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Two New Diphenyl Ethers and a New Depside from the Lichen *Micarea prasina* Fr.

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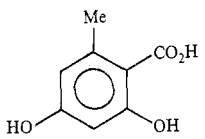
Abstract

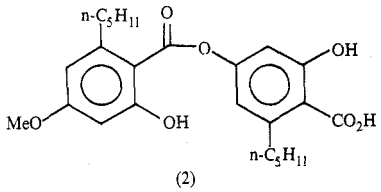
Two new diphenyl ethers, 4-(2-carboxy-3-heptyl-5-methoxyphenoxy)-2-heptyl-6-hydroxybenzoic acid (micareic acid) (13), 4-(2-carboxy-3-heptyl-5-methoxyphenoxy)-2-heptyl-6-hydroxy-3-methoxybenzoic acid (methoxymicareic acid) (27) and a new depside, 4-(2-heptyl-6-hydroxy-4-methoxybenzoyloxy)-2-heptyl-6-hydroxybenzoic acid (prasinic acid) (34) have been detected in chemical races of the lichen *Micarea prasina* Fr. and isolated and characterized as the corresponding methyl esters. The structure of the latter compounds has been confirmed by total synthesis. The key steps in the synthesis of the diphenyl ethers (14), (26) involved Ullmann-like condensation between the 3-chloro 2-enone (17) and the phenols (11), (31), and subsequent aromatization of the enol ethers (23) and (32). A biomimetic-type synthesis of methyl micareate (48) has also been achieved by treatment of the depside (33) with sodium hydride in dimethylformamide.

Introduction

Lichens produce a wide variety of metabolites but undoubtedly the aromatic polyketides are most typical, in particular the depsides, depsidones and dibenzofurans. Orsellinic acid (1) and its homologues form the most common mononuclear structural unit, while metabolites derived from phloroacetophenone (through an alternative cyclization of a linear C_8 polyketide) are very limited in number.[1,2] Diphenyl ethers derived along either biogenetic pathway constitute a relatively rare group of lichen products with only six examples known prior to the present work. We now describe the isolation of the new depside, prasinic acid (34) and two unique diphenyl ethers, methoxymicareic acid (27) and micareic acid (13) from chemical races of the lichen



(1)



(2)

[1] Mosbach, K., *Angew. Chem.*, 1969, **81**, 233.
[2] Mosbach, K., in 'The Lichens' (Eds V. Ahmadjian and M. E. Hale, Jr) Ch. 16 (Academic Press: New York 1973).

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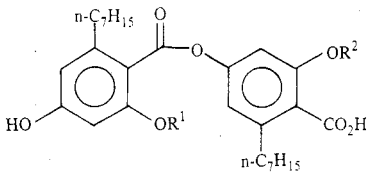
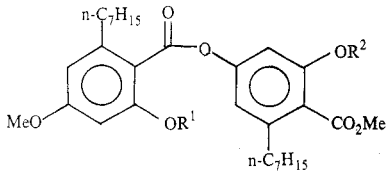
Micarea prasina Fr. Coppins and James[3] had previously examined extracts of this lichen by thin-layer chromatography and confirmed that it occurred in three distinct chemical races, each of which produced a metabolite of unknown constitution.

Micareic Acid (13)

A small-scale extraction of the lichen *Micarea prasina* Fr. (chemical race B)[3] with acetone led to the recovery of crude micareic acid. The mass spectrum of the crude acid showed a weak molecular ion at *m/z* 500 and a base peak at *m/z* 456 ($M - CO_2$, $^{12}C_{28}{}^{1}H_{40}{}^{16}O_5$), while the ^1H n.m.r. spectrum indicated the presence of four aromatic protons, a methoxy group and two n-heptyl groups. In fact the ^1H n.m.r. spectrum was very similar to that of the common depside, perlatolic acid (2).[4] Given the paucity of material, the crude acid was converted into the corresponding methyl ester (by brief treatment with ethereal diazomethane) in order to facilitate purification. The ^1H n.m.r. spectrum of the methyl ester so obtained revealed not only four aromatic protons and two heptyl groups but one intramolecularly hydrogen-bonded hydroxy group and a total of three *O*-methyl groups. This led us to propose that micareic acid was a depside containing both a free carboxylic acid group and a phenolic group (i.e. (3) or (4)), and that methylation with diazomethane gave rise to the corresponding methyl ester (either (5) or (6)). To establish which of the structures (3), (4) corresponded to the natural material, the methyl esters (5) and (6) were synthesized unambiguously by the well established procedures.[4]

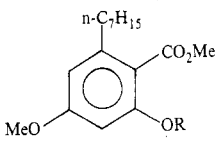


	R^1	R^2
(3)	Me	H
(4)	H	Me

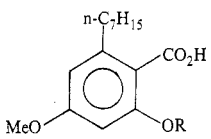


	R^1	R^2
(5)	Me	H
(6)	H	Me

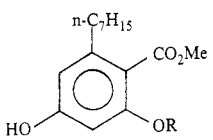
Hence methylation of methyl 2-heptyl-4,6-dihydroxybenzoate[5] (12) with one molar proportion of dimethyl sulfate in the presence of potassium carbonate gave methyl 2-heptyl-6-hydroxy-4-methoxybenzoate (7) while methylation with excess dimethyl sulfate gave methyl 2-heptyl-4,6-dimethoxybenzoate (8). The esters (7) and (8) were then hydrolysed by treatment with an aqueous dimethyl sulfoxide solution of



(7) R = H
(8) R = Me

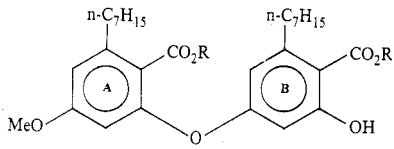


(9) R = H
(10) R = Me

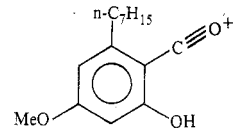


(11) R = Me
(12) R = H

[3] Coppins, B. J., *Bull. Br. Mus. (Nat. Hist.), Bot.*, 1983, **11**, 85.
[4] Elix, J. A., *Aust. J. Chem.*, 1974, **27**, 1767.
[5] Djura, P., and Sargent, M. V., *Aust. J. Chem.*, 1976, **29**, 899.



(13) R = H
(14) R = Me



(15)

Table 1. ^{13}C n.m.r. chemical shifts of (5), (6), (14), (26), (33) (ppm)

(5)	(6)	(14)	(26)	(33)	Assnt.
171·65	169·94	171·80	171·69	171·53	Ar q,[A] C=O
165·89	168·30	167·41	167·47	169·52	
164·24	166·49	164·99	161·42	166·57	
162·02	164·82	162·29	160·03	164·88	
158·69	157·57	161·37	156·02	164·29	
155·32	151·46	153·71	153·76	154·08	
148·13	148·48	148·54	144·61	148·48	
143·85	142·99	144·64	141·39	148·40	
			140·06		
115·15	121·61	119·28	118·73	110·04	
109·61	103·87	106·61	106·77	103·74	
115·96	114·39	112·19	111·75	115·80	Ar
108·69	111·33	111·97	104·24	111·38	
106·16	102·92	104·16	103·40	108·77	
96·32	99·05	103·26		99·02	
56·05	56·14		61·30	55·41	OMe
55·41	55·40	55·48	55·47		
52·17	52·25	51·97	52·07	52·29	CO_2Me
		51·97	51·96		
36·78	37·36	36·84	33·98	37·27	CH_2
34·08	33·57	33·93	31·77	36·75	
31·86	32·45	31·85	31·58	32·29	
31·86	31·84	31·85	31·25	31·86	
31·86	31·76	31·78	30·29	31·82	
31·43	30·88	31·24	29·69	31·61	
29·85	29·92	29·78	29·48	29·82	
29·59	29·45	29·47	29·15	29·65	
29·19	29·33	29·18	29·08	29·23	
29·19	29·05	29·09	28·28	29·16	
22·67	22·66	22·66	22·68	22·65	
22·67	22·66	22·66	22·68	22·65	
14·07	14·05	14·08	14·10	14·04	CH_3C
14·07	14·05	14·08	14·10	14·04	

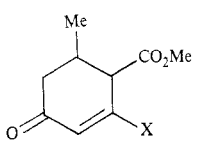
[A] We have attempted to use additivity parameters to assign the aromatic ring carbon resonances but in our experience there is sufficient ambiguity in such analyses to preclude definitive structural assignments unless closely analogous structural models are available.

potassium hydroxide to give the corresponding acids, 2-heptyl-6-hydroxy-4-methoxybenzoic acid (9) and 2-heptyl-4,6-dimethoxybenzoic acid (10). The condensation of the acid (9) with methyl 2-heptyl-4-hydroxy-6-methoxybenzoate (11),[5] and the acid (10) with methyl 2-heptyl-4,6-dihydroxybenzoate (12) in the presence of trifluoroacetic anhydride gave rise to the depside esters (6) and (5) respectively. Surprisingly, neither of these synthetic compounds corresponded to that derived by methylation of micareic acid. Subsequent examination of the ^{13}C n.m.r. spectra of the depside esters (5) and (6) not only confirmed that they were structurally similar to the methylated natural acid, but established that the latter contained two methyl ester groups and only one methyl ether group (Table 1). This new evidence indicated that micareic acid was the uniquely substituted diphenyl ether (13), and the methylated product the corresponding dimethyl ester, (14). High-resolution measurement on the mass spectral molecular ion established the molecular formula $C_{31}H_{44}O_7$ for dimethyl micareate (14). The prominent nature of the molecular ion in the mass spectrum [*m/z* 528 (100%)] and of the daughter ion (15) [*m/z* 249] due to A-ring fragmentation were consistent with this proposal. The structure of micareic acid (13) was subsequently confirmed by total synthesis as outlined below.

