Naturally Occurring Dibenzofurans. Part 5.[1] Synthesis of Melacarpic Acid

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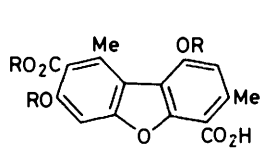
The total synthesis of the lichen dibenzofuran melacarpic acid (**5**) [1-heptyl-3-hydroxy-7-methoxy-9-methyldibenzofuran-2-carboxylic acid] was achieved by intramolecular Ullmann coupling of methyl 5-bromo-4-(2-bromo-5-methoxy-3-methylphenoxy)-6-heptyl-2-methoxybenzoate (**48**) or methyl 6-heptyl-5-iodo-4-(2-iodo-5-methoxy-3-methyl-4-nitrophenoxy)-2-methoxybenzoate (**46**) followed by appropriate transformations.

The lichen dibenzofurans may be regarded as being derived biogenetically by C–C phenolic oxidative coupling of two units of orsellinic acid or its homologues, followed by dehydration of the resultant biphenyl-2,2′-diols and further conventional biochemical modifications. Two modes of oxidative coupling are apparent, as typified by pannaric acid (**1**),[2] schizopeltic acid (**2**),[3] and porphyrilic acid (**3**)[4] on the one hand, and by didymic acid (**4**),[5] melacarpic acid (**5**),[6] condidymic acid (**6**),[7] subdidymic acid (**7**),[8] and strepsilin (**8**)[9] on the other.

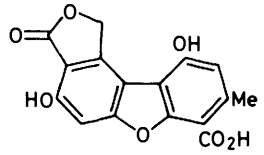
The structures of pannaric acid (**1**)[10] and schizopeltic acid (**2**)[11] have been confirmed by synthesis. Confirmation of the structures of some of the other group of lichen dibenzofurans by total synthesis has been hampered by the unavailability of suitable methods for this purpose. Di-*O*-methylstrepsilin, however, has been synthesized in poor overall yield by methods based on the annelation of suitably substituted 2-vinylbenzofurans by Diels–Alder reactions with dimethyl acetylenedicarboxylate and further transformations.[12] The synthesis of condidymic acid (**6**)[7] was a relatively easy task on account of the symmetry of the intermediate (**9**), which is readily available by Ullmann biaryl synthesis of the appropriate 2,2′-dimethoxybiphenyl followed by cyclization with boiling hydrobromic acid. This type of synthesis cannot be applied to melacarpic acid or didymic acid since carboxy groups are lost under the severe conditions required for ring closure. Consequently, we have adopted a different strategy for the synthesis of melacarpic acid (**5**), which is the subject of this paper, and of didymic acid (**4**), which is described in the following paper.

Melacarpic acid (**5**) was isolated from the lichen *Gymnoderma melacarpum* (Wils.) Yoshim. by Chester and Elix.[6] The structure followed from its mass and ^{1}H n.m.r. spectra. The mass spectrum indicated that melacarpic acid was an *ortho*-hydroxy acid and the ^{1}H n.m.r. spectrum indicated the nature and location of the remaining substituents. The heptyl group was placed at the 1-position *ortho* to the carboxy function rather than at the alternative 9-position on account of the characteristic chemical shift of the α-methylene protons of the heptyl chain in such a location.

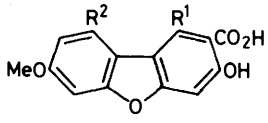
We have found that dibenzofurans are amenable to synthesis by intramolecular Ullmann reaction of di-2-halogenophenyl ethers; thus compound (**10**) is cyclized to the dibenzofuran (**11**) in 88% yield by this method.[13] To adapt this method to the synthesis of didymic or melacarpic acids an intermediate of the type (**12**), where X is halogen, would be required. A possible precursor to such an intermediate might be a nitro-compound of type (**13**). The nitro function would serve to direct halogenation into the ring bearing the ester substituent, and also as a precursor to another halogeno-substituent. Since methyl 2,4-dimethoxy-6-methylbenzoate (**14**) is known to undergo bromination at the 5-position[14] it was reasoned that halogenation of a compound of type (**13**) would proceed in the desired sense. We decided to test these predictions for compounds where the alkyl substituents were methyl groups.



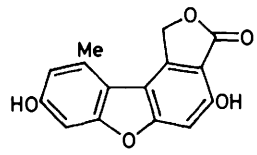
(**1**) R = H
(**2**) R = Me



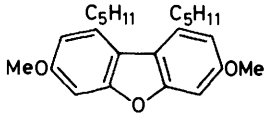
(**3**)



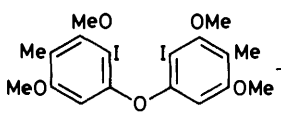
(**4**) $R^1 = C_5H_{11}$, $R^2 = C_3H_7$
(**5**) $R^1 = C_7H_{15}$, R^2 = Me
(**6**) $R^1 = R^2 = C_5H_{11}$
(**7**) $R^1 = R^2 = C_3H_7$



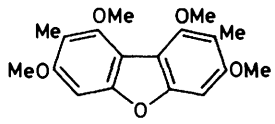
(**8**)



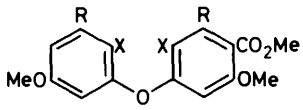
(**9**)



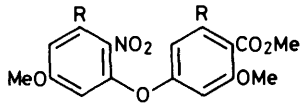
(**10**)



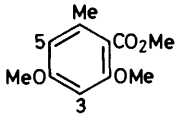
(**11**)



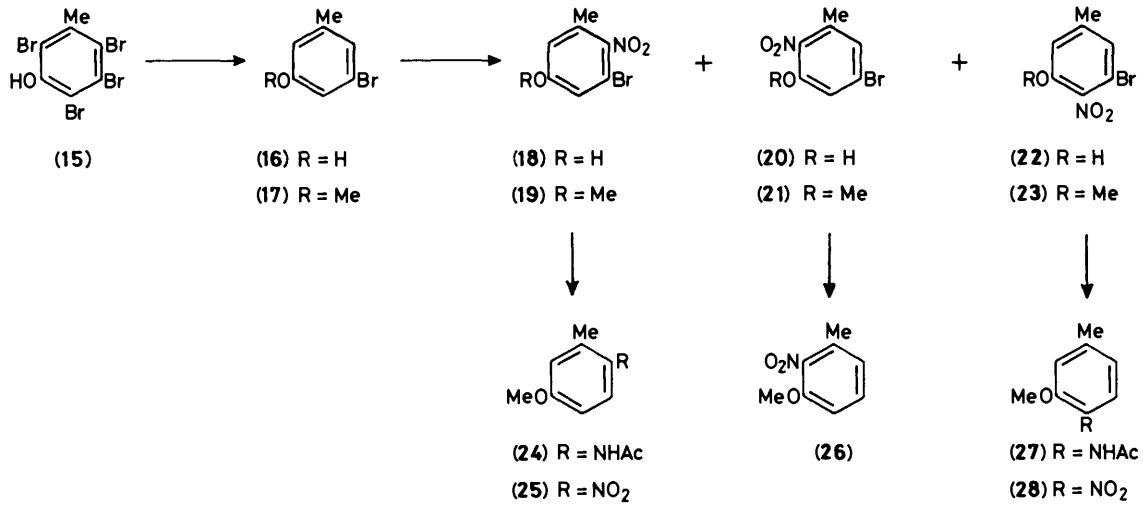
(**12**)



