Depsidone Synthesis. Part 11.[1] Synthesis of Some Fungal Depsidones related to Nidulin

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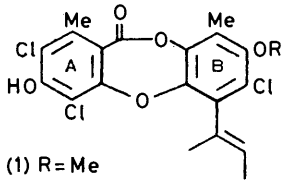
The synthesis of 3-hydroxy-8-methoxy-1,9-dimethyl-6-(s-butyl)dibenzo[*b*,*e*][1,4]dioxepin-11-one (tridechlorodihydronidulin) (34), a derivative of the fungal depsidone nidulin (1), and of 3,8-dihydroxy-1,9-dimethyl-6-(s-butyl)dibenzo[*b*,*e*][1,4]dioxepin-11-one (tridechlorodihydro-*O*-nornidulin) (39), a derivative of the fungal depsidone tridechloro-*O*-nornidulin (4), by oxidative coupling of 5-bromo-2,2',4'-trihydroxy-4-methoxy-3,6'-dimethyl-6-(s-butyl)benzophenone (30) is described.

In contrast to the lichen depsidones,[2] their fungal counterparts are rare; at present their source is confined to the morphologically indistinguishable[3] fungi *Aspergillus nidulans* (NRRL 2006) and *A. unguis* Emile-White and Gaudin (NRRL 5250). *A. nidulans* grown on a Czapek–Dox medium produces nidulin (1) as a major metabolite[4] as well as the minor metabolites *O*-nornidulin (2) and dechloro-*O*-nornidulin (3).[5] The structures of these metabolites were established by classical degradative methods whereby fragments due to both rings A and B with their pendant substituents were identified.[6] When grown on a Czapek–Dox

[1] P. Djura, M. V. Sargent, and P. D. Clark, *Austral. J. Chem.*, 1977, **30**, 1545.
[2] C. F. Culberson, 'Chemical and Botanical Guide to Lichen Products,' University of North Carolina Press, Chapel Hill, 1969.
[3] F. H. Stodola, R. F. Vesonder, D. I. Fennell, and D. Weisleder, *Phytochemistry*, 1972, **11**, 2107.
[4] F. M. Dean, D. S. Deorha, A. D. T. Erni, D. W. Hughes, and J. C. Roberts, *J. Chem. Soc.*, 1960, 4829.
[5] F. M. Dean, A. D. T. Erni, and A. Robertson, *J. Chem. Soc.*, 1956, 3545.
[6] B. W. Bycroft, J. A. Knight, and J. C. Roberts, *J. Chem. Soc.*, 1963, 5148.

medium free from chloride, *A. nidulans* produces tridechloro-*O*-nornidulin [7] (unguinol; [3] yasimin [8]) (4), the structure of which followed from degradative experiments [8] and from its general similarity [3,7] to nidulin. *A. unguis* also produces the above mentioned metabolites and in addition four minor depsidones have been isolated, and assigned structures (5)—(8).[9] The biosynthesis of nidulin has been studied.[10]

We now report the synthesis of tridechlorodihydronidulin (34) and tridechlorodihydro-*O*-nornidulin (39). We used a route based on the oxidative coupling of an appropriate benzophenone. This type of route was developed by Hendrickson [11] and used for a synthesis of diploicon; we have since used the method for the synthesis of caloploicin [12] and vicanicin.[13] We consequently required the phenylbutane (13), which had been synthesised previously [14,15] in a lengthy route from *p*-toluic acid. By a modification of this route methyl 4-methyl-3,5-dimethoxybenzoate (9) [16] was condensed with methylsulphonylmethanide ion under the conditions of House and Larson.[17] The intermediate β-oxo-sulphone (10) was reduced to the acetophenone



(1) R = Me
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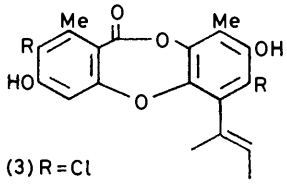
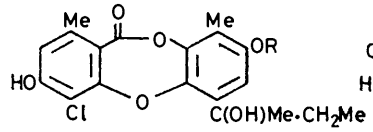


(3) R = Cl
(4) R = H



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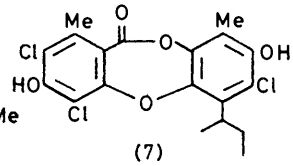

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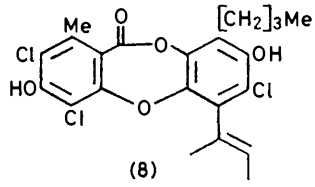
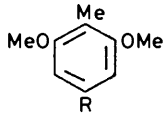
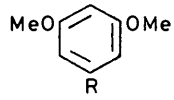


(8)

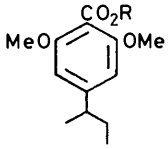
(11) with zinc dust in acetic acid and ethyl acetate. These conditions prevent the formation of pinacolic products.[18] A Grignard reaction of the acetophenone (11) then furnished the tertiary alcohol (12) [14] which was smoothly reduced with lithium aluminium hydride and aluminium chloride to the required intermediate (13).



