

Naturally Occurring Dibenzofurans. Part 6.<sup>1</sup> Synthesis of Didymic Acid

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The synthesis of the lichen dibenzofuran didymic acid (1) (3-hydroxy-7-methoxy-1-pentyl-9-propyldibenzofuran-2-carboxylic acid) by intramolecular Ullmann coupling of methyl 5-bromo-4-(2-bromo-5-methoxy-3-propylphenoxy)-2-methoxy-6-pentylbenzoate (34) and methyl 5-iodo-4-(2-iodo-5-methoxy-4-nitro-3-propylphenoxy)-2-methoxy-6-pentylbenzoate (32) and appropriate further transformations, is described.

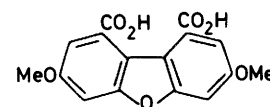
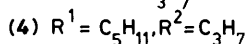
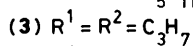
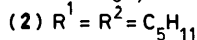
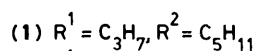
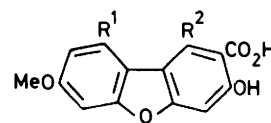
Didymic acid (1)<sup>2</sup> occurs in many lichens of the genus *Cladonia*, where it often co-occurs with varying amounts of condidymic acid (2)<sup>3,4</sup> and subdidymic acid (3).<sup>4</sup>

The structure of didymic acid (1) was solved by Shibata by classical degradative techniques.<sup>2</sup> The overall substitution pattern was indicated by degradation to the dicarboxylic acid (5), which was identified by synthesis. Didymic acid was presumably a salicylic acid since it gave a blue colour with Fe<sup>III</sup>, and one of the alkyl chains was pentyl since caproic acid was isolated on oxidation; the other chain was assumed to be propyl. The location of the carboxy group was investigated by controlled permanganate oxidation of methyl *O*-methyl-didymate (6): a compound assigned structure (7) was obtained, which on hydrolysis yielded a dicarboxylic acid giving a positive phthalein reaction. The controlled oxidation product was also characterized by conversion into its methyl ester (8)

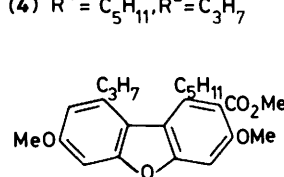
It is known that toluenes substituted in the *ortho*- or *para*-positions by electron-withdrawing substituents are oxidized by permanganate at an appreciably lower rate than toluene itself,<sup>5</sup> so that structure (7) for the partial oxidation product appeared to us to be unlikely. A more reasonable structure would be (9), and the elemental analytical data for this compound and its methyl ester (10) would still be in keeping with this. Hence the possibility existed that didymic acid should be represented by structure (4).

We communicated these misgivings concerning the structure of didymic acid to Professor Shibata and he and his co-workers have re-examined the structure of the methyl ester of the controlled oxidation product. X-Ray crystallography revealed it to be the oxoester (11).<sup>6</sup> Furthermore Professor Shibata has permitted us to record the spectral data of his original sample of this ester which are in accord with structure (11). Thus the high resolution mass spectrum was in accord with the molecular formula C<sub>24</sub>H<sub>26</sub>O<sub>8</sub>, rather than C<sub>21</sub>H<sub>22</sub>O<sub>7</sub> as required by structure (8). The i.r. spectrum (KBr) exhibited carbonyl stretching bands at 1740, 1735, and 1695 cm<sup>-1</sup> which were assigned to the ester carbonyl of an  $\alpha$ -oxoester, an aromatic ester, and the oxo group of an  $\alpha$ -oxoester. The <sup>1</sup>H n.m.r. spectrum (CDCl<sub>3</sub>; 80 MHz) showed signals assigned to a pentyl group at  $\delta$  0.81 (3 H, distorted t, [CH<sub>2</sub>]<sub>4</sub>CH<sub>3</sub>), 1.00–1.83 (6 H, m, CH<sub>2</sub>[CH<sub>2</sub>]<sub>3</sub>Me), and 2.66 (2 H, distorted t, CH<sub>2</sub>[CH<sub>2</sub>]<sub>3</sub>Me), and to four methoxy groups at 3.92 (9 H, s, 3  $\times$  OMe) and 3.98. The 4-proton afforded a singlet at  $\delta$  6.98, and the signals due to the 6- and 8-protons, shifted to lower field on account of the electron-withdrawing substituent at the 9-position, appeared as an AB system at  $\delta$  7.02 and 7.07 with a *meta*-coupling constant of 3.0 Hz. Hence the original structural proposal for didymic acid (1) was correct and we now describe the total synthesis of this natural product which confirms this.

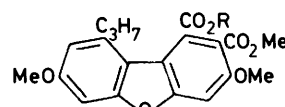
For the synthesis of didymic acid (1) we adopted a similar strategy to that used in our synthesis of melacarpic acid.<sup>1</sup> Consequently in order to construct the requisite diaryl ether (28) (Scheme) the bromo-nitro-compound (21) and the phenol



(5)

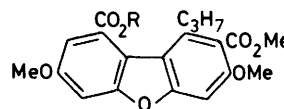


(6)



