Natural Benzofurans: Synthesis of the Arylbenzofuran Constituents of *Sophora tomentosa*

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The structure, 2-(2',4'-dihydroxyphenyl)-5,6-methylenedioxybenzofuran (1), suggested for *Sophora* compound I has been confirmed by a synthesis in which the benzofuran heterocycle was constructed by an intramolecular Wittig reaction of an *o*-bromomethylphenyl aroyl ester. The congeneric *Sophora* compound II, 2-(2'-hydroxy-4'-methoxyphenyl)-5,6-methylenedioxybenzofuran (2) was synthesized by formation of the benzofuran *via* the reaction of a copper(I) arylacetylide with an *o*-iodophenyl ester.

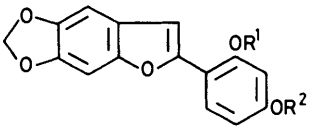
From the aerial parts of *Sophora tomentosa* L., the isolation of two benzofurans (compounds I and II) was reported and the respective structures 2-(2',4'-dihydroxyphenyl)-5,6-methylenedioxybenzofuran (1) and 2-(2'-hydroxy-4'-methoxyphenyl)-5,6-methylenedioxybenzofuran (2) were suggested largely on the basis of spectroscopic evidence.[1] We report here the synthesis of each of these products by disparate pathways. The natural products are representative of a group which includes pterofuran [2] (3), isopterofuran [3] (4), vignafuran [4] (5), 6-demethylvignafuran [5] (6), 2-(2',4'-dihydroxyphenyl)-5,6-dimethoxybenzofuran,[6] 6,3',5'-trihydroxybenzofuran,[7] and moracins A—H.[8-10] These benzofurans are of increasing interest since it has been recognised that several are antifungal phytoalexins.

For the synthesis of *Sophora* compound I (1) we employed a pathway in which the key step, the construction of the benzofuran heterocycle, was achieved by the intramolecular Wittig reaction [11] of a phenolic ester, several interesting examples of which have recently been recorded.[12]

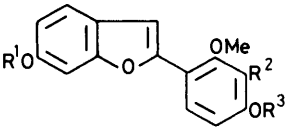
The starting phenol, 2-hydroxy-4,5-methylenedioxybenzaldehyde (7) is readily obtained from sesamol by Gattermann, formylation,[13] and was esterified with 2,4-dibenzyloxybenzoyl chloride to yield the aldehyde ester (11) (Scheme 1). The acid chloride was prepared from methyl 2,4-dihydroxybenzoate (8) [14] by standard benzylation of the latter to give the diether (9) followed by saponification to the acid (10) and treatment with oxalyl chloride. On catalytic hydrogenation, the aldehyde (11) was smoothly reduced, with removal of the benzyl protecting groups, to yield the benzylic alcohol (12). The alcohol was then converted into the benzylphosphonium bromide (13) by successive treatment with triphenylphosphine hydrobromide and acetic anhydride. This salt, without purification or isolation, was heated with triethylamine in toluene to give 2-(2',4'-diacetoxyphenyl)-5,6-methylenedioxybenzofuran (14); this had constants in excellent agreement with those reported for the diacetate derivative of *Sophora* compound I. Reductive hydrolysis of compound (14) with lithium aluminium hydride gave the natural product (1).

A shorter, alternative pathway to (1) from the aldehyde ester (11) involved reduction of the latter to the benzyl alcohol (15) with retention of the benzyl protecting groups. After experiencing some difficulties in effecting this simple reduction, it was cleanly effected by the use of neutral alumina-supported sodium borohydride.[15] Conversion of the alcohol (15) into the phosphonium salt (16) followed by Wittig cyclization gave the *Sophora* compound dibenzyl ether (17) and then the diol (1) by hydrogenolysis of the protecting group.

