# Depsidone Synthesis. Part II.[1] Diploicin and Gangaleoidin

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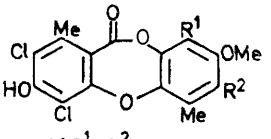
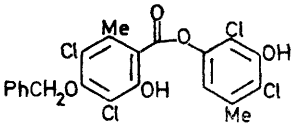
A new synthesis of the lichen depsidone diploicin (2,4,7,9-tetrachloro-3-hydroxy-8-methoxy-1,6-dimethyldibenzo[*b,e*][1,4]dioxepin-11-one) (1), and a synthesis of the lichen depsidone gangaleoidin (methyl 2,4-dichloro-3-hydroxy-8-methoxy-1,6-dimethyl-11-oxo-11*H*-dibenzo[*b,e*][1,4]dioxepin-7-carboxylate) (2) are described. The key step in both syntheses was an Ullmann reaction.

THE depsidones constitute a group of about thirty natural products based on the dibenzo[*b,e*][1,4]dioxepin-11-one system.[2] When we commenced our work in this area only the simplest member, diploicin (1),[3] had been totally synthesised.[4,5] Ollis' route [4] involved oxidative coupling of the depside (3) but we have been unable to effect similar oxidative couplings.[1] Hendrickson,[5] who questioned the generality of this seven-membered ring closure, used as the key step the solvolytic cleavage of a grisan, itself the product of an oxidative coupling. This route is again of limited generality since the oxidative coupling step was only successful with highly halogenated benzophenones. We therefore sought a more general route for the synthesis of depsidones and now describe a




(1) $R^1 = R^2 = Cl$

(2) $R^1 = H, R^2 = CO_2Me$




(3)

new synthesis of diploicin (1) and a synthesis of gangaleoidin (2), the structure of which we recently proved,[6] as examples of this method.

[1] Part I, T. M. Cresp, P. Djura, M. V. Sargent, J. A. Elix, U. Engkaninan, and D. P. H. Murphy, *Austral. J. Chem.*, 1975, in the press; see also P. Djura, J. A. Elix, U. Engkaninan, and M. V. Sargent, *J.C.S. Chem. Comm.*, 1975, 276.

[2] F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, p. 564; C. F. Culberson, 'Chemical and Botanical Guide to Lichen Products,' University of North Carolina Press, Chapel Hill, 1969.

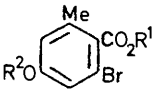
[3] T. J. Nolan, J. Algar, E. P. McCann, W. A. Manahan, and N. Nolan, *Sci. Proc. Royal Dublin Soc.*, 1948, **24**, 319.

[4] C. J. Brown, D. E. Clarke, W. D. Ollis, and P. L. Veal, *Proc. Chem. Soc.*, 1960, 393.

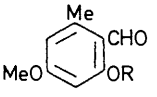
[5] J. B. Hendrickson, M. V. J. Ramsay, and T. R. Kelly, *J. Amer. Chem. Soc.*, 1972, **94**, 6834.

[6] M. V. Sargent, P. Vogel, and J. A. Elix, *J.C.S. Perkin I*, 1975, 1986.

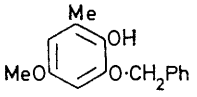
We chose to construct the diaryl ether linkage of diploicin (1) by an Ullmann reaction between the *o*-bromo-ester (7) and the phenol (11). The *o*-bromo-ester (4), available from previous work,[6] on hydrolysis



(4) $R^1=R^2=Me$
(5) $R^1=H, R^2=Me$
(6) $R^1=R^2=H$
(7) $R^1=R^2=CH_2Ph$



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



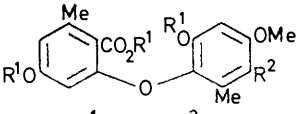
(11)

gave the acid (5), which on demethylation with boron tribromide [7] gave the hydroxy-acid (6). This on benzylation then gave the required *o*-bromo-ester (7).

