

## Naturally Occurring Dibenzofurans. Part 1. A Synthesis of Cannabifuran

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The synthesis of dibenzofurans from diphenyl ethers by non-phenolic oxidative coupling, u.v. irradiation, and by reaction with palladium(II) acetate has been investigated. 9-Isopropyl-6-methyl-3-pentylidibenzofuran-1-ol (cannabifuran) (35), a minor cannabis constituent, has been synthesized by annulation of 4-isopropyl-7-methylbenzofuran-2-carbaldehyde (28) by Wittig reaction with 2-carboxy-1-methoxycarbonylethyltriphenylphosphorane and ring closure and functional-group modification of the resultant (*E*)-4-(4-isopropyl-7-methylbenzofuran-2-yl)-3-methoxycarbonylbut-3-enoic acid (29).

DIBENZOFURANS are comparatively rare natural products: nine are known to occur in lichens,<sup>1,2</sup> and five have been isolated from higher plants.<sup>3-5</sup> We are interested in developing syntheses of some of these compounds since there is a dearth of good general synthetic methods available for dibenzofurans. The classical methods of synthesis involve Pschorr cyclization of 2-phenoxyanilines,<sup>6</sup> or cyclization of 2,2'-dihydroxybiphenyls or their methyl ethers under acidic conditions.<sup>3,7</sup> Owing to the difficulty of preparation of many of these intermediates these methods are not easily adapted to the synthesis of the natural products. Some success has been achieved by Diels-Alder annulation of 2-vinylbenzofurans<sup>8</sup> and by rearrangement of 3-(2-methylbenzofuran-3-yl)prop-1,2-dienones<sup>9</sup> but these methods are of limited use.<sup>10</sup>

Non-phenolic oxidative coupling of suitably substituted diphenyl ethers appeared to be an attractive method for the synthesis of dibenzofurans. Consequently we prepared the diphenyl ethers (1) and (3) by conventional methods and attempted to convert them into dibenzofurans by treating them with vanadium trifluoride oxide<sup>11</sup> or thallium(III) trifluoroacetate<sup>12</sup> under a variety of conditions. In no case was any dibenzofuran detected. The diphenyl ether (4) was recovered unchanged from an attempted reaction with vanadium trifluoride oxide under conditions whereby the methyl phosphinate analogue undergoes smooth cyclization to the dibenzophosphole.<sup>13,†</sup>

The preparation of a number of alkylidibenzofurans by u.v. irradiation of diphenyl ethers in the presence of iodine has been reported.<sup>14</sup> We investigated this method using the diphenyl ethers (1) and (3). In the first example poor yields of the isomeric dibenzofurans (5) and (7) were isolated. Their structures were deduced from their <sup>1</sup>H n.m.r. spectra. Similarly the diphenyl ether (3) gave the three possible products (9), (11), and (12) in poor yield. Again their structures were deduced from their <sup>1</sup>H n.m.r. spectra. An attempt was made to convert the diphenyl ether (2), which contains an ester function as a blocking group, into the dibenzofuran (8). The only product which was isolated from this irradiation was the xanthone (13).

It has been reported that diphenyl ether is converted

into dibenzofuran on treatment with palladium(II) acetate in boiling acetic acid.<sup>15</sup> We investigated this reaction for a number of diphenyl ethers but the results do not suggest that this would be a useful method for the synthesis of the natural products. Thus, the diphenyl ether (1) gave a mixture of the dibenzofurans (5) and (7) in moderate yield. The dibenzofurans (6) and (10) were also secured in moderate yield from the diphenyl ethers (14) and (4). The ester (2), in which one possible site of cyclization is blocked, gave the expected dibenzofuran (8), but in low yield.

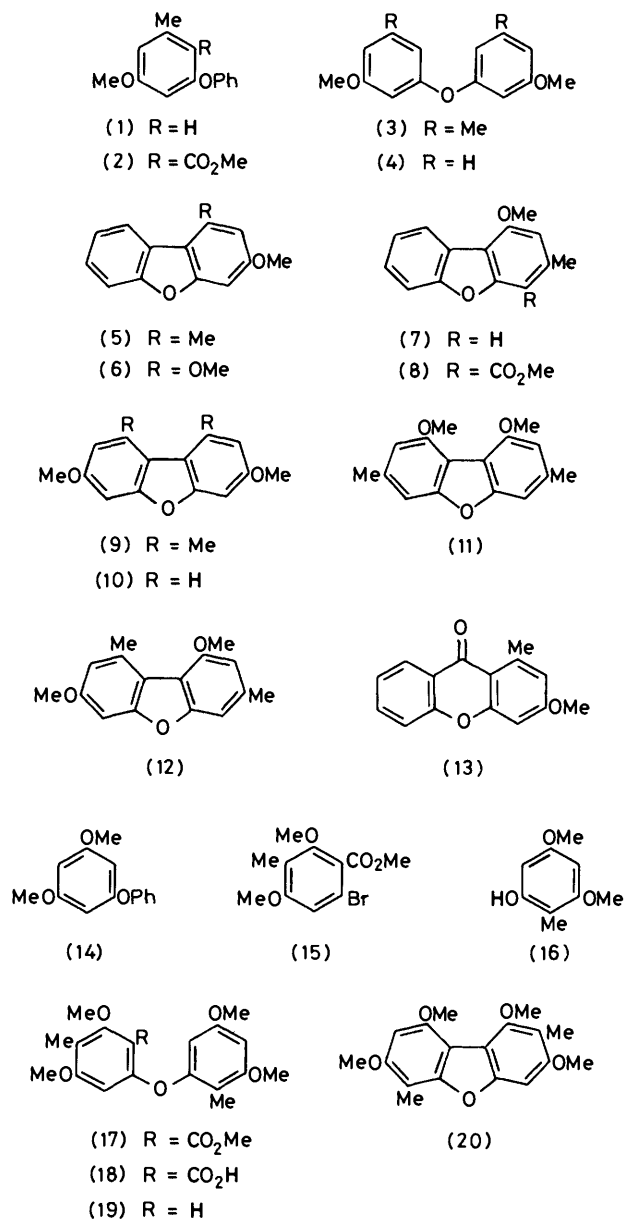
In order to discover if this method of cyclization could be applied to a highly substituted diphenyl ether, compound (19) was synthesized. Ullmann reaction between the *o*-bromo-ester (15)<sup>16</sup> and the phenol (16)<sup>17</sup> gave the diphenyl ether (17). The derived acid (18), on decarboxylation with copper(II) chromite in hot quinoline, gave the required ether (19). Cyclization was effected in only poor yield and the product (20) was identical (m.p., <sup>1</sup>H n.m.r.) with that previously prepared by Ollis and his co-workers by a more conventional route.<sup>3</sup>

In view of these results we thus decided to develop a method of dibenzofuran synthesis by annulation of benzofurans, and we chose as our initial target the minor cannabis constituent cannabifuran (35)<sup>4</sup> (see Scheme). Retrosynthetic analysis suggested that a Wittig reaction between the benzofuran-2-carbaldehyde (28) and 2-carboxy-1-methoxycarbonylethyltriphenylphosphorane<sup>18</sup> should yield the itaconic half-ester (29). Cyclization and functional-group manipulation should then yield cannabifuran (35).

