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The Synthesis of Notatic Acid and 4-*O*-Methylhypoprotocetraric Acid*

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Abstract

The total synthesis of the depsidones, notatic acid (1′-carboxy-2′-hydroxy-4-methoxy-3,6,6′-trimethyldepsidone) and 4-*O*-methylhypoprotocetraric acid (1′-carboxy-2′-hydroxy-4-methoxy-3,3′,6,6′-tetramethyldepsidone) is reported.

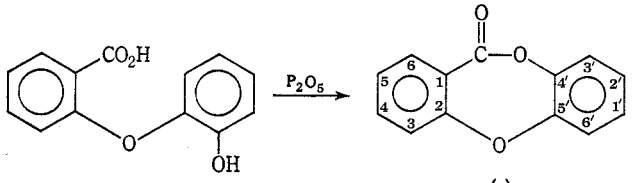
Introduction

Depsidone (11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-one) (1) is the parent compound of the depsidones, the second largest group of lichen metabolites.[1–3] Although there are about thirty known naturally occurring depsidones, up to the present time only one such compound has been synthesized chemically.[4,5] Despite the fact that the depsidone ring system can readily be synthesized[6–8] (Scheme 1) the preparation of the natural derivatives is complicated by the number of reactive functional groups. Biogenetically depsidones are believed to be derived by intramolecular oxidative coupling of a depside [i.e. (2) → (3)] or oxidative coupling without participation of the free depside intermediate.[9]

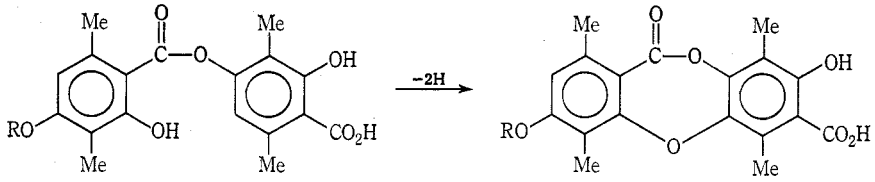
The first reported synthesis of diploicin (4)[4] utilized activated manganese dioxide to effect such an intramolecular oxidative coupling (Scheme 2) but, unfortunately, the details of this process have not been published. Moreover the generality and efficacy

* A preliminary communication describing a portion of this work has been published (*J. Chem. Soc., Chem. Commun.*, 1975, 276).

[1] Asahina, Y., and Shibata, S., 'Chemistry of Lichen Substances' (Japanese Society for Promotion of Science: Tokyo 1954).
[2] Dean, F. M., 'Naturally Occurring Oxygen Ring Compounds' Ch. 30 (Butterworths: London 1963).
[3] Culberson, C. F., 'Chemical and Botanical Guide to Lichen Products' (University of North Carolina Press: Chapel Hill 1969); Supplement to 'Chemical and Botanical Guide to Lichen Products' *Bryologist*, 1970, **73**, 177–377.
[4] Brown, C. J., Clark, D. E., Ollis, W. D., and Veal, P. L., *Proc. Chem. Soc.*, 1960, 393.
[5] Hendrickson, J. B., Ramsay, M. V., and Kelly, T. R., *J. Amer. Chem. Soc.*, 1972, **94**, 6834.
[6] Neelakantan, S., Padmasani, R., and Seshadri, T. R., *Curr. Sci.*, 1964, **33**, 365.
[7] Tomita, M., Inubuse, Y., and Kusuda, F., *Yakugaku Zasshi*, 1944, **64**, 173 (*Chem. Abstr.*, 1951, **45**, 6173b).
[8] Noyce, D. S., and Weldon, J. W., *J. Amer. Chem. Soc.*, 1952, **74**, 401, 5144.
[9] Mosbach, K., in 'The Lichens' (Eds V. Ahmadjian and M. E. Hale) (Academic Press: New York 1973).



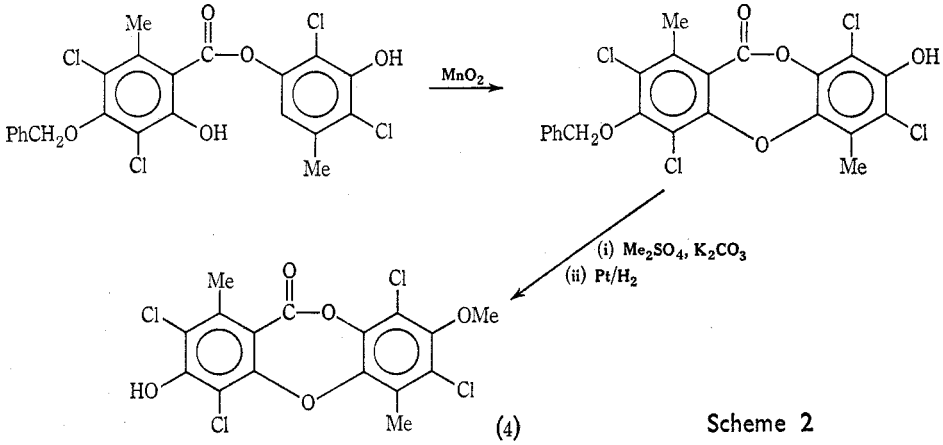
(1)



(2) R = H
(10) R = Me

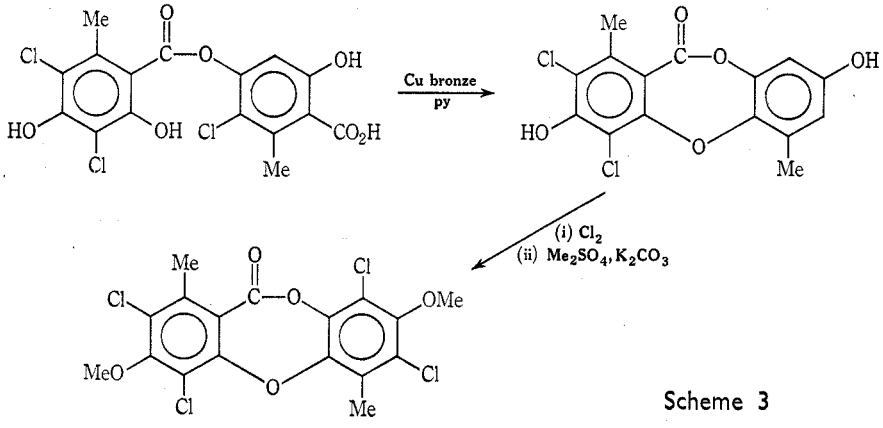
(3) R = H
(5) R = Me

Scheme 1



(4)

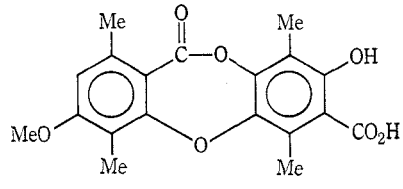
Scheme 2



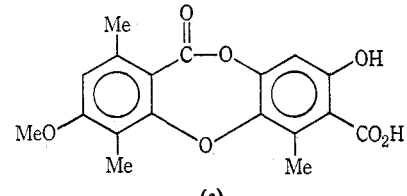
Scheme 3

of this seven-membered ring closure process have been questioned.[5] Seshadri and coworkers[6] encountered considerable difficulties when they investigated an alternative chemical route to achieve this cyclization and only traces of product could be identified (Scheme 3). Again full experimental details were not published.

In 1968 Hendrickson and Ramsay[5,10] reported a much more elegant route to diploicin, which utilized the solvolytic cleavage of a grisan in the key step. However, this method had only limited applicability since the critical phenolic oxidation was only successful for highly halogenated intermediates. We have endeavoured to develop a more general route to these compounds and have concentrated our efforts on the synthesis of 4-*O*-methylhypoprotocetraric acid (5) and notatic acid (6), two new depsidones we recently isolated from *Parmelia notata* Kurok.[11,12]



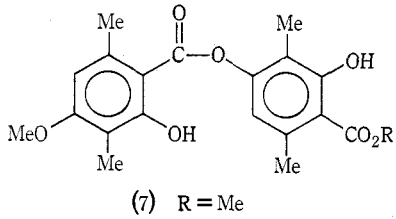
(5)



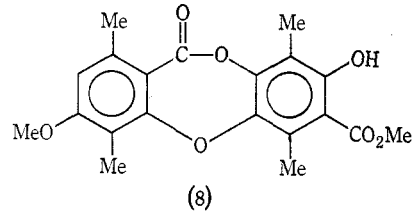
(6)

Discussion

Three basic synthetic routes to depsidones were investigated. Initially we attempted to effect the intramolecular oxidation of methyl barbatate (7) with a variety of oxidizing agents including activated manganese dioxide, alkaline potassium ferricyanide, potassium permanganate, lead dioxide and tris(acetylacetonato)manganese(III). No traces of methyl 4-*O*-methylhypoprotocetrarate (8) could be detected in these reaction mixtures.



(7) R = Me
(24) R = $PhCH_2$



(8)

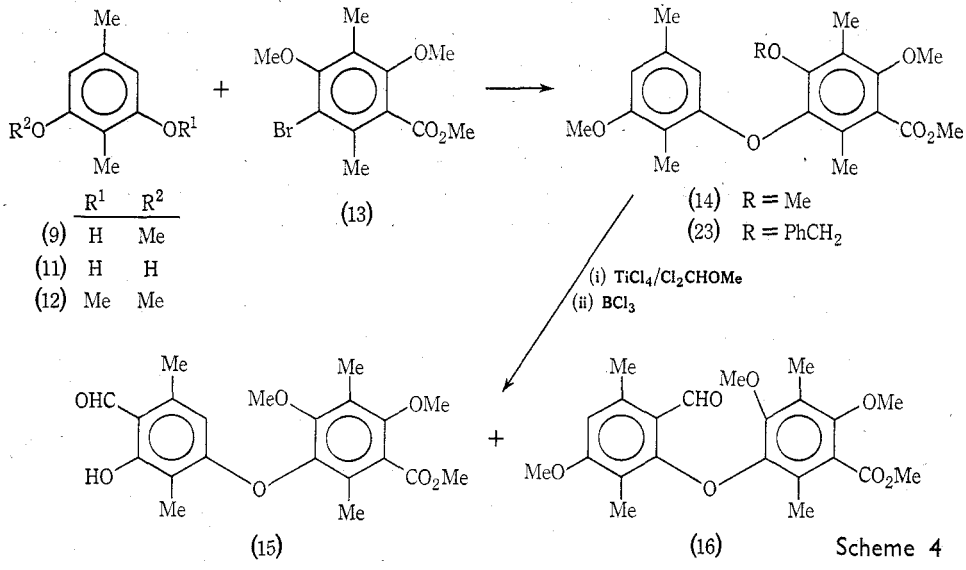
Subsequently we have attempted to modify and improve Seshadri's route[6] to these compounds through the corresponding bromo depsides. Although this method proved successful in the synthesis of 4-*O*-methylhypoprotocetraric acid (5), the key Ullmann cyclization failed in a variety of other instances.