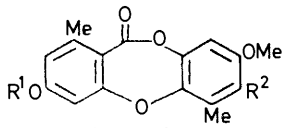
For the synthesis of the phenol (11) the starting material was di-*O*-methylorsellinaldehyde (8).[8] Selective demethylation of this with boron trichloride [9] gave everninaldehyde (9), which was converted into the benzyl ether (10). Baeyer–Villiger oxidation [8] of this intermediate and hydrolysis of the resultant formate then gave the required phenol (11).

Ullmann reaction, under the conditions of Tomita,[10] between the *o*-bromo-ester (7) and the phenol (11) furnished the diaryl ether (12) in 51% yield. Hydrogenolysis of the protecting groups gave the dihydroxy-acid (13). Of the reagents studied, hot acetic anhydride was the best for lactonisation of (13) and the depsidone acetate (16) resulted. The major product of this reaction arose by intramolecular electrophilic substitution and was the grisan (20), the structure of which followed from its microanalysis and spectroscopic properties. It was isomeric with the depsidone acetate (16), exhibiting a mass spectral molecular ion at *m/e* 328. The i.r. spectrum ($CHCl_3$) had carbonyl stretching bands at 1 780 (acetate), 1 720 (3-one), and 1 670 $cm^{-1}$ (2′-one). The last value is typical of cyclohexa-2,4-dienones.[11] The electronic spectrum was also in accord with the assigned structure.[12]

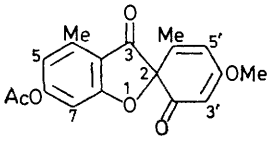
Treatment of the depsidone acetate (16) with hot wet pyridine furnished the hydroxydepsidone (17), which on chlorination with an excess of *N*-chlorosuccinimide [13] and toluene-*p*-sulphonic acid as catalyst gave a trichlorodepsidone (21); this was not further chlorinated on re-subjection to these conditions. Two of the chlorine atoms must be located on ring A of this compound since the ions (23) and (25) are present in its mass spectrum. The exact location of the third chlorine atom on ring B is not known. Chlorination of the trichloro-compound (21) with chlorine in acetic acid at room temperature then gave synthetic diploicin (1), identical (mixed m.p., $R_F$ values, and mass and n.m.r. spectra) with the natural material.



(12) $R^1=CH_2Ph, R^2=H$
(13) $R^1=R^2=H$
(14) $R^1=CH_2Ph, R^2=CO_2Me$
(15) $R^1=H, R^2=CO_2Me$



(16) $R^1=Ac, R^2=H$
(17) $R^1=R^2=H$
(18) $R^1=Ac, R^2=CO_2Me$
(19) $R^1=H, R^2=CO_2Me$



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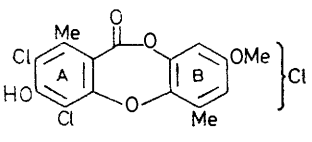

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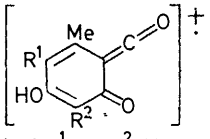
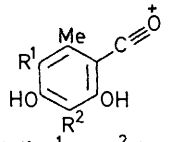
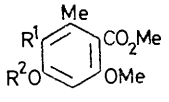


(22) $R^1=Cl, R^2=H$
or $R^1=H, R^2=Cl$
(23) $R^1=R^2=Cl$



(24) $R^1=Cl, R^2=H$
or $R^1=H, R^2=Cl$
(25) $R^1=R^2=Cl$

The synthesis of gangaleoidin (2) closely paralleled that of diploicin (1). The starting material for the ring B intermediate (30) was methyl isoeverninate (26),[14] readily available by hydrogenolysis of the known benzyl compound (27).[1] Formylation [15] of methyl isoeverninate (26) gave the aldehyde (28), which on benzylation furnished the ether (30). This on Baeyer–Villiger oxidation and subsequent hydrolysis gave the required ring B intermediate (30).



