Structure of the Lichen Depsidone Pannarin †

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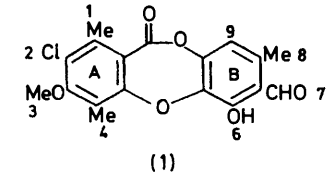
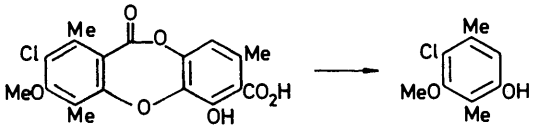
The published structure of pannarin{2-chloro-6-hydroxy-3-methoxy-1,4,8-trimethyl-11-oxo-11*H*-dibenzo[*b*,*e*]-[1,4]dioxepin-7-carbaldehyde} (1) is revised to 2-chloro-3-hydroxy-8-methoxy-1,6,9-trimethyl-11-oxo-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-4-carbaldehyde (21), in the light of a combination of degradative, spectroscopic, and synthetic studies. The utility of mass spectrometry and high resolution n.m.r. spectroscopy in depsidone structural determination is discussed.

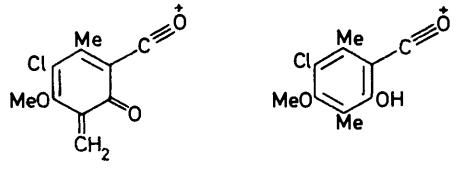
THE structure (1) for the lichen depsidone pannarin was proposed by Yosioka.[1] The substitution pattern of ring



(1)



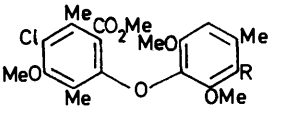
(2) (3)



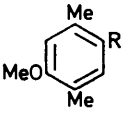
(4) (5)

A followed from oxidation of pannarin to an acid, assigned structure (2) of which on dry distillation allegedly afforded the phenol (3), identified by synthesis. The nature of ring A appeared to be confirmed by the mass spectrum of pannarin, which exhibited ions at *m/e* 211/213 and 213/215, assigned structures (4) and (5) by Djerassi and his co-workers.[2] Yosioka's structure for ring B of pannarin relies ' heavily on colour reactions, the provenance of which is not always clearly defined.' [3] Furthermore ring B of pannarin was unusual since among almost 30 known depsidones only pannarin and variolaric acid [4] possessed the diaryl ether linkage *ortho* to the hydroxy-group of ring B.

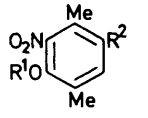
As a preliminary to the synthesis of pannarin we decided to verify the structure (1) by synthesis of the degradation product (7). We chose the Ullmann reaction as the key step in this synthesis. Previous results with *o*-hydroxy-esters in such reactions had been poor.[5] We therefore sought a synthesis of the *o*-bromo-ester (17). This was prepared from 2,5-xylenol methyl ether (8), which on bromination gave the bromo-anisole (9). This on Grignard reaction and carboxylation gave the known acid (10).[6] The derived methyl ester (11) on nitration afforded the nitro-ester (12) and a little of the demethylation product (13), which was easily removed by treatment with base. The structure of the nitro-ester



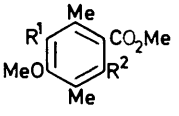
(6) R = H
(7) R = CHO



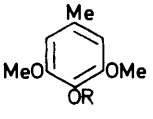
(8) R = H
(9) R = Br
(10) R = CO_2H
(11) R = CO_2Me



(12) R^1 = Me, R^2 = CO_2Me
(13) R^1 = H, R^2 = CO_2Me
(14) R^1 = Me, R^2 = H



(15) R^1 = NH_2, R^2 = H
(16) R^1 = NH_2, R^2 = Br
(17) R^1 = Cl, R^2 = Br
(18) R^1 = H, R^2 = Br



(19) R = H
(20) R = Me

(12) followed from its hydrolysis and decarboxylation to the nitro-compound (14), the n.m.r. spectrum of which

† Preliminary communication, J. A. Elix, D. A. Jackman, and M. V. Sargent, *J.C.S. Chem. Comm.*, 1974, 892.

[1] I. Yosioka, *Yakagaku Zasshi*, 1941, **61**, 332.
[2] S. Huneck, C. Djerassi, D. Becher, M. Barber, M. von Ardenne, K. Steinfelder, and R. Tümmler, *Tetrahedron*, 1968, **24**, 2707.
[3] F. M. Dean, ' Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, p. 576.
[4] N. M. Rana, M. V. Sargent, and J. A. Elix, *J.C.S. Perkin I*, 1975, 1922.
[5] T. M. Cresp, J. A. Elix, S. Kurokawa, and M. V. Sargent, *Austral. J. Chem.*, 1972, **25**, 2167.
[6] G. R. Clemo, R. D. Haworth, and E. Walton, *J. Chem. Soc.*, 1929, 2368.

revealed the aromatic protons as an *o*-coupled AB system. Reduction of the nitro-ester (12) gave the amine (15), which on bromination gave the bromo-amine (16). This on diazotisation followed by treatment with copper(I) chloride then gave the desired ester (17) accompanied by some deamination product (18), which was also prepared by treatment of the diazonium salt with phosphinous acid.

For ring B of structure (1) we required the phenol (19) which had previously been isolated from birch and beech tars [7,8] but never apparently synthesised. It was readily prepared by partial demethylation [9] of the known tri-*O*-methyl ether (20).[10]

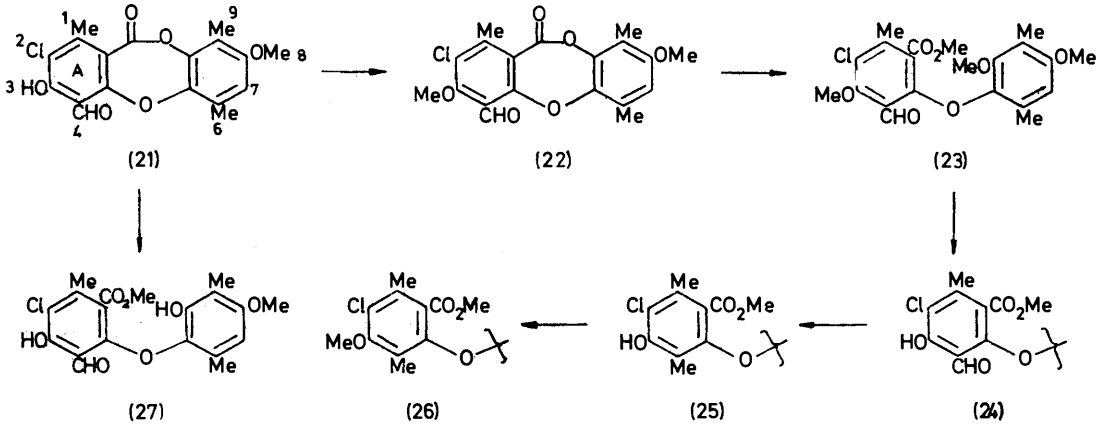
Ullmann reaction of the phenol (19) and the *o*-bromo-ester (17) then gave the diaryl ether (6). This underwent smooth formylation with dichloromethyl methyl ether and titanium(IV) chloride and gave the desired aldehyde (7). Were Yosioka's structure for pannarin correct then methanolysis and methylation of pannarin should also have provided the aldehyde (7). The two products were different.