Both *Sophora* compounds (1) and (2), on methylation with diazomethane, had given the dimethoxyphenylbenzofuran (18).[1] This compound had been known previously as a degradation product of medicagol [16] and flemichapparin-C [17] and we have reported a synthesis by which the benzofuran



(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = Me$
(18) $R^1 = R^2 = Me$



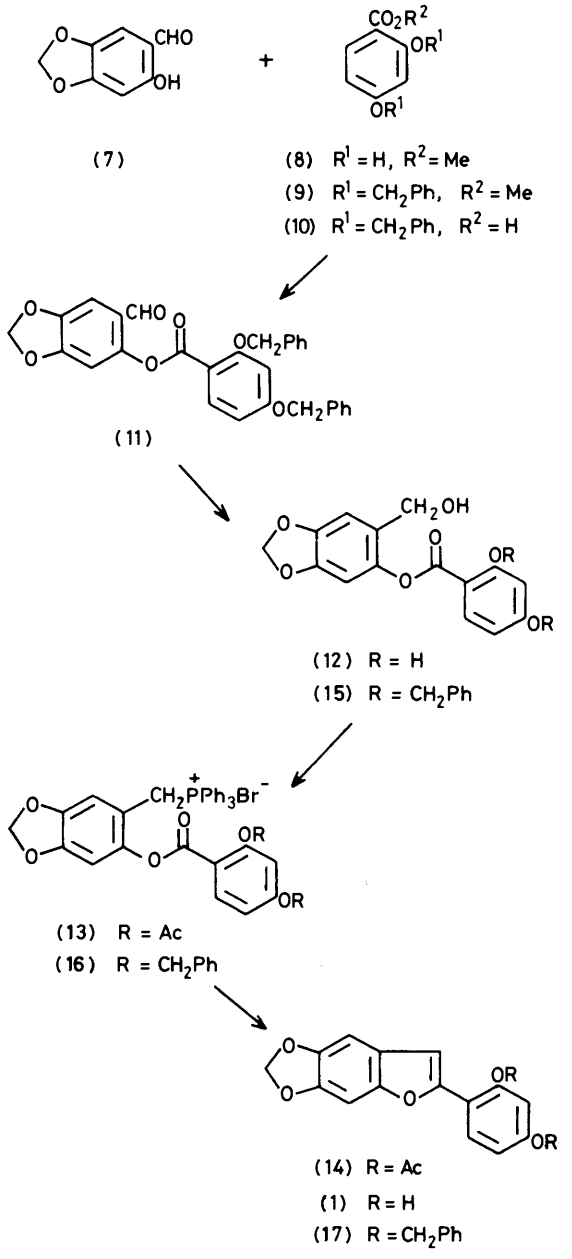
(3) $R^1 = H$, $R^2 = OH$, $R^3 = Me$
(4) $R^1 = H$, $R^2 = OMe$, $R^3 = H$
(5) $R^1 = Me$, $R^2 = R^3 = H$
(6) $R^1 = R^2 = R^3 = H$

heterocycle was constructed by reaction of an *o*-halogenophenol ester with a copper(I) acetylide.[18]

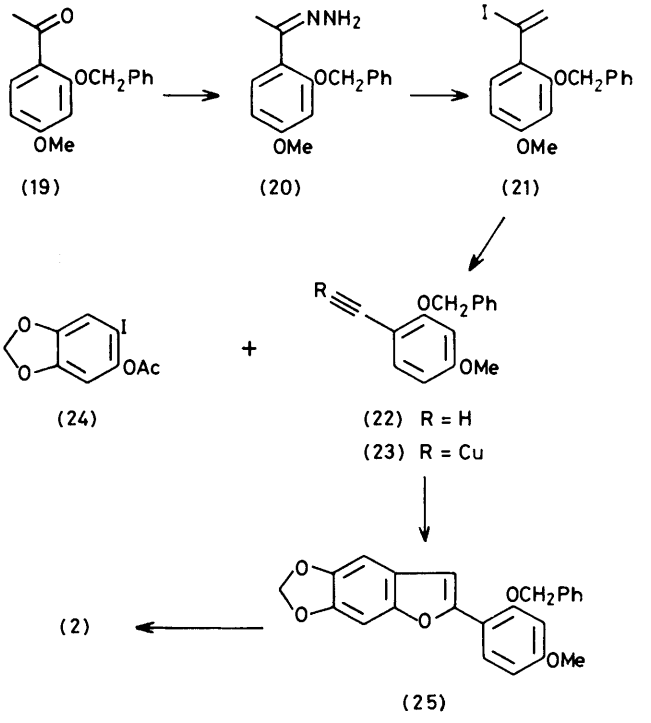
We now report the synthesis of *Sophora* compound II (2) using this pathway (Scheme 2). The required arylacetylene, 2-benzyloxy-4-methoxyphenylacetylene (22), was prepared from the corresponding acetophenone (19) by a modification of procedures developed by Barton *et al.*[19] and Oliveto *et al.*[20] Iodination of the hydrazone derivative (20) in the presence of triethylamine gave the vinyl iodide (21) from which hydrogen iodide was eliminated by treatment with sodium hydride, thus affording the alkyne (22). The cuprous salt (23) was then obtained in the standard manner [21] and the reaction with iodosesamol acetate (24) [22] was examined. When these components were heated together in pyridine, a mixture was obtained from which three products, in addition to the unchanged iodo-ester (24), were isolated by column chromatography on silica gel. These were readily identified from their ^1H n.m.r. spectra as the desired benzofuran, *Sophora* compound II benzyl ether (25), the acetylene oxidation product (26), and the bisarylacetylene product (27) formed by the coupling of compounds (23) and (24) without concomitant or subsequent cyclization. The synthesis of compound (2) was then completed by catalytic hydrogenolysis of the benzyl ether (25).