(9) R = CO_2Me
(10) R = $CO \cdot CH_2SO_2Me$
(11) R = COMe
(12) R = $C(OH)Me \cdot CH_2Me$
(13) R = $CHMe \cdot CH_2Me$



(14) R = $CO \cdot CH_2SO_2Me$
(15) R = COMe
(16) R = $C(OH)Me \cdot CH_2Me$
(17) R = $CHMe \cdot CH_2Me$



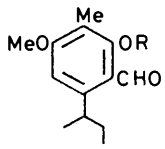
(18) R = H
(19) R = Me

In view of the inacessibility of the ester (9) [19] we developed an alternative synthesis of the phenylbutane (13). The readily available β-oxo-sulphone (14) [20] on reduction as before furnished the acetophenone (15).[21] A Grignard reaction then gave the tertiary alcohol (16). Attempted reduction of this alcohol with lithium aluminium hydride and aluminium chloride gave a mixture of products.[22] Apparently only benzyl alcohols possessing an electron-releasing group at the *o*- or *p*-position are reduced smoothly to alkylbenzenes. However the required phenylbutane (17) was produced in good yield by dehydration of the alcohol (16) and hydrogenation of the mixture of alkenes thus produced. On treatment of compound (17) with phenyl-lithium, lithium–hydrogen exchange took place, as expected,[23] at the position *ortho* to both methoxy-groups, and carboxylation then gave the acid (18). The derived ester (19) on reduction with lithium aluminium hydride and aluminium chloride then gave the phenylbutane (13).

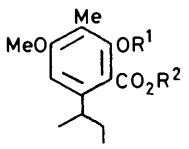
Formylation of the phenylbutane (13) with dichloromethyl methyl ether and titanium(IV) chloride gave the aldehyde (20), which underwent selective demethylation on treatment with boron trichloride, thus furnishing the *o*-hydroxy-aldehyde (21). The derived acetate (22) on oxidation with permanganate gave the intermediate

[7] J. Sierankiewicz and S. Gatenbeck, *Acta Chem. Scand.*, 1972, **26**, 455.
[8] A. Kamal, Y. Haider, Y. A. Khan, I. H. Qureshi, and A. A. Qureshi, *Pakistan J. Sci. Ind. Research*, 1970, **13**, 244.
[9] A. Kamal, Y. Haider, A. A. Qureshi, and Y. A. Khan, *Pakistan J. Sci. Ind. Research*, 1970, **13**, 364.
[10] J. Sierankiewicz and S. Gatenbeck, *Acta Chem. Scand.*, 1973, **27**, 2710, and references. therein.
[11] J. B. Hendrickson, M. V. J. Ramsay, and T. R. Kelly, *J. Amer. Chem. Soc.*, 1972, **94**, 6834.
[12] M. V. Sargent and P. Vogel, *Austral. J. Chem.*, 1976, **29**, 907.
[13] M. V. Sargent, P. Vogel, J. A. Elix, and B. A. Ferguson, *Austral. J. Chem.*, 1976, **29**, 2263.
[14] D. H. Johnson, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1950, 2971.
[15] A. H. Frye, E. S. Wallis, and G. Dougherty, *J. Org. Chem.*, 1949, **14**, 397.
[16] S. Huneck and M. V. Sargent, *Austral. J. Chem.*, 1976, **29**, 1059.
[17] H. O. House and J. K. Larson, *J. Org. Chem.*, 1968, **33**, 61.
[18] L. Pavlickova, B. Koutek, and M. Soucek, *Coll. Czech. Chem. Comm.*, 1974, **39**, 1216.
[19] D. R. Briggs and W. B. Whalley, *J.C.S. Perkin I*, 1976, 1382.
[20] J. R. Cannon, P. K. Cheong, B. H. Hamilton, I. A. McDonald, and G. Vinciguerra, *Austral. J. Chem.*, 1973, **26**, 799.
[21] J. P. Brown, N. J. Cartwright, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1949, 859.
[22] J. H. Brewster, H. O. Bayer, and S. F. Osman, *J. Org. Chem.*, 1964, **29**, 110.
[23] G. Wittig in 'Newer Methods of Preparative Organic Chemistry,' Interscience, New York, 1948, p. 571.

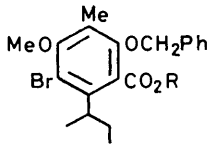
(23), and thence the acid (24). Attempts to chlorinate the acid (24) or the derived di-*O*-benzyl compound (25) gave complex mixtures under a variety of conditions. However treatment of the di-*O*-benzyl compound (25) with an excess of bromine in acetic acid containing anhydrous sodium acetate in the absence of light smoothly gave the bromo-compound (26). On hydrolysis the latter afforded the acid (27).