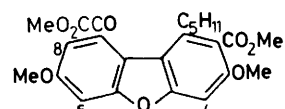
(7) R = H

(8) R = Me



(9) R = H

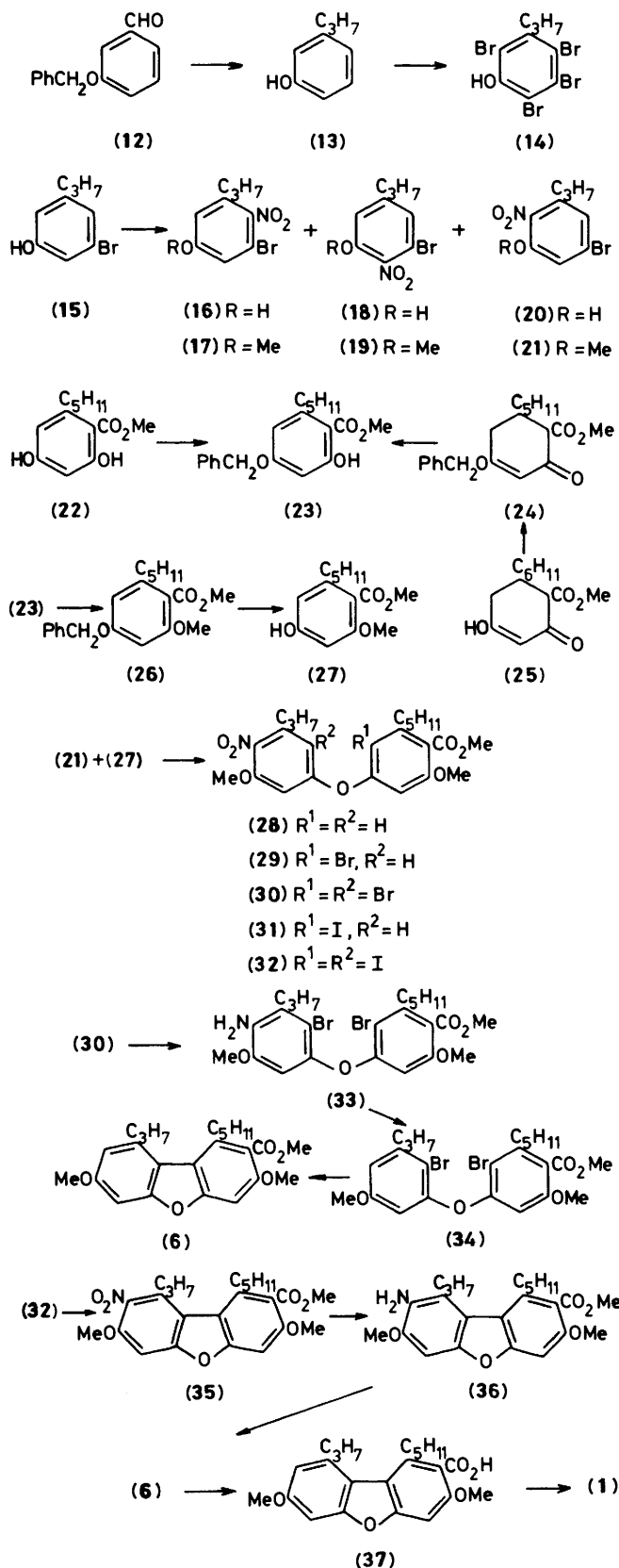
(10) R = Me



(11)

(27) were required as the components in the Ullmann reaction. 3-Propylphenol (13) was easily synthesized from 3-benzyloxybenzaldehyde (12)<sup>7</sup> by Grignard reaction with ethylmagnesium bromide and subsequent catalytic hydrogenolysis of the resultant secondary alcohol. In an adaptation of the method of Kohn and Weissberg<sup>8</sup> for the synthesis of 3-bromo-5-methylphenol,<sup>1</sup> we converted 3-propylphenol (13) into the tetrabromo-compound (14). On treatment of this compound with aluminium chloride in boiling benzene a high yield of the required 3-bromo-5-propylphenol (15) was obtained. Nitration of the bromophenol (15) with concentrated nitric acid in acetic gave a mixture of the three possible nitro-compounds (16), (18), and (20). The *ortho*-nitrophenols (18) and (20) were conveniently separated from the *para*-isomer (16) by steam distillation. The nitrophenols (16), (18), and (20) were converted by methylation into their respective methyl ethers (17), (19), and (21). The structures of the nitrophenols and their methyl ethers were readily assigned by comparison of the n.m.r. spectral signals of the aromatic protons with those of their methyl analogues, described in the previous paper,<sup>1</sup> the structures of which followed from inter-relationship with known compounds.

The phenol (27) required as the other component in the projected Ullmann synthesis was readily prepared from methyl 2,4-dihydroxy-6-pentylbenzoate (22) or the dihydro-compound (25).<sup>9</sup> The former compound was treated with 1 mol equiv. of



Scheme.

potassium carbonate and benzyl bromide and this reaction gave selectively the 4-benzyloxy-compound (23). An alternative synthesis of this compound used the dihydro-olivitol derivative

(25)<sup>9</sup> as the starting material: this was converted into the benzyl enol ether (24) by treatment with benzyl alcohol in the presence of toluene-*p*-sulphonic acid.<sup>10</sup> The benzyl enol ether (24) was then treated with 1 mol equiv. of bromine in acetic acid in the presence of an excess of anhydrous sodium acetate. Dehydrobromination of the crude product with 1,5-diazabicyclo[3.4.0]non-5-ene then afforded the benzyl ether (23). Methylation of the benzyl ether (23) gave compound (26), which on catalytic hydrogenolysis furnished the required phenol (27).

When the phenol (27) reacted with the bromo-nitro-compound (21) under the conditions of the Ullmann reaction a good yield of the diaryl ether (28) was obtained. As in the synthesis of melacarpic acid<sup>1</sup> bromination with 1 mol equiv. of bromine gave the monobromo-compound (29), and with 2 mol equiv. of bromine the dibromo-compound (3) was obtained. Transfer hydrogenation of the latter compound provided the amine (33), and the derived diazonium salt on treatment with phosphinic acid afforded the dibromo-compound (34). On treatment with activated copper bronze this compound gave the dibenzofuran (6) in only 14% yield.

The alternative strategy in which iodine was used as substituent was also explored. Sequential iodination of the diaryl ether (28) gave first the monoiodo-compound (31) and then the di-iodo-compound (32). Ring closure of this intermediate with activated copper bronze gave the dibenzofuran (35) in 23% yield. This compound was reduced to the amine (36), which on deamination gave methyl *O*-methylididymate (6), identical with that prepared by the alternative route.