Experimental

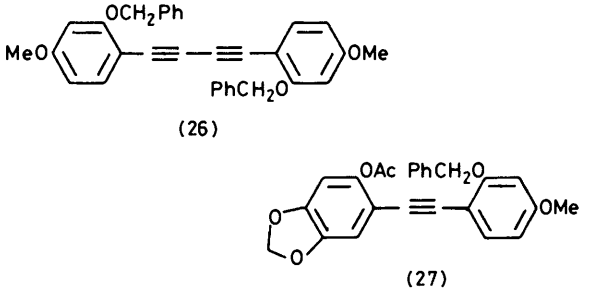
M.p.s were determined with a Gallenkamp and Fisher-Johns apparatus and are uncorrected. Varian EM-390, Perkin-Elmer R-32, and Bruker FT (90 MHz) spectrometers were employed for the determination of ^1H n.m.r. spectra, with tetramethylsilane (TMS) as internal standard and deuteriochloroform as solvent unless otherwise stated. The i.r. spectra were obtained using a Perkin-Elmer 683 IR spectrophotometer as KBr pellets or neat samples. Silica gel used for chromatography was from J. T. Baker (40—140 mesh), Davidson (28—200 mesh), or E. Merck (silica gel 60) (70—230 mesh). Ether refers to diethyl ether throughout.



Scheme 1.



Scheme 2.



2-Hydroxy-4,5-methylenedioxybenzaldehyde (7).—This compound was prepared in 52—64% yield as previously described,[13] m.p. 124—126 °C (lit.,[13] m.p. 125—126 °C); δ_H 6.02 (s, OCH_2O), 6.48 (s, 3-H), 6.87 (s, 6-H), 9.67 (s, CHO), and 11.83 (s, OH).

Methyl 2,4-Dihydroxybenzoate (8).—This compound was prepared in 81% yield as previously described,[14] m.p. 116—118 °C (lit.,[14] m.p. 118—119 °C); δ_H 3.90 (s, CO_2Me), 6.37—6.49 (m, 3- and 5-H), and 7.72 (d, *J* 10 Hz, 6-H).

Methyl 2,4-Dibenzyloxybenzoate (9).—Anhydrous potassium carbonate (66 g) and benzyl chloride (32 ml) were added to a solution of the ester (8) (13.2 g) in acetone (200 ml) and the mixture heated under reflux for 3 days. After work-up by evaporation, and washing of a chloroform extract, the product was distilled (0.5 mmHg, 60 °C bath-temp.) to give an oil (66%) which solidified (m.p. 62—65 °C) on standing. Crystallization from methanol gave the *dibenzyl diether* (9), m.p. 68—69.5 °C (Found: C, 75.5; H, 5.6. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%); δ_H 3.88 (s, CO_2Me), 5.10 (s, $ArCH_2O$), 5.16 (s, $ArCH_2O$), 6.56—6.66 (m, 3- and 5-H), 7.35—7.49 (m, 10 ArH), and 7.88 (d, *J* 9 Hz, 6-H).