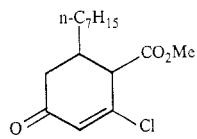
Synthesis of Micareic Acid (13) and Dimethyl Micareate (14)

In the past diphenyl ethers have normally been prepared by the Ullmann ether synthesis involving the reaction between a phenol (or phenolate salt) and a halobenzene in the presence of a tertiary amine and catalysed by copper, cuprous or cupric salts. Such a synthetic approach to a highly substituted diphenyl ether such as (14) is feasible but the preparation of a suitably substituted halobenzene involves numerous steps.[5] Recently Buchi and coworkers[6,7] have circumvented this difficulty by utilizing the more accessible methyl 2-halo-4-oxo-6-methylcyclohex-2-enecarboxylates (16; X = Br, Cl) in an Ullmann-type reaction with the appropriate phenol. We have now developed an efficient route to the corresponding heptyl derivatives (17) and utilized the compound as key intermediate in the synthesis of the diphenyl ethers (13) and (14).

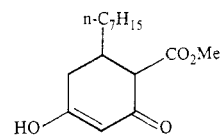
The logical starting material for the synthesis of the chloro ketone (17) is methyl 6-heptyl-4-hydroxy-2-oxocyclohex-3-enecarboxylate (18), available from the base-catalysed condensation of methyl 2-decenoate and methyl acetoacetate.[5] When the



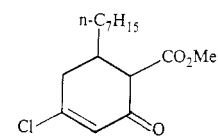
(16)



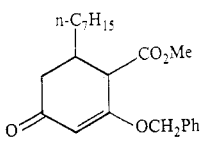
(17)



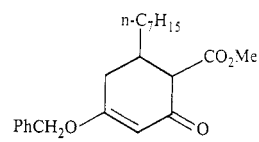
(18)



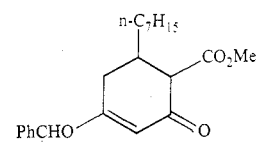
(19)



(20)



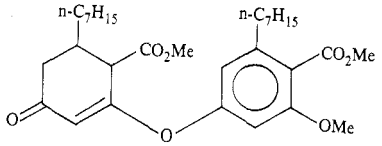
(21)



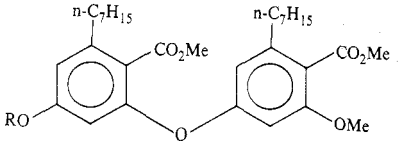
(22)

[6] Büchi, G., and Willard, P. G., *Heterocycles*, 1978, **11**, 437.
[7] Büchi, G., personal communication to M. V. Sargent.

enol (18) was treated directly with oxalyl chloride only the unwanted isomer, methyl 4-chloro-6-heptyl-2-oxocyclohex-3-enecarboxylate (19), was obtained. Consequently the enol (18) was converted into an enol ether by treatment with benzyl alcohol and *p*-toluenesulfonic acid. This procedure yielded a 2 : 3 mixture of methyl 2-benzyloxy-6-heptyl-4-oxocyclohex-2-enecarboxylate (20) and methyl 4-benzyloxy-6-heptyl-2-oxocyclohex-3-enecarboxylate (21) which could not be separated chromatographically. Hence the mixture of (20) and (21) was treated directly with oxalyl chloride to give a 2 : 3 mixture of the 4-chloro ketone (19) and the 2-chloro ketone (17). Although the latter chloro ketones could be readily separated by fractional distillation a more efficient route to the required isomer (17) was desirable. Hence the enol (18) was treated with 1-phenylethanol and *p*-toluenesulfonic acid and the predominant product was methyl 6-heptyl-2-oxo-4-(1-phenylethyl)cyclohex-2-enecarboxylate (22), favoured presumably for steric reasons. Treatment of the enol ether (22) with oxalyl chloride then smoothly afforded the required 2-chloro ketone (17). The reaction between the chloro ketone (17) and methyl 2-heptyl-4-hydroxy-6-methoxybenzoate (11) in the presence of potassium carbonate yielded the dihydrodiphenyl ether (23) in 88% yield. Aromatization of (23) was achieved by a modification of an efficient one-step procedure we have recently developed.[8] In this process a mixture of the dihydro compound (23) was treated with one equivalent of bromine in acetic anhydride, acetic acid and carbon tetrachloride to give the diphenyl ether (24) in good yield. Subsequent methylation of (24) gave (25) and selective demethylation of the latter compound with boron trichloride afforded dimethyl micareate (14), identical in all respects with that derived from the natural material. Finally the diester (14) was hydrolysed by treatment with an aqueous dimethyl sulfoxide solution of potassium hydroxide to give the corresponding dicarboxylic acid, micareic acid (13). Comparative thin-layer chromatography in three independent solvent systems confirmed that this synthetic material was identical with the metabolite produced by *Micarea prasina* (i.e. *prasina* unknown B).[3]



(23)



(24) R = H
(25) R = Me

Extractives from *Micarea prasina* (Chemical Race A)[3]

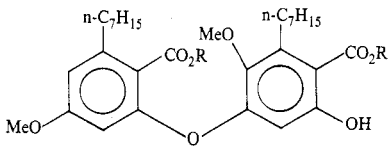
A similar small-scale extraction of the second chemical race of the lichen *Micarea prasina* led to the isolation of two new metabolites closely related to micareic acid (13). Treatment of the crude extractives with excess ethereal diazomethane for a brief period afforded the methyl esters of the unknown acids, and these were separated by preparative-layer chromatography.

The ^{1}H n.m.r. spectrum of the major methyl ester (dimethyl methoxymicareate (26)) exhibited three aromatic proton signals, and signals due to two heptyl groups, an intramolecularly hydrogen bonded hydroxy group and four *O*-methyl groups.

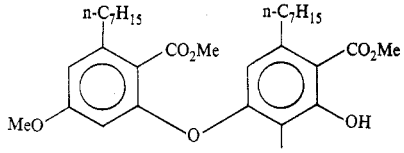
[8] Elix, J. A., Marcuccio, S. M., and Whitton, A. A., unpublished data.

The ^{13}C n.m.r. spectrum of this compound revealed three aromatic C–H carbons and four *O*-methyl carbons, two of which occurred at 52·07 and 51·96 ppm, indicative of methyl ester groups (Table 1). A third *O*-methyl group resonated at 55·47 and was comparable with that of dimethyl micareate (14) while the remaining signal occurred at 61·30, consistent with a sterically crowded *O*-methyl group.[9–11]

The mass spectrum of this compound exhibited a prominent molecular ion at *m/z* 558 ($^{12}C_{32}{}^{1}H_{46}{}^{16}O_8$) and daughter ions at *m/z* 280, 279 and 249. From the above evidence this compound was obviously a methoxy derivative of methyl micareate (14), with additional substitution most probably occurring in the B ring [since the mass spectrum still exhibited the A-ring fragment (15)]. Hence the alternative structures (26) and (28) seemed likely possibilities. The former structure (26) was favoured since the benzylic methylene protons are indistinguishable in the ^1H n.m.r. spectrum of (14) but are quite distinct (δ 2·66, 2·91) in the corresponding spectrum of dimethyl methoxymicareate (26). This evidence suggested that the two heptyl groups of dimethyl methoxy micareate experienced significantly different chemical environments, consistent with structure (26). The total synthesis of methyl methoxymicareate (26) indeed confirmed this to be correct.