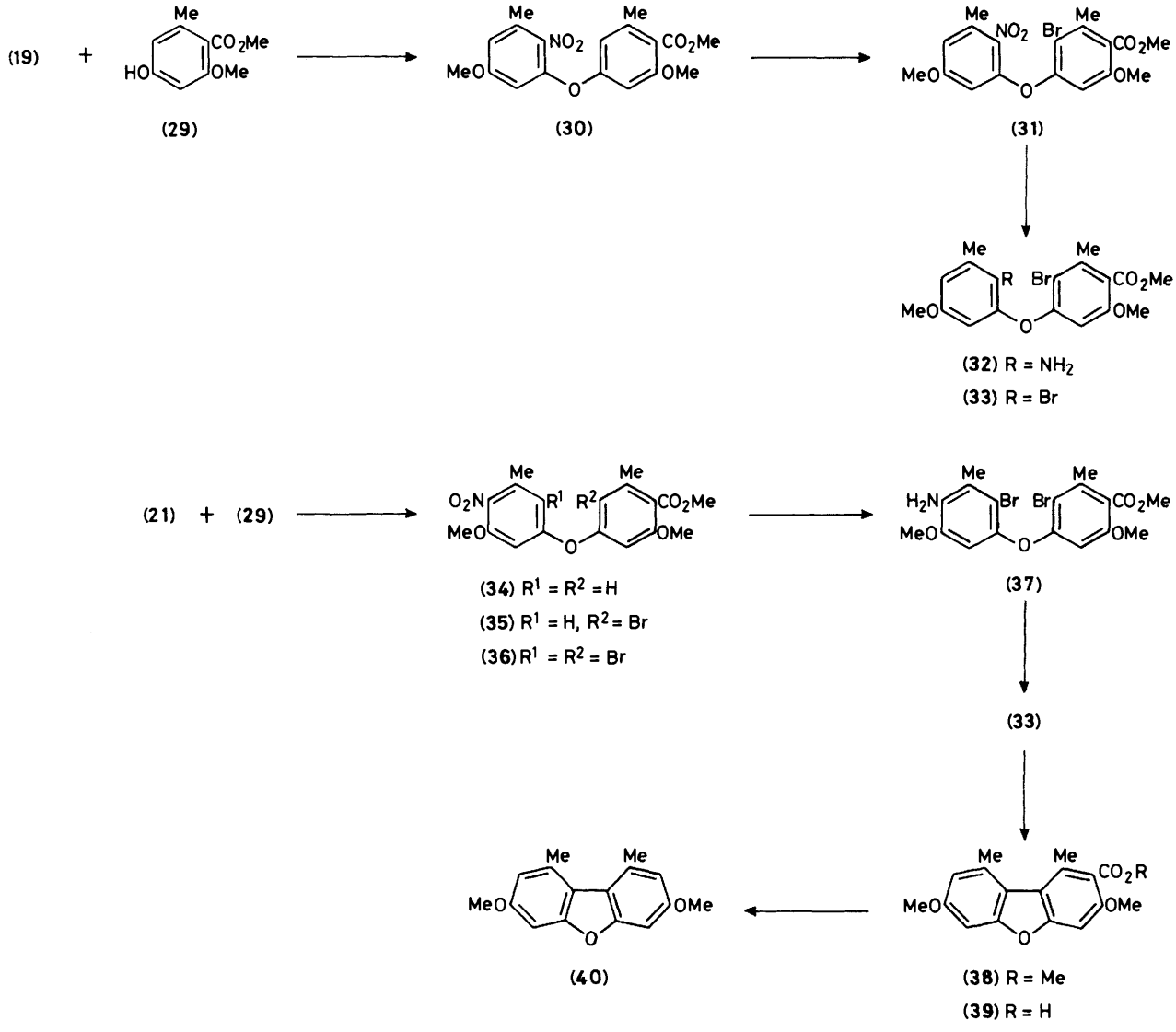
(**13**)



(**14**)



Scheme 1.

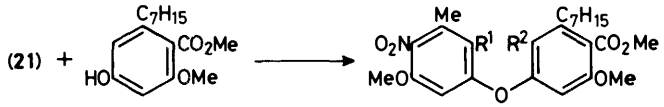


Scheme 2.

For this purpose it was necessary to synthesize the *ortho*-bromo-nitro-compound (**19**) (Scheme 1). The bromocresol (**16**) was consequently required. Kohn and Weissberg[15] described a synthesis of this compound by first treating *m*-cresol with an excess of bromine thus producing the tetrabromocresol (**15**), which was then selectively debrominated at the positions *ortho* and *para* to the hydroxy group on being treated with aluminium chloride and boiling benzene. By careful attention to the reaction conditions this method was adapted to provide a high yield of the required bromocresol (**16**). Nitration of this cresol with concentrated nitric acid in acetic acid gave a 74% yield of a mixture of the three possible nitrophenols (**18**), (**20**), and (**22**) in the ratio 1.84:1.19:1. The *ortho*-nitrophenols (**20**) and (**22**) were conveniently separated from the *para*-isomer by steam distillation. When this reaction was carried out in a two-phase system containing ether, hydrochloric acid, and sodium nitrate in presence of lanthanum ions[16] the yield of nitro-compounds was 69% and the ratios of products were little altered, now being 2.08:1.47:1. Nitration of the methyl ether (**17**) with copper(II) nitrate trihydrate in acetic anhydride was also studied. The total yield of nitro-compounds was 94% and much less nitration *para* to the oxygen function now occurred, the ratios of the products (**19**), (**21**), and (**23**) being 1:1.65:3.26. The interrelationship of the nitrophenols with the methyl ethers was established by methylation. The structures of the methyl ethers (**19**) and (**23**) were proved by their conversion into the known acetanilides (**24**) and (**27**)[17] by catalytic reduction and acetylation. Further evidence for the structures of the bromo-nitro-compounds (**19**), (**21**), and (**23**) was provided by the isolation of the known[17] debromo-nitro-compounds (**25**), (**26**), and (**28**) as by-products when the bromo-nitro-compounds were used in Ullmann diaryl ether reactions.

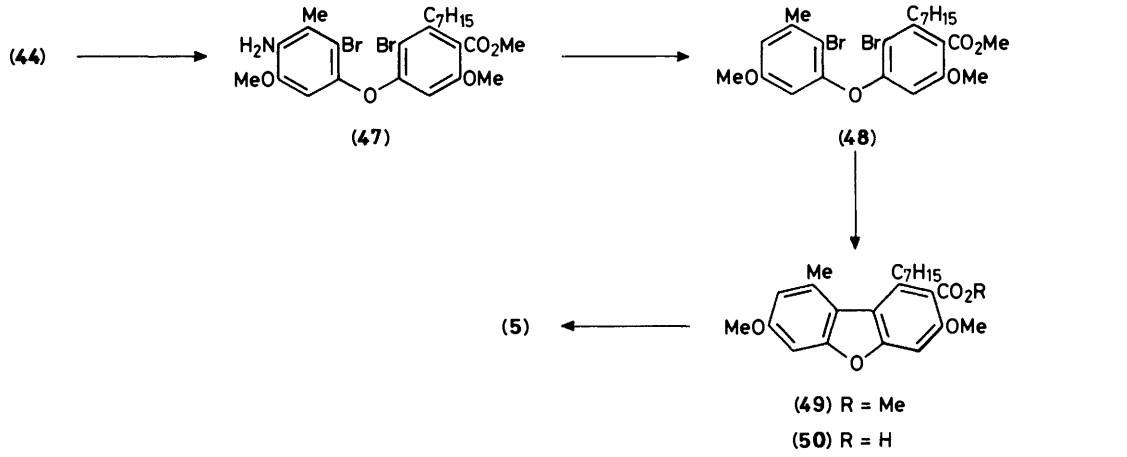
The bromonitroanisole (**19**) (Scheme 2) was treated with methyl isoeverninate (**29**)[18] in an Ullmann reaction. The resultant diaryl ether, formed in high yield, on treatment with 1 mol equiv. of bromine, gave only one bromo-compound, which was tentatively assigned structure (**31**) on the grounds of its ^{1}H n.m.r. spectrum. This compound was reduced with tin(II) chloride and hydrochloric acid to the amine (**32**). On treatment with copper(II) bromide and isopentyl nitrite in acetonitrile at 65 °C the amine (**32**) underwent substitutive deamination[19] and a moderate yield of the dibromo-compound (**33**) resulted. However this product was contaminated by a tribromo-compound of unknown structure which we were unable to remove. Doyle *et al.*[19] have observed similar substitution of bromine at an aromatic ring position during substitutive deamination reactions. We were encouraged to seek a better synthesis of the dibromo-compound (**33**) since treatment of the impure compound with activated copper bronze at 260 °C under dry nitrogen gave the dibenzofuran (**38**) in 31% yield.

