Depsidone Synthesis. Part 14.[1] The Total Synthesis of Psoromic Acid: Isopropyl Ethers as Useful Phenolic Protective Groups

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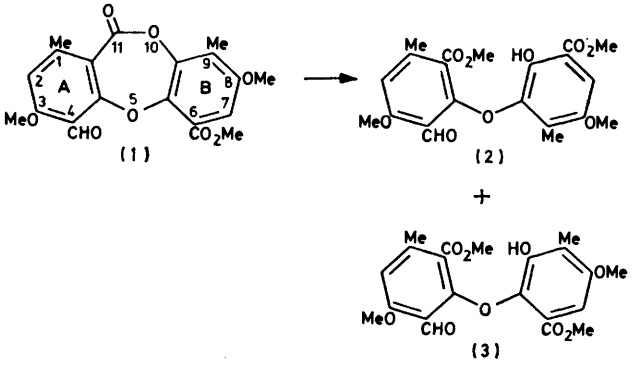
The total synthesis of 4-formyl-3-hydroxy-8-methoxy-1,9-dimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-6-carboxylic acid (psoromic acid) (28), a lichen depsidone, by selective functionalization of synthetic methyl 3,8-dimethoxy-1,4,9-trimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-6-carboxylate (methyl *O*-methylhypopsoromate) (23) and subsequent steps, is described. Attention is drawn to the use of isopropyl ethers as phenol protective groups.

THE total synthesis of the lichen depsidone psoromic acid (28) [2] presents a considerable challenge first because of the difficulty inherent in the construction of the substitution pattern and oxidation level of the C_1 substituents, and secondly because these features confer on the molecule the propensity to undergo a base-induced Smiles rearrangement. Thus treatment of methyl *O*-methylpsoromate (1) with methanolic sodium methoxide yields predominantly the rearranged cleavage product (2) as well as a trace of its unrearranged isomer (3) [2] (Scheme 1). For these reasons it was decided to

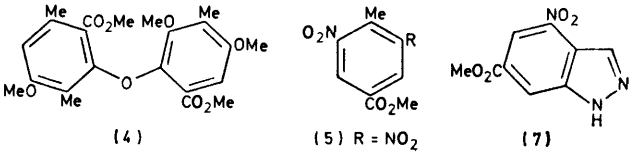


SCHEME 1

synthesize psoromic acid (28) by functionalization of methyl *O*-methylhypopsoromate (23).

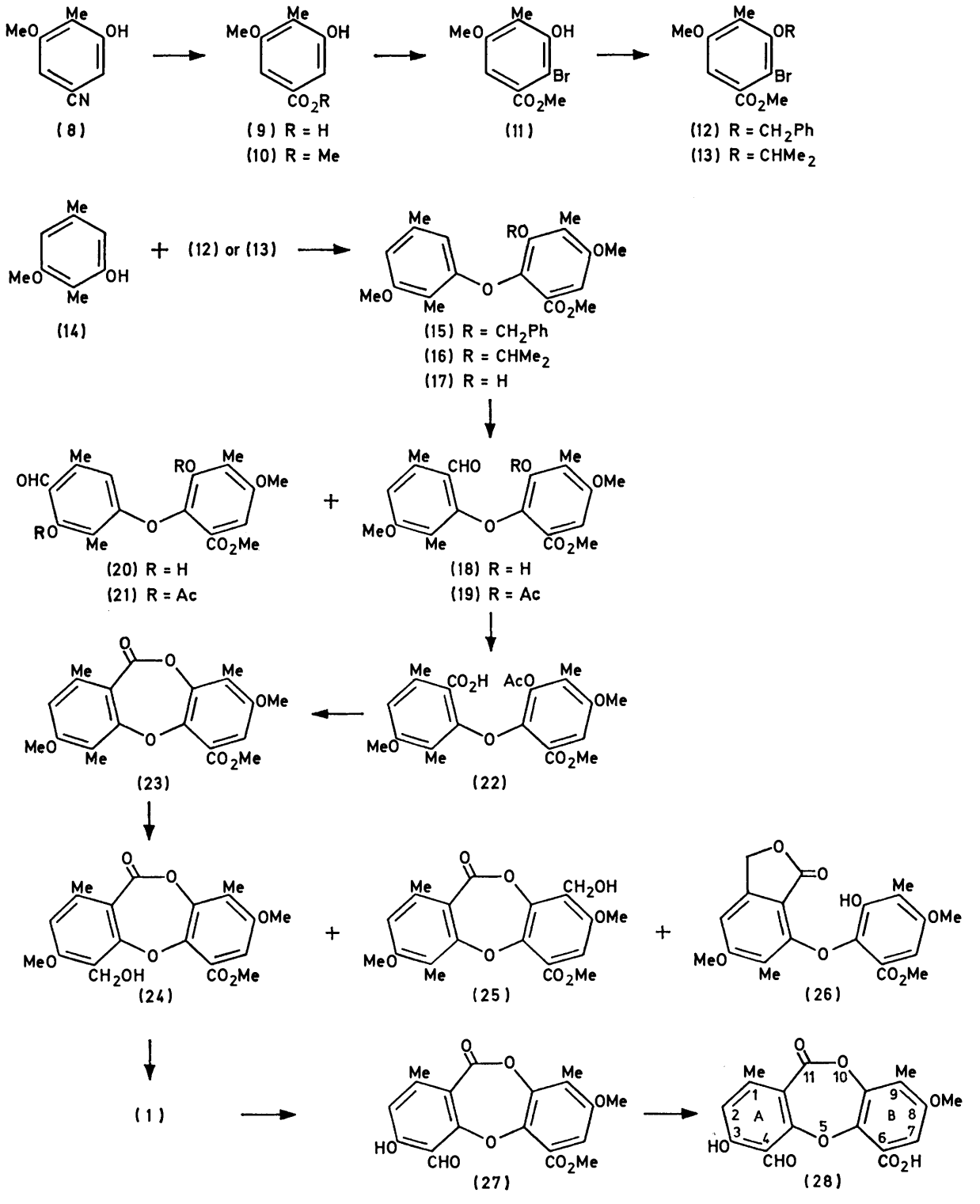
We have developed two general methods for the synthesis of depsidones: one based on the oxidation of suitably substituted benzophenones to grisadienediones and subsequent base catalysed rearrangement to depsidones,[3] and the other employing an Ullmann reaction to construct the diaryl ether linkage.[1] Methyl *O*-methylhypopsoromate (23) appeared to be more amenable to synthesis by the Ullmann route. The method employed was closely modelled on that used by us for the synthesis of methyl di-*O*-methylhypoparellinate (4), a degradation product of psoromic acid.[2] Consequently the bromo-compound (12) was required as the B ring component. The ester (10), readily available by hydrolysis of 3-hydroxy-5-methoxy-4-methylbenzonitrile (8) [4] to the acid (9) and subsequent selective methylation, appeared to be an appropriate starting material for the synthesis of the bromo-compound (12). Since the nitrile (8) can only be prepared in moderate yield [4] an alternative synthetic route to the ester (10) was investigated. Methyl 4-methyl-3,5-dinitrobenzoate (5) [5] was partially reduced to the amine (6) by transfer hydrogenation.[6] Diazotization of the amine (6) and treatment of the diazonium salt with warm sulphuric acid gave only the indazole (7),[7] and none of the desired phenol; this route was therefore abandoned. Accordingly the bromination of the ester (10) was investigated. Treatment of this compound with bromine in dichloromethane at 25 °C gave only one bromo-compound. This was assigned structure (11) since its i.r. spectrum in dilute carbon tetrachloride solution exhibited a sharp band at 3 501 cm^{-1} attributed to the OH stretching frequency of an intramolecularly hydrogen bonded phenol.[8] The frequency of this band did not change with increasing dilution. Benzylation of the phenol (11) then gave the required bromo-compound (12).