Hydrolysis of methyl *O*-methylididymate (6) followed by treatment of the crude acid (37), so obtained, with boron trichloride gave synthetic didymic acid. An authentic sample of didymic acid was secured by extraction of the lichen *Cladonia sydneysensis* and the synthetic and natural materials proved identical by all the usual criteria.

## Experimental

General directions are given in Part 4.<sup>11</sup>

**3-Benzyloxybenzaldehyde (12).**—Benzyl bromide (114.0 g) in anhydrous *N,N*-dimethylformamide (40 ml) was added over 15 min to a stirred mixture of 3-hydroxybenzaldehyde (Fluka, tech.; 73.2 g), anhydrous potassium carbonate (114 g), and anhydrous *N,N*-dimethylformamide (200 ml) under dry nitrogen. The mixture was stirred at room temperature under dry nitrogen for 7 h and then poured into ice-water. The crude product was isolated with diethyl ether and the extract was washed twice with water; the solvent and excess of benzyl bromide were removed in steam. The crude product was crystallized from dichloromethane–light petroleum (charcoal), and then from hexane–cyclohexane (charcoal): material (99.4 g, 78%) sufficiently pure for the following step was obtained. A sample crystallized several more times from light petroleum formed plates, m.p. 56–57 °C (lit.,<sup>7</sup> 54 °C).

**3-Propylphenol (13).**—The Grignard reagent was prepared in the customary manner from bromoethane (39.5 ml), magnesium (8.75 g), and anhydrous diethyl ether (200 ml). The aldehyde (12) (58.75 g) in anhydrous diethyl ether (200 ml) was added dropwise at 0 °C to a stirred solution of the Grignard reagent over 1 h. The mixture was then stirred at room temperature for 1 h, and then heated under reflux for 1 h. The solution was then cooled to 0 °C and treated dropwise with an excess of saturated aqueous ammonium chloride. The crude oily product (66.3 g), isolated with ethyl acetate in the usual way, was dissolved in glacial acetic acid (130 ml), containing concentrated hydro-

chloric acid (10 drops) and stirred under hydrogen with palladized charcoal (Engelhard; 10%; 3.0 g) until absorption ceased. The catalyst was separated by filtration through Celite and was washed with ethyl acetate. The filtrate was diluted with more ethyl acetate and washed in turn with water, saturated aqueous sodium hydrogen carbonate, and finally saturated brine. The crude product was distilled under diminished pressure and was obtained as an oil (30.5 g, 81%), b.p. 122—124 °C at 24 mmHg (lit.,<sup>12</sup> 110 °C at 10 mmHg).

**2,4,5,6-Tetrabromo-3-propylphenol (14).**—Aluminium powder (3.0 g) was added slowly in portions with stirring at 0 °C to bromine (85 ml). The mixture was then stirred for a further 10 min and the phenol (13) (37.2 g) was added slowly dropwise. When the reaction had subsided the excess of bromine was removed by heating and stirring at 80 °C (bath) under reduced pressure (water pump). The residue was triturated with warm hydrochloric acid (5%; 300 ml) and then poured on ice and water. Isolation with ethyl acetate gave the crude product, which was crystallized from light petroleum (charcoal), and formed needles (93.2 g, 75%) of the phenol (14), m.p. 95—96 °C (Found: C, 24.1; H, 1.75; Br, 71.05. C<sub>9</sub>H<sub>8</sub>Br<sub>4</sub>O requires C, 23.95; H, 1.8; Br, 70.75%); δ 1.04 (3 H, t, Me), 1.52 (2 H, m, CH<sub>2</sub>CH<sub>2</sub>Me), 3.07 (2 H, t, with further fine coupling, CH<sub>2</sub>Et), and 6.12 (1 H, s, D<sub>2</sub>O-exchangeable OH).

**3-Bromo-5-propylphenol (15).**—The tetrabromophenol (14) (95 g) and powdered aluminium chloride (Fluka tech.; 185.5 g) were stirred together and heated under reflux in anhydrous benzene (181 ml) for 0.5 h. T.l.c. then indicated that the starting material had been consumed. The mixture was poured with caution into an excess of ice and water and the crude product was isolated with ethyl acetate. The ethyl acetate layer was washed with water and with saturated brine and dried. The crude product left on removal of the solvent was dissolved in light petroleum and extracted with Claisen's alkali. The extracts were diluted with water, cooled to 0 °C, and acidified with hydrochloric acid. Isolation with ethyl acetate gave the crude product, which was distilled under diminished pressure and was obtained as an oil (41.9 g, 93%), b.p. 180 °C at 22 mmHg (Kugelrohr) (Found: C, 50.15; H, 5.1; Br, 37.3. C<sub>9</sub>H<sub>11</sub>BrO requires C, 50.25; H, 5.15; Br, 37.15%); δ 0.89 (3 H, t, Me), 1.57 (2 H, sextet with further fine coupling, CH<sub>2</sub>CH<sub>2</sub>Me), 2.47 (2 H, t, CH<sub>2</sub>Et), 5.81br (1 H, D<sub>2</sub>O-exchangeable OH), and 6.56, 6.86, and 6.90 (each 1 H, narrow m, ArH).