In the third alternative method we utilized an Ullmann diphenyl ether synthesis and then modified the ether so obtained by the selective introduction and conversion of substituents. Such a route eventually yielded notatic acid (6).

[10] Hendrickson, J. B., and Ramsay, M. V., *Chem. Commun.*, 1968, 1101.
[11] Kurokawa, S., Elix, J. A., Watson, P. L., and Sargent, M. V., *J. Jap. Bot.*, 1971, **46**, 33.
[12] Cresp, T. M., Elix, J. A., Kurokawa, S., and Sargent, M. V., *Aust. J. Chem.*, 1972, **25**, 2167.

Synthetic Approaches to 4-O-Methylhypoprotocetraric Acid (5)

To test whether the Ullmann approach to hypoprotocetraric acid was viable we undertook the sequence of reactions outlined in Scheme 4.



	R^1	R^2
(9)	H	Me
(11)	H	H
(12)	Me	Me

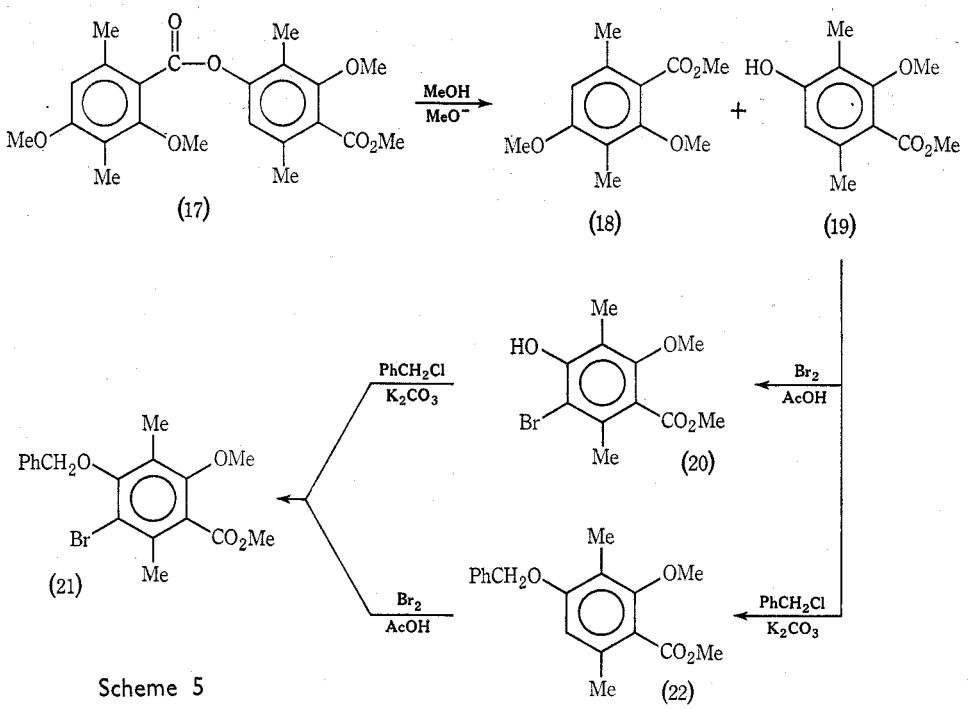
Scheme 4

3-Methoxy-2,5-dimethylphenol (9) had previously been synthesized by a multistep procedure from *p*-xylenol,[13] but we utilized natural barbatic acid (10) as a convenient precursor to this compound. Alkaline hydrolysis of barbatic acid yielded a mixture of 3-methoxy-2,5-dimethylphenol (9) and 2,5-dimethylresorcinol (11) which could be separated chromatographically. Alternatively this mixture of phenols could be fully methylated to give 1,3-dimethoxy-2,5-dimethylbenzene (12), and then this compound selectively demethylated with sodium thioethoxide in dimethylformamide[14] to yield the required phenol (9). The Ullmann reaction of (9) with 5-bromo-2,4-dimethoxy-3,6-dimethylbenzoate[12] (13) led to the formation of methyl 2,4-dimethoxy-5-(3′-methoxy-2′,4′-dimethylphenoxy)-3,6-dimethylbenzoate (14) and formylation of this compound followed by selective demethylation[15] with boron trichloride yielded a mixture of the aldehydes (15) and (16). The success of this reaction sequence suggested that by suitable protection of the substituents such a scheme could possibly lead to the synthesis of 4-*O*-methylhypoprotocetraric acid (5).

Hence barbatic acid was permethylated to yield methyl 2,2′,4-tri-*O*-methylbarbatate (17) and subsequent methanolysis of this compound gave a readily separable mixture of methyl 2,4-dimethoxy-3,6-dimethylbenzoate (18) and methyl 4-hydroxy-2-methoxy-3,6-dimethylbenzoate (19) (Scheme 5). The latter compound has previously been obtained by a lengthy total synthesis from methyl 2,4-dihydroxy-3,6-dimethylbenzoate.[16] Bromination of the phenol (19) with bromine in acetic acid, followed by treatment of the derived methyl 5-bromo-4-hydroxy-2-methoxy-3,6-dimethylbenzoate

[13] Sonn, A., *Ber. Deut. Chem. Ges.*, 1916, **49**, 2589.
[14] Feutrill, G. I., and Mirrington, R. N., *Aust. J. Chem.*, 1972, **25**, 2167.
[15] Dean, F. M., Goodchild, J., Houghton, L. E., Martin, J. A., Morton, R. B., Parton, B., Price, A. W., and Somvichein, N., *Tetrahedron Lett.*, 1966, 4153.
[16] Robertson, A., and Stephenson, R. J., *J. Chem. Soc.*, 1932, 1675.

(20) with benzyl chloride and potassium carbonate in dimethylformamide solution readily yielded methyl 4-benzyloxy-5-bromo-2-methoxy-3,6-dimethylbenzoate (21) in high yield. Alternatively methyl 4-hydroxy-2-methoxy-3,6-dimethylbenzoate (19) could be benzylated initially to form methyl 4-benzyloxy-2-methoxy-3,6-dimethylbenzoate (22) and subsequently brominated to form the bromo ester (21).



(17) (18) (19) (20) (21) (22)

Scheme 5

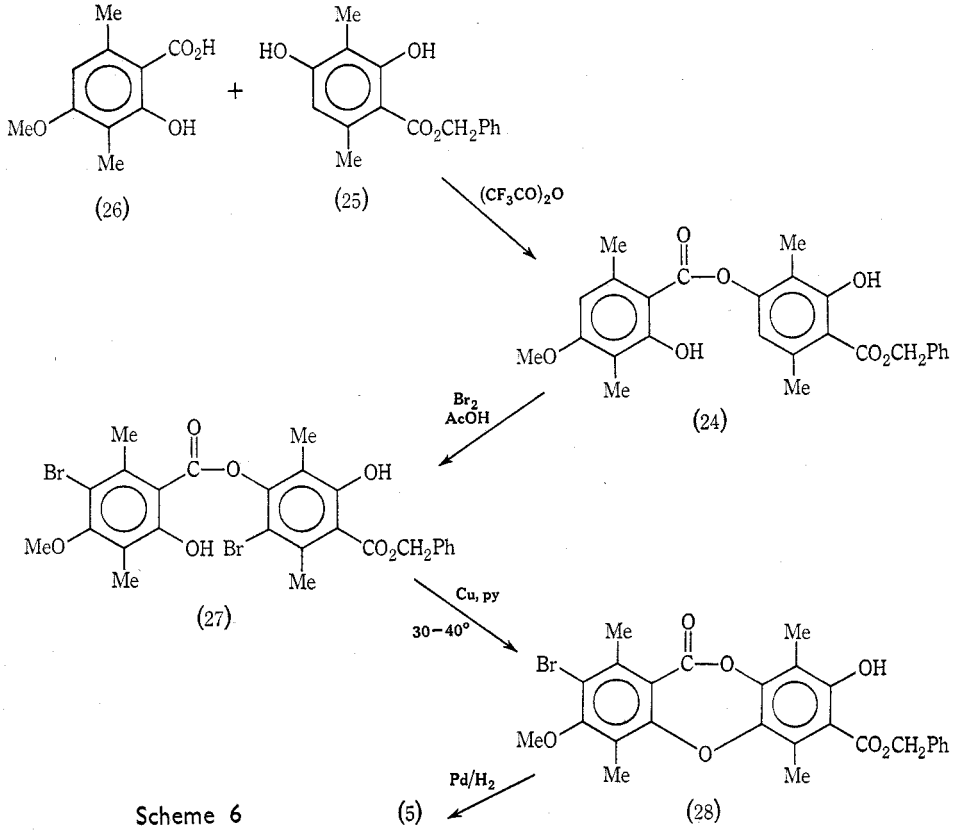
The Ullmann reaction of the bromo ester (21) with 3-methoxy-2,5-dimethylphenol (9) produced methyl 4-benzyloxy-6-methoxy-3-(3′-methoxy-2′,5′-dimethylphenoxy)-2,5-dimethylbenzoate (23) in 11% yield. However, after formylation and attempted demethylation of this diphenyl ether, the desired aldehyde could not be isolated. The fact that this formylation was carried out at room temperature probably effected debenzylation of this ether and hence consequent complications.

