Structure of the Lichen Depsidone Gangaleoidin †

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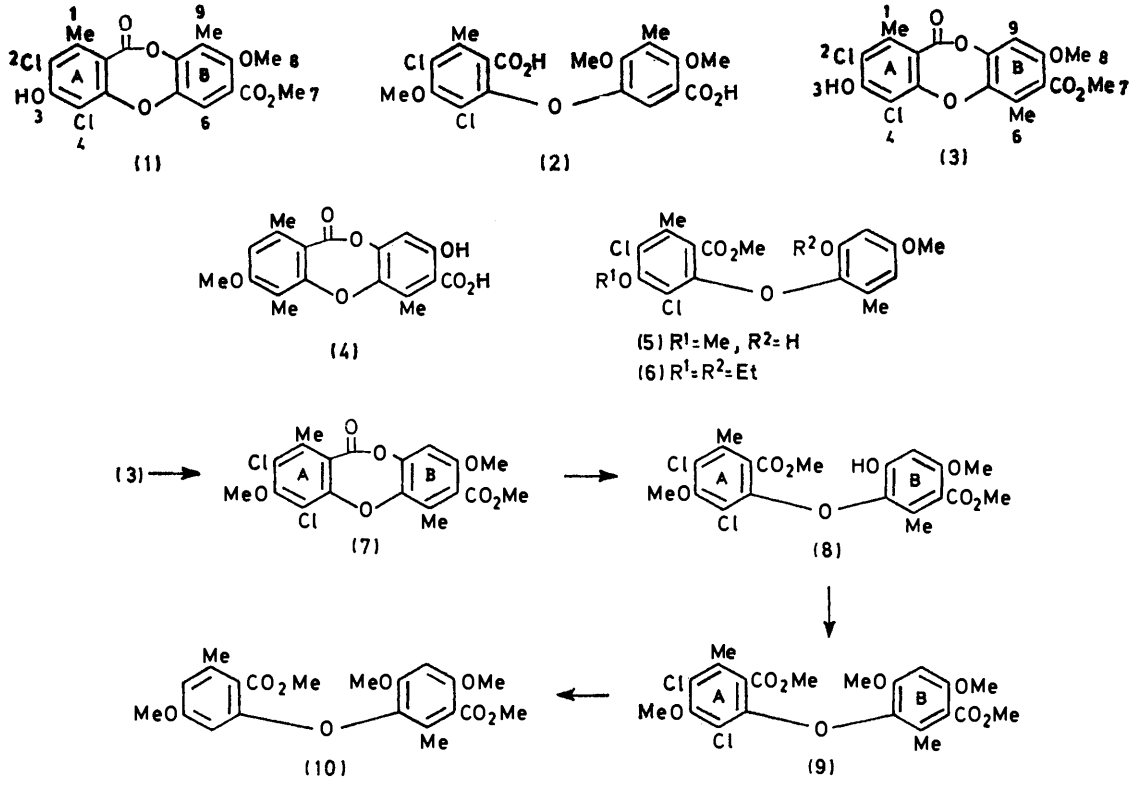
As a result of degradative, spectroscopic, and synthetic evidence the structure of the lichen depsidone gangaleoidin is revised to methyl 2,4-dichloro-3-hydroxy-8-methoxy-1,6-dimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-carboxylate. Gangaleoidin was degraded to methyl 3-(2-methoxycarbonyl-5-methoxy-3-methylphenoxy)-4,6-dimethoxy-2-methylbenzoate (10), which was synthesised in 70% yield by Ullmann reaction between methyl 2-bromo-4-methoxy-6-methylbenzoate (22) and methyl 3-hydroxy-4,6-dimethoxy-2-methylbenzoate (30). The bromination of methyl dihydro-orsellinate(23) was studied.

STRUCTURE (1) for the lichen depsidone gangaleoidin was proposed by Nolan on the grounds of classical degradation results.[1] The superchlorination technique was used to elucidate the structure of ring A. The structure of ring B rested on the following, apparently sound, evidence. Methanolysis of gangaleoidin and subsequent the dicarboxylic acid (2) also yielded a monocarboxylic acid which underwent re-lactonisation on treatment with sulphuric acid and acetic anhydride. The methanolysis product of this new depsidone gave a positive Gibb's test hence the ring B carboxy-group was *para* to the depside linkage.



methylation and hydrolysis yielded a dicarboxylic acid, assigned structure (2), which underwent partial decarboxylation and ring-closure to a xanthone on pyrolysis. This evidence indicated that the position *ortho* to the diaryl ether linkage in ring B was vacant. Pyrolysis of

The biogenesis of ring B of structure (1), which is unique among depsidones, would presumably involve a unit of β-orcinolcarboxylic acid which has lost the methyl group derived from acetyl-coenzyme A, and retained that derived from *S*-adenosylmethionine.[2] Hendrickson [3] therefore proposed structure (3) for ganga-