For the synthesis of the benzofuran (28) we required the aldehyde (24) which had previously been synthesized by Duff.<sup>19</sup> A better synthesis of salicylaldehydes is the recently reported method of Zwanenburg and Reynen.<sup>20</sup> Consequently, carvacrol (21) was acylated with oxalyl chloride in the presence of 4-(*N,N*-dimethylamino)pyridine in boiling chloroform and the intermediate was cyclized upon treatment with aluminium chloride. The resultant benzofurandione (22) was reduced with lithium aluminium hydride to the triol (23) which afforded the aldehyde (24) in high overall yield on periodate oxidation. *O*-Alkylation and subsequent intramolecular aldol-type reaction were achieved by treatment of the aldehyde (24) with diethyl bromomalonate in boiling acetone<sup>21</sup> to afford the intermediate (25), which was smoothly de-

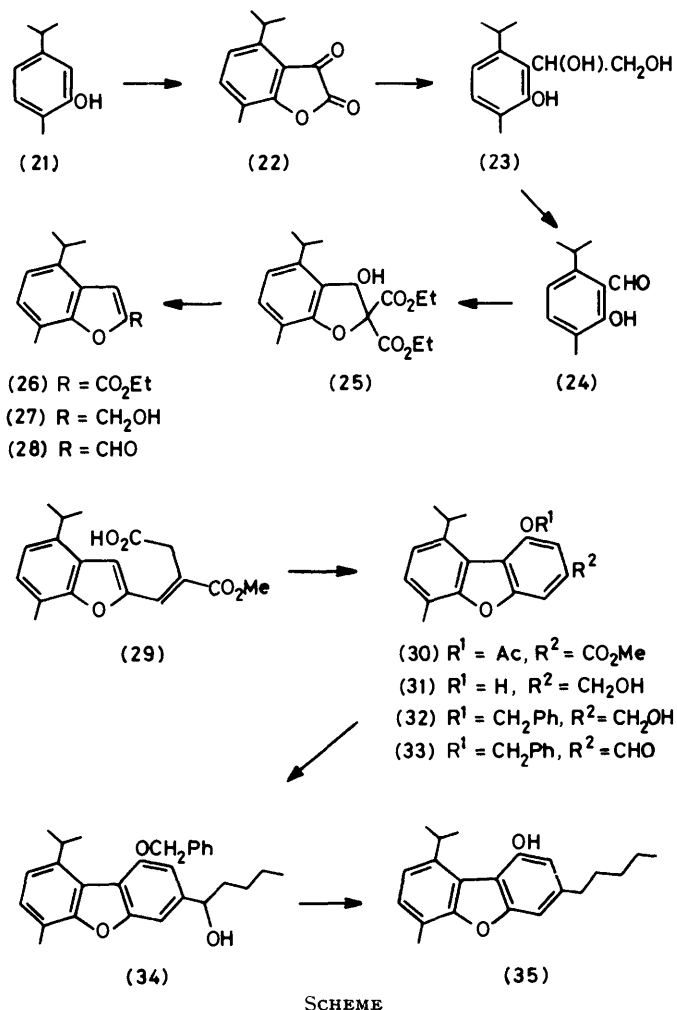
† We thank Dr. A. Sierakowski for these experimental details.

ethoxycarbonylated and dehydrated on heating with lithium chloride in wet dimethyl sulphoxide (DMSO)<sup>22</sup> to give the ester (26). This was converted, *via* the alcohol (27), into the aldehyde (28). Wittig reaction of



the aldehyde (28) and 2-carboxy-1-methoxycarbonyl-ethyltriphenylphosphorane in anhydrous tetrahydrofuran (THF) at room temperature gave the itaconic half-ester (29) which cyclized to the dibenzofuran (30) on treatment with hot acetic anhydride. Reduction of the ester (30) with lithium aluminium hydride gave the diol (31). The derived benzyl ether (32) was then converted, by oxidation with activated manganese dioxide,<sup>23</sup> into the aldehyde (33). This was allowed to react with butylmagnesium bromide to give the secondary alcohol (34). Debenzylation and hydrogenolysis of the benzylic alcohol

function of compound (34) were achieved by catalytic hydrogenation and furnished compound (35), m.p. 78—79 °C. Cannabifuran is reported as an oil but only a minute quantity was obtained from the natural source.<sup>4</sup> The mass- and <sup>1</sup>H n.m.r.-spectra of compound (35) are, however, in close agreement with the data published for cannabifuran.<sup>4</sup>



#### EXPERIMENTAL

General directions have been given before.<sup>24</sup> Photochemical reactions were carried out using a 450 W Hanovia medium-pressure mercury lamp surrounded by a silica cooling jacket. Palladium(II) acetate was prepared by the method of Stephenson *et al.*<sup>25</sup> Light petroleum refers to that fraction boiling in the range 58—65 °C.