In order to synthesize the dibromo-compound (**33**) by a better method we prepared the diaryl ether (**34**) from the bromo-nitro-compound (**21**) and methyl isoeverninate (**29**). Reaction of this diaryl ether with 1 mol equiv. of bromine gave only one bromo-compound tentatively assigned structure (**35**) on the grounds of its ^{1}H n.m.r. spectrum. When this compound was allowed to react with a further mol equiv. of bromine a dibromo-compound resulted, which was similarly assigned structure (**36**). This was converted into the pure dibromo-compound (**33**) by first reduction to the amine (**37**) by transfer hydrogenation,[20] and then by treatment of the derived diazonium salt with phosphinic acid. When the pure dibromo-compound (**33**) was



(**41**)

(**42**) $R^1 = R^2 = H$
(**43**) $R^1 = H$, $R^2 = Br$
(**44**) $R^1 = R^2 = Br$
(**45**) $R^1 = H$, $R^2 = I$
(**46**) $R^1 = R^2 = I$



Scheme 3.

treated with copper bronze a 48% yield of the dibenzofuran (**38**) resulted. In order to verify the positions of the bromo-substituents in the dibromo-compound (**33**) the dibenzofuran (**38**) was hydrolysed to the acid (**39**), which on decarboxylation afforded the known dibenzofuran (**40**)[21] identical with an authentic sample.[22]

We now sought to apply this method of dibenzofuran synthesis to the case of melacarpic acid. Reaction of the bromo-nitro-compound (**21**) (Scheme 3) with methyl 6-heptyl-4-hydroxy-2-methoxybenzoate (**41**), available from previous work,[23] gave the diaryl ether (**42**) in good yield. Sequential bromination gave first the monobromo-compound (**43**) and then the dibromo-compound (**44**). The latter compound was reduced to the amine (**47**) by transfer hydrogenation and the derived diazonium salt on treatment with phosphinic acid gave the required dibromo-compound (**48**). On treatment with activated copper bronze under dry nitrogen at 260 °C this last-mentioned compound provided the dibenzofuran (**49**) in 29% yield.

In order to secure a higher yield of the dibenzofuran (**49**) the diaryl ether (**42**) was sequentially iodinated with iodine and silver trifluoroacetate in chloroform thus providing the monoido-compound (**45**) and then the di-iodo-compound (**46**). Although the di-iodo-compound (**46**) was smoothly converted by transfer hydrogenation into the corresponding amine, this compound proved impossible to deaminate in satisfactory yield. Consequently we attempted ring closure of the di-iodo-compound (**46**) to the nitrodibenzofuran (**51**) and this reaction was achieved in 37% yield. The nitrodibenzofuran (**51**) was now converted into the amine (**52**) which on diazotization and treatment with phosphinic acid provided the dibenzofuran (**49**).

The conversion of the dibenzofuran (**49**) into synthetic melacarpic acid (**5**) was readily achieved by hydrolysis to the acid (**50**), which on treatment with boron trichloride underwent selective demethylation thus affording the natural product. The synthetic material was identical with an authentic sample of the natural product by all the usual criteria.

Experimental

General directions are given in Part 4.[1]

2,4,5,6-*Tetrabromo*-3-*methylphenol* (**15**).—Aluminium powder (5.0 g) was added slowly to bromine (142.5 ml) with stirring at 0 °C. The mixture was then stirred at room temperature for 10 min and then *m*-cresol (50 g) was added dropwise with stirring. The excess of bromine was then removed under reduced pressure with warming on a steam-bath. The solid residue was covered with warm dilute hydrochloric acid and triturated. The crude product was separated by filtration, washed with water, and then crystallized from ethanol; it formed needles of the product (**15**) (152.0 g, 77%), m.p. 194—196 °C (lit.,[15] 196 °C).

3-*Bromo*-5-*methylphenol* (**16**).—The tetrabromophenol (**15**) (54.5 g), finely divided aluminium chloride (Fluka prakt; 113.3 g), and anhydrous benzene (110 ml) were stirred and heated under reflux for 0.5 h. The termination of the reaction is indicated when the addition of a sample of the reaction mixture to water produces an orange-red colour in the organic layer. The mixture was poured into ice and water and then extracted with ether. The crude product was isolated by extraction with aqueous 10% sodium hydroxide in the usual way. Distillation of the oily product under reduced pressure gave the bromophenol (**16**) (19.95 g, 83%), b.p. 85 °C at 0.6 mmHg (Kugelrohr), which soon crystallized as needles, m.p. 57—58 °C (lit.,[15] 54 °C).