Following the failure of this route to 4-*O*-methylhypoprotocetraric acid (5) we investigated Seshadri's method[6] of depsidone synthesis as a route to this compound. Previously we have described the synthesis of benzyl barbatate (24) by the condensation of benzyl 2,4-dihydroxy-3,6-dimethylbenzoate (25) and rhizonic acid (26) in the presence of trifluoroacetic anhydride.[17] Bromination of this ester with bromine in glacial acetic acid gave the corresponding dibromo compound, benzyl 5,5′-dibromobarbatate (27). This compound was cyclized by treatment with copper bronze in pyridine at 30–40° to give benzyl 5-bromo-4-*O*-methylhypoprotocetrarate (28) in 13% yield. Treatment of the bromo depsidone (28) with palladized carbon and hydrogen ultimately yielded 4-*O*-methylhypoprotocetraric acid (5) (Scheme 6). This synthetic material was shown to be identical with the natural metabolite.

[17] Elix, J. A., and Norfolk, S., *Aust. J. Chem.*, 1975, **28**, 1113.

Synthetic Approaches to Notatic Acid (6)

Following the success of the above route to 4-*O*-methylhypoprotocetraric acid (5), we attempted an analogous synthesis of notatic acid (6). Thus bromination of methyl 2,4-dibenzyloxy-6-methylbenzoate (29)[18] with bromine in acetic acid yielded methyl 2,4-dibenzyloxy-5-bromo-6-methylbenzoate (30). The structure of the latter compound was confirmed by hydrogenolysis of the *O*-benzyl groups and methylation of the phenol obtained to give the known ester, methyl 5-bromo-2,4-dimethoxy-6-methylbenzoate.[19] Transesterification of the methyl ester (30) by treatment with sodium benzyloxide in benzyl alcohol led to the formation of benzyl 2,4-dibenzyloxy-6-methylbenzoate (31). Subsequent hydrogenolysis of this ester followed by benzylation of the crude acid produced with phenyldiazomethane yielded benzyl 5-bromo-2,4-dihydroxy-6-methylbenzoate (32) (Scheme 7).

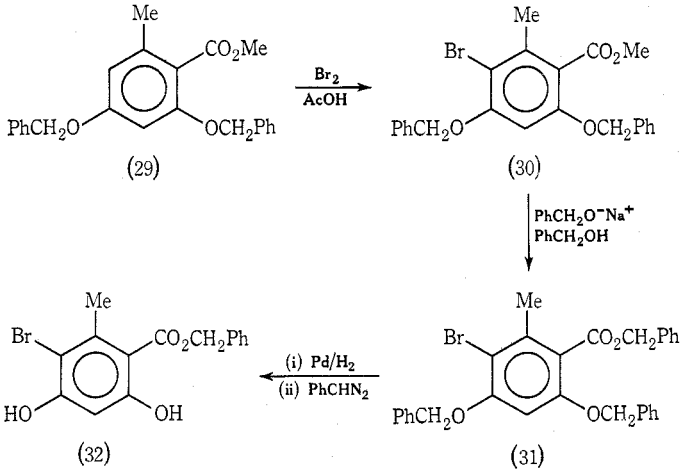


Scheme 6

Condensation of rhizonic acid (26) with benzyl 5-bromo-2,4-dihydroxy-6-methylbenzoate (32) in the presence of trifluoroacetic anhydride then yielded benzyl 5′-bromoobtusatate (33). However, after treatment of this compound with copper bronze in pyridine, no trace of the required cyclized product could be detected. A

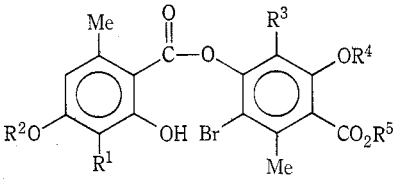
[18] Jayalakshmi, V., Neelakantan, S., and Seshadri, T. R., *Indian J. Chem.*, 1969, **7**, 56.
[19] Cannon, J. R., Cresp, T. M., Metcalf, B. W., Sargent, M. V., Vinciguerra, G., and Elix, J. A., *J. Chem. Soc., C*, 1971, 3495.

variety of other bromodepsides, (34)–(37), also failed to cyclize under these reaction conditions.[20]

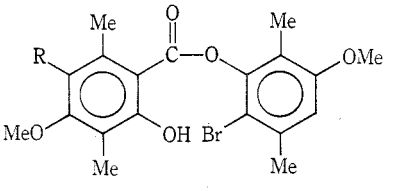


Scheme 7

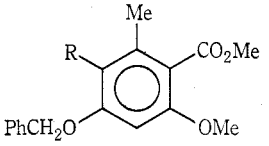
Following this setback we reverted to the alternative Ullmann route for the synthesis of notatic acid (6). Thus bromination of methyl 4-benzyloxy-2-methoxy-6-methylbenzoate (38) with bromine in acetic acid gave methyl 4-benzyloxy-3-bromo-6-



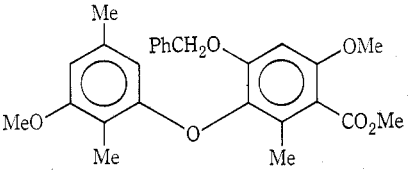
	R^1	R^2	R^3	R^4	R^5
(33)	Me	Me	H	H	CH_2Ph
(36)	H	CH_2Ph	H	Me	Me
(37)	CHO	H	Me	H	CH_2Ph



(34) R = H
(35) R = Cl



(38) R = H
(39) R = Br

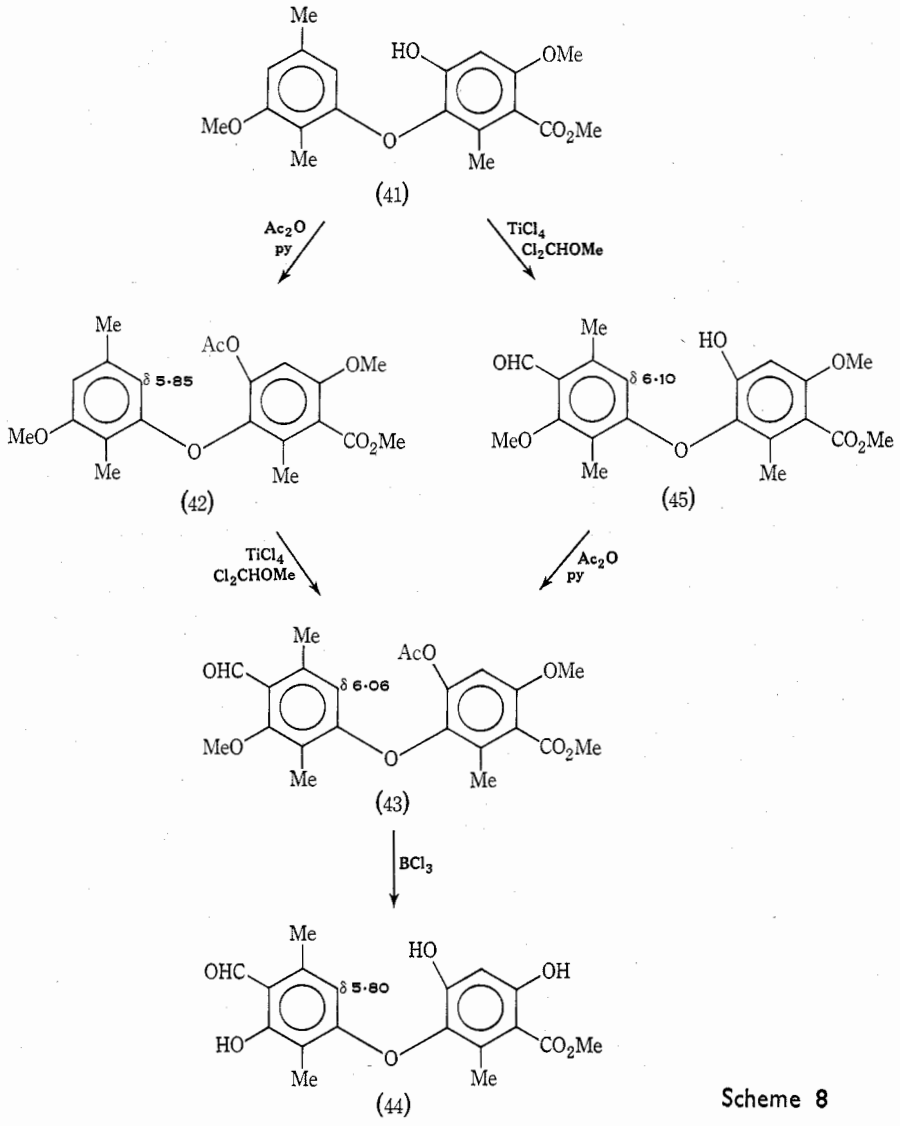


(40)

methoxy-2-methylbenzoate (39). The structure of this bromo compound was confirmed by subsequent hydrogenolysis followed by methylation, whereby it was converted into the known ester, methyl 5-bromo-2,4-dimethoxy-6-methylbenzoate.[19] The

[20] Elix, J. A., and Sargent, M. V., unpublished data.

Ullmann reaction of the bromo ester (39) and 3-methoxy-2,5-dimethylphenol (9) proved particularly troublesome under a variety of standard conditions. However, by modifying the procedure of Tomita and coworkers[21] so that the pyridine solvent is slowly removed from the reaction mixture, a 38% yield of methyl 4-benzyloxy-6-methoxy-3-(3′-methoxy-2′,5′-dimethoxyphenoxy)-2-methylbenzoate (40) could be



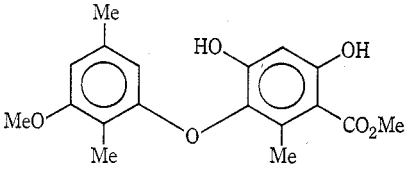
Scheme 8

obtained. This diphenyl ether was then treated with palladized carbon and hydrogen, to give the corresponding phenol (41) (Scheme 8). Formylation of the corresponding acetate (42) with dichloromethyl methyl ether and titanium tetrachloride gave only one aldehyde, methyl 4-acetoxy-3-(4′-formyl-3′-methoxy-2′,5′-dimethylphenoxy)-6-methoxy-2-methylbenzoate (43). The structure of this compound was deduced by the

[21] Tomita, M., Fujitani, K., and Aoyagi, Y., *Chem. Pharm. Bull.*, 1965, **13**, 1341.

