Depsidone Synthesis. Part 19.[1] Some β-Orcinol Depsidones

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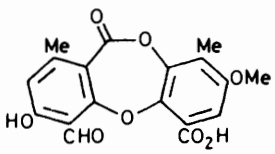
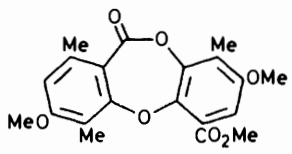
The synthesis of the lichen depsidones 3,8-dihydroxy-1,4,6,9-tetramethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]-dioxepin-7-carboxylic acid (hypoprotocetraric acid) (4), 8-hydroxy-3-methoxy-1,4,6,9-tetramethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-carboxylic acid (*O*-methylhyprprotocetraric acid) (5), 4-formyl-3,8-dihydroxy-1,6,9-trimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-carboxylic acid (virensic acid) (6), and 4-formyl-3,8-dihydroxy-9-hydroxymethyl-1,6-dimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-carboxylic acid (protocetraric acid) (7) is described.

In Part 14 [2] we described a synthesis of the lichen depsidone psoromic acid (1) which depended on selective functionalization of the depsidone (2) by photobromination. We now describe the extension of this work to the photobromination of other depsidones of the β-orcinol group such as (3) which possess four methyl substituents. The aim of the present work was to devise a synthesis of the lichen depsidones virensic acid (6) [3] and protocetraric acid (7) [4] the structures of which had been determined by classical methods but never confirmed by synthesis. Thus the substitution pattern of virensic acid (6) followed from its hydrogenation to hypoprotocetraric acid (4) and the position of the formyl group was fixed by recourse to degradation and the judicious use of i.r. spectroscopic data and colour tests. The structure of protocetraric acid (7) was determined by similar means.



(1)



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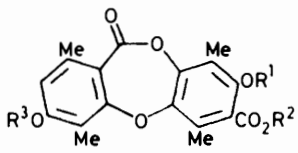
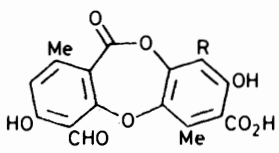