(26) $R^1=R^2=H$
(27) $R^1=H, R^2=CH_2Ph$
(28) $R^1=CHO, R^2=H$
(29) $R^1=CHO, R^2=CH_2Ph$
(30) $R^1=OH, R^2=CH_2Ph$

Ullmann reaction between the *o*-bromo-ester (7) and the phenol (30) yielded the diaryl ether (14) (68.5%). Hydrogenolysis of the protecting groups of the ether (14) gave the dihydroxy-acid (15), which on cyclisation as before gave the depsidone acetate (18) and thence the hydroxy-depsidone (19).

[7] J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, 1968, **24**, 2289.
[8] I. M. Godfrey, M. V. Sargent, and J. A. Elix, *J.C.S. Perkin I*, 1974, 1353.
[9] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.
[10] M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1341.
[11] E. C. Friedrich, *J. Org. Chem.*, 1968, **33**, 413; A. Meisels, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 700.
[12] O. Jeger, R. Rüegg, and L. Ruzicka, *Helv. Chim. Acta*, 1947, **30**, 1294.
[13] E. L. Lambert, W. D. Ellis, and R. J. Parry, *J. Org. Chem.*, 1965, **30**, 304.
[14] E. M. Howells and G. T. Newbold, *J. Chem. Soc.*, 1965, 4592.
[15] T. M. Cresp, M. V. Sargent, J. A. Elix, and D. P. H. Murphy, *J.C.S. Perkin I*, 1973, 340.

Treatment of the hydroxy-depsidone (19) with an excess of *N*-chlorosuccinimide in boiling dioxan with toluene-*p*-sulphonic acid as catalyst gave a mixture of ring A monochlorodepsidones; the mass spectrum of the mixture exhibited molecular ions at *m/e* 378/380 and prominent ring A fragments at *m/e* 184/186 and 185/187 due to the ions (22) and (24), respectively. Resubjection of this mixture to the same conditions gave only a ring A dichlorination product which exhibited the characteristic ions (23) and (25) in its mass spectrum. This material was identical (mixed m.p., $R_F$ values, and n.m.r. and mass spectra) with gangaleoidin (2).

## 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 sodium sulphate. Silica gel was B.D.H. 60—120 mesh and preparative layer chromatography (p.l.c.) plates (20 × 20 × 0.1 cm) were coated with Merck Keiselgel $GF_{254}$. N.m.r. spectra were determined for solutions in deuteriochloroform unless stated otherwise at 60 MHz with a Varian A-60-A spectrometer. For spectra at 90 MHz a Bruker HX-90 spectrometer was used. Mass spectra were determined with a Varian MAT CH-7 (low resolution) or a Varian MAT 311 instrument (high resolution). I.r. spectra were determined with a Perkin-Elmer 137 spectrophotometer. Electronic spectra were determined for ethanolic solutions with a Unicam SP 800 spectrophotometer.

*2-Bromo-4-methoxy-6-methylbenzoic Acid* (5).—Methyl 2-bromo-4-methoxy-6-methylbenzoate (4) [6] (28.0 g) and potassium hydroxide (17.4 g) in dimethyl sulphoxide (400 ml) and water (100 ml) were heated on a steam-bath for 6 h. Work-up in the usual way gave the *acid* (5) (24.0 g, 94%) as prisms (from ether–light petroleum), m.p. 143—144° (Found: C, 44.2; H, 4.05; Br, 32.0. $C_9H_9BrO_3$ requires C, 44.1; H, 3.7; Br, 32.6%).

*2-Bromo-4-hydroxy-6-methylbenzoic Acid* (6).—Boron tribromide (76 g) in dry dichloromethane (380 ml) was added at −78 °C to a stirred solution of the acid (5) (24.0 g) in dry dichloromethane (1 l). The mixture was stirred at −78 °C for 5 h and at room temperature for 20 h. Work-up in the usual way gave the *acid* (6) (21.5 g), as needles (from ether–light petroleum), m.p. 177—178.5° (Found: Br, 34.75%; $M^+$, 230/232. $C_8H_7BrO_3$ requires Br, 34.6%; *M*, 230/232).