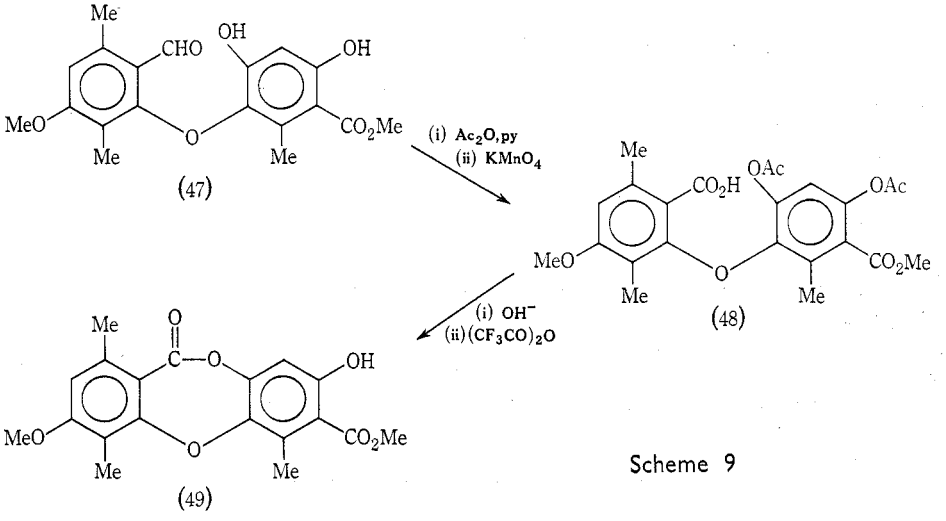
fact that selective demethylation with boron trichloride (which is effective in removing alkoxy groups adjacent to a carbonyl functionality) produced the trihydric phenol (44), in which two of the phenolic protons were engaged in intramolecular hydrogen-bonding (from the p.m.r. spectrum). Furthermore the diphenyl ether (42) adopted an H-inside conformation[22–26] as indicated by the presence of a highly shielded aromatic proton in the p.m.r. spectrum of this compound (Scheme 8). Such a proton was also present in the aldehydes (43) and (44) thus confirming formylation had not taken place in this position.

Similarly, formylation of the phenol (41) gave only the 4′-formyl compound (45), since on acetylation this produced the compound (43). In marked contrast, formylation of the 4-benzyloxy compound (40) at −70°, followed by demethylation with boron trichloride, produced the dihydric phenol (46) and a mixture of two aldehydes, methyl 3-(6′-formyl-3′-methoxy-2′,5′-dimethylphenoxy)-4,6-dihydroxy-2-methylbenzoate (47) and the corresponding 4′-formyl compound (44).



(46)

Subsequent acetylation of the aldehyde (47) followed by oxidation with potassium permanganate gave the intermediate carboxylic acid (48). Then hydrolytic removal of the acetoxy groups of (48) followed by cyclization with trifluoroacetic anhydride produced methyl notatate (49). This ester was successfully hydrolysed by treatment



Scheme 9

[22] Jackman, D. A., Sargent, M. V., and Elix, J. A., *J. Chem. Soc. Perkin Trans. 1*, 1975, in press.
[23] Bergmann, J. J., Griffith, E. A. H., Robertson, B. E., and Chandler, W. D., *Can. J. Chem.*, 1973, **51**, 162.
[24] Bergmann, J. J., and Chandler, W. D., *Can. J. Chem.*, 1972, **50**, 353.
[25] Bergmann, J. J., Chandler, W. D., and Moir, R. Y., *Can. J. Chem.*, 1971, **49**, 223.
[26] Chandler, W. D., Smith, W. M., and Moir, R. Y., *Can. J. Chem.*, 1964, **42**, 2549.

with potassium hydroxide in aqueous dimethyl sulphoxide at 0–5°. The crude acid so obtained was recyclized by treatment with trifluoroacetic anhydride to yield notatic acid (6), identical with the natural material (Scheme 9).

Experimental

P.m.r. spectra were recorded at 60 MHz on a Varian A-60-A instrument, at 90 MHz on a Bruker HX-90 spectrometer or at 100 MHz on a Jeol JNM-MH-100 spectrometer, and chemical shifts were measured on the δ scale relative to tetramethylsilane as an internal standard. Mass spectra were determined on a Varian MAT CH7 instrument operating at 70 eV. Melting points are uncorrected. Microanalyses were carried out by the A.N.U. Microanalytical Laboratory under the direction of Dr J. E. Fildes and Miss B. Stevenson. Preparative layer chromatograms were carried out on thick-layer plates (20 by 20 by 0·1 cm) with silica gel (Merck GF_{254}) as adsorbent. Bands were detected by exposure to short-wavelength ultraviolet light. Column chromatography utilized silica gel (B.D.H 60–120 mesh) as absorbent and all organic extracts were dried over Na_2SO_4. Light petroleum refers to that fraction boiling between 58 and 65°.

Methyl Barbatate (7)

Barbatic acid (10) was treated with diazomethane after the manner of Robertson and Stephenson.[16] The ester formed blades (from dichloromethane/light petroleum), m.p. 166–168° (lit.[16] 170°). P.m.r. ($CDCl_3$) δ 2·10 (6H, s, 2× Me), 2·53 and 2·69 (each 3H, s, Me), 3·89 and 3·97 (each 3H, s, OMe), 6·37 and 6·53 (each 1H, s, ArH), 11·54 and 12·00 (each 1H, s, OH).

Attempted Oxidation of Methyl Barbatate

Methyl barbatate (7) (200 mg) in an appropriate solvent was treated with the oxidizing reagent and subsequently worked up in the usual manner (Table 1). The crude 'product' was then adsorbed on a thick-layer plate and eluted with 30% ethyl acetate/light petroleum. In all instances only unchanged methyl barbatate (together with mononuclear hydrolysis products in several cases) could be isolated. No trace of methyl 4-*O*-methylhypoprotocetrarate[12] was obtained.

Table 1. Attempted oxidation of methyl barbatate

All reactions under nitrogen

Solvent	Oxidizing reagent	Time (h)	Conditions
Chloroform	activated MnO_2 [A]	24	reflux
Chloroform	activated MnO_2 [B]	24	reflux
Chloroform	B.D.H. MnO_2 (precipitated)	24	reflux
Chloroform	Ajax MnO_2 (technical)	24	reflux
Chloroform	May & Baker MnO_2 (lot 80658)	24	reflux
Chloroform	B.D.H. PbO_2	24	reflux
Chloroform	HgO (yellow)	24	reflux
Aqueous K_2CO_3 (5%)	$K_3Fe(CN)_6$	4	15–20°
Dioxan	2,3-dichloro-5,6-dicyano-*p*-benzoquinone	20	reflux
Aqueous acetone (10%)	$KMnO_4$	15	15–20°
Carbon disulphide	tris(acetylacetonato)manganese(III)	26	reflux
Benzene	$VOCl_3$	24	reflux

[A] Attenburrow, J., Cameron, A. F. B., Chapman, J. H., Evans, R. M., Hems, B. A., Jensen, A. B. A., and Walker, T., *J. Chem. Soc.*, 1952, 1094.
[B] Harnfeist, M., Bavely, A., and Lazier, W. A., *J. Org. Chem.*, 1954, **19**, 1608.

3-Methoxy-2,5-dimethylphenol (9) *by Degradation of Barbatic Acid* (10)

(i) Crude barbatic acid (22·0 g), from the lichen *Siphula coriacea*, was heated under reflux with sodium hydroxide (15 g) and water (150 ml) for 5 h and then acidified with concentrated hydrochloric

acid whilst still hot. The suspension was extracted exhaustively with ethyl acetate and the extract was washed in turn with saturated sodium hydrogen carbonate solution and with water and dried. The crude product was chromatographed over silica gel with 15–25% ethyl acetate/light petroleum as eluent. This gave firstly 3-methoxy-2,5-dimethylphenol (7·0 g) (9) as blades (from light petroleum), m.p. 64–65·5° (lit.[27] 67·5–68°). P.m.r. (CCl_4) δ 2·00 and 2·25 (each 3H, s, Me), 3·76 (3H, s, OMe), 4·65 (1H, s, OH), and 6·15 (2H, s, ArH); mass spectrum *m/e* 152 (M^+). Further elution gave 1,3-dihydroxy-2,5-dimethylbenzene (β-orcinol) (11) (4·8 g) as needles (from ether/light petroleum), m.p. 161° (lit.[28] 163°); p.m.r. ($(CD_3)_2SO$) δ 1·92 and 2·10 (each 3H, s, Me), 6·12 (2H, s, ArH), and 8·82 (2H, s, OH); mass spectrum *m/e* 138 (M^+).

(ii) Crude barbatic acid (200 g) was treated with sodium hydroxide as before and the crude product was methylated in the usual way with methyl sulphate and potassium carbonate in acetone. The crude product was distilled under diminished pressure and the fraction of b.p. 108–118°/9 mm was crystallized from cold pentane and afforded prisms (137 g), m.p. 46–47° (lit.[29] 49–50°) of 1,3-dimethoxy-2,5-dimethylbenzene (12). P.m.r. (CCl_4) δ 1·99 and 2·29 (each 3H, s, Me), 3·72 (6H, s, 2×OMe), 6·24 (2H, s, ArH). This was selectively demethylated by the method of Feutrill and Mirrington.[14] Ethanethiol (100 g) in dry dimethylformamide (250 ml) was added to a suspension of sodium hydride (73·5 g of a 50% dispersion in oil) in dry dimethylformamide (500 ml) under dry nitrogen. The solution was then stirred for 45 min and the dimethoxy compound (12) (100 g) in dimethylformamide (100 ml) was added. The solution was then stirred and heated under reflux for 3 h. The cooled solution was acidified with dilute hydrochloric acid and extracted with ether. The ether layer was extracted with 5% aqueous sodium hydroxide and the alkaline extracts were acidified and extracted with ether. The extract was washed with water and saturated brine. The crude product was purified by steam distillation and then crystallized from light petroleum when it formed blades (82·1 g, 91%) of the phenol (9), m.p. 64–65·5°.