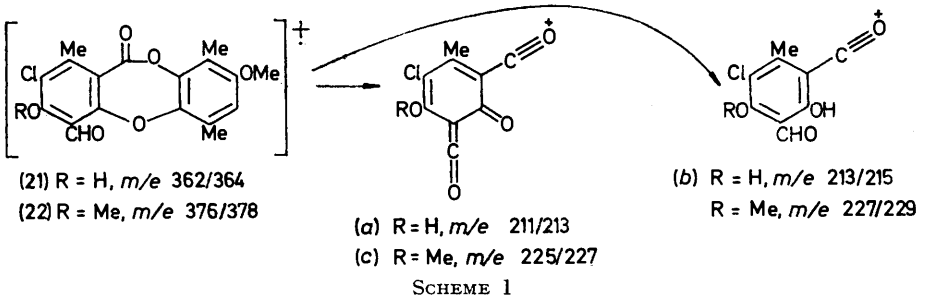
A systematic spectroscopic investigation of pannarin and its degradation products then ensued which culminated in the assignment of structure (21) to pannarin, which was verified by synthesis of the degradation product (26).

Pannarin (21) on methylation gave the methyl ether (22). and on methanolysis gave the known 'pannarin methoxide' (27).[1] Methanolysis of the methyl ether (22) and subsequent methylation gave the diaryl ether (23). This on demethylation with boron trichloride [11] furnished the *o*-hydroxy-aldehyde (24). On hydrogenation over platinum under acidic conditions the aldehyde group was reduced to yield the product (25). Methylation then gave (26).

The i.r. spectrum of pannarin confirmed that it was a depsidone, and exhibited a band at 1 650 cm^{-1} due to an *o*-hydroxy-aldehyde. This was confirmed by the n.m.r. spectrum (90 MHz; $CDCl_3$) which showed sharp singlets at τ −2.77 (OH) and −0.66 (CHO). High resolution mass spectrometry revealed that the ring A fragment at *m/e* 210.9798 had the composition $^{12}C_9{}^{1}H_4{}^{35}Cl^{16}O_4$; hence the ring A fragments were now ascribed the structures (*a*) and (*b*) (see Scheme 1). The ring A fragments of the products (22)—(27) were also in keeping with the assignment of the ring A of structure (21) (see Schemes 1—5).

The mass spectra of the diaryl ether degradation products (23)—(25) and (27) revealed the gross structure of ring B. Thus the mass spectra of the diaryl ethers (23)—(25) had in common the ions (*d*) and (*e*), and in addition (24) and (25) showed the ion (*f*), all due to ring B frag-

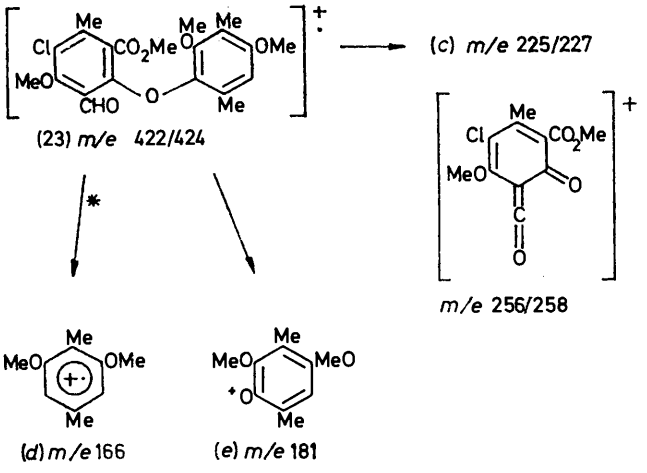




SCHEME 1

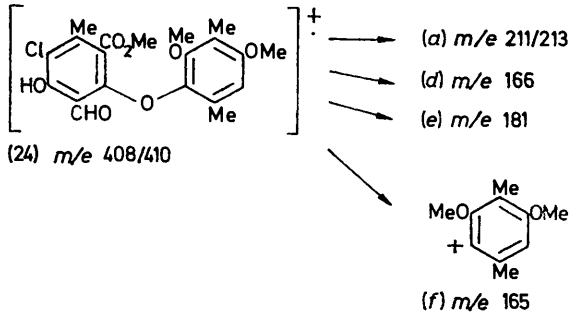
[7] A. W. Hofmann, *Ber.*, 1879, **12**, 1371.
[8] V. E. Tishchenko, M. I. Lishkevich, and L. A. Sulskaya, *Zhur. priklad. Khim.*, 1930, **3**, 375 (*Chem. Abs.*, 1930, **25**, 5145).
[9] C. D. Hurd and H. E. Winberg, *J. Amer. Chem. Soc.*, 1942, **64**, 2085.
[10] H. Sugihara, M. Watanabe, Y. Kawamatsu, and H. Morimoto, *Annalen*, 1972, **763**, 109.
[11] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. M. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

ments. The mass spectrum of ' pannarin methoxide ' (27) exhibited the ring B ions (*g*) and (*h*).

