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A Novel Synthesis of the Lichen Depsidones Divaronic Acid and Stenosporonic Acid, and the Biosynthetic Implications

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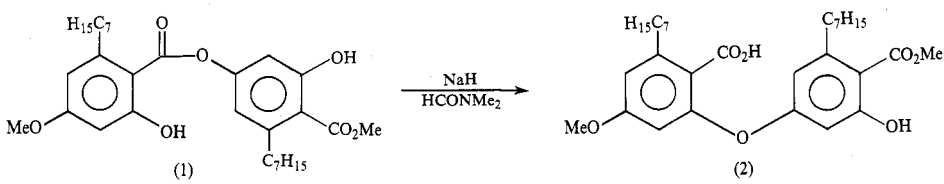
Abstract

The depsidones divaronic acid (24) (8-hydroxy-3-methoxy-1,6-dipropyl-11-oxo-11*H*-dibenzo[*b,e*][1,4]dioxepin-7-carboxylic acid) and stenosporonic acid (25) (8-hydroxy-3-methoxy-6-pentyl-1-propyl-11-oxo-11*H*-dibenzo[*b,e*][1,4]dioxepin-7-carboxylic acid) have been prepared by unambiguous synthesis, and have been shown to cooccur with colensoic acid, atranorin and chloroatranorin in the lichen *Paraparmelia mongaensis*. The syntheses employed a novel biomimetic-type approach which involved a Smiles rearrangement of a precursor *meta*-depside in the key step. This rearrangement has important biosynthetic implications and may account for the natural occurrence of isostructural depside–depsidone pairs.

Introduction

The biosynthetic interrelationship between the common lichen polyketides, the depsides, the depsidones, the diphenyl ethers and the dibenzofurans has been a subject of speculation for some time.[1–3] Following the key discovery that *para*-depsides such as methyl prasinate (1) could be readily converted into the isomeric diphenyl ether (2) through an intramolecular Smiles rearrangement under mild conditions,[4] plausible routes to potential catabolites of such depsides became evident.



Using such a rationale we recently developed a biomimetic-type synthesis of the lichen dibenzofurans pannaric acid and schizopeltic acid,[5] but undoubtedly the

[1] Culberson, C. F., 'Chemical and Botanical Guide to Lichen Products' (University of North Carolina Press: Chapel Hill 1969).
[2] Mosbach, K., *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 240.
[3] Mosbach, K., in 'The Lichens' (Eds V. Amadjian and M. E. Hale, Jr) Ch. 16 (Academic Press: New York 1973).
[4] Elix, J. A., Jones, A. J., Lajide, L., Copins, B. J., and James, P. W., *Aust. J. Chem.*, 1984, **7**, 2349.
[5] Elix, J. A., and Parker, J. L., *Aust. J. Chem.*, 1987, **40**, 187.

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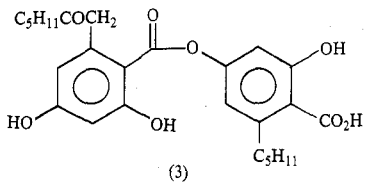
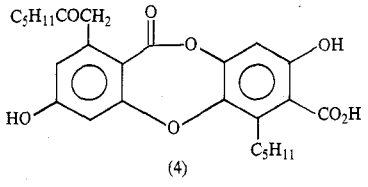


(3)



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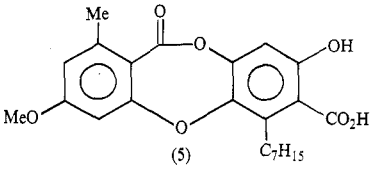
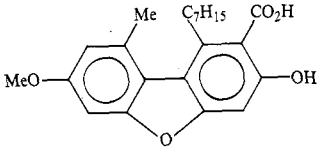


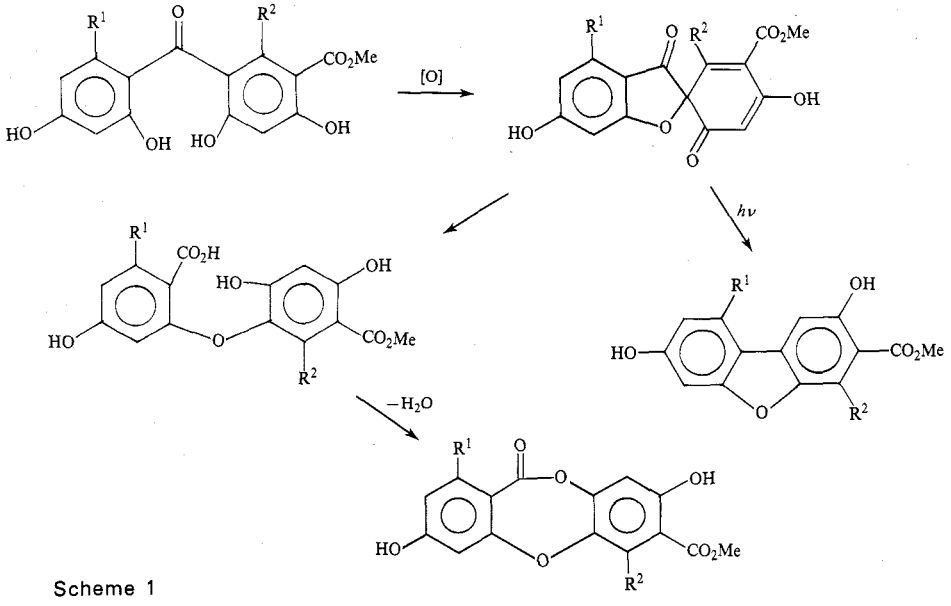
(5)



(6)

biosynthesis of the corresponding depsidones has elicited most interest. Circumstantial evidence exists for such a biosynthetic interrelationship in the form of the cooccurrence of isostructural depside–depsidone pairs such as olivetoric acid (3) and physodic acid (4),[1-3,6] and depsidone–dibenzofuran pairs such as grayanic acid (5) and melacarpic acid (6),[7] in the same organism.

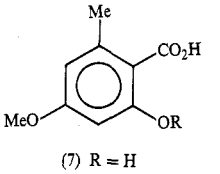
Subsequently Sala and Sargent[8] suggested that depsidones are derived independently of depsides, through the phenolic coupling of benzophenones and the intermediacy of spirobenzofuran-3-ones (Scheme 1). However, neither of the suggested precursors has been demonstrated to occur naturally in lichens, and, although such a scheme proceeds well in a laboratory synthesis, it does not lead to the appropriately substituted dibenzofuran (see Scheme 1).



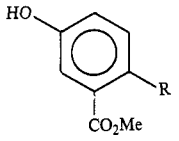
Scheme 1

[6] Culberson, C. F., *Bryologist*, 1965, **68**, 435.
[7] Elix, J. A., and Chester, D. O., *Aust. J. Chem.*, 1980, **33**, 1153.
[8] Sala, T., and Sargent, M. V., *J. Chem. Soc., Perkin Trans. 1*, 1981, 855.

