3.92 (each 3 H, s, OMe), and 6.62 (3 H, $W_{\frac{1}{2}}$ 3.0 Hz, ArH).

*Photobromination and Subsequent Hydrolysis of the Depsidone* (12).—A solution of the depsidone (12) (650 mg) in carbon tetrachloride (100 ml) was boiled under reflux over a 150 W tungsten lamp whilst bromine (306 mg) in carbon tetrachloride (10 ml) was added dropwise over 0.5 h. The solution was then heated under reflux for 2 h, cooled, and diluted with ethyl acetate and worked up in the usual way. The crude product was heated under reflux in aque-

ous dioxan (azeotropic mixture; 100 ml) for 24 h. The cooled solution was diluted with ethyl acetate and worked up in the usual way. The crude product was chromatographed over silica gel with 1.5—2.5% ethyl acetate–benzene as eluant. This gave first the starting material (155 mg) which crystallized from chloroform–methanol as needles (135 mg). Further elution gave 4,7-*dimethoxy*-9-*methyl*-10H-*isobenzofuro*[5,6-b][1,4]*benzodioxepin*-3,10(1H)-*dione* (2) (197 mg) which crystallized from dichloromethane–light petroleum as needles (175 mg), m.p. 267—269° (decomp.), with slight sweating from 245° (lit.,[3] 260—261°) (Found: C, 62.85; H, 4.1. $C_{18}H_{14}O_7$ requires C, 63.15; H, 4.1%). For the $^1$H n.m.r. see the Discussion section, $\nu_{max.}$ ($CHCl_3$) 1 765 (phthalide CO) and 1 752 (depsidone CO) $cm^{-1}$; *m/e* 343 (23%, $M^+ + 1$), 342 (100, $M^+$, $C_{18}H_{14}O_7$), 341 (14), 313 (20), 312 (16), 299 (59), 298 (18), 284 (17), 283 (16), 243 (24), 227 (20), 215 (17), 165 (30, $C_9H_9O_3$), and 164 (20, $C_{19}H_8O_3$). The column was then stripped with ethyl acetate and the residue (265 mg) was separated by p.l.c. with benzene–dioxan–acetic acid (200 : 22.5 : 2.5 v/v) as developing solvent. Two bands developed and the faster band was extracted with boiling dichloromethane and gave *methyl* 3-[(1,3-*dihydro*-6-*methoxy*-3-*oxoisobenzofuran*-4-*yl*)*oxy*]-4-*hydroxy*-2-*methoxy*-6-*methylbenzoate* (27) (121 mg) as prisms (from chloroform–ether), m.p. 203—205° with resolidification to needles, m.p. 221—225° (Found: C, 59.55; H, 5.1. $C_{19}H_{18}O_8,\frac{1}{2}H_2O$ requires C, 59.55; H, 5.0%); δ(90 MHz; $CD_3COCD_3$) 2.26 (3 H, s, $W_{\frac{1}{2}}$ 2.0 Hz, Me), 3.80, 3.82, and 3.84 (each 3 H, s, OMe), 5.28 (2 H, s, $W_{\frac{1}{2}}$ 3.0 Hz, $CH_2$), 6.09 and 6.83 (2 H, ABq, *J* 2.4 Hz, 5- and 7-H), and 6.72 (1 H, s, 5′-H). Irradiation at δ 2.26 sharpened the 5′-H signal, and irradiation at δ 5.28 sharpened the AB system, $\nu_{max.}$ ($CHCl_3$) 1 745 (phthalide CO) and 1 733 (ester CO) $cm^{-1}$; *m/e* 375 (16%, $M^+ + 1$), 374 (45, $M^+$, $C_{12}H_{18}O_8$), 343 (37), 342 (100), 164 (38, $C_9H_8O_3$), and 163 (16, $C_9H_7O_3$). The slower band was extracted with boiling acetone and gave 6-[(1,3-*dihydro*-6-*methoxy*-3-*oxoisobenzofuran*-4-*yl*)*oxy*]-5-*hydroxy*-7-*methoxyisobenzofuran*-1(3H)-*one* (30) (97 mg) as platelets (from acetone–water–dimethyl sulphoxide), m.p. 290—297° (decomp.) (Found: C, 59.1; H, 4.2. $C_{18}H_{14}O_8\cdot\frac{1}{2}H_2O$ requires C, 58.9; H, 4.1%); δ(90 MHz; $CD_3SOCD_3$) 3.74 and 3.88 (each 3 H, s, OMe), 5.24 and 5.32 (each 2 H, s, $CH_2$), 5.91 (1 H, d, *J* 2.2 Hz, 5-H), and 6.86 (2 H, m, ArH); $\nu_{max.}$ (Nujol) 1 746 and 1 723 (phthalide CO) $cm^{-1}$; *m/e* 359 (15%, $M + 1$), 358 (44, $M^+$, $C_{18}H_{14}O_8$), 296 (30), 178 (67), 177 (100), 165 (11), and 164 (33).