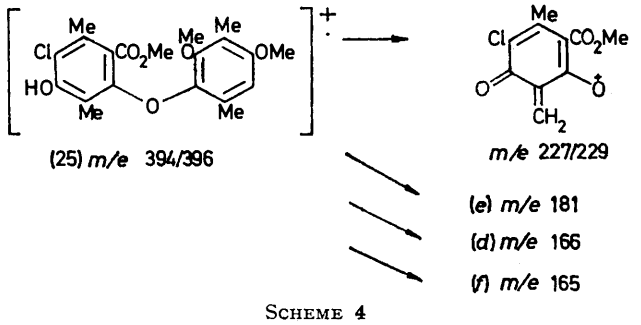


SCHEME 2

In the mass spectra of depsidones ring A fragments are usually prominent but those due to ring B are not observed.[2] In the above-mentioned diaryl ether degradation products it is apparent that, in addition to ring A fragments, those due to ring B are responsible for much of the ion current. We have observed that this behaviour is typical of most of the methanolysis products of depsidones and of their synthetic analogues, as is evident in the mass spectrum of the synthetic diaryl ether (7) shown in



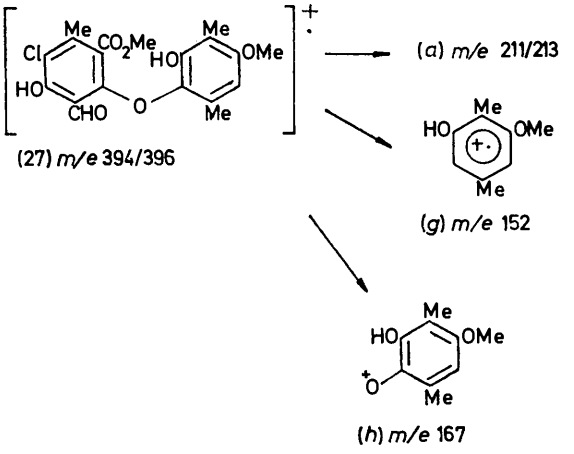
SCHEME 3



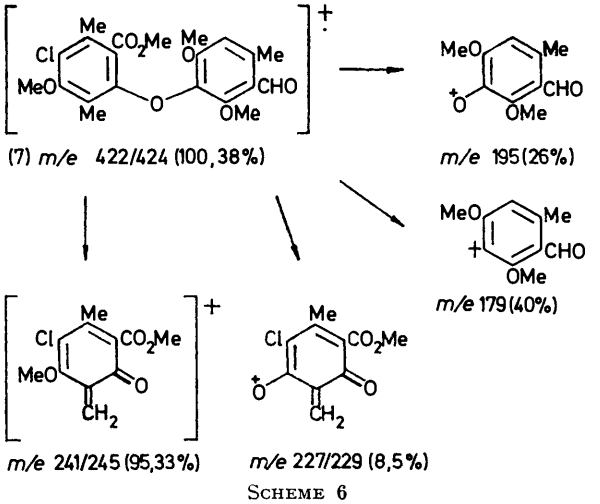
SCHEME 4

Scheme 6. This observation should prove useful in depsidone structural determination, and coupled with high resolution n.m.r. spectroscopy, should obviate recourse to oxidative degradation [12] as a means of determination of the character of ring B.

By use of decoupling and nuclear Overhauser effect (n.O.e.) experiments the precise location of five of the seven substituents on the depsidone nucleus of pannarin



SCHEME 5



SCHEME 6

was determined. In addition to the features mentioned above the n.m.r. spectrum of pannarin (21) exhibited a broad 1 H singlet at τ 3.56 ($W_{\frac{1}{2}}$ 2.0 Hz) due to H-7, a sharp 3 H singlet at 6.21 due to 8-OMe, a sharp 3 H singlet at 7.44 (1-Me), and broad 3 H singlets at 7.64 and 7.80 (each $W_{\frac{1}{2}}$ 2.0 Hz). Irradiation at τ 7.80 caused sharpening of the aromatic proton signal ($W_{\frac{1}{2}}$ 1.7 Hz), and irradiation at 7.64 caused greater sharpening ($W_{\frac{1}{2}}$ 1.0 Hz). That the methyl groups were mutually coupled was evident since irradiation at the frequency of the aromatic proton caused the broad singlets at 7.64 and 7.80 to appear as two finely split doublets. These data were tentatively accommodated by the *para*-arrangement of

[12] F. M. Dean, D. S. Deorha, A. D. T. Erni, D. W. Hughes, and J. C. Roberts, *J. Chem. Soc.*, 1960, 4829.

the methyl groups on ring B, the aromatic proton being *ortho* to the methyl group giving rise to the signal at 7.64. This interpretation was confirmed by the fact that saturation of the signal at 7.64 gave a 10% enhancement in the integral for the aromatic proton, and a 27% n.O.e. at the formyl proton. Since mass spectrometry had indicated that the formyl group was on ring A, the latter effect indicated that the formyl proton and the 6-Me are in close proximity. This is undoubtedly due to the presence of the formyl group at the 4-position and a hydroxy-group at the 3-position, the formyl proton being held close to the 6-Me by intramolecular hydrogen bonding.

Nuclear Overhauser effects

Compound	Signal irradiated	Signal(s) observed	% N.O.e.*
(23)	6′-Me	CHO	7
	6′-Me	5′-H	9
	3′-Me	CHO;5′-H	Nil; nil
	4′-OMe	5′-H	21
	4′-OMe	CHO	Nil
	2′-OMe	CHO	11
	2′-OMe	5′-H	Nil
	1-CO_2Me	CHO;5′-H	Nil; nil
	4-OMe	CHO;5′-H	Nil; nil
(24)	6′-Me	CHO	13
	6′-Me	5′-H	19
	3′-Me	CHO;5′-H	Nil; nil
	2′-OMe	CHO	20
	2′-OMe	5′-H	Nil
	4′-OMe	CHO	Nil
	4′-OMe	5′-H	22

* % Increase in integrated intensity on irradiation.