*Benzyl 4-Benzyloxy-2-bromo-6-methylbenzoate* (7).—The acid (6) (21.5 g), potassium carbonate (48 g), and benzyl bromide (32 g) were stirred at 50 °C (bath) in *NN*-dimethylformamide (500 ml) for 3.5 h. The mixture was poured into ice-cold dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and saturated brine. The excess of benzyl bromide was removed in steam and the crude product was filtered through a column of silica gel with 5% ethyl acetate–light petroleum as eluant. The *ester* (7) (34.1 g, 89%) was obtained as an oil (Found: $M^+$, 410.0510. $^{12}C_{22}{}^{1}H_{19}{}^{79}Br^{16}O_3$ requires *M*, 410.0518), τ ($CCl_4$) 2.76 (10 H, s, ArH), 3.09 and 3.38 (2 H, ABq, $J_{3,5}$ 2.0 Hz, 3- and 5-H), 4.74 and 5.07 (each 2 H, s, $CH_2$), and 7.84 (3 H, s, Me).

*2-Hydroxy-4-methoxy-6-methylbenzaldehyde* (*Everninaldehyde*) (9).—2,4-Dimethoxy-6-methylbenzaldehyde (8) [8] (82.0 g) in dry dichloromethane (200 ml) was added with stirring at −10 °C to a solution of boron trichloride (161 g) in dichloromethane (500 ml). After 0.5 h, work-up in the usual way gave everninaldehyde (9) (68.3 g, 90%) as blades (from methanol), m.p. 63—64° (lit.,[15] 63—64°).

*2-Benzyloxy-4-methoxy-6-methylbenzaldehyde* (10).—The aldehyde (9) (45.8 g), potassium carbonate (80 g), and benzyl chloride (35 g) in *NN*-dimethylformamide were stirred on a steam-bath for 12 h. Work-up as before gave the *aldehyde* (10) (57.2 g, 81%) as prisms (from light petroleum), m.p. 77° (Found: C, 75.15; H, 6.45. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%), τ ($CCl_4$) −0.50 (1 H, s, CHO), 2.67 (5 H, s, ArH), 3.72 (2 H, narrow m, 3- and 5-H), 4.93 (2 H, s, $CH_2$), 6.22 (3 H, s, OMe), and 7.47 (3 H, s, Me).

*2-Benzyloxy-4-methoxy-6-methylphenol* (11).—The aldehyde (10) (26.0 g) and *m*-chloroperoxybenzoic acid (85%; 29.0 g) in dry dichloromethane (500 ml) were stirred at room temperature for 2.5 h. Work-up in the usual way [8] gave the crude formate which was stirred at 0 °C for 1 h under nitrogen with sodium hydroxide (28 g) in water (280 ml) and methanol (280 ml). Acidification and extraction with ethyl acetate gave the crude product, which was chromatographed over silica gel with 2.5—5% ethyl acetate–light petroleum as eluant. The *phenol* (11) crystallised from ether–light petroleum as needles (21.0 g, 85%), m.p. 63.5—64° (Found: C, 73.85; H, 6.65. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%), τ ($CCl_4$) 2.68 (5 H, s, ArH), 7.80 (2 H, narrow m, 3- and 5-H), 4.92 (1 H, s, OH), 4.99 (2 H, s, $CH_2$), 6.35 (3 H, s, OMe), and 7.81 (3 H, s, Me).

*Benzyl 4-Benzyloxy-2-(2-benzyloxy-4-methoxy-6-methylphenoxy)-6-methylbenzoate* (12).—The *o*-bromo-ester (7) (5.0 g), the phenol (11) (2.96 g), and dry finely ground potassium carbonate (5.0 g) in dry pyridine (15 ml) were stirred and heated under dry nitrogen to 120 °C (bath). Copper(II) oxide (1.0 g) was then added, the temperature was raised to 150 °C (bath), and the mixture was stirred for 18 h. The cooled mixture was diluted with ethyl acetate and filtered through kieselguhr. The filtrate was washed in turn with dilute hydrochloric acid, dilute aqueous sodium hydroxide, water, and finally saturated brine. The combined crude products from two such reactions were applied in a little benzene to a column of silica gel, which was eluted with 5—7.5% ethyl acetate–light petroleum. This afforded the *diaryl ether* (12) (7.1 g, 51%) as a viscous oil (Found: $M$,[+] 574.2346. $^{12}C_{37}{}^{1}H_{34}{}^{16}O_6$ requires *M*, 574.2355), τ (90 MHz) 2.74 (10 H, s, ArH), 2.83 (5 H, s, ArH), 3.58—3.69 (3 H, m, 3′-, 5′-, and 5-H), 4.04 (1 H, arm of ABq, $J_{3,5}$ 2.1 Hz, 3-H), 4.65, 5.08, and 5.15 (each 2 H, s, $CH_2$), 6.26 (3 H, s, OMe), and 7.68 and 7.93 (each 3 H, s, Me).