The A-ring component (14) had been synthesized previously,[9] but a number of improvements in this method are detailed in the Experimental section. Ullmann reaction between the bromo-compound (12) and the phenol (14) gave the diaryl ether (15). This was formylated with dichloromethyl methyl ether in the presence of titanium(IV) chloride at −78 °C and the crude product was treated with boron trichloride in order to facilitate separation of the isomeric aldehydes produced. This sequence gave the aldehydes (18) and (20) the structures of which followed readily from their



spectroscopic and elementary analytical data and those of their derived acetates (19) and (21). The major product, however, was the phenol (17). Presumably the benzyl ether protective group is cleaved by titanium(IV) chloride under the conditions of the formylation reaction, and the phenol (17) produced, or its formate, are inert to formylation.

We reasoned that an isopropyl ether protective group would be more stable to Lewis acids than the benzyl ether group. The former group has rarely been used for the protection of phenols and has usually been removed by brief treatment with concentrated aqueous

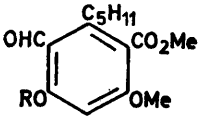

(8)
(9) R = H
(10) R = Me
(11)
(12) R = CH2Ph
(13) R = CHMe2
(14)
(12) or (13)
(15) R = CH2Ph
(16) R = CHMe2
(17) R = H
(20) R = H
(21) R = Ac
(18) R = H
(19) R = Ac
(23)
(22)
(24)
(25)
(26)
(1)
(27)
(28)

SCHEME 2

hydrobromic acid in boiling acetic acid;[10] it has, however, been used more frequently for the protection of the enols of β-keto-aldehydes.[11,12] Reaction of the phenol (11) with 2-bromopropane and potassium carbonate in dry *NN*-dimethylformamide [12] smoothly gave the isopropyl ether (13). These conditions appear to be quite general for the conversion of phenols to their isopropyl ethers. Ullmann reaction of the isopropyl ether (13) and the phenol (14) then gave the diaryl ether (16). The protective group in compound (16) was cleaved rapidly by boron trichloride in dichloromethane at 0 °C, and more slowly by titanium(IV) chloride in dichloromethane at 0 °C, but it was stable to tin(IV) chloride in dichloromethane at 0 °C. These properties make the isopropyl ether function a phenolic protective group capable of selective manipulation. For example, treatment of compound (29) with titanium(IV) chloride at 0—25 °C smoothly yielded the phenol (30).[13]

Consequently formylation of the diaryl ether (16) with dichloromethyl methyl ether in the presence of tin(IV) chloride at 0 °C followed by treatment of the crude product with boron trichloride gave only a readily separable mixture of the aldehydes (18) and (20) in which the desired product (18) predominated. The derived acetate (19) proved difficult to oxidize to the acid (22). It was stable to potassium permanganate in buffered aqueous acetone at 25 °C, and to tetrabutylammonium permanganate in pyridine at 25 °C,[14] but it was oxidized smoothly to the acid (22) by sodium chlorite in aqueous dioxan in the presence of sulphamic acid as a chlorine scavenger.[15]