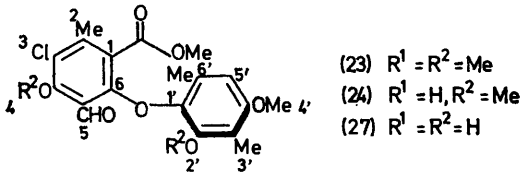


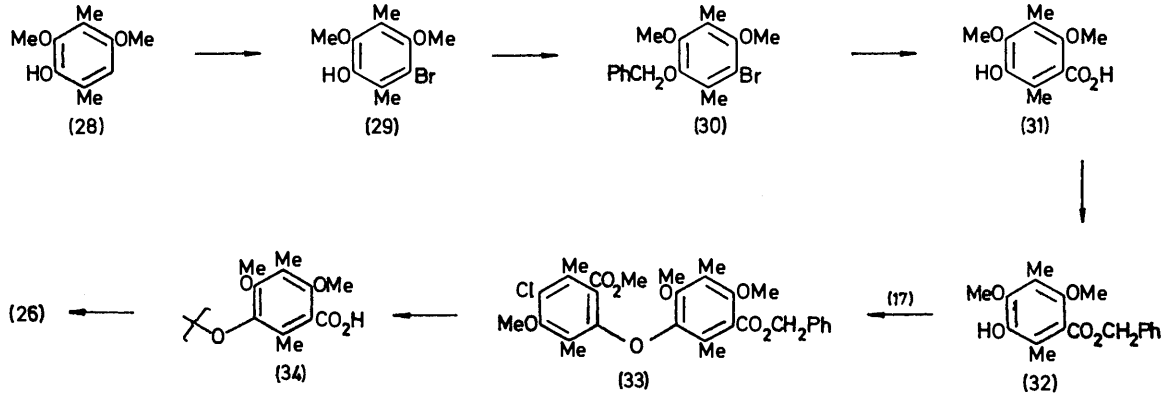
FIGURE Preferred conformations of diaryl ethers

Saturation of the signal at 7.80 gave no n.O.e. at either the aromatic or the formyl proton.

Further confirmation of the above structural assignments came from n.O.e. experiments with the diaryl ethers (23) and (24) (see Table). Much is now known about the conformational preferences of highly hindered diaryl ethers.[13] ' Pannarin methoxide ' (27) exhibits a very high field methoxy-signal at τ 6.58 and similar signals are also present in the spectra of the diaryl ethers (23) and (24) at 6.66 and 6.73. These are attributed on the grounds of the n.O.e. experiments shown in the Table to the ester methoxy-group. This therefore indicates, since the ester methoxy-group is highly shielded, that in these compounds the ' ester inside ' conformations (see Figure) are highly populated.

The positions of only a methyl and a chloro-substituent on ring A of pannarin were now in doubt. From biogenetic considerations they can be safely assigned to the 1- and 2-positions, respectively.

Although we regarded the above spectroscopic evidence as providing a strong case for structure (21) for pannarin, the synthesis of the degradation product (26) was undertaken to provide conclusive proof. The Ullmann reaction of the *o*-bromo-ester (17) and the phenol (28) [14] unexpectedly gave none of the desired product. From other work it appeared that the phenol (32) might successfully undergo Ullmann reaction with the *o*-bromo-ester (17). Accordingly the bromo-compound (29), available from bromination of (28), was benzylated and afforded the ether (30). Lithium–halogen exchange followed by carboxylation and hydrogenolysis then gave the acid (31). Selective benzylation of the latter afforded the ester (32), which gave the desired product (33) on Ullmann reaction. Hydrogenolysis of (33) then gave the acid (34) which on decarboxylation gave the diaryl ether (26), identical with the degradation product. Pannarin therefore has structure (21), and is thus of the common depsidone type in which both rings are based on β-orcinol-carboxylic acid.

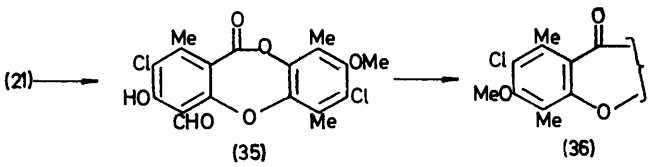


After we had privately communicated our structure for pannarin to Huneck he was able to confirm our proposal

[13] J. J. Bergman, E. A. H. Griffith, B. E. Robertson, and W. D. Chandler, *Canad. J. Chem.*, 1973, **51**, 162; J. J. Bergman, W. D. Chandler, *ibid.*, 1972, **50**, 353; J. J. Bergman, W. D. Chandler, and R. Y. Moir, *ibid.*, 1971, **49**, 223; W. D. Chandler, W. M. Smith, and R. Y. Moir, *ibid.*, 1964, **42**, 2549; and references therein.

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

by chlorination of pannarin (21) to give agropsin (35),[15] the structure of which had recently been proved by degradation to vicanicin (36).[16] The structure of vicanicin was known from *X*-ray analysis of the iodo-acetate.[17]



EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. Light petroleum was a fraction of b.p. 58—65°. All organic extracts were dried over sodium sulphate. Silica gel was B.D.H. 60—120 mesh and all solid products were preadsorbed from dichloromethane on this material prior to chromatography. Preparative layer chromatography (p.l.c.) plates (20 × 20 × 0.1 cm) were coated with Merck Kieselgel GF_{254}. N.m.r. spectra were determined for solutions in deuteriochloroform, unless stated otherwise, at 60 MHz with a Varian A-60 spectrometer. For those at 90 MHz a Bruker HX-90 spectrometer was used. Solutions for nuclear Overhauser experiments were degassed. Mass spectra were determined with a Varian M.A.T. CH-7 instrument (low resolution) or an A.E.I. MS-902 instrument (high resolution) at 70 eV. I.r. spectra were determined with a Perkin-Elmer 137 spectrophotometer.

4-Bromo-2,5-dimethylanisole (9).—Methylation of 2,5-xylenol with methyl sulphate and potassium carbonate in acetone yielded the anisole (8) (93%) as an oil, b.p. 91—92° at 26 mmHg (lit.,[6] 186—188° at 760 mmHg). Bromine (38.7g) in dichloromethane (90 ml) was added to a stirred solution of the anisole (8) (32.9 g) in dichloromethane (200 ml) over 40 min. After stirring for a further 10 min work-up gave the crude product which was fractionated under diminished pressure and afforded the *bromo-compound* (9) (50.4 g, 82%) as an oil, b.p. 82—83° at 0.4 mmHg (Found: C, 50.65; H, 5.35. $C_9H_{11}BrO$ requires C, 50.25; H, 5.15%).

4-Methoxy-2,5-dimethylbenzoic Acid (10).—The bromo-compound (9) (287.2 g) and 1,2-dibromoethane (125 g) in dry ether (600 ml) were added dropwise over 2 h to a stirred suspension of magnesium turnings (50 g) in dry ether (600 ml) so that gentle reflux was maintained. Heating under reflux was continued for a further 20 min and the stirred solution was cooled to −5 °C. A stream of carbon dioxide was passed over the solution at −2 to −5 °C until the exothermic reaction ceased. Work-up in the usual way gave the acid (10) (153.1 g, 66%) as plates, m.p. 167—168° (lit.,[6] 163—165°) (from methanol). The *methyl ester* (11) formed prisms, m.p. 51—52° (from pentane) (Found: C, 67.75; H, 7.15. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25%), τ (CCl_4) 2.33 (1 H, s, 6-H), 3.49 (1 H, s, 3-H), 6.20 and 6.23 (each 3 H, s, OMe), and 7.45 and 7.86 (each 3 H, s, Me).