(3) $R^1 = R^2 = R^3 = Me$
(4) $R^1 = R^2 = R^3 = H$
(5) $R^1 = R^2 = H$, $R^3 = Me$



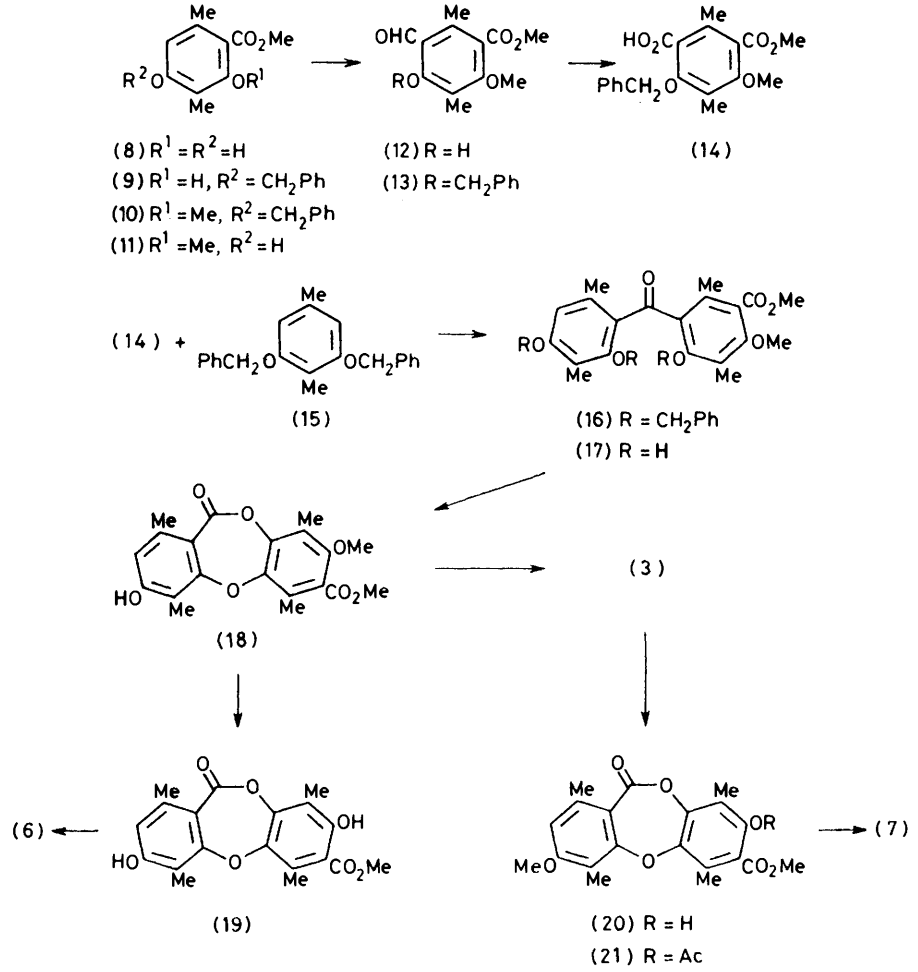
(6) R = Me
(7) R = CH_2OH

It was argued, because of the electronic effects of the substituents,[5] that photobromination of the depsidone (3) with 1 mol equiv. of bromine would occur preferentially at the methyl group at the 4-position, and with 2 mol equiv. of bromine preferentially at the methyl groups at the 4- and 9-positions. In order to test these predictions we required an efficient synthesis of the depsidone (4). We have previously described a synthesis of the *O*-methylhypoprotocetraric acid (5) by intramolecular Ullmann reaction of a depside and subsequent steps but the yield was very low.[6] We therefore decided to use the method based on benzophenone–grisadienedione–depsidone interconversion.[7] Consequently we required a synthesis of the benzophenone (17) (see Scheme) and therefore of the acid (14). Methyl β-orcinolcarboxylate (8),[2] on benzylation with 1 mol equiv. each of benzyl bromide and potassium carbonate in acetone, gave the benzyl ether (9). The derived methyl ether (10) on hydrogenolytic debenzylation afforded the known methyl isorhizinonate (11).[6] Attempts to formylate this compound by treating it with dichloromethyl methyl ether and titanium(IV) chloride in dichloromethane or by the Vilsmeier–Haack method were fruitless. Although methyl β-orcinolcarboxylate (8) undergoes smooth formylation by the Gattermann method in the presence of aluminium chloride its *O*-methyl derivatives also suffer demethylation under these conditions.[8] Formylation of compound (11) was successfully achieved by the modified Duff method.[9] The resultant aldehyde (12) was converted into its benzyl ether (13) which on oxidation with tetrabutylammonium permanaganate in pyridine [10] gave the required acid (14).

Friedel–Crafts reaction of the acid (14) and di-*O*-benzyl-β-orcinol (15) [11] in the presence of trifluoroacetic anhydride gave the tri-*O*-benzylbenzophenone (16) which on hydrogenolytic debenzylation furnished the trihydroxybenzophenone (17). Oxidation of this benzophenone with potassium hexacyanoferrate(III) in aqueous potassium carbonate gave directly the depsidone (18). This compound was readily converted into the natural products hypoprotocetraric acid (4) [12,13] and *O*-methylhypoprotocetraric acid (5).[14] Thus treatment of the depsidone (18) with boron trichloride gave methyl hypoprotocetrarate (19) which on treatment with lithium iodide in hot hexamethylphosphoric triamide gave hypoprotocetraric acid (6), identical with an authentic sample isolated from the lichen *Parmelia hypoprotocetrarica* Kurok.[15] Methylation of the depsidone (18) gave methyl di-*O*-methylhypoprotocetrarate (3). This was treated first with boron trichloride affording compound (20), and then with lithium iodide in hot hexamethylphosphoric triamide thus affording *O*-methylhypoprotocetraric acid (7), identical with an authentic sample.[14]

Photobromination with 1 mol equiv. of bromine and subsequent hydrolysis of the depsidone (3) yielded a mixture of two hydroxymethyl compounds in the ratio 1.9 : 1. The major component was formulated as the hydroxymethyl compound (22) since its mass spectrum exhibited a prominent fragment at *m/e* 177 ascribed to the ring-A ion (26). In contrast the mass spectrum of the isomer (24) exhibited prominent fragments at *m/e* 179 and 178 ascribed to the ions (27) and (28). Oxidation of the hydroxymethyl compound (22) with pyridinium chlorochromate [16] gave the aldehyde (29) which had the same m.p. as methyl di-*O*-methylvirensate.[3]

It was reasoned that photobromination of the acetate (21), readily available by acetylation of the depsidone (20), would occur with greater selectivity at the methyl group at the 4-position since the methyl group at the 9-position is now *ortho* to a less-electron-releasing substituent than in the depsidone (3). In the event photobromination of the depsidone (21) with 1 mol equiv. of bromine and subsequent hydrolysis gave two hydroxymethyl compounds in the ratio 7.6 : 1. The major isomer again exhibited a prominent fragment ion at *m/e* 177 and was thus assigned structure (23); the minor isomer was assigned structure (25). Oxidation of compound (23) with pyridinium chlorochromate gave the aldehyde (30). Treatment of this compound with lithium iodide in hot hexamethylphosphoric triamide gave virensic acid (6) identical with an authentic sample. Presumably the facile cleavage of the acetate under these conditions is due to the assistance of the neighbouring carboxylate ion.

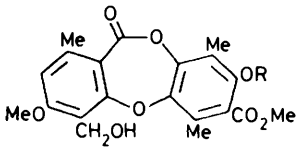


SCHEME

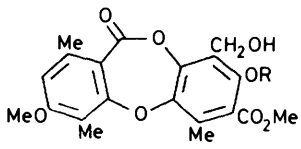
Natural virensic acid has been converted [3] into methyl virensate [3] (granulatin) [17] (31) a depsidone which occurs in *Pseudocyphellaria granulata* and *P. flaveolata*.[17] This depsidone on chlorination [17] yielded physciosporin [18] (chlorogranulatin) [17] (32) which occurs in various *Pseudocyphellaria* species. Hence the synthesis of virensic acid (6) constitutes a formal synthesis of these depsidones.