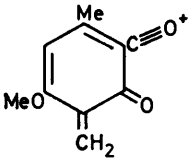
Treatment of the acid (22) with an excess of boron trichloride in dichloromethane caused deacetylation and lactonization and gave directly the depsidone (23). This reaction presumably involved the intermediacy of the acid chloride since benzoic acid yielded some benzoyl chloride, identified by its i.r. spectrum, under similar conditions. Photobromination of the depsidone (23) was expected,[16] because of the electronic effects of the



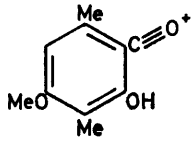
(29) R = $CHMe_2$
(30) R = H

substituents, to occur preferentially at the methyl group at the 4-position. This expectation was realized since the crude product of the reaction on hydrolysis in boiling aqueous dioxan gave chiefly the hydroxymethyl compound (24). Traces of the hydroxymethyl compound (25) and the phthalide (26) were also produced in this reaction. The isomeric hydroxymethyl compounds (24) and (25) were differentiated on the grounds of their high resolution mass spectra. The mass spectrum of compound (24) exhibited the intense ring A ion (31) whilst that of compound (25) exhibited the intense ring A ion (32).

Oxidation of the hydroxymethyl compound (24) with pyridinium chlorochromate [17] in dichloromethane gave methyl *O*-methylpsoromate (1), which on treatment with an excess of boron trichloride in dichloromethane at 0 °C gave methyl psoromate (27). Treatment of methyl psoromate (27) with an excess of lithium iodide [18] in hot



(31)



(32)

hexamethylphosphoric triamide gave psoromic acid (28), identical with the natural product by all the usual criteria.

EXPERIMENTAL

General directions have been given before.[1]

Methyl 3-Amino-4-methyl-5-nitrobenzoate (6).—Nitration [19] of *p*-toluic acid gave 4-methyl-3,5-dinitrobenzoic acid (95%) which was converted into the methyl ester (5) [5] with methanol and sulphuric acid in the usual way. The ester (5) (10 g) was boiled under reflux with ethanol (80 ml), cyclohexene (175 ml), and 10% palladized charcoal (200 mg) for 24 h. The catalyst was separated by filtration and the solvents were removed from the filtrate under reduced pressure. The residue crystallized from ethanol as yellow prisms (6.0 g) of the *amine* (6), m.p. 172—174° (Found: C, 51.6; H, 4.9; N, 13.55%, M^+, 210. $C_9H_{10}N_2O_4$ requires C, 51.45; H, 4.8; N, 13.35%; *M*, 210); δ ($CDCl_3$; 60 MHz) 2.25 (3 H, s, Me), 3.91 (3 H, s, OMe), 4.20br (2 H, s, NH_2), and 7.51 and 7.81 (2 H, AB, *J* 2 Hz, ArH).

Methyl 4-Nitro-1H-indazole-6-carboxylate (7).—The amine (6) (7.0 g) was suspended in water (200 ml) and concentrated hydrochloric acid (30 ml) and cooled to 0 °C, and stirred rapidly during the dropwise addition of sodium nitrite (2.7 g) dissolved in a little water. The cooling bath was removed and the suspension was stirred at room temperature for 1.25 h, filtered, and treated with a little urea. The filtrate was diluted with water (1 l) containing concentrated sulphuric acid (35 ml) and the mixture was stirred at 50 °C for 15 min. The cooled mixture was extracted with ethyl acetate and the crude product was crystallized from methanol (charcoal), and formed cream needles (3.2 g) of the *indazole* (7), m.p. 203—203.5° (Found: C, 49.0; H, 3.4; N, 19.45%; M^+, 221. $C_9H_7N_3O_4$ requires C, 48.9; H, 3.2; N, 19.0%; *M*, 221); δ ($CDCl_3$–CD_3SOCD_3; 90 MHz) 4.00 (3 H, s, OMe), 8.63 (3 H, m, ArH), and 8.70 (1 H, d, *J* 1.0 Hz, ArH).

3-Hydroxy-5-methoxy-4-methylbenzoic Acid (9).—The nitrile (8) (18.1 g), m.p. 178—179° (lit.,[4] 178—179°), water (18 ml), concentrated sulphuric acid (18 ml), and glacial acetic acid (72 ml) were heated under reflux under nitrogen for 7 h. The usual work-up gave the *acid* (9) (17.8 g) as needles from aqueous methanol), m.p. 228—230° (Found: C, 59.6; H, 5.6%; M^+, 182. $C_9H_{10}O_4$ requires C, 59.35; H, 5.55%; *M*, 182).

Methyl 3-Hydroxy-5-methoxy-4-methylbenzoate (10).—Iodomethane (14.0 g) in *NN*-dimethylformamide (50 ml) was added with stirring to the acid (9) (17.8 g) and dry potassium hydrogen carbonate (10.0 g) suspended in *NN*-dimethyl-

formamide (100 ml). Work-up after 6.5 h gave the crude product which was filtered through a column of silica gel with 20% ethyl acetate–light petroleum as eluant. The *ester* (10) (16.8 g) formed prisms (from dichloromethane–light petroleum), m.p. 136—137° (Found: C, 61.3; H, 5.95%; M^+, 196. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.15%, *M*, 196); δ ($CDCl_3$; 90 MHz) 2.16 (3 H, s, Me), 3.85 and 3.90 (each 3 H, s, OMe), 6.21br (1 H, OH), and 7.11 and 7.29 (2 H, AB, *J* 1.9 Hz, ArH).

