Dihydrostilbenes of *Cannabis*. Synthesis of Canniprene

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Canniprene (10) is synthesised *via* reaction of a phenolate-anion ylide with a benzyl-protected aldehyde. Benzoylation, followed by hydrogenation and hydrogenolysis of the resulting stilbene, leads to a half-benzoylated bibenzyl which is converted into its *O*-dimethylprop-2-ynyl derivative. Semi-hydrogenation, Claisen rearrangement, and debenzoylation gives canniprene. In a second synthesis the prenylated (3-methylbut-2-enylated) and benzyl-protected ring-B section is made first and converted by Wittig reaction into a dibenzyl-protected stilbene. The stilbene is reduced and the benzyl groups removed in one step, without affecting the prenyl group, by sodium in butanol: magnesium in methanol is capable of stilbene reduction without debenzylation. This practical synthesis proceeds in 19% overall yield from the dimethylprop-2-ynyl ether of isovanillin (14) and is applicable to isotope-labelling. The use of *p*-bromophenacyl (PBP) ether and methoxyethoxymethyl (MEM) ether protection as the basis for canniprene synthesis is also considered.

Other bibenzyls relevant to the natural products of *Cannabis* are made and the methylated chroman (37) derived from canniprene is also synthesised.

CANNIPRENE (10) is the member of the bibenzyl (dihydrostilbene)-spiran-dihydrophenanthrene group of metabolites of *Cannabis sativa* which occurs in largest amount (0.5—1.5 g/kg in Thailand Δ^1-THC strain).[1] Since its contribution to the effects of the smoked drug is undetermined, we have undertaken synthesis[2] of the compound (Scheme 1) to make it more readily available, and to make provision for isotopic labelling.

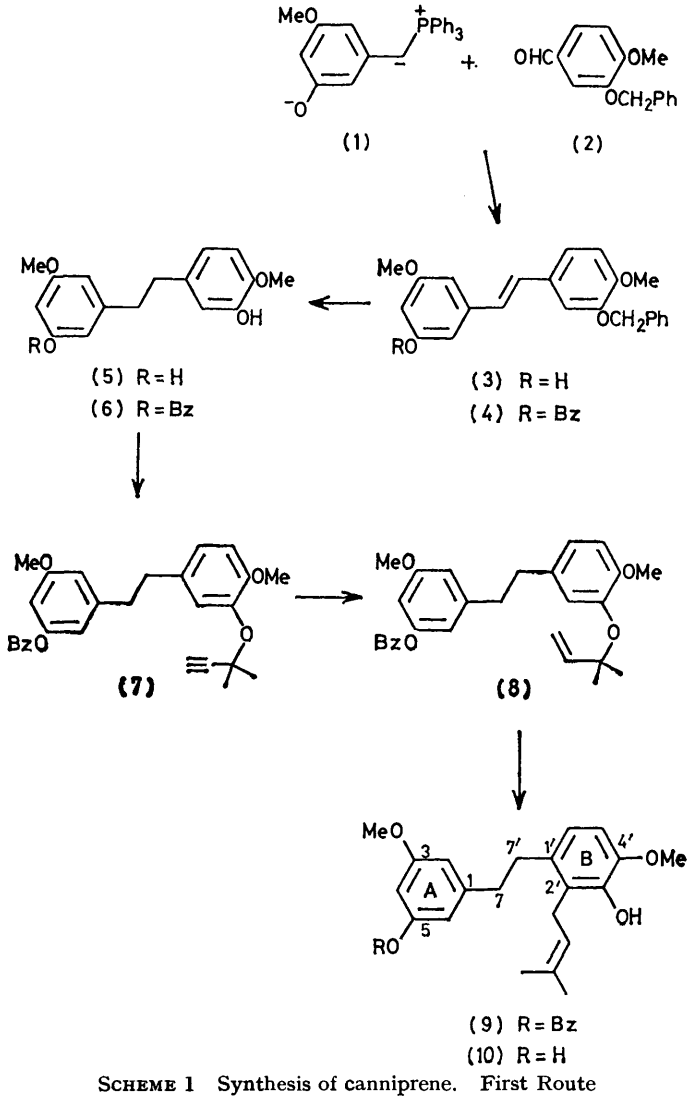
Wittig reagents containing an unblocked phenolic hydroxy-group can be successfully employed if made from the phosphonium salt using 2 mol equiv. of n-butyllithium.[3] The phenolate bis-anion (1) condensed successfully with 3-benzyloxy-4-methoxybenzaldehyde (2) to give the stilbene (3), a mixture of geometrical isomers, (73%). On benzoylation the crystalline stilbene derivative was obtained as a single isomer (4) in 71% yield, and by hydrogenation over Pd–C this was hydrogenated and hydrogenolised to the ring-A protected bibenzyl (6) (97%). Treatment with 3-chloro-3-methylbutyne in the presence of potassium iodide and potassium carbonate gave the *O*-dimethylprop-2-ynyl ether (7), though in rather poor yield (24%). The acetylenic ether was semi-hydrogenated over Lindlar catalyst to give the olefinic ether (8) which was identified on the basis of its n.m.r. spectrum and M^+ value but not further purified. Claisen rearrangement[4] of this material at 150 °C gave the A-ring benzoate of canniprene (9) in a yield of 50% for the combined hydrogenation/rearrangement steps. Deprotection gave, in 90% yield, the crystalline bibenzyl (10), identical in all respects with natural canniprene.[1]