Nitration of 3-*Bromo*-5-*methylphenol* (**16**).—(*a*) *With concentrated nitric acid.* A solution of concentrated nitric acid (70% w/w; 11.1 g) in acetic acid (100 ml) was added dropwise with stirring over 4 h to a solution of the phenol (**16**) (18.1 g) in acetic acid (100 ml) so that the reaction temperature was 15—16 °C. The mixture was stirred for a further 20 min at 15 °C and then poured into ice and water and extracted with ether. Most of the acetic acid was removed by washing with saturated sodium hydrogen carbonate solution. The ethereal layer was then washed with water and the crude product was subjected to steam distillation until no more material passed over. Isolation of the pot residue with ethyl acetate gave 3-*bromo*-5-*methyl*-4-*nitrophenol* (**18**) (7.55 g, 34%), which formed glistening yellow plates (from dichloromethane–light petroleum), m.p. 129—129.5 °C (Found: C, 36.0; H, 2.55; Br, 34.35; N, 5.70%; M^+, 231/233. $C_7H_6BrNO_3$ requires C, 36.25; H, 2.6; Br, 34.45; N, 6.05%; *M*, 231/233); δ 2.30 (3 H, d, $J_{6\text{-H,Me}}$ 0.5 Hz, Me), 5.93br (1 H, OH), and 6.67 and 6.95 (2 H, AB, *J* 2.5 Hz, 6- and 2-H) (the signal due to the 6-H was further split by coupling to the methyl protons and this splitting was removed by irradiation at δ 2.30). On methylation with methyl iodide and potassium carbonate in *N*,*N*-dimethylformamide at room temperature under dry nitrogen during 14 h this compound gave the *methyl ether* (**19**) (97%) which formed pale yellow laths (from light petroleum), m.p. 46.5—47 °C (Found: C, 38.9; H, 3.25; Br, 32.45; N, 5.4%, M^+, 245/247. $C_8H_8BrNo_3$ requires C, 39.05; H, 3.3; Br, 32.45; N, 5.7%; *M*, 245/247); δ2.34 (3 H, d, $J_{6\text{-H,Me}}$ 0.5 Hz, Me), 3.81 (3 H, s, OMe), and 6.71 and 6.97 (2 H, AB, *J* 2.5 Hz, 6- and 2-H) (the signal due to the 6-H was further split by coupling to the methyl protons and this splitting was removed by irradiation at δ 2.34). The methyl ether (**19**) (200 mg) was stirred in ethanol (5 ml) with 10% palladized charcoal (25 mg) under hydrogen for 18 h. The crude amine, so obtained, was converted into 4′-methoxy-2′-methylacetanilide (**24**) in the usual way. An authentic sample of this compound was prepared by sequential methylation, catalytic hydrogenation and acetylation of 3-methyl-4-nitrophenol.[24] The acetanilide (**24**) formed needles (from dichloromethane–light petroleum), m.p. and mixed m.p. 133—134 °C (lit.,[17] 132 °C). The steam-volatile material from the steam distillation was isolated with ethyl acetate and chromatographed over silica gel with 2.5—5% ethyl acetate–light petroleum as eluant. The first material eluted was 5-*bromo*-3-*methyl*-2-*nitrophenol* (**20**) (4.90 g, 22%), which was distilled under diminished pressure and yielded a yellow oil, b.p. 135 °C at 0.5 mmHg (Kugelrohr) (Found: C, 36.2; H, 2.65; Br, 34.0; N, 5.6. $C_7H_6BrNO_3$ requires C, 36.25; H, 2.6; Br, 34.45; N, 6.05%); δ 2.58 (3 H, narrow m, Me), 6.95 and 7.15 (2 H, AB with further coupling to Me, 4- and 6-H), and 10.42br (1 H, D_2O exchangeable OH) (irradiation at δ 2.58 caused collapse of the aromatic proton signals to an AB system with J_m 2.5 Hz). On methylation in the manner described for compound (**18**) this gave the *methyl ether* (**21**) as pale green laths (from light petroleum), m.p. 116.5—117 °C (Found: C, 39.4; H, 3.3; Br, 32.5; N, 5.7. $C_8H_8BrNO_3$ requires C, 39.05; H, 3.3; Br, 32.45; N, 5.7%); δ 2.26 (3 H, narrow m, Me), 3.85 (3 H, s, OMe), and 7.00 (2 H, br s, ArH) (irradiation at δ 2.26 sharpened the signal of the aromatic protons). Further elution yielded 3-*bromo*-5-*methyl*-2-*nitrophenol* (**22**) (4.10 g, 18%), which formed yellow needles (from light petroleum), m.p. 74—75 °C (Found: C, 36.4: H, 2.55; Br, 34.05; N, 6.0. $C_7H_6BrNO_3$ requires C, 36.25; H, 2.6; Br, 34.45; N, 6.05%); δ 2.33 (3 H, narrow m, Me), 6.88 and 7.11 (2 H, AB with further coupling to Me, ArH), and 10.85br (1 H, D_2O-exchangeable OH) (irradiation at δ 2.33 caused collapse of the aromatic signals to an AB system with J_m 2.0 Hz). On methylation as for compound (**18**) this gave the *methyl ether* (**23**) as fine pale yellow needles (from light petroleum), m.p. 73—74.5 °C (Found: C, 39.2; H, 3.3; N, 5.65%; M^+, 245/247. $C_8H_8BrNO_3$ requires C, 39.05; H, 3.3; N, 5.7%; *M*, 245/247); δ 2.35 (3 H, narrow m, Me), 3.84 (3 H, s, OMe), 6.77 (1 H, br s, 6-H), and 6.99 (1 H, narrow m, 4-H) (irradiation at δ 2.35 caused

collapse of the aromatic proton signals to an AB system). On hydrogenation and acetylation in the same manner as described for compound (**19**) this methyl ether gave 2′-methoxy-4′-methylacetanilide (**27**) as needles (from dichloromethane–light petroleum), m.p. 125—126 °C (lit.,[17] 131 °C).

(*b*) *In the presence of lanthanum ions* (*with* **Albert V. Russo**).—The bromophenol (**16**) (5.0 g) in ether (80 ml) was stirred with concentrated hydrochloric acid (22 ml) and water (22 ml) containing sodium nitrate (2.39 g) and lanthanum carbonate (126 mg) for 9 h. The mixture was then diluted with ethyl acetate and the organic layer was separated and washed with water. The crude product was then subjected to steam distillation. Isolation of the pot residue with ethyl acetate gave 3-bromo-5-methyl-4-nitrophenol (**18**) (1.84 g, 30%), which formed yellow plates (from dichloromethane–light petroleum), m.p. and mixed m.p. 129—129.5 °C. The steam-volatile material was methylated with methyl iodide and potassium carbonate in anhydrous *N,N*-dimethylformamide at room temperature under dry nitrogen. The crude product was chromatographed over silica gel with 2.5—5% ethyl acetate–light petroleum as eluant. The first material eluted was the methyl ether (**21**) (1.48 g, 22%), which formed pale green laths (from light petroleum), m.p. and mixed m.p. 116.5—117 °C. Further elution afforded the methyl ether (**19**) (130 mg, 2%), which formed pale yellow laths (from light petroleum), m.p. and mixed m.p. 46.5—47 °C. The final compound to be eluted was the methyl ether (**23**) (1.0 g, 15%), which formed pale yellow needles (from light petroleum), m.p. and mixed m.p. 73—74.5 °C.

1-*Bromo*-3-*methoxy*-5-*methylbenzene* (**17**).—The bromophenol (**16**) (9.90 g) and anhydrous potassium carbonate (8.77 g) were stirred in anhydrous acetone (50 ml) during the dropwise addition of dimethyl sulphate (8.00 g). The mixture was then heated and stirred under reflux for 4 h. The usual work-up gave the methyl ether (**17**) (10.53 g, 99%) as an oil, b.p. 94 °C at 0.8 mmHg (Kugelrohr) (lit.,[25] 139—140 °C at 20 mmHg).

Nitration of 1-*Bromo*-3-*methoxy*-5-*methylbenzene* (**17**).—Copper(II) nitrate trihydrate (8.62 g) was added in portions over 1 h to a stirred solution of the methyl ether (**17**) (7.17 g) in acetic anhydride (40 ml) and the reaction temperature was kept below 30 °C by cooling in water. The mixture was stirred for 1 h longer and then diluted with water and ice; stirring was continued for a further 0.5 h. The lime-green waxy solid was separated by filtration, dried *in vacuo*, and then chromatographed over silica gel with 1—5% ethyl acetate–light petroleum as eluant. The first material eluted was the methyl ether (**21**) (4.57 g, 52%), which formed pale green laths (from light petroleum), m.p. and mixed m.p. 116.5—117 °C. This was followed by the methyl ether (**19**) (1.40 g, 16%) which formed pale yellow laths (from light petroleum), m.p. and mixed m.p. 46.5—47 °C. The final material to be eluted was the methyl ether (**23**) (2.31 g, 26%), which formed pale yellow needles (from light petroleum), m.p. and mixed m.p. 73—74.5 °C.