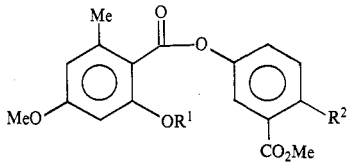
No *para*-depsides bearing an additional oxygen atom in the B-ring (i.e. an oxygen atom not implicit in the acetate–polymalonate route to such compounds) are known although a number of analogues with oxidized A-rings are.[1,9–11] If such oxidation were to occur in the 3′-position, subsequent rearrangement of the *para*-depside formed has very recently been shown to lead to the well known family of *meta*-depsides[12] by acyl



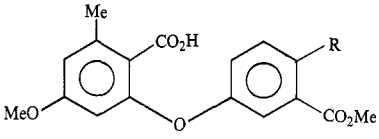
(7) R = H
(8) R = CH_2Ph



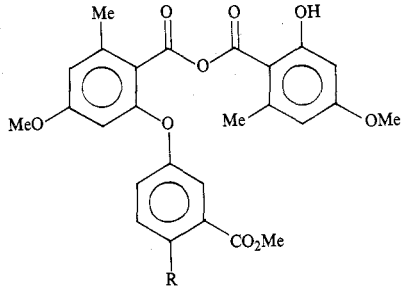
(9) R = H
(10) R = OH



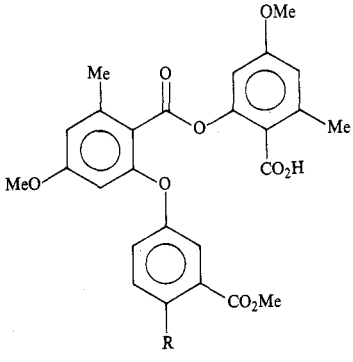
	R^1	R^2
(11)	H	H
(12)	CH_2Ph	OH
(13)	CH_2Ph	OAc
(14)	H	OH
(15)	H	OAc



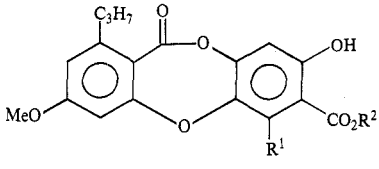
(16) R = H
(17) R = OH
(18) R = OAc



(19) R = H
(20) R = OH
(21) R = OAc

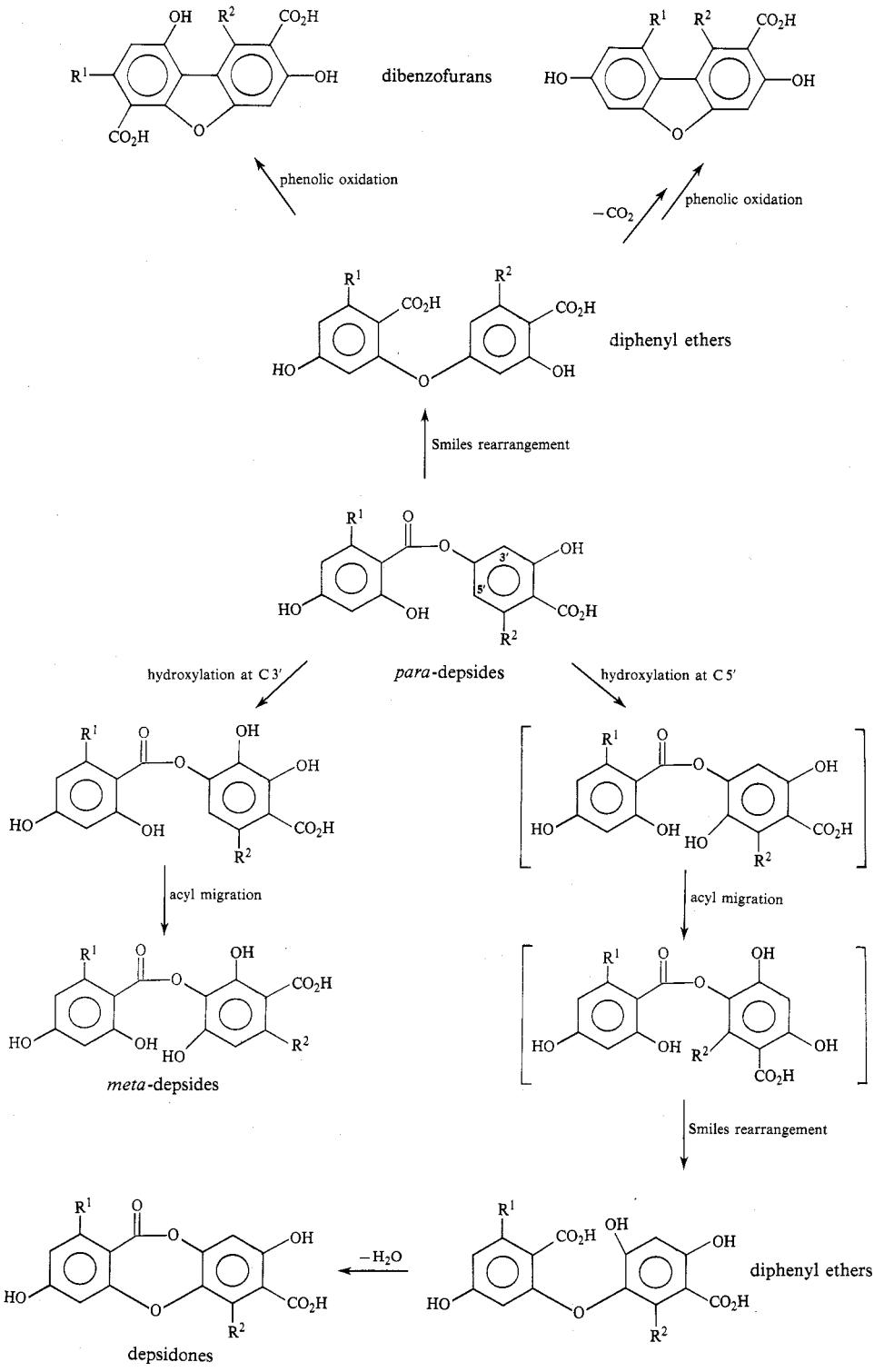


(22) R = H
(23) R = OAc



	R^1	R^2
(24)	C_3H_7	H
(25)	C_5H_{11}	H
(26)	C_3H_7	Me

[9] Culberson, C. F., Supplement to 'Chemical and Botanical Guide to Lichen Products' *Bryologist*, 1970, **73**, 177.
[10] Culberson, C. F., Second Supplement to 'Chemical and Botanical Guide to Lichen Products' (American Bryological and Lichenological Society: St. Louis 1977).
[11] Elix, J. A., Whitton, A. A., and Sargent, M. V., *Fortschr. Chem. Org. Naturst.*, 1984, **45**, 104.
[12] Elix, J. A., and Gaul, K. L., *Aust. J. Chem.*, 1986, **39**, 613.


dibenzofurans
phenolic oxidation
−CO2
phenolic oxidation
diphenyl ethers
Smiles rearrangement
para-depsides
hydroxylation at C3′
hydroxylation at C5′
acyl migration
acyl migration
meta-depsides
Smiles rearrangement
−H2O
diphenyl ethers
depsidones

Scheme 2

migration. Alternative hydroxylation of the 5′-position, followed by an analogous acyl migration and subsequent Smiles rearrangement of the *meta*-depside formed, could well lead to the corresponding orcinol depsidones (Scheme 2). We believe that such a route could be involved in the biosynthesis of these compounds and have employed a biomimetic-type approach to synthesize the new depsidones divaronic acid (24) and stenosporonic acid (25).[13]