Preliminary tests of the prenylation (3-methylbut-2-enylation) step were made using 3-hydroxy-4-methoxytoluene (Clemmensen reduction of isovanillin) as substrate. The dimethylprop-2-ynyl ether was obtained in 47% yield by the above method, semi-hydrogenated (60%) and rearranged (60%) to (11). It is of interest that the two *ortho*-protons appear as a singlet in the ^{1}H n.m.r. spectrum of (11) and of its chroman (12) formed by cyclisation with 1% BF_3: a parallel situation is found in the case of canniprene and its chroman.[1]

The poor yield in the dimethylprop-2-ynylation to form (7) in Scheme 1, occurring at a comparatively late stage, is a limitation on its use as a practical synthesis. We have therefore devised a second and more convergent route (Scheme 2). In this, the dimethylprop-2-ynylation is re-positioned to the first stage where a low yield involves only readily accessible starting material. This now causes a new difficulty, as after semi-hydrogenation and rearrangement, catalytic hydrogenation cannot be used at any stage because of the presence of the prenyl group, which would be difficult to protect. Isovanillin can be converted into the dimethylprop-2-ynyl ether (14) in 23% yield and this is viewed as a starting material, available in quantity. Semi-hydrogenation (91%) and Claisen rearrangement at 135 °C for 6 min gave 2-prenylated isovanillin (15) (86%). This was benzylated (83%) and the benzyl derivative (16) was used as the aldehyde component in a Wittig reaction with the benzylated phosphonium salt (13) to give the doubly benzylated stilbene (17) (63%). Catalytic reduction being contraindicated, other methods were examined for the reduction of the stilbene double bond. When compound (4) was used as a model compound it was found that magnesium in dry methanol reduced the stilbene, causing elision of the benzoate ester function but not reducing the benzyl protecting group, to give the 3'-benzyl ether of (5) in 65% yield. On the other hand, sodium in ethanol performed the same reactions and caused partial debenzylation as well. Sodium and butanol however caused complete debenzylation, debenzoylation, and stilbene reduction, to give compound (5). When the latter reagent was employed on compound (17) it gave selective reduction of the stilbene double bond whilst leaving the prenyl intact: at the same time the two benzyl groups were cleaved and canniprene (10), identical with natural material,[1] was formed directly in 46% yield. The overall yield of canniprene from (14) was 19%.

For biological evaluation, it was desirable to prepare canniprene isotopically labelled with deuterium by a

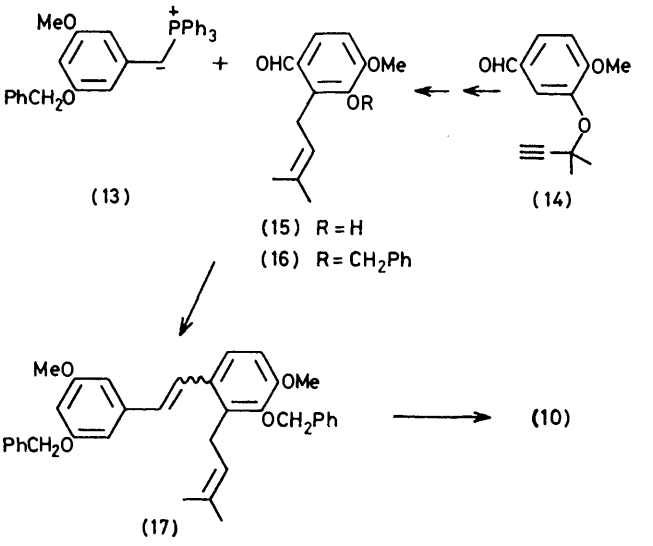
method which could be readily extended to tritium labelling. This was done by reducing the aldehyde (18) to the deuterio-alcohol (19) with sodium borodeuteride (90%), and then re-oxidising it with manganese dioxide [5] to give the deuterio-aldehyde (20) (80%). Though convenient, this procedure involves some loss of isotope: however the isotope effect considerably favours deuterium



