Cannabis. Part 28.[1] A New Route to the Synthesis of Cannabifuran

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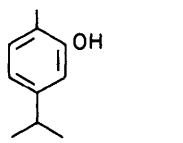
The total synthesis of the naturally occurring dibenzofuran cannabifuran (9-isopropyl-6-methyl-3-pentyldibenzofuran-1-ol) (25) is presented. In the key step, starting from 2,3-dimethoxy-*p*-toluic acid and 2-bromo-1,3-dimethoxy-5-pentylbenzene, the aryl–aryl bond was formed *via* a methoxy displacement in the aryldihydro-oxazole (17). The final furan ring closure in the trimethoxybiphenyl (23) to cannabifuran was accomplished by use of HI–Ac_2O. Investigations of other approaches resulted in an improved synthesis of 2,6-dimethoxybiphenyl using modifications of nickel-catalysed Grignard cross-coupling syntheses.

The dibenzofuran cannabifuran (25) was isolated [2] in 1975 from the cyclohexane extract of green Afghan hashish by micro-preparative gas chromatography followed by thin layer chromatography. The structural assignment was based on mass and ^1H n.m.r. spectral data and some microchemical reactions. Since cannabifuran represents a unique structure among the cannabinoids, we undertook its synthesis to confirm the proposed structure as well as to obtain a quantity useful for pharmacological research. We report here an unambiguous structure proof by the total synthesis of cannabifuran. After completion of our work on this subject, which started in 1978, a synthesis of cannabifuran appeared,[3] which was followed by our preliminary communication [4] of a different synthesis of this compound.

From the known synthetic methods available for dibenzofurans, a number appeared possibly adaptable to the cannabifuran synthesis, such as the condensation of a cyclohexane-1,3-dione with an α-halogenated cyclohexanone,[5] the cyclization of a 2-cyclohex-2-enylcyclohexane-1,3-dione,[6] the Diels–Alder annelation of a 2-isopropenylbenzofuran,[7] the photochemical synthesis of dibenzofuran from a depsidone,[8] the photochemical [9] or palladium(II) acetate [10] mediated cyclization of a diphenyl ether, and the cyclization of a 2-iodo-2′-acetoxybiphenyl [11] or a 2,2′-dimethoxybiphenyl.[12,13] The use of a cannabielsoin-derived compound [14–16] as a precursor might have been attractive; however, the syntheses of these compounds are lengthy involving various chromatographic separations. In view of the substitution pattern of cannabifuran the reported synthesis [17,18] of methyl 4-acetoxybenzofuran-6-carboxylate from furfural using the Stobbe reaction followed by cyclization seemed particularly suited for its preparation. Thus, for an extension of this method to the annelation of the benzofuran (4) we required the aldehyde (2). To achieve this end, we chose the *ortho*-formylation of carvacrol (1) using the method of Casiraghi *et al.*[19] which is based on the reaction of formaldehyde with an aryloxymagnesium bromide complexed with hexamethylphosphoramide. Our yield was significantly lower than that stated and the aldehyde was isolated from the resulting mixture *via* its semicarbazone. The transformation of the aldehyde (2) into the new benzofurancarbaldehyde (4) was mainly based on the work of Descamps and Henaux.[20] The phenolic group in compound (2) was converted into an ether group by bromoacetaldehyde diethyl acetal, giving compound (3). The following acetal cleavage and cyclization to the carbaldehyde (4) was carried out as a one-pot reaction in boiling acetic acid. Subsequently, we investigated the Stobbe reaction of this aldehyde with dimethyl succinate to obtain the required itaconic half-ester (5). This reaction was attempted several times using different reaction conditions; however, the best yield obtained was 20%. We have also tried the condensation with ethyl laevulinate [21] instead of dimethyl succinate but the yields were equally disappointing. In the recently published [3] synthesis of cannabifuran, using a quite similar approach, a Wittig reaction was successfully applied instead of the above mentioned Stobbe reaction.