Methyl 2-Bromo-3-hydroxy-5-methoxy-4-methylbenzoate (11).—Bromine (13.7 g) in carbon tetrachloride (100 ml) was added dropwise over 15 min with stirring and ice-cooling to the ester (10) (16.75 g) in dichloromethane (500 ml). After a further 5 min the usual work-up gave the *bromo-ester* (11) (22.1 g) as prisms (from dichloromethane–light petroleum), m.p. 84—85° (Found: C, 43.85; H, 4.35; Br, 28.65%; M^+, 274, 276. $C_{10}H_{11}BrO_4$ requires C, 43.65; H, 4.05; Br, 29.05%; *M*, 274, 276); δ ($CDCl_3$; 90 MHz) 2.20 (3 H, s, Me), 3.83 and 3.92 (each 3 H, s, OMe), 6.12 (1 H, s, D_2O exchangeable OH), and 7.02 (1 H, s, ArH).

Methyl 3-Benzyloxy-2-bromo-5-methoxy-4-methylbenzoate (12).—The phenol (11) (22.1 g), potassium carbonate (22.5 g), and benzyl bromide (15.1 g) were stirred in dry *NN*-dimethylformamide (225 ml) under dry nitrogen at room temperature for 4 h. The excess of benzyl bromide was removed from the crude product by steam distillation. The *ether* (12) (28.6 g) formed clusters of prisms (from dichloromethane–light petroleum), m.p. 73—74° (Found: C, 56.05; H, 4.6; Br, 21.95%; M^+, 364, 366. $C_{17}H_{17}BrO_4$ requires C, 55.9; H, 4.7; Br, 21.9%; *M*, 364, 366); δ ($CDCl_3$; 90 MHz) 2.20 (3 H, s, Me), 3.83 and 3.92 (each 3 H, s, OMe), 4.89 (2 H, s, CH_2), 7.07 (1 H, s, ArH), and 7.33—7.64 (5 H, m, Ph).

Methyl 2-Bromo-3-isopropoxy-5-methoxy-4-methylbenzoate (13).—The phenol (11) (6.5 g), potassium carbonate (6.5 g), and 2-bromopropane (10.0 g) were stirred in dry *NN*-dimethylformamide (100 ml) under dry nitrogen for 19 h. The usual work-up gave the *ether* (13) (7.4 g) which formed large prisms (from pentane), m.p. 47.5—48.5° (Found: C, 49.35; H, 5.4; Br, 24.8%; M^+, 316, 318. $C_{13}H_{17}BrO_4$ requires C, 49.25; H, 5.4; Br, 25.2%; *M*, 316, 318); δ ($CDCl_3$; 60 MHz) 1.25 (6 H, d, *J* 5.8 Hz, Me_2C), 2.10 (3 H, s, Me), 3.72 and 3.79 (each 3 H, s, OMe), 4.40 (1 H, heptet, *J* 5.8 Hz, CH), and 6.80 (1 H, s, ArH).

Methyl 4-Hydroxy-3,6-dimethyl-2-oxocyclohex-3-enecarboxylate.—This method is an adaptation of that of Elix and Norfolk [20] for the ethyl ester. Methyl crotonate (100 g) was added dropwise with stirring to a solution of sodium methoxide [from sodium (23 g)] in methanol (300 ml) and methyl 3-oxopentanoate (130 g), prepared in 68% yield from Meldrum's acid and propionyl chloride.[21] The mixture was boiled and stirred under reflux for 24 h, and then most of the methanol was removed by distillation. The residue was dissolved in water and then extracted with ether. The extracts were discarded and the aqueous layer was cooled to 0 °C and acidified with ice-cold concentrated hydrochloric acid. The crystalline precipitate (128.7 g) was separated by filtration and washed with water and dried *in vacuo*. A sample formed prisms of the *ester* (from ethyl acetate), m.p. 155.5—157.5° (Found: C, 60.4; H, 7.2%; M^+, 198. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%; *M*, 198).

Methyl 5-Bromo-2,4-dihydroxy-3,6-dimethylbenzoate.—Bromine (81 g) in acetic acid (200 ml) was added dropwise with stirring to a suspension of the foregoing dihydro-compound (50 g) in acetic acid (500 ml) at room temperature. The mixture was then stirred for 2.25 h and poured into ice–water (6 l). The precipitate (68 g) was separated by filtration, washed with water, and dried *in vacuo*. A sample formed *prisms* (from dichloromethane–light petroleum), m.p. 87—88° (Found: C, 43.55; H, 4.0; Br, 28.85%; M^+, 274, 276. $C_{10}H_{11}BrO_4$ requires C, 43.65; H, 4.05; Br, 29.05%; *M*, 274, 276); δ ($CDCl_3$; 60 MHz) 2.13 and 2.55 (each 3 H, s, Me), 3.83 (3 H, s, OMe), and 6.03 and 11.52 (each 1 H, s, OH).

Methyl 2,4-Dihydroxy-3,6-dimethylbenzoate.—Raney nickel–aluminium alloy (60 g) was added portionwise with stirring and ice-cooling to a solution of the foregoing bromo-compound (50 g) in aqueous sodium hydroxide (2M; 1 400 ml). After the addition the suspension was stirred at 0 °C for 1.75 h and then filtered through Kieselguhr. The acidified filtrate was extracted with ethyl acetate and the crude product was crystallized from aqueous methanol and afforded rods (34 g), m.p. 142—143° (lit.,[22] 142.5—143.5°), δ ($CDCl_3$; 60 MHz) 2.07 and 2.43 (each 3 H, s, Me), 3.86 (3 H, s, OMe), 5.10 (1 H, s, OH), 6.10 (2 H, s, ArH), and 11.90 (1 H, s, OH).