**Nitration of 3-Bromo-5-propylphenol (15).**—A solution of concentrated nitric acid (70% w/w; 12.65 g) in acetic acid (100 ml) was added dropwise to the phenol (15) (30.2 g) in acetic acid (100 ml) with stirring and intermittent cooling in ice and water so that the reaction temperature was 10—15 °C. The reaction exhibited an induction period after which it became exothermic so that close control of the temperature was important. After the addition the mixture was poured on ice and water and extracted with light petroleum—diethyl ether (4:1). The extract was washed successively with water (2×), saturated aqueous sodium hydrogen carbonate (1×), and finally saturated brine. The crude product was distilled in steam and 15 l of distillate were collected. Extraction of the pot residue with ethyl acetate gave a crude product which was filtered through silica gel with 15% ethyl acetate—light petroleum as eluant and afforded 3-bromo-4-nitro-5-propylphenol (16) (13.5 g, 37%) as an orange oil, b.p. 170 °C at 0.5 mmHg (Found: C, 41.1; H, 3.9; Br, 30.6; N, 5.0. C<sub>9</sub>H<sub>10</sub>BrNO<sub>3</sub> requires C, 41.55; H, 3.9; Br, 30.7; N, 5.4%); δ 0.91 (3 H, t, Me), 1.59, (2 H, sextet, CH<sub>2</sub>CH<sub>2</sub>Me), 2.50 (2 H, t, CH<sub>2</sub>Et), 5.53br (1 H, OH), and 6.71 and 6.98 (2 H, AB, *J* 2.5 Hz, 6- and 2-H). On methylation with iodomethane and potassium carbonate in *N,N*-dimethylformamide at room temperature

under dry nitrogen this afforded the methyl ether (17) as pale yellow prisms (from light petroleum), m.p. 44—44.5 °C (Found: C, 43.8; H, 4.45; Br, 29.1; N, 4.85%; *M*<sup>+</sup>, 273/275. C<sub>10</sub>H<sub>12</sub>BrNO<sub>3</sub> requires C, 43.8; H, 4.4; Br, 29.15; N, 5.1%; *M*, 273/275); δ 0.94 (3 H, t, Me), 1.63 (2 H, sextet, CH<sub>2</sub>CH<sub>2</sub>Me), 2.54 (2 H, t, CH<sub>2</sub>CH<sub>2</sub>Me), 3.81 (3 H, s, OMe), and 6.73 and 6.98 (2 H, AB, *J* 2.5 Hz, ArH). The material isolated from the steam distillate with ethyl acetate was chromatographed over a column of silica gel with 0—5% ethyl acetate—light petroleum as eluant. The first material eluted was 5-bromo-2-nitro-3-propylphenol (20) (8.7 g, 24%) as a yellow oil, b.p. 150 °C at 0.5 mmHg (Kugelrohr) (Found: C, 41.5; H, 3.85. C<sub>9</sub>H<sub>10</sub>BrNO<sub>3</sub> requires C, 41.55; H, 3.9%; δ 1.00 (3 H, t, Me), 1.63 (2 H, sextet, CH<sub>2</sub>CH<sub>2</sub>Me), 2.86 (2 H, t, CH<sub>2</sub>Et), 6.97 and 7.17 (2 H, AB, *J* 2.5 Hz, 4- and 6-H), and 10.17 (1 H, s, D<sub>2</sub>O-exchangeable OH). The methyl ether (21) formed yellow prisms (from methanol), m.p. 40.5—41 °C (Found: C, 43.75; H, 4.25; Br, 29.0; N, 4.95%; *M*<sup>+</sup>, 273/275. C<sub>10</sub>H<sub>12</sub>BrNO<sub>3</sub> requires C, 43.8; H, 4.4; Br, 29.15; N, 5.1%; *M*, 273/275). Further elution gave 3-bromo-2-nitro-5-propylphenol (18) (7.3 g, 20%) as a yellow oil, b.p. 155 °C at 0.5 mmHg (Found: C, 41.9; H, 4.1; Br, 30.9; N, 5.25. C<sub>9</sub>H<sub>10</sub>BrNO<sub>3</sub> requires C, 41.55; H, 3.9; Br, 30.7; N, 5.4%); δ 0.96 (3 H, t, Me), 1.65 (2 H, sextet, CH<sub>2</sub>CH<sub>2</sub>Me), 2.55 (2 H, t, CH<sub>2</sub>Et), 6.89 and 7.12 (2 H, AB, *J* 2.5 Hz, 6- and 4-H), and 9.77br (1 H, OH). The methyl ether (19) was obtained as a yellow oil, b.p. 155 °C at 0.6 mmHg (Kugelrohr) (Found: C, 44.0; H, 4.6; N, 5.3. C<sub>10</sub>H<sub>12</sub>BrNO<sub>3</sub> requires C, 43.8; H, 4.4; N, 5.1%); δ 0.95 (3 H, t, Me), 1.64 (2 H, sextet, CH<sub>2</sub>CH<sub>2</sub>Me), 2.59 (2 H, t, CH<sub>2</sub>Et), 3.85 (3 H, s, OMe), and 6.78 and 7.01 (2 H, broadened AB, ArH) (irradiation at δ 2.59 caused sharpening of the AB system).

**Methyl 4-Benzoyloxy-2-oxo-6-pentylcyclohex-3-enecarboxylate (24).**—Methyl 4-hydroxy-2-oxo-6-pentylcyclohex-3-enecarboxylate (25) (4.0 g), benzyl alcohol (1.71 g), toluene-*p*-sulphonic acid (50 mg), and anhydrous benzene (125 ml) were heated under reflux in a Dean-Stark apparatus for 5 h. The cooled solution was washed in turn with dilute aqueous sodium hydroxide, water, and saturated brine. The product (24) (4.5 g, 86%) was obtained as a thick oil which crystallized from cold methanol as laths, m.p. 64—65 °C (Found: C, 73.05; H, 8.15%; *M*<sup>+</sup>, 330. C<sub>20</sub>H<sub>26</sub>O<sub>4</sub> requires C, 72.7; H, 7.9%; *M*, 330).