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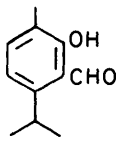

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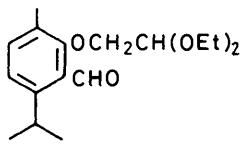

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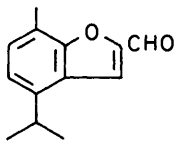

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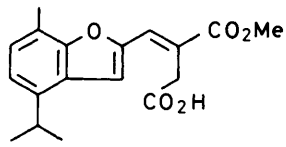
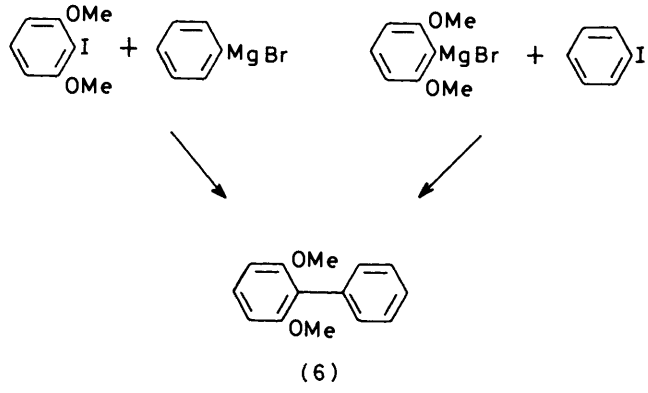


(5)

A re-evaluation of the possible synthetic approaches showed then that a route proceeding *via* a 2,2′-dimethoxybiphenyl should be preferable; thus the biphenyl (23) became our next target. For selective formation of the aryl–aryl bond a Grignard cross-coupling reaction was chosen. As a model reaction we first studied the synthesis of 2,6-dimethoxybiphenyl (6). The synthesis of (6) has been reported twice; [22,23] the former method proceeds in low yield, while the latter is not generally applicable to the synthesis of other biphenyls. For cross-coupling between aromatic Grignard reagents and aryl halides various catalysts have been proposed in the last few years, based mainly on nickel [24,25] or palladium [26] complexes or salts. Thus, for example, the reaction between mesitylmagnesium bromide and bromobenzene catalysed by dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) [Ni(dppp)Cl_2] gave 2-phenylmesitylene in 78% yield according to Tamao *et al.*[27] However, when their conditions were applied to the reaction between 2,6-dimethoxyphenylmagnesium bromide and bromobenzene, the desired product was not formed at all. Interchanging the Grignard reagent and the aryl halide, thus coupling 2-bromo-1,3-dimethoxybenzene with phenylmagnesium bromide, was likewise disappointing, only 13% of 2,6-dimethoxybiphenyl being formed. Studying first the latter combination, a significant improvement, to 50% yield, was found on substituting 2-iodo-1,3-dimethoxybenzene for the corresponding bromo derivative. The use of other Ni(II) catalysts did not affect the yield [the yield with $Ni(Ph_3P)_2Cl_2$ was 49% and with bis(dipivaloylmethanato)-nickel(II), 52%]. Less useful catalysts were $Ni(Ph_3P)_4$ (23%)



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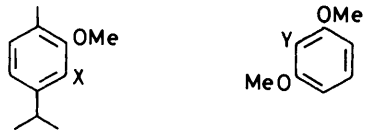
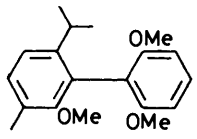


(7) a ; X = MgBr
b ; X = I

(8) a ; Y = I
b ; Y = MgBr



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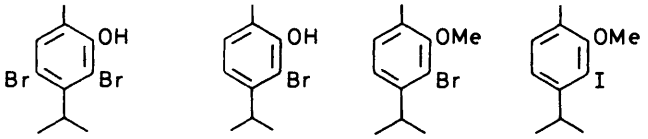
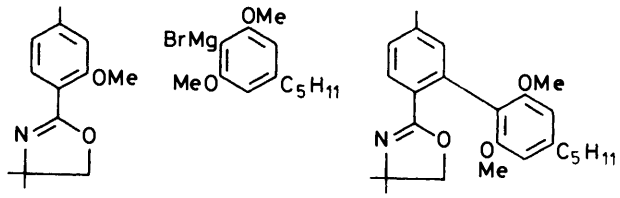