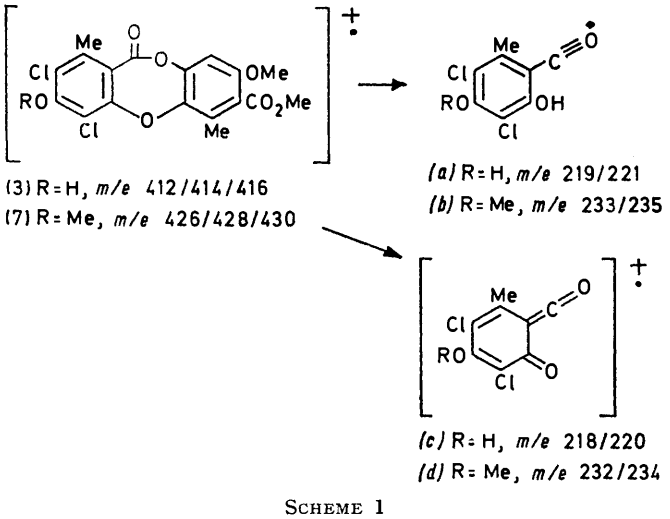
† Preliminary communication, J. A. Elix, M. V. Sargent, and P. Vogel, *J.C.S. Chem. Comm.*, 1974, 1023.

[1] J. Keane and T. J. Nolan, *Sci. Proc. Roy. Dublin Soc.*, 1935, **21**, 141; 1940, **22**, 199; V. E. Davidson, J. Keane, and T. J. Nolan, *ibid.*, 1943, **23**, 143.

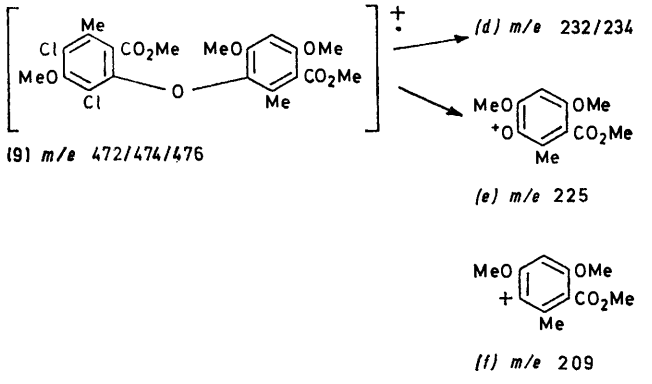
[2] C. F. Culberson, 'Chemical and Botanical Guide to Lichen Products,' University of North Carolina Press, Chapel Hill, 1969, p. 43.

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

leiodin in which ring B is similar to that of notatic acid (4),[4] and is of the usual orsellinic acid type. The formation of the above-mentioned xanthone would then involve a grisan intermediate which could yield the



SCHEME 1



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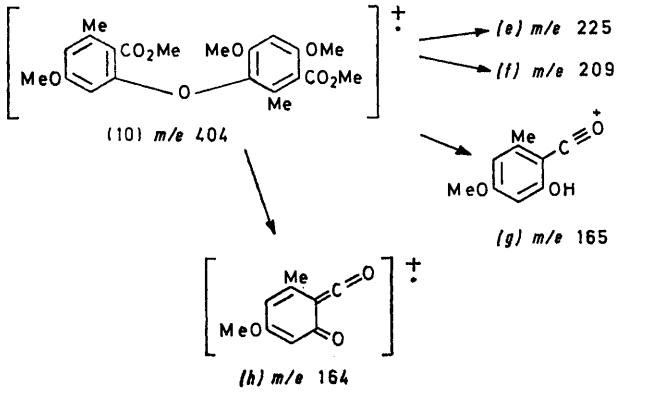


SCHEME 3

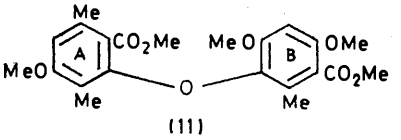
observed product after dienone–phenol rearrangements.[3] Hendrickson synthesised the degradation products (5) and (6) of the gangaleoidin of structure (3), but these had different m.p.s from those recorded by Nolan. A direct comparison was impossible since Nolan's samples are lost, and no lichen material was available. The structure (1) therefore appeared to be correct when we commenced our work.

We now present degradative, spectroscopic, and synthetic evidence for the revised structure (3) for gangaleoidin, which was extracted from the same species, *Lecanora gangaleoides* Nyl., as used by Nolan.[1] The mass spectrum of gangaleoidin (3) (see Scheme 1) showed the expected ring A ions (*a*) and (*c*). In the mass spectrum (Scheme 1) of *O*-methylgangaleoidin (7) the ring A fragments were (*b*) and (*d*), in keeping with the presence of a hydroxy-group on ring A of gangaleoidin. Methanolysis of *O*-methylgangaleoidin (7) gave the phenolic diaryl ether (8) which on methylation afforded the diaryl ether (9). This on hydrogenolysis afforded the dechloro-compound (10). The mass spectra of both (9) and (10) (Schemes 2 and 3) showed the prominent ions (*e*) and (*f*) due to ring B fragments, thus indicating the gross structure of this ring. The mass spectrum of (9) again exhibited the ion (*d*) due to ring A, and in the mass spectrum of (10) the ring A fragments were (*g*) and (*h*), in keeping with the location of the chloro-substituents on ring A of gangaleoidin.