**Methyl 4-Benzoyloxy-2-hydroxy-6-pentylbenzoate (23).**—(a) (with Lynette J. Cullen). Methyl 2,4-dihydroxy-6-pentylbenzoate (22) (30.0 g), anhydrous potassium carbonate (17.9 g), and benzyl bromide (15.0 ml) were stirred and heated under reflux in anhydrous acetone (250 ml) for 24 h. The cooled mixture was poured into an excess of ice-cold dilute hydrochloric acid. The crude product, isolated with ethyl acetate in the usual way was chromatographed over silica gel with 2.5% ethyl acetate—light petroleum as eluant. The benzyl ether (23) (31.9 g, 77%) formed prisms (from dichloromethane—light petroleum), m.p. 44—46 °C (Found: C, 72.85; H, 7.2%; *M*<sup>+</sup>, 238. C<sub>20</sub>H<sub>24</sub>O<sub>4</sub> requires C, 73.15; H, 7.35%; *M*, 328); δ (80 MHz) 0.89 (3 H, distorted t, Me), 0.97—1.77 (6 H, m, [CH<sub>2</sub>]<sub>3</sub>), 2.85 (2 H, distorted t, CH<sub>2</sub>Ar), 3.91 (3 H, s, OMe), 5.04 (2 H, s, CH<sub>2</sub>Ph), 6.34 (2 H, s, ArH), 7.38 (5 H, s, Ph), and 11.72 (1 H, s, D<sub>2</sub>O-exchangeable OH).

(b) Bromine (966 mg) in acetic acid (15 ml) was added rapidly dropwise with stirring to the enol ether (24) (1.99 g) in acetic acid (10 ml) containing anhydrous sodium acetate (1.0 g). After the addition the solution was diluted with water and extracted with diethyl ether. The extract was washed in turn with aqueous sodium hydrogen carbonate solution, water, and finally saturated brine. The crude product in anhydrous dichloromethane (10 ml) was cooled in ice and 1,5-diazabicyclo-[3.4.0]non-5-ene (1.2 g) was added. The mixture was set aside at room temperature for 24 h and then diluted with diethyl ether

and washed successively with dilute hydrochloric acid, saturated sodium hydrogen carbonate solution, and finally saturated brine. The crude product was chromatographed over silica gel with 2.5% ethyl acetate–light petroleum as eluant. This gave the benzyl ether (**23**) (1.16 g, 59%) as prisms (from dichloromethane–light petroleum), m.p. and mixed m.p. 44–46 °C.

**Methyl 4-Benzoyloxy-2-methoxy-6-pentylbenzoate (26)** (with Lynette J. Cullen).—The benzyl compound (**23**) (31.9 g), dimethyl sulphate (10.2 ml), and anhydrous potassium carbonate (21.5 g) were stirred and heated under reflux in dry acetone (1 300 ml) for 34 h. The usual work-up gave the ester (**26**) as an oil (32.9 g, 99%) (Found:  $M^+$ , 342.183.  $^{12}C_{21}^{1}H_{26}^{16}O_4$  requires  $M$ , 342.193);  $\delta$  (80 MHz) 0.87 (3 H, distorted t, Me), 1.00–1.81 (6 H, m,  $[CH_2]_3$ ), 2.54 (2 H, t,  $CH_2Ar$ ), 3.76 and 3.86 (each 3 H, s, OMe), 5.04 (2 H, s,  $CH_2Ph$ ), 6.39 (2 H, s, ArH), and 7.34 (5 H, m, Ph).

**Methyl 4-Hydroxy-2-methoxy-6-pentylbenzoate (27)**.—The benzyl ether (**26**) (18.1 g) and 10% palladized charcoal (0.5 g) were stirred under hydrogen in ethyl acetate (200 ml) containing concentrated hydrochloric acid (3 drops) until absorption ceased. The usual work-up gave the ester (**27**) (13.3 g, 100%) as an oil,<sup>13</sup> b.p. 160 °C at 0.01 mmHg (Kugelrohr) (Found: C, 66.75; H, 7.85%;  $M^+$ , 252.  $C_{14}H_{20}O_4$  requires C, 66.65; H, 8.0%  $M$ , 252);  $\delta$  0.87 (3 H, distorted t, Me), 1.09–1.68 (6 H, m,  $[CH_2]_3$ ), 2.48 (2 H, distorted t,  $CH_2Ar$ ), 3.63 and 3.87 (each 3 H, s, OMe), 6.21 and 6.24 (2 H, AB,  $J$  2.5 Hz, ArH), and 6.92 (1 H, s, OH).

**Methyl 2-Methoxy-4-(5-methoxy-4-nitro-3-propylphenoxy)-6-pentylbenzoate (28)**.—The bromo-compound (**21**) (3.13 g), the phenol (**27**) (3.17 g), and finely ground anhydrous potassium carbonate (1.89 g) were stirred and heated to 140 °C (bath) in anhydrous pyridine (9.0 ml) under dry nitrogen. Copper(II) oxide (910 mg) was then added and the mixture was stirred and heated at 140 °C (bath) for 18 h. The mixture was cooled and diluted with ether and filtered through Celite. The filtrate was washed in turn with dilute hydrochloric acid, dilute sodium hydroxide solution, water, and finally saturated brine. The crude product was steam distilled; work-up of the distillate gave 6-methoxy-1-nitro-2-propylbenzene (200 mg, 9%) as a yellow oil, b.p. 90 °C at 0.35 mmHg (Kugelrohr) (Found: C, 61.5; H, 6.75%;  $M^+$ , 195.  $C_{10}H_{13}NO_3$  requires C, 61.55; H, 6.7%;  $M$ , 195);  $\delta$  0.93 (3 H, t, Me), 1.62 (2 H, sextet,  $CH_2CH_2Me$ ), 2.53 (2 H, t,  $CH_2Et$ ), 3.84 (3 H, s, OMe), and 6.82–7.41 (3 H, m, ArH). The pot residue was extracted with ethyl acetate and the extract filtered through alumina with 5% ethyl acetate–light petroleum as eluant; this gave the product (**28**) (3.42 g, 67%) as a yellow viscous oil (Found: C, 64.3; H, 7.1; N, 3.4%;  $M^+$ , 445.  $C_{24}H_{31}NO_7$  requires C, 64.7; H, 7.0; N, 3.15%;  $M$ , 445);  $\delta$  0.81–1.00 (6 H, m,  $[CH_2]_4CH_3$  and  $[CH_2]_2CH_3$ ), 1.12–1.80 (8 H, m,  $CH_2CH_2Me$  and  $CH_2[CH_2]_3Me$ ), 2.43–2.64 (4 H, m,  $CH_2CH_2Me$  and  $CH_2[CH_2]_3Me$ ), 3.78, 3.82, and 3.91 (each 3 H, s, OMe), 6.42 and 6.52 (2 H, AB,  $J$  2.5 Hz, 6- and 2-H), and 6.48 (2 H, s, 3- and 5-H).