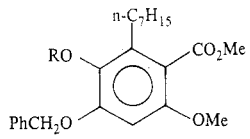


(26) R = Me
(27) R = H

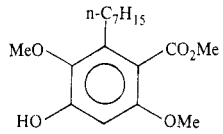


(28)

The key intermediate phenol (31) required for this synthesis was obtained in two steps from methyl 4-benzyloxy-2-heptyl-3-hydroxy-6-methoxybenzoate (29), previously prepared by Djura and Sargent.[5] Hence methylation of (29) with methyl iodide and potassium carbonate produced the ester (30) and subsequent hydrogenolysis gave the required phenol (31).



(29) R = H
(30) R = Me

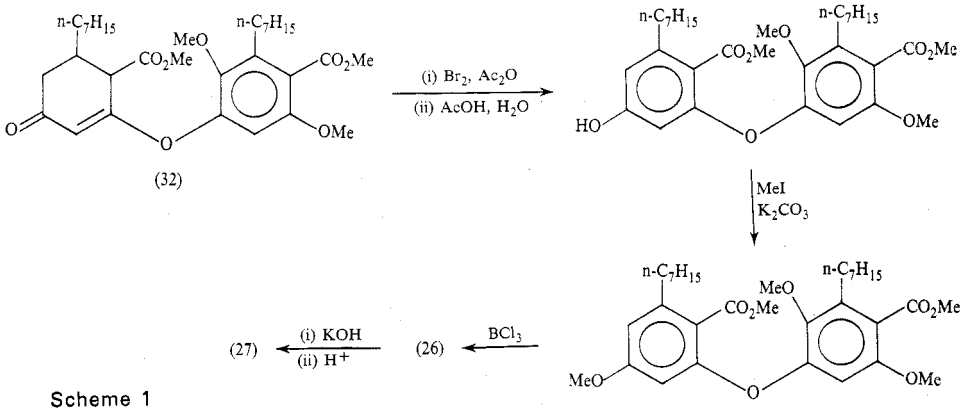


(31)

The base-catalysed condensation of the phenol (31) and the chloro ketone (17) gave the dihydro diphenyl ether (32) in good yield. Aromatization of (32) followed by methylation and subsequent selective demethylation of the successive products proceeded as discussed previously and outlined in Scheme 1 to yield dimethyl

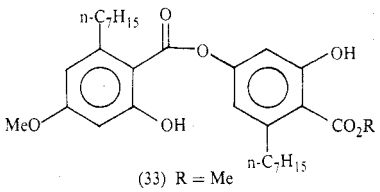
[9] Elix, J. A., Jayanthi, V. K., Jones, A. J., and Lennard, C. J., *Aust. J. Chem.*, 1984, **37**, 1531.
[10] Elix, J. A., Engkaninan, U., Jones, A. J., Raston, C. L., Sargent, M. V., and White, A. H., *Aust. J. Chem.*, 1978, **31**, 2057.
[11] Jones, A. J., Elix, J. A., and Engkaninan, U., *Aust. J. Chem.*, 1976, **29**, 1947.

methoxymicareate (26) and ultimately methoxymicareic acid (27). Synthetic (26) was found to be identical in all respects with that obtained on methylation of the natural acid. Comparative thin-layer chromatography in three independent solvent systems confirmed that synthetic methoxymicareic acid (27) was identical with the major metabolite present in *Micarea prasina* (i.e. *prasina* unknown A).[3]

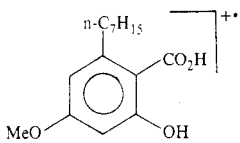


Scheme 1

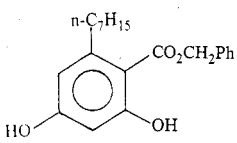
The ^{1}H n.m.r. spectrum of the minor methyl ester (methyl prasinate) originating from this chemical race of the lichen *M. prasina*, confirmed the presence of four aromatic protons, two *O*-methyl groups, two heptyl groups and two intramolecular hydrogen-bonded hydroxy groups in this compound. The ^{13}C n.m.r. spectrum established that one methyl ester group and one methyl ether group were present (Table 1) thus confirming that this compound was in fact a depside. Further evidence was provided by the mass spectrum of this compound. Although depsides rarely exhibit molecular ions in the positive ion spectra,[4,12] daughter ions originating from ring A were always observed and naturally are indicative of the substitution in this ring. In this particular case fragment ions (15) and (36) indicated that methyl prasinate had structure (33) and thus the natural depside, prasinic acid, structure (34). The structure of (33) and (34) was subsequently confirmed by synthesis.



(33) R = Me
(34) R = H
(35) R = CH_2Ph



(36) *m/z* 266

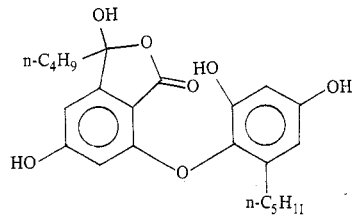


(37)

Condensation of 2-heptyl-6-hydroxy-4-methoxybenzoic acid (9) with methyl 2-heptyl-4,6-dihydroxybenzoate (12) in the presence of trifluoroacetic anhydride gave methyl prasinate (33), identical in all respects with the naturally derived material.

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

When the ester (12) was treated with sodium benzyloxide in excess benzyl alcohol, benzyl 2-heptyl-4,6-dihydroxybenzoate (37) was obtained. Condensation of the acid (9) with the benzyl ester (37) in the usual manner produced benzyl prasinate (35), and subsequent hydrogenolysis of the latter compound yielded prasinic acid (34).



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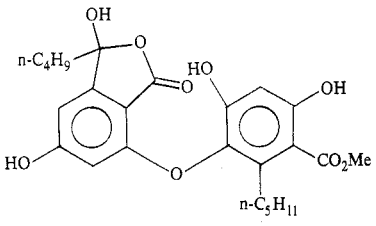

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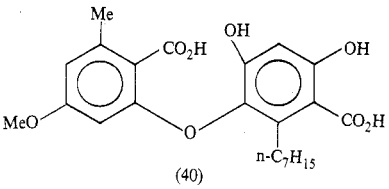

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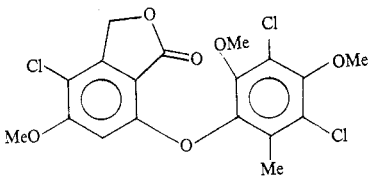
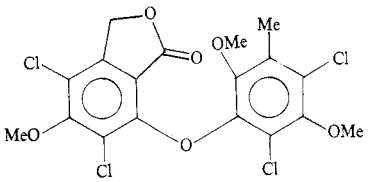
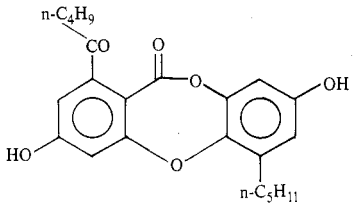


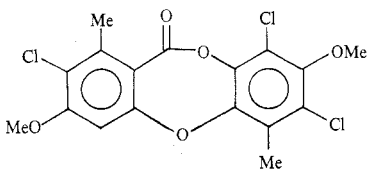
(41)



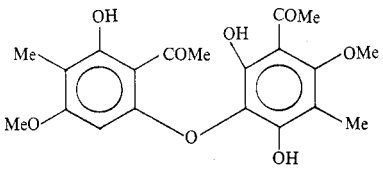
(42)



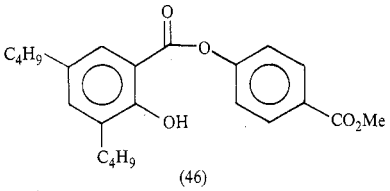
(43)



(44)



(45)



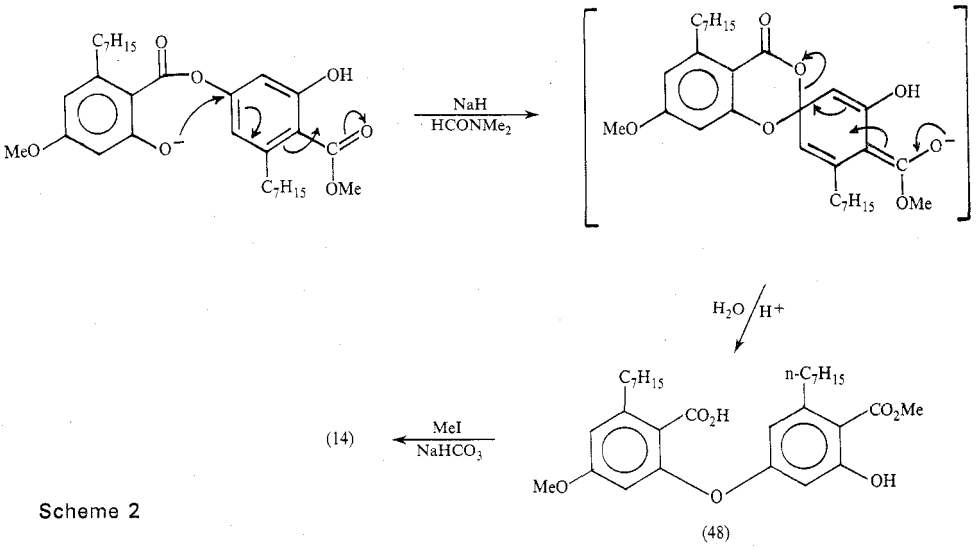
(46)