(20) R=Me
(21) R=H
(22) R=Ac



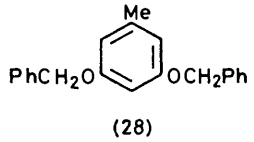
(23) R^1=Ac, R^2=H
(24) R^1=R^2=H
(25) R^1=R^2=CH_2Ph



(26) R=CH_2Ph
(27) R=H

A Friedel–Crafts reaction between the acid (27) and 3,5-bisbenzyloxytoluene (28) [24] with trifluoroacetic anhydride as catalyst gave the tri-*O*-benzylbenzophenone (29). This on hydrogenolysis furnished the trihydroxybenzophenone (30). Oxidative coupling of this benzophenone was expected to occur with oxidative entry into the ring bearing the bromo-substituent [11-13,25] and thus afford the grisan (31). The crystalline product of this reaction, obtained in high yield, was assigned the depsidone structure (32). Its i.r. and electronic spectra were compatible with this structure but not with a grisan.[16,25] The grisan intermediate (31) must therefore undergo hydrolysis and lactonisation under the conditions of the oxidative coupling reaction.* An analogous reaction was observed in our synthesis of vicanicin.[13] Had oxidative entry occurred into the orcinol ring then the isolated depsidone would possess structure (35). That this was not the case followed from the mass spectra of the depsidone (32) and its acetate (33) which exhibited the characteristic ring A daughter ions (36) at *m/e* 151. Cleavage of the depside linkage of the depsidone (32) with potassium hydroxide gave a dihydroxy-acid which must have structure (37) rather than (38) on the folowing grounds. The *ortho*-protons of tri-*o*-substituted diaryl ethers resonate at unusually high field in their n.m.r. spectra since they adopt an 'H-inside' conformation.[26] The dihydroxy-acid in question exhibited such a signal at δ 5.86.

Hydrogenolysis of the bromo-substituent of depsidone 32) gave synthetic tridechlorodihydronidulin (34), identical with a sample obtained by hydrogenation of the double bond and hydrogenolysis of the chloro-substituents of nidulin (1). Demethylation of the depsidone (32) with boron tribromide followed by hydrogenolytic removal of the bromo-substituent gave synthetic tridechlorodihydro-*O*-nornidulin (39), identical with a sample prepared from natural tridechloro-*O*-nornidulin (4) by hydrogenation of the double bond.



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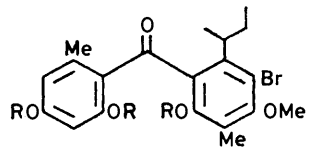
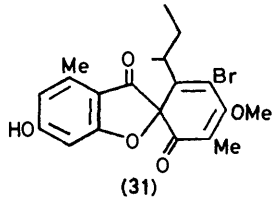


(29) R=CH_2Ph
(30) R=H



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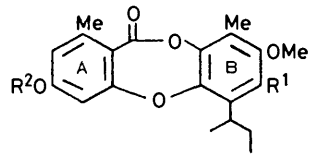
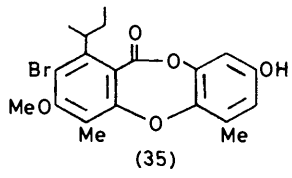
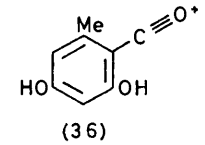




(35)

(32) R^1=Br, R^2=H
(33) R^1=Br, R^2=Ac
(34) R^1=R^2=H



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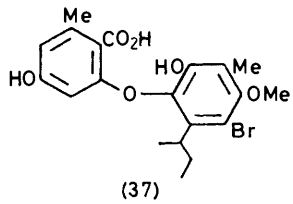

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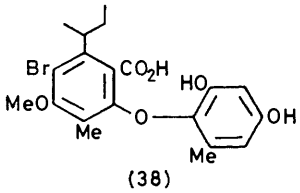

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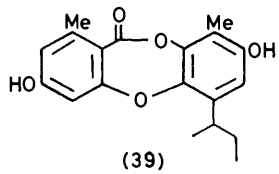

(39)

EXPERIMENTAL

General directions have been given before.[27] Unless stated otherwise n.m.r. spectra were recorded at 90 MHz.

3′,5′-Dimethoxy-4′-methylacetophenone (11).—Dimethyl sulphone (17.9 g) was added with stirring to sodium hydride (4.6 g) in dry dimethyl sulphoxide (85 ml) and the mixture was stirred under dry nitrogen at 65 °C (bath) for 2 h. Dry tetrahydrofuran (60 ml) was then added, and a solution of methyl 3,5-dimethoxy-4-methylbenzoate (9) [16] (20.0 g) in dry tetrahydrofuran (70 ml) was then added dropwise at room temperature. The mixture was stirred at 65 °C (bath) for 2 h and then poured on ice. The precipitate was

* The ease of the lactonisation of the acid (37) may be due to relief of strain: see C. Danforth, A. W. Nicholson, J. C. James, and G. M. Loudon, *J. Amer. Chem. Soc.*, 1976, **98**, 4275.

[24] J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, and J. A. Elix, *J.C.S. Perkin I*, 1972, 1200.

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[26] T. M. Cresp, P. Djura, M. V. Sargent, J. A. Elix, U. Engkaninan, and D. P. H. Murphy, *Austral. J. Chem.*, 1975, **28**, 2417.