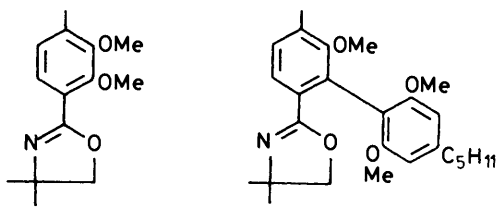
(10) (11) (12) (13)

and $PdCl_2$ (19%). The use of 2 equiv. of the Grignard reagent brought a major improvement. The yield reached was 93% with $Ni(dppp)Cl_2$ and 87% with the more easily accessible $Ni(Ph_3P)_2Cl_2$. Stimulated by this success we also tried to optimize the above mentioned coupling of 2,6-dimethoxyphenylmagnesium bromide with a halogenobenzene. The use of 3 equiv. of iodobenzene and substitution of tetrahydrofuran (THF) for diethyl ether brought the yield up to 39%. The use of only half of the original amount of THF was unexpectedly beneficial (72%). The last improvement was achieved by using only 2 equiv. of iodobenzene. The 88% yield thus obtained makes both coupling routes almost comparable in practice.

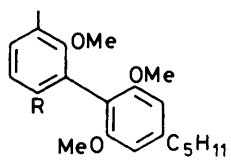
Having improved the synthesis of 2,6-dimethoxybiphenyl, we investigated the coupling of *o*-bromo- and *o*-iodo-carvacrol methyl ethers (12) and (13) with 2-bromo- and 2-iodo-1,3-dimethoxybenzene which should afford the biphenyl (9). The required bromocarvacrol ether was synthesized by converting carvacrol into dibromocarvacrol [28] (10), reducing the *p*-bromine atom selectively with zinc powder in 10% aqueous NaOH [29] to the new *o*-bromocarvacrol (11), and methylating this phenol with methyl iodide–K_2CO_3 in acetone. The *o*-iodocarvacrol ether (13) was prepared from the bromo compound (12) by bromine–lithium exchange with butyl-lithium



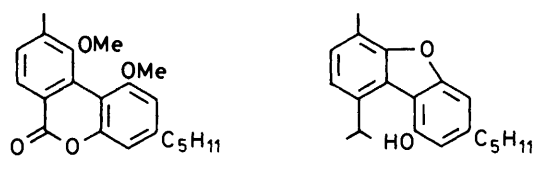
(14) (15) (16)



(17) (18)



(19) R = CO_2H
(20) R = CO_2Me
(21) R = $CH(OH)Me_2$
(22) R = $C(Me)=CH_2$
(23) R = $CHMe_2$



(24) (25)

followed by iodination with I_2. We have investigated both the possible coupling modes, *i.e.* the coupling of (7a) with (8a) as well as the coupling of (7b) with (8b); the yields achieved were, however, quite disappointing (10 and 1% respectively). These results showed a great sensitivity of the cross-coupling reaction to the *o*-substituents of both reactants, and we therefore looked for a means to circumvent the steric hindrance present, especially that due to the isopropyl group.

The recent report [30] on dihydro-oxazole-facilitated methoxy substitution in *o*-methoxyaryl-dihydro-oxazoles by organometallics offered a unique method for synthesizing the required aryl–aryl bond selectively by replacing the sterically hindering isopropyl group by the activating dihydro-oxazole moiety. This method was first tried with the model dihydro-oxazole (14). The reaction with the Grignard reagent (15) using general reaction conditions [30] (THF, 20 °C), however, resulted in a very low conversion into the biphenyl (16) (only 4%). As already reported in a previous publication [31] on a new synthesis of cannabinol, the yield could be dramatically improved to 87% by performing the reaction in refluxing THF. This modification was therefore applied to the synthesis of cannabifuran.