4-*Hydroxy*-7-*methoxy*-9-*methyl*-10H-*isobenzofuro*[5,6-b][1,4]*benzodioxepin*-3,10(1H)-*dione* (3).—The depsidone (2) (20 mg) and anhydrous lithium iodide (40 mg) in dry hexamethylphosphoric triamide (6 ml) were stirred and heated at 90 °C (bath) under dry nitrogen for 1.5 h when more lithium iodide (40 mg) was added. After a further 3.5 h lithium iodide (60 mg) was added and heating was continued for a further 28 h. The cooled solution was then diluted with hydrochloric acid (3M) and extracted with ethyl acetate. The extract was washed in turn with water, sodium thiosulphate solution, water, and finally with saturated brine. The crude product was applied to a p.l.c. plate which was developed with 30% ethyl acetate–light petroleum and then with chloroform. The major band gave the *product* (3) which crystallized from acetone–methanol as needles (10.6 mg), m.p. 265—267.5° (decomp.) (Found: $M^+$, 328.058 7. $^{12}C_{17}{}^1H_{12}{}^{16}O_7$ requires *M*, 328.058 3); δ(80 MHz; $CDCl_3$–$CD_3SOCD_3$) 2.47 (3 H, s, Me), 3.84 (3 H, s, OMe), 5.18 (2 H, s, $CH_2$), 6.66 and 7.10 (2 H, ABq, *J* 2.3 Hz, 6- and 8-H), and 6.79 (1 H, s, 12-H); irradiation at δ 2.47 sharpened the AB system, whilst irradiation at δ 5.18 sharpened the 12-H signal, *m/e* 329 (33%, $M + 1$), 328 (100, $M^+$), 165 (13, $C_9H_9O_3$), and 151 (25).

7-*Hydroxy*-4-*methoxy*-9-*methyl*-10H-*isobenzofuro*[5,6b]-[1,4]*benzodioxepin*-3,10(1H)-*dione* (4).—The depsidone (2) (37 mg) in dry dichloromethane (70 ml) was stirred under dry nitrogen at −78 °C and treated dropwise with boron tribromide (500 mg) in dry dichloromethane (10 ml). The mixture was then stirred at room temperature for 12 h. The crude product, obtained as usual, was applied to a p.l.c. plate which was developed with chloroform–acetic acid (10 : 1 v/v). The fastest band gave the starting material (5.0 mg). The major band was resubjected to p.l.c. [chloroform–ethyl acetate (5 : 1 v/v)] which gave the *product* (4) (10.4 mg) which crystallized from acetone–light petroleum as prisms (6.4 mg), m.p. 273—276° (decomp.) (Found: $M^+$, 328.057 4. $^{12}C_{17}{}^1H_{12}{}^{16}O_7$ requires *M*, 328.058 3); δ(60 MHz; $CD_3COCD_3$–$CD_3SOCD_3$) 2.36 (3 H, s, Me), 4.16 (3 H, s, OMe), 5.20 (2 H, s, $CH_2$), 6.60 (2 H, narrow m, 6- and 8-H), and 7.09 (1 H, s, 12-H), *m/e* 329 (26%, $M + 1$), 328 (100, $M^+$), 285 (64), 151 (33, $C_8H_7O_3$), 150 (26, $C_8H_6O_3$), 123 (44), and 106 (61).

4,7-*Dihydroxy*-9-*methyl*-10H-*isobenzofuro*[5,6-b][1,4]*benzodioxepin*-3,10(1H)-*dione* (*Variolaric Acid*) (1).—The depsidone (4) (6.3 mg) and anhydrous lithium iodide (50 mg) in hexamethylphosphoric triamide (3 ml) were heated and stirred at 90 °C (bath) under dry nitrogen for 6 h. Lithium iodide (50 mg) was added and heating was continued for a further 17 h. Work-up as before gave the crude product which was applied to a p.l.c. plate (20 × 20 × 0.05 cm) which was developed with 20% ethyl acetate–chloroform. The major band gave *variolaric acid* (1) which crystallized from methanol as large needles (4.4 mg), m.p. 294—296° (decomp.) [lit.,[3] 296° (decomp.)], undepressed on admixture with authentic material (Found: $M^+$, 314.040 7. $^{12}C_{16}{}^1H_{10}{}^{16}O_7$ requires *M*, 314.042 6); δ(80 MHz; $CDCl_3$–$CD_3SOCD_3$) 2.41 (3 H, s, Me), 5.18 (2 H, s, $CH_2$), 6.59 and 6.98 (2 H, ABq, *J* 2.3 Hz, 6- and 8-H), and 6.79 (1 H, s, 12-H); irradiation at δ 2.41 sharpened the AB systems, and irradiation at δ 5.18 sharpened the 12-H signal. The mass spectrum [2] and the $R_F$ values in four solvent systems were identical with those of an authentic sample.

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