The n.m.r. spectra of the degradation products were also highly informative. The *meta*-relationship of the chloro-substituents on ring A was apparent since the n.m.r. spectrum of the hydrogenolysis product (10) exhibited an AB system due to two aromatic protons with J_m 2.3 Hz. The chemical shifts of the ring B aromatic protons, τ 3.65 and 3.56, in the n.m.r. spectra of the diaryl ethers (9) and (10) were very similar to the chemical shift (τ 3.69) of the ring B proton of the diaryl ether (11), which had been obtained both by synthesis and by degradation of notatic acid. Structure (1) for gangaleoidin, and hence structure (12) for the *O*-methylated methanolysis product, were rejected since in the n.m.r. spectrum of the synthetic diaryl ether (13) [5] the signal of the ring B aromatic proton was at much lower field (τ 3.22) than in the spectra of the natural derivatives (9) and (10). Structure (3) for gangaleoidin was therefore preferred.

The synthesis of the degradation product (10) would thus constitute a complete proof of the structure of gangaleoidin. For this purpose the bromo-ester (22) was required. Nitration of the known acid (14) [6] gave a mixture of neutral and acidic products. The neutral products were identified as the known dinitro-compounds (15) [7] and (16).[8] The acidic products were methylated and the desired nitro-compound (17) was easily separated from its isomer (18) and the dinitro-compound (19). Reduction of the nitro-compound (17) gave the amine (20), which underwent smooth bromination affording the bromo-amine (21). Deamination of the latter then gave the bromo-ester (22).

[4] T. M. Cresp, J. A. Elix, S. Kurokawa, and M. V. Sargent, *Austral. J. Chem.*, 1972, **25**, 2167.
[5] M. V. Sargent, unpublished work.
[6] A. M. Van Arendonk and M. E. Cupery, *J. Amer. Chem. Soc.*, 1931, **53**, 3184.
[7] R. B. Drew, *J. Chem. Soc.*, 1920, 1615.
[8] R. de Capeller, *Helv. Chim. Acta*, 1928, **11**, 426.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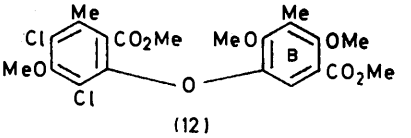
A
Me
O
MeO
OMe
B
CO2Me
Me

(11)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Cl
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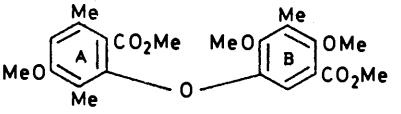
CO2Me

(12)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O
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Me
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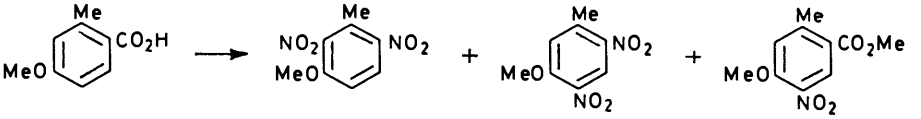
B
CO2Me

(13)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(14)
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NO2
NO2
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+
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NO2
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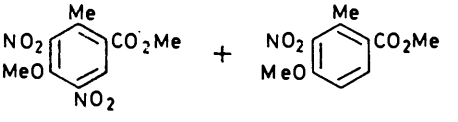
NO2
(16)
+
Me
CO2Me
MeO
NO2
(17)

+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MeO
NO2
(19)
+
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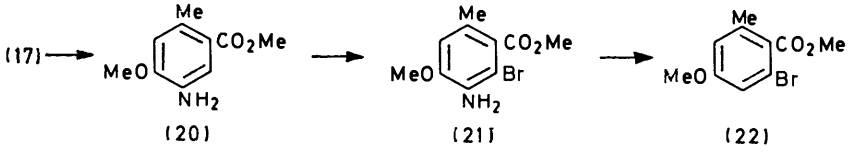
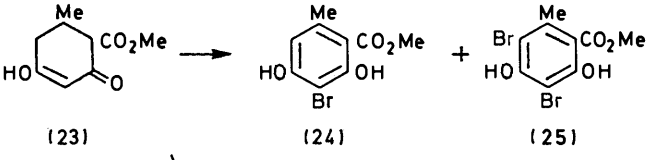
CO2Me
MeO
(18)


(17)
Me
CO2Me
MeO
NH2
(20)
Me
CO2Me
MeO
Br
NH2
(21)
Me
CO2Me
MeO
Br
(22)


Me
CO2Me
HO
O
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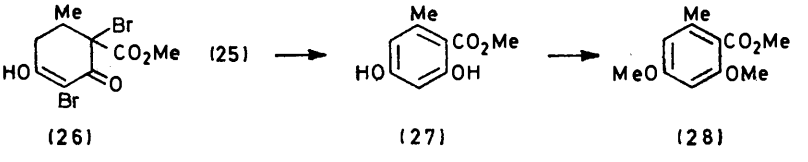
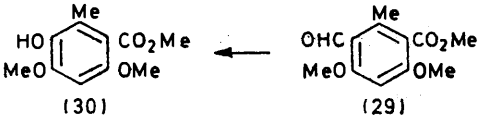
Me
CO2Me
HO
OH
Br
(24)
+
Br
Me
CO2Me
HO
OH
Br
(25)


Me
Br
CO2Me
HO
O
Br
(26)
(25)
Me
CO2Me
HO
OH
(27)
Me
CO2Me
MeO
OMe
(28)


Me
HO
CO2Me
MeO
OMe
(30)
Me
OHC
CO2Me
MeO
OMe
(29)

The ring B precursor (30) of the diaryl ether (10) was prepared from methyl orsellinate (27) which on methylation gave the ester (28). Formylation [9] of the latter afforded the aldehyde (29), which on Baeyer–Villiger oxidation and hydrolysis of the formate so produced [10] gave the desired phenol (30).