Methyl 2-*Methoxy*-4-(3-*methoxy*-5-*methyl*-2-*nitrophenoxy*)-6-*methylbenzoate* (*with* **Albert V. Russo**).—Methyl 4-hydroxy-2-methoxy-6-methylbenzoate (**29**) (2.10 g), the methyl ether (**23**) (2.78 g), and anhydrous finely divided potassium carbonate (1.25 g) were stirred and heated gradually to 140 °C (bath) under dry nitrogen. Finely divided anhydrous copper(II) oxide (990 mg)[26] was then added, and the mixture was stirred and heated at 140 °C (bath) for 16 h. The cooled mixture was diluted with ether and filtered through Celite. The filtrate was washed in turn with cold dilute hydrochloric acid, dilute aqueous sodium hydroxide, water, and finally saturated brine. The crude product was subjected to steam distillation. Extraction of the distillate with ethyl acetate afforded 2-methoxy-4-methyl-1-nitrobenzene (**28**) (322 mg, 17%), which formed yellow needles (from light petroleum), m.p. 55—56 °C (lit.,[17] 60—61 °C); δ 2.41 (3 H, s, Me), 3.92 (3 H, s, OMe), 6.74 (1 H, m, $W_{\frac{1}{2}}$ 3.0 Hz, 3-H), and 6.86 (2 H, m, $W_{\frac{1}{2}}$ 5.0 Hz, 5- and 6-H). The pot residue was isolated with ethyl acetate and filtered through alumina with 10% ethyl acetate–light petroleum as eluant. The *product* (2.29 g, 59%) formed yellow needles (from dichloromethane–light petroleum), m.p. 132—133 °C (Found: C, 59.85; H, 5.25; N, 3.9%; M^+, 361. $C_{18}H_{19}NO_7$ requires C, 59.85; H, 5.3; N, 3.9%; *M*, 361); δ 2.30 and 2.25 (each 3 H, s, Me), 3.76 (3 H, s, OMe), 3.89 (6 H, s, 2 × OMe), 6.36 and 6.60 (2 H, broadened AB, *J* 1.5 Hz, 6′- and 4′-H), and 6.47 and 6.50 (2 H, broadened AB, *J* 2.0 Hz, 3- and 5-H) (irradiation at δ 2.30 sharpened the AB system at δ 6.47 and 6.50, and irradiation at δ 2.25 sharpened the other AB system).

Methyl 2-*Methoxy*-4-(5-*methoxy*-3-*methyl*-2-*nitrophenoxy*)-6-*methylbenzoate* (**30**).—This was prepared (75%) from the phenol (**29**) and the bromo-compound (**19**) as for the foregoing diphenyl ether. The steam distillate afforded 4-methoxy-2-methyl-1-nitrobenzene (**25**) (8%) which formed needles (from light petroleum), m.p. 49—50 °C (lit.,[17] 54—55 °C) undepressed on admixture with an authentic sample; δ (60 MHz) 2.60 (3 H, s, Me), 3.80 (3 H, s, OMe), 6.70 (2 H, m, 3- and 5-H), and 7.98 (1 H, m, 6-H). The *diphenyl ether* (**30**) formed glistening buff prisms (from dichloromethane–light petroleum), m.p. 96.5—98.5 °C (Found: C, 60.2; H, 5.4; N, 3.85%; M^+, 361. $C_{18}H_{19}NO_7$ requires C, 59.85; H, 5.3; N, 3.9%; *M*, 361); δ 2.25 and 2.36 (each 3 H, s, Me), 3.73, 3.76, and 3.88 (each 3 H, s, OMe), 6.32 and 6.53 (2 H, AB, *J* 2.5 Hz, 6′- and 4′-H), and 6.45 and 6.49 (2 H, AB, *J* 2.0 Hz, 5- and 3-H) (irradiation at δ 2.25 sharpened the AB system at δ 6.45 and 6.49, and irradiation at δ 2.36 sharpened the other AB system).

Methyl 5-*Bromo*-2-*methoxy*-4-(5-*methoxy*-3-*methyl*-2-*nitrophenoxy*)-6-*methylbenzoate* (**31**).—Bromine (293 mg) in dichloromethane (3 ml) was added dropwise over 10 min to a stirred solution of the diphenyl ether (**30**) (660 mg) in dichloromethane (6 ml). The solution was stirred for a further 5 min and then diluted with ethyl acetate and washed with water. The product was obtained as a viscous yellow gum, which was crystallized from dichloromethane–light petroleum whereupon it formed pale yellow *needles* (720 mg, 90%), m.p. 93—95 °C (Found: C, 49.3; H, 4.1; Br, 18.1; N, 3.0%; M^+, 439/441. $C_{18}H_{18}BrNO_7$ requires C, 49.1; H, 4.1; Br, 18.15; N, 3.2%; *M*, 439/441); δ 2.37 (6 H, s, 2 × Me), 3.72, 3.74, and 3.94 (each 3 H, s, OMe), 6.10 and 6.49 (2 H, AB, *J* 2.5 Hz, 6′- and 4′-H), and 6.57 (1 H, s, 3-H).

Methyl 2-*Methoxy*-4-(3-*methoxy*-5-*methyl*-4-*nitrophenoxy*)-6-*methylbenzoate* (**34**).—Ullmann reaction between the phenol (**29**) (2.23 g) and the bromo-compound (**21**) (2.80 g) gave the *diphenyl ether* (**34**) (77%), which formed yellow needles (from dichloromethane–light petroleum), m.p. 132.5—133.5 °C (Found: C, 59.4; H, 5.3; N, 3.7%; M^+, 361. $C_{18}H_{19}NO_7$ requires C, 59.85; H, 5.3; N, 3.9%; *M*, 361); δ 2.26 and 2.28 (each 3 H, s, Me), 3.77, 3.81, and 3.91 (each 3 H, s, OMe), 6.38 and 6.51 (2 H, AB, *J* 2.5 Hz, 6′- and 2′-H), and 6.47 (2 H, s, 3- and 5-H). Extraction of the steam distillate with ethyl acetate gave 2-methoxy-6-methyl-1-nitrobenzene (**26**) (16%) as an oil, b.p. 185 °C at 22 mmHg (Kugelrohr), which crystallized from cold light petroleum as blades, m.p. 48—49 °C (lit.,[17] 49 °C).

Methyl 5-*Bromo*-2-*methoxy*-4-(3-*methoxy*-5-*methyl*-4-*nitrophenoxy*)-6-*methylbenzoate* (**35**).—Bromination of the diphenyl ether (**34**) as for compound (**30**) gave the *diphenyl ether* (**35**) (97%), which formed glistening yellow prisms (from light petroleum), m.p. 180—181 °C (Found: C, 48.7; H, 4.1; N, 3.2%;

M^+, 439/441. $C_{18}H_{18}BrNO_7$ requires C, 49.1; H, 4.1; N, 3.2%; *M*, 439/441); δ 2.24 and 2.40 (each 3 H, s, Me), 3.75, 3.83, and 3.93 (each 3 H, s, OMe), 6.25 and 6.50 (2 H, AB, *J* 2.5 Hz, 6′- and 2′-H), and 6.54 (1 H, s, 3-H).

Methyl 5-Bromo-4-(2-bromo-5-methoxy-3-methyl-4-nitrophenoxy)-2-methoxy-6-methylbenzoate (**36**).—Bromine (440 mg) was added to a solution of the monobromo-compound (**35**) (1.10 g) in dichloromethane (20 ml) and the solution was set aside with exclusion of light for 19.5 h. The solution was then diluted with ethyl acetate and was washed successively with saturated sodium hydrogen carbonate solution, water, and finally saturated brine. The crude product formed needles (1.10 g, 85%) of the *dibromo-compound* (**36**) (from dichloromethane–light petroleum), m.p. 191.5—192.5 °C (Found: C, 41.7; H, 3.3; N, 2.7%; M^+, 517/519/521. $C_{18}H_{17}Br_2NO_7$ requires C, 41.65; H, 3.3; N, 2.7%; *M*, 517/519/521); δ 2.41 (6 H, s, 2 × Me), 3.72, 3.74, and 3.93 (each 3 H, s, OMe), and 6.28 and 6.43 (each 1 H, s, ArH).