[27] P. Djura, M. V. Sargent, and P. Vogel, *J.C.S. Perkin I*, 1976, 147.

separated by filtration and washed in turn with water, saturated aqueous sodium hydrogen carbonate, and saturated brine. The crude sulphone (10) (24.2 g) was dried by azeotropic distillation with benzene. This product in glacial acetic acid (300 ml) and ethyl acetate (300 ml) was stirred and treated with zinc dust (31 g) in portions over 2 h. The temperature was maintained below 30 °C by intermittent cooling. The mixture was filtered and the solid was washed with ethyl acetate. The filtrate was concentrated to small volume, under reduced pressure, and the residue was diluted with ethyl acetate and then washed in turn with water, saturated aqueous sodium hydrogen carbonate, and saturated brine. The acetophenone (11) formed blades (14.9 g, 80%) (from dichloromethane–light petroleum), m.p. 99—100° (lit.,[14] 104°); δ (60 MHz; $CDCl_3$) 2.28 (3 H, s, Me), 2.57 (3 H, s, MeCO), 3.85 (6 H, s, 2 × OMe), and 7.10 (2 H, s, 2 × ArH).

2-(3,5-*Dimethoxy*-4-*methylphenyl*)*butan*-2-*ol* (12).—Prepared (98%) by the method of Robertson and his co-workers,[14] this was obtained as an oil; δ (60 MHz; CCl_4), 0.75 (3 H, t, 4-Me), 1.43 (3 H, s, 1-Me), 1.73 (2 H, q, CH_2), 1.83br (1 H, s, OH), 1.97 (3 H, s, ArMe), 3.75 (6 H, s, 2 × OMe), and 6.45 (2 H, s, 2 × ArH).

3′,5′-*Dimethoxyacetophenone* (15).—The sulphone (14) [20] (75.0 g) in glacial acetic acid (300 ml) and ethyl acetate (400 ml) was reduced with zinc dust (40.8 g) during 2.5 h as above. The residue from filtration was washed with light petroleum and the filtrate was diluted with more light petroleum, and washed as above. The acetophenone (15) (40.9 g, 95%) was obtained as an oil, b.p. 101—103° at 0.05 mmHg (lit.,[21] 122° at 0.5 mmHg), which solidified on cooling.

2-(3,5-*Dimethoxyphenyl*)*butan*-2-*ol* (16).—The Grignard reagent was prepared in the usual way from magnesium (8.3 g), iodoethane (28 ml), and dry ether (200 ml). The acetophenone (15) (41.4 g) in dry ether (50 ml) was added dropwise and the mixture was stirred and heated under reflux for 2 h, and then poured into an excess of ice-cold saturated aqueous ammonium chloride. The *alcohol* (16) (44.4 g, 92%) was obtained as an oil, b.p. 108—109° at 0.05 mmHg (Found: C, 68.35; H, 8.65. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65%); δ(CCl_4) 0.75 (3 H, t, 4-Me), 1.42 (3 H, s, 1-Me), 1.71 (2 H, q, CH_2), 2.10 (1 H, s, OH), 3.69 (6 H, s, 2 × OMe), 6.17 (1 H, t, *J* 2.5 Hz, 4-H), and 6.45 (2 H, d, *J* 2.5 Hz, 2- and 6-H).

2-(3,5-*Dimethoxyphenyl*)*butane* (17).—The alcohol (16) (50.0 g), toluene-*p*-sulphonic acid (250 mg), and benzene (500 ml) were heated under reflux in a Dean–Stark apparatus for 2 h. The cooled solution was washed with water and saturated brine. The crude mixture of alkenes in ethyl acetate (250 ml) was stirred under hydrogen with 10% palladised charcoal (2.5 g) until absorption ceased. The crude product was distilled under diminished pressure and afforded the *product* (17) (39.0 g, 85%) as an oil, b.p. 152—154° at 23 mmHg (Found: C, 74.25; H, 9.4. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.35%), δ(CCl_4) 0.81 (3 H, t, 4-Me), 1.19 (3 H, d, 1-Me), 1.55 (2 H, quintet, CH_2), 2.46 (1 H, sextet, CH), 3.69 (6 H, s, 2 × OMe), and 6.20 (3 H, m, ArH).

2,6-*Dimethoxy*-4-*s*-*butylbenzoic Acid* (18).—The ether (17) (25.0 g) in dry ether (50 ml) was treated with phenyllithium (1 equiv.) in dry ether (125 ml) under dry nitrogen. The flask was sealed and set aside for 60 h and the contents were then added to crushed solid carbon dioxide (500 g). When the carbon dioxide had disappeared the mixture was treated with dilute hydrochloric acid. The *acid* (18) was obtained by extraction with sodium hydrogen carbonate in the usual way; it formed prisms (19.5 g, 64%) (from ether–light petroleum), m.p. 133—135° (Found: C, 65.5; H, 7.7. $C_{13}H_{18}O_4$ requires C, 65.55; H, 7.6%), δ($CDCl_3$) 0.83 (3 H, t, 4-Me), 1.21 (3 H, d, 1-Me), 1.58 (2 H, quintet, CH_2), 2.56 (1 H, sextet, CH), 3.84 (6 H, s, 2 × OMe), 6.39 (2 H, s, 2 × ArH), and 11.36br (1 H, s, OH). The methyl ester (19) was obtained as an oil by methylation of the acid with iodomethane and potassium carbonate in dry acetone; *m/e* 252 (M^+).