Photobromination of the depsidone (3) with 2 mol equiv. of bromine and subsequent hydrolysis gave a good yield of a bishydroxymethyldepsidone (33). Again the mass spectrum of this depsidone exhibited a prominent fragment at *m/e* 177 ascribed to the ion (26). On

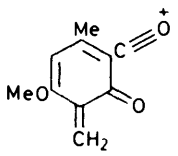
treatment with an excess of boron trichloride, followed by hydrolysis of the mixture of chloromethyl compounds produced, this depsidone (**33**) gave the demethylated product (**34**). It was desired to effect preferential oxidation of the primary alcohol at the 4-position of this



(22) R = Me
(23) R = Ac



(24) R = Me
(25) R = Ac



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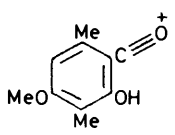

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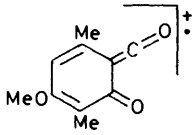

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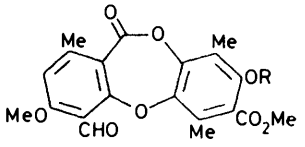
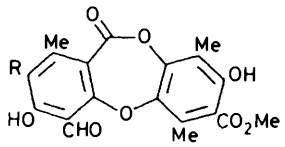
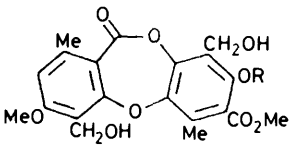


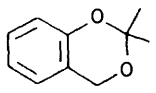
(29) R = Me
(30) R = Ac



(31) R = H
(32) R = Cl



(33) R = Me
(34) R = H



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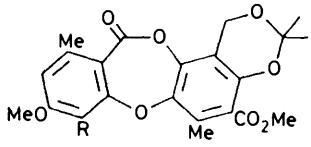
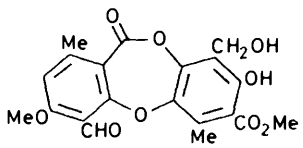


(36) R = CH_2OH
(37) R = CHO



(38)

depsidone. Ring B of the depsidone contains an *o*-hydroxymethylphenol functionality. This functionality is also found in pyridoxine where it has been protected by conversion into an acetonide.[19,20] In order to verify the stability of such an acetonide to pyridinium chlorochromate the simplest system (**35**) was prepared by treatment of saligenin with 2,2-dimethoxypropane and a trace of toluene-*p*-sulphonic acid. The depsidone (**34**) was then converted into the acetonide (**36**) which on oxidation with pyridinium chlorochromate gave the aldehyde (**37**). Removal of the protecting group with warm aqueous acetic acid afforded the depsidone (**38**) which on treatment with lithium iodide as before furnished protocetraric acid (**7**), identical with an authentic sample.

EXPERIMENTAL

General directions have been given before.[21]

Methyl 4-Benzyloxy-2-hydroxy-3,6-dimethylbenzoate (**9**).—Methyl 2,4-dihydroxy-3,6-dimethylbenzoate (**8**)[2] (3.4 g), benzyl bromide (3.3 g), and dry potassium carbonate (2.6 g) were stirred together in acetone (75 ml) under dry nitrogen for 15 h at room temperature. The mixture was then poured into cold dilute hydrochloric acid. The crude product, obtained as usual, was chromatographed over silica gel with 2.5% ethyl acetate–light petroleum as eluant. The *benzyl ether* (**9**) crystallized from pentane as needles (3.75 g), m.p. 79.5—80 °C (Found: C, 71.25; H, 6.5%; M^+, 286. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.35%; *M*, 286), δ($CDCl_3$, 90 MHz) 2.14 and 2.55 (each 3 H, s, Me), 3.89 (3 H, s, OMe), 5.08 (2 H, s, CH_2), 6.32 (1 H, s, ArH), 7.37 (5 H, narrow m, Ph), and 11.83 (1 H, s, OH).

Methyl 4-Hydroxy-2-methoxy-3,6-dimethylbenzoate (**11**).—Methylation of the foregoing compound (**9**) with methyl sulphate and potassium carbonate in acetone gave methyl 4-benzyloxy-2-methoxy-3,6-dimethylbenzoate (**10**) as prisms (from light petroleum), m.p. 73—74 °C (lit.,[6] 73—74 °C). This compound (3.6 g) in ethyl acetate (200 ml) containing concentrated hydrochloric acid (2 drops) was stirred under hydrogen with 10% palladium charcoal (0.5 g) until absorption ceased. The usual work-up gave the product as prisms (2.16 g) (from ether–light petroleum), m.p. 144—145 °C (lit.,[6] 144 °C).

Methyl 3-Formyl-4-hydroxy-6-methoxy-2,5-dimethylbenzoate (**12**).—Methyl isorhizinonate (**11**) (5.6 g), hexamethylenetetramine (4.0 g), and trifluoroacetic acid (75 ml) were heated under reflux for 2.5 h. The solvent was removed under reduced pressure and the residue was stirred in water (200 ml) for 12 h and then heated on a steam-bath for 15 min. The cooled mixture was extracted with ethyl acetate and the crude product was chromatographed over silica gel with 10—15% ethyl acetate–light petroleum as eluant. The *aldehyde* (**12**) formed blades (2.84 g) (from dichloromethane–light petroleum), m.p. 83—84 °C (Found: C, 60.4; H, 6.05%; M^+, 238. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%; *M*, 238), δ($CDCl_3$, 90 MHz) 2.09 and 2.45 (each 3 H, s, Me), 3.79 and 3.91 (each 3 H, s, OMe), 10.17 (1 H, s, CHO), and 12.62 (1 H, s, D_2O exchangeable OH).