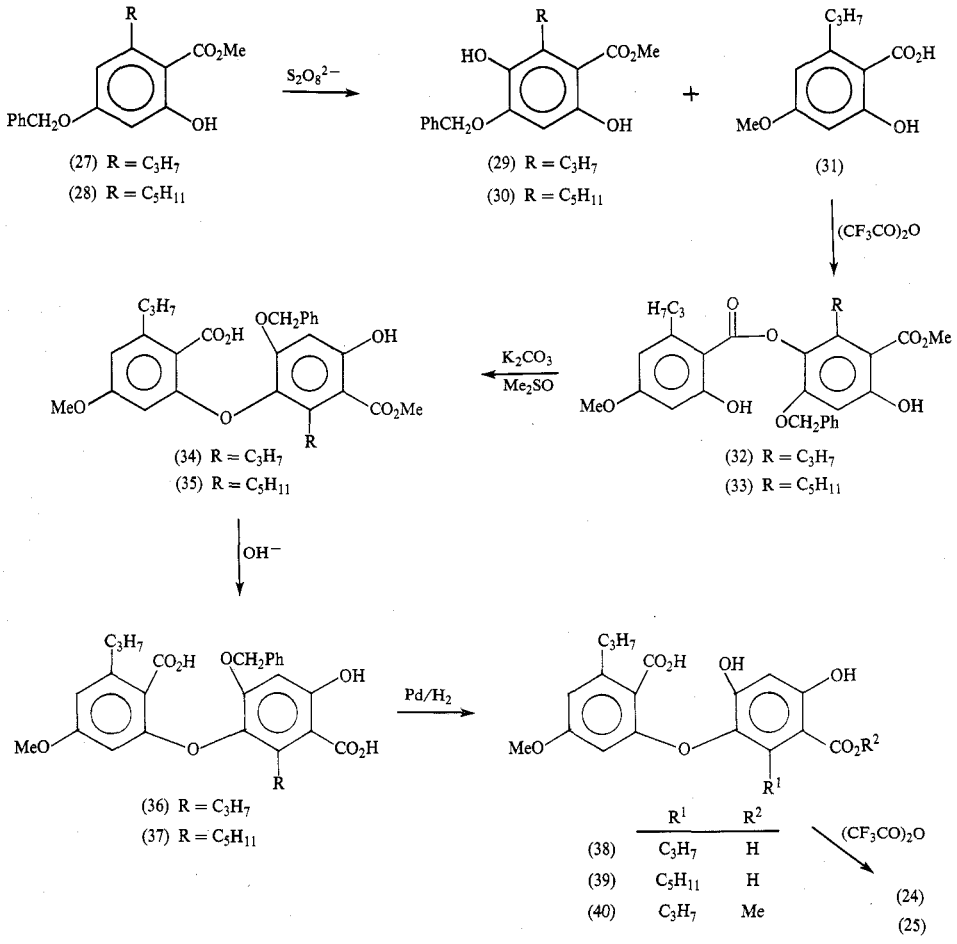
Model Reactions: Smiles Rearrangement of Unactivated *meta*-Depsides

Before the synthesis of the natural depsidones was undertaken, it was necessary to establish the viability of the Smiles rearrangement in unactivated *meta*-depsides. This internal nucleophilic substitution reaction is facilitated by activation of the aromatic ring by the presence of electron-withdrawing groups in the *ortho*- or *para*-positions, and in all previously reported rearrangements of depsides there was an electron-withdrawing ester substituent *para* to the site of substitution. To determine whether this rearrangement was more generally applicable we prepared the depside esters (11), (14) and (15). Thus condensation of 2-hydroxy-4-methoxy-6-methylbenzoic acid (7) with methyl 3-hydroxybenzoate (9) in the presence of trifluoroacetic anhydride afforded the depside ester (11) in good yield. Similarly condensation of 2-benzyloxy-4-methoxy-6-methylbenzoic acid (8) with methyl 2,5-dihydroxybenzoate (10) gave the depside ester (12) and subsequent treatment of this compound with acetic anhydride in pyridine gave the corresponding acetate (13). Hydrogenolysis of (12) and (13) over palladium on charcoal then gave the depside esters (14) and (15) respectively. The Smiles rearrangement of the depside esters (11), (14) and (15) was carried out by treatment with anhydrous lithium carbonate in dry dimethyl sulfoxide solution at room temperature. It was expected that the corresponding diphenyl ethers (16), (17) and (18) respectively, would result from such treatment. In actual fact the ether anhydrides (19)–(21) were isolated as the major products of these reactions. The structures of the products (19)–(21) were established from microanalytical evidence and spectroscopic analysis, in particular from the ^{1}H n.m.r. and mass spectral data. These ether anhydrides were presumed to be derived from the initial Smiles products (16)–(18) respectively, by subsequent nucleophilic attack on the unreacted starting depsides. We attribute these further reactions to the lack of a bulky substituent at the 5-position of the B-ring (see below).

If the Smiles rearrangement of (11) and (15) was carried out with anhydrous potassium carbonate instead of lithium carbonate, the ether acids (22) and (23) were obtained. The compounds (22) and (23) were obviously formed by further rearrangement of the ether anhydrides (19) and (21) respectively. Indeed the intermediacy of (19) and (21) was confirmed by thin-layer chromatographic examination of the reaction mixture at intervals throughout the reaction. Although the expected diphenyl ethers (16)–(18) were only observed as intermediates in these reactions, at least the Smiles rearrangement was occurring and the resultant anhydrides (19)–(21) could be converted into the desired products by hydrolysis. As expected, the rearrangement of the depside ester (14) was least satisfactory, with only 9% yield of product. This is probably due to the electronic effect of the hydroxy group at the position *para* to the depside–ester linkage inhibiting nucleophilic attack on the B-ring. When the electronic effect of this hydroxy group was modified by acetylation, the

[13] Culberson, C. F., Culberson, W. L., and Johnson, A., *Bryologist*, 1985, **88**, 380.

yield of the rearranged product increased (18%) although it was still lower than that observed for the depside ester (11). These model experiments confirmed that such *meta*-depside derivatives would undergo Smiles rearrangement to the corresponding diphenyl ether derivatives under appropriate basic conditions. Secondly it appeared that the electronic effect of a hydroxy group at the position *para* to the depside–ester linkage inhibited but did not prevent the Smiles rearrangement from proceeding. Hence it was considered that such an approach would be feasible for the synthesis of the natural depsidones.



Scheme 3

Synthesis of the Depsidones

The synthetic route to the depsidones (24) and (25) is outlined in Scheme 3.

For the syntheses, 2-hydroxy-4-methoxy-6-propylbenzoic acid (31), methyl 4-benzyloxy-2-hydroxy-6-propylbenzoate (27) and methyl 4-benzyloxy-2-hydroxy-6-pentylbenzoate (28) were used as starting materials. Nuclear hydroxylation of (27) and (28) was achieved by treatment with potassium persulfate in aqueous dimethyl sulfoxide to afford the corresponding dihydroxy compounds (29) and (30) in moderate

yield. The depside esters (32) and (33) were then synthesized by treating a mixture of the benzoic acid (31) and the dihydroxy esters (32) and (33), respectively, with trifluoroacetic anhydride in anhydrous toluene. The conversion of the depside esters (32) and (33) into the corresponding diphenyl ethers (34) and (35) was effected by a Smiles rearrangement in the presence of anhydrous potassium carbonate in dimethyl sulfoxide at 75–76° as these particular deside esters did not react with lithium carbonate under these conditions.

The structure of the respective ethers (34) and (35) followed from the normal microanalytical evidence and spectroscopic properties of these compounds. For instance the ^{1}H n.m.r. spectrum of (34) exhibited all the features expected for this structure and in particular showed two doublets at δ 6·57 and 6·03 (J 2·6 Hz), which correspond to protons H 5 and H 3 respectively. The downfield position of these signals compared with those of the corresponding protons of the depside (32) was consistent with the diphenyl ether formulation of (34). Furthermore the compound (34) exhibited a molecular ion peak at *m/z* 508 and the observed fragmentation pattern was consistent with this structure. The fact that this key Smiles rearrangement occurs readily under such mild conditions gives credence to our suggestion that this is a key step in the biosynthesis of such depsidones, but ultimate confirmation of this proposal must await detailed biosynthetic investigations.

Hydrolysis of the ester groups of (34) and (35) with potassium hydroxide in aqueous dimethyl sulfoxide gave the corresponding diacids (36) and (37). Subsequent hydrogenolysis of (36) and (37) by using palladium on charcoal as a catalyst yielded the corresponding phenolic acids (38) and (39). The latter compounds were cyclized by treatment with trifluoroacetic anhydride in toluene at room temperature to give divaronic acid (24) and stenosporonic acid (25) respectively. Methyl divaronate (26) was obtained in a similar manner by omitting the penultimate hydrolysis step.