The starting compound in our synthetic sequence was the known [32] 2,3-dimethoxy-*p*-toluic acid, which was converted into the new dihydro-oxazole (17) in 78% yield by the procedure of Meyers *et al.*[30] In the key step this dihydro-oxazole reacted with the Grignard reagent [31] (15) from 2-bromo-1,3-dimethoxy-5-pentylbenzene (2 equiv.) in boiling THF for 22 h to afford the highly hindered biphenyldihydro-oxazole (18) in 83% yield. The cleavage of the dihydro-oxazole moiety to give the carboxylic acid (19) under standard conditions [30] (boiling 4.5M-hydrochloric acid, 16 h) was accompanied by a partial ether cleavage leading to a mixture of the acid (19) (major product) and the lactone (24) in 100% yield. Performing the reaction on a larger scale promoted more lactone formation. This mixture was methylated by dimethyl sulphate and aqueous NaOH to give the methyl ester (20) in 83% yield. The ester function was transformed quantitatively into the hydroxy-isopropyl group in compound (21) by excess of methyl-magnesium iodide. This carbinol was directly and quantitatively dehydrated by trifluoroacetic acid and the resulting st rene (22) was reduced catalytically to the isopropyl-biphenyl (23) in 92% yield. In the final, remarkably smooth synthetic operation (HI–Ac_2O, 5 h reflux), cleavage of the three methoxy groups in compound (23) and dehydration leading to cyclization took place simultaneously to afford the crystalline cannabifuran (25), m.p. 80—81 °C, in 90% yield, identical with the natural oily [2] material.

Experimental

General directions are given in ref. 1.

2-Hydroxy-6-isopropyl-3-methylbenzaldehyde (2).—To a solution of ethylmagnesium bromide [from ethyl bromide (44 g) and magnesium (8.4 g)] in diethyl ether (250 ml) was added dropwise a solution of carvacrol (1) (48 g) in diethyl ether (50 ml). Most of the ether was distilled off and benzene was added. Distillation was continued until the temperature reached 80 °C. The volume was then adjusted to 250 ml with benzene, and hexamethylphosphoramide (72 g) was added followed by paraformaldehyde (28 g). The mixture was heated under reflux with stirring for 3 h, cooled, acidified with 6M-hydrochloric acid, and extracted with diethyl ether. The extract was washed twice with water, dried, evaporated to dryness, and distilled to give the product (38.5 g), b.p. 115—145 °C/12 mmHg. According to the ^1H n.m.r. analysis, the product was a mixture of the aldehyde (2), carvacrol, and *o*-methoxymethylcarvacrol in the ratio 50 : 35 : 15; the yield of aldehyde (2) was thus 35 and 47% based on converted carvacrol. The aldehyde was isolated *via* its semicarbazone. To a mixture of semicarbazide hydrochloride (100 g), sodium acetate (150 g), and water (500 ml) was added the obtained crude aldehyde (130 g) and ethanol (650 ml). After standing overnight at −20 °C, the crystalline semicarbazone was collected (quantitative yield) and recrystallized from ethanol, m.p. 176—177 °C (lit.,[3] m.p. 177—178 °C). Steam distillation of a mixture of the semicarbazone (10 g), oxalic acid dihydrate (20 g), and water (200 ml) gave the aldehyde (2) as a pale yellow oil (6.5 g, 86%); ^1H n.m.r. data were identical with the published values.[3]

4-Isopropyl-7-methylbenzofuran-2-carbaldehyde (4).—A stirred mixture of the aldehyde (2) (14.4 g), bromoacetaldehyde diethyl acetal (17.6 g), potassium carbonate (12 g), and *N,N*-dimethylformamide (40 ml) was refluxed for 90 min, then cooled, filtered, and the dimethylformamide evaporated under reduced pressure. To the residue was added acetic acid (48 ml) and the solution was refluxed for 43 h. The acetic acid was evaporated under reduced pressure and the crude product was distilled, b.p. 137 °C/1 mmHg, to afford the aldehyde (4) as an oil which quickly solidified (9.5 g, 58%), m.p. 54 °C from hexane (lit.,[3] m.p. 49—50 °C); ^1H n.m.r. data were identical with the published values; [3] δ_C ($CDCl_3$) 14.5, 23.1 (2 C), 31.2, 116.6, 119.8, 120.0, 124.8, 129.8, 141.9, 152.0, 155.4, and 179.5 p.p.m.