**3-Methoxy-5-methylphenyl 2'-Nitrophenyl Ether.**—3-Methoxy-5-methylphenol<sup>26</sup> (9.1 g), 2-bromonitrobenzene (15.0 g), and dry potassium carbonate (31.5 g) in anhydrous pyridine (200 ml) were stirred and heated under dry nitrogen at 130 °C (bath) and copper(II) oxide (6.0 g) was then added.<sup>27</sup> The mixture was then stirred and heated under reflux for 18 h. The cooled mixture was diluted with ether and filtered through kieselguhr. The filtrate was washed in turn with dilute hydrochloric acid, dilute sodium hydroxide,

water, and finally, saturated brine. Chromatography of the crude product over silica gel with 3% ethyl acetate–light petroleum as eluant afforded the *diphenyl ether* (14.85 g) as an oil, b.p. 152 °C (bath) at 0.1 mmHg (Found: C, 65.0; H, 5.15, N, 5.4%;  $M^+$ , 259.  $C_{14}H_{13}NO_4$  requires C, 64.85; H, 5.05; N, 5.4%;  $M$ , 259);  $\delta$  (CDCl<sub>3</sub>, 90 MHz) 2.87 (3 H, s, Me), 3.74 (3 H, s, OMe), 6.42 (2 H, deformed s,  $w/2$  3.2 Hz, 2- and 6-H), 6.54 (1 H, deformed s,  $w/2$  4.9 Hz, 4-H), and 6.96–7.97 (4 H, ABCD, 3', 4', 5', and 6'-H).

*2-(3-Methoxy-5-methylphenoxy)aniline*.—The foregoing nitro-compound (10.0 g) in ethyl acetate (100 ml) was shaken under hydrogen at 4 atm with 10% palladium–charcoal (1.0 g) until absorption ceased. The usual work-up and distillation of the crude product under reduced pressure gave the *aniline* (7.9 g) as an oil, b.p. 160 °C at 0.3 mmHg (Found: C, 73.05; H, 6.5; N, 6.3%;  $M^+$ , 224.  $C_{14}H_{15}NO_2$  requires C, 73.35; H, 6.6; N, 6.1%;  $M$ , 224).

*3-Methoxy-5-methylphenyl Phenyl Ether* (1).—A solution of sodium nitrite (1.3 g) in water (40 ml) was added dropwise to a stirred solution of the foregoing aniline (4.0 g) in a mixture of water (65 ml), dioxan (35 ml), and concentrated hydrochloric acid (7.5 ml), at 0 °C. The mixture was stirred for a further 15 min at 0 °C after which urea (170 mg) was added to it, followed by the dropwise addition of phosphinous acid (50%; 40 ml) at 0 °C. The solution was stirred at 0 °C for a further 2 h, and then set aside at 0 °C for 18 h. The mixture was extracted with ether and the extract was washed in turn with dilute ammonia, dilute hydrochloric acid, water, and saturated brine. The crude product was chromatographed over silica gel with 2.5% ethyl acetate–light petroleum as eluant. The *diphenyl ether* (1) (3.14 g) was obtained as an oil ( $M^+$ , 214.0963.  $C_{14}H_{14}O_2$  requires  $M$ , 214.0994);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.20 (3 H, s, Me), 3.59 (3 H, s, OMe), 6.29 (3 H, s, 3 × ArH), and 6.72–7.36 (5 H, m, 5 × ArH).

*Methyl 4-Methoxy-5-methyl-2-phenoxybenzoate* (2).—Ullmann reaction between phenol and methyl 2-bromo-4-methoxy-6-methylbenzoate<sup>28</sup> by the method described above gave a crude product which was subjected to steam distillation. The involatile residue was then chromatographed over silica gel with 5% ethyl acetate–light petroleum as eluant. The *ester* (2) (78%) was obtained as an oil, b.p. 115 °C (bath) at 0.01 mmHg (Found: C, 70.4; H, 5.95%;  $M^+$ , 272.  $C_{16}H_{16}O_4$  requires C, 70.5; H, 5.9%;  $M$ , 272);  $\delta$  (CDCl<sub>3</sub>, 90 MHz) 2.36 (3 H, s, Me), 3.70 and 3.76 (each 3 H, s, OMe), 6.27 and 6.50 (2 H, AB,  $J$  2.5 Hz, 3- and 5-H), and 6.88–7.45 (5 H, m, 5 × ArH).

*Benzyl 4-Methoxy-2-(3-methoxy-5-methylphenoxy)-6-methylbenzoate*.—Ullmann reaction between 3-methoxy-5-methylphenol and benzyl 2-bromo-4-methoxy-6-methylbenzoate<sup>29</sup> by the method described above gave the *ester* (58%) as an oil, b.p. 180 °C (bath) at 0.005 mmHg (Found: C, 73.35; H, 6.15%;  $M^+$ , 392.  $C_{24}H_{24}O_5$  requires C, 73.45; H, 6.15%;  $M$ , 392);  $\delta$  (CDCl<sub>3</sub>, 90 MHz) 2.32 and 2.35 (each 3 H, s, Me), 3.67 (6 H, s, 2 × OMe), 5.22 (2 H, s, CH<sub>2</sub>), 6.26–6.55 (5 H, m, 5 × ArH), and 7.35 (5 H, s, Ph).

*4-Methoxy-2-(3-methoxy-5-methylphenoxy)-6-methylbenzoic Acid*.—The foregoing ester (2.3 g) and 10% palladium–charcoal (200 mg) in ethyl acetate (100 ml) containing concentrated hydrochloric acid (2 drops) were stirred under hydrogen until absorption ceased. The usual work-up gave the *acid* which crystallized from ethyl acetate–light petroleum as prisms (1.3 g), m.p. 142–143 °C (Found: C, 68.0; H, 6.3.  $C_{17}H_{18}O_5$  requires C, 67.55; H, 6.0%).

*Bis-(3-methoxy-5-methylphenyl) Ether* (3).—The foregoing acid (1.25 g) and copper(II) chromite (640 mg) were suspended in anhydrous quinoline (20 ml) and the mixture was stirred and heated under dry nitrogen at 210 °C (bath) for 2 h. The cooled mixture was diluted with ethyl acetate and filtered through kieselguhr. The filtrate was washed in turn with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, water, and finally with saturated brine. The crude product was chromatographed over silica gel with 2% ethyl acetate–light petroleum as eluant. The *diphenyl ether* (3) (620 mg) was obtained as an oil, b.p. 130 °C (bath) at 0.005 mmHg (Found: C, 74.8; H, 6.85%;  $M^+$ , 258.  $C_{16}H_{18}O_3$  requires C, 74.4; H, 7.0%;  $M$ , 258);  $\delta$  (CDCl<sub>3</sub>, 90 MHz) 2.26 (6 H, s,  $w/2$  2.1 Hz, 2 × Me), 3.73 (6 H, s, 2 × OMe), and 6.40br and 6.44br (total 6 H, each s, 6 × ArH).