2,4-Dibenzyloxybenzoic Acid (10).—This compound was prepared in quantitative yield by standard saponification of the ester (9). Crystallization from ethanol gave the acid (10) as fine needles, m.p. 120—121 °C (lit.,[23] m.p. 180 °C) (Found: C, 75.2; H, 5.3. Calc. for $C_{21}H_{18}O_4$: C, 75.4; H, 5.4%); δ_H 5.13 (s, $ArCH_2O$), 5.24 (s, $ArCH_2O$), 6.72—6.82 (m, 3- and 5-H), 7.42—7.48 (m, 10 ArH), and 8.20 (d, *J* 10 Hz, 6-H).

2-Formyl-4,5-methylenedioxyphenyl 2',4'-Dibenzyloxybenzoate (11).—Oxalyl chloride (1.5 ml) was added to a suspension of the acid (10) (2.42 g) in benzene (15 ml) and the mixture was heated under reflux for 5 h, then evaporated under reduced pressure. To the residue was added a solution of the phenolic aldehyde (7) (1.20 g) in pyridine (40 ml) and the mixture was stirred at room temperature for 7 days. Work-up in the usual way, with dichloromethane extraction and

filtration of the extract through silica gel (40 g), gave the *ester* (11) (63%) as a solid which crystallized from ethanol as fine needles, m.p. 153—154 °C (Found: C, 72.0; H, 4.7. $C_{29}H_{22}O_7$ requires C, 72.2; H, 4.6%); δ_H 5.13 (s, $ArCH_2O$), 5.18 (s, $ArCH_2O$), 6.08 (s, OCH_2O), 6.63—6.78 (m, 3 ArH), 7.30—7.45 (m, 2 $C_6H_5CH_2O$ and 1 ArH), 8.10 (d, *J* 10 Hz, 6'-H), and 10.10 (s, ArCHO).

2-*Hydroxymethyl*-4,5-*methylenedioxyphenyl* 2',4'-*Dihydroxybenzoate* (12).—A solution of the aldehyde (11) (1.29 g) in ethyl acetate (150 ml) was stirred with palladium–carbon (5%, 1.26 g) under hydrogen for 13 h. After filtration and evaporation, the residual solid was recrystallized from methanol–benzene to give the *benzyl alcohol* (12) (87%) as fine needles, m.p. 187—188 °C (Found: C, 59.1; H, 4.05. $C_{15}H_{12}O_7$ requires C, 59.2; H, 4.0%); δ_H [$(CD_3)_2CO$] 4.55 (br s, $ArCH_2OH$), 6.08 (s, OCH_2O), 6.45 (d, *J* 2 Hz, 3'-H), 6.55 (dd, *J* 8.5, 2 Hz, 5'-H), 6.86 (s, 3- or 6-H), 7.07 (s, 6- or 3-H), and 7.98 (d, *J* 8.5 Hz, 6'-H).

2-(2',4'-*Diacetoxyphenyl*)-5,6-*methylenedioxbenzofuran* (14).—A solution of triphenylphosphine hydrobromide [24] (160 mg) and the benzyl alcohol (12) (135 mg) in acetonitrile (30 ml) was heated under reflux in a nitrogen atmosphere for 2 h and the solvent then removed under reduced pressure. Acetic anhydride (2.5 ml) and pyridine (2.5 ml) were then added, and the mixture was heated under reflux for 5 h. The residue obtained after solvent evaporation was triturated with ether, and the ether soluble fraction decanted. The residual crude semi-solid salt (13) was suspended in toluene (30 ml) and triethylamine (0.45 ml), heated under reflux under nitrogen for 16 h, then cooled and filtered. Evaporation of the filtrate yielded an oil which was dissolved in dichloromethane and chromatographed on silica gel. Elution with this solvent gave a solid which on recrystallization from chloroform–methanol yielded *Sophora* compound I diacetate (14) (38%) as fine needles, m.p. 187—188 °C (lit.,[1] m.p. 187—189 °C); δ_H 2.31 (s, OAc), 2.41 (s, OAc), 5.99 (s, OCH_2O), 6.92 (s, 7-H), 6.95 (s, 4-H), 6.99 (s, 3-H), 7.02—7.17 (m, 3'- and 5'-H), and 7.93 (d, *J* 9 Hz, 6'-H).