Methyl 2,4-Dimethoxy-5-(3′-methoxy-2′,4′-dimethylphenoxy)-3,6-dimethylbenzoate (14)

Methyl 5-bromo-2,4-dimethoxy-3,6-dimethylbenzoate[15] (13) (2·0 g), the foregoing phenol (9) (0·92 g), and finely divided potassium carbonate (2 g) in dry pyridine (15 ml) under dry nitrogen were stirred and heated to 130° (bath); copper(II) oxide[21] (0·3 g) was then added and the mixture was stirred for 24 h at 150° (bath). The cooled mixture was diluted with ether and filtered through kieselguhr. The filtrate was washed in turn with dilute hydrochloric acid, dilute sodium hydroxide solution, water and saturated brine. The crude product was preadsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel (total 3·5 by 40 cm) with 2·5% (8 l.) and then 5% ethyl acetate/light petroleum as eluent; 200-ml fractions were collected. Fractions 43–61 gave the diaryl ether (14) (390 mg, 17%) which crystallized from methanol as *prisms*, m.p. 117–118° (Found: C, 67·6; H, 7·1. $C_{21}H_{26}O_8$ requires C, 67·4; H, 7·0%). P.m.r. ($CDCl_3$) δ 2·05 (3H, s, Me), 2·18 (6H, s, 2×Me), 2·25 (3H, s, Me), 3·68 (3H, s, OMe), 3·77 (6H, s, 2×OMe), 3·85 (3H, s, OMe), 5·80 (1H, br s, H2′), and 6·32 (1H, br s, H4′); mass spectrum *m/e* 374 (M^+).

Formylation and Subsequent Selective Demethylation of Diaryl Ether (14)

The foregoing diaryl ether (160·4 mg) and dichloromethyl methyl ether (0·25 ml) in dry dichloromethane (3 ml) were stirred and treated slowly at 0° by dropwise addition of titanium(IV) chloride (0·44 ml) in dry dichloromethane (3 ml). The mixture was stirred at 0° for 15 min and then at room temperature for 15 min. The mixture was poured into ice-water and extracted with ether; the extracts were washed with saturated sodium hydrogen carbonate solution and with water. The crude product in dichloromethane (30 ml) was treated at −10° with an excess of boron trichloride for 15 min with stirring. The mixture was poured into ice-water and extracted with ether. The extract was washed with water and with saturated brine. The crude product was applied to two layer plates which were developed with 5% ethyl acetate/light petroleum. The faster band yielded *methyl 5-(4′-formyl-3′-hydroxy-2′,5′-dimethylphenoxy)-2-hydroxy-4-methoxy-3,6-dimethylbenzoate* (15) (65·1 mg, 38%) as blades (from dichloromethane/light petroleum), m.p. 178–179° (Found: C, 64·1; H, 5·8. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%). P.m.r. ($CDCl_3$) δ 2·23 (3H, s, Me), 2·37 (6H, s, 2×Me), 2·47 (3H, s

[27] Pfau, A. St., *Helv. Chim. Acta*, 1928, **11**, 864.
[28] Kostanecki, St. von, *Ber. Deut. Chem. Ges.*, 1886, **19**, 1238.
[29] Ridley, D. D., Ritchie, E., and Taylor, W. C., *Aust. J. Chem.*, 1968, **21**, 2979.

Me), 3·81 and 4·03 (each 3H, s, OMe), 5·77 (1H, s, H 6′), 10·17 (1H, s, CHO), 11·70 and 12·85 (each 1H, s, D_2O exchangeable OH); mass spectrum *m/e* 374 (M^+). The slower band yielded *methyl 5-(2′-formyl-5′-methoxy-3′,6′-dimethylphenoxy)-2-hydroxy-4-methoxy-3,6-dimethylbenzoate* (16) (58·6 mg, 33%) as blades (from methanol), m.p. 134–136° (Found: C, 64·9; H, 6·3. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%). P.m.r. ($CDCl_3$) δ 1·73, 2·05, 2·51 and 2·53 (each 3H, s, Me), 3·27, 3·83 and 3·95 (each 3H, s, OMe), 6·40 (1H, s, H 4′), 10·41 (1H, s, CHO), 11·31 (1H, s, D_2O exchangeable OH).

Methanolysis of Methyl Di-O-methylbarbatate (17)

Methyl di-*O*-methylbarbatate (17) was obtained as described previously.[12] It formed prisms from light petroleum, m.p. 101–102° (lit.[30] 106–107°). P.m.r. ($CDCl_3$) δ 2·15, 2·22, 2·30 and 2·47 (each 3H, s, Me), 3·80 (3H, s, OMe), 3·83 (6H, s, 2 × OMe), 3·91 (3H, s, OMe), and 6·53 and 6·83 (each 1H, s, ArH). The depside (70·1 g) in warm dry methanol (300 ml) was added under dry nitrogen to a stirred solution of potassium hydroxide in dry methanol (300 ml) and the mixture was heated under gentle reflux for 3 h and then poured into ice-water. The suspension was extracted exhaustively with ether and the extract was washed with water and with saturated brine. This crude product (33·5 g) was distilled under reduced pressure and gave methyl 2,4-dimethoxy-3,6-dimethylbenzoate (18) as an oil, b.p. 112–114°/0·15 mm (lit.[27] 161–163°/12 mm). A sample on keeping for 2 years slowly crystallized. It formed prisms (from light petroleum), m.p. 42–43°. The aqueous layer was acidified and extracted with ethyl acetate. The extract was washed with water and with saturated brine. This gave methyl 4-hydroxy-2-methoxy-3,6-dimethylbenzoate (methyl isorhizonate) (19) (33·4 g), as needles (from light petroleum), m.p. 144° (lit.[30] 146°). P.m.r. ($CDCl_3$) δ 2·10 and 2·18 (each 3H, s, Me), 3·73 and 3·88 (each 3H, s, OMe), 6·25 (1H, b, OH), and 6·35 (1H, s, ArH); mass spectrum *m/e* 210 (M^+).

Methyl 4-Benzyloxy-2-methoxy-3,6-dimethylbenzoate (22)

Methyl isorhizonate (7·3 g), dry potassium carbonate (15 g) and benzyl chloride (4·6 g) were stirred at 70° (bath) in dry dimethylformamide (60 ml) for 12 h. The mixture was poured into cold dilute hydrochloric acid and extracted with ether. The extract was washed with water and with saturated brine. The *product* (22) crystallized from light petroleum as prisms (10·1 g, 97%), m.p. 73–74° (Found: C, 71·8; H, 6·7. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%). P.m.r. (CCl_4) δ 2·01 and 2·22 (each 3H, s, Me), 3·70 and 3·80 (each 3H, s, OMe), 4·99 (2H, s, CH_2), 6·43 (1H, s, H 5) and 7·32 (5H, s, ArH); mass spectrum *m/e* 300 (M^+).

Methyl 3-Bromo-4-hydroxy-6-methoxy-2,5-dimethylbenzoate (20)

Bromine (6·3 g) in acetic acid (25 ml) was added over 15 min with stirring and ice-cooling to a mixture of methyl isorhizonate (8·3 g) and anhydrous sodium acetate (6 g) in acetic acid (40 ml). After stirring for a further 5 min at room temperature the mixture was poured into water containing a little sodium metabisulphite and the precipitate was extracted into ether. The extract was washed exhaustively with saturated sodium hydrogen carbonate solution and with water and with saturated brine. The crude product crystallized from light petroleum as blades (10·0 g, 88%) of the *bromo compound* (20), m.p. 69–71° (Found: C, 45·9; H, 4·7; Br, 27·3. $C_{11}H_{13}BrO_4$ requires C, 45·7; H, 4·5; Br, 27·6%). P.m.r. ($CDCl_3$) δ 2·20 and 2·33 (each 3H, s, Me), 3·75 and 3·90 (each 3H, s, OMe), 5·92 (1H, b, OH); mass spectrum *m/e* 288, 290 (M^+).

Methyl 3-Bromo-4-benzyloxy-6-methoxy-2,5-dimethylbenzoate (21)

(i) Bromination of the benzyl ether (22) (8·5 g), as above, gave the *bromo compound* (21) (10·2 g, 95%) as needles (from light petroleum), m.p. 50–51° (Found: C, 57·1; H, 5·0; Br, 20·8. $C_{18}H_{19}BrO_4$ requires C, 57·0; H, 5·0; Br, 21·1%). P.m.r. (CCl_4) δ 2·15 and 2·32 (each 3H, s, Me), 3·68 and 3·85 (each 3H, s, Me), 4·88 (2H, s, CH_2), 7·38 (5H, m, ArH); mass spectrum *m/e* 378, 380 (M^+).

(ii) Benzylation of the bromo phenol (20) as above gave the benzyl ether (21) (95%).

[30] Asahina, Y., and Fuzikawa, F., *Ber. Deut. Chem. Ges.*, 1932, **65**, 175.

Methyl 4-Benzyloxy-6-methoxy-3-(3′-methoxy-2′,5′-dimethylphenoxy)-2,5-dimethylbenzoate (23)

The Ullmann reaction (16 h) was performed twice, as described above, between the phenol (9) (2·04 g) and the bromo compound (21) (5·08 g) and the combined crude products were preadsorbed from dichloromethane on silica gel and chromatographed over a column of silica gel (total 4·5 by 50 cm) with 2·5% ethyl acetate/light petroleum as eluent; 200-ml fractions were collected. Fractions 63–80 yielded the product (883·5 mg) and fractions 46–62 were mixtures which on rechromatography yielded more *product* (23) (total 1·359 g, 11%) which formed prisms (from methanol), m.p. 84–85° (Found: C, 72·2; H, 6·7. $C_{27}H_{30}O_6$ requires C, 72·0; H, 6·7%). P.m.r. ($CDCl_3$) δ 2·08 and 2·22 (each 6H, bs, 2×Me), 3·77, 3·80, and 3·90 (each 3H, s, OMe), 4·93 (2H, s, CH_2), 5·87 (1H, bs, H 6′), 6·38 (1H, bs, H 4′), 7·23 (5H, s, ArH); mass spectrum *m/e* 450 (M^+).