SCHEME 1 Synthesis of canniprene. First Route

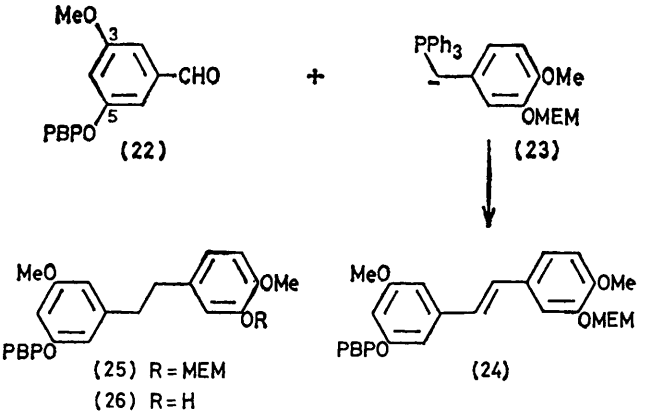
retention. Wittig reaction with the ylide (13) gave the stilbene (17) (56%) carrying one olefinic deuterium at C-7′ adjacent to ring B. Sodium in butanol reduction (60% yield) produced crystalline deuteriated canniprene (21). The ^{1}H n.m.r. showed approximately 3 hydrogens on the two bridge methylene carbons (singlet δ 2.81) and mass spectral analysis indicated that the sample contained *ca.* 85% of one deuterium atom. This was entirely located at the bridge position, from the single broadened signal at δ 2.84 in the deuterium n.m.r. spectrum.

Some experiments were also carried out on the use, on rings-A and -B, of blocking groups having differential



SCHEME 2 Synthesis of canniprene. Second Route

reactivities, as a basis for canniprene synthesis (Scheme 3). These involved *p*-bromophenacyl ether (PBP) [6] and methoxyethoxymethyl (MEM) protection.[7] The *p*-bromophenacyl ether is stable to catalytic hydrogenation [(27) is smoothly converted into (28)] and natural canniprene was found to be stable to the zinc–acetic acid conditions which removed the PBP-ether from (28) to give (29). The PBP-ether is stable to cleavage conditions required to remove the MEM grouping, as was shown by treating a mixture of PBP-protected isovanillin and

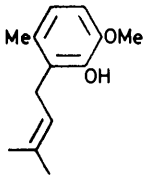


SCHEME 3 Use of PBP- and MEM-protected components

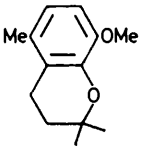
MEM-protected isovanillin with zinc bromide in dichloromethane at 20 °C: the latter was deprotected but the former was not. These reactions would allow us to remove the MEM group from (25), carry through the ring-B prenylation and then develop the A ring hydroxy-group by removing PBP-ether protection.

The B-ring section was prepared from isovanillin by MEM-protection (NaH–MEM chloride in dimethoxyethane) (80%) and reduction to the alcohol with lithium aluminium hydride (97%). Phosphorus tribromide could not be used to convert the alcohol into the bromide

since it acted as a Lewis acid and removed the MEM grouping. Consequently the bromide was made (88%) by the dimethyl sulphide–*N*-bromosuccinimide method:[8] it was converted into the phosphonium salt (83%). Reduction of methyl 3-hydroxy-5-methoxybenzoate with lithium aluminium hydride gave the corresponding



(11)



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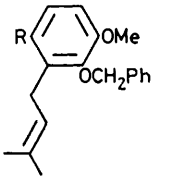
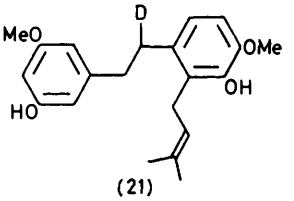


(18) R = CHO
(19) R = CHDOH
(20) R = CDO



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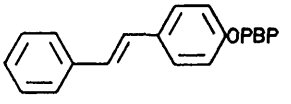