2-Benzyloxy-5-methoxycarbonyl-4-methoxy-3,6-dimethylbenzoic Acid (**14**).—The phenol (**12**) (3.25 g), potassium carbonate (4.0 g), and benzyl bromide (2.6 g) were stirred together under dry nitrogen in *NN*-dimethylformamide (30 ml) for 16 h. The crude product was freed from benzyl bromide by steam distillation which gave methyl 4-benzyloxy-3-formyl-6-methoxy-2,5-dimethylbenzoate (**13**) as an oil (5.3 g). Tetrabutylammonium permanganate[10] (3.4 g) in pyridine (50 ml) was added dropwise over 1.25 h to a stirred solution of the aldehyde (**13**) (4.2 g) in pyridine (80 ml). After 7 h the usual work-up gave the *acid* (**14**) as prisms (4.0 g) (from dichloromethane–light petroleum), m.p. 103—105 °C (Found: C, 66.05; H, 5.6%; M^+, 344. $C_{19}H_{20}O_6$ requires C, 66.25; H, 5.85%; *M*, 344), δ($CDCl_3$, 90 MHz) 2.20 and 2.30 (each 3 H, s, Me), 3.79 and 3.92

(each 3 H, s, OMe), 4.94 (2 H, s, CH_2), 7.33 (5 H, m, Ph). and 10.25br (1 H, OH).

Methyl 4-Benzyloxy-3-(2,4-bisbenzyloxy-3,6-dimethylbenzoyl)-6-methoxy-2,5-dimethylbenzoate (16).—Trifluoroacetic anhydride (12.5 ml) in dry dichloromethane (30 ml) was added dropwise at 0 °C over 20 min to a stirred solution of the acid (14) (3.0 g) and 1,3-bisbenzyloxy-2,5-dimethylbenzene (15) [11] (11.1 g) in dry dichloromethane (60 ml). The solution was then stirred at room temperature for 2 h and diluted with ether and washed in turn with water, dilute aqueous ammonium hydroxide, water, and finally saturated brine. The crude product was chromatographed over silica gel with 5—15% ethyl acetate–light petroleum as eluant. The *benzophenone* (16) (2.35 g) formed yellow prisms (from ether–pentane), m.p. 109—112° (Found: C, 76.2; H, 6.4. $C_{41}H_{40}O_7$ requires C, 76.35; H, 6.25%), δ($CDCl_3$, 90 MHz) 1.82, 2.10, 2.17, and 2.21 (each 3 H, s, Me), 3.91 and 4.02 (each 3 H, s, OMe), 4.61 and 4.68 * (total 2 H, each s, CH_2), 4.80 (2 H, s, $W_{\frac{1}{2}}$ 5.0 Hz, CH_2), 5.09 (2 H, s, CH_2), 6.24 (1 H, s, ArH), 7.23 (10 H, s, Ph), and 7.37 (5 H, s, Ph).

Methyl 3-(2,4-Dihydroxy-3,6-dimethylbenzoyl)-4-hydroxy-6-methoxy-2,5-dimethylbenzoate (17).—The benzophenone (16) (1.45 g) in ethyl acetate (100 ml) containing concentrated hydrochloric acid (2 drops) was stirred with 10% palladium–charcoal (250 mg) under hydrogen until absorption ceased. The usual work-up gave the *benzophenone* (17) as yellow blades (820 mg) (from dichloromethane–light petroleum), m.p. 164—165° (Found: C, 64.2; H, 5.95%; M^+, 374. $C_{20}H_{22}O_7$ requires C, 64.15; H, 5.9%; *M*, 374), δ($CDCl_3$–CD_3SOCD_3, 90 MHz) 1.79, 1.98, 2.06, and 2.14 (each 3 H, s, Me), 3.75 and 3.86 (each 3 H, s, OMe), and 6.21 (1 H, s, ArH).

Methyl 3-Hydroxy-8-methoxy-1,4,6,9-tetramethyl-11-oxo-11H-dibenzo[b,e][1,4]*dioxepin-7-carboxylate* (18).—Potassium hexacyanoferrate(III) (1.1 g) in water (65 ml) was added in one portion to a stirred solution of the benzophenone (17) (550 mg) and potassium carbonate (4.4 g) in water (140 ml). The solution was stirred for 1 h and then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The product crystallized from dichloromethane–light petroleum as prisms (430 mg) of the *depsidone* (18), m.p. 170—171 °C with resolidification to rods, m.p. 220—221 °C (Found: C, 64.75; H, 5.7%; M^+, 372. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%; *M*, 372), δ($CDCl_3$, 90 MHz) 2.27 and 2.31 (each 3 H, s, Me), 2.37 (6 H, s, 2 × Me), 3.73 and 3.93 (each 3 H, s, OMe), 6.47 (1 H, s, ArH), and 6.83 (1 H, s, D_2O exchangeable OH). The *methyl ether* (3), prepared by methylation of (18) with iodomethane and potassium carbonate in *NN*-dimethylformamide, formed needles (from dichloromethane–light petroleum) which changed into prisms at 145—150 °C which then had m.p. 176—177.5 °C undepressed on admixture with an authentic sample [lit.,[12] 144—145 and 172—173 °C (dimorphic)] (Found: C, 65.55; H, 5.85%; M^+, 386. $C_{21}H_{22}O_7$ requires C, 65.3; H, 5.75%; *M*, 386), δ($CDCl_3$, 90 MHz) 2.28, 2.31, 2.37, and 2.50 (each 3 H, s, Me), 3.73, 3.85, and 3.97 (each 3 H, s, OMe), and 6.57 (1 H, s, ArH).