Ullmann reaction of the phenol (30) and the bromo-compound (22) then gave the diaryl ether (10), identical with the degradation product. Gangaleoidin therefore has structure (3).

Certain aspects of the synthesis of methyl orsellinate (27) deserve comment. Methyl dihydro-orsellinate * (23) was readily prepared by a modification of the literature method.[12] The best method for the conversion of the dihydro-compound (23) into methyl orsellinate (27) appeared to be bromination and subsequent debromination.[13,14] Some confusion [14,15] is apparent in the literature concerning the products of bromination of ethyl dihydro-orsellinate; hence we present our results for the bromination of the methyl ester (23). Contrary to the results of Santesson [14] with the ethyl ester, rapid bromination of the methyl ester (23) with 2 mol. equiv. of bromine gave an alicyclic dibromo-compound formulated as (26) on the grounds of its n.m.r. spectrum. If the mixture resulting from the rapid addition of 2 mol. equiv. of bromine to the ester (23) was allowed to remain in contact with the hydrogen bromide generated in the reaction then the chief product isolated was the bromo-compound (24), accompanied by a little of the dibromo-compound (25); [16] evidently elimination occurs under these conditions. The structure of the bromo-compound (24) followed from its conversion into the corresponding known di-*O*-methyl compound.[17] Treatment of the dihydro-ester (23) with 3 mol. equiv. of bromine for an extended period gave the dibromo-derivative (25) in agreement with the results of Ansell and Culling.[16] This underwent smooth debromination [14] and afforded methyl orsellinate (27).

EXPERIMENTAL

General directions have been given before.[18] N.m.r. spectra at 100 MHz were determined with a JEOL JNM-MH-100 spectrometer.

Extraction of Lecanora gangaleoides *Nyl.*—The dry finely ground lichen (9.5 g) was extracted (Soxhlet) with ether (500 ml) for 24 h. The residue on crystallisation from toluene furnished gangaleoidin (3) (283 mg) as needles, m.p. 211—212° (lit.,[1] 213—214°) (Found: M^+, 412.0115. Calc. for $^{12}C_{18}{}^{1}H_{14}{}^{35}Cl_2{}^{16}O_7$: *M*, 412.0116), τ [$CDCl_3$, $(CD_3)_2CO$; 100 MHz] 3.26 (1 H, s, ArH), 6.11 and 6.17 (each 3 H, s, OMe), and 7.53 (6 H, s, 2 × Me), *m/e* 416 (M^+, 13%), 415(14), 414 (M^+, 69), 413(22), 412(M^+, 100), 399(23), 397(35), 386(18), 385(10), 384(32), 383(25), 382(22), 381(37), 380(26), 371(7), 369(13), 367(13), 365(18), 356(8), 355(11), 354(18), 353(14), 352(15), 351(10), 349(10), 341(10), 339(14), 338(6), 337(16), 327(12), 326(11), 325(23), 324(14), 323(7), 311(8), 310(5), 309(8), 298(5), 297(9), 296(8), 295(8), 294(6), 284(5), 283(5), 282(7), 281(5), 273(6), 271(8), 221(3), 220(6), 219(5), 218(4), 194(38), 191(19), 190(22), 177(6), 176(9), 174(7), 173(11), 166(8), and 151(5). The lichen was then further extracted with acetone (500 ml) for 24 h and the material obtained was combined with that left in the toluene mother liquor and chromatographed over a p.l.c. plate (100 × 20 × 0.1 cm) developed with 50% ethyl acetate–light petroleum (b.p. 60—80°). Four bands were removed; these yielded (in order of decreasing R_F), atranorin (45 mg), the artefact methyl β-orcinolcarboxylate (20 mg), chloroatranorin (17 mg) and crude gangaleoidin contaminated with an unknown orange metabolite (total 99 mg).

Methylation of Gangaleoidin (3).—Gangaleoidin (3) (30 mg) in ethyl acetate (2 ml) was treated with an excess of ethereal diazomethane. After 15 min the solvents were removed under diminished pressure and the residue was crystallised from cyclohexane–benzene to give the methyl ether (7) in quantitative yield as rosettes, m.p. 180—181° (lit.,[1] 181°) (Found: M^+, 426.0269. Calc. for $^{12}C_{19}{}^{1}H_{16}{}^{35}Cl_2{}^{16}O_7$: *M*, 426.0273), τ (100 MHz) 3.28 (1 H, s, ArH), 6.05, 6.07, and 6.19 (each 3 H, s, OMe), and 7.48 (6 H, s, 2 × Me); *m/e* 430 (14%, M^+), 429(15), 428(70, M^+), 427(23), 426(100, M^+), 413(14), 411(22), 400(11), 399(7), 398(21), 397(19), 396(16), 395(27), 394(15), 391(10), 385(6), 383(10), 381(7), 379(10), 370(6), 369(8), 368(10), 367(11), 366(7), 365(7), 363(9), 355(7), 353(9), 351(10), 341(11), 340(8), 339(18), 338(8), 337(6), 311(6), 309(6), 294(5), 287(5), 285(7), 235(2), 234(2), 233(3), 232(3), 199(9), 198(9), 197(14), 194(19), 181(5), 180(11), 166(6), 147(6), 145(6), 123(5), and 109(5).