This synthetic product and the natural material exhibited identical chromatographic behaviour. Further, comparative thin-layer chromatography confirmed that prasinic acid was the only metabolite produced by the third race of *Micarea prasina* (≡ *prasina* unknown C).[3]

Biogenetic Considerations

As mentioned previously, diphenyl ethers constitute a relatively rare group of lichen metabolites. Five of the six known derivatives, norlobariol (38),[13] loxodinol (39),[14] congrayanic acid (40),[15] buellolide (41)[16] and canesolide (42)[16] appear to be derived catabolically from co-occurring depsidones. For instance norlobariol (38) co-occurs with norlobaridone (43)[13] and buellolide (41) with dechloro-*O*-methyldiploicin (44).[16] Leprolomin (45)[10] on the other hand appears to have a distinctly different biogenetic origin, apparently arising by direct oxidative coupling of two molecules of *C*-methylphloroacetophenone.[10]

In contrast to all these compounds, micareic acid (13) and methoxymicareic acid (27) have a distinctly different substitution pattern—and presumably biogenetic origin. One intriguing possibility is that micareic acid (13) arises by an enzymatically induced Smiles rearrangement of the depside, prasinic acid (34). A chemically analogous rearrangement of a synthetic depside (46) has recently been achieved by treatment with sodium hydride in dimethylformamide to give a diphenyl ether.[17] When methyl prasinate (33) was made to react under analogous conditions, methyl micareate (48) was obtained (Scheme 2). This rearrangement was also accompanied by a minor amount of depside cleavage. Subsequent methylation of the acid (48) gave dimethyl micareate (14), identical in all respects with the authentic material. This synthesis gives credence to the proposal that Smiles rearrangement of the appropriate depside provides a viable biosynthetic pathway to these uniquely substituted diphenyl ethers.



Scheme 2

The additional methoxy group present in methoxymicareic acid (27) is not inherent in the acetate–polymalonate pathway to this compound,[1,2] but is apparently the result of nuclear hydroxylation followed by *O*-methylation. The actual sequence of these

[13] Foo, L. Y., and Gwyn, S. A., *Experientia*, 1978, **34**, 970.
[14] Foo, L. Y., and Galloway, D. J., *Phytochemistry*, 1979, **18**, 1977.
[15] Chester, D. O., and Elix, J. A., *Aust. J. Chem.*, 1980, **33**, 1153.
[16] Sala, T., Sargent, M. V., and Elix, J. A., *J. Chem. Soc., Perkin Trans. 1*, 1981, 849.
[17] Pfister, J. R., *J. Heterocycl. Chem.*, 1982, **19**, 1255.

processes (i.e. before or after Smiles rearrangement of the depside precursor) remains a matter for conjecture, but a number of depsides with additional nuclear hydroxy (or methoxy) groups are known.[18]

Experimental

General directions[19] and details regarding ^{13}C n.m.r. spectral acquisition[11] have been described earlier.

Extraction of Micarea prasina *Fr. (Chemical Race B)*[3]

The lichen material was collected on the underside of decorticate *Corylus*, Milton wood, East Perthshire (v.c. 89), Scotland, *B. J. Coppins 8718* (ANUC).

The dried lichen thallus (and adhering lignin) (2·75 g) was boiled in dry acetone (100 ml) for 0·75 h and the solution filtered. The filtrate was concentrated to give the crude acid (50 mg). A portion of the crude acid (40 mg) was redissolved in acetone and treated with an excess of ethereal diazomethane for 1 min. The excess diazomethane was then quenched (acetic acid) and the solution concentrated. The residue so obtained was applied to a thin-layer chromatographic plate (20 by 20 by 0·1 cm) and eluted with 30% ethyl acetate/hexane. The major band yielded *methyl 2-heptyl-4-(3-heptyl-2-methoxycarbonyl-5-methoxyphenoxy)-6-hydroxybenzoate* (*dimethyl micareate*) (14) (15 mg, 0·5%) as a colourless oil (Found: $M^{+\cdot}$, 528·3090. $^{12}C_{31}{}^{1}H_{44}{}^{16}O_7$ requires $M^{+\cdot}$, 528·3087). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 3400 (OH); 1725, 1655 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·88, bt, CCH_3; 1·25, m, CH_2; 2·08–2·84, bt, $ArCH_2$; 3·72, 3·76, 3·93, 3s, OMe; 6·18, 6·19, 2d, J 2·5 Hz, H3,5; 6·39, 6·60, 2d, J 2·5 Hz, H4′,6′; 11·54, s, bonded OH; mass spectrum m/z 528 (M, 100%), 498 (6), 497 (24), 496 (36), 495 (20), 445 (12), 444 (45), 437 (16), 426 (11), 425 (31), 412 (26), 411 (43), 384 (14), 360 (8), 279 (54), 249 (10), 165 (20), 149 (80), 113 (17).

Extraction of Micarea prasina *Fr. (Chemical Race A)*[3]

The lichen material was collected on peaty turf on rock, near Garvard, Colonsay, South Ebudes (v.c. 102), Scotland, *B. J. Coppins 8767, F. Rose & R. Ashby* (ANUC).

The dried lichen thallus and adhering turf (3·0 g) was boiled in dry acetone (100 ml) for 0·75 h and the solution filtered. The filtrate was concentrated to 20 ml and treated with excess of ethereal diazomethane for 1 min. The excess diazomethane was then quenched (acetic acid) and the solution concentrated. The oily residue obtained was applied to four silica gel plates (20 by 20 by 0·1 cm) and eluted with 30% ethyl acetate–hexane. The faster moving (major band) afforded *methyl 4-(3-heptyl-2-methoxycarbonyl-5-methoxyphenoxy)-2-heptyl-6-hydroxy-3-methoxybenzoate* (*dimethyl methoxymicareate*) (26) (25 mg, 0·8%) as a colourless oil (Found: $M^{+\cdot}$, 558·3193. $^{12}C_{32}{}^{1}H_{46}{}^{16}O_8$ requires $M^{+\cdot}$, 558·3178). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 3400 (OH); 1725, 1650 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·88, 0·89, 2bt, CH_2CH_3; 1·30, m, CH_2; 2·66, 2·91, 2bt, $ArCH_2$; 3·74, s, 2×OMe; 3·79, 3·94, 2s, OMe; 6·26, s, H5; 6·34, 6·59, 2d, J 2·5 Hz, H4′,6′; 11·16, s, OH; mass spectrum m/z 558 (M, 100%), 526 (34), 455 (11), 318 (4), 280 (3), 279 (20), 256 (20), 224 (20), 210 (30), 193 (20), 178 (85), 149 (61), 131 (4), 121 (8), 113 (12).

The minor slower moving band yielded *methyl 4-(2-heptyl-6-hydroxy-4-methoxybenzoyloxy)-2-heptyl-6-hydroxybenzoate* (*methyl prasinate*) (33) (5 mg, 0·25%) which crystallized from hexane in colourless needles, m.p. 37–39° (Found: C, 70·0; H, 8·4. $C_{30}H_{42}O_7$ requires C, 70·3; H, 8·2%). ^1H n.m.r. ($CDCl_3$) δ 0·88, bt, CH_2CH_3; 1·25, m, CH_2; 2·83–3·03, 2bt, $ArCH_2$; 3·83, 3·97, 2s, OMe; 6·37, s, H3,5; 6·56, 6·70, 2d, J 2·4 Hz, H3′,5′; 11·33, 11·41, 2s, OH; mass spectrum m/z 266 (6%), 252 (15), 249 (50), 179 (12), 165 (16), 164 (100), 150 (20), 138 (70), 124 (60).