**Methyl 5-Bromo-4-(5-methoxy-4-nitro-3-propylphenoxy)-2-methyl-6-pentylbenzoate (29)**.—Bromine (124 mg) in dichloromethane (3.8 ml) was added dropwise with stirring to a solution of the diphenyl ether (**28**) (344.5 mg) in dichloromethane (5 ml). The mixture was stirred for a further 10 min after the addition and was then diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate solution, and with saturated brine. The crude product (386.5 mg, 95%) formed stout needles of the bromo-compound (**29**) (from methanol), m.p. 80.5–82.5 °C (Found: C, 55.45; H, 5.7; Br, 15.2; N, 2.5%;  $M^+$ ,

523/525.  $C_{24}H_{30}BrNO_7$  requires C, 54.95; H, 5.75; Br, 15.25; N, 2.65%;  $M$ , 523/525);  $\delta$  0.91 (6 H, t,  $[CH_2]_2CH_3$  and  $[CH_2]_4CH_3$ ), 1.31–1.91 (8 H, m,  $CH_2CH_2Me$  and  $CH_2[CH_2]_3Me$ ), 2.40–2.82 (4 H, m,  $CH_2CH_2Me$  and  $CH_2[CH_2]_3Me$ ), 3.74, 3.84, and 3.94 (each 3 H, s, OMe), 6.28 and 6.49 (2 H, AB,  $J$  2.5 Hz, 6- and 2-H), and 6.51 (1 H, s, 3-H).

**Methyl 5-Bromo-4-(2-bromo-5-methoxy-4-nitro-3-propylphenoxy)-2-methoxy-6-pentylbenzoate (30)**.—Bromine (2.30 g) in dichloromethane (20 ml) was added dropwise with stirring to a solution of the diphenyl ether (**28**) (3.05 g) in dichloromethane (50 ml). After the addition the mixture was set aside with exclusion of light for 26 h. The solution was then diluted with ethyl acetate and washed in turn with saturated sodium hydrogen carbonate solution, dilute sodium pyrosulphite solution, water, and finally saturated brine. The crude product (3.88 g, 94%) crystallized from methanol as needles of the dibromo-compound (**30**), m.p. 95–97 °C (Found: C, 47.45; H, 4.85; Br, 26.3; N, 2.15%;  $M^+$ , 601/603/605.  $C_{24}H_{29}Br_2O_7$  requires C, 47.8; H, 4.85; Br, 26.5; N, 2.3%;  $M$ , 601/603/605);  $\delta$  0.84–1.09 (6 H, m,  $[CH_2]_2CH_3$  and  $[CH_2]_4CH_3$ ), 1.23–1.84 (8 H, m,  $CH_2CH_2Me$  and  $CH_2[CH_2]_3Me$ ), 2.61–2.80 (4 H, m,  $CH_2Et$  and  $CH_2[CH_2]_3Me$ ), 3.73, 3.74, and 3.94 (each 3 H, s, OMe), 6.26 (1 H, s, 6-H), and 6.41 (1 H, s, 3-H).

**Methyl 5-Bromo-4-(2-bromo-5-methoxy-3-propylphenoxy)-2-methoxy-6-pentylbenzoate (34)**.—Palladized charcoal (10%; Engelhard; 1.8 g) was slowly added under dry nitrogen to a slurry of the dibromo-nitro-compound (**30**) (3.65 g) in methanol (70 ml) and phosphinic acid (50% w/w; 24 ml). The mixture was stirred and heated under reflux for 25 min, then cooled, and the catalyst was separated by filtration. The usual work-up gave the amine (**33**) (3.33 g, 96%) as a gum. This material (3.23 g) was dissolved in a mixture of dioxane (150 ml), water (20 ml), and concentrated hydrochloric acid (20 ml). The solution was stirred and cooled to 7 °C and diazotized by dropwise addition of sodium nitrite (670 mg) in water (20 ml) so that the temperature did not exceed 7 °C. The solution was then stirred at 8 °C for 2 h and ice-cold phosphinic acid (50% w/w; 34 ml) was added slowly dropwise so that the temperature did not exceed 7 °C. The mixture was then set aside at 0 °C for 21 h. After this time the mixture was diluted with water and extracted with ethyl acetate. The extract was washed in turn with water, saturated sodium hydrogen carbonate solution, and finally saturated brine. The crude product was filtered through alumina with 5% ethyl acetate–light petroleum as eluant. The dibromo-compound (**34**) (1.35 g, 43%) formed needles (from methanol), m.p. 79–80 °C (Found: C, 51.9; H, 5.5; Br, 28.95%;  $M^+$ , 556/558/560.  $C_{24}H_{30}Br_2O_5$  requires C, 51.65; H, 5.4; Br, 28.6%;  $M$ , 556/558/560);  $\delta$  0.84–1.14 (6 H, m,  $[CH_2]_2CH_3$  and  $[CH_2]_4CH_3$ ), 1.14–1.88 (8 H, m,  $CH_2CH_2Me$  and  $CH_2[CH_2]_3Me$ ), 2.64–2.84 (4 H, m,  $CH_2Et$  and  $CH_2[CH_2]_3Me$ ), 3.66, 3.72, and 3.91 (each 3 H, s, OMe), 6.27 (1 H, s, 3-H), and 6.27 and 6.62 (2 H, AB,  $J$  3.0 Hz, 6- and 4-H).