*Photochemical Reaction of 3-Methoxy-5-methylphenyl Phenyl Ether* (1).—The ether (1) (1.0 g) and iodine (0.6 g) in cyclohexane (1 l) were irradiated for 15.5 h. The solution was washed with aqueous sodium thiosulphate and then evaporated. The residue was subjected to p.l.c. over silica gel with hexane as developing solvent. This gave three compounds in order of decreasing  $R_F$  value: *1-methoxy-3-methyl-dibenzofuran* (7) (136 mg) as rods (from light petroleum, m.p. 69 °C (Found: C, 79.4; H, 5.6%;  $M^+$ , 212.  $C_{14}H_{12}O_2$  requires C, 79.25; H, 5.7%;  $M$ , 212);  $\delta$  (CDCl<sub>3</sub>, 90 MHz) 2.48 (3 H, s, Me), 3.99 (3 H, s, OMe), 6.58 (1 H, s,  $w/2$  3.0 Hz, 2-H), 6.98 (1 H, s,  $w/2$  3.0 Hz, 4-H), 7.17–7.57 (3 H, m, 6-, 7-, and 8-H), and 7.99–8.13 (1 H, m, 9-H); starting material (480 mg); and *3-methoxy-1-methyl-dibenzofuran* (5) (220 mg) as prisms (from light petroleum, m.p. 74 °C (Found: C, 79.1; H, 5.8%;  $M^+$ , 212.  $C_{14}H_{12}O_2$  requires C, 79.25; H, 5.7%;  $M$ , 212);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 2.73 (3 H, s, Me), 3.88 (3 H, s, OMe), 6.73 and 6.94 (total 2 H, AB,  $J$  2.0 Hz, 2- and 4-H), 7.05 and 7.58 (total 3 H, m, 6-, 7-, and 8-H), and 7.70–7.90 (1 H, m, 9-H). Compound (7) (80 mg) in anhydrous dichloromethane (15 ml) was stirred and treated dropwise at –78 °C with boron tribromide (470 mg) in dichloromethane (5 ml). The solution was then stirred at room temperature for 15 h. The usual work-up gave *3-methyl-dibenzofuran-1-ol* (67 mg) as needles (from benzene–pentane, m.p. 115 °C (Found: C, 78.75; H, 5.15%;  $M^+$ , 198.  $C_{13}H_{10}O_2$  requires C, 78.75; H, 5.1%;  $M$ , 198);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.38 (3 H, s, Me), 6.38 (1 H, s, 2-H), 6.86 (1 H, s, 4-H), 7.10–7.59 (3 H, m, 6-, 7-, and 8-H), and 7.76–8.11 (1 H, m, 9-H).

*Photochemical Reaction of Methyl 4-Methoxy-6-methyl-2-phenoxybenzoate* (2).—Compound (2) was photolysed by the method described above for compound (1) for 45 h. Chromatography of the product over silica gel using gradient elution with 0–2.5% ethyl acetate–light petroleum as eluant gave the starting material (65%). This was followed by *3-methoxy-1-methyl-xanthen-9-one* (13) (9.5%) which formed rods (from ethyl acetate), m.p. 181 °C (Found: C, 74.85; H, 5.1%;  $M^+$ , 240.  $C_{15}H_{12}O_3$  requires C, 75.0; H, 5.05%;  $M$ , 240);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 2.84 (3 H, s, Me), 3.97 (3 H, s, OMe), 6.91 (1 H, A part of AB,  $J$  1.7 Hz, 2-H), 7.16–7.57 (4 H, m, 4-, 5-, 6-, and 7-H), and 7.90–8.03 (1 H, m, 8-H).

*Photochemical Reaction of Bis-(3-methoxy-5-methylphenyl) Ether* (3).—Compound (3) was photolysed for 9 h by the method described above for compound (1). P.l.c. of the crude product over silica gel with hexane as developing solvent gave three compounds in order of decreasing  $R_F$  value: *1,7-dimethoxy-3,9-dimethyl-dibenzofuran* (12) (10%)

as prisms (from light petroleum), m.p. 92–93 °C (lit.<sup>30</sup> 94.5–95.5 °C);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.45 (3 H, s, 3-Me), 2.80 (3 H, s, 9-Me), 3.80 and 3.89 (each 3 H, s, OMe), 6.48 (1 H, s, 2-H), 6.50 and 6.76 (total 2 H, AB, *J* 2.0 Hz, 8- and 6-H), and 6.86 (1 H, s, 4-H); 1,9-dimethoxy-3,7-dimethyldibenzofuran (11) (3%) as needles (from light petroleum), m.p. 107–108 °C (Found: C, 75.1; H, 6.3%; *M*<sup>+</sup>, 256. C<sub>16</sub>H<sub>16</sub>O<sub>3</sub> requires C, 75.0; H, 6.3%; *M*, 256);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.40 (6 H, s, 2 × Me), 3.89 (6 H, s, 2 × OMe), 6.44 (2 H, s, 2- and 8-H), and 6.80 (2 H, s, 4- and 6-H); and 3,7-dimethoxy-1,9-dimethyldibenzofuran (9) (4%) as plates (from light petroleum), m.p. 158–159 °C (lit.<sup>31</sup> 159–160 °C);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.78 (6 H, s, 2 × Me), 3.78 (6 H, s, 2 × OMe), and 6.56 and 6.76 (total 4 H, AB, *J* 2.0 Hz, 2-, 8-, 4-, and 6-H).

*Reaction of 3-Methoxy-5-methylphenyl Phenyl Ether (1) with Palladium(II) Acetate.*—The ether (1) (200 mg) was heated under reflux in acetic acid (30 ml) with palladium(II) acetate (200 mg) for 10 h. The cooled mixture was diluted with ethyl acetate and washed with aqueous sodium hydrogen carbonate. P.l.c. of the crude product gave the dibenzofuran (7) (49 mg), m.p. and mixed m.p. 69 °C, starting material (83 mg), and the dibenzofuran (5) (46 mg), m.p. and mixed m.p. 74 °C.