Formylation and Subsequent Demethylation of Diaryl Ether (23)

This was carried out as described previously for methyl 2,4-dimethoxy-5-(3′-methoxy-2′,4′-dimethylphenoxy)-3,6-dimethylbenzoate (14). The desired aldehyde could not be isolated from the complex mixture of products obtained.

Benzyl 5,5′-Dibromobarbatate (27)

A solution of bromine (0·2 ml) in CCl_4 (3 ml) was added dropwise to a suspension of benzyl barbatate (24) (0·57 g) in glacial acetic acid (5 ml) with stirring. Stirring was continued for 16 h and then the solvent was evaporated under reduced pressure. The residue was crystallized from benzene/cyclohexane to afford the *product* (27) (0·71 g, 92%) as colourless prisms, m.p. 171° (Found: Br, 26·4. $C_{26}H_{24}Br_2O_7$ requires Br, 26·3%). P.m.r. ($CDCl_3$) δ 2·12, 2·24, 2·67 and 2·91 (each 3H, s, Me), 3·83 (3H, s, OMe), 5·41 (2H, s, CH_2), 7·36 (5H, s, ArH), 11·10 and 11·27 (each 1H, s, OH); mass spectrum *m/e* 608 (M^+).

Benzyl 5-Bromo-4-O-methylhypoprotocetrarate (28)

A mixture of benzyl 5,5′-dibromobarbatate (0·26 g), copper bronze (0·1 g) and anhydrous pyridine (5 ml) was stirred at 37° under anhydrous conditions for 7 days. The mixture was then filtered and the filtrate diluted with ether and washed in turn with dilute hydrochloric acid and water and then dried (Na_2SO_4). The residue obtained on evaporation of the ether was applied to a silica gel plate and eluted with 20% ethyl acetate/light petroleum (b.p. 60–80°). The faster moving band was removed, extracted and the residue crystallized from acetone/cyclohexane to give the *product* (28) (30 mg, 13%) as colourless needles, m.p. 173° (Found: C, 59·0; H, 4·5. $C_{26}H_{23}BrO_7$ requires C, 59·2; H, 4·4%). P.m.r. ($CDCl_3$) δ 2·26, 2·46, 2·55 and 2·66 (each 3H, s, Me), 3·84 (3H, s, OMe), 5·43 (2H, s, CH_2), 7·46 (5H, s, ArH), 11·54 (1H, s, OH); mass spectrum *m/e* 528 (M^+).

4-O-Methylhypoprotocetraric Acid (5)

Benzyl 5-bromo-4-*O*-methylhypoprotocetrarate (200 mg) and 10% palladium on carbon (50 mg) were suspended in glacial acetic acid (15 ml) and stirred in an atmosphere of hydrogen for 24 h. The precipitated solid was dissolved by addition of acetone and the catalyst was filtered. The filtrate was then concentrated under reduced pressure and the residue dissolved in water (10 ml) and dioxan (5 ml) containing potassium hydrogen carbonate (160 mg). Palladium on carbon (10%; 25 mg) was then added and the suspension stirred in a hydrogen atmosphere for 2 h. The catalyst was filtered and the filtrate acidified with cold, dilute hydrochloric acid. The precipitated acid was filtered, air-dried and crystallized from dimethylformamide to give 4-*O*-methylhypoprotocetraric acid (5) (120 mg, 88%) as colourless needles, m.p. 228–229° (dec.) alone or admixed with a portion of the natural material. The p.m.r. and mass spectra of the two samples were identical.[12]

Methyl 2,4-Dibenzyloxy-6-methylbenzoate (29)

Methyl orsellinate[31] (15·0 g), benzyl chloride (42·0 g) and potassium carbonate (45·5 g) in acetone (200 ml) were stirred and boiled under reflux for 60 h. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and then subjected

[31] Sargent, M. V., Vogel, P., and Elix, J. A., *J. Chem. Soc., Perkin Trans 1*, 1975, in press.

to steam distillation to remove the excess of benzyl chloride. The dried residue was crystallized from ether/light petroleum and afforded prisms (25·0 g, 85%) of the *orsellinate*, m.p. 67–68° (Found: C, 76·3; H, 6·2. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%). P.m.r. ($CDCl_3$) δ 2·30 (3H, s, Me), 3·85 (3H, s, OMe), 4·97 and 5·00 (each 2H, s, CH_2), 6·38 (2H, s, ArH), 7·31 (10H, s, ArH); mass spectrum *m/e* 362 (M^+).

Methyl 3-Bromo-4,6-dibenzyloxy-2-methylbenzoate (30)

Bromine (1·76 g) in glacial acetic acid (20 ml) was added rapidly to a stirred mixture of methyl 2,4-dibenzyloxy-6-methylbenzoate (29) (4·0 g) and anhydrous sodium acetate (1·35 g) in glacial acetic acid (60 ml). The mixture was then stirred for a further 2 min and poured into ice-water and extracted with ethyl acetate. The extract was washed in turn with saturated aqueous sodium hydrogen carbonate, water and with saturated brine. The crude product crystallized from dichloromethane/light petroleum as *prisms* (4·55 g, 94%), m.p. 117–118° (Found: C, 62·9; H, 5·1; Br, 18·4. $C_{23}H_{21}BrO_4$ requires C, 62·6; H, 4·8; Br, 18·1%). P.m.r. ($CDCl_3$) δ 2·41 (3H, s, Me), 3·87 (3H, s, OMe), 4·98 and 5·08 (each 2H, s, CH_2), 6·36 (1H, s, ArH), 7·28 and 7·32 (each 5H, s, ArH); mass spectrum *m/e* 440, 442 (M^+).

Methyl 3-Bromo-4,6-dihydroxy-2-methylbenzoate

The foregoing dibenzyl compound (30) (5·0 g) and concentrated hydrochloric acid (3 drops) were stirred in a hydrogen atmosphere until uptake ceased with 10% palladized charcoal (0·9 g). The crude product crystallized from ether/light petroleum as prisms (2·25 g, 76%) of *methyl 3-bromo-4,6-dihydroxy-6-methylbenzoate*, m.p. 111–113° (Found: C, 41·7; H, 3·8; Br, 30·9. $C_9H_9BrO_4$ requires C, 41·4; H, 3·4; Br, 30·6%). P.m.r. ($CDCl_3$) δ 2·64 (3H, s, Me), 3·93 (3H, s, OMe), 6·15 (1H, s, OH), 6·51 (1H, s, ArH), 11·36 (1H, s, OH). On methylation with methyl sulphate and potassium carbonate in acetone methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate,[19] m.p. and mixed m.p. 120–122° (lit.[19] 121–122°), was produced.

Benzyl 3-Bromo-4,6-dibenzyloxy-2-methylbenzoate (31)

The methyl ester (30) (35·0 g) in freshly distilled benzyl alcohol (450 ml) was stirred under dry nitrogen and treated with sodium (3·68 g). The stirred mixture was heated at 75° (bath) for 40 h, cooled, and poured into ice and dilute hydrochloric acid, and then extracted with ethyl acetate. The extract was washed with water and with saturated brine and the excess of benzyl alcohol was removed under diminished pressure. The residue was crystallized from dichloromethane/methanol and afforded the *benzyl ester* (31) (29·0 g, 71%), m.p. 97·5–99° (Found: C, 67·6; H, 5·1; Br, 15·3. $C_{21}H_{25}BrO_4$ requires C, 67·3; H, 4·9; Br, 15·4%). P.m.r. (CCl_4) δ 2·28 (3H, s, Me), 4·82, 4·88 and 5·18 (each 2H, s, CH_2), 6·25 (1H, s, ArH), 7·20 (15H, m, ArH).

Benzyl 3-Bromo-4,6-dihydroxy-2-methylbenzoate (32)

The benzyl ester (5·0 g) in acetic acid (200 ml) was stirred in hydrogen with 10% palladized charcoal (0·9 g) until absorption ceased. The crude acid crystallized from chloroform as needles (1·95 g, 82%), m.p. 174–175° (dec.). P.m.r. ($(CD_3)_2SO$) δ 2·43 (3H, s, Me), 6·42 (1H, s, ArH). A stirred suspension of the crude acid (5·26 g) in ether (60 ml) was treated dropwise with phenyldiazomethane [from *N*-benzyl-*N*-nitroso-*p*-toluenesulphonamide[32] (18·5 g)] in ether (70 ml) at room temperature. After 5 min a slight excess of glacial acetic acid was added and the solution was washed in turn with saturated sodium hydrogen carbonate solution, water and saturated brine. The crude product was chromatographed over silica gel with 5% ethyl acetate/light petroleum as eluent. The *benzyl ester* (32) formed needles (2·3 g, 32%), from ether/light petroleum, m.p. 102° (Found: C, 53·5; H, 3·9; Br, 23·5. $C_{15}H_{13}BrO_4$ requires C, 53·4; H, 3·9; Br, 23·7%). P.m.r. (CCl_4) δ 2·60 (3H, s, Me), 5·32 (2H, s, CH_2), 6·07 (1H, br, OH), 6·48 (1H, s, ArH), 7·32 (5H, s, ArH), 11·28 (1H, s, OH).

[32] Overberger, C. G., and Anselme, J.-P., *J. Org. Chem.*, 1963, **28**, 592.