Methyl 3,8-Dihydroxy-1,4,6,9-tetramethyl-11-oxo-11H-dibenzo[b,e][1,4]*dioxepin-7-carboxylate* (19).—Boron trichloride (1.0 g) in dichloromethane (20 ml) was added dropwise over 15 min to a stirred solution of the depsidone (18) (200 mg) in dichloromethane (20 ml). The solution was then stirred at room temperature for 4.25 h. The usual work-up gave the *depsidone* (19) which crystallized from acetone–light petroleum as prisms (180 mg) which changed into needles at 200 °C and then had m.p. 259.5—261.5 °C (decomp.) [lit.,[12,13] 257—260 (decomp.), 260—261 °C (decomp.)] (Found: C, 63.6; H, 5.4%; M^+, 358. $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.05%; *M*, 358), δ($CDCl_3$–CD_3SOCD_3, 90 MHz) 2.19, 2.29, 2.37, and 2.60 (each 3 H, s, Me), 3.94 (3 H, s, OMe), and 6.60 (1 H, s, ArH).

3,8-Dihydroxy-1,4,6,9-tetramethyl-11-oxo-11H-dibenzo[b,e][1,4]*dioxepin-7-carboxylic Acid* (*Hypoprotocetraric Acid*) (4).—The depsidone (19) (100 mg) and anhydrous lithium iodide (1.0 g) were suspended in dry hexamethylphosphoric triamide (17 ml) and stirred under dry nitrogen at 90 °C (bath) for 20 h. The mixture was diluted with water and extracted with ethyl acetate. The aqueous layer was acidified and extracted with ethyl acetate. The extract was washed in turn with water, aqueous sodium thiosulphate, and finally saturated brine. The depsidone (4) crystallized from acetone–hexane (charcoal) as prisms (40 mg), m.p. 242—245 °C (decomp.) (block preheated to 230 °C) [lit.,[12,4,22] 242—243 (decomp.), 241 (decomp.), 250—251 °C (decomp.)], identical (mixed m.p., mass and n.m.r. spectra, and R_F values in three solvent systems) with an authentic sample; δ($CDCl_3$–CD_3SOCD_3, 90 MHz) 2.17, 2.28, 2.35, and 2.66 (each 3 H, s, Me), and 6.59 (1 H, s, ArH).

Methyl 8-Hydroxy-3-methoxy-1,4,6,9-tetramethyl-11-oxo-11H-dibenzo[b,e][1,4]*dioxepin-7-carboxylate* (20).—Boron trichloride (1.0 g) in dichloromethane (20 ml) was added over 10 min to a solution of the depsidone (3) (200 mg) in dichloromethane (20 ml) at 0 °C. The solution was then stirred at room temperature for 5 h and then worked up in the usual way. The depsidone (20) crystallized from chloroform–methanol as needles (171 mg), m.p. 225—226 °C (lit.,[13,14] 219, 219—220 °C); δ($CDCl_3$–CD_3SOCD_3, 90 MHz) 2.19, 2.30, 2.45, and 2.57 (each 3 H, s, Me), 3.86 and 3.93 (each 3 H, s, OMe), and 6.65 (1 H, s, ArH). The *acetate* (21) (pyridine, acetic anhydride, 90 °C, 3 h) crystallized from dichloromethane–light petroleum (charcoal) as laths (96%), m.p. 188—189 °C (Found: C, 63.9; H, 5.5%; M^+, 414. $C_{22}H_{22}O_8$ requires C, 63.75; H, 5.35%; *M*, 414), δ($CDCl_3$, 90 MHz) 2.16 (3 H, s, Me), 2.26 (3 H, s, MeCO), 2.30, 2.45, and 2.48 (each 3 H, s, Me), 3.85 and 3.86 (each 3 H, s, OMe), and 6.57 (1 H, s, ArH).

8-Hydroxy-3-methoxy-1,4,6,9-tetramethyl-11-oxo-11H-dibenzo[b,e][1,4]*dioxepin-7-carboxylic Acid* (*3-O-Methylhypoprotocetraric Acid*) (5).—The depsidone (20) (100 mg) was treated with lithium iodide (1.0 g) in hexamethylphosphoric triamide as before. The crude product was crystallized from chloroform–methanol and formed needles (47 mg) of the *depsidone* (5), m.p. 229—231 °C (decomp.) (block preheated to 210 °C) [lit.,[14] 228—229 °C (decomp.)], identical (mixed m.p., mass and n.m.r. spectra, and R_F values in three solvent systems) with an authentic sample (Found: C, 63.35; H, 5.35; M^+, 358. $C_{19}H_{18}O_7$ requires C, 63.7; H, 5.05%; *M*, 358), δ($CDCl_3$, 90 MHz) 2.18, 2.31, 2.45, and 2.67 (each 3 H, s, Me), 3.86 (3 H, s, OMe), and 6.65 (1 H, s, ArH).