2-(3,5-*Dimethoxy*-4-*methylphenyl*)*butane* (13).—(a) *From* 2-(3,5-*dimethoxy*-4-*methylphenyl*)*butan*-2-*ol* (12) (with Dr. P. Vogel). Aluminium chloride (18.8 g) in dry ether (30 ml) was added dropwise under dry nitrogen to a stirred suspension of lithium aluminium hydride (3.2 g) in dry ether (30 ml) at 0 °C. The nitrogen stream was then discontinued and the alcohol (12) (15.0 g) in dry ether (40 ml) was added dropwise over 10 min. The mixture was then stirred and heated under reflux for 1 h. The cooled (0 °C) mixture was then treated with saturated aqueous sodium sulphate in the usual way. The crude product was steam distilled, and was obtained as an oil (11.2 g, 80%). A sample was distilled under diminished pressure; b.p. 130° (bath) at 0.2 mmHg (lit.,[14] 105° at 1 mmHg) (Found: C, 75.2; H, 10.1%; M^+, 208. Calc. for $C_{13}H_{20}O_2$: C, 74.95; H, 9.7%; *M*, 208), δ(CCl_4) 0.83 (3 H, t, 4-Me), 1.21 (3 H, d, 1-Me), 1.56 (2 H, quintet, CH_2), 1.97 (3 H, s, ArMe), 2.48 (1 H, sextet, CH), 3.75 (6 H, s, 2 × OMe), and 6.22 (2 H, s, 2 × ArH).

(b) *From methyl* 2,6-*dimethoxy*-4-*s*-*butylbenzoate* (19). Reduction of the ester (19) (23.3 g) with lithium aluminium hydride (3.5 g) and aluminium chloride (12.1 g) in dry ether (250 ml) as above gave the product (13) (16.0 g, 83%).

2,4-*Dimethoxy*-3-*methyl*-6-*s*-*butylbenzaldehyde* (20).—Titanium(IV) chloride (27.4 g) in dry dichloromethane (120 ml) was added dropwise at 0 °C over 15 min to the ether (13) (10.0 g) and dichloromethyl methyl ether (16.6 g) in dry dichloromethane (200 ml). The mixture was stirred at 0 °C for 0.5 h, and at room temperature for 0.5 h, poured on ice and dilute hydrochloric acid, and then extracted with ethyl acetate. The crude product was steam-distilled and afforded the *aldehyde* (20) (9.6 g, 85%). A sample was distilled under reduced pressure; b.p. 175° (bath) at 0.3 mmHg (Found: C, 70.8; H, 8.5%; M^+, 236. $C_{14}H_{20}O_3$ requires C, 71.15; H, 8.55%; *M*, 236); δ(CCl_4) 0.85 (3 H, t, 4-Me), 1.17 (3 H, d, 1-Me), 1.53 (2 H, d of quintets, $J_{3,2} = J_{3,4} = 7.0$ Hz, $J_{3,3}$ 2.0 Hz, diastereotopic CH_2), 2.08 (3 H, s, ArMe), 3.75 and 3.86 (each 3 H, s, OMe), 6.60 (1 H, s, ArH), and 10.32 (1 H, s, CHO); the signal due to the CH was partially obscured by the OMe resonances.

2-*Hydroxy*-4-*methoxy*-3-*methyl*-6-*s*-*butylbenzaldehyde* (21).—Boron trichloride (13.8 g) in dry dichloromethane (120 ml) was added at −78 °C to a stirred solution of the aldehyde (20) (9.4 g) in dry dichloromethane (120 ml). The mixture was stirred at −78 °C for 15 min and at room temperature for 3 h. The usual work-up, followed by steam distillation, gave the *aldehyde* (21) (6.4 g, 72%) as an oil. A sample was distilled under reduced pressure; b.p. 106—108° (bath) at 0.05 mmHg (Found: C, 70.6; H, 8.4%; M^+, 222. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.15%; *M*, 222), δ(CCl_4) 0.88 (3 H, t, 4-Me), 1.28 (3 H, d, 1-Me), 1.66 (2 H, quintet, CH_2), 1.99 (3 H, s, ArMe), 3.31 (1 H, sextet, CH), 3.87 (3 H, s, OMe), 6.31 (1 H, s, ArH), 10.14 (1 H, s, CHO), and 12.58 (1 H, s, OH).

2-*Acetoxy*-4-*methoxy*-3-*methyl*-6-*s*-*butylbenzaldehyde*

(22).—The phenol (21) was converted into the oily *acetate* (22) with pyridine and acetic anhydride (3 h; 90 °C). A sample was distilled under reduced pressure; b.p. 135—138° (bath) at 0.05 mmHg (Found: C, 68.35; H, 7.8%; M^+, 264. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%; *M*, 264); δ(CCl_4) 0.85 (3 H, t, 4-Me), 1.21 (3 H, d, 1-Me), 1.59br (2 H, quintet, diastereotropic CH_2), 1.94 (3 H, s, ArMe), 2.25 (3 H, s, MeCO), 3.70 (1 H, sextet, CH), 3.80 (3 H, s, OMe), 6.68 (1 H, s, ArH), and 10.18 (1 H, s, CHO).