Methanolysis of the Ether (7).—The ether (7) (60 mg) in dry methanol (25 ml) containing sodium (10 mg) was stirred at room temperature for 2 h. The solution was poured into ice and dilute hydrochloric acid and then extracted with chloroform. The crude product was applied to a p.l.c. plate which was developed with 20% ethyl acetate–light petroleum. This gave methyl 3,5-dichloro-2-(6-hydroxy-3-methoxycarbonyl-4-methoxy-2-methylphenoxy)-4-methoxy-6-methylbenzoate(8) (50 mg) as prisms (from benzene–cyclohexane), m.p. 167—168° (with resolidification and m.p. 185—186°) (lit.,[1] 186—187°) (Found: M^+, 458.0531. Calc. for $^{12}C_{20}{}^{1}H_{20}{}^{35}Cl_2{}^{16}O_8$: *M*, 458.0259), τ (100 MHz) 2.99br (1 H, OH) 3.54 (1 H, s, ArH), 6.13 (6 H, s, 2 × OMe), 6.22 (3 H, s, OMe) and 7.73 and 7.81 (each 3 H, s, Me); *m/e* 462 (15%, M^+), 461 (17), 460 (70, M^+), 459(25), 458(100, M^+), 431(5), 430(14), 429(26), 428(60), 427(37), 426(82), 413(20), 412(6), 411(28), 400(16), 399(10), 398(30), 397(22), 396(20), 395(29), 394(21), 393(6), 391(15), 385(7), 383(10), 381(7), 379(10), 370(6), 369(11), 368(12), 367(15), 366(9), 365(8), 364(5), 363(10), 355(6), 353(7), 351(8), 341(8), 340(7), 339(14), 338(8), 337(6), 235(1), 234(2), 233(1), 232(3), 211(2), 194(4), 179(4), and 151(4).

Methylation of the Diaryl Ether (8).—Treatment of the

* The n.m.r. spectrum of this compound was very similar to that of the ethyl ester.[11] Hence the methyl 4-hydroxy-6-methyl-2-oxocyclohex-3-enecarboxylate structure (23) predominates.

[9] T. M. Cresp, M. V. Sargent, J. A. Elix, and D. P. H. Murphy, *J.C.S. Perkin I*, 1973, 340.

[10] I. M. Godfrey, M. V. Sargent, and J. A. Elix, *J.C.S. Perkin I*, 1974, 1353.

[11] R. N. Mirrington, E. Ritchie, C. W. Shoppee, S. Sternhell and W. C. Taylor, *Austral. J. Chem.*, 1966, **19**, 1265.

[12] A. Sonn, *Ber.*, 1929, **64**, 3012.

[13] R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 1945, 311.

[14] J. Santesson, *Acta Chem. Scand.*, 1970, **24**, 3373.

[15] R. A. Kloss and D. A. Clayton, *J. Org. Chem.*, 1965, **30**, 3566.

[16] M. F. Ansell and G. C. Culling, *J. Chem. Soc.*, 1961, 2908.

[17] J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, G. Vinciguerra, and J. A. Elix, *J. Chem. Soc.* (*C*), 1971, 3495.

[18] D. A. Jackman, M. V. Sargent, and J. A. Elix, *J.C.S. Perkin I*, preceding paper.

ether (8) in ethyl acetate, as before, with ethereal diazomethane gave methyl 3,5-dichloro-4-methoxy-2-(3-methoxycarbonyl-4,6-dimethoxy-2-methylphenoxy)-6-methylbenzoate (9), in quantitative yield as needles (from hexane–cyclohexane), m.p. 112—113° (on cooling and solidification, m.p. 138—140°) (lit.,[1] 141—142°) (Found: M^+, 472.0688. Calc. for $^{12}C_{21}{}^{1}H_{22}{}^{35}Cl_2{}^{16}O_8$: M, 472.0692), τ (100 MHz) 3.65 (1 H, s, ArH), 6.08, 6.11, 6.19, 6.38, and 6.52 (each 3 H, s, OMe), and 7.78 and 7.80 (each 3 H, s, Me); *m/e* 476 (14%, M^+), 475(17), 474(70, M^+), 473(26), 472(100, M^+), 442(14), 441(6), 440(21), 406(4), 404(9), 389(7), 382(17), 381(6), 380(24), 263(1), 261(1), 234(2), 232(3), 225(16), 209(15), 193(10), and 165(10).