1,3-Dimethoxydibenzofuran (6).—3,5-Dimethoxyphenyl phenyl ether<sup>32</sup> (14) (200 mg) and palladium(II) acetate (200 mg) were heated under reflux in acetic acid (30 ml) for 10 h. The usual work-up gave a crude product which was subjected to p.l.c. over silica gel with hexane as developing solvent. This gave the dibenzofuran (6) (104 mg) as needles (from pentane), m.p. 72 °C (Found: C, 73.9; H, 5.5%; *M*<sup>+</sup>, 228. C<sub>14</sub>H<sub>12</sub>O<sub>2</sub> requires C, 73.65; H, 5.3%; *M*, 228);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 3.77 and 3.88 (each 3 H, s, OMe), 6.35 and 6.57 (total 2 H, AB, *J* 2.0 Hz, 2- and 4-H), 7.04–7.47 (3 H, m, 6-, 7-, and 8-H), and 7.69–8.01 (1 H, m, 9-H).

3,7-Dimethoxydibenzofuran (10).—Bis-(3-methoxyphenyl) ether<sup>33</sup> (4) (140 mg) and palladium(II) acetate (80 mg) were heated under reflux in acetic acid (10 ml) for 48 h. The usual work-up and p.l.c. over silica gel (hexane as developer) gave the dibenzofuran (10) (47 mg) as prisms (from light petroleum), m.p. 149–150 °C (lit.<sup>34</sup> 150 °C);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 3.88 (6 H, s, 2 × OMe), 6.90 (2 H, dd, *J*<sub>1,2</sub> = *J*<sub>8,9</sub> = 8.3 Hz, *J*<sub>2,4</sub> = *J*<sub>6,8</sub> = 2.0 Hz, 2- and 8-H), 7.06 (2 H, d, *J*<sub>2,4</sub> = *J*<sub>6,8</sub> = 2.0 Hz, 4- and 6-H), and 7.70 (2 H, d, *J*<sub>1,2</sub> = *J*<sub>8,9</sub> = 8.3 Hz, 1- and 9-H); *m/z* 228 (*M*<sup>+</sup>).

Methyl 1-Methoxy-3-methyldibenzofuran-4-carboxylate (8).—The ester (2) (250 mg) and palladium(II) acetate (465 mg) in acetic acid (30 ml) were heated at 115 °C (bath) for 48 h. The usual work-up and p.l.c. of the crude product over silica gel (8% ethyl acetate–light petroleum) gave the dibenzofuran (8) (87 mg) as rods (from ether–pentane), m.p. 98–99 °C (Found: C, 71.3; H, 5.25%; *M*<sup>+</sup>, 270. C<sub>16</sub>H<sub>14</sub>O<sub>4</sub> requires C, 71.1; H, 5.2%; *M*, 270);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.66 (3 H, s, Me), 3.94 (6 H, s, 2 × OMe), 6.51 (1 H, s, 2-H), 7.11–7.62 (3 H, s, 6-, 7-, and 8-H), and 7.84–8.06 (1 H, m, 9-H).

Methyl 6-(3,5-Dimethoxy-2-methylphenoxy)-2,4-dimethoxy-3-methylbenzoate (17).—Methyl 6-bromo-2,4-dimethoxy-3-methylbenzoate (15)<sup>16</sup> and 3,5-dimethoxy-2-methylphenol (16)<sup>17</sup> were allowed to react under Ullmann conditions in the manner described above. The crude product was chromatographed over silica gel with 2.5% ethyl acetate–light petroleum as eluant to give the ester (17) (53%) as prisms (from ether–pentane), m.p. 85–86 °C (Found: C, 63.85; H, 6.45%; *M*<sup>+</sup>, 376. C<sub>20</sub>H<sub>24</sub>O<sub>5</sub> requires C, 63.8; H, 6.45%;

*M*, 376);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.00 and 2.07 (each 3 H, s, Me), 3.59 and 3.62 (each 3 H, s, OMe), 3.79 (9 H, s, 3 × OMe), 5.09 (1 H, s, 5-H), and 6.03 and 6.17 (2 H, AB, *J* 2.0 Hz, 6'- and 4'-H).

6-(3,5-Dimethoxy-2-methylphenoxy)-2,4-dimethoxy-3-methylbenzoic Acid (18).—The ester (17) (1.15 g), DMSO (25 ml), water (5 ml), and potassium hydroxide (1.4 g) were heated on a steam-bath for 3.5 h. The usual work-up gave the acid (18) (1.01 g) as needles (from ether–pentane), m.p. 144–145 °C (Found: C, 63.0; H, 6.25%; *M*<sup>+</sup>, 362. C<sub>18</sub>H<sub>22</sub>O<sub>7</sub> requires C, 63.0; H, 6.1%; *M*, 362).

3,5-Dimethoxy-2-methylphenyl 3,5-Dimethoxy-4-methylmethylphenyl Ether (19).—The acid (18) (950 mg) and copper(II) chromite (550 mg) were stirred and heated in anhydrous quinoline (40 ml) at 200 °C (bath) for 4 h. The usual work-up gave the diphenyl ether (19) (730 mg) as prisms (from light petroleum), m.p. 98–99 °C (Found: C, 68.1; H, 6.9%; *M*<sup>+</sup>, 318. C<sub>18</sub>H<sub>22</sub>O<sub>5</sub> requires C, 67.9; H, 6.95%; *M*, 318);  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 2.00 (6 H, s, 2 × Me), 3.62 (9 H, s, 3 × OMe), 3.84 (3 H, s, OMe), 6.00 and 6.15 (total 2 H, AB, *J* 2.0 Hz, 4- and 6-H), and 6.02 (2 H, s, 2'- and 6'-H).

1,3,7,9-Tetramethoxy-2,6-dimethyldibenzofuran (20).—The diaryl ether (19) (100 mg) and palladium(II) acetate (85 mg) were heated at 80 °C (bath) for 35 min with acetic acid (40 ml) and methanesulphonic acid (1.5 ml). The usual work-up gave the dibenzofuran (20) (9.7 mg) as needles (from light petroleum), m.p. 115–116 °C (lit.<sup>3</sup> 116 °C);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 2.25 and 2.34 (each 3 H, s, Me), 3.85, 3.89, 3.93, and 4.03 (each 3 H, s, OMe), and 6.45 and 6.89 (each 1 H, s, 8- and 4-H); *m/z* 316 (*M*<sup>+</sup>).