Nitration of Methyl 4-methoxy-2,5-dimethylbenzoate (11).—The ester (11) (5.0 g) was added in portions over 20 min to stirred fuming nitric acid (25 ml) at 0 °C. After a further 20 min the mixture was poured into ice–water and extracted with ether. The extract was washed with water and with brine and the crude product was chromatographed over silica gel with 5—10% ethyl acetate–light petroleum. The first material eluted was *methyl 4-methoxy-2,5-dimethyl-3-nitrobenzoate* (12) (3.10 g, 50%), which formed needles, m.p. 44—45° (from light petroleum) (Found: C, 55.4; H, 5.45; N, 6.2. $C_{11}H_{13}NO_5$ requires C, 55.25; H, 5.5; N, 5.85%), τ (CCl_4) 2.20 (1 H, s, ArH), 6.15 and 6.18 (each 3 H, s, OMe), and 7.63 and 7.70 (each 3 H, s, Me). Further elution gave *methyl 4-hydroxy-2,5-dimethyl-3-nitrobenzoate* (13) (648 mg, 11%) as leaflets, m.p. 135—136° (from dichloromethane–light petroleum) (Found: C, 53.65; H, 4.95; N, 5.85. $C_{10}H_{11}NO_5$ requires C, 53.35; H, 4.9; N, 6.2%), τ −0.42br (1 H, s, OH), 2.29 (1 H, s, ArH), 6.13 (3 H, s, Me), and 7.38 and 7.71 (each 3 H, s, Me). This material could be removed from the crude product by exhaustive washing with aqueous sodium hydrogen carbonate. On methylation with methyl sulphate and potassium carbonate in dimethylformamide it afforded the nitro-compound (12).

3,6-Dimethyl-2-nitroanisole (14).—The ester (12) was hydrolysed with aqueous methanolic sodium hydroxide in the usual way. The *acid* formed needles, m.p. 154—156° (from dichloromethane–light petroleum) (Found: C, 53.65; H, 5.15; N, 6.05. $C_{10}H_{11}NO_5$ requires C, 53.35; H, 4.9; N, 6.2%). The acid (1.45 g) and copper bronze (420 mg) were suspended in dry quinoline (20 ml) and stirred and heated under nitrogen at 220 °C (bath) for 15 min. Work-up in the usual way gave the crude product, which was chromatographed over silica gel and then distilled under reduced pressure to afford the bright yellow, oily *nitro-compound* (14) (170 mg), b.p. 98° (bath) at 0.05 mmHg (Found: C, 59.75; H, 6.25; N, 7.7%; M^+, 181. $C_9H_{11}NO_3$ requires C, 59.65; H, 6.1; N, 7.75%; *M*, 181), τ (CCl_4) 2.90 and 3.13 (2 H, ABq, *J* 8 Hz, ArH), 6.22 (3 H, s, OMe), and 7.73 and 7.79 (each 3 H, s, Me).

Methyl 3-Amino-4-methoxy-2,5-dimethylbenzoate (15).—The nitro-compound (12) (6.5 g) and 10% palladised charcoal were stirred in methanol (100 ml) under hydrogen until absorption ceased. The catalyst was separated by filtration and the methanol removed under reduced pressure. The residue was diluted with ether and the oily amine (15) (5.11 g, 89%) was extracted into acid in the usual way; τ (CCl_4) 2.94 (1 H, s, ArH), 6.21 and 6.29 (each 3 H, s, OMe), and 7.68 and 7.78 (each 3 H, s, Me). The *N-acetyl derivative* formed needles, m.p. 145—146° (from dichloromethane–light petroleum) (Found: C, 61.75; H, 6.75; N, 5.4. $C_{13}H_{17}NO_4$ requires C, 62.15; H, 6.8; N, 5.55%). The *NN-diacetyl derivative* formed prisms, m.p. 102—103° (from dichloromethane–light petroleum) (Found: C, 61.55; H, 6.8; N, 4.65. $C_{15}H_{19}NO_5$ requires C, 61.4; H, 6.55; N, 4.75%). On a larger scale this reaction was more conveniently carried out at 3 atm.

Methyl 3-Amino-6-bromo-4-methoxy-2,5-dimethylbenzoate (16).—Bromine (16.0 g) in dichloromethane (200 ml) was added at −78 °C to a stirred solution of the amine (15) (20.6 g) in dichloromethane (200 ml). Work-up in the usual way gave the product (25.2 g, 89%) as needles, m.p. 105—108°, of the *bromo-compound* (16) (from dichloromethane–light petroleum) (Found: C, 46.05; H, 4.85; N, 4.65. $C_{11}H_{14}BrNO_3$ requires C, 45.85; H, 4.9; N, 4.55%), τ 6.14 and 6.33 (each 3 H, s, OMe), and 7.74 and 8.00 (each 3 H, s, Me).

Sandmeyer Reaction of the Amine (16).—The amine (16) (14.4 g) was suspended in water (150 ml) and concentrated

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hydrochloric acid (18.5 ml) and stirred at 0—5 °C during dropwise addition of sodium nitrite (3.7 g) in water (14 ml). The suspension was stirred at 0—5 °C for 15 min and then filtered and added in a thin stream at 0 °C to a freshly prepared solution of copper(I) chloride (5.6 g) in water (40 ml) and concentrated hydrochloric acid (12.2 ml). The cooling bath was removed and the mixture was stirred at room temperature for 1 h and at 60 °C for 1 h. The cooled suspension was extracted with ether and the extract was washed in turn with dilute aqueous sodium hydroxide, water, and saturated brine. The crude product was chromatographed over silica gel with 5% ethyl acetate–light petroleum as eluant. The first material (10.3 g, 67%) eluted was *methyl 6-bromo-3-chloro-4-methoxy-2,5-dimethylbenzoate* (17) which formed prisms, m.p. 57—58° (from pentane), τ (CCl_4) 6.08 and 6.22 (each 3 H, s, OMe), and 7.63 and 7.70 (each 3 H, s, Me). The corresponding *acid* formed prisms (from dichloromethane), m.p. 165—166° (Found: C, 40.95; H, 3.7. $C_{10}H_{10}BrClO_3$ requires C, 40.9; H, 3.45%). Further elution afforded *methyl 2-bromo-4-methoxy-3,6-dimethylbenzoate* (18) (1.75 g), as an oil, τ 3.42 (1 H, s, ArH), 6.12 and 6.25 (each 3 H, s, OMe), and 7.75 (6 H, s, 2 × Me). The derived *acid* formed rods (from dichloromethane), m.p. 188—190° (Found: C, 46.3; H, 4.3. $C_{10}H_{11}BrO_3$ requires C, 46.35; H, 4.3%).