Methyl 2-Heptyl-6-hydroxy-4-methoxybenzoate (7)

A mixture of methyl 2-heptyl-4,6-dihydroxybenzoate (12)[5] (9·6 g), anhydrous potassium carbonate (15 g), and dimethyl sulfate (5·5 g) in anhydrous acetone (100 ml) was refluxed for 18 h. The cooled

[18] Elix, J. A., Whitton, A. A., and Sargent, M. V., *Fortschr. Chem. Org. Naturst.*, in press.
[19] Elix, J. A., and Lajide, L., *Aust. J. Chem.*, 1981, **34**, 583.

reaction mixture was poured into dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, saturated brine solution, and dried ($MgSO_4$). Evaporation of the solvent gave an oily residue which was purified by column chromatography on silica gel using 10% ethyl acetate/hexane as eluent.

The faster moving band yielded the *product* (7) (6·0 g, 59%) as a colourless oil; ^{1}H n.m.r. ($CDCl_3$) δ 0·86, bt, CH_2CH_3; 1·26, m, CH_2; 2·90, bt, $ArCH_2$; 3·80, 3·96, 2s, OMe; 6·38, s, ArH; 11·81, s, OH.

2-Heptyl-6-hydroxy-4-methoxybenzoic Acid (9)

The methyl ester (7) (4 g) was added to a solution of potassium hydroxide (4 g) in 50 ml of dimethyl sulfoxide and water (10 ml). The mixture was heated at 100° for 3 h, cooled, and then diluted with water. This was followed by extraction with ether and the aqueous layer acidified with cold dilute hydrochloric acid. The crude acid was extracted into ethyl acetate, washed with water and saturated brine solution, and dried ($MgSO_4$). The solvent was then evaporated to give the *acid* (9) which recrystallized from cyclohexane as colourless prisms, m.p. 129–130° (Found: C, 67·8; H, 8·6. $C_{15}H_{22}O_4$ requires C, 67·7; H, 8·3%). ^{1}H n.m.r. ($CDCl_3$) δ 0·88, bt, CH_2CH_3; 1·30, m, CH_2; 3·00, bt, $ArCH_2$; 3·92, s, OMe; 6·38, s, ArH; 10·98, bs, OH and CO_2H.

Methyl 2-Heptyl-4,6-dimethoxybenzoate (8)

Methylation of methyl 2-heptyl-4,6-dihydroxybenzoate (12)[5] (9·6 g) with excess dimethyl sulfate (12 g) and potassium carbonate (30 g) in refluxing acetone followed by the usual workup as described above for (7) gave the *ester* (8) (10 g, 94%) as a colourless oil; ^{1}H n.m.r. ($CDCl_3$) δ 0·80, bt, CH_2CH_3; 1·25, m, CH_2; 3·64, bt, $ArCH_2$; 3·75, s, 2OMe; 3·85, s, OMe; 6·30, s, ArH.

2-Heptyl-4,6-dimethoxybenzoic Acid (10)

The ester (8) (4 g) was added to a solution of potassium hydroxide (4 g) in dimethyl sulfoxide (40 ml) and water (10 ml) and the mixture heated at 90° for 3 h. Acidification of the cooled reaction mixture with cold dilute hydrochloric acid gave the crude acid. The acid was extracted with ethyl acetate, washed with water, saturated brine solution, and dried ($MgSO_4$). The solvent was evaporated to give the *acid* (10) (3·4 g, 89%) which crystallized from cyclohexane as colourless flakes, m.p. 66–67° (Found: C, 68·7; H, 8·7. $C_{16}H_{24}O_4$ requires C, 68·6; H, 8·6%). ^{1}H n.m.r. ($CDCl_3$) δ 0·85, bt, CH_2CH_3; 1·28, m, CH_2; 2·50, bt, $ArCH_2$; 3·76, 3·80, 2s, OMe; 6·35, 6·40, 2d, J 2·0 Hz, ArH; 8·9, bs, CO_2H.

Benzyl 2-Heptyl-4,6-dihydroxybenzoate (37)

Methyl 2-heptyl-4,6-dihydroxybenzoate (12)[5] (8 g) was added to a solution of sodium (0·92 g) in redistilled benzyl alcohol (90 ml) in an atmosphere of dry nitrogen. The mixture was heated at 130° for 16 h, then cooled, acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure while the excess benzyl alcohol was distilled in a vacuum. The oily residue was purified on a short silica gel column using 10% ethyl acetate/hexane as eluent to give the *benzyl ester* (37) (9·6 g, 90%) which crystallized from light petroleum in colourless needles, m.p. 94–95° (Found: C, 73·4; H, 7·8. $C_{22}H_{26}O_4$ requires C, 73·7; H, 7·6%). ^{1}H n.m.r. ($CDCl_3$) δ 0·86, bt, CH_2CH_3; 1·10, m, CH_2; 2·80, bt, $ArCH_2$; 5·42, s, OCH_2; 6·29, 6·35, 2d, J 2·5 Hz, H 3,5; 7·40, s, C_6H_5; 11·79, s, OH.

Methyl 2-Benzyloxy-6-heptyl-4-oxocyclohex-2-enecarboxylate (20) and Methyl 4-Benzyloxy-6-heptyl-2-oxocyclohex-3-enecarboxylate (21)

A mixture of methyl 6-heptyl-4-hydroxy-2-oxocyclohex-3-enecarboxylate[5] (18 g), benzyl alcohol (50 ml), and *p*-toluenesulfonic acid (360 mg) in benzene (100 ml) was boiled under reflux for 3 h. The benzene was then removed under reduced pressure and the residue diluted with ether. The ether extract was washed with 2 M potassium hydroxide solution, water and saturated brine solution, and then dried ($MgSO_4$). The solvent was removed and the excess benzyl alcohol was removed in a vacuum. Thin-layer chromatography of the oily residue showed the presence of one major and

one minor compound, but these were difficult to separate. The residue was purified on a silica gel column with 20% ethyl acetate/hexane as eluent to give the mixture of (20) and (21) (21 g, 87%) as a colourless oil (Found: $M^{+\cdot}$, 358·2133. Calc. for $^{12}C_{22}{}^{1}H_{30}{}^{16}O_4$: $M^{+\cdot}$, 358·2144). ^{1}H n.m.r. ($CDCl_3$) δ 0·86, bt, CH_2CH_3; 1·31, m, CH_2; 2·30–3·71, m, ring CH, CH_2; 4·82, s, OCH_2; 5·46, s, =CH; 7·30, s, C_6H_5.

Methyl 6-Heptyl-2-oxo-4-(1-phenylethyl)cyclohex-3-enecarboxylate (22)

A mixture of methyl 6-heptyl-4-hydroxy-2-oxocyclohex-3-enecarboxylate[5] (18) (30 g), 1-phenylethanol (25 ml) and *p*-toluenesulfonic acid (500 mg) in cyclohexane (150 ml) was boiled under reflux for 1 h. After being cooled, the reaction mixture was concentrated and the residue diluted with ether and then extracted with ether. The ether layer was washed with 2 M potassium hydroxide solution, water, and then dried ($MgSO_4$). The solvent was removed under reduced pressure while the excess alcohol was distilled in a vacuum. The oily residue crystallized on standing to give the desired *product* (22) (32 g, 80%), m.p. 38–40° (Found: $M^{+\cdot}$, 372·2290. $^{12}C_{23}{}^{1}H_{32}{}^{16}O_4$ requires $M^{+\cdot}$, 372·2301). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems). ^{1}H n.m.r. ($CDCl_3$) δ 0·85, bt, CH_2CH_3; 1·30, m, CH_2; 1·58, d, J 4·0 Hz, CH_3CHO; 2·25–3·08, m, ring CH, CH_2; 3·79, s, OMe; 5·18–5·46, m, CH_3CH; 5·31, s, =CH and 7·25, s, C_6H_5; mass spectrum m/z (M, 7%), 104 (100).

Methyl 4-Chloro-6-heptyl-2-oxocyclohex-3-enecarboxylate (19)

Oxalyl chloride (10 g) was added to a solution of methyl 6-heptyl-4-hydroxy-2-oxocyclohex-3-enecaroxylate (18)[5] (7·5 g) in benzene (50 ml) and chloroform (50 ml) and the resulting mixture was boiled under reflux for 1 h. The solution was then cooled and water (50 ml) was added slowly and the mixture stirred for 1 h at room temperature. The organic layer was then separated and washed with 2 M potassium hydroxide solution, water, saturated brine, and dried ($MgSO_4$). The solvent was removed and the yellow oily residue was distilled under reduced pressure to give the *product* (19) (4 g, 50%) as a colourless liquid, b.p. 166–176°/0·25 mm (Found: $M^{+\cdot}$, 286·1330. $^{12}C_{15}{}^{1}H_{23}{}^{16}O_3{}^{35}Cl$ requires $M^{+\cdot}$, 286·1336). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 1735, 1680 (C=O) cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 0·87, bt, CH_2CH_3; 1·24, m, CH_2; 2·40–3·66, m, $CH_2C_6H_{13}$, ring CH, CH_2; 3·77, s, OMe; 6·38, s, and 6·18, s, =CH.