2,6-Dimethoxybiphenyl (6).—(*a*) To a stirred mixture of 2-iodo-1,3-dimethoxybenzene [33] (1.3 g), $Ni(Ph_3P)_2Cl_2$ (65 mg), and diethyl ether (20 ml), the Grignard reagent from magnesium (0.3 g), bromobenzene (1.6 g), and diethyl ether (10 ml) was added dropwise. The black solution was refluxed for 22 h and worked up *via* ether extraction. Crystallization of the crude product from cyclohexane yielded pure 2,6-dimethoxybiphenyl (87%), m.p. 88—89 °C (lit.,[22] m.p. 88—89 °C); δ_H ($CDCl_3$) 3.7 (6 H, s, 2 × OMe), 6.6 (2 H, d, *J* 8 Hz, ArH), 7.25 (1 H, t, *J* 8 Hz, ArH), and 7.35 (5 H, s, 5 × ArH); δ_C ($CDCl_3$) 55.7 (2 C), 104.1 (2 C), 119.5, 126.6, 127.4 (2 C), 128.5, 130.7 (2 C), 134.0, and 157.5 p.p.m. (2 C).

(*b*) To a stirred mixture of iodobenzene (4.1 g) and Ni(dppp)Cl_2 (110 mg) the Grignard reagent from magnesium (0.3 g), 2-bromo-1,3-dimethoxybenzene [34] (2.2 g), and THF (7 ml) was added dropwise. The dark solution was refluxed for 22 h and worked up to afford the crystallized product (88%).

2-Bromo-1-hydroxy-3-isopropyl-6-methylbenzene (11).—To a suspension of zinc powder (10 g) in 10% NaOH (50 ml) was added dibromocarvacrol [28] (10) (6 g). After being stirred at 100 °C for 5 min, the unchanged zinc was filtered off, the filtrate was acidified (HCl) and extracted with diethyl ether. The extract was washed with water, dried, concentrated under reduced pressure, and distilled, b.p. 120—122 °C/12 mmHg, to afford the oily phenol (11) (60%); δ_H (CCl_4) 1.2 (6 H, d, *J* 7 Hz, 2 × Me), 2.25 (3 H, s, ArMe), 3.2 (1 H, septet, *J* 7 Hz, C*H*Me_2), 6.65 (1 H, d, *J* 8 Hz, ArH), and 6.95 (1 H, d, *J* 8 Hz, ArH). Working on a larger scale led to lower selectivity.

2-Bromo-3-isopropyl-1-methoxy-6-methylbenzene (12).—A mixture of *o*-bromocarvacrol (11) (37.2 g), methyl iodide (20 ml), potassium carbonate (28 g), and acetone (280 ml) was stirred at room temperature for 18 h. The salts were filtered off, the filtrate was concentrated under reduced pressure and redissolved in diethyl ether. The ethereal solution was washed with 10% aqueous KOH and water, dried, and evaporated to dryness. Distillation afforded the ether (12) (38.0 g, 96%), b.p. 124 °C/12 mmHg; δ_H (CCl_4) 1.2 (6 H, d, *J* 7 Hz, 2 × Me), 2.25 (3 H, s, ArMe), 3.35 (1 H, septet, *J* 7 Hz, C*H*Me_2), 3.75 (3 H, s, OMe), 6.85 (1 H, d, *J* 8 Hz, ArH), and 7.0 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 16.1 (q), 22.8 (q, 2 C), 32.7 (d), 59.7 (q), 112.8 (s), 119.5 (s), 121.6 (d), 129.7 (d), 146.6 (s), and 155.0 p.p.m. (s).