4-Isopropyl-7-methylbenzofuran-2,3-dione (22).—Carvacrol (21) (5.0 g), oxalyl chloride (9.25 g), and 4-(*NN*-dimethylamino)pyridine (165 mg) in chloroform (150 ml) were heated under reflux for 2.5 h. The solvent was removed under reduced pressure and the residue, dissolved in anhydrous 1,2-dichloroethane (100 ml), was slowly added dropwise to a stirred suspension of aluminium chloride (13.35 g) in 1,2-dichloroethane (100 ml) at room temperature. The mixture was then stirred for a further 10 min and then poured into ice-water. The usual work-up gave the crude product (6.7 g) as a crystalline solid. A sample was recrystallized from light petroleum and formed needles of the dione (22), m.p. 104–105 °C (Found: C, 70.4; H, 6.1%; *M*<sup>+</sup>, 204. C<sub>12</sub>H<sub>12</sub>O<sub>3</sub> requires C, 70.6; H, 5.9%; *M*, 204);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.27 (6 H, d, *J* 6.7 Hz, Me<sub>2</sub>C), 2.31 (3 H, s, Me), 3.73 (1 H, septet, *J* 6.7 Hz, Me<sub>2</sub>CH), and 7.12 and 7.50 (total 2 H, AB, *J* 8.0 Hz, ArH).

1-(2-Hydroxy-6-isopropyl-3-methylphenyl)ethane-1,2-diol (23).—A solution of the crude dione (22) (6.7 g) in anhydrous ether (150 ml) was added to a stirred suspension of lithium aluminium hydride (4.4 g) in ether (200 ml). The mixture was then heated under reflux for 10 min, cooled in ice, and treated with an excess of saturated aqueous sodium sulphate. The usual work-up gave the crude product as a crystalline solid (6.8 g). A sample was recrystallized from benzene–light petroleum to give needles of the triol (23), m.p. 89 °C (Found: C, 68.3; H, 8.45%; *M*<sup>+</sup>, 210. C<sub>12</sub>H<sub>18</sub>O<sub>3</sub> requires C, 68.55; H, 8.65%; *M*, 210);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.22 (6 H, d, *J* 6.3 Hz, Me<sub>2</sub>C), 2.19 (3 H, s, Me), 3.00 (1 H, septet, *J* 6.3 Hz, Me<sub>2</sub>CH), 3.33br (1 H, D<sub>2</sub>O-exchangeable OH), 3.66–4.08 (2 H, AB-part of ABX, *J*<sub>AB</sub> 10.0 Hz, CH<sub>2</sub>OH), 5.28–5.45 (1 H, X-part of ABX, CHOH), 6.73 and 6.08 (total 2 H, AB, *J* 8.0 Hz, ArH), and 8.65 (1 H, s, D<sub>2</sub>O-exchangeable OH).

*2-Hydroxy-6-isopropyl-3-methylbenzaldehyde* (24).—A solution of the crude triol (23) (6.7 g) in ethanol (50 ml) and water (50 ml) was slowly added dropwise to a stirred solution of potassium metaperiodate (10.0 g) in 1M sulphuric acid (100 ml) at 0 °C. The mixture was stirred at 0 °C for 2 h, allowed to warm to room temperature, then diluted with water and extracted with ethyl acetate. Steam distillation gave the aldehyde (24) as an oil (5.2 g),  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 1.25 (6 H, d, *J* 6.5 Hz, Me<sub>2</sub>C), 2.12 (3 H, s, Me), 3.53 (1 H, septet, *J* 6.5 Hz, Me<sub>2</sub>CH), 6.59 and 7.16 (total 2 H, AB, *J* 8.0 Hz, ArH), 10.29 (1 H, s, CHO), and 12.23 (1 H, s, OH). The semicarbazone formed needles from ethanol, m.p. 177—178 °C (lit.<sup>19</sup> 180 °C).

*Diethyl 3-Hydroxy-4-isopropyl-7-methyl-2,3-dihydrobenzofuran-2,2-dicarboxylate* (25).—The aldehyde (24) (4.9 g) and anhydrous potassium carbonate (7.6 g) in dry acetone (100 ml) were stirred under dry nitrogen and treated dropwise with diethyl bromomalonate (8.0 g) in acetone (50 ml). The mixture was then heated under reflux for 3 h. The salts were filtered off and washed with acetone. The filtrate was evaporated under reduced pressure and the residue taken up in ether and washed with water and then with saturated brine. After evaporation under reduced pressure the crude product crystallized from light petroleum as rosettes of needles (9.5 g) of the *benzofuran* (25), m.p. 102—103 °C (Found: C, 64.35; H, 7.25%; *M*<sup>+</sup>, 336. C<sub>18</sub>H<sub>24</sub>O<sub>6</sub> requires C, 64.25; H, 7.2%; *M*, 336);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.10—1.50 (12 H, m, Me<sub>2</sub>C and 2 × CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.26 (3 H, s, Me), 2.39 (1 H, d, *J* 8.6 Hz, D<sub>2</sub>O-exchangeable OH), 3.17 (1 H, septet, *J* 6.9 Hz, Me<sub>2</sub>CH), 4.25 and 4.34 (each 2 H, q, 2 × CO<sub>2</sub>CH<sub>2</sub>Me), 5.95 (1 H, d, *J* 8.6 Hz, CHOH, collapsing to a singlet on addition of D<sub>2</sub>O), and 6.81 and 7.09 (total 2 H, AB, *J* 8.0 Hz, ArH).

*Ethyl 4-Isopropyl-7-methylbenzofuran-2-carboxylate* (26).—The diester (25) (30.0 g), lithium chloride (4.5 g), and water (3.3 ml) were heated in DMSO (400 ml) at 165 °C (bath) for 2 h. The cooled solution was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and then with saturated brine. Removal of the solvent gave the crude product (18.6 g). A sample was distilled under reduced pressure whereupon the *ester* (26) was obtained as an oil, b.p. 100—105 °C (bath) at 0.05 mmHg (Found: C, 73.1; H, 7.6%; *M*<sup>+</sup>, 246. C<sub>15</sub>H<sub>18</sub>O<sub>3</sub> requires C, 73.15; H, 7.35%; *M*, 246);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.34 (6 H, d, *J* 6.8 Hz, Me<sub>2</sub>C), 1.43 (3 H, t, CH<sub>2</sub>Me), 2.54 (3 H, s, Me), 3.25 (1 H, septet, *J* 6.8 Hz, Me<sub>2</sub>CH), 4.44 (2 H, q, CH<sub>2</sub>), 7.03 and 7.20 (total 2 H, AB, *J* 7.4 Hz, ArH), and 7.62 (1 H, s, 3-H).