Treatment of a Mixture of (20), (21) with Oxalyl Chloride

A 2 : 3 mixture of enol ethers (20), (21) was treated with oxalyl chloride in the manner described above. Fractional distillation of the crude product under reduced pressure yielded a more volatile fraction containing *methyl 2-chloro-6-heptyl-4-oxocyclohex-2-enecarboxylate* (17) (60%). This compound was obtained as a colourless liquid, b.p. 140–150° (0·25 mm) (Found: $M^{+\cdot}$, 286·1330. $^{12}C_{15}{}^{1}H_{23}{}^{16}O_3{}^{35}Cl$ requires $M^{+\cdot}$, 286·1336). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 1735, 1675 (C=O) cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 0·88, bt, CH_2CH_3; 1·26, m, CH_2; 2·42–3·66, m, ring CH, CH_2, $CH_2C_6H_{13}$; 3·80, s, OMe; 6·25, s, =CH.

A higher boiling fraction yielded the isomer (19) (40%) as a colourless liquid, b.p. 166–176°/0·25 mm, identical in all respects with the material prepared above.

Methyl 2-Chloro-6-heptyl-4-oxocyclohex-2-enecarboxylate (17)

When a solution of methyl 6-heptyl-2-oxo-4-(1-phenylethyl)cyclohex-3-enecarboxylate (22) (30 g) in cyclohexane (100 ml) was treated with oxalyl chloride (60 g) in the manner described above and the crude product distilled, the chloro ketone (17) (24 g, 80%) was obtained as a colourless liquid, b.p. 140–150°/0·25 mm, identical in all respects with the material prepared above.

Methyl 4-Benzyloxy-2-heptyl-3,6-dimethoxybenzoate (30)

A solution of methyl 4-benzyloxy-2-heptyl-3-hydroxy-6-methoxybenzoate (29)[5] (5·0 g) in dry acetone (50 ml) was treated with anhydrous potassium carbonate (10 g) and methyl iodide (2 ml) and boiled under reflux for 6 h. The reaction mixture was then cooled, poured into cold dilute

hydrochloric acid and extracted with ether. The ether extract was washed with 10% sodium hydroxide solution, water, saturated brine solution, and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give the *product* (30) (5·0 g, 96%) as a colourless oil (Found: $M^{+\cdot}$, 400·2238. $^{12}C_{24}{}^{1}H_{32}{}^{16}O_5$ requires $M^{+\cdot}$, 400·2250). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 1730 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·85, bt, CH_2CH_3; 1·25, m, CH_2; 2·48, bt, $ArCH_2$; 3·68, 3·76, 3·80, 3s, OMe; 5·09, s, OCH_2; 6·38, s, H3; 7·35, s, C_6H_5; mass spectrum *m/z* 400 (M, 35%), 91 (100).

Methyl 2-Heptyl-4-hydroxy-3,6-dimethoxybenzoate (31)

10% Palladium-on-charcoal (0·5 g) was added to a solution of methyl 4-benzyloxy-2-heptyl-3,6-dimethoxybenzoate (30) (5·0 g) in ethyl acetate (75 ml) and the mixture was stirred in an atmosphere of hydrogen for 6 h. The catalyst was then filtered and the filtrate concentrated to give an oily residue which on crystallization from pentane afforded the *phenol* (31) (3·75 g, 90%) as colourless flakes, m.p. 43–45° (Found: C, 65·4; H, 8·5. $C_{17}H_{26}O_5$ requires C, 65·8; H, 8·4%). ^1H n.m.r. ($CDCl_3$) δ 0·89, bt, CH_2CH_3; 1·25, s, CH_2; 2·60, bt, $ArCH_2$; 3·80, s, 2×OMe; 3·95, s, OMe; 6·10, bs, OH; 6·40, s, ArH.

Synthesis of Depside Esters

General procedure.—The appropriate carboxylic acid (1 mmol) and phenol (1 mmol) were dissolved in a solution of anhydrous toluene or benzene (4 ml) and trifluoroacetic anhydride (1 ml), and the solution was allowed to stand at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue applied to a thick-layer silica gel plate and eluted with 20% ethyl acetate/hexane, unless stated otherwise. The major faster moving band yielded the appropriate depside ester which was extracted and crystallized.

Methyl 4-(2-heptyl-4,6-dimethoxybenzoyloxy)-2-heptyl-6-hydroxybenzoate (5) (55%) was obtained by condensation of the acid (10) and methyl 2-heptyl-4,6-dihydroxybenzoate (12)[5] and crystallized from hexane as colourless needles, m.p. 50–52° (Found: C, 70·7; H, 8·4. $C_{31}H_{44}O_7$ requires C, 70·5; H, 8·4%). ^1H n.m.r. ($CDCl_3$) δ 0·88, bt, CH_2CH_3; 1·25, m, CH_2; 2·58, 2·96, 2bt, $ArCH_2$; 3·80, s, 2×OMe; 3·90, s, OMe; 6·32, s, H3,5; 6·60, 6·79, 2d, *J* 3·0 Hz, H3′,5′; 11·60, s, OH; mass spectrum *m/z* 528 (M, 1%), 280 (33), 250 (57), 210 (9), 196 (100), 177 (34), 138 (23).

Methyl 4-(2-heptyl-6-hydroxy-4-methoxybenzoyloxy)-2-heptyl-6-hydroxybenzoate (methyl prasinate) (33) (54%) was obtained by condensation of the acid (9) and ester (12) and crystallized from pentane in colourless needles, m.p. 37–39°, alone or admixed with the authentic sample. This synthetic compound exhibited ^1H n.m.r. and mass spectra and t.l.c. behaviour identical with that of the naturally derived ester described above.

Benzyl 4-(2-heptyl-6-hydroxy-4-methoxybenzoyloxy)-2-heptyl-6-hydroxybenzoate (benzyl prasinate) (35) (81%) was obtained by condensation of the acid (9) and benzyl 2-heptyl-4,6-dihydroxybenzoate (37) and crystallized from pentane in colourless prisms, m.p. 60–61° (Found: C, 73·0; H, 8·0. $C_{36}H_{46}O_7$ requires C, 73·2; H, 7·8%). ^1H n.m.r. ($CDCl_3$) δ 0·83, 0·86, 2bt, CH_2CH_3; 1·14, 1·25, 2m, CH_2; 2·50–2·90, m, $ArCH_2$; 3·82, s, OMe; 5·39, s, OCH_2; 6·36, s, H3,5; 6·54, 6·60, 2d, *J* 3·0 Hz, H3′,5′; 11·33, 11·47, 2s, OH.

4-(2-Heptyl-6-hydroxy-4-methoxybenzoyloxy)-2-heptyl-6-hydroxybenzoic Acid (Prasinic Acid) (34)

A solution of benzyl prasinate (35) (0·96 g) in ethyl acetate (30 ml) containing 10% palladium-on-charcoal (100 mg) was stirred in an atmosphere of hydrogen for 3 h. The catalyst was then filtered and the filtrate concentrated to give the *acid* (34) (0·7 g, 86%) which crystallized from acetone/hexane in colourless needles, m.p. 93–94° (Found: C, 69·3; H, 8·1. $C_{29}H_{40}O_7$ requires C, 69·6; H, 8·0%). ^1H n.m.r. ($CDCl_3$) δ 0·84, 0·88, 2bt, CH_2CH_3; 1·28, m, CH_2; 2·93, 2·99, 2bt, $ArCH_2$; 3·84, s, OMe; 6·38, s, H3,5; 6·63, 6·75, 2d, *J* 2·5 Hz, H3′,5′; 11·28, bs, OH, CO_2H; 11·34, s, OH. Mass spectrum *m/z* 267 (8%), 266 (50), 252 (12), 249 (13), 248 (62), 234 (16), 222 (15), 208 (13), 206 (15), 205 (10), 193 (9), 192 (42), 191 (21), 182 (95), 179 (12), 178 (26), 177 (39), 168 (19), 165 (16), 164 (100), 151 (21), 150 (25), 149 (13), 138 (82), 137 (32), 135 (22), 124 (60). Comparative t.l.c. in three independent solvent systems[20] confirmed that this acid occurred in acetone extracts of the lichen *Micarea prasina* (chemical strain C).[3]

[20] Culberson, C. F., *J. Chromatogr.*, 1972, **72**, 113.