2-Acetoxy-4-methoxy-3-methyl-6-s-butylbenzoic Acid (23).—A solution of potassium permanganate (10.5 g) and magnesium sulphate monohydrate (18.3 g) in water (250 ml) was added dropwise to a stirred solution of the aldehyde (22) (5.0 g) in acetone (50 ml) at such a rate that the reaction temperature was 20—25 °C. The mixture was then stirred at room temperature for 1.5 h, cooled to 0 °C, and clarified by passage of sulphur dioxide. The mixture was then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The *acid* (23) was obtained by extraction with sodium hydrogen carbonate solution in the usual way, and formed prisms (3.0 g, 57%) (from ether–light petroleum), m.p. 123—125° (Found: C, 64.05; H, 7.3. $C_{15}H_{20}O_5$ requires C, 64.25; H, 7.2%).

2-Hydroxy-4-methoxy-3-methyl-6-s-butylbenzoic Acid (24).—The acid (23) (9.3 g) in methanol (75 ml) was added dropwise to stirred aqueous potassium hydroxide (5%; 150 ml) at 0 °C under nitrogen. The solution was stirred at 0 °C for 1 h, acidified with dilute hydrochloric acid, and then worked up in the usual way. The *acid* (24) formed needles (7.0 g, 89%) (from aqueous methanol), m.p. 123—125° (Found: C, 65.45; H, 7.8%; M^+, 238. $C_{13}H_{18}O_4$ requires C, 65.55; H, 7.6%; *M*, 238).

Benzyl 2-Benzyloxy-4-methoxy-3-methyl-6-s-butylbenzoate (25).—The acid (24) (6.3 g), dry potassium carbonate (24.0 g), and benzyl bromide (8.7 g) were stirred in dry *NN*-dimethylformamide (60 ml) at room temperature for 24 h. More benzyl bromide (2.5 g) was then added and stirring was continued for a further 6 h. The excess of benzyl bromide was removed from the crude product (obtained in the usual fashion) by steam distillation; the product was obtained as a thick *oil* (10.5 g, 95%) (Found: M^+, 418.210 3. $^{12}C_{27}{}^1H_{30}{}^{16}O_4$ requires *M*, 418.214 4); δ(CCl_4) 0.76 (3 H, t, 4-Me), 1.15 (3 H, d, 1-Me), 1.52 (2 H, d of quintets, $J_{3.2} = J_{3.4} = 7.0$ Hz, $J_{3.3}$ 2.0 Hz, diastereotopic CH_2), 2.08 (3 H, s, ArMe), 2.54 (1 H, sextet, CH), 3.74 (3 H, s, OMe), 4.80 and 5.14 (each 2 H, s, CH_2Ph), 6.40 (1 H, s, ArH), and 7.20 (10 H, m, 2 × Ph).

Benzyl 2-Benzyloxy-5-bromo-4-methoxy-3-methyl-6-s-butylbenzoate (26).—The ester (25) (5.0 g), dry sodium acetate (8.0 g), and bromine (9.6 g) in glacial acetic acid (60 ml) were kept for 18 h in the dark. The mixture was poured into water and extracted with ethyl acetate. The usual work-up gave the *product* (26) (5.8 g, 98%) as an oil (Found: M^+, 496.125 0. $^{12}C_{27}{}^1H_{29}{}^{79}Br^{16}O_4$ requires *M*, 496.125 0).

2-Benzyloxy-5-bromo-4-methoxy-3-methyl-6-s-butylbenzoic Acid (27).—The ester (26) (12.0 g), potassium hydroxide (13.0 g), water (60 ml), and dimethyl sulphoxide (150 ml) were heated and stirred at 90 °C (bath) for 18 h, then more potassium hydroxide (5 g) was added and stirring and heating were continued for a further 54 h. The usual work-up gave the crude product, which was chromatographed over silica gel with 10% ethyl acetate–light petroleum as eluent. The *acid* (27) formed prisms (6.9 g, 70%) (from ether–light petroleum), m.p. 126—128° (Found: C, 59.0; H, 5.7; Br, 19.45. $C_{20}H_{23}BrO_4$ requires C, 59.0; H, 5.7; Br, 19.45%), δ($CDCl_3$) 0.85 (3 H, t, 4-Me), 1.37 (3 H, d, 1-Me), 1.71 (2 H, broadening quintet, diastereotopic CH_2), 2.27 (3 H, s, ArMe), 3.0vbr (1 H, CH), 3.79 (3 H, s, OMe), 4.92 (2 H, s, CH_2Ph), 7.32 (5 H, m, Ph), and 9.65br (1 H, s, OH).

2,2′,4′-Trisbenzyloxy-5-bromo-4-methoxy-3,6′-dimethyl-6-s-butylbenzophenone (29).—3,5-Bisbenzyloxytoluene (28) [24] (3.75 g) in dry dichloromethane (100 ml) was added dropwise to a stirred solution of the acid (27) (5.0 g) and trifluoroacetic anhydride (12.5 ml) in dry dichloromethane (80 ml) at room temperature, and stirring was continued for 2.5 h after the addition. The mixture was poured into water and the separated organic phase was washed in turn with saturated aqueous sodium hydrogen carbonate, water, and saturated brine. The crude product was chromatographed over a column of silica gel with 2.5—10% ethyl acetate–light petroleum as eluent. The *benzophenone* (29) (6.9 g, 81%) was obtained as a thick pale yellow oil, homogeneous on t.l.c. in several solvent systems (Found: M^+, 692.213 5. $^{14}C_{41}{}^1H_{41}{}^{79}Br^{16}O_5$ requires *M*, 692.213 6).