Chromatographic comparisons (thin-layer and high-performance liquid chromatography) have subsequently confirmed that the behaviour of the synthetic depsidones (24) and (25) was identical with that of a minor and major constituent, respectively, of the lichen *Paraparmelia mongaensis*.[13] The presence of the known depsides atranorin and chloroatranorin, and the depsidone colensoic acid, in extracts of this lichen was confirmed by comparison with authentic samples.

Experimental

General experimental details have been reported previously.[14]

3′-Methoxycarbonylphenyl 2-Hydroxy-4-methoxy-6-methylbenzoate (11)

A solution of 2-hydroxy-4-methoxy-6-methylbenzoic acid (7)[15] (152·7 mg, 0·84 mmol) and methyl 3-hydroxybenzoate (9) (127·7 mg, 0·84 mmol) in anhydrous toluene (4 ml) and trifluoroacetic anhydride (1 ml) was allowed to stand at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The extract was washed with water, saturated brine and dried ($MgSO_4$). The solvent was then evaporated, and the residue was purified over a silica gel plate on the Chromatotron, 40% dichloromethane/light petroleum being used as eluent. The major, faster moving band yielded the *depside ester* (11) (200 mg, 75%), which was crystallized from dichloromethane/light petroleum as colourless crystals, m.p. 89–91° (Found: C, 64·3; H, 5·2.

[14] Elix, J. A., Jenie, U. A., Arvidsson, L., Jörgensen, P. M., and James, P. W., *Aust. J. Chem.*, 1986, **39**, 719.

[15] Wederkind, E., and Fleischer, K., *Ber. Dtsch. Chem. Ges.*, 1923, **56**, 2556.

$C_{17}H_{16}O_6$ requires C, 65·5; H, 5·1%). ^{1}H n.m.r. ($CDCl_3$) δ 2·70, s, ArMe; 3·86, 3·96, 2s, OMe; 6·41, s, H 3,5; 7·43, dq, *J* 7·8, 1·2 Hz, H 6′; 7·56, td, *J* 7·8, 0·6 Hz, H 5′; 7·90, td, *J* 1·2, 0·6 Hz, H 2′; 8·03, dt, *J* 7·8, 1·2 Hz, H 4′; 11·43, s, bonded OH. Mass spectrum *m/z* 316 (M, 0·2%), 285 (0·8), 261 (0·4), 121 (100).

4′-Hydroxy-3′-methoxycarbonylphenyl 2-Benzyloxy-4-methoxy-6-methylbenzoate (12)

A solution of 2-benzyloxy-4-methoxy-6-methylbenzoic acid (8)[16] (1·36 g, 5 mmol) and methyl 2,5-dihydroxybenzoate (10) (0·84 g, 5 mmol) in anhydrous toluene (24 ml) and trifluoroacetic anhydride (6 ml) was allowed to stand at room temperature for 2 h. The solvent was then removed under reduced pressure, and the residue was diluted with water and extracted with ethyl acetate. The extract was washed with water, saturated brine and dried ($MgSO_4$). The solvent was then evaporated, and the residue was subjected to column chromatography over silica gel, with 60% dichloromethane/light petroleum as eluent. The major faster moving fraction yielded the *depside ester* (12) (1·80 g, 85%) which was crystallized from dichloromethane/light petroleum as colourless crystals, m.p. 89–91° (Found: C, 68·5; H, 5·4. $C_{24}H_{22}O_7$ requires C, 68·2; H, 5·2%). ^{1}H n.m.r. ($CDCl_3$) δ 2·44, s, ArMe; 3·83, 3·93, 2s, OMe; 5·13, s, CH_2; 6·37, 6·41, 2d, *J* 2·8 Hz, H 3,5; 6·90, d, *J* 9·1 Hz, H 5′; 7·10, dd, *J* 9·1, 2·8 Hz, H 6′; 7·23–7·44, m, C_6H_5; 7·56, d, *J* 2·8 Hz, H 2′; 10·70, s, OH. Mass spectrum *m/z* 391 (1·5%), 335 (0·2), 255 (100).

4′-Acetoxy-3′-methoxycarbonylphenyl 2-Benzyloxy-4-methoxy-6-methylbenzoate (13)

A solution of 4′-hydroxy-3′-methoxycarbonylphenyl 2-benzyloxy-4-methoxy-6-methylbenzoate (12) (422 mg, 1 mmol) and acetic anhydride (0·2 ml) in dry pyridine (5 ml) was stirred at room temperature for 3·5 h. The cooled reaction mixture was then diluted with dilute hydrochloric acid (5%, 10 ml) and water (10 ml), then extracted with ethyl acetate. This extract was washed with water, saturated brine and dried ($MgSO_4$). Evaporation of the solvent followed by crystallization of the residue from dichloromethane/light petroleum afforded the *acetate* (13) (417 mg, 90%) as colourless crystals, m.p. 80–82° (Found: C, 66·9; H, 5·0. $C_{26}H_{24}O_8$ requires C, 67·2; H, 5·2%). ^{1}H n.m.r. ($CDCl_3$) δ 2·40, s, OAc; 2·48, s, ArMe; 3·86, 3·90, 2s, OMe; 5·18, s, CH_2; 6·48, 6·52, 2br s, H 3,5; 7·12, dd, *J* 9, 0·9 Hz, H 5′; 7·30, dd, *J* 9, 4 Hz, H 6′; 7·38–7·54, m, C_6H_5; 7·84, dd, *J* 4, 0·9 Hz, H 2′. Mass spectrum *m/z* 463 (M−H, 0·03%), 255 (100).

4′-Hydroxy-3′-methoxycarbonylphenyl 2-Hydroxy-4-methoxy-6-methylbenzoate (14)

A solution of 4′-hydroxy-3′-methoxycarbonylphenyl 2-benzyloxy-4-methoxy-6-methylbenzoate (12) (422 mg) in ethyl acetate (10 ml) containing 10% palladium on charcoal (40 mg) was stirred in an atmosphere of hydrogen for 16 h. The catalyst was then filtered off and the filtrate concentrated to give the *depside ester* (14) (312 mg, 94%) which crystallized from dichloromethane/light petroleum as colourless needles, m.p. 122–124° (Found: C, 61·3; H, 5·1. $C_{17}H_{16}O_7$ requires C, 61·4; H, 4·9%). ^{1}H n.m.r. ($CDCl_3$) δ 2·66, s, ArMe; 3·86, 4·00, 2s, OMe; 6·40, s, H 3,5; 7·11, d, *J* 9·1 Hz, H 5′; 7·36, dd, *J* 9·1, 2·8 Hz, H 6′; 7·72, d, *J* 2·8 Hz, H 2′; 10·76, 11·46, 2s, OH. Mass spectrum *m/z* 332 (M, 0·7%), 165 (100).

4′-Acetoxy-3′-methoxycarbonylphenyl 2-Hydroxy-4-methoxy-6-methylbenzoate (15)

Hydrogenolysis of 4′-acetoxy-3′-methoxycarbonylphenyl 2-benzyloxy-4-methoxy-6-methylbenzoate (13) (260 mg) by the method described above yielded the *depside ester* (15) (194 mg, 98%) which crystallized from dichloromethane/light petroleum in colourless needles, m.p. 134–135° (Found: C, 61·3; H, 5·0. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%). ^{1}H n.m.r. ($CDCl_3$) δ 2·40, s, OAc; 2·63, s, ArMe; 3·86, 3·90, 2s, OMe; 6·40, s, H 3,5; 7·27, d, *J* 9·1 Hz, H 5′; 7·48, dd, *J* 9·1, 2·1 Hz, H 6′; 7·92, d, *J* 2·1 Hz, H 2′; 11·36, s, OH. Mass spectrum *m/z* 374 (M, 0·3%), 136 (100).

Smiles Rearrangement of Depside Esters

A solution of the depside ester (0·25 mmol) in anhydrous dimethyl sulfoxide and lithium or potassium carbonate (0·25 mmol) was stirred at room temperature for a period of time.