Bromination and Subsequent Hydrolysis of Methyl 3,8-Dimethoxy-1,4,6,9-tetramethyl-11-oxo-11H-dibenzo[b,e][1,4]*dioxepin-7-carboxylate* (3).—A solution of the depsidone (3) (500 mg) in carbon tetrachloride (10 ml) was boiled under reflux over a 100 W tungsten lamp whilst bromine (211 mg) in carbon tetrachloride (10 ml) was added dropwise over 45 min. The solution was heated under reflux for 15 min then

* The splitting of the signal due to these benzylic protons is presumably due to rotational isomerism.

cooled and diluted with ether and washed with water and with saturated brine. The crude product in dioxan (60 ml) and water (30 ml) was heated under reflux for 4.25 h. The usual work-up gave a crude product which was purified by preparative t.l.c. over 5 plates which were multiply developed with 10—30% ethyl acetate–light petroleum. The fastest moving band gave the starting material (149 mg). A band of lower R_F was resubjected to preparative t.l.c. (dichloromethane). The faster band yielded *methyl* 4-*hydroxymethyl*-3,8-*dimethoxy*-1,6,9-*trimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (22) (149 mg) which formed prisms (from dichloromethane–hexane), m.p. 157—158.5 °C (Found: C, 62.75; H, 5.75. $C_{21}H_{22}O_8$ requires C, 62.7; H, 5.5%), δ($CDCl_3$, 80 MHz) 2.28, 2.41, and 2.52 (each 3 H, s, Me), 3.74, 3.90, and 3.93 (each 3 H, s, OMe), 4.95 (2 H, s, CH_2), and 6.64 (1 H, s, ArH); *m/e* 402 (M^+, 100%, $C_{21}H_{22}O_8$), 374 (64), and 177 (29, $C_{10}H_9O_3$). The slower band yielded *methyl* 9-*hydroxymethyl*-3,8-*dimethoxy*-1,4,6-*trimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (24) (80 mg) which formed prisms (from dichloromethane–light petroleum), m.p. 140—141 °C (Found: C, 62.9; H, 5.6. $C_{21}H_{22}O_8$ requires C, 62.7; H, 5.5%); δ($CDCl_3$, 80 MHz) 2.31, 2.39, and 2.49 (each 3 H, s, Me), 3.85 (6 H, s, 2 × OMe), 3.91 (3 H, s, OMe), 4.79 (2 H, s, CH_2), and 6.57 (1 H, s, ArH); *m/e* 402 (M^+, 59%), 344 (100), 179 (24), and 178 (18).

Methyl 4-*Formyl*-3,8-*dimethoxy*-1,6,9-*trimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (*Methyl Di-O-methylvirensate*) (29).—The alcohol (22) (86 mg) in dichloromethane (5 ml) was added rapidly to a stirred suspension of pyridinium chlorochromate (80 mg) in dichloromethane (5 ml). After 2 h a further portion of pyridinium chlorochromate (20 mg) was added and after a further 2.5 h ethanol (5 ml) was added. The mixture was then diluted with ethyl acetate and worked up as usual. The crude product was crystallized from dichloromethane–light petroleum (charcoal) and gave the *virensate* (29) (60.5 mg) as rosettes of needles, m.p. 160—162 °C (lit.,[3] 160—162 °C) (Found: C, 62.8; H, 5.15%; M^+, 400. $C_{21}H_{20}O_8$ requires C, 63.0; H, 5.05%; *M*, 400), δ($CDCl_3$, 80 MHz) 2.22, 2.29, and 2.56 (each 3 H, s, Me), 3.74, 3.90, and 3.96 (each 3 H, s, OMe), 6.65 (1 H, s, ArH), and 10.64 (1 H, s, CHO).