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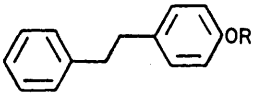
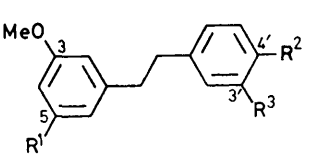


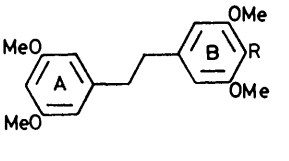
(28) R = PBP
(29) R = H

benzyl alcohol (89%) which was converted into the *p*-bromophenacyl ether (*p*-bromophenacyl bromide, potassium carbonate, potassium iodide, and 18-crown-6)[9] (74%). Oxidation (MnO_2)[5] gave the protected aldehyde (22) (50%). The Wittig reagent (23) was added (reverse addition) to the aldehyde and gave the desired stilbene (24) (61%) as a mixture of *cis–trans*-isomers. On hydrogenation (10% Pd–C) a dihydrostilbene was isolated but, in addition, it was found that the MEM grouping had unexpectedly cleaved, giving (26) direct. Although not disadvantageous, the yield of (26) was poor (26%). Since the subsequent dimethylprop-2-ynylation reaction also gave poor yields, and attempts to employ more forcing conditions were apparently affecting the PBP ether, this approach was discontinued in favour of the two methods described above.

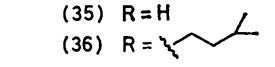
During our work on the bibenzyls of *Cannabis* and their metabolites,[1] a number of bibenzyls having significance for this investigation were made, and are listed as compounds (30)—(34). They were all prepared *via* Wittig reactions using either compound (13) or the corresponding dimethoxy-reagent as the ylide component, together with the appropriate methoxylated or benzyl-



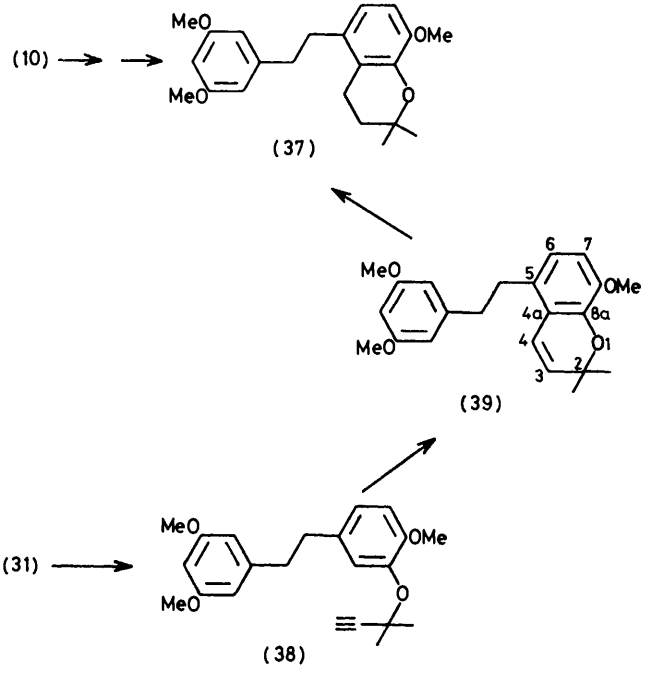
(30) $R^1 = R^2 = R^3 = OMe$
(31) $R^1 = R^2 = OMe$, $R^3 = OH$
(32) $R^1 = R^2 = OH$, $R^3 = H$
(33) $R^1 = R^3 = OH$, $R^2 = OMe$
(34) $R^1 = R^2 = OH$, $R^3 = OMe$



(35) R = H
(36) R =



ated aldehyde: hydrogenolysis of the benzyl groups, accompanied by hydrogenation of the stilbene olefin, was done in one step over Pd–C. A related method has been used for similar compounds in connection with the batatasins,[10] and synthesis of (32) and (33) has been independently reported.[11] Direct comparisons with the two unprenylated stilbenes (32) and (33) from *Cannabis*[1] confirmed their identification. A further bibenzyl of interest to us was (36), carrying a saturated prenyl group: this model compound made it clear (from ^1H n.m.r. and ^{13}C n.m.r. spectra) that despite the singlet



SCHEME 4 Synthesis of canniprene chroman methyl ether

arising from the ring-B protons, canniprene could not have 3′,4′,5′-substitution of the type shown. It was made by self coupling 3,5-dimethoxybenzyl bromide which gave (35) in 95% yield. Treatment with 1 equiv. of butyl-lithium gave a green 4-mono-anion which was alkylated with isopentyl bromide.