[16] Elix, J. A., and Wardlaw, J. H., *Aust. J. Chem.*, 1987, **40**, 425.

The reaction mixture was then acidified with cold, dilute hydrochloric acid and extracted with ethyl acetate. The combined organic fractions were washed with several portions of water, saturated brine, then dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product so obtained was purified by chromatography over silica gel on the Chromatotron with an appropriate eluent.

2″-Hydroxy-4″-methoxy-6″-methylbenzoic 4-Methoxy-2-(3′-methoxycarbonylphenoxy)-6-methylbenzoic Anhydride (19)

When the rearrangement of (11) was carried out for 4 h by using anhydrous lithium carbonate, the *ether anhydride* (19) (21%) was separated with 10% ethyl acetate/5% glacial acetic acid/light petroleum as eluent and obtained as a colourless sticky gum. [Found: *m/z* 452·1473. $^{12}C_{25}{}^{1}H_{24}{}^{16}O_8$ ($M^+ - CO$) requires *m/z* 452·1471]. The homogeneity of this compound was confirmed by thin-layer chromatography and ^1H n.m.r. spectroscopy. ^1H n.m.r. ($CDCl_3$) δ 2·62, 2·64, 2s, ArMe; 3·83, 3·90, 2s, OMe; 6·40, s, H 3″,5″; 6·55, 6·91, 2d, *J* 3 Hz, H 5,3; 7·10, dq, *J* 7·8, 1·2 Hz, H 6′; 7·31, td, *J* 7·8, 0·6 Hz, H 5′; 7·56, td, *J* 1·2, 0·6 Hz, H 2′; 7·80, dt, *J* 7·8, 1·2 Hz, H 4′; 11·40, s, OH. Mass spectrum *m/z* (c.i.) 498 ($M+NH_4$,1%), 335 (27), 336 (100), 317 (13), 300 (4), 182 (14), 165 (62); *m/z* (e.i.) 452 ($M-CO$, 0·2%), 410 (0·6), 353 (0·9), 165 (61), 149 (98), 121 (100). ν_{max} (KBr) 1730–1720 (CO ester, anhydride), 1660–1650 cm^{-1} (bonded CO).

2-[4′-Methoxy-2′-(3″-methoxycarbonylphenoxy)-6′-methylbenzoyloxy]-4-methoxy-6-methylbenzoic Acid (22)

When the rearrangement of (11) was carried out for 6 h by using anhydrous potassium carbonate, the *acid* (22) (27%) was separated with 10% ethyl acetate/5% glacial acetic acid/light petroleum as eluent and obtained as a colourless gum [Found: *m/z* 463·1392. $^{12}C_{26}{}^{1}H_{23}{}^{16}O_8$ ($M^+ - OH$) requires *m/z* 463·1393]. The homogeneity of this compound was confirmed by thin-layer chromatography and ^1H n.m.r. spectroscopy. ^1H n.m.r. ($CDCl_3$) δ 2·50, 2·60, 2s, ArMe; 3·76, 3·83, 3·93, 3s, OMe; 6·24, 6·52, 6·55, 6·67, 4d, *J* 2·1 Hz, H 5,5′,3,3′; 7·16, dq, *J* 7·7, 1·4 Hz, H 6″; 7·40, td, *J* 7·7, 0·7 Hz, H 5″; 7·60, td, *J* 1·4, 0·7 Hz, H 2″; 7·90, dt, *J* 7·7, 1·4 Hz, H 4″. Mass spectrum *m/z* (c.i.) 498 ($M+NH_4$, 39%), 480 (5), 463 (4), 454 (9), 346 (20), 286 (19), 285 (100); *m/z* (e.i.) 479 ($M-H$, 0·02%), 463 (0·5), 311 (2), 285 (100). ν_{max} (KBr) 3400–2900 (OH), 1720 cm^{-1} (CO).

2″-Hydroxy-4″-methoxy-6″-methylbenzoic 2-(4′-Hydroxy-3′-methoxycarbonylphenoxy)-4-methoxy-6-methylbenzoic Anhydride (21)

Rearrangement of the depside (14) by using anhydrous lithium carbonate for 24 h followed by purification of the crude product by chromatography with 15% ethyl acetate/light petroleum as eluent gave the *anhydride* (21) (9%) as a colourless gum [Found: *m/z* 328·0948. $^{12}C_{18}{}^{1}H_{16}{}^{16}O_6$ ($M^+ - C_8H_8O_4$) requires *m/z* 328·0947]. The homogeneity of this compound was confirmed by thin-layer chromatography and ^1H n.m.r. spectroscopy. ^1H n.m.r. ($CDCl_3$) δ 2·60, 2·63, 2s, ArMe; 3·84, 3·90, 3·91, 3s, OMe; 6·36, s, H 3″,5″; 6·64, 6·80, 2d, *J* 2·4 Hz, H 5,3; 6·94, d, *J* 9 Hz, H 5′; 7·12, dd, *J* 9, 3 Hz, H 6′; 7·42, d, *J* 3 Hz, H 2′; 10·66, 11·40, 2s, OH. Mass spectrum *m/z* (c.i.) 514 ($M+NH_4$, 8%), 359 (86), 333 (100), 182 (18·5), 165 (74); *m/z* (e.i.) 329 ($M-C_8H_7O_4$, 1%), 328 (1), 255 (0·8), 165 (100).

2-(4′-Acetoxy-3′-methoxycarbonylphenoxy)-4-methoxy-6-methylbenzoic 2″-Hydroxy-4″-methoxy-6″-methylbenzoic Anhydride (20)

When the rearrangement of (15) was carried out for 16 h by using anhydrous lithium carbonate, the crude product so obtained was purified by chromatography over silica gel on the Chromatotron with 10% ethyl acetate/light petroleum as eluent, and the *anhydride* (20) (18%) was obtained as a colourless gum [Found: *m/z* 492·14300. $^{12}C_{27}{}^{1}H_{24}{}^{16}O_9$ ($M^+ - CO - H_2O$) requires *m/z* 492·141990]. The homogeneity of this compound was confirmed by thin-layer chromatography and ^1H n.m.r. spectroscopy. ^1H n.m.r. ($CDCl_3$) δ 2·36, s, OAc; 2·62, 2·66, 2s, ArMe; 3·85, 3·90, 3·92, 3s, OMe; 6·36, s, H 3″,5″; 6·65, 6·86, 2d, *J* 2·4 Hz, H 5,3; 7·02, d, *J* 8·4 Hz, H 5′; 7·22, dd, *J* 8·4, 2·4 Hz, H 6′; 7·63, d, *J* 2·4 Hz, H 2′; 11·40, s, OH. Mass spectrum *m/z* (c.i.) 556 ($M+NH_4$, 11%), 510 (17), 434 (32), 393 (21), 392 (100), 346 (14), 329 (31), 228 (37), 165 (41); *m/z* (e.i.) 492 ($M-CO-H_2O$, 1%), 165 (100).

2-[2′-(4″-Acetoxy-3″-methoxycarbonylphenoxy)-4′-methoxy-6′-methylbenzoyloxy]-4-methoxy-6-methylbenzoic Acid (23)

When the rearrangement of (15) was carried out for 3 h by using anhydrous potassium carbonate, and the crude product so obtained was purified by preparative t.l.c. over silica gel with 15% glacial acetic acid/toluene as eluent, the *acid* (23) (10%) was obtained as a colourless gum [Found: *m/z* 521·1447. $^{12}C_{28}{}^{1}H_{25}{}^{16}O_{10}$ ($M^+ - OH$) requires *m/z* 521·1448]. The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 2·36, s, OAc; 2·50, 2·56, 2s, ArMe; 3·76, 3·85, 3·90, 3s, OMe; 6·24, 6·53, 6·56, 6·70, 4d, *J* 2·4 Hz, H 5,5′,3,3′; 7·10, d, *J* 8·4 Hz, H 5″; 7·18, dd, *J* 8·4, 2·4 Hz, H 6″; 7·63, d, *J* 2·4 Hz, H 2″. Mass spectrum *m/z* (c.i.) 556 ($M+NH_4$, 54%), 521 (8), 346 (16), 285 (100), 228 (46); *m/z* (e.i.) 537 ($M-H$, 0·01%), 521 (0·5), 507 (0·9), 329 (1·5), 285 (100).

