Depsidone Synthesis. XXII*  
An Alternative Synthesis of Gangaleoidin

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Abstract  
A new synthesis of the lichen depsidone gangaleoidin (1) (methyl 2,4-dichloro-3-hydroxy-8-methoxy-1,6-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepin-7-carboxylate) is described. It depends on the oxidation of methyl 4-hydroxy-3-(4',6'-dihydroxy-2'-methylbenzoyl)-6-methoxy-2-methylbenzoate (7) to methyl 6-hydroxy-4,6'-dimethyl-4'-methoxy-2',3-dioxo-2,3-dihydrospiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-5'-carboxylate (8), and the thermolysis of this compound to methyl 3-hydroxy-8-methoxy-1,6-dimethyl-11-oxo-11H-dibenzo[b,e][1,4]dioxepin-7-carboxylate (2), which had been previously converted into gangaleoidin (1) by chlorination.

A number of years ago we reported the synthesis1 of the lichen depsidone gangaleoidin (1)2 by chlorination of the synthetic depsidone (2) which had been obtained by the lactonization of the dihydroxy acid (3), obtained in turn by an Ullmann synthesis. More recently we have developed a method of depsidone synthesis which depends on the oxidative coupling of benzophenones to form linearly conjugated

grisadiendiones which undergo ready rearrangement to depsidones under a number of conditions. We have also suggested that the biosynthesis of depsidones may follow this course.

We now report that the depsidone (2) is conveniently obtained by the oxidative coupling method and gangaleoidin (1) is hence available by this alternative route. Friedel–Crafts reaction of 4,6-dibenzyloxy-2-methylbenzoic acid (4) and methyl 4-benzyloxy-6-methoxy-2-methylbenzoate (5) in presence of trifluoroacetic anhydride readily gave the benzophenone (6). Hydrogenolytic debenzylation then afforded the trihydroxybenzophenone (7). As expected from our previous results oxidative coupling of this trihydroxybenzophenone (7) yielded the linearly conjugated grisadiendione (8), as evidenced by its 'H n.m.r. spectrum, rather than its isomer resulting from oxidative entry into the ring bearing two hydroxy groups. Thermolysis of this grisadiendione (8) yielded the depsidone (2), identical with an authentic sample, which had previously been converted into gangaleoidin (1) by chlorination.

Experimental

General directions have been given before.

Methyl 4-Benzyloxy-3-(4',6'-dibenzyloxy-2'-methylbenzoyl)-6-methoxy-2-methylbenzoate (6)

Trifluoroacetic anhydride (1.2 ml) was added dropwise to a stirred solution of 4,6-dibenzyloxy-2-methylbenzoic acid (4) (1.2 g) in dry nitromethane (10 ml) at -10°. The solution was stirred for 10 min at -10° and then methyl 4-benzyloxy-6-methoxy-2-methylbenzoate (5) (2.0 g) in nitromethane (10 ml) was added dropwise at -10°. The reaction mixture was then stirred at room temperature for 80 min and poured into ethyl acetate. The solution was washed in turn with water, saturated sodium hydrogen carbonate, and saturated brine and dried. The crude product was chromatographed over silica gel with 0-20% ethyl acetate/light petroleum as eluent. The benzophenone (6) (480 mg) crystallized from dichloromethane/light petroleum as prisms, m.p. 147-149° (Found: C, 75.9; H, 5.8. C32H32O5 requires C, 76.0; H, 5.9%). δ (CDCl3, 60 MHz) 2.06 and 2.11, each 3H, s, Me; 3.67 and 3.77, each 3H, s, OMe; 4.62, 4H, s, 2×PhCH2; 4.89, 2H, s, PhCH2; 6.08, 1H, s, H5; 6.19, 2H, bs, H3',5'; 6.61-7.19, 10H, m, 2×Ph; 7.23, 5H, s, Ph.

Methyl 4-Hydroxy-3-(4',6'-dihydroxy-2'-methylbenzoyl)-6-methoxy-2-methylbenzoate (7)

The benzophenone (6) (475 mg) and 10% palladized charcoal (200 mg) in ethyl acetate (50 ml), containing concentrated hydrochloric acid (2 drops), were stirred under hydrogen until absorption ceased. The usual workup gave the trihydroxybenzophenone (7) (204 mg) (from dichloromethane/light petroleum), m.p. 202-205° (Found: C, 62.1; H, 5.4. C18H18O7 requires C, 62.4; H, 5.2%). δ (CD3COCD3, 60 MHz) 1.82 and 1.87, each 3H, s, Me; 3.71, 6H, s, 2×OMe; 6.13, 2H, bs, H3',5'; 6.37, 1H, s, H5; mass spectrum m/z 346 (M).

Methyl 6-Hydroxy-4,6'-dimethyl-4'-methoxy-2,3-dioxo-2,3-dihydrospiro[benzofuran-2,1'-cyclohexa-3',5'-diene]-5'-carboxylate (8)

Potassium hexacyanoferrate(m) (244 mg) in water (15 ml) was rapidly added dropwise to a stirred solution of the trihydroxybenzophenone (7) (100 mg) and potassium carbonate (917 mg) in water
(31 ml). The reaction mixture was stirred for 2 min after the addition and then acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed successively with water, saturated aqueous sodium hydrogen carbonate, and finally with saturated brine, and dried. The grisadiendione (8) (54.3 mg) crystallized from acetone as pale yellow plates, m.p. 182-190° with resolidification to prisms, m.p. 217-218° (Found: C, 62.5; H, 4.8. C_{18}H_{16}O_{7} requires C, 62.8; H, 4.7%). δ (CD_{3}COCD_{3}, 60 MHz) 1.70, 3H, s, C=CMe; 2.35, 3H, s, &Me; 3.75 and 3.81, each 3H, s, OMe; 5.36, 1H, s, C=CH; 6.39, 2H, s, H 5,7; mass spectrum m/z 344 (M).

Methyl 3-Hydroxy-8-methoxy-1,6-dimethyl-11-oxo-1H-dibenzo[b,e][1,4]dioxepin-7-carboxylate (2)

The grisadiendione (8) (130 mg) in dry phenetole (5 ml) was heated under reflux under dry nitrogen for 20 min. The phenetole was removed by steam distillation and the residue was subjected to p.l.c. with 10% ethyl acetate/light petroleum as developing solvent. The depsidone (2) (33 mg) crystallized from dichloromethane/light petroleum as prisms, m.p. and mixed m.p. 218-220° (lit.1 219-220°), identical (mass and ^1H n.m.r. spectra and R_f values in three different solvent systems) with an authentic sample; δ (CD_{3}COCD_{3}, 60 MHz) 2·30 and 2·37, each 3H, s, Me; 3·76, 6H, s, 2×OMe; 6·58, 2H, s, H 2,4; 6·72, 1H, s, H 9.

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