5-Bromo-2,2′,4′-trihydroxy-4-methoxy-3,6′-dimethyl-6-s-butylbenzophenone (30).—The benzophenone (29) (5.0 g) and 10% palladised charcoal (0.5 g) were stirred under hydrogen in ethyl acetate (100 ml) containing concentrated hydrochloric acid (5 drops) until absorption ceased. The usual work-up gave the *benzophenone* (30) as prisms (2.7 g, 89%) (from aqueous methanol), m.p. 97—101°, presumably a hydrate. A sample crystallised several times from ether–light petroleum formed prisms, which were dried *in vacuo*; m.p. 185—188° (Found: C, 56.6; H, 5.4; Br, 18.9%; M^+, 422.069 1. $C_{20}H_{23}BrO_5$ requires C, 56.75; H, 5.5; Br, 18.9%. $^{12}C_{20}{}^1H_{23}{}^{79}Br^{16}O_5$ requires *M*, 422.072 9); δ [60 MHz; CCl_4–$(CD_3)_2SO$] 0.73 (3 H, t, 4-Me), 1.19 (3 H, d, 1-Me), 1.82 (3 H, s, ArMe), 2.00 (2 H, m, partially obscured by 2 × ArMe, CH_2), 2.19 (3 H, s, ArMe), 2.70 (1 H, m, CH), 3.73 (3 H, s, OMe), 6.01 and 6.11 (2 H, ABq, *J* 2.0 Hz, ArH), and 6.89, 8.50, and 13.34 (each 1 H, s, OH).

7-Bromo-3-hydroxy-8-methoxy-1,9-dimethyl-6-s-butyldibenzo[b,e][1,4]*dioxepin-11-one* (32).—Potassium hexacyanoferrate(III) (5.0 g) in water (250 ml) was added dropwise to a stirred solution of the benzophenone (30) (2.5 g) and potassium carbonate (18.7 g) in water (625 ml) at room temperature. The mixture was then stirred at room temperature for 3 h and poured into an excess of ice-cold dilute hydrochloric acid. The precipitate was extracted with ethyl acetate and the crude product was chromatographed over silica gel with 2.5—10% ethyl acetate–light petroleum as eluent. The *depsidone* (32) formed prisms (2.0 g, 80%) (from ether–light petroleum), m.p. 161—163° (Found: C, 56.7; H, 5.25; Br, 18.7. $C_{20}H_{21}BrO_5$ requires C, 57.0; H, 5.0; Br, 18.95%), $\nu_{max.}$ (Nujol) 1 690 (C=O), 1 620 (C=C), and 1 578 cm^{-1} (C=C); *m/e* 422 (8%), 420 (8, M^+), 394 (8), 392 (9), 342 (24), 341 (100), 313 (17), and 151 (14); δ(CCl_4) 0.85 (3 H, t, 4-Me), 1.38 (3 H, d, 1-Me), 1.85 (2 H, m, CH_2), 2.29 (3 H, s, 9-Me), 2.48 (3 H, s, 1-Me), 3.58 (1 H, m, CH), 3.72 (3 H, s, OMe), and 6.59 and 6.54 (2 H, ABq, 2.5 Hz, 2- and 4-H) (irradiating at δ 2.48 sharpened the AB system); $\lambda_{max.}$ (EtOH) 268 nm (ε, 13 000). The *acetate* (33) (acetic anhydride; 90 °C; 1 h) formed prisms (from aqueous methanol), m.p. 104—106° (Found: C, 57.05; H, 5.2; Br, 17.35. $C_{22}H_{23}BrO_6$ requires C, 57.05; H, 5.0; Br, 17.25%), δ (60 MHz; CCl_4) 0.88 (3 H, t, 4-Me), 1.37 (3 H, d, 1-Me), 1.93 (2 H, quintet, CH_2), 2.22, 2.29, and

2.49 (each 3 H, s, MeCO and 2 × ArMe), 3.57 (1 H, m, CH), 3.65 (3 H, s, OMe), and 6.70 and 6.84 (2 H, ABq, J 2.5 Hz, ArH); m/e 464 (10%), 462 (10, M^+), 436 (10), 434 (10), 384 (29), 383 (100), 341 (21), 313 (15), and 151 (10).