Bromination and Subsequent Hydrolysis of Methyl 8-*Acetoxy*-3-*methoxy*-1,4,6,9-*tetramethyl*-11-*oxo*-11H-*dibenzo*-[b,e][1,4]*dioxepin*-7-*carboxylate* (21).—The depsidone (21) (1.200 g) in carbon tetrachloride (120 ml) was boiled under reflux over a 100 W tungsten lamp whilst bromine (503 mg) in carbon tetrachloride (60 ml) was added dropwise over 1 h. The mixture was worked up in the usual way after a further 15 min. The oily product was then boiled under reflux for 4.5 h in a mixture of dioxan (180 ml) and water (90 ml). The crude product was chromatographed over silica gel with 5—40% ethyl acetate–light petroleum as eluant to give at first starting material (21) (204 mg). Later fractions gave *methyl* 8-*acetoxy*-4-*hydroxymethyl*-3-*methoxy*-1,6,9-*trimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (23) which crystallized from dichloromethane–light petroleum as plates (545 mg), m.p. 202—205 °C (Found: C, 61.65; H, 5.5. $C_{22}H_{22}O_9$ requires C, 61.4; H, 5.15%), δ($CDCl_3$, 90 MHz) 2.16 (3 H, s, Me), 2.27 (3 H, s, MeCO), 2.49 and 2.51 (each 3 H, s, Me), 3.87 and 3.93 (each 3 H, s, OMe), 4.95 (2 H, s, CH_2), and 6.65 (1 H, s, ArH); *m/e* 430 (M^+, 31%), 388 (100), 328 (88), 274 (51), and 177 (31, $C_{10}H_9O_3$). This was followed by *methyl* 8-*acetoxy*-9-*hydroxymethyl*-3-*methoxy*-1,4,6-*trimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (25) which crystallized from dichloromethane–light petroleum as small prisms (72 mg), m.p. 190—193 °C (Found: C, 61.5; H, 5.55. $C_{22}H_{22}O_9$ requires C, 61.4; H, 5.15%), δ($CDCl_3$, 90 MHz) 1.86 (3 H, s, Me), 2.06 (6 H, s, 2 × Me), 2.26 (3 H, s, MeCO), 3.78 and 3.92 (each 3 H, s, OMe), 5.12 (2 H, s, CH_2), 6.52 (1 H, s, ArH), and 6.67 (1 H, s, D_2O exchangeable OH); *m/e* 430 (M^+, 15%, $C_{22}H_{22}O_9$), 388 (69), 356 (100), 179 (7, $C_{10}H_{11}O_3$), 178 (14, $C_{10}H_{10}O_3$), and 164 (55).

Methyl 8-*Acetoxy*-4-*formyl*-3-*methoxy*-1,6,9-*trimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (30).—The alcohol (23) (288 mg) in dichloromethane (16 ml) was added rapidly to a stirred suspension of pyridinium chlorochromate (320 mg) in dichloromethane (16 ml). After 3 h the usual work-up gave the *aldehyde* (30) which crystallized from dichloromethane–light petroleum as needles (210 mg), m.p. 224—225 °C (Found: C, 61.8; 4.95%; M^+, 428. $C_{22}H_{20}O_9$ requires C, 61.7; H, 4.7%; *M*, 428), δ($CDCl_3$, 90 MHz) 2.17 (3 H, s, Me), 2.27 (3 H, s, MeCO), 2.29 and 2.56 (3 H, s, Me), 3.86 and 3.96 (each 3 H, s, OMe), 6.73 (1 H, s, ArH), and 10.63 (1 H, s, CHO).

4-*Formyl*-3,8-*dihydroxy*-1,6,9-*trimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylic Acid* (*Virensic Acid*) (6).—The depsidone (30) (74 mg) and dry lithium iodide (1.5 g) were heated and stirred under dry nitrogen for 40 h at 100 °C (bath) in hexamethylphosphoric triamide (20 ml). The reaction mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with aqueous sodium thiosulphate and then exhaustively with sodium hydrogencarbonate solution. The recovered acid was applied to a preparative t.l.c. plate which was developed with 10% methanol–chloroform. The purified *virensic acid* (6) (67 mg) crystallized from acetone as needles, m.p. 248—250 °C (decomp.) (sealed tube, electrical coil apparatus) (lit.,[3] 245—247 °C), identical (mixed m.p., mass and n.m.r. spectra, and R_F values in three solvent systems) with an authentic sample; δ(CD_3COCD_3, 80 MHz) 2.21, 2.52, and 2.70 (each 3 H, s, Me), 6.81 (1 H, s, ArH), and 10.79 (1 H, s, CHO); *m/e* 359 (24%), 358 (M^+, 100, $C_{18}H_{14}O_8$), 341 (13), 340 (49), 314 (17), 313 (23), 312 (87), 311 (15), 286 (9), 285 (29), 284 (25), 283 (11), 273 (10), 272 (49), 259 (13), 258 (60), 257 (27), 256 (30), 245 (25), 230 (21), 209 (10), 207 (13), 180 (15), 179 (42, $C_9H_7O_4$), 177 (27, $C_9H_5O_4$), 170 (17), 152 (9), 151 (10), 150 (10), 134 (12), 131 (13), 106 (30), and 105 (18).

Methyl 4,9-*Bishydroxymethyl*-3,8-*dimethoxy*-1,6-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (33).—The ester (3) (2.000 g) in carbon tetrachloride (100 ml) was boiled under reflux over a 100 W tungsten lamp during the dropwise addition over 20 min of bromine (1.674 g). After a further 5 min work-up gave the crude product which was boiled under reflux with dioxan (200 ml) and water (80 ml) for 4 h. The usual work-up and chromatography of the crude product over silica gel with 20—100% ethyl acetate–light petroleum as eluant gave the *diol* (33) as prisms (1.1 g) (from dichloromethane–light petroleum), m.p. 155—160 °C with slight previous sweating (Found: C, 57.9; H, 5.6. $C_{21}H_{22}O_9 \cdot H_2O$ requires C, 57.8; H, 5.55%), δ($CDCl_3$, 60 MHz) 2.36 and 2.43 (each 3 H, s, Me), 3.74 (3 H, s, OMe), 3.82 (6 H, s, 2 × OMe), 4.64 and 4.82 (each 2 H, s, CH_2), and 6.49 (1 H, s, ArH); *m/e* 418 (M^+, 60%), 360 (100), 177 (63).