Benzyl 3-Bromo-6-hydroxy-4-(2'-hydroxy-4'-methoxy-3',6'-dimethylbenzoyloxy)-2-methylbenzoate (33)

Rhizonic acid[17] (26) (1·16 g) and the benzyl ester (32) (2·0 g) were stirred in dry toluene (30 ml) and trifluoroacetic anhydride (6 ml) at room temperature for 12 h. The solvents were removed under reduced pressure and the residue was preadsorbed from dichloromethane and chromatographed over silica gel with 10% ethyl acetate/light petroleum as eluent. The *depside* (33) (1·3 g, 44%) crystallized from ether/light petroleum as prisms, m.p. 136–138° (Found: C, 58·5; H, 4·8; Br, 15·6. $C_{25}H_{23}BrO_7$ requires C, 58·3; H, 4·5; Br, 15·5%). P.m.r. ($CDCl_3$, 90 MHz) δ 2·10 (3H, s, Me), 2·70 (6H, s, 2× Me), 3·82 (3H, s, OMe), 5·43 (2H, s, CH_2), 6·37 and 6·78 (each 1H, s, ArH), 7·41 (5H, s, ArH), 11·10 and 11·30 (each 1H, s, D_2O exchangeable OH).

Attempted Cyclization of the Bromodepside (33)

The bromodepside (33) (200 mg) was treated with copper bronze and anhydrous pyridine as described above for the synthesis of benzyl 5-bromo-4-*O*-methylhypoprotocetrarate (28). After the normal workup followed by chromatography, no trace of benzyl notatate could be detected.

Methyl 4-Benzyloxy-6-hydroxy-2-methylbenzoate

Methyl orsellinate[31] (39·6 g), potassium carbonate (92 g) and benzyl chloride (28·0 g) were stirred and heated under reflux in dry acetone (480 ml) for 23 h. The cooled mixture was poured into dilute sulphuric acid and extracted with ethyl acetate. The extract was washed with water and with saturated brine. The crude product was chromatographed over a column of silica gel with light petroleum as eluent. The ester (33·0 g, 48%) formed needles (from light petroleum), m.p. 64–66° (lit.[18] 68–69°) (Found: C, 70·9; H, 6·1. Calc. for $C_{16}H_{16}O_4$: C, 70·6; H, 6·1%). P.m.r. (CCl_4) δ 2·46 (3H, s, Me), 3·88 (3H, s, OMe), 4·97 (2H, s, CH_2), 6·28 (2H, apparent s, ArH), 7·30 (5H, s, ArH), 11·17 (1H, s, OH); mass spectrum *m/e* 272 (M^+).

Methyl 4-Benzyloxy-3-bromo-6-methoxy-2-methylbenzoate (39)

The foregoing product was methylated in the usual way with methyl sulphate and potassium carbonate in acetone. The product, methyl 4-benzyloxy-6-methoxy-2-methylbenzoate (38), was obtained as an oil in quantitative yield. P.m.r. (CCl_4) δ 2·08 (3H, s, Me), 3·63 and 3·73 (each 3H, s, OMe), 4·90 (2H, s, CH_2), 6·25 (2H, apparent s, ArH), and 7·26 (5H, s, ArH). The ester (38) (28·0 g), anhydrous sodium acetate (90 g) and acetic acid (560 ml) were stirred and treated rapidly with bromine (15·05 g) in acetic acid (100 ml). After a further 2·5 min the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with 5% aqueous sodium hydroxide and with water and with saturated brine. The crude product was crystallized from ether/light petroleum and formed prisms and plates of the *bromo compound* (39) (34·0 g, 83%), m.p. 101–104° (Found: C, 56·1; H, 5·0; Br, 21·7. $C_{17}H_{17}BrO_4$ requires C, 55·9; H, 4·7; Br, 21·9%). P.m.r. ($CDCl_3$) δ 2·28 (3H, s, Me), 3·64 and 3·77 (each 3H, s, OMe), 5·06 (2H, s, CH_2), 6·28 (1H, s, ArH), 7·32 (5H, s, ArH); mass spectrum *m/e* 366 (M^+), 364 (M^+).

Methyl 3-Bromo-4-hydroxy-6-methoxy-2-methylbenzoate

The foregoing bromo compound (39) (2·0 g) and 10% palladized charcoal (0·2 g) in ethyl acetate (50 ml) were stirred under hydrogen until absorption ceased. The crude product was crystallized from ether/light petroleum and gave the *phenol* (1·2 g, 80%) as needles, m.p. 122–123° (Found: C, 43·8; H, 4·3; Br, 28·8. $C_{10}H_{11}BrO_4$ requires C, 43·7; H, 4·0; Br, 29·0%). P.m.r. (CCl_4) δ 2·31 (3H, s, Me), 3·79 and 3·82 (each 3H, s, OMe), 5·74 (1H, s, OH), 6·43 (1H, s, ArH). On methylation with methyl sulphate and potassium carbonate in acetone, methyl 5-bromo-2,4-dimethoxy-6-methylbenzoate,[19] m.p. and mixed m.p. 120–122° (lit.[19] 121–122°), was produced.

Methyl 4-Benzyloxy-6-methoxy-3-(3'-methoxy-2',5'-dimethoxyphenoxy)-2-methylbenzoate (40)

The phenol (9) (4·2 g), the bromo compound (39) (4·8 g) and dry, finely divided potassium carbonate (5 g) in dry pyridine (15 ml) were stirred and heated to 120° (bath) under dry nitrogen. Copper(II) oxide (1·0 g) was then added and the temperature was raised to 150° (bath). The nitrogen flow was

adjusted so that the pyridine evaporated through a short air condenser over 4 h. The residue was heated for 1 h longer and then cooled and diluted with ether. The extract was filtered through kieselguhr and then washed in turn with dilute hydrochloric acid, 5% aqueous sodium hydroxide, water and saturated brine. T.l.c. indicated that the crude product consisted of a mixture of the bromo compound (39), the debromo compound (38) and the product (40) which all had almost identical R_F values. The combined products from three reactions were preadsorbed from dichloromethane and chromatographed over a column of silica gel (total 7 by 70 cm) with 1% (1 l.), 1·5% (1 l.), 2% (1 l.), 2·5% (184 l.) and 10% ethyl acetate/light petroleum as eluents; 200-ml fractions, monitored by n.m.r. spectroscopy, were collected. Fractions 935–1010 were combined and afforded the *diaryl ether* (40) (8·4 g, 38%) which formed prisms (from ether/light petroleum), m.p. 117–119° (Found: C, 71·7; H, 6·4. $C_{26}H_{28}O_6$ requires C, 71·5; H, 6·5%). P.m.r. ($CDCl_3$) δ 2·11 (3H, s, Me), 2·16 (6H, s, 2 × Me), 3·66 (3H, s, OMe), 3·78 (6H, s, 2 × OMe), 4·91 (2H, s, CH_2), 5·81 (1H, bs, H 6′), 6·24 (1H, bs, H 4′), 6·32 (1H, s, H 5), 7·15 (5H, narrow m, ArH); mass spectrum *m/e* 436 (M^+).

Methyl 4-Hydroxy-6-methoxy-3-(3′-methoxy-2′,5′-dimethylphenoxy)-2-methylbenzoate (41)

The foregoing diaryl ether (50) (3·0 g) and 10% palladized charcoal (0·3 g) in glacial acetic acid (50 ml) containing concentrated hydrochloric acid (3 drops) were stirred under hydrogen until absorption ceased. Workup in the usual way gave the *phenol* (41) (2·1 g, 89%) as prisms (from ether/light petroleum), m.p. 148–149·5° (Found: C, 66·1; H, 6·4. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%). P.m.r. (90 MHz, $CDCl_3$) δ 1·99 (3H, s, $W_{h/2}$ 1·1 Hz, 2-Me), 2·19 and 2·24 (each 3H, s, $W_{h/2}$ 2·0 Hz, 2′- and 5′-Me), 3·81, 3·82, and 3·88 (each 3H, s, OMe), 5·48 (1H, s, OH), 5·92 (1H, m, $W_{h/2}$ 3·0 Hz, H 6′), 6·39 (1H, m, $W_{h/2}$ 2·5 Hz, H 4′), 6·52 (1H, s, $W_{h/2}$ 1·9 Hz, H 5); mass spectrum *m/e* 346 (M^+). The derived *methyl ether* formed needles (from ether/light petroleum), m.p. 139–140° (Found: C, 67·0; H, 6·6. $C_{20}H_{24}O_6$ requires C, 66·7; H, 6·7%).

Methyl 4-Acetoxy-6-methoxy-3-(3′-methoxy-2′,5′-dimethylphenoxy)-2-methylbenzoate (42)

The foregoing phenol (41) was acetylated with pyridine and acetic anhydride (90°/1·5 h). The *acetate* (42) (91%) formed needles (from ether/light petroleum), m.p. 125–126° (Found: C, 65·0; H, 6·1. $C_{21}H_{24}O_7$ requires C, 64·9; H, 6·2%). P.m.r. (90 MHz, $CDCl_3$) δ 1·99 and 2·11 (each 3H, s, Me), 2·19 (6H, s, 2 × Me), 3·81 (6H, s, 2 × OMe), 3·91 (3H, s, OMe), 5·85 and 6·35 (each 1H, m, $W_{h/2}$ 3·0 Hz, H 6′,4′), 6·61 (1H, s, $W_{h/2}$ 1·8 Hz, H 5); mass spectrum *m/e* 388 (M^+).

Methyl 4-Acetoxy-3-(4′-formyl-3′-methoxy-2′,5′-dimethylphenoxy)-6-methoxy-2-methylbenzoate (43)

The foregoing diaryl ether (42) (700 mg) and dichloromethyl methyl ether (260 mg) in dichloromethane (15 ml) were stirred at 0° during the dropwise addition of titanium(IV) chloride (430 mg) in dichloromethane (10 ml). The mixture was stirred at 0° for 0·5 h and at room temperature for 0·5 h. The usual workup gave the crude product which was chromatographed over silica gel with 10% ethyl acetate/light petroleum as eluent. The *aldehyde* (43) (420 mg, 59%) formed prisms (from methanol), m.p. 132–134° (Found: C, 63·2; H, 6·0. $C_{22}H_{24}O_8$ requires C, 63·4; H, 5·8%). P.m.r. (90 MHz, $CDCl_3$) δ 2·03 (3H, s, $W_{h/2}$ 1·2 Hz, OCOMe), 2·11 (3H, s, $W_{h/2}$ 1·7 Hz, 2-Me), 2·29 (3H, s, $W_{h/2}$ 2·1 Hz, 2′-Me), 2·44 (3H, s, $W_{h/2}$ 2·4 Hz, 5′-Me), 3·84, 3·87 and 3·93 (each 3H, s, OMe), 6·06 (1H, s, $W_{h/2}$ 2·2 Hz, H 6′), 6·67 (1H, s, $W_{h/2}$ 1·9 Hz, H 5), 10·42 (1H, s, CHO); mass spectrum *m/e* 416 (20%, M^+), 374 (100%).