*4-Hydroxy-2-(2-hydroxy-4-methoxy-6-methylphenoxy)-6-methylbenzoic Acid* (13).—The benzyl compound (12) (6.2 g) and 10% palladised charcoal (2.0 g) in ethyl acetate (450 ml) containing concentrated hydrochloric acid (3 drops) were stirred in hydrogen until absorption ceased. The filtered solution was washed with saturated brine. The *acid* (13) (3.0 g) crystallised from chloroform as prisms, m.p. 158—160° (Found: C, 63.3; H, 5.15%; $M^+$, 304. $C_{16}H_{16}O_6$ requires C, 63.15; H, 5.3%; *M*, 304) τ [90 MHz; $(CD_3)_2SO$–$CDCl_3$] 3.64—3.75 (3 H, m, 3′-, 5′-, and 5-H), 4.03 (1 H, arm of ABq, $J_{3,5}$ 2.0 Hz, 3-H), 6.28 (3 H, s, OMe), and 7.64 and 7.86 (each 3 H, s, Me).

*Treatment of the Acid* (13) *with Acetic Anhydride.*—The acid (13) (2.57 g) and acetic anhydride (100 ml) were heated on a steam-bath for 1 h and the solvent was then removed under reduced pressure. The residue was preabsorbed from dichloromethane on silica gel and chromatographed over silica gel with 0—5% ethyl acetate–benzene as eluant.

Early fractions afforded *3-acetoxy-8-methoxy-1,6-dimethyldibenzo*[b,e][1,4]*dioxepin-11-one* (16) (473 mg) as prisms (from dichloromethane–light petroleum), m.p. 120—121° (Found: C, 64.7; H, 5.15%; $M^+$, 328. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.9%; *M*, 328), τ (90 MHz) 3.09 and 3.15 (2 H, ABq, $J_{2,4}$ 2.2 Hz, 2- and 4-H), 3.39 and 3.48 (2 H, ABq, $J_{7,9}$ 3.0 Hz, 7- and 9-H), 6.27 (3 H, s, OMe), 7.50 and 7.59 (each 3 H, s, Me), and 7.71 (3 H, s, MeCO). Further elution gave material (1.20 g) which after several crystallisations from dichloromethane–light petroleum afforded *6-acetoxy-4′-methoxy-4,6′-dimethylspiro*[*benzofuran*-2,1′-*cyclohexa*-3′,5′-*diene*]-2′,3-*dione* (20) as plates, m.p. 189—191° (Found: C, 65.85, 66.25; H, 5.0, 5.05. $C_{18}H_{16}O_6$ requires C, 65.85; H, 4.9%) τ (90 MHz; assignments made by spin decoupling) 3.03 (1 H, m, $W_{\frac{1}{2}}$ 4.0 Hz, 5- or 7-H), 3.36 (1 H, m, $W_{\frac{1}{2}}$ 4.0 Hz, 5- or 7-H), 3.87 (1 H, m, $W_{\frac{1}{2}}$ 4.1 Hz, 5′-H), 4.59 (1 H, apparent d, $W_{\frac{1}{2}}$ 3.8 Hz, 3′-H), 6.18 (3 H, s, OMe), 7.49 (3 H, s, $W_{\frac{1}{2}}$ 2.5 Hz, 4-Me), 7.68 (3 H, s, MeCO), and 8.21 (3 H, apparent d, $W_{\frac{1}{2}}$ 3.0 Hz, 6′-Me); $\lambda_{max.}$ 269 and 324 nm (ε 19 000 and 9 200).