Methyl 4-(4-Amino-2-bromo-5-methoxy-3-methylphenoxy)-5-bromo-2-methoxy-6-methylbenzoate (**37**).—Palladized charcoal (Engelhard; 10%; 400 mg) was added in portions to a suspension of the nitro-compound (**36**) (760 mg) in methanol (10 ml) and phosphinic acid (50%; 5 ml) under dry nitrogen and the mixture was then stirred and heated under reflux for 25 min. The cooled solution was diluted with ethyl acetate and the catalyst was recovered by filtration. The filtrate was washed in turn with saturated sodium hydrogen carbonate solution, water, and finally saturated brine. Removal of the solvent under reduced pressure gave the crude product which formed needles (680 mg, 95%) of the *amine* (**37**) from dichloromethane–light petroleum), m.p. 175—176 °C (Found: C, 44.0; H, 3.9; Br, 32.35; N, 3.15%; M^+, 487/489/491. $C_{18}H_{19}Br_2NO_5$ requires C, 44.2; H, 3.9; Br, 32.65; N, 2.85%; *M*, 487/489/491); δ 2.32 and 2.40 (each 3 H, s, Me), 3.41—3.96br (2 H, NH_2), 3.56, 3.76, and 3.87 (each 3 H, s, OMe), and 6.05 and 6.50 (each 1 H, s, ArH).

Methyl 5-Bromo-4-(2-bromo-5-methoxy-3-methylphenoxy)-2-methoxy-6-methylbenzoate (**33**).—(*a*) To a warm solution of tin(II) chloride dihydrate (5.5 g) in concentrated hydrochloric acid (6 ml) and methanol (6 ml) was added a solution of the nitro-compound (**31**) (1.5 g) in methanol (4 ml) over 15 min. The mixture was then heated on a steam-bath for 4 h, cooled and poured into an excess of dilute aqueous sodium hydroxide. Isolation with ether yielded the amine (**32**) (1.15 g, 69%) as a pale yellow gum; δ (60 MHz) 2.13 and 2.33 (each 3 H, s, Me), 3.57, 3.58, and 3.80 (each 3 H, s, OMe), 3.73br (2 H, NH_2), 6.17 and 6.39 (2 H, AB, *J* 2.5 Hz, 4′- and 6′-H), and 6.25 (1 H, s, 3-H). The amine (**32**) (1.00 g) in dry acetonitrile (2 ml) was added dropwise over 5 min to a stirred mixture of isopentyl nitrite (430 mg) and anhydrous copper(II) bromide (600 mg) in dry acetonitrile (6 ml) at 65 °C (bath). The mixture was stirred and heated at this temperature for 13 h, cooled, and poured into dilute hydrochloric acid and extracted with ether. The extract was washed with water and with saturated brine. The crude product was filtered through a plug of alumina with 5% ethyl acetate–light petroleum as eluant. This afforded the product as an oil (530 mg), which crystallized from methanol as prisms, m.p. 115—116 °C. Analysis of this material by g.l.c.–mass spectrometry indicated that it was the dibromo-compound (**33**), contaminated by 20% of a tribromo-compound. It migrated as one spot on t.l.c. on silica or alumina in a variety of solvent systems and it was not obtained pure after numerous crystallizations.

(*b*) Sodium nitrite (121 mg) in water (3 ml) was added dropwise to a stirred solution of the amine (**37**) (500 mg) in dioxane (20 ml), water (3 ml), and concentrated hydrochloric acid (3 ml) so that the reaction temperature was 0—5 °C. The mixture was stirred at 0 °C for 0.5 h and then cold phosphinic acid (50%; 5 ml) was added dropwise. The mixture was set aside at 0 °C for 21 h and then diluted with water and extracted with ether. The extract was washed in turn with dilute aqueous ammonia, water, and finally saturated brine. The crude product was filtered through alumina with 5% ethyl acetate–light petroleum as eluant. The *dibromo-compound* (**33**) (481 mg, 99%) crystallized from methanol as prisms, m.p. 112.5—114 °C (Found: C, 45.1; H, 3.7; Br, 34.3%; M^+, 472/474/476. $C_{18}H_{18}Br_2O_5$ requires C, 45.6; H, 3.85; Br, 33.7%; *M*, 472/474/476); δ 2.39 and 2.43 (each 3 H, s, Me), 3.66, 3.70, and 3.90 (each 3 H, s, OMe), 6.24 and 6.62 (2 H, AB, *J* 3.0 Hz, 6′-and 4′-H), and 6.31 (1 H, s, 3-H).

Methyl 3,7-Dimethoxy-1,9-dimethyldibenzofuran-2-carboxylate (**38**).—An intimate mixture of the pure dibromo-compound (**33**) (330 mg) and activated copper bronze (1.0 g) was heated at 260 °C (bath) under dry nitrogen for 2 h. The cooled mixture was exhaustively extracted with boiling ethyl acetate, and the crude product was filtered through alumina with 10% ethyl acetate–light petroleum as eluant. The product was then subjected to p.l.c. over silica with 5% ethyl acetate–light petroleum as developer. The band of higher R_F afforded the debromo-compound (33 mg) and the band of lower R_F gave the *dibenzofuran* (**38**) (104.5 mg, 48%), which formed prisms (from dichloromethane–light petroleum), m.p. 154—155 °C (Found: C, 69.2; H, 5.9%; M^+, 314. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.75%; *M*, 314); δ (80 MHz) 2.78 (3 H, s, 9-Me), 2.83 (3 H, s, 1-Me), 3.87, 3.89, and 3.95 (each 3 H, s, OMe), 6.70 and 6.89 (2 H, AB, *J* 2.0 Hz, 8- and 6-H), and 6.92 (1 H, s, 4-H); $\lambda_{max.}$(MeOH) 226, 225infl, and 306 nm (ε 33 400, 14 400, and 20 000). When the dibromo-compound (**33**) which was contaminated with tribromo-compound was used in this reaction the yield fell to 31%.

3,7-Dimethoxy-1,9-dimethyldibenzofuran-2-carboxylic Acid (**39**).—The ester (**38**) (117 mg) and potassium hydroxide (220 mg) in dimethyl sulphoxide (10 ml) and water (0.5 ml) were heated on a steam-bath for 1.67 h. The solution was then diluted with water and extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid and the product was isolated with ethyl acetate. The *acid* (**39**) (110 mg, 98%) formed pale yellow prisms (from ethyl acetate–light petroleum), m.p. 248—249 °C (Found: C, 67.85; H, 5.35%; M^+, 300. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.35%; *M*, 300).

3,7-Dimethoxy-1,9-dimethyldibenzofuran (**40**).—Copper chromite (60 mg) was added to a stirred solution of the acid (**39**) (110 mg) in anhydrous quinoline (2 ml) under dry nitrogen at 180 °C (bath). The mixture was stirred and heated at this temperature for 1.5 h and then cooled and diluted with ethyl acetate and washed successively with dilute hydrochloric acid, water, and finally with saturated brine. The crude product was subjected to p.l.c. over silica with 2.5% ethyl acetate–light petroleum as developer. The major band gave the product (**40**) (10 mg, 11%) as plates (from light petroleum), m.p. 158—159.5 °C (lit.,[22] 158—159 °C; lit.,[21] 159—160 °C), undepressed on admixture with an authentic sample; δ 2.81 (6 H, s, 2 × Me), 3.83 (6 H, s, 2 × OMe), 6.65 and 6.85 (4 H, AB, *J* 2.5 Hz, 2-, 8-, and 4-, 6-H); $\lambda_{max.}$(MeOH) 218infl, 226, 264, 298infl, and 308 nm (ε 23 400, 24 400, 10 200, 13 200, and 14 800).

Methyl 6-Heptyl-2-methoxy-4-(3-methoxy-5-methyl-4-nitrophenoxy)benzoate (**42**).—Ullmann reaction between the bromo-compound (**21**) (2.10 g) and methyl 6-heptyl-4-hydroxy-2-methoxybenzoate (**41**) (2.87 g)[23] gave the *diphenyl ether* (**42**) (61%), which formed prisms (from methanol), m.p. 108.5—110.5 °C (Found: C, 64.65; H, 6.75; N, 3.35%. M^+, 415.