2-(2',4'-*Dihydroxyphenyl*)-5,6-*methylenedioxybenzofuran* (Sophora *Compound* I) (1).—(*a*) Lithium aluminium hydride (*ca.* 3 mg) was added to a solution of the diacetate (14) (7 mg) in ether (20 ml) and the mixture was heated under reflux for 30 min and worked up in the usual way after quenching with ethyl acetate. Separation of the product (3 mg) from aqueous methanol gave *Sophora* compound I (1) as an amorphous solid, m.p. 233—236 °C (lit.,[1] m.p. 235—237 °C), δ_H [$(CD_3)_2SO$] 6.01 (s, OCH_2O), 6.35 (dd, *J* 8.5, 2 Hz, 5'-H), 6.46 (d, *J* 2 Hz, 3'-H), 7.06 (s, 4- and 7-H), 7.18 (s, 3-H), 7.56 (d, *J* 8.5 Hz, 6'-H), 9.55 (br s, ArOH), and 10.11 (br s, ArOH).

(*b*) A solution of the dibenzyl ether (17) (70 mg) in ethyl acetate (15 ml) was stirred with palladium–carbon (10%, 100 mg) under hydrogen for 2.5 h. Removal of the catalyst and solvent gave a solid, which, on crystallization from aqueous methanol, gave compound (1) (71%), m.p. 235—237 °C, identical with that obtained in (*a*).

2-*Hydroxymethyl*-4,5-*methylenedioxyphenyl* 2',4'-*Dibenzyloxybenzoate* (15).—Alumina supported sodium borohydride (*ca.* 10%, 1.72 g, Alfa Products) was added to a solution of the aldehyde (11) (0.83 g) in tetrahydrofuran (THF), stirred at room temperature for 20 min, filtered and washed with ethyl acetate. Evaporation of the combined filtrate and washings gave an oil which was chromatographed on silica gel, eluted with ethyl acetate–dichloromethane (1 : 9) and recrystallized from aqueous ethanol to yield the *alcohol* (15) (83%) as fine needles, m.p. 106—107 °C (Found: C, 71.7; H, 5.1. $C_{29}H_{24}O_7$ requires C, 71.9; H, 5.0%); δ_H 4.49 (s, $ArCH_2OH$) 5.24 (s, OCH_2Ph), 5.29 (s, OCH_2Ph), 6.03 (s, OCH_2O), 6.71—6.93 (m, 3'-, 5'-, 6'-, or 3-H), 7.03 (s, 3- or 6-H), 7.29—7.59 (m, 10 ArH), and 8.03 (d, *J* 9 Hz, 6'-H).

2-(2',4'-*Dibenzyloxyphenyl*)-5,6-*methylenedioxybenzofuran* (Sophora *Compound* I *Dibenzyl Ether*) (17).—A solution of triphenylphosphine hydrobromide (370 mg) and the alcohol (15) (460 mg) in acetonitrile (25 ml) was heated under reflux for 3 h and then evaporated under reduced pressure. The residual crude product (16) was dissolved in toluene (40 ml) containing triethylamine (1.0 ml), heated under reflux for 12 h, then cooled and filtered. Evaporation of the filtrate gave a dark oil, which was chromatographed on silica gel. Elution with carbon tetrachloride gave unchanged triphenylphosphine, followed by a solid (21%) which on crystallization from ethanol–dichloromethane gave the *dibenzyl diether* (17) as needles, m.p. 164—166 °C (Found: C, 76.9; H, 4.9. $C_{29}H_{22}O_5$ requires C, 77.3; H, 4.9%); δ_H 5.08 (s, OCH_2Ph), 5.18 (s, OCH_2Ph), 5.96 (s, OCH_2O), 6.65—6.72 (3'- and 5'-H), 6.86 (s, 3-H), 6.98 (s, 4-H), 7.04 (s, 7-H), 7.40 (m, 10 ArH), and 7.91 (d, *J* 9 Hz, 6'-H).

2-*Benzyloxy*-4-*methoxyacetophenone* (19).—This compound was prepared in 71% yield, as described,[25] from 2-hydroxy-4-methoxyacetophenone had m.p. 85—86.5 °C (lit.,[25] m.p. 82.5—84 °C), δ_H 2.53 (s, $COCH_3$), 3.78 (s, OMe), 5.08 (s, OCH_2Ph), 6.48 (dd, *J* 9, 2 Hz, 5-H), 6.48 (d, *J* 2 Hz, 3-H), 7.37 (m, 5 ArH), and 7.81 (d, *J* 9 Hz, 6-H).