*3-Hydroxy-8-methoxy-1,6-dimethyldibenzo*[b,e][1,4]-*dioxepin-11-one* (17).—The depsidone acetate (16) (380 mg), pyridine (16 ml), and water (2 ml) were heated on a steam-bath for 2.5 h. The cooled solution was acidified with cold dilute hydrochloric acid and then extracted exhaustively with ethyl acetate. The extract was washed with water and with saturated brine. The crude product (342 mg) crystallised from chloroform as needles of the *depsidone* (17), m.p. 198—199° (Found: C, 67.35; H, 4.9%; $M^+$, 286. $C_{16}H_{14}O_5$ requires C, 67.15; H, 4.95%; *M*, 286), τ (90 MHz; $CDCl_3$ at 50 °C) τ 3.45 (4 H, m, ArH), 6.28 (3 H, s, OMe), and 7.54 and 7.61 (each 3 H, s, Me).

*The Trichlorodepsidone* (21).—The depsidone (17) (330 mg), *N*-chlorosuccinimide (740 mg), and toluene-*p*-sulphonic acid (57 mg) were stirred and heated under reflux in dioxan (8 ml) for 2 h. The solution was diluted with water and extracted with ethyl acetate. The extract was washed with water and saturated brine. The n.m.r. spectrum of the crude product indicated it to be incompletely chlorinated. The crude product was treated as before with *N*-chlorosuccinimide (390 mg) and toluene-*p*-sulphonic acid (25 mg) in dioxan (10 ml). The product obtained by the usual work-up was preadsorbed from chloroform on silica gel and chromatographed over a small column of silica gel with benzene as eluant. The depsidone (21) (301 mg) crystallised from chloroform–cyclohexane as small rosettes of needles, m.p. 238—240° (Found: $M^+$, 387.9670. Calc. for $^{12}C_{16}{}^{1}H_{11}{}^{35}Cl_3{}^{16}O_5$: *M*, 387.9671), τ [$(CD_3)_2SO$] 2.91 (1 H, s, ArH), 6.12 (3 H, s, OMe), and 7.42 and 7.60 (each 3 H, s, Me).

*2,4,7,9-Tetrachloro-3-hydroxy-8-methoxy-1,6-dimethyldibenzo*[b,e][1,4]*dioxepin-11-one* (*Diploicin*) (1).—The depsidone (21) (20 mg) in glacial acetic acid (7 ml) was stirred in the dark with chlorine (7 mg) in glacial acetic acid (2 ml) for 24 h. The solution was diluted with water and extracted with ethyl acetate and the extract was washed with aqueous sodium hydrogen carbonate and saturated brine. The crude product was applied in ethyl acetate to two p.l.c. plates which were multiply developed with 0—2% ethyl acetate–benzene. The faster-running band yielded the starting material (1.6 mg). The slower-running band yielded diploicin (1), which crystallised from ethanol as needles (5.6 mg), m.p. and mixed m.p. 231—232° (lit.,[16] 232°), τ [90 MHz; $(CD_3)_2SO$] 6.17 (3 H, s, OMe) and 7.42 and 7.61 (each 3 H, s, Me); the mass spectrum [17] and the $R_F$ in three solvent systems were identical with those of the natural product.

*Methyl 4-Hydroxy-6-methoxy-2-methylbenzoate* (26).—Methyl 4-benzyloxy-6-methoxy-2-methylbenzoate (27) [1] (34.0 g), 10% palladised charcoal (4 g), concentrated hydrochloric acid (10 drops), and ethyl acetate (600 ml) were stirred together under hydrogen until absorption ceased. The usual work-up gave the isoeverninate (26) (24.0 g). A sample formed needles (from dichloromethane–light petroleum), m.p. 111—112° (lit.,[14] 111—112°), τ 3.47br (1 H, OH), 3.77 (2 H, s, ArH), 6.12 and 6.35 (each 3 H, s, OMe), and 7.80 (3 H, s, Me).