2-Iodo-3-isopropyl-1-methoxy-6-methylbenzene (13).—To a solution of the bromoether (12) (2.4 g) in diethyl ether (10 ml) was added a solution of 1.5M-butyl-lithium in hexane (8.8 ml). After being stirred at room temperature for 21 h, a solution of iodine (2.5 g) in diethyl ether (25 ml) was added dropwise and the mixture was refluxed for 2 h. The resulting mixture was washed with 10% aqueous sodium thiosulphate and water, dried, concentrated under reduced pressure, and distilled, b.p. 140—145 °C/12 mmHg, to give the oily iodoether (13) (56%); δ_H (CCl_4) 1.2 (6 H, d, *J* 7 Hz, 2 × Me), 2.3 (3 H, s, ArMe), 3.25 (1 H, septet, *J* 7 Hz, C*H*Me_2), 3.7 (3 H, s, OMe), 6.8 (1 H, d, *J* 8 Hz, ArH), and 7.0 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 16.6 (q), 23.0 (q, 2 C), 37.9 (d), 59.8 (q), 99.6 (s), 121.4 (d), 129.0 (s), 131.0 (d), 150.0 (s), and 157.5 p.p.m. (s).

Methyl 2-(2,6-*Dimethoxy*-4-*pentylphenyl*)-3-*methoxy*-4-*methylbenzoate* (20).—A mixture of the dihydro-oxazole [1] (18) (18.6 g) and 4.5M-hydrochloric acid (1 l) was stirred and refluxed for 7 h. After being cooled, the mixture was extracted with ethyl acetate (2 × 300 ml), the organic extracts were washed with water, dried and evaporated to dryness to yield yellow crystals (17.54 g). According to the ^{1}H n.m.r. analysis, this was a mixture of the acid (19) and the lactone (24) in the ratio 57 : 43, as calculated from the characteristic peaks at δ_H 7.65 (1 H, d, *J* 8 Hz, ArH) and δ_H 7.8 (1 H, d, *J* 8 Hz, ArH), respectively. To the acid–lactone mixture (9.3 g) was added 30% aqueous NaOH (50 g) and dimethyl sulphate (10 ml) and the mixture was stirred for 1 h. Then, more dimethyl sulphate (3 × 10 ml) was added during 2 h, and after a further 1 h 30% NaOH (25 g) was added and the resulting mixture was heated at 100 °C for 1 h. After being cooled and acidified, the product was extracted with ethyl acetate. Work-up afforded the crystalline methyl ester (20) (83% overall), m.p. 79—80 °C (from cyclohexane); δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.2—1.9 (6 H, m, 3 × CH_2), 2.35 (3 H, s, ArMe), 2.65 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 3.4 (3 H, s, OMe), 3.55 (3 H, s, CO_2Me), 3.7 (6 H, s, 2 × OMe), 6.45 (2 H, s, 2 × ArH), 7.2 (1 H, d, *J* 8 Hz, ArH), and 7.65 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 13.9 (q), 16.6 (q), 22.4 (t), 30.8 (t), 31.4 (t), 36.6 (t), 51.3 (q), 55.8 (q, 2 C), 59.7 (q), 104.1 (d, 2 C), 112.5 (s), 125.2 (d), 129.7 (s and d, 2 C), 130.5 (s), 135.3 (s), 143.8 (s), 157.1 (s), 157.2 (s, 2 C), and 167.4 p.p.m. (s).

6′-(1-*Hydroxy*-1-*methylethyl*)-2,2′,6-*trimethoxy*-3′-*methyl*-4-*pentylbiphenyl* (21).—To a stirred solution of methylmagnesium iodide prepared from methyl iodide (8.8 ml) and magnesium (3.2 g) in diethyl ether (80 ml) was added dropwise a solution of the methyl ester (20) (4.0 g) in THF (160 ml). The mixture was stirred and refluxed for 70 min, then cooled and poured onto saturated aqueous ammonium chloride (200 ml). The mixture was extracted with diethyl ether (2 × 160 ml); the extracts were washed with water, dried, and concentrated under reduced pressure at room temperature to yield the biphenyl (21) as a viscous oil that slowly crystallized (4.0 g, 100%); δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.2—1.85 (6 H, m, 3 × CH_2), 1.4 (6 H, s, 2 × Me), 2.3 (3 H, s, ArMe), 2.65 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 3.4 (3 H, s, OMe), 3.7 (6 H, s, 2 × OMe), 6.45 (2 H, s, 2 × ArH), 7.15 (1 H, d, *J* 8 Hz, ArH), and 7.3 (1 H, d, *J* 8 Hz, ArH). The unstable product was used directly for the next step.