3-Methoxy-2,5-dimethylphenol (14).—The foregoing ester was hydrolysed and decarboxylated by the method of St. Pfau.[22] The resultant 1,3-dihydroxy-2,5-dimethylbenzene was converted into the di-*O*-methyl ether (methyl sulphate–potassium carbonate–acetone) which was partially demethylated to (14) by the method of Cresp *et al.*[9]

Methyl 3-Benzyloxy-5-methoxy-2-(3-methoxy-2,5-dimethylphenoxy)-4-methylbenzoate (15).—The bromo-compound (12) (8.8 g), the phenol (14) (3.7 g), and finely ground dry potassium carbonate (5.3 g) were stirred and heated under dry nitrogen in dry pyridine (35 ml) at 140 °C (bath). Copper(II) oxide (1.8 g) was added and the mixture was heated for 20 h. The cooled mixture was diluted with ether and filtered through Kieselguhr and the filtrate was washed in turn with dilute hydrochloric acid, dilute aqueous sodium hydroxide, water, and finally saturated brine. Chromatography of the crude product over silica gel, with 5—15% ethyl acetate–light petroleum as eluant gave first *methyl 3-benzyloxy-5-methoxy-4-methylbenzoate* (1.8 g) as prisms (from dichloromethane–light petroleum), m.p. 86—87° (Found: C, 70.95; H, 6.2%; M^+, 286. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.35%; *M*, 286); δ ($CDCl_3$; 90 MHz) 2.19 (3 H, s, Me), 3.84 and 3.88 (each 3 H, s, OMe), 5.09 (2 H, s, CH_2), and 7.28 (7 H, m, ArH). This was followed by the *diaryl ether* (15) (6.2 g) as prisms (from dichloromethane–methanol), m.p. 154—155° (Found: C, 71.65; H, 6.5%; M^+, 436. $C_{26}H_{28}O_6$ requires C, 71.55; H, 6.45%; *M*, 436); δ ($CDCl_3$; 90 MHz) 2.11 (3 H, s, 4-Me), 2.14br (3 H, s, Me), 2.27 (3 H, apparent d, Me), 3.67, 3.81, and 3.86 (each 3 H, s, OMe), 4.95 (2 H, s, CH_2), 5.82 (1 H, m, $W_{1/2}$ 3.0 Hz, 6′-H), 6.33 (1 H, m, $W_{1/2}$ 3.2 Hz, 4′-H), 7.21 (1 H, s, 6-H), and 7.24 (5 H, s, Ph).

Methyl 3-Isopropyloxy-5-methoxy-2-(3-methoxy-2,5-dimethylphenoxy)-4-methylbenzoate (16).—Ullmann reaction as above between the bromo-compound (13) (4.0 g) and the phenol (14) (1.95 g) gave a crude product which was chromatographed over silica gel with 1—15% ethyl acetate–light petroleum as eluant. Early fractions furnished *methyl 3-isopropoxy-5-methoxy-4-methylbenzoate* (0.54 g) as an oil, b.p. 120—121° (bath) at 0.01 mmHg (Found: C, 65.8; H, 7.6%; M^+, 238. $C_{13}H_{18}O_4$ requires C, 65.55; H, 7.6%; *M*, 238); δ ($CDCl_3$; 90 MHz) 1.33 (6 H, d, *J* 5.8 Hz, Me_2C), 2.13 (3 H, s, Me), 3.85 and 3.89 (each 3 H, s, OMe), 4.56 (1 H, heptet, *J* 5.8 Hz, CH), 7.18 and 7.24 (2 H, AB, *J* 1.9 Hz, ArH). Later fractions gave the *diaryl ether* (16) (2.58 g) as

prisms (from light petroleum), m.p. 99—100° (Found: C, 68.0; H, 7.35%; M^+, 388. $C_{22}H_{28}O_6$ requires C, 68.0; H, 7.25%; M, 388); δ ($CDCl_3$; 90 MHz) 1.17 (6 H, d, J 6.5 Hz, Me_2C), 2.13 (3 H, s, $W_{1/2}$ 2.1 Hz, Me), 2.20 (3 H, s, 4-Me), 2.25 (3 H, s, $W_{1/2}$ 2.0 Hz, Me), 3.65, 3.81, and 3.88 (each 3 H, s, OMe), 4.52 (1 H, heptet, J 6.5 Hz, CH), 5.72 (1 H, m, $W_{1/2}$ 3.0 Hz, 6'-H), 6.31 (1 H, m, $W_{1/2}$ 3.7 Hz, 4'-H), and 7.17 (1 H, s, 6-H).