*4-Isopropyl-7-methylbenzofuran-2-methanol* (27).—A solution of the crude ester (26) (18.0 g) in anhydrous ether (230 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.8 g) in anhydrous ether (230 ml). The mixture was then stirred and heated under reflux for 2 h, cooled in ice, and stirred during the addition of an excess of saturated aqueous sodium sulphate. The usual work-up gave the crude product (14.6 g). A sample was distilled under reduced pressure to afford the *alcohol* (27) as an oil, b.p. 90 °C (bath) at 0.08 mmHg (Found: C, 76.3; H, 7.95%; *M*<sup>+</sup>, 204. C<sub>13</sub>H<sub>16</sub>O<sub>2</sub> requires C, 76.45; H, 7.9%; *M*, 204);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.33 (6 H, d, *J* 7.4 Hz, Me<sub>2</sub>C), 1.89br. (1 H, D<sub>2</sub>O-exchangeable OH), 2.48 (3 H, s, Me), 3.19 (1 H, septet, *J* 7.4 Hz, Me<sub>2</sub>CH), 4.79 (2 H, s, CH<sub>2</sub>), 6.74 (1 H, s, 3-H), and 7.00 (2 H, s, ArH).

*4-Isopropyl-7-methylbenzofuran-2-carbaldehyde* (28).—The crude alcohol (27) (14.0 g) and activated manganese di-

oxide<sup>23</sup> (50 g) in benzene (1.2 l) were heated and stirred under reflux in a Dean–Stark apparatus for 12 h. The manganese dioxide was filtered off and washed with boiling benzene. The filtrate was evaporated to dryness under reduced pressure to give the crude product (11.4 g). A sample gave prisms of the *aldehyde* (28) (from light petroleum), m.p. 49—50 °C (Found: C, 77.35; H, 6.95%; *M*<sup>+</sup>, 202. C<sub>13</sub>H<sub>14</sub>O<sub>2</sub> requires C, 77.2; H, 7.0%; *M*, 202);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.37 (6 H, d, *J* 6.9 Hz, Me<sub>2</sub>C), 2.54 (3 H, s, Me), 3.27 (1 H, septet, *J* 6.9 Hz, Me<sub>2</sub>CH), 7.09 and 7.26 (total 2 H, AB, *J* 8.0 Hz, ArH), 7.66 (1 H, s, 3-H), and 9.88 (1 H, s, CHO).

(E)-4-(4-Isopropyl-7-methylbenzofuran-2-yl)-3-methoxycarbonylbut-3-enoic Acid (29).—The crude aldehyde (28) (11.0 g) and 2-carboxy-1-methoxycarbonyltriphenylphosphorane<sup>18</sup> (21.1 g) in dry THF (130 ml) were stirred at room temperature for 20 h. The solution was then poured into water and extracted with ethyl acetate. Acidic material was recovered with aqueous sodium hydrogen carbonate in the usual way. The extracts were washed with a little ethyl acetate and then acidified. Extraction with ethyl acetate and evaporation gave the crude product (12.65 g). A sample formed plates of the *acid* (29) (from ether–light petroleum), m.p. 152—154 °C (Found: C, 68.2; H, 6.4%; *M*<sup>+</sup>, 316. C<sub>18</sub>H<sub>20</sub>O<sub>5</sub> requires C, 68.35; H, 6.35%; *M*, 316);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.32 (6 H, d, *J* 6.9 Hz, Me<sub>2</sub>C), 2.40 (3 H, s, Me), 3.20 (1 H, septet, *J* 6.9 Hz, Me<sub>2</sub>CH), 3.83 (3 H, s, CO<sub>2</sub>Me), 4.06 (2 H, s, CH<sub>2</sub>), 7.01 (2 H, s, ArH), 7.07 (1 H, s, olefinic H), and 7.70 (1 H, s, furan H).

*Methyl 1-Acetoxy-9-isopropyl-6-methylidibenzofuran-3-carboxylate* (30).—The crude acid (29) (12.0 g) in acetic anhydride (100 ml) was heated on a steam-bath for 0.5 h. The solution was poured into an excess of aqueous sodium hydrogen carbonate and stirred until the acetic anhydride was decomposed. Extraction with ethyl acetate gave the crude product (12.2 g). A sample formed prisms of the *dibenzofuran* (30) (from ether), m.p. 162—163 °C (Found: C, 70.85; H, 5.9%; *M*<sup>+</sup>, 340. C<sub>20</sub>H<sub>20</sub>O<sub>5</sub> requires C, 70.6; H, 5.9%; *M*, 340);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.37 (6 H, d, *J* 6.9 Hz, Me<sub>2</sub>C), 2.45 (3 H, s, COMe), 2.56 (3 H, s, Me), 3.91 (1 H, septet, *J* 6.9 Hz, Me<sub>2</sub>CH), 3.96 (3 H, s, CO<sub>2</sub>Me), 7.22 and 7.32 (total 2 H, AB, *J* 8.0 Hz, 8- and 7-H), and 7.76 and 8.16 (total 2 H, AB, *J* 1.4 Hz, 2- and 4-H).

*3-Hydroxymethyl-9-isopropyl-6-methylidibenzofuran-1-ol* (31).—A solution of the foregoing crude ester (30) (3.7 g) in anhydrous THF (100 ml) was added dropwise with stirring to lithium aluminium hydride (1.2 g) in anhydrous THF (100 ml). The mixture was then heated under reflux for 2 h, then worked up in the usual way (aqueous sodium sulphate). The crude product was crystallized from ether–light petroleum to give needles of the *diol* (31) (2.9 g), m.p. 161—162 °C (Found: C, 75.65; H, 6.7%; *M*<sup>+</sup>, 270. C<sub>17</sub>H<sub>18</sub>O<sub>3</sub> requires C, 75.55; H, 6.7%; *M*, 270);  $\delta$  (CDCl<sub>3</sub>, 80 MHz) 1.34 (6 H, d, *J* 6.9 Hz, Me<sub>2</sub>C), 1.96 (1 H, t, *J* 5.7 Hz, D<sub>2</sub>O-exchangeable CH<sub>2</sub>OH), 2.53 (3 H, s, Me), 4.42 (1 H, septet, *J* 6.9 Hz, Me<sub>2</sub>CH), 4.78 (2 H, d, *J* 5.7 Hz, CH<sub>2</sub>OH, collapsing to a singlet on addition of D<sub>2</sub>O), 5.95 (1 H, s, D<sub>2</sub>O-exchangeable phenolic OH), 6.75 (1 H, s, 2-H), 7.16 (1 H, s, 4-H), and 7.19 (2 H, s, 7- and 8-H).