Methyl 2-Bromo-4-methoxy-3,6-dimethylbenzoate (18) (with Dr. T. M. Cresp).—The diazonium salt was prepared from the amine (16) (2.5 g) as above and was added at 0 °C to stirred 30% phosphinous acid (50 ml). The mixture was stirred at 0 °C for 2 h and then worked up in the usual way. This gave the title ester (1.4 g), identical with that described before.

2,6-Dimethoxy-4-methylphenol (19).—This method is based on that of Hurd and Winberg [9] for the selective demethylation of tri-*O*-methylpyrogallol. The Grignard reagent was prepared in the usual way from methyl iodide (47.3 g), magnesium (8.03 g), and dry ether (140 ml). A solution of 3,4,5-trimethoxytoluene (20) [10] (15.0 g) in dry toluene (100 ml) was added with stirring to the Grignard reagent and the ether was removed by distillation and replaced by an equal volume of dry toluene. The mixture was heated under reflux for 18 h and then cooled and acidified. The phenol (19) was obtained by extraction with dilute sodium hydroxide. It crystallised as prisms (11.7 g, 84%), m.p. 39.5—40.5° (lit.,[7] 36°) (from pentane), τ (CCl_4) 3.75 (2 H, s, ArH), 4.68 (1 H, s, OH), 6.30 (6 H, s, 2 × OMe), and 7.82 (3 H, s, Me). The benzoyl derivative formed prisms, m.p. 122—123° (lit.,[8] 118°) (from dichloromethane–light petroleum) (Found: C, 70.6; H, 6.05. Calc. for $C_{16}H_{16}O_4$: C, 70.55; H, 5.9%).

Methyl 3-Chloro-6-(2,6-dimethoxy-4-methylphenoxy)-4-methoxy-2,5-dimethylbenzoate (6).—The bromo-compound (17) (3.40 g), the phenol (19) (1.87 g), and dry finely ground potassium carbonate (4.5 g) in dry pyridine (15 ml) were stirred under dry nitrogen and gradually heated to 130 °C (bath); copper(II) oxide (0.8 g) was then added. The temperature was raised to 150 °C (bath) and the mixture was stirred under dry nitrogen for 20 h. The cooled mixture was diluted with ether and filtered through kieselguhr and the filtrate was washed in turn with dilute hydrochloric acid, aqueous sodium hydroxide, water, and saturated brine. The crude product was chromatographed over silica gel with 5% ethyl acetate–light petroleum as eluant. The *diaryl ether* (6) (1.05 g, 24%) formed prisms m.p. 77—78° (from dichloromethane–light petroleum) (Found: C, 60.8; H, 6.2%; M^+, 394/396. $C_{20}H_{23}ClO_6$ requires C, 60.85; H, 5.85; *M*, 394/396), τ (CCl_4) 3.74 (2 H, s, ArH), 6.22 (3 H, s, OMe), 6.33 (6 H, s, 2 × OMe), 6.70 (3 H, s, OMe), 7.71 (3 H, s, Me), and 7.82 (6 H, s, 2 × Me).

Methyl 3-Chloro-4-methoxy-6-(3-formyl-2,6-dimethoxy-4-methylphenoxy)-2,5-dimethylbenzoate (7).—The diaryl ether (6) (850 mg) and dichloromethyl methyl ether (0.55 ml) in dry dichloromethane (2 ml) were stirred at 0 °C and treated over 0.5 h with a solution of titanium(IV) chloride (1.0 ml) in dry dichloromethane (1.2 ml). The mixture was then stirred at room temperature for 1 h and poured into dilute hydrochloric acid. The mixture was extracted with ether and the extract washed in turn with saturated aqueous sodium hydrogen carbonate, water, and saturated brine. The crude product formed *prisms* (814 mg, 76%) (from dichloromethane–light petroleum), m.p. 100—102° (Found: C, 60.1; H, 5.3; Cl, 8.35. $C_{21}H_{23}ClO_7$ requires C, 59.65; H, 5.5; Cl, 8.4%), τ (90 MHz) −0.39 (1 H, d, $J_{5',CHO}$ 0.8 Hz, CHO), 3.52 (1 H, s, $W_{\frac{1}{2}}$ 2.1 Hz, 5'-H), 6.11, 6.19, 6.27, and 6.57 (each 3 H, s, OMe), 7.42 (3 H, d, $J_{5',4'\text{-Me}}$ 0.9 Hz, 4'-Me), and 7.67 and 7.77 (each 3 H, br,s, 2- and 5-Me). Irradiation at the frequency of 5'-H caused the CHO and the 4'-Me signals to collapse to sharp singlets.

Degradation of Pannarin.—Pannarin (21). The sample was in the form of needles, m.p. 216.5—218° (lit.,[1] 216—217°); for n.m.r. see Discussion section; mass spectrum identical with that reported; [2] $\nu_{max.}$ ($CHCl_3$) 1 730 (depsidone) and 1 650 cm^{-1} (*o*-hydroxy-aldehyde).

O-Methylpannarin (22).—Pannarin (62.6 mg), potassium carbonate (2.5 g), methyl iodide (2 ml), and dry dimethylformamide (5 ml) were stirred at room temperature for 16 h. The usual work up gave the *methyl ether* (22) in quantitative yield. It formed needles (from dichloromethane–hexane), m.p. 192—194° (Found: M^+, 376.0713. $^{12}C_{19}{}^1H_{17}{}^{35}Cl^{16}O_6$ requires *M*, 376.0713), τ −0.69 (1 H, s, CHO), 3.54br (1 H, s, ArH), 6.05 and 6.21 (each 3 H, s, OMe), and 7.44, 7.70, and 7.80 (each 3 H, s, Me).