6′-*Isopropenyl*-2,2′,6-*trimethoxy*-3′-*methyl*-4-*pentylbiphenyl* (22).—Trifluoroacetic acid (0.6 ml) was added to a stirred solution of the alcohol (21) (4.0 g) in chloroform (25 ml). After 3 h at room temperature the solution was evaporated to dryness to give the slowly crystallizing styrene (22) (100%); δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.2—1.8 (6 H, m, 3 × CH_2), 1.7 (3 H, s, *Me*C=CH_2), 2.3 (3 H, s, ArMe), 2.65 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 3.4 (3 H, s, OMe), 3.7 (6 H, s, 2 × OMe), 4.65br (1 H, s, CH=), 4.8br (1 H, s, CH=), 6.4 (2 H, s, 2 × ArH), 6.95 (1 H, d, *J* 8 Hz, ArH), and 7.15 (1 H, d, *J* 8 Hz, ArH). The product was used without purification for the next step.

6′-*Isopropyl*-2,2′,6-*trimethoxy*-3′-*methyl*-4-*pentylbiphenyl* (23).—Hydrogenation of the styrene (22) (3.35 g) using PtO_2 (40 mg) in ethyl acetate (100 ml) at room temperature under H_2 (1 atm) for 2 h, followed by filtration and evaporation of the solvent, afforded the isopropylbiphenyl (23) (3.1 g, 92%), m.p. 75—76 °C from hexane; δ_H ($CDCl_3$) 0.9 (3 H, t, ω-Me), 1.05 (6 H, d, *J* 7 Hz, 2 × Me), 1.2—1.85 (6 H, m, 3 × CH_2), 2.3 (3 H, s, ArMe), 2.45—2.8 (3 H, m, benzylic CH_2 and *CH*Me_2), 3.4 (3 H, s, OMe), 3.7 (6 H, s, 2 × OMe), 6.45 (2 H, s, 2 × ArH), 7.05 (1 H, d, *J* 8 Hz, ArH), and 7.2 (1 H, d, *J* 8 Hz, ArH); δ_C ($CDCl_3$) 13.9 (q), 16.0 (q), 22.4 (t), 23.7 (q, 2 C), 30.0 (d), 30.9 (t), 31.6 (t), 36.6 (t), 55.4 (q, 2 C), 59.5 (q), 103.8 (d, 2 C), 112.2 (s), 120.1 (d), 127.0 (s), 127.3 (s), 130.3 (d), 143.8 (s), 147.3 (s), 156.2 (s), and 157.7 p.p.m. (s, 2 C).

9-*Isopropyl*-6-*methyl*-3-*pentyldibenzofuran*-1-*ol* (*Cannabifuran*) (25).—Aqueous 57% HI (50 ml) was added dropwise with cooling (20 °C) to a stirred solution of the biphenyl (23) (2 g) in acetic anhydride (50 ml). The mixture was stirred and refluxed for 5 h, cooled, diluted with water (250 ml), and extracted with diethyl ether (2 × 200 ml). Work-up gave cannabifuran (25) (90%), m.p. 80—81 °C from hexane (lit.,[3] m.p. 78—79 °C); ^{1}H n.m.r. data were identical with the published values; [2,3] δ_C ($CDCl_3$) 14.0 (q), 15.0 (q), 22.5 (t), 24.3 (q, 2 C), 30.4 (d), 31.0 (t), 31.4 (t), 35.8 (t), 104.1 (d), 109.7 (d), 110.7 (s), 118.3 (s), 118.8 (d), 121.4 (s), 127.4 (d), 142.0 (s), 143.2 (s), 149.8 (s), 154.4 (s), and 158.3 p.p.m. (s).