*1-Benzyloxy-9-isopropyl-6-methylidibenzofuran-3-ylmethanol* (32).—The diol (31) (4.0 g), benzyl bromide (2.63 g), and potassium carbonate (4.38 g) were stirred and heated under reflux in dry acetone (50 ml) for 2.5 h. Work-up in the usual way and removal of the excess of benzyl bromide by steam distillation afforded the *alcohol* (32) as prisms (5.2 g)

(from light petroleum), m.p. 149–150 °C (Found: C, 80.34; H, 6.95%;  $M^+$ , 360.  $C_{24}H_{24}O_3$  requires C, 79.95; H, 6.7%;  $M$ , 360);  $\delta$  ( $CDCl_3$ , 80 MHz) 0.98 (6 H, d,  $J$  6.9 Hz,  $Me_2C$ ), 1.82br. (1 H,  $D_2O$ -exchangeable OH), 2.52 (3 H, s, Me), 4.29 (1 H, septet,  $J$  6.9 Hz,  $Me_2CH$ ), 4.81 (2 H, s,  $w/2$  5.5 Hz,  $CH_2OH$ ), 5.22 (2 H, s,  $CH_2Ph$ ), 6.91 (1 H, s, 2-H), 7.12 and 7.04 (total 2 H, AB,  $J$  8.0 Hz, 8- and 7-H), 7.24 (1 H, s, 4-H), and 7.44 (5 H, m, Ph).

1-Benzoyloxy-9-isopropyl-6-methyl-dibenzofuran-3-carbaldehyde (33).—The alcohol (32) (5.4 g) and activated manganese dioxide (30 g) were heated and stirred under reflux in benzene (500 ml) in a Dean–Stark apparatus for 2 h. The usual work-up gave the aldehyde (33) (3.9 g) as prisms (from light petroleum), m.p. 141–142 °C (Found: C, 80.25; H, 6.3%;  $M^+$ , 358.  $C_{24}H_{22}O_3$  requires C, 80.4; H, 6.2%;  $M$ , 358);  $\delta$  ( $CDCl_3$ , 80 MHz) 0.98 (6 H, d,  $J$  6.9 Hz,  $Me_2C$ ), 2.55 (3 H, s, Me), 4.30 (1 H, septet,  $J$  6.9 Hz,  $Me_2CH$ ), 5.30 (2 H, s,  $CH_2Ph$ ), 7.26 and 7.14 (total 2 H, AB,  $J$  8.0 Hz, 8- and 7-H), 7.46 (6 H, m, Ph and 2-H), 7.73 (1 H, A-part of AB,  $J$  1.1 Hz, 4-H), and 10.07 (1 H, s, CHO).

1-(1-Benzoyloxy-9-isopropyl-6-methyl-dibenzofuran-3-yl)-pentan-1-ol (34).—A solution of butylmagnesium bromide [from magnesium (495 mg) and 1-bromobutane (2.45 g)] in anhydrous ether (30 ml) was added dropwise to a stirred solution of the aldehyde (33) (2.0 g) in ether (150 ml) under dry nitrogen. The mixture was then stirred and heated under reflux for 20 min. The usual work-up gave the dibenzofuran (34) (2.3 g) as needles (from light petroleum), m.p. 82–84 °C (Found: C, 80.75; H, 7.55%;  $M^+$ , 416.  $C_{18}H_{22}O_3$  requires C, 80.75; H, 7.75%;  $M$ , 416);  $\delta$  ( $CDCl_3$ , 80 MHz) 0.89 (3 H, t, Me), 0.99 (6 H, d,  $J$  6.9 Hz,  $Me_2C$ ), 1.15–2.08 (6 H, m,  $3 \times CH_2$ ), 2.52 (3 H, s, Me), 4.31 (1 H, septet,  $J$  6.9 Hz,  $Me_2CH$ ), 4.78 (1 H, t,  $CHOH$ ), 5.23 (2 H, s,  $CH_2Ph$ ), 6.90 (1 H, s, 2-H), 7.08 and 7.16 (total 2 H, AB,  $J$  8.3 Hz, 8- and 7-H), 7.21 (1 H, s, 4-H), and 7.43 (5 H, m, Ph).

9-Isopropyl-6-methyl-3-pentyl-dibenzofuran-1-ol (35).—The alcohol (34) (1.00 g) and 10% palladium–charcoal (250 mg) were shaken in deoxygenated methanol (100 ml) containing concentrated hydrochloric acid (4 drops), under hydrogen at 4 atm until absorption ceased. The usual work-up gave the crude product (740 mg). A sample was distilled under diminished pressure, b.p. 190 °C (kugelrohr) at 0.01 mmHg, and then crystallized from pentane to give prisms of *cannabinifuran* (35), m.p. 78–79 °C (Found: C, 81.55; H, 8.65.  $C_{21}H_{26}O_2$  requires C, 81.25; H, 8.44%);  $\delta$  ( $CCl_4$ , 90 MHz) 0.89 (3 H, t, Me), 1.31 (6 H, d,  $J$  6.8 Hz,  $Me_2C$ ), 1.59 (6 H, m,  $3 \times CH_2$ ), 2.49 (3 H, s, Me), 2.57 (2 H, t,  $J$  7.0 Hz,  $CH_2$ ), 4.33 (1 H, septet,  $J$  6.8 Hz,  $Me_2CH$ ), 5.11br (1 H,  $D_2O$ -exchangeable OH), 6.23 (1 H, s,  $w/2$  3.0 Hz, 2-H), 6.91 (1 H, s,  $w/2$  2.9 Hz, 4-H), and 7.05 (2 H, s, 7- and 8-H); mass spectrum (Hewlett–Packard 5986 instrument)  $m/z$  311 (11.7), 310 (54.9,  $M^+$ ), 296 (20.3), 295 (100), 254 (19.8), 253 (16.6), 239 (8.5), 238 (14.9), 237 (9.6), 225 (8.5), 224 (4.0), 223 (7.8), 211 (12.2), 210 (3.1), 165 (9.5), and 119 (8.2).

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