Methanolysis and Subsequent Methylation of O-Methylpannarin (22).—The depsidone (22) (61 mg) and absolute methanol (15 ml) in which sodium (28 mg) had been dissolved were heated under gentle reflux under dry nitrogen for 1.25 h. The solution was poured into dilute hydrochloric acid and the crude product, obtained as usual, was methylated as before. P.l.c. over one plate developed with 5% ethyl acetate–light petroleum gave *methyl 3-chloro-6-(2,4-dimethoxy-3,6-dimethylphenoxy)-5-formyl-4-methoxy-2-methylbenzoate* (23) (41.4 mg) as prisms (from methanol), m.p. 94—96° (Found: M^+, 422.1139. $^{12}C_{21}{}^1H_{23}{}^{35}Cl^{16}O_7$ requires *M*, 422.1132), τ (90 MHz) −0.41 (1 H, s, CHO), 3.55 (1 H, s, $W_{\frac{1}{2}}$ 2.1 Hz, ArH), 6.07 (3 H, s, 4-OMe), 6.20 (3 H, s, 4'-OMe), 6.48 (3 H, s, 2'-OMe), 6.66 (3 H, s, ester OMe), 7.73 (3H, s, 2-Me), 7.76 (3H, s, $W_{\frac{1}{2}}$ 2.2 Hz, 6'-Me), and 7.92 (3H, s, $W_{\frac{1}{2}}$ 2.0 Hz, 3'-Me); *m/e* 424 (15%, M^+), 429 (9), 422 (38, M^+), 391 (6), 258 (3), 256 (6) 227 (4), 225 (8), 181 (7), 167 (25), 166 (100), 165 (17), 153 (7), 151 (17), 138 (9), 137 (8), 136 (6), 135 (17), 124 (9), 107 (5), and 105 (6).

Methyl 3-Chloro-5-formyl-4-hydroxy-6-(2-hydroxy-4-methoxy-3,6-dimethylphenoxy)-2-methylbenzoate ('*Pannarin Methoxide*') (27).—Prepared by the method of Yosioka,[1] this formed pale yellow prisms (from methanol), m.p. 197—198° (lit.,[1] 201°), τ (90 MHz), −2.64 (1 H, s, 4-OH), −0.35 (1 H, s, CHO), 3.83 (1 H, s, $W_{\frac{1}{2}}$ 2.0 Hz, ArH), 4.03 (1 H, s, 2'-OH), 6.21 (3 H, s, 4'-OMe), 6.58 (3 H, s, ester OMe), 7.70 (3 H, s, 2-Me), 7.89 (3 H, s, $W_{\frac{1}{2}}$ 2.0 Hz, Me), and 8.01 (3 H, s, $W_{\frac{1}{2}}$ 2.5 Hz, Me); *m/e* 396 (12%, M^+), 395 (9), 394 (35, M^+),

365 (12), 364 (13), 363 (27), 347 (8), 345 (6), 309 (12), 308 (7), 306 (11), 305 (5), 303 (5), 292 (7), 291 (9), 213 (9), 211 (14), 181 (13), 179 (6), 178 (19), 169 (4), 167 (7), 153 (9), 152 (20), 151 (12), 141 (7), 139 (9), 137 (6), 127 (8), 125 (5), 124 (7), 123 (10), 122 (24), 121 (6), 113 (11), 112 (5), 111 (8), 109 (6), 107 (10), and 57 (100).

Selective Demethylation of the Diaryl Ether (23).—The ether (23) (80 mg) in dry dichloromethane (10 ml) was added to boron trichloride (2.0 g) in dry dichloromethane (20 ml) at −10 °C with stirring. After 0.5 h the usual work-up gave the crude product, which was purified by p.l.c. over one plate developed with 2.5% ethyl acetate–light petroleum. This gave *methyl 3-chloro-6-(2,4-dimethoxy-3,6-dimethylphenoxy)-5-formyl-4-hydroxy-2-methylbenzoate* (24) (41 mg) as yellow prisms (from cyclohexane), m.p. 152—154° (Found: M^+, 408.0972. $^{12}C_{20}{}^{1}H_{21}{}^{35}Cl^{16}O_7$ requires M, 408.0976), τ (90 MHz) −2.67 (1 H, s, OH), −0.47 (1 H, s, CHO), 3.54 (1 H, s, $W_{\frac{1}{2}}$ 2.0 Hz, ArH), 6.19 (3 H, s, 4′-OMe), 6.48 (3 H, s, 2′-OMe), 6.73 (3 H, s, ester OMe), 7.74 (6 H, s, 6′- and 2-Me), and 7.91 (3 H, s, $W_{\frac{1}{2}}$ 2.0 Hz, 3′-Me); *m/e* 410 (10%, M^+), 409 (6), 408 (27, M^+), 213 (2), 211 (4), 184 (3), 181 (4), 167 (14), 166 (100), 165 (11), 153 (4), 151 (9), 135 (7), 123 (5), and 121 (5).

Reduction of the Diaryl Ether (24).—The diaryl ether (24) (7.7 mg), platinum oxide (40 mg), perchloric acid (1 drop), and acetic acid (3 ml) were stirred under hydrogen for 12 h. P.l.c. over one plate developed with 15% ethyl acetate–light petroleum gave *methyl 3-chloro-6-(2,4-dimethoxy-3,6-dimethylphenoxy)-4-hydroxy-2,5-dimethylbenzoate* (25) (5.0 mg) as prisms (from light petroleum), m.p. 130—131° (Found: M^+, 394.1175. $^{12}C_{20}{}^{1}H_{23}{}^{35}Cl^{16}O_6$ requires M, 394.1183), τ 3.56 (1 H, s, ArH), 4.14 (1 H, s, D_2O-exchangeable OH), 6.21 (3 H, s, 4′-OMe), 6.46 (3 H, s, 2′-OMe), 6.67 (3 H, s, ester OMe), 7.80 (3 H, s, 5-Me), 7.82 (6 H, s, 2- and 6′-Me), and 7.92 (3 H, s, 3′-Me); *m/e* 397 (8%), 396 (38, M^+), 395 (24), 394 (100, M^+), 365 (3), 363 (9), 349 (2), 347 (7), 333 (4), 331 (6), 229 (2), 227 (6), 167 (11), 166 (40), 165 (51), 153 (15), 138 (9), 135 (6), 123 (5), 121 (6), and 107 (7).