2-*Benzyloxy*-α-*iodo*-4-*methoxystyrene* (21).—A solution of the ketone (19) (500 mg), triethylamine (5 ml), and hydrazine (95%, 0.6 ml) in ethanol (10 ml) was stirred at room temperature overnight and then poured into ice and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated to give the hydrazone (20) (87%) as a pale yellow oil, δ_H 2.03 (s, Me), 3.71 (s, OMe), 4.98 (s, OCH_2Ph), 5.15 (br s, NH_2), 6.36—6.47 (m, 3- and 5-H), and 7.25—7.38 (m, 6-H and 5 ArH). A solution of iodine (23 g) in THF (75 ml) was added dropwise during 1 h to a solution of the hydrazone (20) (9.78 g) in triethylamine (250 ml) and THF (500 ml). The mixture was stirred for an additional hour, then diluted with water (200 ml) and extracted with ether (3 × 200 ml). The extract was washed successively with water, aqueous sodium thiosulphate, brine, and water, and then dried. Evaporation of the solvent gave a black residual oil which was dissolved in carbon tetrachloride and filtered through silica gel to yield a colourless oil, which on standing yielded the *vinyl iodide* (21) 90% as a solid, m.p. 51—52.5 °C (Found: C, 52.7; H, 4.2. $C_{16}H_{15}IO_2$ requires C, 52.5; H, 4.1%); δ_H 3.68 (s, OMe), 5.04 (s, OCH_2Ph), 6.05 (d, *J* 1 Hz, vinyl H), 6.20 (d, *J* 1 Hz, vinyl H), 6.30—6.40 (m, 3- and 5-H), 7.15 (d, *J* 9 Hz, 6-H), and 7.23—7.50 (m, 5 ArH). Warming in solvents for attempted recrystallization resulted in deposition of a dark oil.

2-*Benzyloxy*-4-*methoxyphenylacetylene* (22).—To a stirred suspension of sodium hydride (1.86 g, from a 60% oil dispersion washed several times with pentane) in THF (200 ml) under nitrogen was added a solution of the iodide (21) (10.95 g) in THF (60 ml), and the mixture heated under reflux overnight. The reaction was quenched by the addition of ethanol and then diluted with water and extracted with ether. Evaporation of the washed and dried extract gave a residual black oil (7.08 g) which was distilled (1.1 mmHg, 155 °C bath-temp.) to give a yellow oil (4.45 g) which was chromatographed on silica gel. Elution with carbon tetrachloride–benzene (1 : 1) and benzene gave the *alkyne* (22) as a pale yellow oil (23%),

b.p. 140 °C at 0.5 mm Hg (bath temp.) (Found: C, 80.8; H, 6.1. $C_{16}H_{14}O_2$ requires C, 80.6; H, 5.9%); $\nu_{max.}$ (neat) 3 275 (C≡CH) and 2 110 cm^{-1} (C≡C); δ_H 3.18 (s, C≡CH), 3.67 (s, OMe), 5.07 (s, OCH_2Ph), 6.31—6.41 (m, 3- and 5-H), and 7.27—7.39 (m, 6-H and 5 ArH).

Copper(I) *2-Benzyloxy-4-methoxyphenylacetylide* (23).—Hydroxylamine hydrochloride (580 mg) was added in portions with stirring during 5 min to a cooled (ice-bath) solution of cupric sulphate pentahydrate (1.05 g) in concentrated ammonium hydroxide solution (4 ml) and water (15 ml). The mixture was stirred for a further 10 min (until the deep blue colour faded) and then a solution of the alkyne (22) (1.05 g) in ethanol (25 ml) was added in one portion. A voluminous yellow precipitate appeared immediately which, after further dilution with water (15 ml), was filtered off. After being washed with water, ethanol, and ether, and dried (P_2O_5) under reduced pressure, the salt (23) was obtained as a yellow powder (59%), m.p. 187—190 °C (decomp.)