**Methyl 5-Iodo-4-(5-methoxy-4-nitro-3-propylphenoxy)-2-methyl-6-pentylbenzoate (31)**.—Iodine (2.15 g) in chloroform (100 ml) was added dropwise to a stirred solution of the diphenyl ether (**28**) (3.42 g) in chloroform (50 ml) containing suspended silver trifluoroacetate (1.87 g). After the iodine colour had disappeared the silver iodide was separated by filtration and washed with chloroform, and the filtrate was washed in turn with saturated sodium hydrogen carbonate solution, dilute sodium thiosulphate solution, water, and finally saturated brine. The crude product (4.40 g, 100%) formed brilliant yellow prisms (from methanol) of the iodo-compound (**31**), m.p. 99–101 °C (Found: C, 50.75; H, 5.35; I, 22.0; N, 2.5%;  $M^+$ , 571.  $C_{24}H_{30}INO_7$  requires C, 50.45; H, 5.3; I, 22.2; N, 2.45%;  $M$ ,

571);  $\delta$  0.91 (6 H, distorted t,  $[\text{CH}_2]_2\text{CH}_3$  and  $[\text{CH}_2]_4\text{CH}_3$ ), 1.13–1.79 (8 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 2.49 (2 H, t,  $\text{CH}_2\text{Et}$ ), 2.76 (2 H, distorted t,  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 3.76, 3.83, and 3.94 (each 3 H, s, OMe), 6.29 and 6.50 (2 H, AB,  $J$  2.25 Hz, 6- and 2-H), and 6.47 (1 H, s, 3-H).

**Methyl 5-Iodo-4-(2-iodo-5-methoxy-4-nitro-3-propylphenoxy)-2-methoxy-6-pentylbenzoate (32).**—A mixture of the monoiodo-compound (31) (2.67 g), iodine (1.19 g), and silver trifluoroacetate (1.14 g) was stirred and heated under reflux in chloroform (100 ml) for 0.5 h. Work-up as for compound (31) gave the crude product (3.15 g, 97%) which crystallized from methanol as needles of the *di-iodo-compound* (32), m.p. 137.5–139 °C (Found: C, 41.65; H, 4.05; I, 36.6; N, 1.95%;  $M^+$ , 697.  $\text{C}_{24}\text{H}_{29}\text{I}_2\text{NO}_7$  requires C, 41.35; H, 4.2; I, 36.4; N, 2.0%;  $M$ , 697);  $\delta$  0.98 (3 H, distorted t,  $[\text{CH}_2]_4\text{CH}_3$ ), 1.03 (3 H, distorted t,  $[\text{CH}_2]_2\text{CH}_3$ ), 1.17–1.86 (8 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_2\text{Me}$ ), 2.65–2.83 (4 H, m,  $\text{CH}_2\text{Et}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 3.72, 3.76, and 3.93 (each 3 H, s, OMe), 6.20 (1 H, s, 6-H), and 6.33 (1 H, s, 3-H).

**Methyl 3,7-Dimethoxy-8-nitro-1-pentyl-9-propyldibenzofuran-2-carboxylate (35).**—An intimate mixture of the powdered substrate (32) (1.00 g) and activated copper bronze (5.0 g) was heated at 200 °C for 7 h under dry nitrogen. The cooled mixture was exhaustively extracted with boiling ethyl acetate and the extract was filtered through Celite. The crude product was subjected to flash chromatography over silica gel with 10% ethyl acetate–light petroleum as eluant. The first material to be eluted was the diiodo-compound (28) (332 mg, 52%). Later fractions gave the *dibenzofuran* (35) (144 mg, 23%), which formed pale yellow needles (from methanol), m.p. 205.5–207 °C (Found: C, 65.25; H, 6.45; N, 3.15%;  $M^+$ , 443.  $\text{C}_{24}\text{H}_{29}\text{NO}_7$  requires C, 65.0; H, 6.6; N, 3.15%;  $M$ , 443);  $\delta$  (80 MHz) 0.88 (3 H, distorted t,  $[\text{CH}_2]_4\text{CH}_3$ ), 0.98 (3 H, t,  $[\text{CH}_2]_2\text{CH}_3$ ), 1.15–1.82 (8 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 2.76–3.01 (4 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 3.91 (3 H, s, OMe), 3.96 (6 H, s, 2  $\times$  OMe), and 6.98 and 7.05 (each 1 H, s, 4- and 6-H).

**Methyl 3,7-Dimethoxy-1-pentyl-9-propyldibenzofuran-2-carboxylate (6).**—(a) An intimate mixture of the dibromo-compound (32) (200 mg) and activated copper bronze (1.0 g) was heated at 260 °C under dry nitrogen for 43 h. The usual work-up gave the crude product, which was subjected to p.l.c. with 5% ethyl acetate–light petroleum as developer. The band of higher  $R_F$  gave the debromo-compound (51.0 mg) and the band of lower  $R_F$  gave the *dibenzofuran* (6) (20.0 mg, 14%), which formed prisms (from aqueous methanol), m.p. 94.5–96.5 °C (lit.,<sup>2</sup> 109 °C) (Found: C, 72.0; H, 7.25%;  $M^+$ , 398.  $\text{C}_{24}\text{H}_{30}\text{O}_5$  requires C, 72.35; H, 7.6%;  $M$ , 398);  $\delta$  (80 MHz) 0.82–1.09 (6 H, m,  $[\text{CH}_2]_2\text{CH}_3$  and  $[\text{CH}_2]_4\text{CH}_3$ ), 1.14–2.14 (8 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 2.84–3.09 (4 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 3.89 (6 H, s, 2  $\times$  OMe), 3.96 (3 H, s, OMe), 6.75 and 6.92 (2 H, AB,  $J$  2.5 Hz, 8- and 6-H), and 6.92 (1 H, s, 4-H).