Hydrogenolysis of the Diaryl Ether (9).—The ether (9) (14.0 mg) and 10% palladised charcoal (0.5 g) were shaken in methanol (25 ml) and triethylamine (1 ml) under hydrogen at 3 atm for 18 h. Work-up in the usual way followed by chromatography over one plate developed with 10% ethyl acetate–light petroleum gave *methyl 3-(2-methoxycarbonyl-5-methoxy-3-methylphenoxy)-4,6-dimethoxy-2-methylbenzoate* (10) (10.1 mg) as rods (from methanol), m.p. 127—128° (Found: M^+, 404.1474. $^{12}C_{21}{}^{1}H_{24}{}^{16}O_8$ requires M, 404.1471), τ (90 MHz), 3.56 (1 H, s, 5-H), 3.65 and 4.16 (2 H, ABq, $J_{4,6}$ 2.3 Hz, 4- and 6-H), 6.12, 6.14, 6.18, 6.25, and 6.36 (each 3 H, s, OMe), and 7.67 and 7.89 (each 3 H, s, Me); *m/e* 406(5%), 405(28), 404(100, M^+), 374(10), 373(35), 372(7), 341(17), 340(8), 329(5), 327(6), 314(15), 313(53), 299(8), 297(7), 295(6), 285(9), 284(7), 283(8), 271(6), 270(7), 269(6), 255(5), 253(7), 241(8), 240(20), 226(7), 225(23), 211(6), 210(7), 209(32), 197(9), 195(6), 194(8), 193(28), 179(10), 178(7), 171(17), 165(22), 164(10), 163(6), 151(7), 149(15), 148(6), 136(11), 135(12), 123(8), 121(11), 120(9), 115(6), 109(6), 107(6), and 105(6).

4-Methoxy-2-methylbenzoic Acid (14).—Sodium hydroxide (26.6 g) in water (37 ml) was cooled to 0 °C and ice (153 g) was added. Chlorine (19.7 g) was rapidly passed through the stirred solution which was then warmed to 55 °C. 4′-Methoxy-2′-methylacetophenone [19] (10.0 g) was then added and the temperature was kept at 60—70 °C by intermittent cooling. After the exothermic reaction had ceased the solution was stirred for a further 0.5 h and the excess of hypochlorite was destroyed by the addition of aqueous sodium disulphite. The cooled solution was acidified and the precipitated acid was collected by filtration. It formed needles (8.0 g, 79%), m.p. 177.5—178° (lit.,[6] 175°) (from methanol).

Nitration of 4-Methoxy-2-methylbenzoic Acid (14) (with N. M. Rana).—The acid (14) (77.6 g) was nitrated in portions. Each (5 g) was added slowly over 15 min to stirred fuming nitric acid (25 ml) at 0—5 °C. After stirring at room temperature for a further 15 min the mixture was poured into ice–water and the precipitated product was collected by filtration and washed with iced water. The total product was suspended in a warm aqueous solution of anhydrous sodium carbonate (100 g) and the yellow insoluble material (30.8 g) was extracted into ether. This appeared to be a mixture of 3-methoxy-2,6-dinitrotoluene (15) [7] (55%), τ 1.82 and 2.97 (2 H, ABq, $J_{4,5}$ 9 Hz, 5- and 4-H), 6.00 (3 H, s, OMe), and 7.50 (3 H, s, Me); and 5-methoxy-2,4-dinitrotoluene (16) [8] (45%), τ 1.34 (1 H, s, 3-H), 2.97 (1 H, s, 6-H), 5.92 (3 H, s, OMe), and 7.24 (3 H, s, OMe); *m/e* (of mixture) 212 (M^+). The sodium carbonate solution was acidified and the crude acidic products were esterified in the usual way (methanol–sulphuric acid). The esters (55.5 g) so obtained were crystallised from methanol. The first crop afforded *methyl 4-methoxy-2-methyl-5-nitrobenzoate* (17) (24.5 g) as pale yellow needles, m.p. 132—133° (Found: C, 53.05; H, 4.9; N, 5.9. $C_{10}H_{11}NO_5$ requires C, 53.35; H, 4.9; N, 6.2%), τ 1.53 (1 H, s, 6-H), 3.08 (1 H, s, 3-H), 5.99 and 6.10 (each 3 H, s, OMe), and 7.31 (3 H, s, Me). The second crop (13.18 g) was chromatographed over silica gel with 7.5—10% ethyl acetate–light petroleum as eluant. This gave first *methyl 4-methoxy-2-methyl-3,5-dinitrobenzoate* (19) (9.20 g), which formed rods (from methanol), m.p. 75° (Found: C, 44.35; H, 3.75; N, 10.4%; M^+, 270. $C_{10}H_{10}N_2O_7$ requires C, 44.45; H, 3.75; N, 10.35%; M, 270), τ 1.36 (1 H, s, ArH), 5.96 and 6.03 (each 3 H, s, OMe), and 7.42 (3 H, s, Me). Further elution gave a mixture of mononitro-esters (4.0 g) which was added in a little warm methanol to a stirred solution of tin(II) chloride dihydrate (9.0 g) in concentrated hydrochloric acid (9 ml) at room temperature. The mixture was stirred in ice for 5 min until the reaction moderated and then for 0.5 h at room temperature. The mixture was poured into ice–water and basified with sodium hydroxide. It was extracted with ethyl acetate and the extract was washed with dilute hydrochloric acid. The organic phase yielded *methyl 4-methoxy-2-methyl-3-nitrobenzoate* (18) (2.33 g), which formed very pale yellow needles (from methanol), m.p. 161—161.5° (Found: C, 53.0; H, 5.2; N, 5.9%; M^+, 225. $C_{10}H_{11}NO_5$ requires C, 53.35; H, 4.9; N, 6.2%, M, 225), τ 1.95 and 3.10 (2 H, ABq, $J_{5,6}$ 9 Hz, 6- and 5-H), 6.07 and 6.11 (each 3 H, s, OMe), and 7.49 (3 H, s, Me). Basification of the acid extract and extraction with ethyl acetate afforded *methyl 5-amino-4-methoxy-2-methylbenzoate* (20) (0.55 g) as prisms (from dichloromethane–light petroleum), m.p. 82° (Found: C, 61.25; H, 6.5; N, 7.0. $C_{10}H_{13}NO_3$ requires C, 61.55; H, 6.7; N, 7.15%), τ 2.68 (1 H, s, 6-H), 3.40 (1 H, s, 3-H), 6.13 and 6.16 (each 3 H, s, OMe), and 7.47 (3 H, s, Me).