Methyl 2-(3-Heptyl-5-methoxy-4-methoxycarbonylphenoxy)-6-heptyl-4-oxocyclohex-2-enecarboxylate (23)

Freshly roasted potassium carbonate (1·5 g) was added to a solution of methyl 2-chloro-6-heptyl-4-oxocyclohex-2-enecarboxylate (17) (2·8 g) and methyl 2-heptyl-4-hydroxy-2-methoxybenzoate (11) (2·7 g) in dry t-butyl alcohol (20 ml) and the mixture boiled under reflux for 16 h. The mixture was then cooled, concentrated, and the dark oily residue was diluted with water and extracted with ether. The ethereal layer was separated, washed with water, saturated brine solution and then dried ($MgSO_4$). The solvent was removed, under reduced pressure and the oily residue purified by column chromatography using cyclohexane/chloroform/acetone (10 : 8 : 1) as eluent to give the desired *product* (23) (4·4 g, 86%) as a colourless oil (Found: $M^{+\bullet}$, 530·3244. $^{12}C_{31}{}^{1}H_{46}{}^{16}O_7$ requires $M^{+\bullet}$, 530·3245). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 1730, 1640 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·89, bt, CH_2CH_3; 1·30, m, CH_2; 2·50, bt, $ArCH_2$; 2·40–3·40, m, ring CH, CH_2; 3·79, 3·87, 3·92, 3s, OMe; 5·30, s, =CH; 6·55, 6·62, 2d, J 2·4 Hz, ArH. Mass spectrum m/z 530 (M, 25%), 57 (100).

Methyl 2-Heptyl-4-(3-heptyl-5-hydroxy-2-methoxycarbonylphenoxy)-6-methoxybenzoate (24)

The dihydro compound (23) was dissolved in a mixture of acetic anhydride (15 ml) and carbon tetrachloride (15 ml) and the solution cooled to 0°. Bromine (1·2 g) in glacial acetic acid (5 ml) was added with stirring over 10 min. Stirring was continued at room temperature for a further 0·5 h after which the reaction mixture was refluxed under dry nitrogen for 3 h. After the mixture was cooled, water (10 ml) and hydrobromic acid (0·5 ml) were added and the mixture refluxed for 2 h. The reaction mixture was then poured into water and extracted with ether; the organic layer so obtained was washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure and the oily residue was chromatographed on a short silica gel column with cyclohexane/chloroform/acetone (10 : 8 : 1) as eluent. The slowest major band gave the *phenol* (24) (2·5 g, 63%) as a colourless oil (Found: $M^{+\bullet}$, 528·3090. $^{12}C_{31}{}^{1}H_{44}{}^{16}O_7$ requires $M^{+\bullet}$, 528·3087). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ^1H n.m.r. ($CDCl_3$) δ 0·87, bt, CH_2CH_3; 1·26, m, CH_2; 2·41–2·70, m, $ArCH_2$; 3·70, 3·80, 3·89, 3s, OMe; 5·80, bs, OH; 6·39, s, H 3,5; 6·16, 6·45, 2d, J 2·4 Hz, H 4′,6′; mass spectrum m/z 528 (M, 100%), 500 (50).

Methyl 2-Heptyl-4-(3-heptyl-5-methoxy-2-methoxycarbonylphenoxy)-6-methoxybenzoate (25)

A mixture of the phenol (24) (2 g), anhydrous potassium carbonate (2 g) and methyl iodide (1 ml) in dimethylformamide (10 ml) was stirred at room temperature for 3 h. Ethyl acetate (25 ml) and water (50 ml) were then added in turn. The organic layer was washed with water, 10% sodium hydroxide solution, saturated brine and dried ($MgSO_4$). The solvent was evaporated to give the desired *product* (25) (2 g, 97%) as a colourless oil (Found: $M^{+\bullet}$, 542·3236. $^{12}C_{32}{}^{1}H_{46}{}^{16}O_7$ requires $M^{+\bullet}$, 542·3244). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ^1H n.m.r. ($CDCl_3$) δ 0·88, bt, CH_2CH_3; 1·27, m, CH_2; 2·41–2·71, m, $ArCH_2$; 3·72, 3·74, 3·78, 3·85, 4s, OMe; 6·28, 6·54, 2d, J 2·4 Hz, H 4′,6′; 6·43, s, H 3,5.

Methyl 2-Heptyl-4-(3-heptyl-5-methoxy-2-methoxycarbonylphenoxy)-6-hydroxybenzoate (Dimethyl Micareate) (14)

A stirred solution of the diphenyl ether (25) (1 g) in anhydrous dichloromethane (25 ml) was cooled to −78° and a 2 M solution of boron trichloride in dichloromethane (1 ml) was added dropwise over 5 min. The mixture was then stirred at −78° for a further 0·5 h and at room temperature for 0·5 h. The reaction mixture was poured into cold water and extracted with ethyl acetate. The organic layer was washed with water, saturated sodium hydrogen carbonate solution, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give the dimethyl micareate (14) (0·8 g, 92%) as a colourless oil. The infrared, ^1H n.m.r., mass spectrum and t.l.c. behaviour of this synthetic compound were identical with that observed for the naturally derived material.

Methyl 2-(3-Heptyl-2,5-dimethoxy-4-methoxycarbonylphenoxy)-6-heptyl-4-oxocyclohex-2-enecarboxylate (32)

A solution of methyl 2-chloro-6-heptyl-4-oxocyclohex-2-enecarboxylate (17) (3 g) and methyl 2-heptyl-4-hydroxy-3,6-dimethoxybenzoate (31) (3·2 g) in t-butanol (20 ml) was treated with freshly

roasted potassium carbonate (1·75 g) in the manner described above for the preparation of (23). Workup in the usual way afforded the *dihydro ether* (*32*) (4·6 g, 78%) as a colourless oil (Found: $M^{+\bullet}$, 560·3329. $^{12}C_{32}{}^{1}H_{48}{}^{16}O_8$ requires $M^{+\bullet}$, 560·3349). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 1730, 1660 (C=O) cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 0·88, bt, CH_2CH_3; 1·25, m, CH_2; 2·00–2·90, m, ring CH, CH_2; 2·55, bt, $ArCH_2$; 3·71, 3·75, 3·85, 3·90, 4s, OMe; 5·28, s, =CH; 6·53, s, ArH. Mass spectrum *m/z* 560 (M, 100%).

Methyl 2-Heptyl-4-(3-heptyl-5-hydroxy-2-methoxycarbonylphenoxy)-3,6-dimethoxybenzoate

Aromatization of the dihydro ether (32) (4 g) in the manner described for the preparation of (24) gave *methyl 2-heptyl-4-(3-heptyl-5-hydroxy-2-methoxycarbonylphenoxy)-3,6-dimethoxybenzoate* (3·4 g, 85%) as a colourless oil (Found: $M^{+\bullet}$, 558·3173. $^{12}C_{32}{}^{1}H_{46}{}^{16}O_8$ requires $M^{+\bullet}$, 558·3193). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ^{1}H n.m.r. ($CDCl_3$) δ 0·87, bt, CH_2CH_3; 1·29, m, CH_2; 2·58, bt, $ArCH_2$; 3·66, 3·76, 3·83, 3·89, 4s, OMe; 6·41, s, H5; 6·02, 6·41, 2d, *J* 2·0 Hz, H4′,6′; 6·80, bs, OH. Mass spectrum *m/z* 558 (M, 100%).

Methyl 2-Heptyl-4-(3-heptyl-5-methoxy-2-methoxycarbonylphenoxy)-3,6-dimethoxybenzoate

Methylation of the above phenol (2·5 g) with methyl iodide, anhydrous potassium carbonate (2 g) in dimethylacetamide (10 ml) in the manner described for the synthesis of (25) yielded *methyl 2-heptyl-4-(3-heptyl-5-methoxy-4-methoxycarbonylphenoxy)-3,6-dimethoxybenzoate* (2·4 g, 94%) as a colourless oil (Found: $M^{+\bullet}$, 572·3347. $^{12}C_{33}{}^{1}H_{48}{}^{16}O_8$ requires $M^{+\bullet}$, 572·3349). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ^{1}H n.m.r. ($CDCl_3$) δ 0·85, bt, CH_2CH_3; 1·26, m, CH_2; 2·50–2·80, 2bt, $ArCH_2$; 3·60, s, 2×OMe; 3·71, 3·78, 3·82, 3s, OMe; 6·10, 6·45, 2d, *J* 2·0 Hz, H4′,6′; 6·39, s, H5′. Mass spectrum *m/z* 572 (M, 100%).