Methyl 3-(4′-Formyl-3′-hydroxy-2′,5′-dimethylphenoxy)-4,6-dihydroxy-2-methylbenzoate (44)

The foregoing aldehyde (43) (150 mg) in 1,2-dichloroethane (10 ml) was added at −10° to a stirred solution of boron trichloride (340 mg) in 1,2-dichloroethane (25 ml). After 15 min at −10° and 15 min at room temperature the usual workup gave the *phenol* (44) (110 mg, 91%) as needles (from methanol), m.p. 118–120° (Found: C, 62·3; H, 5·2. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2%). P.m.r. (90 MHz, $CDCl_3$) δ 2·24, 2·26 and 2·40 (each 3H, s, Me), 3·92 (3H, s, OMe), 5·80 (1H, s, H 6′), 6·53 (1H, s, H 5), 10·08 (1H, s, CHO), 11·59 and 12·47 (each 1H, s, D_2O exchangeable OH); mass spectrum *m/e* 346 (43%, M^+), 149 (100).

Methyl 3-(4′-Formyl-3′-methoxy-2′,5′-dimethylphenoxy)-4-hydroxy-6-methoxy-2-methylbenzoate (45)

Titanium(IV) chloride (690 mg) in dichloromethane (10 ml) was added dropwise at 0° to a stirred solution of the diaryl ether (41) (1·0 g) and dichloromethyl methyl ether (420 mg) in dichloromethane (15 ml). After 0·5 h at 0° and 1 h at room temperature the usual workup gave the crude product which was chromatographed over a column of silica gel with 10–20% ethyl acetate/light petroleum as eluent. The *diaryl ether* (45) (670 mg, 62%) formed needles (from methanol), m.p. 188·5–189·5° (Found: C, 63·9; H, 6·0. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%). P.m.r. (90 MHz, $CDCl_3$) δ 1·98 (3H, s, $W_{h/2}$ 2·0 Hz, 2-Me), 2·30 (3H, s, $W_{h/2}$ 2·0 Hz, 2′-Me), 2·39 (3H, s, $W_{h/2}$ 2·8 Hz, 5′-Me), 3·80, 3·81 and 3·88 (each 3H, s, OMe), 6·10 (1H, s, $W_{h/2}$ 2·6 Hz, H 6′), 6·53 (1H, s, $W_{h/2}$ 1·9 Hz, H 5), 6·57 (1H, s, D_2O exchangeable OH), 10·30 (1H, s, CHO); mass spectrum *m/e* 374 (100%, M^+). On acetylation with pyridine and acetic anhydride it afforded the diaryl ether (43), m.p. and mixed m.p. 132–134° (from methanol).

Formylation and Subsequent Demethylation of Diaryl Ether (40)

A solution of titanium(IV) chloride (9·2 g) in dichloromethane (80 ml) was added with stirring at −70° over 1·5 h to the diaryl ether (40) (4·21 g) and dichloromethyl methyl ether (5·6 g) in dichloromethane (80 ml). Workup in the usual way gave the crude product which was stirred in 1,2-dichloroethane (100 ml) and treated at −10° with a solution of boron trichloride (13 g) in 1,2-dichloroethane (100 ml). After 15 min the solution was poured into ice-water and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The solvents were removed from the dried combined extracts and the residue was triturated with hot dichloromethane. The solid product was collected by filtration and crystallized from ethyl acetate. This afforded *methyl 3-(6′-formyl-3′-methoxy-2′,5′-dimethylphenoxy)-4,6-dihydroxy-2-methylbenzoate* (47) (730 mg, 21%) as prisms, m.p. 241–242° (dec.) (Found: C, 63·1; H, 5·4. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·6%). P.m.r. (90 MHz, $(CD_3)_2SO$) δ 1·82 and 2·21 (each 3H, s, $W_{h/2}$ 2·0 Hz, 2- and 2′-Me), 2·48 (3H, s, $W_{h/2}$ 2·8 Hz, 5′-Me), 3·79 and 3·85 (each 3H, s, OMe), 6·23 (1H, s, $W_{h/2}$ 1·9 Hz, H 5), 6·67 (1H, s, $W_{h/2}$ 2·3 Hz, H 4′), 9·92 (2H, b, 2 × OH, solvent bonded), 10·32 (1H, s, CHO); mass spectrum *m/e* 360 (M^+). The dichloromethane solution was preadsorbed on silica gel and chromatographed over a column of silica gel. This gave firstly *methyl 4,6-dihydroxy-3-(3′-methoxy-2′,5′-dimethylphenoxy)-2-methylbenzoate* (46) (1·01 g, 31%) as prisms (from cyclohexane), m.p. 146–148° (Found: C, 65·0; H, 6·3. $C_{18}H_{20}O_6$ requires C, 65·0; H, 6·1%). P.m.r. (90 MHz, $CDCl_3$) δ 2·18 (3H, s, Me), 2·24 (6H, s, 2 × Me), 3·71 and 3·89 (each 3H, s, OMe), 5·87 (1H, m, $W_{h/2}$ 3·2 Hz, H 6′), 5·93 (1H, s, D_2O exchangeable OH), 6·38 (1H, m, $W_{h/2}$ 3·0 Hz, H 4′), 6·50 (1H, s, $W_{h/2}$ 1·7 Hz, H 5), 11·55 (1H, s, D_2O exchangeable OH); mass spectrum *m/e* 332 (M^+). Further elution gave the aldehyde (44) (1·57 g, 47%), m.p. and mixed m.p. 118–120°.

Methyl 4,6-Diacetoxy-3-(6′-formyl-3′-methoxy-2′,5′-dimethylphenoxy)-2-methylbenzoate

The aldehyde (47) was acetylated with acetic anhydride and pyridine (1·5 h/90°) in the usual way. The product was obtained as a glass. P.m.r. ($CDCl_3$) δ 1·53 (3H, s, OCOMe), 1·80 (3H, s, 2′-Me), 2·20 (3H, s, OCOMe), 2·43 (3H, s, 2-Me), 2·62 (3H, s, 5′-Me), 3·85 and 3·90 (each 3H, s, OMe), 6·57 (1H, s, $W_{h/2}$ 2·0 Hz, H 4′), 6·75 (1H, s, $W_{h/2}$ 1·5 Hz, H 5), 10·42 (1H, s, CHO); mass spectrum *m/e* 444 (M^+).

Methyl Notatate (49)

The foregoing acetate (873 mg) was stirred in acetone (80 ml) and treated dropwise over 1·3 h with potassium permanganate (1·11 g) and magnesium sulphate monohydrate (1·10 g) in water (40 ml). Stirring was continued for a further 1 h and then the cooled (ice) mixture was clarified by the passage of sulphur dioxide. The acidified mixture was exhaustively extracted with ethyl acetate and the extracts were washed with aqueous sodium hydrogen carbonate. The acidified washings were extracted with ethyl acetate. The crude product, so obtained, in methanol (20 ml) was treated with stirring at 0° under nitrogen with sodium hydroxide (2·0 g) in water (20 ml). After 1 h the mixture was acidified with dilute hydrochloric acid and extracted exhaustively with ethyl acetate. The crude product was stirred at room temperature with trifluoroacetic anhydride (5 ml) and dry toluene (30 ml). After 17 h the solvents were removed under diminished pressure and the residue in ethyl acetate was washed successively with water, saturated sodium hydrogen carbonate solution (twice) and

with saturated brine. The crude product was preadsorbed from dichloromethane and chromatographed over a column of silica gel (total 2·2 by 38 cm) with 10–12% ethyl acetate/light petroleum as eluent. This afforded 2′-hydroxy-4-methoxy-1′-methoxycarbonyl-3,6,6′-trimethyldepsidone (49) (194 mg, 29%) as rosettes of small needles (from dichloromethane/light petroleum), m.p. and mixed m.p. 203–204° (lit.[12] 203–204°) (Found: C, 63·5; H, 5·3. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·1%). P.m.r. (90 MHz, $CDCl_3$) δ 2·32 (3H, s, $W_{h/2}$ 2·0 Hz, 3-Me), 2·48 (3H, s, $W_{h/2}$ 2·1 Hz, 6-Me), 2·68 (3H, s, $W_{h/2}$ 1·6 Hz, 6′-Me), 3·84 and 3·94 (each 3H, s, OMe), 6·55 (1H, s, $W_{h/2}$ 2·2 Hz, H 5), 6·70 (1H, s, $W_{h/2}$ 1·8 Hz, H 3′), and 11·11 (1H, s, D_2O exchangeable OH); mass spectrum *m/e* 358 (M^+). The R_F in several solvent systems and the n.m.r. and mass spectra were identical with those of an authentic sample.

Notatic Acid (*6*)

Methyl notatate (49) (132 mg) and potassium hydroxide (320 mg) were stirred under nitrogen in Me_2SO (5 ml) and water (1 ml) for 40 h at 0–5°. The mixture was diluted with iced water and acidified with hydrochloric acid and extracted with ethyl acetate. The crude product was treated with trifluoroacetic anhydride (5 ml) in dry toluene (30 ml) as before. The residue left on removal of the solvents was applied in a little dioxan to 2 silica plates which were developed with benzene/dioxan/acetic acid (90 : 20 : 1). The band corresponding in R_F to notatic acid was separated and extracted with boiling acetone. Removal of the solvent and crystallization of the residue from acetone gave 2′-carboxy-2′-hydroxy-4-methoxy-3,6,6′-trimethyldepsidone (6) (4·2 mg) as needles, m.p. and mixed m.p. 225–226° (dec.) (Found: mol. wt., 328·0941. Calc. for $^{12}C_{18}{}^{1}H_{16}{}^{16}O_6$: mol. wt., 328·0947). The mass spectrum and the R_F in two solvent systems were identical with those of notatic acid.

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