Methyl 5-Amino-4-methoxy-2-methylbenzoate (20) (with N. M. Rana).—Reduction of the pure nitro-ester (17), as before, yielded the amine (20 (88%), m.p. 82°.

Methyl 3-Amino-2-bromo-4-methoxy-6-methylbenzoate (21) (with N. M. Rana).—Bromine (17.1 g) in dichloromethane (210 ml) was added dropwise to a stirred solution of the amine (20) (20.8 g) in dichloromethane (670 ml) at −70 °C. The cooling bath was removed and the mixture was stirred for a further 5 min and then poured into aqueous sodium carbonate. The usual work-up gave the *bromo-compound* (21) as an oil (28.7 g, 98%), τ 3.50 (1 H, s, ArH), 5.85br (2 H, NH_2), 6.12 and 6.22 (each 3 H, s, OMe), and 7.78 (3 H, s, Me). The N-*benzoyl derivative* formed plates (from methanol), m.p. 217.5—218° (Found: N, 4.0. $C_{17}H_{16}BrNO_4$ requires N, 3.7%).

Methyl 2-Bromo-4-methoxy-6-methylbenzoate (22) (with P. Djura and N. M. Rana).—At 0.5 °C a solution of sodium nitrite (11.0 g) in water (30 ml) was added dropwise to a stirred suspension of the amine (21) (43.0 g) in water (800 ml) and concentrated hydrochloric acid (80 ml). The mixture was then stirred at 0 °C for 2.5 h and rapidly filtered. The stirred filtrate was cooled to 0 °C and treated with urea (1.2 g) and then with ice-cold 50% phosphinous acid (340 ml), dropwise, over 0.5 h at 0.5 °C. The solution was stirred at 0 °C for a further 2 h and then set aside at 0 °C for 16 h. The usual work-up afforded the crude product which was filtered through a column of silica gel with 2.5—5% ethyl acetate–light petroleum as eluant. The *bromo-ester* (22) (33.6 g, 80%) was obtained as prisms (from pentane), m.p.

[19] C. R. Noller and R. Adams, *J. Amer. Chem. Soc.*, 1924, **46**, 1889.

31° (Found: Br, 31.15%; M^+, 258/260. $C_{10}H_{11}BrO_3$ requires Br, 30.85%; M, 258/260), τ (CCl_4) 3.18 and 3.45 (2 H, ABq, $J_{3.5}$ 2.7 Hz, 3- and 5-H), 6.20 and 6.31 (each 3 H, s, OMe), and 7.88 (3 H, s, Me).

Methyl Dihydro-orsellinate (23).—Sodium (69 g) was added with stirring to dry methanol (1 020 ml). After the reaction had subsided methyl acetoacetate (348 g) and methyl crotonate (300 g) were added in turn and the mixture was stirred and heated under reflux for 44 h. The bulk of the methanol was removed by distillation and ether (1 500 ml) was added to the stirred and ice-cooled residue. The precipitated salt was collected by filtration and washed with ether (500 ml). It was dissolved in water (1 l), cooled to 0 °C, and acidified with ice-cold concentrated hydrochloric acid. The crystalline precipitate (362 g, 67%) was separated by filtration, washed with ice-cold water (1.5 l), and dried *in vacuo*. A sample formed prisms (from cold methanol), m.p. 122—124° (with sweating from 112°) (lit.,[12] 125—126°) (Found: C, 58.5; H, 6.8. Calc. for $C_9H_{12}O_4$: C, 58.65; H, 6.55%).

Bromination of the Dihydro-orsellinate (23) *with* 2 *Mol. Equiv. of Bromine*.—(*a*) Bromine (17.6 g) in acetic acid (40 ml) was added over 5 min to a stirred solution of the dihydro-orsellinate (23) (10.11 g) in acetic acid (40 ml). The mixture was poured into ice–water and the crude product was collected by filtration, washed with iced water, and dried *in vacuo*. It crystallised from methanol as prisms (13.5 g, 72%) of *methyl 1,3-dibromo-4-hydroxy-6-methyl-2-oxocyclohex-3-enecarboxylate* (26), m.p. 124—125.5° (with sweating from 112°) (Found: C, 31.55; H, 2.95; Br, 46.8%; M^+, 340/342/344. $C_9H_{10}Br_2O_4$ requires C, 31.6; H, 2.95; Br, 46.75%; M, 340/342/344), τ (90 MHz) 6.14 (3 H, s, OMe), 7.38 (3 H, m, 5- and 6-H), and 8.90 (3 H, d, $J_{6.Me}$ 6.0 Hz, Me).