Formylation and Subsequent Treatment with Boron Trichloride of the Diaryl Ether (15).—Titanium(IV) chloride (2.7 g) in dichloromethane (10 ml) was added dropwise with stirring at −78 °C over 1.5 h to a solution of the diaryl ether (15) (1.06 g) in dichloromethane (20 ml) and dichloromethyl methyl ether (1.7 g). The reaction mixture was then poured into ice-cold dilute hydrochloric acid and extracted with ethyl acetate. The crude product, so obtained, in dichloromethane (50 ml) was stirred at −10 °C and treated with a solution of boron trichloride (6.0 g) in 1,2-dichloroethane (20 ml). After 20 min the usual work-up gave the crude product which was chromatographed over silica gel with 5—20% ethyl acetate–light petroleum as eluant. This gave first *methyl 3-hydroxy-5-methoxy-2-(3-methoxy-2,5-dimethylphenoxy)-4-methylbenzoate* (17) (319 mg) which formed prisms (from methanol), m.p. 178—179.5 °C (Found: C, 65.75; H, 6.5%; M^+, 346. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%; M, 346); δ ($CDCl_3$; 90 MHz) 2.15 (3 H, s, $W_{1/2}$ 2.4 Hz, Me), 2.21 (3 H, s, 4-Me), 2.26 (3 H, s, $W_{1/2}$ 2.0 Hz, Me), 3.60 3.82, and 3.88 (each 3 H, s, OMe), 5.76 (1 H, s, D_2O exchangeable OH), 5.83 (1 H, m, $W_{1/2}$ 3.2 Hz, 6'-H), 6.35 (1 H, m, $W_{1/2}$ 3.1 Hz, 4'-H), and 7.01 (1 H, s, 6-H). Further elution furnished *methyl 2-(4-formyl-3-hydroxy-2,5-dimethylphenoxy)-3-hydroxy-5-methoxy-4-methylbenzoate* (20) (159 mg) as prisms (from chloroform–methanol), m.p. 235—240° (decomp.) (Found: C, 63.7; H, 5.9%, M^+, 360. $C_{19}H_{20}O_7$ requires C, 63.35; H, 5.6%; M, 360); δ ($CDCl_3$; 60 MHz) 2.19, 2.22, and 2.33 (each 3 H, s, Me), 3.56 and 3.80 (each 3 H, s, OMe), 5.40 (1 H, s, D_2O exchangeable OH), 5.61 (1 H, s, 6'-H), 6.90 (1 H, s, 6-H), 10.15 (1 H, s, CHO), and 12.49 (1 H, s, D_2O exchangeable OH). The *diacetate* (21) (pyridine–acetic anhydride–90°) formed prisms (from methanol), m.p. 169—170° (Found: C, 62.05; H, 5.6%; M^+, 444. $C_{23}H_{24}O_9$ requires C, 62.15; H, 5.45%; M, 444). Later fractions gave *methyl 2-(6-formyl-3-methoxy-2,5-dimethylphenoxy)-3-hydroxy-5-methoxy-4-methylbenzoate* (18) (291 mg) as needles (from dichloromethane–light petroleum), m.p. 156—158° (Found: C, 64.15; H, 6.0%; M^+, 374. $C_{20}H_{22}O_7$ requires C, 64.15; H, 5.9%; M, 374); δ ($CDCl_3$; 90 MHz) 1.66 (3 H, s, $W_{1/2}$ 1.9 Hz, Me), 2.22 (3 H, s, 4-Me), 2.56 (3 H, s, $W_{1/2}$ 2.0 Hz, Me), 3.33, 3.81, and 3.82 (each 3 H, s, OMe), 6.42 (1 H, s, $W_{1/2}$ 2.4 Hz, 4'-H), 6.61 (1 H, s, 6-H), 6.67 (1 H, s, D_2O exchangeable OH), and 10.43 (1 H, s, CHO). The *acetate* (19) formed prisms (from dichloromethane–light petroleum), m.p. 133—134° (Found: C, 63.6; H, 5.9%; M^+, 416. $C_{22}H_{24}O_8$ requires C, 63.45; H, 5.8%; M, 416); δ ($CDCl_3$; 90 MHz) 1.82 (6 H, s, 2 × Me), 1.98 and 2.62 (each 3 H, s, Me), 3.71 (3 H, s, OMe), 3.85 (6 H, s, 2 × OMe), 6.48 (1 H, s, 4'-H), 7.15 (1 H, s, 6-H), and 10.43 (1 H, s, CHO).

Formylation and Subsequent Treatment with Boron Trichloride of the Diaryl Ether (16).—Tin(IV) chloride in dichloromethane (10 ml) was added dropwise over 5 min with stirring and ice-cooling to a solution of the diaryl ether (16) (7.0 g) in dichloromethane (125 ml) and dichloromethyl methyl ether (4.0 g). The solution was stirred at 0 °C for 0.5 h and worked up as before. The crude product in dichloromethane (25 ml) was added with stirring at −10 °C to a solution of boron trichloride (17 g) in 1,2-dichloroethane. After 0.5 h at −10 °C work-up gave the crude product which was boiled with carbon tetrachloride (150 ml) and then filtered. The solid residue was the pure (t.l.c.) aldehyde (20) (2.0 g). The filtrate was evaporated under reduced pressure and the residue was heated for 1 h on a steam-bath with pyridine (15 ml) and acetic anhydride (15 ml). The solvents were removed under reduced pressure and the residue was chromatographed over silica gel with 5—15% ethyl acetate–light petroleum as eluant. This gave the acetate (19) (4.4 g) as prisms (from aqueous methanol), m.p. 133—134°.