Finally, synthesis of the chroman (37), formed when canniprene is treated with 1% BF_3,[1] and then methylated, was effected. Bibenzyl (31), treated with 3-

chloro-3-methylbutyne, gave the dimethyl prop-2-ynyl ether (38) in 36% yield. Heated at 218 °C for 2 h in diethylaniline, the latter underwent the acetylene version of the Claisen rearrangement [12,4b] to give chromen (39) (56%). It was catalytically hydrogenated over palladium producing the chroman (37) (76%), identical in all respects with the chroman, derived from natural canniprene. This placed the structure of canniprene, based at the time mainly on spectral information, beyond any doubt.[2]

EXPERIMENTAL

Unless stated otherwise, ^{1}H n.m.r. data refer to $CDCl_3$ solutions.

3-Hydroxy-5-methoxybenzyl Alcohol.—Methyl 3,5-dihydroxybenzoate (92 g, 0.55 mol), m.p. 163—164 °C (lit.,[13] m.p. 165 °C) was added to potassium carbonate (75 g, 0.57 mol) in dry acetone (680 ml). Dimethyl sulphate (29 ml, 38 g, 0.3 mol) was then added in portions to the stirred mixture which was refluxed for 16 h. H.p.l.c. monitoring of the reaction mixture showed a substantial amount of starting material still remaining so more dimethyl sulphate (7 ml, 9.25 g, 0.07 mol) was added; the mixture was then stirred and refluxed for a further 2 h. Cooling, filtration, evaporation, and extraction with ether gave, after washing, drying, and evaporation, a brown oil (102.3 g) which solidified. Chromatography by preparative h.p.l.c. (Waters cartridge instrument: Porasil cartridge) using ether–hexane (2 : 5) as eluant gave methyl 3-hydroxy-5-methoxybenzoate (31.4 g, 32%), m.p. 94—95 °C from ether–hexane (lit.,[14] m.p. 97 °C) (M^+, 182.0578. Calc. for $C_9H_{10}O_4$: M, 182.0579), $\nu_{max.}$ (mull) 1 690 cm^{-1}; ^{1}H n.m.r.: δ 7.16 (m, 2 H), 6.64 (m, 1 H), 5.80 (br s, 1 H, D_2O exchange), 3.93 (s, 3 H), and 3.82 (s, 3 H). Also isolated were methyl 3,5-dihydroxybenzoate (34.4 g) and methyl 3,5-dimethoxybenzoate (16.9 g).

Methyl 3-hydroxy-5-methoxybenzoate (6 g, 0.033 mol) in dry ether (60 ml) was added to stirred lithium aluminium hydride (4.5 g, 0.12 mol) in ether (120 ml) and refluxed for 3 h. After cooling it was stirred (16 h) and worked up by addition of dilute hydrochloric acid and ether extraction. 3-Hydroxy-5-methoxybenzyl alcohol (4.5 g, 89%) had m.p. 84—85 °C from ether–hexane (lit.,[15] m.p. 83—85 °C), M^+, 154.0623 (Calc. for $C_8H_{10}O_3$: M, 154.0630), ^{1}H n.m.r. (CD_3COCD_3): δ 6.96 (br s, 2 H), 6.75 (m, 1 H), 4.87 (s, 2 H), and 4.02 (s, 3 H).

3-Hydroxy-5-methoxybenzyltriphenylphosphonium Bromide.—3-Hydroxy-5-methoxybenzyl alcohol (8.2 g, 0.053 mol) in dry tetrahydrofuran (35 ml) and dry benzene (75 ml) was treated, with stirring at 0 °C, by dropwise addition of phosphorus tribromide (11 ml, 31.3 g, 0.12 mol) in dry tetrahydrofuran (8 ml) and dry benzene (45 ml). After the reaction mixture had been stirred for 3.5 h at 20 °C it was poured into water and the product extracted with ether. The ether extract was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was dissolved in dry benzene and triphenylphosphine (20 g, 0.077 mol) was added. The mixture was then stirred and refluxed for 6 h, and then cooled and filtered to give *3-hydroxy-5-methoxybenzyltriphenylphosphonium bromide* (15.6 g, 61%), m.p. 254.5—255.5 °C from ethanol–ether (Found: C, 65.0; H, 5.5. $C_{26}H_{24}BrO_2P$ requires C, 65.15; H, 5.05%), ^{1}H n.m.r. (CD_3OD): δ 7.8—7.4 (m, 15 H, Ar), 6.20 (m, 1 H, Ar), 6.00 (m, 1 H, Ar), 5.90 (m, 1 H, Ar), 4.72 (d, 2 H, CH_2P, J 15 Hz), and 3.44 (s, 3 H, OMe).