Methyl 8-*Hydroxy*-4,9-*bishydroxymethyl*-3-*methoxy*-1,6-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (34).—Boron trichloride (2.6 g) was passed into a stirred solution of the diol (33) (460 mg) in dichloromethane (40 ml). The solution was stirred at room temperature for 4.5 h. The crude product, obtained as usual, was boiled under

reflux with dioxan (50 ml) and water (20 ml) for 4 h. The crude product crystallized from acetone–light petroleum (charcoal) as prisms (240 mg) of the *triol* (34), m.p. 201—204 °C (Found: C, 59.5; H, 5.15%; M^+, 404. $C_{20}H_{20}O_9$ requires C, 59.4; H, 5.0%; M, 404), δ($CDCl_3$, 60 MHz) 2.49 and 2.72 (each 3 H, s, Me), 3.89 and 3.90 (each 3 H, s, OMe), 4.80 (4 H, s, 2 × CH_2), and 6.59 (1 H, s, ArH).

2,2-*Dimethyl*-4H-1,3-*benzodioxin* (35).—2-Hydroxymethylphenol (1.25 g) and toluene-*p*-sulphonic acid monohydrate (20 mg) were dissolved in dry *NN*-dimethylformamide (20 ml) and 2,2-dimethoxypropane (1.6 g) and set aside at room temperature for 24 h. The usual work-up gave the *acetonide* (35) as an oil (1.4 g), b.p. 110 °C (bath) at 0.01 mmHg (Found: C, 73.15; H, 7.35%; M^+, 164. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.35%; M, 164), δ($CDCl_3$, 90 MHz) 1.53 (6 H, s, 2 × Me), 4.82 (2 H, s, CH_2), and 6.72—7.26 (4 H, m, ArH).

Methyl 8-*Formyl*-9-*methoxy*-2,2,6,11-*tetramethyl*-12-*oxo*-1H,12H-[1,3]*benzodioxino*[6,5-b][1,4]*benzodioxepin*-5-*carboxylate* (37.)—The triol (34) (188 mg), toluene-*p*-sulphonic acid monohydrate (5 mg), and 2,2-dimethoxypropane (250 mg) were dissolved in dry *NN*-dimethylformamide (8 ml) and set aside for 70 h. A further portion of 2,2-dimethoxypropane (140 mg) was added and the reaction was worked up after a further 12 h. The crude acetonide (36) in dry dichloromethane (20 ml) was added to a stirred suspension of pyridinium chlorochromate (400 mg) and anhydrous sodium acetate (400 mg) in dry dichloromethane (20 ml). Work-up after 4 h gave the crude product which was applied to a preparative t.l.c. plate and then immediately eluted from the plate. Crystallization of the product from dichloromethane–light petroleum gave the *acetonide* (37) as needles (146 mg), m.p. 184—186 °C (Found: C. 62.7; H, 5.3%; M^+, 442. $C_{23}H_{22}O_9$ requires C, 62.45; H, 5.0%; M, 442), δ($CDCl_3$, 60 MHz) 1.49 (6 H, s, 2 × Me), 2.19 and 2.49 (each 3 H, s, Me), 3.78 and 3.79 (each 3 H, s, OMe), 4.80 (2 H, s, CH_2), 6.68 (1 H, s, ArH), and 10.58 (1 H, s, CHO).

Methyl 4-*Formyl*-8-*hydroxy*-9-*hydroxymethyl*-3-*methoxy*-1,6-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylate* (38).—The acetonide (37) (72 mg) in aqueous acetic acid (50%; 16 ml) was stirred and heated at 50 °C (bath) for 24 h. The usual work-up gave the *diol* (38) (59 mg) which formed needles (from dichloromethane–light petroleum), m.p. 180—187 °C (Found: C, 59.3; H, 4.85%; M^+, 402. $C_{20}H_{18}O_9$ requires C, 59.7; H, 4.5%; M, 402), δ($CDCl_3$, 60 MHz) 2.47 and 2.51 (each 3 H, s, Me), 3.89 (6 H, s, OMe), 4.80 (2 H, s, CH_2), 6.60 (1 H, s, ArH), 10.77 (1 H, s, CHO), and 11.78 (1 H, s, OH).

4-*Formyl*-3,8-*dihydroxy*-9-*hydroxymethyl*-1,6-*dimethyl*-11-*oxo*-11H-*dibenzo*[b,e][1,4]*dioxepin*-7-*carboxylic Acid* (*Protocetraric Acid*) (7).—The depsidone (38) (17 mg) and anhydrous lithium iodide (300 mg) were stirred in hexamethylphosphoric triamide (3 ml) under dry nitrogen at 80 °C (bath) for 20 h. The usual work-up gave a crude product which was purified by extraction into sodium hydrogencarbonate solution. Crystallization from acetone–light petroleum then gave prisms (6.5 mg) of the acid (7), decomp. >240 °C alone or admixed with authentic material (lit.,[4] decomp. 245—250 °C), identical (n.m.r. spectrum and R_F values in three solvent systems) with an authentic sample; δ(CD_3COCD_3, 80 MHz) 2.51 and 2.70 (each 3 H, s, Me), 4.79 (2 H, s, CH_2), 6.80 (1 H, s, ArH), and 10.79 (1 H, s, CHO).

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