*Methyl 3-Formyl-4-hydroxy-6-methoxy-2-methylbenzoate* (28).—Titanium(IV) chloride (126 g) in dry dichloromethane (250 ml) was added at 0 °C to a stirred solution of the isoeverninate (126) (26.0 g) in dry dichloromethane (500 ml). Dichloromethyl methyl ether (30.7 g) in dry dichloromethane (200 ml) was then added over 15 min at 0 °C and after a further 20 min the cooling bath was removed and the solution was stirred at room temperature for 2 h. The usual work-up gave the crude product, which was chromatographed over silica gel with 10—20% ethyl acetate–light petroleum as eluant. Early fractions gave the *product* (28) (9.0 g), which formed prisms (from dichloromethane–light petroleum), m.p. 134—134.5° (Found: C, 59.7; H, 5.35. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%), τ −2.62 (1 H, s, OH), −0.33 (1 H, s, CHO), 3.70 (1 H, s, ArH), 6.10 and 6.15 (each 3 H, s, OMe), and 7.37 (3 H, s, Me).

*Methyl 4-Benzyloxy-3-formyl-6-methoxy-2-methylbenzoate* (29).—The phenol (28) (6.10 g), benzyl bromide (5.1 g), and potassium carbonate (11.3 g) were stirred in dry *NN*-dimethylformamide (100 ml) for 18.5 h at 50 °C (bath). Work-up in the usual way gave the *benzyl compound* (29) (8.30 g, 97%), which formed plates (from dichloromethane–light petroleum), m.p. 128.5—129.5° (Found: C, 68.9; H, 5.9. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.75%), τ −0.48 (1 H, s, CHO), 2.60 (5 H, s, Ph), 3.57 (1 H, s, ArH), 4.82 (2 H, s, $CH_2$), 6.12 and 6.20 (each 3 H, s, OMe), and 7.50 (3 H, s, Me).

*Methyl 4-Benzyloxy-3-hydroxy-6-methoxy-2-methylbenzoate* (30).—The aldehyde (29) (7.2 g) in dry dichloromethane (35 ml) was added dropwise over 20 min to a stirred solution of *m*-chloroperbenzoic acid (85%; 9.6 g) in dry dichloromethane (130 ml) at room temperature. After 30 min, work-up in the usual way [8] gave the crude formate, which was stirred at 0 °C in methanol (100 ml) with aqueous 10% potassium hydroxide (100 ml) for 30 min under nitrogen. Acidification at 0 °C and extraction with ethyl acetate gave the crude product, which crystallised from dichloromethane–light petroleum as prisms (3.7 g) of the *phenol* (30), m.p. 125.5—126.5° (Found: C, 67.7; H, 6.15. $C_{17}H_{18}O_5$ requires C, 67.55; H, 6.0%), τ 2.62 (5 H, s, Ph), 3.57 (1 H, s, ArH), 4.55 (1 H, s, OH), 4.92 (2 H, s, $CH_2$), 6.13 and 6.28 (each 3 H, s, OMe), and 7.80 (3 H, s, Me).

*Benzyl 4-Benzyloxy-2-(2-benzyloxy-4-methoxy-5-methoxycarbonyl-6-methylphenoxy)-6-methylbenzoate* (14).—The *o*-bromo-ester (7) (4.90 g), and the phenol (30) (3.60 g) were subjected to Ullmann reaction as before. The crude product was chromatographed over silica gel with 10—15% ethyl acetate–light petroleum as eluant. The *diaryl ether* (14) (5.15 g, 68.5%) formed prisms (from methanol), m.p.

[16] P. A. Spillane, J. Keane, and T. J. Nolan, *Sci. Proc. Royal Dublin Soc.*, 1936, **21**, 333.

[17] S. Huneck, C. Djerassi, D. Becher, M. Barber, M. von Ardenne, K. Steinfelder, and R. Tümmler, *Tetrahedron*, 1968, **24**, 2707.