$C_{24}H_{31}NO_7$ requires C, 64.7; H, 7.0; N, 3.15%; *M*, 415); δ 0.87 (3 H, distorted t, $[CH_2]_6CH_3$), 1.12—1.73 (10 H, m, $CH_2[CH_2]_5$-Me), 2.23 (3 H, s, ArMe), 2.56 (2 H, t, CH_2), 3.75, 3.78, and 3.88 (each 3 H, s, OMe), 6.38 and 6.49 (2 H, AB, *J* 2.0 Hz, 6′- and 2′-H), and 6.49 (2 H, s, 3- and 5-H). The steam distillate gave 2-methoxy-6-methyl-1-nitrobenzene (**26**) (16%).

Methyl 5-Bromo-6-heptyl-2-methoxy-4-(3-methoxy-5-methyl-4-nitrophenoxy)benzoate (**43**).—Bromination of the diphenyl ether (**42**) as for compound (**30**) gave the *bromo compound* (**43**) (95%) as prisms (from methanol), m.p. 109.5—110.5 °C (Found: C, 54.6; H, 5.75; Br, 15.35; N, 2.6%; M^+, 523/525. $C_{24}H_{30}BrNO_7$ requires C, 54.95; H, 5.75; Br, 15.25; N, 2.65%; *M*, 523/525); δ 0.89 (3 H, distorted t, $[CH_2]_6CH_3$), 1.10—1.80 (10 H, m, $CH_2[CH_2]_5Me$), 2.24 (3 H, s, ArMe), 2.73 (2 H, distorted t, CH_2), 3.75, 3.83, and 3.93 (each 3 H, s, OMe), 6.26 and 6.49 (2 H, AB *J* 2.5 Hz, 6- and 2-H), and 6.52 (1 H, s, 3-H) (irradiation at δ 2.24 sharpened the AB system).

Methyl 5-Bromo-4-(2-bromo-5-methoxy-3-methyl-4-nitrophenoxy)-6-heptyl-2-methoxybenzoate (**44**).—The bromo-compound (**43**) (2.12 g) in carbon tetrachloride (20 ml) was treated with bromine (1.5 g) and the mixture was set aside with exclusion of light for 18 h. The solution was diluted with ethyl acetate and then washed successively with aqueous sodium pyrosulphite, water, and finally saturated brine. The crude product was filtered through alumina with 5% ethyl acetate–light petroleum as eluant. The resultant gum was crystallized from cold methanol whereupon it formed prisms (2.15 g, 88%) of the *dibromo-compound* (**44**), m.p. 107—108.5 °C (Found: C, 47.5; H, 4.85; Br, 26.4; N, 2.2%; M^+, 601/603/605. $C_{24}H_{29}Br_2NO_7$ requires C, 47.8; H, 4.85; Br, 26.5; N, 2.3%; *M*, 601/603/605); δ 0.89 (3 H, distorted t, $[CH_2]_6CH_3$) 1.12—1.77 (10 H, m, $CH_2[CH_2]_5Me$), 2.40 (3 H, s, ArMe), 2.53—2.70 (2 H, m, CH_2), 3.70, 3.72, and 3.90 (each 3 H, s, OMe), 6.26 (1 H, s, 6′-H), and 6.44 (1 H, s, 3-H) (irradiation at δ 2.40 sharpened the signal at δ 6.26).

Methyl 5-Bromo-4-(2-bromo-5-methoxy-3-methylphenoxy)-6-heptyl-2-methoxybenzoate (**48**).—Under a gentle stream of nitrogen, palladized charcoal (Engelhard; 10%; 1.0 g) was added in portions to a suspension of the nitro-compound (**44**) (3.14 g) in methanol (40 ml) and phosphinic acid (50%; 13 ml). The mixture was then heated under reflux for 20 min, cooled, and diluted with ethyl acetate, and the catalyst was separated by filtration and recovered. The filtrate was washed in turn with saturated sodium hydrogen carbonate solution, water, and finally saturated brine. The amine (**47**) (2.80 g) was obtained as a viscous oil, a sample of which crystallized from the methanol as pink prisms, m.p. 98—103 °C; δ (80 MHz) 0.89 (3 H, distorted t, $[CH_2]_6CH_3$), 1.08—1.89 (10 H, m, $CH_2[CH_2]_5Me$), 2.35 (3 H, s, ArMe), 2.63—2.82 (2 H, m, CH_2), 3.58, 3.79, and 3.89 (each 3 H, s, OMe), 6.04 (1 H, s, 6′-H), and 6.49 (1 H, s, 3-H) (the signal for the NH_2 protons was obscured by the methoxy resonances); *m/z* 571/573/575 (M^+). A solution of the crude amine (2.80 g) in dioxane (75 ml), water (20 ml), and concentrated hydrochloric acid (15 ml) was cooled to 2—3 °C and diazotized by dropwise addition of a solution of sodium nitrite (580 mg) in water (5 ml). The solution was stirred at 3 °C for 1 h and then phosphinic acid (50%; 30 ml) was added slowly so that the temperature of the reaction did not exceed 5 °C. The mixture was set aside at 0 °C for 24 h and the crude product, obtained by the usual work-up, was filtered through alumina with 5% ethyl acetate–light petroleum as eluant. The *dibromo-compound* (**48**) (2.32 g, 80%) formed prisms (from cold methanol), m.p. 36.5—38 °C (Found: C, 51.35; H, 5.45; Br, 29.1%; M^+, 556/558/560. $C_{24}H_{30}Br_2O_5$ requires C, 51.65; H, 5.4; Br, 28.6%; *M*, 556/558/560); δ 0.89 (3 H, distorted t, $[CH_2]_6CH_3$), 1.07—1.81 (10 H, m, $CH_2[CH_2]_5Me$), 2.45 (3 H, s, ArMe), 2.72 (2 H, m, CH_2), 3.67, 3.71, and 3.91 (each 3 H, s, OMe), 6.22 and 6.63 (2 H, AB, *J* 3.0 Hz, 6′- and 4′-H), and 6.30 (1 H, s, 3-H) (irradiation at δ 2.45 sharpened the AB system).

Methyl 6-Heptyl-5-iodo-2-methoxy-4-(3-methoxy-5-methyl-4-nitrophenoxy)benzoate (**45**).—A solution of iodine (1.29 g) in chloroform (50 ml) was added dropwise to a stirred solution of the nitro-compound (**42**) (2.22 g) in chloroform (50 ml) containing a suspension of silver trifluoroacetate (1.12 g). After the addition the silver iodide was separated by filtration and washed with a little chloroform. The chloroform solution was washed in turn with saturated sodium hydrogen carbonate solution, water, and finally saturated brine. The crude product crystallized from methanol as brilliant yellow prisms (2.80 g, 92%) of the *iodo-compound* (**45**), m.p. 116—117 °C (Found: C, 50.6; H, 5.25; I, 22.1; N, 2.35%; M^+, 571. $C_{24}H_{30}INO_7$ requires C, 50.45; H, 5.3; I, 22.2; N, 2.45%; *M*, 571); δ 0.90 (3 H, distorted t, $[CH_2]_6CH_3$), 1.05—1.85 (10 H, m, $CH_2[CH_2]_5Me$), 2.25 (3 H, s, ArMe), 2.76 (2 H, distorted t, CH_2), 3.74, 3.84, and 3.93 (3 H, s, OMe), 6.26 and 6.50 (2 H, AB, *J* 2.5 Hz, 6′- and 2′-H), and 6.48 (1 H, s, 3-H).