Methyl 4-Benzyloxy-2-hydroxy-6-pentylbenzoate (28)

Methyl olivetolcarboxylate[17] (6·66 g, 28 mmol), anhydrous potassium carbonate (13·5 g) and benzyl bromide (5·13 g, 30 mmol) were stirred and heated under reflux in dry acetone (100 ml) for 22 h. The mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, saturated brine and dried ($MgSO_4$). The oily product left on removal of the solvent was passed through column silica gel (6 by 60 cm) with 2·5% ethyl acetate/light petroleum as eluent. Removal of the solvent from the first fraction gave the *methyl 4-benzyloxy-2-hydroxy-6-pentylbenzoate* (28) (4·16 g, 43%) as a colourless liquid (Found: C, 73·3; H, 7·6. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%). ^{1}H n.m.r. ($CDCl_3$) δ 0·89, br t, *J* 7 Hz, Me; 1·10–1·70, m, $(CH_2)_3$; 2·85, t, *J* 7 Hz, ArMe; 3·93, s, OMe; 5·05, s, OCH_2; 6·43, s, H 3,4; 7·46, s, C_6H_5; 11·86, s, OH. Mass spectrum *m/z* 328 (M, 4%), 91 (100).

Methyl 4-Benzyloxy-2,5-dihydroxy-6-propylbenzoate (29)

A saturated solution of potassium persulfate (4·34 g, 16·05 mmol) was added dropwise over 3 h to a stirred solution of methyl 4-benzyloxy-2-hydroxy-6-propylbenzoate[18] (27) (4·30 g, 14·33 mmol) in 20% aqueous sodium hydroxide (35 ml) and dimethyl sulfoxide (45 ml) in an atmosphere of nitrogen. The temperature of the reaction mixture was maintained at 10° throughout the addition. The stirred reaction mixture was then stored at room temperature for 24 h, then acidified to pH 4–5 by addition of concentrated hydrochloric acid. Unchanged starting material (27) was then extracted with ether, and was recovered (2·20 g). A further quantity of concentrated hydrochloric acid (27 ml) and solid sodium sulfite (3 g) was then added to the aqueous layer and the mixture was stirred and warmed to 80° for 30 min in an atmosphere of nitrgen. After cooling, the solution was extracted with ether, the combined organic fractions then washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was crystallized from dichloromethane/light petroleum to give the *diol* (29) (1·73 g, 38%) as colourless plates, m.p. 98–100° (Found: C, 68·4; H, 6·5. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%). ^{1}H n.m.r. ($CDCl_3$) δ 0·99, t, *J* 7·5 Hz, $CH_2CH_2CH_3$; 1·46–1·62, m, $CH_2CH_2CH_3$; 2·88, t, *J* 7 Hz, $CH_2CH_2CH_3$; 3·96, s, OMe; 5·12, s, $ArCH_2O$; 5·35, s, 5OH; 6·46, s, H 3; 5·43, s, C_6H_5; 11·30, s, 2OH. Mass spectrum *m/z* 316 (M, 21%), 193 (100).

Methyl 4-Benzyloxy-2,5-dihydroxy-6-pentylbenzoate (30)

This compound was prepared from methyl 4-benzyloxy-2-hydroxy-6-pentylbenzoate (28) by the method described above. Crystallization of the crude product from dichloromethane/light petroleum gave the *diol* (30) (0·80 g, 19%) as colourless plates, m.p. 88–91° (Found: C, 69·5; H, 7·0. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%). ^{1}H n.m.r. ($CDCl_3$) δ 0·90, t, *J* 7 Hz, $(CH_2)_4CH_3$; 1·30–1·52, m, $CH_2(CH_2)_3CH_3$; 2·55, t, *J* 7 Hz, $ArCH_2$; 3·92, s, OMe; 5·12, s, $ArCH_2O$; 5·35, s, 5OH; 6·46, s, H 3; 7·43, s, C_6H_5; 11·30, s, 2OH. Mass spectrum *m/z* 344 (M, 33%), 221 (100).

[17] Djura, P., and Sargent, M. V., *Aust. J. Chem.*, 1976, **29**, 1069.
[18] Elix, J. A., and Norfolk, S., *Aust. J. Chem.*, 1975, **28**, 399.

Methyl 4-Benzyloxy-3-[2′-hydroxy-4′-methoxy-6′-propylbenzoyloxy)-6-hydroxy-2-propylbenzoate (32)

A solution of 2-hydroxy-4-methoxy-6-propylbenzoic acid[19] (31) (210 mg, 1 mmol) and methyl 4-benzyloxy-2,5-dihydroxy-6-propylbenzoate (29) (316 mg, 1 mmol) in anhydrous toluene (4 ml) and trifluoroacetic anhydride (1 ml) was stood at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue was purified with the chromatotron using 20% dichloromethane/light petroleum followed by 50% dichloromethane/light petroleum as eluent. The *depside ester* (32) (345·5 mg, 69%) was obtained as a colourless sticky gum (Found: C, 69·0; H, 6·3. $C_{29}H_{32}O_8$ requires C, 68·5; H, 6·3%). ^{1}H n.m.r. ($CDCl_3$) δ 0·83–0·96, m, CH_2CH_3; 1·40–1·70, m, CH_2CH_3; 2·70, 2·94, 2br, $ArCH_2CH_2$; 3·77, 3·91, 2s, OMe; 5·06, s, CH_2O; 6·34, br s, H 3,5; 6·50, s, H 3′; 7·22, s, C_6H_5; 11·49, 11·72, 2s, OH. Mass spectrum *m/z* 508 (M, 14%), 193 (100).

Methyl 4-Benzyloxy-3-[2′-hydroxy-4′-methoxy-6′-propylbenzoyloxy)-6-hydroxy-2-pentylbenzoate (33)

The condensation of 2-hydroxy-4-methoxy-6-propylbenzoic acid[19] (31) (210 mg, 1 mmol) and methyl 4-benzyloxy-2,5-dihydroxy-6-pentylbenzoate (30) (344 mg, 1 mmol) was carried out by the method described above. The *depside ester* (33) (409·3 mg, 76%) was obtained as a colourless sticky gum (Found: C, 69·5; H, 6·5. $C_{31}H_{36}O_8$ requires C, 69·4; H, 6·8%). ^{1}H n.m.r. ($CDCl_3$) δ 0·84–0·88, m, CH_2CH_3; 1·28–1·80, m, $(CH_2)_3CH_3$ and $CH_2CH_2CH_3$; 2·60–3·20, m, $ArCH_2CH_2$; 3·86, 3·97, 2s, OMe; 5·12, s, CH_2O; 6·38, 6·41, 2d, *J* 2·2 Hz, H 3,5; 6·53, s, H 3′; 7·27, s, C_6H_5; 11·50, 11·76, 2s, OH. Mass spectrum *m/z* 536 (M, 10%), 193 (100).