118—119° (Found: C, 74.35; H, 5.7. $C_{39}H_{36}O_8$ requires C, 74.05; H, 5.75%), τ ($CCl_4$) 2.83 (15 H, m, 3 × Ph), 3.67 and 4.13 (2 H, ABq, $J_{3.5}$ 2.1 Hz, 5- and 3-H), 3.70 (1 H, s, 3'-H), 4.77, 5.17, and 5.23 (each 2 H, s, $CH_2$), 6.25 and 6.38 (each 3 H, s, OMe), and 7.75 and 7.83 (each 3 H, s, Me).

*4-Hydroxy-2-(2-hydroxy-4-methoxy-5-methoxycarbonyl-6-methylphenoxy)-6-methylbenzoic Acid* (15).—The diaryl ether (14) (5.10 g) was hydrogenolysed as before. The crude product (3.19 g), obtained in the usual way, formed clusters of prisms of the *acid* (15) (from ether–light petroleum), m.p. *ca.* 185° with much softening from 165° (Found: C, 60.0; H, 5.3. $C_{18}H_{18}O_8$ requires C, 59.65; H, 5.75%).

*Methyl 3-Hydroxy-8-methoxy-1,6-dimethyl-11-oxo-11H-dibenzo*[b,e][1,4]*dioxepin-7-carboxylate* (19).—The acid (15) (3.0 g) and acetic anhydride (200 ml) were heated on a steam-bath for 1 h. The acetic anhydride was removed under reduced pressure and the residue was heated on a steam-bath with water (200 ml) for 15 min. The mixture was extracted with ethyl acetate and the extract was washed several times with aqueous potassium carbonate, with water, and with saturated brine. The crude product was pre-adsorbed from dichloromethane and chromatographed over silica gel with 0—2.5% ethyl acetate–benzene as eluant. The crude depsidone acetate (18) (547 mg) was heated on a steam-bath with pyridine (23 ml) and water (3 ml) for 2.5 h. Work-up in the usual way gave the *depsidone* (19) (496 mg), which crystallised from dichloromethane–light petroleum as plates, m.p. 219—220° (Found: C, 62.45; H, 4.85%; $M^+$, 344. $C_{18}H_{16}O_7$ requires C, 62.8; H, 4.7%; *M*, 344) τ [$CDCl_3$–$(CD_3)_2CO$] 3.34 (1 H, s, ArH), 3.38 (2 H, s, ArH), 6.11 and 6.23 (each 3 H, s, OMe), and 7.54 and 7.63 (each 3 H, s, Me).

*Methyl 2,4-Dichloro-3-hydroxy-8-methoxy-1,6-dimethyl-11-oxo-11H-dibenzo*[b,e][1,4]*dioxepin-7-carboxylate* (*Gangaleoidin*) (2).—The depsidone (19) (100 mg), *N*-chlorosuccinimide (93.5 mg), and toluene-*p*-sulphonic acid (8 mg) were heated under reflux in dioxan (6 ml) for 2.5 h. The cooled solution was diluted with ethyl acetate and washed with water and with saturated brine. The n.m.r. spectrum of the product indicated that starting material was still present. The product was treated exactly as before and the crude material was applied to two p.l.c. plates, which were developed with 5% ethyl acetate–benzene. This gave a mixture of ring-A-monochlorinated depsidones (65.4 mg), which was heated under reflux in dioxan (4 ml) with *N*-chlorosuccinimide (61 mg) and toluene-*p*-sulphonic acid (8 mg) for 2.5 h. The crude product was applied to two p.l.c. plates which were developed with benzene, then 2% ethyl acetate–benzene. The faster-running band gave the starting monochloro-compounds (32.7 mg) and the slower-running band gave *gangaleoidin* (2) (14.0 mg), which crystallised from dichloromethane–light petroleum as needles, m.p. and mixed m.p. 211—212° (lit.,[6] 211—212°) (Found: C, 52.0; H, 3.65%; $M^+$, 412/414/416. $C_{18}H_{14}Cl_2O_7$ requires C, 52.3; H, 3.4%; *M*, 412/414/416). It was identical ($R_F$ values in three systems; n.m.r. and mass spectra) with an authentic sample.

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