Methyl 6-Heptyl-5-iodo-4-(2-iodo-5-methoxy-3-methyl-4-nitrophenoxy)-2-methoxybenzoate (**46**).—Iodine (1.35 g) was added to a stirred solution of the monoiodo-compound (**45**) (2.53 g) in chloroform (50 ml) containing suspended silver trifluoroacetate (1.18 g). The mixture was stirred for 20 h. The silver salts were separated by filtration and washed with a little chloroform. The filtrate was diluted with ethyl acetate and washed successively with saturated sodium hydrogen carbonate solution, aqueous sodium pyrosulphite, water, and finally saturated brine. The crude product crystallized from methanol as bright yellow platelets (3.00 g, 97%) of the *di-iodo-compound* (**46**), m.p. 131—133 °C (Found: C, 41.35; H, 4.1; I, 36.4; N, 1.9%; M^+, 697. $C_{24}H_{29}I_2NO_7$ requires C, 41.35; H, 4.2; I, 36.4; N, 2.0%; *M*, 697); δ 0.91 (3 H, distorted t, $[CH_2]_6CH_3$), 1.29—2.00 (10 H, m, $CH_2[CH_2]_5Me$), 2.49 (3 H, s, ArMe), 2.74 (2 H, distorted t, CH_2), 3.72, 3.74, and 3.93 (each 3 H, s, OMe), and 6.21 and 6.34 (each 1 H, s, 3- and 6′-H).

Methyl 1-Heptyl-3,7-dimethoxy-9-methyl-8-nitrodibenzofuran-2-carboxylate (**51**).—An intimate mixture of the di-iodo-compound (**46**) (874 mg) and activated copper bronze (5.00 g) was heated at 210 °C (bath) for 3.5 h under dry nitrogen. The cooled mixture was extracted with boiling ethyl acetate and the crude product was subjected to flash chromatography with 20% ethyl acetate–light petroleum as eluant. The first material eluted was the deiodo-compound (**42**) (306.5 mg); this was followed by the *dibenzofuran* (**51**) (203.2 mg, 37%), which formed yellow laths (from methanol), m.p. 121.5—123.5 °C (Found: C, 64.75; H, 6.55; N, 3.25%; M^+, 443. $C_{24}H_{29}NO_7$ requires C, 65.0; H, 6.6; N, 3.15%; *M*, 443); δ (80 MHz) 0.87 (3 H, distorted t, $[CH_2]_6CH_3$), 1.06—1.90 (10 H, m, $CH_2[CH_2]_5Me$), 2.70 (3 H, s, ArMe), 3.04 (2 H, distorted t, CH_2), 3.91 (3 H, s, OMe), 3.96 (6 H, s, 2 × OMe), and 6.97 and 7.04 (each 1 H, s, 4- and 6-H) (irradiation at δ 2.70 sharpened the signal at δ 7.04).

Methyl 1-Heptyl-3,7-dimethoxy-9-methyldibenzofuran-2-carboxylate (**49**).—(*a*) An intimate mixture of the dibromo-compound (**48**) (863.5 mg) and activated copper bronze (3.0 g) was heated at 260 °C (bath) under dry nitrogen for 2 h. The cooled mixture was extracted with boiling ethyl acetate and the crude product was subjected to flash chromatography with 5% ethyl acetate–light petroleum as eluant. The major fraction was subjected to p.l.c. over silica with 2.5% ethyl acetate–light petroleum as developer. The major band gave a gum which on crystallization from methanol gave the *dibenzofuran* (**49**) (179.5 mg, 29%) as needles, m.p. 94—95 °C (Found: C, 72.0; H, 7.6%;

M^+, 398. $C_{24}H_{30}O_5$ requires C, 72.35; H, 7.6%; *M*, 398); δ (80 MHz) 0.87 (3 H, distorted t, $[CH_2]_6CH_3$), 1.08—1.91 (10 H, m, $CH_2[CH_2]_5Me$), 2.80 (3 H, s, ArMe), 2.89—3.17 (2 H, m, CH_2), 3.87, 3.88, and 3.94 (each 3 H, s, OMe), 6.73 and 6.91 (2 H, AB, *J* 2.0 Hz, 8- and 6-H), and 6.94 (1 H, s, 4-H) (irradiation at δ 2.80 sharpened the AB system).

(*b*) The nitrodibenzofuran (**51**) (169.5 mg) was reduced during 20 min with phosphinic acid (50%; 1.1 ml) and palladized charcoal (10%; 60 mg) in boiling methanol (5 ml) as for the preparation of compound (**37**). The crude amine (**52**) (142 mg), so obtained, in dioxane (5 ml), water (3 ml), and concentrated hydrochloric acid (1 ml), was stirred and diazotized at 2—3 °C by dropwise addition of sodium nitrite (36 mg) in water (0.5 ml). The solution was stirred at 3 °C for 1 h longer and phosphinic acid (50%; 2 ml) was added dropwise; the mixture was then set aside at 0 °C for 13 h. The usual work-up gave a crude product which was subjected to p.l.c. over silica with 10% ethyl acetate–light petroleum as eluant. The major band yielded the dibenzofuran (**49**) (34.8 mg, 23%), which formed needles (from methanol), m.p. and mixed m.p. 94—95 °C.

1-*Heptyl*-3,7-*dimethoxy*-9-*methyldibenzofuran*-2-*carboxylic Acid* (**50**).—The ester (**49**) (43.0 mg) and potassium hydroxide (60 mg) in dimethyl sulphoxide (5 ml) and water (0.3 ml) were heated on a steam-bath for 20.5 h. The cooled solution was diluted with water and extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The crude product crystallized from dichloromethane–light petroleum as pale yellow needles (35 mg, 84%) of the acid (**50**), m.p. 134—136 °C; δ (80 MHz) 0.86 (3 H, distorted t, $[CH_2]_6CH_3$), 1.04—1.93 (10 H, m, $CH_2[CH_2]_5Me$), 2.82 (3 H, s, ArMe), 3.25 (2 H, distorted t, CH_2), 3.88 and 3.94 (each 3 H, s, OMe), 6.74 and 6.92 (2 H, AB, *J* 2.5 Hz, 8- and 6-H), and 6.97 (1 H, s, 4-H); *m/z* 384 (M^+).

1-*Heptyl*-3-*hydroxy*-7-*methoxy*-9-*methyldibenzofuran*-2-*carboxylic Acid* (*Melacarpic Acid*) (**5**).—A solution of boron trichloride (107 mg) in dichloromethane (0.20 ml) was added to a stirred solution of the acid (**50**) (70 mg) in dichloromethane (2 ml) at −10 °C under dry nitrogen. The solution was stirred for 22 h without further addition of ice to the cooling bath. The solution was diluted with ethyl acetate and then washed with water and with saturated brine. Removal of the solvent left the crude product (60.0 mg, 89%), which formed pale yellow needles (from dichloromethane–light petroleum), m.p. 153—154.5 °C (lit.,[6] 148—149 °C) (Found: C, 71.3; H, 7.0. $C_{22}H_{26}O_5$ requires C, 71.35; H, 7.05%); δ (80 MHz) 0.85 (3 H, distorted t, $[CH_2]_6CH_3$), 1.02—1.87 (10 H, m, $CH_2[CH_2]_5Me$), 2.83 (3 H, s, ArMe), 3.65 (2 H, distorted t, CH_2), 3.87 (3 H, s, OMe), 6.12—8.78 (2 H, br, CO_2H and OH), 6.74 and 6.87 (2 H, AB, *J* 2.3 Hz, 8-H and 6-H), and 6.95 (1 H, s, 4-H); *m/z* 370 (M^+, 12%), 352 (12), 327 (27), and 326 (100), identical with the natural product (n.m.r. and mass spectra, R_F values in three solvent systems, and mixed m.p.).

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