References

1 Part 27, J. Novák and C. A. Salemink, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
2 J. Friedrich-Fiechtl and G. Spiteller, *Tetrahedron*, 1975, **31**, 479.
3 M. V. Sargent and P. O. Stransky, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1605.
4 J. Novák and C. A. Salemink, *Tetrahedron Lett.*, 1983, **24**, 101.
5 H. Stetter and R. Lauterbach, *Liebigs Ann. Chem.*, 1962, **652**, 40.
6 R. Verhé, N. Schamp, L. De Buyck, N. De Kimpe, and M. Sadones, *Bull. Soc. Chim. Belg.*, 1975, **84**, 747.
7 W. J. Davidson and J. A. Elix, *Aust. J. Chem.*, 1970, **23**, 2119.
8 S. R. Lele and B. D. Hosangadi, *Indian J. Chem.*, 1978, **16B**, 415.
9 K.-P. Zeller and S. Berger, *J. Chem. Soc., Perkin Trans. 2*, 1977, 54.
10 B. Åkermark, L. Eberson, E. Jonsson, and E. Pettersson, *J. Org. Chem.*, 1975, **40**, 1365.
11 R. C. Fuson and R. L. Albright, *J. Am. Chem. Soc.*, 1959, **81**, 487.
12 B. Åkermark, H. Erdtman, and C. A. Wachtmeister, *Acta Chem. Scand.*, 1959, **13**, 1855.
13 J.-P. Bachelet, P. Demerseman, and R. Royer, *J. Heterocycl. Chem.*, 1977, **14**, 1409.
14 D. B. Uliss, R. K. Razdan, and H. C. Dalzell, *J. Am. Chem. Soc.*, 1974, **96**, 7372.
15 A. Shani and R. Mechoulam, *Tetrahedron*, 1974, **30**, 2437.
16 N. Lander, Z. Ben-Zvi, R. Mechoulam, B. Martin, M. Nordqvist, and S. Agurell, *J. Chem. Soc., Perkin Trans. 1*, 1976, 8.
17 S. M. Abdel-Wahhab and L. S. El-Assal, *J. Chem. Soc. C*, 1968, 867.
18 S. M. Abdel-Wahhab and N. R. El-Rayyes, *J. Prakt. Chem.*, 1972, **314**, 213.
19 G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, G. Puglia, G. Sartori, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 1*, 1978, 318.
20 M. Descamps and F. Henaux, F.P. 1 537 206 (*Chem. Abstr.*, 1969, **71**, 61198h).
21 B. V. Swaminathan, *Indian J. Chem.*, 1976, **14B**, 620.
22 W. Kern, H. W. Ebersbach, and I. Ziegler, *Makromol. Chem.*, 1959, **31**, 154.
23 G. Ehrhart, *Chem. Ber.*, 1963, **96**, 2042.
24 K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1958 and references cited.
25 E. Ibuki, S. Ozasa, Y. Fujioka, and Y. Yanagihara, *Chem. Pharm. Bull.*, 1982, **30**, 802 and references cited.
26 A. Minato, K. Tamao, T. Hayashi, K. Suzuki, and M. Kumada, *Tetrahedron Lett.*, 1980, **21**, 845 and references cited.

27 K. Tamao, A. Minato, N. Miyake, T. Matsuda, Y. Kiso, and M. Kumada, *Chem. Lett.*, 1975, 133.
28 G. Dahmer, *Liebigs Ann. Chem.*, 1904, **333**, 346.
29 M. Tashiro and G. Fukata, *J. Org. Chem.*, 1977, **42**, 835.
30 A. I. Meyers, R. Gabel, and E. D. Mihelich, *J. Org. Chem.*, 1978, **43**, 1372.
31 J. Novák and C. A. Salemink, *Tetrahedron Lett.*, 1982, **23**, 253.
32 J. A. Gainor and S. M. Weinreb, *J. Org. Chem.*, 1982, **47**, 2833.
33 K.-H. Boltze, H.-D. Dell, and H. Jansen, *Liebigs Ann. Chem.*, 1967, **709**, 63.
34 H. Lettré and A. Jahn, *Chem. Ber.*, 1952, **85**, 346.

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