(b) The nitrodibenzofuran (35) (124 mg) was reduced to the amine (36) with palladized charcoal (60 mg) and phosphinic acid (1.0 ml) in methanol (2 ml) during 10 min as described for compound (30). The crude amine (106.5 mg), so obtained was dissolved in dioxane (5 ml), water (2 ml), and concentrated hydrochloric acid (1 ml) and stirred and cooled to 2–3 °C during the dropwise addition of sodium nitrite (27 mg) in water (0.4 ml). The mixture was stirred at 2–3 °C for 1 h and then treated dropwise with phosphinic acid (1.0 ml). The solution was set aside at 0 °C for 18 h and then worked up in the usual way. P.l.c. of the crude product with 10% ethyl acetate–light

petroleum as developer gave the *dibenzofuran* (6) (14.0 mg, 13%), identical with that described under (a).

**3-Hydroxy-7-methoxy-1-pentyl-9-propyldibenzofuran-2-carboxylic Acid (Didymic Acid) (1).**—Methyl *O*-methyl didymate (6) (44 mg) was heated on a steam-bath for 20.5 h with potassium hydroxide (60 mg), water (0.3 ml), and dimethyl sulphoxide (5 ml). The cooled solution was diluted with water and extracted with diethyl ether; this extract was discarded. The aqueous layer was acidified with dilute hydrochloric acid and the crude acid (37) (40 mg) was isolated with diethyl ether in the usual way. This acid in dichloromethane (1 ml) was cooled and stirred at –10 °C and treated with a solution of boron trichloride (61 mg) in dichloromethane (0.1 ml). The solution was then stirred at room temperature for 21 h and then diluted with ethyl acetate and washed with water, and with saturated brine. The crude product crystallized from dichloromethane–light petroleum as needles (30.0 mg, 81%) of *didymic acid* (1), m.p. 165–167 °C (decomp.) [lit.,<sup>2,6</sup> 172–173 °C (decomp., capillary), 164 °C (decomp., Kofler hot stage)] (Found: C, 71.3; H, 7.0.  $\text{C}_{22}\text{H}_{26}\text{O}_5$  requires C, 71.35; H, 7.05%;  $\delta$  (80 MHz) 0.87 (3 H, distorted t,  $[\text{CH}_2]_4\text{CH}_3$ ), 1.01 (3 H, distorted t,  $[\text{CH}_2]_2\text{CH}_3$ ), 1.14–1.97 (8 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 3.05 (2 H, distorted t,  $\text{CH}_2\text{Et}$ ), 3.56 (2 H, distorted t,  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 3.88 (3 H, s, OMe), 6.78 and 6.91 (2 H, AB,  $J$  2.0 Hz, 8- and 6-H), 6.96 (1 H, s, 4-H), and 11.03 (1 H, br s,  $\text{D}_2\text{O}$ -exchangeable OH);  $m/z$  370 ( $M^+$ , 21%) 353 (25), 352 (100), 327 (12), 326 (46), 295 (15), 280 (15), 267 (12), and 241 (15), identical with a sample of natural didymic acid (mixed m.p.,  $R_F$  values in three different solvent systems, n.m.r. and mass spectra).

**Isolation of Didymic Acid (1) from Cladonia sydneyensis.**—The dried lichen and adhering bark (180 g), collected by J. A. Elix on Black Mountain, Canberra, A.C.T. [voucher specimen: J. A. Elix, 2473 (ANUC)], was exhaustively extracted (Soxhlet) with diethyl ether (2.5 l) during 18 h. The solvent was removed from the extract under reduced pressure and the residue was boiled with ethyl acetate (100 ml). The extract was allowed to cool and then filtered. Removal of the solvent from the filtrate left a brown gum (2.17 g) which was dissolved in *N,N*-dimethylacetamide (30 ml) and stirred with benzyl bromide (0.71 ml) and anhydrous potassium hydrogen carbonate (600 mg) at room temperature for 19 h. The solution was diluted with water and extracted with ethyl acetate in the usual way. The brown gum (2.0 g) left on removal of the solvent was chromatographed over silica gel with 5% ethyl acetate–light petroleum as eluant. The fractions (104 mg) enriched in benzyl didymate were subjected to p.l.c. with 5% ethyl acetate–light petroleum as developer. This gave pure benzyl didymate (53 mg) as a crystalline solid;  $\delta$  (60 MHz) 0.74 (3 H, distorted t,  $[\text{CH}_2]_4\text{CH}_3$ ), 0.95 (3 H, distorted t,  $[\text{CH}_2]_2\text{CH}_3$ ), 1.22–1.94 (8 H, m,  $\text{CH}_2\text{CH}_2\text{Me}$  and  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 2.94 (2H, distorted t,  $\text{CH}_2\text{Et}$ ), 3.31 (2H, distorted t,  $\text{CH}_2[\text{CH}_2]_3\text{Me}$ ), 3.96 (3 H, s, OMe), 5.51 (2 H, s,  $\text{CH}_2\text{Ph}$ ), 6.77 and 6.91 (2 H, AB,  $J$  2.0 Hz, 8- and 6-H), 6.96 (1 H, s, 4-H), 7.25 (5 H, s, Ph), and 10.05 (1 H, s, OH). This material was stirred under hydrogen with 10% palladized charcoal (30 mg) and ethyl acetate (20 ml) containing concentrated hydrochloric acid (1 drop) for 12 h. The usual work-up gave didymic acid (1) (38 mg), which formed needles (from dichloromethane–light petroleum), m.p. 165–167 °C (decomp.).

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