2-(6′-Benzyloxy-4′-hydroxy-3′-methoxycarbonyl-2′-propylphenoxy)-4-methoxy-6-propylbenzoic Acid (34)

A solution of methyl 4-benzyloxy-3-[2′-hydroxy-4′-methoxy-6′-propylbenzoyloxy]-6-hydroxy-2-propylbenzoate (32) (304 mg, 0·6 mmol) was dissolved in a solution of anhydrous potassium carbonate (82·9 mg, 0·6 mmol) and anhydrous dimethyl sulfoxide (10 ml). This reaction mixture was stirred and heated slowly until the temperature reached 75–76°, then maintained overnight at this temperature. The reaction mixture was then acidified with cold dilute hydrochloric acid and extracted with ethyl acetate. The combined organic fractions were washed with several portions of water, saturated brine and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was purified using the chromatotron with 20% dichloromethane/10% ethyl acetate/0·5% glacial acetic acid/light petroleum as eluent. The first fraction contained unreacted starting material (32) (82 mg). The second fraction was concentrated, and crystallization of the residue from dichloromethane/light petroleum yielded the *acid* (34) (106·4 mg, 35%) as colourless plates, m.p. 138–140° (Found: mol. wt, 508·2096. $^{12}C_{29}{}^{1}H_{32}{}^{16}O_8$ requires mol. wt, 508·2097). The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 0·92–1·04, m, CH_2CH_3; 1·40–1·80, m, CH_2CH_3; 2·60–3·10, m, $ArCH_2CH_2$; 3·71, 4·00, 2s, OMe; 5·00, s, CH_2O; 6·03, 6·57, 2d, *J* 2·6 Hz, H 5,3; 6·61, s, H 3′; 7·02–7·38, m, C_6H_5; 11·75, s, 4′-OH. Mass spectrum *m/z* 508 (M, 71%), 193 (100).

2-(2′-Benzyloxy-4′-hydroxy-5′-methoxycarbonyl-6′-pentylphenoxy)-4-methoxy-6-propylbenzoic Acid (35)

A solution of methyl 4-benzyloxy-3-(2′-hydroxy-4′-methoxy-6′-propylbenzoyloxy)-6-hydroxy-2-pentylbenzoate (33) (184·7 mg, 0·34 mmol) in dry dimethyl sulfoxide (5 ml) was treated with anhydrous potassium carbonate (47·7 mg, 0·34 mmol) in the manner described above. The crude product was purified by using the Chromatotron with 20% dichloromethane/10% ethyl acetate/0·5% glacial acetic acid/light petroleum as eluent. The first fraction contained unreacted starting material (33) (45 mg). The second fraction was concentrated, and crystallization of the residue from dichloromethane/light petroleum yielded the *acid* (35) (23 mg, 13%) as colourless plates, m.p. 160–162° (Found: mol. wt, 536·2411. $^{12}C_{31}{}^{1}H_{36}{}^{16}O_8$ requires mol. wt, 536·2410). The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r.

[19] Asahina, Y., and Hiraiwa, M., *Ber. Dtsch. Chem. Ges.*, 1937, **70**, 1826.

spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 0·85, 0·97, 2t, *J* 6, 7 Hz, CH_2CH_3; 1·20–1·40, m, $CH_2(CH_2)_2CH_3$; 1·40–1·80, m, $ArCH_2CH_2$; 2·60–3·10, m, $ArCH_2$; 3·69, 3·97, 2s, OMe; 5·00, s, CH_2O; 5·95, 6·50, 2d, *J* 2·4 Hz, H 5,3; 6·53, s, H 3′; 6·96–7·30, m, C_6H_5; 11·75, s, OH. Mass spectrum *m/z* 536 (M, 3%), 91 (100).

2-(2′-Benzyloxy-5′-carboxy-4′-hydroxy-6′-propylphenoxy)-4-methoxy-6-propylbenzoic Acid (36)

A mixture of 2-(6′-benzyloxy-4′-hydroxy-3′-methoxycarbonyl-2′-propylphenoxy)-4-methoxy-6-propylbenzoic acid (34) (91 mg, 0·175 mmol), potassium hydroxide (39 mg), water (0·35 ml) and dimethyl sulfoxide (1·75 ml) were stirred and heated at 90–95° for 8 h. The solution was then cooled and poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The combined organic fractions were washed with several portions of water, saturated brine and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was purified over a silica gel plate on the Chromatotron, with 20% dichloromethane/10% ethyl acetate/0·5% glacial acetic acid/light petroleum as eluent. The major band yielded the *diacid* (36) (40·8 mg, 48%) which crystallized from dichloromethane/light petroleum as colourless needles, m.p. 86–88°, with resolidification and m.p. 176–177° (Found: mol. wt, 494·1940. $^{12}C_{28}{}^1H_{30}{}^{16}O_8$ requires mol. wt, 494·1940). The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 0·92–1·04, m, CH_2CH_3; 1·58–1·80, m, $CH_2CH_2CH_3$; 2·80–3·00, m, $ArCH_2CH_2$; 3·72, s, OMe; 5·03, s, CH_2O; 6·00, 6·52, 2d, *J* 2·5 Hz, H 5,3; 6·56, s, H 3′; 7·03–7·29, m, C_6H_5. Mass spectrum *m/z* 494 (M, 1%), 91 (100).

2-(2′-Benzyloxy-5′-carboxy-4′-hydroxy-6′-pentylphenoxy)-4-methoxy-6-propylbenzoic Acid (37)

2-(2′-Benzyloxy-4′-hydroxy-5′-methoxycarbonyl-6′-pentylphenoxy)-4-methoxy-6-propylbenzoic acid (35) (176·5 mg, 0·33 mmol) was hydrolysed by the method described above. The crude product was purified over a silica gel plate on chromatotron, using 20% dichloromethane/10% ethyl acetate/0·5% glacial acetic acid/light petroleum as eluent. The first fraction contained unreacted starting material (35) (48·1 mg). The second fraction was concentrated, and crystallization of the residue from dichloromethane/light petroleum yielded the *diacid* (37) (62 mg, 36%) as colourless plates, m.p. 148–150° [Found: *m/z* 478·2355. $^{12}C_{29}{}^1H_{34}{}^{16}O_6$ ($M^+ - CO_2$) requires *m/z* 478·2355]. The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 0·87, 1·00, 2t, *J* 6, 7 Hz, CH_2CH_3; 1·12–1·40, m, $CH_2(CH_2)_2CH_3$; 1·48–1·80, m, $ArCH_2CH_2$; 2·68–3·20, m, $ArCH_2$; 3·70, s, OMe; 5·02, s, CH_2O; 6·00, 6·50, 2d, *J* 2·2 Hz, H 5,3; 6·54, s, H 3′; 7·00–7·27, m, C_6H_5. Mass spectrum *m/z* 522 (M, 0·5%), 91 (100).

2-(5′-Carboxy-2′,4′-dihydroxy-6′-propylphenoxy)-4-methoxy-6-propylbenzoic Acid (38)

2-(2′-Benzyloxy-5′-carboxy-4′-hydroxy-6′-propylphenoxy)-4-methoxy-6-propylbenzoic acid (36) (25 mg, 0·051 mmol) in ethyl acetate (5 ml) containing 10% palladium on charcoal (7·5 mg) was stirred in an atmosphere of hydrogen for 15 h. On removal of the catalyst by filtration, and evaporation of the solvent, the residue was crystallized from dichloromethane/light petroleum to give the corresponding *acid* (38) (19 mg, 92%) as colourless plates, m.p. 155–157° [Found: *m/z* 358·1410. $^{12}C_{20}{}^1H_{22}{}^{16}O_6$ ($M^+ - CO - H_2O$) requires *m/z* 358·1416]. The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. (CD_3COCD_3) δ 0·86–1·03, m, $CH_2CH_2CH_3$; 1·50–1·80, m, $CH_2CH_2CH_3$; 2·75, t, *J* 7 Hz, $ArCH_2CH_2$; 3·00, br t, $ArCH_2CH_2$; 3·70, s, OMe; 6·09, d, *J* 2·5 Hz, H 5; 6·38, s, H 3′; 6·58, d, *J* 2·5 Hz, H 3. Mass spectrum *m/z* 358 ($M - CO - H_2O$, 15%), 341 (25), 340 (100).