Reaction of 2-Iodo-4,5-methylenedioxyphenyl Acetate (24) *with the Copper*(I) *Acetylide* (23).—A mixture of iodosesamol acetate [22] (24) (631 mg) and copper(I) acetylide (23) (616 mg) in pyridine (45 ml) was heated under reflux under nitrogen for 20 h. It was then cooled, diluted with ether (400 ml), stored at 0 °C for 2 h, and then filtered. The filtrate was washed with water (3 × 150 ml) and brine (3 × 150 ml), dried (Na_2SO_4) and evaporated to give a black oily solid (1.08 g) which was fractionated by chromatography on silica gel (100 g). Elution with benzene (525 ml) first gave fraction A (350 mg); further addition of the same solvent (300 ml) yielded fraction B (147 mg). Further elution with benzene (200 ml) and chloroform (3.5 l) gave fraction C (444 mg) as a dark oil.

Fraction A was rechromatographed on silica gel (47 g). Elution with carbon tetrachloride (6 l) and carbon tetrachloride–benzene (1 : 1; 1.5 l) gave a solid (39%) which was recrystallized from methanol to give *2-(2'-benzyloxy-4'-methoxyphenyl)-5,6-methylenedioxybenzofuran* (25) as slender needles, m.p. 141—142.5 °C (Found: C, 73.9; H, 5.05. $C_{23}H_{18}O_5$ requires C, 73.8; H, 4.85%); δ_H 3.78 (s, OMe), 5.15 (s, OCH_2Ph), 5.90 (s, OCH_2O), 6.56 (d, *J* 2 Hz, 3'-H), 6.56 (dd, *J* 9, 2 Hz, 5'-H), 6.82 (s, 4-H), 6.95 (br s, 7-H), 7.01 (d, *J* 1 Hz, 3-H), 7.30—7.49 (m, 5 Ph-H), and 7.98 (d, *J* 9 Hz, 6'-H). Continued elution with carbon tetrachloride–benzene (1 : 1) gave a solid (6%) which on crystallization from methanol gave *1,4-bis(2'-benzyloxy-4'-methoxy)buta-1,3-diyne* (26) as irregular prisms, m.p. 121.5—122.5 °C (Found: C, 80.8; H, 5.7. $C_{32}H_{26}O_4$ requires C, 81.0; H, 5.5%), $\nu_{max.}$ (KBr) 2 152 (C≡C) cm^{-1}; δ_H 3.75 (s, OMe), 5.15 (OCH_2Ph), 6.42 (d, *J* 2 Hz, 3-H), 6.43 (dd, *J* 9, 2 Hz, 5-H), and 7.26—7.45 (m, 6-H and 5 Ph H).

Examination of the ^1H n.m.r. spectrum of fraction B indicated that it was unchanged iodosesamol acetate (24).

Crystallization of fraction C from methanol gave *2-acetoxy-4,5-methylenedioxyphenyl-2'-benzyloxy-4'-methoxyphenylacetylene* (27) (28%) as prisms, m.p. 115.5—116 °C (Found: C, 72.05; H, 5.05. $C_{25}H_{20}O_6$ requires C, 72.1; H, 4.8%); $\nu_{max.}$ (KBr) 2 210 (C≡C) and 1 757 (CO) cm^{-1}; δ_H 2.15 (s, OAc), 3.76 (s, OMe), 5.18 (s, OCH_2Ph), 5.95 (s, OCH_2O), 6.42 (d, *J* 2 Hz, 3'-H), 6.43 (dd, *J* 9, 2 Hz, 5'-H), 6.56 (s, 6-H), 6.89 (s, 3-H), and 7.21—7.46 (m, 6'-H and 5 Ph-H).

2-(2'-Hydroxy-4'-methoxyphenyl)-5,6-methylenedioxybenzofuran (Sophora *Compound* II) (2).—A solution of the benzyl ether (25) (105 mg) in ethyl acetate (15 ml) was stirred with palladium–carbon (10%, 100 mg) under hydrogen for 1.5 h. Removal of the catalyst and solvent gave a pale green solid which on crystallization from methanol gave compound (2) (92%) as prisms, m.p. 182—183.5 °C (lit.,[1] m.p. 179—181 °C); δ_H 3.82 (s, OMe), 5.99 (s, OCH_2O), 6.51—6.62 (m, 3'- and 5'-H), 6.80 (d, *J* 1 Hz, 3-H), 6.93 (s, 4-H), 7.00 (br s, 7-H), and 7.50 (d, *J* 9 Hz, 6'-H).

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