2-(2-Acetoxy-6-methoxycarbonyl-4-methoxy-3-methylphenoxy)-4-methoxy-3,6-dimethylbenzoic Acid (22).—A solution of sodium chlorite (0.40 g; 80% technical) in water (10 ml) was added dropwise with stirring to a solution of the aldehyde (19) (1.00 g) and sulphamic acid (1.4 g) in dioxan (20 ml) and water (10 ml). After 1 h the mixture was diluted with water and extracted with ethyl acetate. The crude product was chromatographed over silica gel with 20% ethyl acetate–dichloromethane as eluant. The *acid* (22) (857 mg) formed prisms (from dichloromethane–light petroleum), m.p. 185—186.5° (Found: C, 60.9; H, 5.65%; M^+, 432. $C_{22}H_{24}O_9$ requires C, 61.1; H, 5.6%; M, 432) δ ($CDCl_3$; 90 MHz) 1.81 (3 H, s, $W_{1/2}$ 2.0 Hz, Me), 2.03 (6 H, s, 3'-Me and MeCO), 2.39 (3 H, s, $W_{1/2}$ 2.0 Hz, Me), 3.67, 3.81, and 3.83 (each 3 H, s, OMe), 6.47 (1 H, s, 5-H), 7.05 (1 H, s, 5'-H), and 7.68br (1 H, OH).

Methyl 3,8-Dimethoxy-1,4,9-trimethyl-11-oxo-11H-dibenzo[b,e][1,4]*dioxepin-6-carboxylate* (*Methyl O-Methylhypopsoromate*) (23).—The acid (22) (790 mg) was stirred at −78 °C in dichloromethane (150 ml) and treated with boron trichloride (4.0 g) in dichloromethane (30 ml). The solution was stirred at −78 °C for 0.5 h and at room temperature for 4.5 h. The usual work-up gave the *hypopsoromate* (23) (568 mg) as needles (from dichloromethane–methanol), m.p. and mixed m.p. 202—203° (lit.,[2] 202—202.2°), identical (mass and n.m.r. spectra and R_F values in three solvent systems) with an authentic sample [2] (Found: C, 64.35; H, 5.3%; M^+, 372. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%; M, 372).

Photobromination and Subsequent Hydrolysis of Methyl O-Methylhypopsoromate (23).—The hypopsoromate (23) (500 mg) was boiled under reflux in carbon tetrachloride (18 ml) over a 100 W tungsten lamp and treated dropwise with bromine (232 mg) in carbon tetrachloride (10 ml) over 1 h. After a further 20 min the solution was cooled, diluted with ethyl acetate, and washed with water. The crude product was boiled under reflux with dioxan (60 ml) and water (30 ml) for 22.5 h. The crude product was chromatographed over silica gel with 10—40% ethyl acetate–light petroleum as eluant. This gave first the starting material (23) (80 mg). Further elution gave *methyl 4-(hydroxymethyl)-3,8-dimethoxy-1,9-dimethyl-11-oxo-11H-dibenzo*[b,e]*dioxepin-6-carboxylate* (24) (120 mg) as needles (from dichloromethane–light petroleum), m.p. 209—210° (Found: C, 61.6; H, 5.1. $C_{20}H_{20}O_8$ requires C, 61.85; H, 5.2%); δ ($CDCl_3$; 90 MHz) 2.26 (3 H, s, 9-Me), 2.51 (3 H, s, 1-Me), 3.83, 3.87, and 4.00 (each 3 H, s, OMe), 4.78 (2 H, s, CH_2), 6.61 (1 H, s, 2-H), and 7.00 (1 H, s, 7-H); irradiation at δ 2.51 sharpened the 2-H signal; *m/e* 388 (100%, M^+, $C_{20}H_{20}O_8$), 177 (28, $C_{10}H_9O_3$). The column was stripped with ethyl acetate and the residue was subjected to p.l.c. [toluene–acetic acid (200 : 5 v/v)]. The faster running

band gave *methyl* 9-(*hydroxymethyl*)-3,8-*dimethoxy*-1,4-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-6-*carboxylate* (25) (23.5 mg) as needles (from dichloromethane–light petroleum), m.p. 220.5—221.5° (Found: C, 61.95; H, 5.45. $C_{20}H_{20}O_8$ requires C, 61.85; H, 5.2%); δ ($CDCl_3$; 90 MHz) 2.15 (3 H, s, 4-Me), 2.48 (3 H, s, 1-Me), 3.83, 3.86, and 3.98 (each 3 H, s, OMe), 4.85 (2 H, s, CH_2), 6.53 (1 H, s, 2-H), and 6.93 (1 H, s, 7-H); irradiation at δ 2.48 sharpened the 2-H signal; *m/e* 388 (72%, M^+, $C_{20}H_{20}O_8$), 329 (100), and 179 (25, $C_{10}H_{11}O_3$). The slower band yielded *methyl* 2-[(1,3-*dihydro*-6-*methoxy*-4-*methyl*-3-*oxoisobenzofuran*-4-*yl*)-*oxy*]-3-*hydroxy*-5-*methoxy*-4-*methylbenzoate* (26) (15.0 mg), as prisms (from chloroform–light petroleum), m.p. 176—178° (Found: M^+, 388.1140. $^{12}C_{20}{}^1H_{20}{}^{16}O_8$ requires M, 388.1158); δ ($CDCl_3$; 90 MHz) 2.09 and 2.22 (each 3 H, s, Me), 3.42, 3.80, and 3.91 (each 3 H, s, OMe), 5.10 (2 H, s, CH_2), 6.60 (1 H, s, 7'-H), and 6.69 (1 H, s, 6-H); $\nu_{max.}$($CHCl_3$) 1 763 (lactone C=O) and 1 723 (ester C=O) cm^{-1}.