2-(5′-Carboxy-2′,4′-dihydroxy-6′-pentylphenoxy)-4-methoxy-6-propylbenzoic Acid (39)

A solution of 2-(2′-benzyloxy-5′-carboxy-4′-hydroxy-6′-pentylphenoxy)-4-methoxy-6-propylbenzoic acid (37) (62 mg, 0·12 mmol) in ethyl acetate (5 ml) containing 10% palladium on charcoal (18·6 mg) was stirred in an atmosphere of hydrogen for 15 h. On removal of the catalyst by filtration, and evaporation of the solvent, the residue was crystallized from dichloromethane/light petroleum to give the *acid* (39) (50·8 mg, 98%) as colourless plates, m.p. 128–130° (Found: mol. wt, 432·1784. $^{12}C_{23}{}^1H_{28}{}^{16}O_8$ requires mol. wt, 432·1784). The

homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. (CD_3COCD_3) δ 0·81, 0·96, 2t, *J* 5·8, 7 Hz, CH_2CH_3; 1·20–1·40, m, $CH_2(CH_2)_2CH_3$; 1·42–1·58, m, $ArCH_2CH_2$; 1·68, sextet, *J* 7 Hz, $CH_2CH_2CH_3$; 2·72, t, *J* 7 Hz, $ArCH_2$; 3·03, br t, $ArCH_2$; 3·71, s, OMe; 6·07, d, *J* 2·4 Hz, H 5; 6·41, s, H 3′; 6·59, d, *J* 2·4 Hz, H 3. Mass spectrum *m/z* 432 (M, 8%), 370 (100).

*8-Hydroxy-3-methoxy-1,6-dipropyl-11-oxo-11*H*-dibenzo*[b,e][*1,4*]*dioxepin-7-carboxylic Acid (Divaronic Acid) (24)*

A solution of 2-(5′-carboxy-2′,4′-dihydroxy-6′-propylphenoxy)-4-methoxy-6-propylbenzoic acid (38) (19·3 mg, 0·05 mmol) in anhydrous toluene (0·2 ml) and trifluoroacetic anhydride (0·05 ml) was permitted to stand at room temperature for 2 h. The solvent was then removed under reduced pressure, and the residue was applied to a silica gel plate (20 by 20 by 0·1 cm) and eluted with 15% glacial acetic acid/toluene. The major band yielded the *depsidone* (24) (3 mg, 17%), which crystallized on standing as colourless prisms, m.p. 110° with resolidification and m.p. 160–162° (Found: mol. wt, 386·1374. Calc. for $^{12}C_{21}{}^1H_{22}{}^{16}O_7$ mol. wt, 386·1365). The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 0·95, 1·06, 2t, *J* 7·5 Hz, CH_2CH_3; 1·43–1·80, m, $CH_2CH_2CH_3$; 2·80, t, *J* 7 Hz, $ArCH_2$; 3·23, br t, $ArCH_2$; 3·83, s, OMe; 6·60, 6·68, 2d, *J* 2·2 Hz, H 2,4; 6·70, s, H 9. Mass spectrum[13] *m/z* 386 (M, 100%), 368 (37), 342 (50), 341 (19), 340 (72), 325 (19), 311 (29), 285 (22), 193 (25), 192 (16), 177 (12).

*8-Hydroxy-3-methoxy-6-pentyl-1-propyl-11-oxo-11*H*-dibenzo*[b,e][*1,4*]*dioxepin-7-carboxylic Acid (Stenosporonic Acid) (25)*

A solution of 2-(5′-carboxy-2′,4′-dihydroxy-6′-pentylphenoxy)-4-methoxy-6-propylbenzoic acid (39) (51·8 mg, 0·12 mmol) in dry toluene (1 ml) and trifluoroacetic anhydride (0·25 ml) was permitted to stand at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue was purified over a silica gel plate on the Chromatotron, by using 20% dichloromethane/10% ethyl acetate/0·5% glacial acetic acid/light petroleum as eluent. The major fraction yielded the depsidone (25) (13·6 mg, 26%), which crystallized on standing as colourless needles, m.p. 139–140° (Found: mol. wt, 414·1679. Calc. for $^{12}C_{23}{}^1H_{26}{}^{16}O_7$: mol. wt, 414·1679). The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 1·00, t, *J* 9·8 Hz, CH_2,CH_3; 1·40–1·70, m, $CH_2CH_2CH_3$ and $CH_2(CH_2)_3CH_3$; 2·86, 3·30, 2t, *J* 7·6 Hz, $ArCH_2$; 3·90, s, OMe; 6·59, 6·64, 2d, *J* 2·8 Hz, H 2,4; 6·71, s, H 9. Mass spectrum[13] *m/z* 414 (M, 100%), 397 (9), 396 (25·5), 370 (70), 354 (7), 353 (14), 341 (21), 340 (25·5), 297 (12), 285 (16), 245 (14), 193 (25·5), 192 (16).

2-(2′,4′-Dihydroxy-5′-methoxycarbonyl-6′-propylphenoxy)-4-methoxy-6-propylbenzoic Acid (40)

A solution of 2-(2′-benzyloxy-4′-hydroxy-5′-methoxycarbonyl-6′-propylphenoxy)-4-methoxy-6-propylbenzoic acid (34) (60 mg) in ethyl acetate (10 ml) containing 10% palladium on charcoal (10 mg) was stirred in an atmosphere of hydrogen for 15 h. On removal of the catalyst by filtration, and evaporation of the solvent under reduced pressure, the residue was recrystallized from dichloromethane/light petroleum to give the *title acid* (40) (46·4 mg, 92%) as yellowish plates, m.p. 48–50° (Found: mol. wt, 418·1628. $^{12}C_{22}{}^1H_{26}{}^{16}O_8$ requires mol. wt, 418·1673). The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 0·90–1·00, m, CH_2CH_3; 1·50–1·80, m, $CH_2CH_2CH_3$; 2·60–3·00, m, $ArCH_2CH_2$; 3·70, 3·92, 2s, OMe; 6·08, 6·49, 2d, *J* 2·2 Hz, H 5,3; 6·50, s, H 3′. Mass spectrum *m/z* 418 (M, 46%), 339 (100).

*Methyl 8-Hydroxy-3-methoxy-1,6-dipropyl-11-oxo-11*H*-dibenzo*[b,e][*1,4*]*dioxepin-7-carboxylate (Methyl Divaronate) (26)*

A solution of 2-(2′,4′-dihydroxy-5′-methoxycarbonyl-6′-propylphenoxy)-4-methoxy-6-propylbenzoic acid (40) (15·20 mg, 0·036 mmol) in anhydrous toluene (1 ml) and trifluoroacetic anhydride (0·25 ml) were allowed to stand at room temperature for 2 h. The solvent was then removed under reduced pressure, and the residue was applied to a silica gel plate (20 by 20

by 0·1 cm) and eluted with 25% ethyl acetate/light petroleum. The major band afforded the *ester* (26) (2·50 mg, 17%), which crystallized on standing as colourless needles, m.p. 108–110° (Found: mol. wt, 400·1542. $^{12}C_{22}{}^{1}H_{24}{}^{16}O_7$ requires mol. wt, 400·1522). The homogeneity of this compound was confirmed by thin-layer chromatography and ^{1}H n.m.r. spectroscopy. ^{1}H n.m.r. ($CDCl_3$) δ 0·99, 1·14, 2t, *J* 7·5 Hz, CH_2CH_3; 1·50–1·72, m, $CH_2CH_2CH_3$; 2·88, 3·18, 2t, *J* 7 Hz, $ArCH_2CH_2$; 3·85, 3·98, 2s, OMe; 6·60, 6·66, 2d, *J* 2·6 Hz, H2,4; 6·74, s, H9; 11·20, s, 8-OH. Mass spectrum *m/z* 400 (M, 100%), 369 (22), 368 (60), 356 (25), 340 (87), 327 (48), 326 (28), 325 (44), 311 (68).

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