Methyl 2-Heptyl-4-(3-heptyl-5-methoxy-2-methoxycarbonylphenoxy)-6-hydroxy-3-methoxybenzoate (Dimethyl Methoxymicareate) (26)

Methyl 2-heptyl-4-(3-heptyl-5-methoxy-4-methoxycarbonylphenoxy)-3,6-dimethoxybenzoate (1·2 g) was demethylated by treatment with boron trichloride as described in the preparation of (14) from (25). Workup in the usual manner gave dimethyl methoxymicareate (26) (0·82 g, 82%) as a colourless oil. The infrared, ^{1}H n.m.r., mass spectrum and t.l.c. behaviour of this synthetic compound were identical with that observed for the naturally derived material.

4-(2-Carboxy-3-heptyl-5-methoxyphenoxy)-2-heptyl-6-hydroxybenzoic Acid (Micareic Acid) (13)

A solution of dimethyl micareate (14) (0·75 g) and potassium hydroxide (2·0 g) in dimethyl sulfoxide (20 ml) and water (5 ml) was heated at 100° for 12 h. The solution was then cooled, acidified with cold dilute hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, saturated brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue crystallized from dichloromethane/cyclohexane to give *micareic acid* (13) (0·58 g, 84%) as colourless needles, m.p. 100–102° (Found: C, 69·3; H, 8·1. $C_{29}H_{40}O_7$ requires C, 69·6; H, 8·1%). ^{1}H n.m.r. (CD_3COCD_3) δ 0·87, bt, CH_2CH_3; 1·29, m, CH_2; 2·65–3·05, m, $ArCH_2$; 3·81, s, OMe; 6·23, 6·39, 2d, *J* 2·5 Hz, H3,5; 6·52, 6·76, 2d, *J* 2·5 Hz, H4′,6′; 8·40, bs, CO_2H and OH. Mass spectrum *m/z* 500 (M, 0·5%), 482 (11), 456 (93), 412 (36), 372 (100), 366 (39), 353 (64), 328 (43), 249 ($^{12}C_{15}{}^{1}H_{21}{}^{16}O_3$, 64%), 165 (79), 150 (31), and 124 (43%). Comparative t.l.c. in three independent solvent systems[20] confirmed that this compound was present in the lichen *Micarea prasina* Fr. (chemical race B).[3]

4-(2-Carboxy-3-heptyl-5-methoxyphenoxy)-2-heptyl-6-hydroxy-3-methoxybenzoic Acid (Methoxymicareic Acid) (27)

Hydrolysis of dimethyl methoxymicareate (26) (0·75 g) in the manner described above yielded *methoxymicareic acid* (27) (0·6 g, 84%) which crystallized from dichloromethane/cyclohexane in colourless needles, m.p. 134–136° (Found: C, 67·7; H, 8·2. $C_{30}H_{42}O_8$ requires C, 67·9; H, 8·0%). ^{1}H n.m.r. (CD_3COCD_3) δ 0·88, bt, CH_2CH_3; 1·33, m, CH_2; 2·77, 3·07, 2bt, $ArCH_2$; 3·81, s, OMe; 6·15, s, H5; 6·49, 6·78, 2d, *J* 2·4 Hz, H4′,6′; 8·78, vb, CO_2H, OH. Mass spectrum *m/z* 530 (M, 1%), 486 ($^{12}C_{29}{}^{1}H_{42}{}^{16}O_6$, 32), 480 (13), 456 (9), 452 (13), 442 (7), 424 (8), 249 (28), 248 (100), 218 (12), 206 (29), 203 (33), 190 (16), 175 (12), 133 (26), 121 (22). Comparative t.l.c. in

three independent solvent systems[20] confirmed that this acid occurred in the lichen *Micarea prasina* Fr. (chemical race A).[3]

Smiles Rearrangement of Methyl Prasinate (33)

Sodium hydride (150 mg, 50% dispersion in oil) was added to a solution of methyl prasinate (0·6 g) (33) in dry dimethylformamide (25 ml) and stirred at room temperature for 16 h. The reaction mixture was then poured into cold dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed repeatedly with water, then with saturated brine, and dried ($MgSO_4$). The solvent was evaporated and the residue applied to two silica gel plates (100 by 20 by 0·2 cm) and eluted with 30% ethyl acetate/hexane. The faster-moving band contained unchanged methyl prasinate (280 mg) and the second band yielded methyl 2-heptyl-4,6-dihydroxybenzoate (12) (40 mg) The third band yielded *2-heptyl-6-(3-heptyl-5-hydroxy-4-methoxycarbonylphenoxy)-4-methoxybenzoic acid* (48) (methyl micareate) (0·1 g, 32%) as a colourless oil (Found: $M^{+\cdot}$, 514·2940. $^{12}C_{30}{}^{1}H_{42}{}^{16}O_7$ requires $M^{+\cdot}$, 514·2931). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems.[20] ν_{max} (film) 1725, 1650 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·86, bt, CH_2CH_3; 1·30, m, CH_2; 2·60–3·00, m, $ArCH_2$; 3·71, 3·90, 2s, OMe; 6·31, s, H2′,6′; 6·35, 6·55, 2d, J 2·5 Hz, H3,5; 10·05, vb, CO_2H, OH. Mass spectrum m/z 514 (M, 1%), 43 (100). The slowest band contained 2-heptyl-6-hydroxy-4-methoxybenzoic acid (9) (40 mg).

Methylation of Methyl Micareate (48)

Methyl micareate (48) (30 mg) was methylated by treatment with methyl iodide (20 mg) and potassium hydrogen carbonate (0·2 g) in boiling acetone for 6 h. Workup in the usual manner (as described for synthesis of (30)) gave dimethyl micareate (14) (25 mg, 81%) as a colourless oil, identical in all respects with the authentic material (^1H n.m.r., mass spectrum, t.l.c.).

Methyl 6-Heptyl-4-(3-heptyl-5-methoxy-4-methoxycarbonylphenoxy)-2-oxocyclohex-3-enecarboxylate

A solution of methyl 4-chloro-6-heptyl-2-oxocyclohex-3-enecarboxylate (19) (2 g) and methyl 2-heptyl-4-hydroxy-6-methoxybenzoate (11) (1·96 g) in t-butanol (20 ml) was treated with freshly roasted potassium carbonate (1·5 g) in the manner described above for the preparation of (23). Workup in the usual way afforded *methyl 6-heptyl-4-(3-heptyl-5-methoxy-4-methoxycarbonylphenoxy)-2-oxocyclohex-3-enecarboxylate* (3 g, 79%) as a colourless oil (Found: $M^{+\cdot}$, 530·3244. $^{12}C_{31}{}^{1}H_{46}{}^{16}O_7$ requires $M^{+\cdot}$, 530·3245). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ν_{max} (film) 1730, 1640 (C=O) cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 0·86, bt, CH_2CH_3; 1·30, m, CH_2; 2·50, bt, $ArCH_2$; 2·30–3·40, m, ring CH, CH_2; 3·78, s, 2 × OMe; 3·88, s, OMe; 5·12, s, =CH; 6·40, 6·42, 2d, J 2·5 Hz, ArH. Mass spectrum m/z 530 (M, 100%).

Methyl 2-Heptyl-4-(3-heptyl-5-methoxy-4-methoxycarbonylphenoxy)-6-hydroxybenzoate

Aromatization of methyl 6-heptyl-4-(3-heptyl-5-methoxy-4-methoxycarbonylphenoxy)-2-oxocyclohex-3-enecarboxylate (2 g) in the manner described for the preparation of (24) gave *methyl 2-heptyl-4-(3-heptyl-5-methoxy-4-methoxycarbonylphenoxy)-6-hydroxybenzoate* (0·85 g, 85%) as a colourless oil (Found: $M^{+\cdot}$, 528·3090. $^{12}C_{31}{}^{1}H_{44}{}^{16}O_7$ requires $M^{+\cdot}$, 528·3087). This compound was shown to be homogeneous by t.l.c. in three independent solvent systems. ^1H n.m.r. ($CDCl_3$) δ 0·86, bt, CH_2CH_3; 1·30, m, CH_2; 2·60–2·98, m, $ArCH_2$; 3·72, s, OMe; 3·90, s, 2 × OMe; 6·20, 6·30, 2d, J 2·5 Hz, H3,5; 6·50, s, H2′,6′; 11·80, s, bonded OH. Mass spectrum m/z 528 (M, 100%).

Note: The intramolecularly hydrogen bonded hydroxyl group observed in this compound confirmed the structure of the starting material, methyl 4-chloro-6-heptyl-2-oxocyclohex-3-enecarboxylate (19).

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