2-(5′-*Bromo*-2′-*hydroxy*-6′-*methyl*-3′-*s*-*butylphenoxy*)-4-*hydroxy*-6-*methylbenzoic Acid* (37).—The depsidone (32) (195 mg), potassium hydroxide (250 mg), and water (10 ml) were heated on a steam-bath for 0.5 h under nitrogen. The cooled solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The crude product was chromatographed over silica gel with 10—25% ethyl acetate–light petroleum as eluent. This afforded the *acid* (37) as a gum (123 mg, 61%), homogeneous on t.l.c. in several solvent systems (Found: M^+, 438.066 7. $^{12}C_{20}{}^{1}H_{23}{}^{79}Br^{16}O_6$ requires M, 438.067 8); δ [60 MHz; CCl_4–$(CD_3)_2SO$] 0.82 (3 H, t, 4-Me), 1.31 (3 H, d, 1-Me), 1.80 (2 H, m, CH_2), 2.11 and 2.39 (each 3 H, s, ArMe), 3.25 (1 H, m, CH), 3.69 (3 H, s, OMe), 5.86 and 6.30 (2 H, ABq, J 2.0 Hz, 3- and 5-H), and 7.55br (3 H, s, 3 × OH).

3-*Hydroxy*-8-*methoxy*-1,9-*dimethyl*-6-*s*-*butyldibenzo*[b,e]-[1,4]*dioxepin*-11-*one* (*Tridechlorodihydronidulin*) (34).—(a) *From the depsidone* (32). The depsidone (32) (370 mg), 10% palladised charcoal (300 mg), and anhydrous sodium acetate (120 mg) were stirred in methanol (60 ml) under hydrogen for 18 h. The usual work-up gave the *depsidone* (34) as prisms (285 mg, 85%) (from ether–light petroleum), m.p. 134—136° (Found: C, 69.85; H, 6.6. $C_{20}H_{22}O_5$ requires C, 70.15; H, 6.5%), identical (mixed m.p.; R_F in three solvent systems; mass and n.m.r. spectra) with that described in (b); δ(CCl_4) 0.83 (3 H, t, 4-Me), 1.17 (3 H, d, 1-Me), 1.56 (2 H, quintet, CH_2), 2.15 and 2.45 (each 3 H, s, 2 × ArMe), 3.35 (1 H, sextet, CH), 3.75 (3 H, s, OMe), 6.37 (1 H, s, 7-H), 6.58 (2 H, s, 2- and 4-H), and 7.50br (1 H, s, OH); m/e 343 (23%), 342 (100, M^+), 314 (22), 313 (19), 299 (16), 298 (10), 286 (12), 285 (26), 269 (15), 259 (13), 258 (71), 257 (20), 253 (10), 190 (12), 164 (28), and 151 (24).

(b) *From nidulin* (1). Nidulin (1) [4] (50 mg) and platinum oxide (25 mg) were stirred in acetic acid (10 ml) under hydrogen until uptake ceased.[28] The crude dihydronidulin, 10% palladised charcoal (100 mg), 5% palladised strontium carbonate (100 mg), and anhydrous sodium acetate (20 mg) in methanol (20 ml) were shaken under 3 ·atm of hydrogen for 50 h. The usual work-up gave the depsidone (34) as prisms (30 mg, 77%), m.p. 134—136° (from ether–light petroleum).

3,8-*Dihydroxy*-1,9-*dimethyl*-6-*s*-*butyldibenzo*[b,e][1,4]-*dioxepin*-11-*one* (*Tridechlorodihydro*-O-*nornidulin*) (39).—(a) *From the depsidone* (32). A stirred solution of the depsidone (32) (500 mg) in dry dichloromethane (50 ml) was cooled to −78 °C and boron tribromide (1.2 g) in dry dichloromethane (25 ml) was added dropwise. After 5 min the cooling bath was removed and the mixture was stirred at room temperature for 40 min, then poured into water, and extracted with ethyl acetate. The extract was washed in turn with water, saturated aqueous sodium hydrogen carbonate, and saturated brine. The crude product, 10% palladised charcoal (300 mg), and anhydrous sodium acetate (120 mg) in methanol (60 ml) were stirred under hydrogen for 18 h. The crude product was chromatographed over silica gel with 5—10% ethyl acetate–light petroleum as eluent. This gave first the depsidone (34) (30 mg), followed by the *depsidone* (39), which formed prisms (81 mg, 21%) (from ether–light petroleum), m.p. 195—197° (lit.,[8] 174°) (Found: C, 69.45; H, 5.95. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.15%), identical (mixed m.p.; R_F in three solvent systems; mass and n.m.r. spectra) with that described in (b); δ[$(CD_3)_2CO$] 0.85 (3 H, t, 4-Me), 1.17 (3 H, d, 1-Me), 1.59 (2 H, quintet, CH_2), 2.15 (3 H, s, 9-Me), 2.42 (3 H, s, 1-Me), 3.38 (1 H, sextet, CH), 6.58 (1 H, s, 7-H), and 6.64 (2 H, s, 2- and 4-H) (irradiating at δ 2.42 sharpened the signal due to the 2- and 4-H); m/e 329 (22%), 328 (100, M^+), 300 (13), 299 (52), 272 (16), 271 (27), 253 (11), 244 (15), 243 (29), 229 (12), 217 (17), 215 (28), and 151 (37).

(b) *From tridechloro*-O-*nornidulin* (4). The ethanol solvate of the depsidone (4) [3] (50 mg) and 10% palladised charcoal (50 mg) in ethyl acetate (25 ml) were stirred under hydrogen until absorption ceased. The usual work-up gave the depsidone (39) as prisms (32 mg, 73%) (from ether–light petroleum), m.p. 195—197°.

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