Methylation of the Diaryl Ether (25).—The diaryl ether (25) (4.9 mg) was treated with an excess of ethereal diazomethane for 2 h. The crude product was applied to a layer plate which was developed with 20% chloroform–hexane. This gave *methyl 3-chloro-6-(2,4-dimethoxy-3,6-dimethylphenoxy)-4-methoxy-2,5-dimethylbenzoate* (26), (3.8 mg) as an oil (Found: M^+, 408.1338. $^{12}C_{21}{}^{1}H_{25}{}^{35}Cl^{16}O_6$ requires M, 408.1339), τ (90 MHz) 3.58 (1 H, s, $W_{\frac{1}{2}}$ 2.1 Hz, ArH), 6.19, 6.23, 6.47, and 6.67 (each 3 H, s, OMe), 7.74 (3 H, s, Me), 7.81 (3 H, s, 2 × Me), and 7.91 (3 H, s, Me).

3-Bromo-4,6-dimethoxy-2,5-dimethylphenol (29).—Bromine (5.65 g) in dichloromethane (100 ml) was added rapidly with stirring to a solution of 2,4-dimethoxy-3,6-dimethylphenol (28) (6.4 g) in dichloromethane (200 ml). The usual work-up gave the *bromophenol* (29) (8.6 g, 93%) as needles (from aqueous methanol), m.p. 75.5—76.5° (Found: C, 46.1; H, 4.8; Br, 30.35. $C_{10}H_{13}BrO_3$ requires C, 46.0; H, 5.0; Br, 30.6%) τ 3.63br (1 H, s, OH), 6.27 (6 H, s, 2 × OMe), and 7.69 and 7.76 (each 3 H, s, Me).

1-Benzyloxy-3-bromo-4,6-dimethoxy-2,4-dimethylbenzene (30).—The phenol (29) (11.0 g), benzyl chloride (9.5 g), dry potassium carbonate (21 g), and dry dimethylformamide (75 ml) were stirred on a steam-bath for 18 h. The mixture was cooled and poured into ice-cold dilute hydrochloric acid. After work-up in the usual way the crude product was chromatographed over silica gel with 2.5% ethyl acetate–light petroleum as eluant; this afforded the *benzyl ether* (30) (13.1 g, 98%) as an oil (Found: M^+, 350.0525/352.0497. $^{12}C_{17}{}^{1}H_{19}Br^{16}O_3$ requires M, 350.0517/352.0493), τ (CCl_4), 2.68 (5 H, m, ArH), 5.18 (2 H, s, CH_2), 6.27 and 6.32 (each 3 H, s, OMe), and 7.76 and 7.81 (each 3 H, s, Me).

Benzyl 3-Hydroxy-4,6-dimethoxy-2,5-dimethylbenzoate (32).—The benzyl ether (30) (9.3 g) in dry ether (70 ml) at 0 °C under dry nitrogen, was treated dropwise over 45 min with butyl-lithium (1 equiv.) in dry ether (100 ml). The solution was then stirred at room temperature for 2 h and then a slow stream of carbon dioxide was passed over the surface at −10 °C for 3 h. The mixture was poured into cold dilute hydrochloric acid and the crude product, obtained as usual (sodium hydrogen carbonate), in ethyl acetate (100 ml) containing concentrated hydrochloric acid (2 drops) was stirred in hydrogen with 10% palladised charcoal (0.2 g) until absorption ceased. The usual work up afforded *3-hydroxy-4,6-dimethoxy-2,5-dimethylbenzoic acid* (31) (2.0 g, 33%) as prisms (from dichloromethane–light petroleum), m.p. 110—113° (Found: C, 58.25; H, 6.2. $C_{11}H_{14}O_5$ requires C, 58.4; H, 6.25%). The acid (1.85 g), dry potassium hydrogen carbonate (820 mg), and benzyl bromide (1.40 g) were stirred in dry dimethylformamide (25 ml) for 18 h. Work-up in the usual way gave the *ester* (32) (2.01 g, 80%) as a viscous oil (Found: M^+, 316.1317. $^{12}C_{18}{}^{1}H_{20}{}^{16}O_5$ requires M, 316.1311), τ 2.65 (5 H, m, ArH), 4.09br (1 H, OH), 6.37 and 6.45 (each 3 H, s, OMe), and 7.88 and 7.93 (each 3 H, s, Me).

3-(4-Chloro-3-methoxy-6-methoxycarbonyl-2,5-dimethylphenoxy)-4,6-dimethoxy-2,5-dimethylbenzoic Acid (34).—The phenol (32) and the bromo-ester (17) were subjected to Ullmann reaction as before. This afforded methyl 2-(3-benzyloxycarbonyl-4,6-dimethoxy-2,5-dimethylphenoxy)-5-chloro-4-methoxy-3,6-dimethylbenzoate (33) (9%), as an oil, τ 2.63 (5 H, m, ArH), 4.65 (2 H, s, CH_2), 6.19, 6.34, 6.55, and 6.62 (each 3 H, s, OMe), 7.77 and 7.80 (each 3 H, s, Me), and 7.88 (6 H, s, 2 × Me). This diaryl ether (319 mg) in ethyl acetate (50 ml) containing concentrated hydrochloric acid (1 drop) was stirred in hydrogen with 10% palladised charcoal (30 mg) until absorption ceased. Work-up in the usual way gave the *acid* (34) (251, mg, 96%) as prisms (from dichloromethane–light petroleum), m.p. 195° (with considerable sweating from 165°) (Found: C, 58.35; H, 5.35. $C_{22}H_{25}ClO_8$ requires C, 58.35; H, 5.55%), τ (90 MHz) 6.18 (6 H, s, 2 × OMe), 6.51 and 6.59 (each 3 H, s, OMe), 7.70 (6 H, s, 2 × Me), and 7.79 and 7.81 (each 3 H, s, Me).

Decarboxylation of Acid (34).—The acid (34) (220 mg), copper(I) oxide (3 mg), and 2,2′-bipyridyl (50 mg) in dry bis-(2-methoxyethyl) ether (5 ml) were stirred and heated under gentle reflux under dry nitrogen for 3 h. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate solution which yielded the starting material (102 mg). The crude product was chromatographed over a layer plate developed with 2.5% ethyl acetate–light petroleum. This gave methyl 3-chloro-6-(2,4-dimethoxy-3,6-dimethylphenoxy)-4-methoxy-2,5-dimethylbenzoate (26) (26.5 mg, 25%) as an oil (Found: M^+, 408.1338. Calc. for $^{12}C_{21}{}^{1}H_{25}{}^{35}Cl^{16}O_6$: M, 408.1339), identical (n.m.r. and mass spectra and R_F in three solvent systems) with that obtained from pannarin.

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