(*b*) Bromine (8.85 g) in acetic acid (20 ml) was added in a thin stream to the stirred dihydro-orsellinate (23) (5.08 g) in acetic acid (20 ml) at room temperature. After 19 h the mixture was poured into ice–water and the crude product was separated by filtration, washed with iced-water, and dried *in vacuo*. It was chromatographed over silica gel with 5—10% ethyl acetate–light petroleum as eluant. Early fractions afforded methyl 3,5-dibromo-2,4-dihydroxy-6-methylbenzoate (25) (1.28 g, 14%) as needles (from dichloromethane–light petroleum), m.p. 105—106° (lit.,[16] 107.5—109°), τ −1.91 (1 H, s, OH), 3.54br (1 H, OH), 6.03 (3 H, s, OMe), and 7.36 (3 H, s, Me). Further elution gave *methyl 3-bromo-2,4-dihydroxy-6-methylbenzoate* (24) (3.33 g, 46%) as needles (from dichloromethane–light petroleum), m.p. 141—142° (Found: C, 41.35; H, 3.65; Br, 30.45%; M^+, 260/262. $C_9H_9BrO_4$ requires C, 41.4; H, 3.45; Br, 30.6%; M, 260/262), τ −2.48 (1 H, s, OH), 3.54 (1 H, s, ArH), 4.06br (1 H, OH), 6.07 (3 H, s, OMe), and 7.52 (3 H, s, Me). On methylation in the usual way with methyl sulphate and potassium carbonate in acetone it gave the di-*O*-methyl ether,[17] m.p. and mixed m.p. 66—67°.

Methyl 3,5-Dibromo-2,4-dihydroxy-6-methylbenzoate (25).—This method was based on that of Anker and Cook.[13] Bromine (131 g) in acetic acid (50 ml) was added to a stirred warm solution of the dihydro-orsellinate (23) (50 g) in acetic acid (160 ml) at such a rate that the temperature was 40—45 °C. The mixture was then stirred for 1 h and set aside for 18 h. Water was added and the product (87.5 g, 95%) was separated by filtration, washed with water, and dried *in vacuo*. The n.m.r. spectrum was identical with that quoted above.

Methyl 2,4-Dihydroxy-6-methylbenzoate (27).—The dibromo-compound (25), or the mixture of bromo-compounds (25) and (26) from (*b*) (above), was debrominated by the method described by Santesson [14] for the ethyl ester. After one crystallisation the product (27) was obtained (90%) as prisms (from light petroleum), m.p. 138—140° (lit.,[20] 138°). The di-*O*-methyl ether (28) (dimethyl sulphate–acetone–potassium carbonate) formed prisms (from cold pentane), m.p. 40.5—41° (lit.,[21] 42—43.5°).

Methyl 3-Formyl-4,6-dimethoxy-2-methylbenzoate (29).—This was prepared by the method of Cresp *et al.*,[9] in 71% yield, except 3 mol. equiv. each of titanium(IV) chloride and dichloromethyl methyl ether were used.

Methyl 3-Hydroxy-4,6-dimethoxy-2-methylbenzoate (30).—A solution of the aldehyde (29) (15.90 g) in dry dichloromethane (80 ml) was added over 0.5 h to a stirred solution of *m*-chloroperbenzoic acid (85%; 25.0 g) in dry dichloromethane (320 ml). The mixture was then heated under reflux for 68.5 h. The crude formate, obtained as usual,[10] was stirred at 0 °C in methanol (150 ml) with potassium hydroxide (11.4 g) in water (160 ml) under nitrogen. After 1.5 h the mixture was acidified with dilute hydrochloric acid and worked up as usual. Chromatography of the crude product over silica gel with 15—20% ethyl acetate–light petroleum as eluant gave the *phenol* (30) (8.88 g, 59%), as glistening prisms (from dichloromethane–light petroleum), m.p. 112—113° (Found: C, 58.7; H, 6.3%; M^+, 226. $C_{11}H_{14}O_5$ requires C, 58.4; H, 6.25%; M, 226), τ 3.71 (1 H, s, ArH), 4.68 (1 H, s, OH), 6.04 (6 H, s, 2 × OMe), 6.27 (3 H, s, OMe), and 7.87 (3 H, s, Me).

Ullmann Reaction between the Bromo-ester (22) *and the Phenol* (30).—The bromo-compound (22) (5.0 g) and the phenol (30) (4.36 g) and finely divided dry potassium carbonate (5.5 g) in dry pyridine (20 ml) were heated gradually with stirring to 130 °C (bath). Copper(II) oxide (1.3 g) was then added and the mixture was stirred and heated at 150 °C (bath) for 17 h. The cooled mixture was diluted with ethyl acetate and filtered through kieselguhr, and the filtrate was washed in turn with dilute hydrochloric acid, dilute sodium hydroxide solution, water, and saturated brine. The crude product was crystallised from methanol and gave methyl 4,6-dimethoxy-3-(2-methoxycarbonyl-5-methoxy-3-methylphenoxy)-2-methylbenzoate (10) (5.40 g, 70%) as rods, m.p. and mixed m.p. 127—128° (Found: C, 62.35; H, 6.1%; M^+, 404. Calc. for $C_{21}H_{24}O_8$: C, 62.35; H, 6.0%, M, 404), identical (t.l.c. in several systems; n.m.r. and mass spectra) with that obtained by degradation of gangaleoidin.

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