Methyl 4-*Formyl*-3,8-*dimethoxy*-1,9-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-6-*carboxylate* (*Methyl* O-*Methylpsoromate*) (1).—The benzyl alcohol (24) (80.0 mg) in dichloromethane (5 ml) was added dropwise to a stirred suspension of pyridinium chlorochromate (70.0 mg) in dichloromethane (2 ml). The mixture was stirred for 2.5 h, and at intervals of 2 h two successive additions of pyridinium chlorochromate (each 10 mg) were made. After a total of 7 h, ethanol (3 ml) was added and the mixture was diluted with ethyl acetate and washed in turn with water, saturated sodium hydrogencarbonate solution, water, and finally with saturated brine. The crude product crystallized from dichloromethane–light petroleum as needles (76.0 mg) of the *psoromate* (1), m.p. and mixed m.p. 232.5—233.5° (lit.,[2] 233—233.5°), identical (mass and n.m.r. spectra and R_F values in three solvent systems) with an authentic sample [2] (Found: C, 62.05; H, 4.75. $C_{20}H_{18}O_8$ requires C, 62.2; H, 4.7%).

Methyl 4-*Formyl*-3-*hydroxy*-8-*methoxy*-1,9-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-6-*carboxylate* (*Methyl Psoromate*) (27).—Boron trichloride (0.5 g) in dichloromethane (20 ml) was added dropwise to a stirred solution of the psoromate (1) (100.0 mg) in dichloromethane at 0 °C. After 5 h the solvent was removed under reduced pressure and cold dilute hydrochloric acid was added to the residue which was then extracted with ethyl acetate. The crude product crystallized from dichloromethane–light petroleum as needles (91.4 mg) of *methyl psoromate*, m.p. and mixed m.p. 215.5—217.5° (lit.,[2] 214—216°), identical (mass and n.m.r. spectra and R_F values in three solvent systems) with an authentic sample [2] (Found: C, 61.2; H, 4.4. $C_{19}H_{16}O_8$ requires C, 61.3; H, 4.35%)

4-*Formyl*-3-*hydroxy*-8-*methoxy*-1,9-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-6-*carboxylic Acid* (*Psoromic Acid*) (28).—Methyl psoromate (1) (42.0 mg) and anhydrous lithium iodide (250 mg) were stirred in dry hexamethylphosphoric triamide (5 ml) at 90 °C (bath) for 5 h, when more lithium iodide (250 mg) was added. Stirring at 90 °C was continued for a further 21 h when the cooled mixture was partitioned between dilute hydrochloric acid and ethyl acetate. The organic extract was washed in turn with water, aqueous sodium thiosulphate, and finally saturated brine. The residue crystallized from aqueous dimethyl sulphoxide as needles (38.2 mg) of *psoromic acid* (28), m.p. and mixed m.p. 264—265° (decomp.) [lit.,[2,23] 265—266° (decomp.), 265° (decomp.)], identical (mass and n.m.r. spectra and R_F values in three solvent systems) with an authentic sample (Found: C, 58.9; H, 4.2. $C_{18}H_{14}O_8 \cdot \frac{1}{2}H_2O$ requires C, 58.9; H, 4.1%); δ (CD_3SOCD_3; 90 MHz) 2.20 and 2.46 (each 3 H, s, Me), 3.83 (3 H, s, OMe), 6.83 (1 H, s, 2-H), 7.08 (1 H, s, 7-H), and 10.46 (1 H, s, CHO).

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REFERENCES

[1] Part 13, R. Jongen, T. Sala, and M. V. Sargent, preceding paper.
[2] S. Huneck and M. V. Sargent, *Austral. J. Chem.*, 1976, **29**, 1059.
[3] T. Sala and M. V. Sargent, *J.C.S. Chem. Comm.*, 1978, 1043.
[4] F. Wessely, J. Swoboda, and V. Guth, *Monatsh.*, 1964, **95**, 649.
[5] K. R. Hargreaves and A. McGookin, *J. Soc. Chem. Ind.*, 1950, **69**, 186 (*Chem. Abs.*, 1951, **45**, 2453).
[6] E. A. Braude, R. P. Linstead, and K. R. H. Woolridge, *J. Chem. Soc.*, 1954, 3586.
[7] L. C. Behr, in 'Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings,' ed. R. H. Wiley, Interscience, New York, 1967.
[8] A. W. Baker, *J. Amer. Chem. Soc.*, 1958, **20**, 3598.
[9] T. M. Cresp, P. Djura, M. V. Sargent, J. A. Elix, U. Engkaninan, and D. P. H. Murphy, *Austral. J. Chem.*, 1975, **28**, 2417.
[10] T. H. Simpson, *J. Org. Chem.*, 1963, **28**, 2107.
[11] W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, 1947, **69**, 1361.
[12] T. M. Cresp and M. V. Sargent, *J.C.S. Perkin I*, 1974, 2145.
[13] M. V. Sargent, unpublished data.
[14] T. Sala and M. V. Sargent, *J.C.S. Chem. Comm.*, 1978, 253.
[15] B. O. Lindgren and T. Nilsson, *Acta Chem. Scand.*, 1973, **27**, 888.
[16] T. Sala and M. V. Sargent, *Austral. J. Chem.*, 1978, **31**, 1383.
[17] E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 2647.
[18] *Cf.* F. Elzinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **49**, 113.
[19] I. K. Barben and H. Suschitzsky, *J. Chem. Soc.*, 1960, 672.
[20] J. A. Elix and S. Norfolk, *Austral. J. Chem.*, 1975, **28**, 1113.
[21] Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem.*, 1978, **43**, 2087.
[22] A. St. Pfau, *Helv. Chim. Acta*, 1926 **9**, 650.
[23] Y. Asahina and H. Hayashi, *Ber.*, 1933, **66**, 1023.