3-Benzyloxy-4-methoxybenzaldehyde (2).—Potassium carbonate (9.25 g, 0.067 mol) and potassium iodide (1.88 g, 0.011 mol) were added to isovanillin (10.0 g, 0.066 mol) in dry acetone (350 ml), and benzyl chloride (8.0 ml, 0.07 mol) in dry acetone (40 ml) was added during 15 min with stirring. After the mixture had been refluxed and stirred (20 h) it was cooled and filtered and the filtrate evaporated. The oily product was dissolved in ether and washed, dried, and evaporated. Chromatography on a dry silica column, with ether–hexane (2 : 1) as eluant gave 3-benzyloxy-4-methoxybenzaldehyde (13.3 g, 84%), m.p. 61—62 °C (lit.,[16] m.p. 62—63 °C), $\nu_{max.}$ (mull) 1 675 cm^{-1}; ^{1}H n.m.r.: δ 9.84 (s, 1 H), 7.46 (m, 7 H), 6.98 (d, 1 H, J 9 Hz), 5.20 (s, 2 H), and 3.98 (s, 3 H).

3′-Benzyloxy-5-hydroxy-3,4′-dimethoxystilbene (3).—n-Butyl-lithium (1.35 molar in hexane; 38 ml, 0.05 mol) was added dropwise to a stirred suspension of 3-hydroxy-5-methoxybenzyltriphenylphosphonium bromide (11.7 g, 0.244 mol) in dry tetrahydrofuran (300 ml) and stirred for 90 min at 20 °C. Addition of 3-benzyloxy-4-methoxybenzaldehyde (6.5 g, 0.0268 mol) in dry tetrahydrofuran (50 ml) discharged the red colour and the solution was stirred at 20 °C for 18 h. The product was just acidified with dilute hydrochloric acid and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. Chromatography of the product on a dry silica column, first with ether–hexane (1 : 1) as eluant and then ether–hexane (2 : 1), gave the title *stilbene* (3) (6.5 g, 73%) as an oily mixture of *cis*- and *trans*-isomers (M^+, 362. $C_{23}H_{22}O_4$ requires M, 362). The later eluted isomer predominated, probably being *trans*-, but overlapping aromatic protons prevented determination of a J value for the olefinic protons in the n.m.r. spectrum. ^{1}H N.m.r.: δ 7.5—7.2 (m, 5 H, OCH_2Ph), 7.15—6.8 (m, 5 H, CH=CH, 2′-H, 5′-H, 6′-H), 6.56 (m, 2 H, 2-H and 6-H), 6.30 (m, 1 H, 4-H), 5.18 (s, 2 H, OCH_2), 3.86 (s, 3 H, OMe), and 3.77 (s, 3 H, OMe).

Benzoylstilbene (4).—The hydroxystilbene (3) (7 g, 0.019 mol) in dry pyridine (40 ml) was stirred with benzoyl chloride (3 g, 0.021 mol) for 6 h. Since t.l.c. showed some hydroxystilbene remaining, benzoyl chloride (0.5 g) was added and stirring continued for a further 16 h. Work-up with dilute hydrochloric acid and extraction with chloroform gave a yellow oil which crystallised on trituration with benzene–hexane. Crystallisation from benzene–hexane gave the *benzoylstilbene* (4) (6.4 g, 71%), m.p. 120—122 °C, M^+, 466.1797 ($C_{30}H_{26}O_5$ requires M, 466.1780), $\nu_{max.}$ (mull) 1 725 cm^{-1}; ^{1}H n.m.r.: δ 8.12—8.00 (m, 2 H, $PhCO_2$), 7.48—7.12 (m, 8 H, $PhCO_2$ + $PhCH_2$), 7.00—6.64 (m, 7 H, Ar and CH=CH), 6.52 (m, 1 H, 4-H), 5.07 (s, 2 H, CH_2Ph), 3.80 (s, 3 H, OMe), and 3.74 (s, 3 H, OMe). The product appears to be a single isomer, probably *trans*.

5-Benzoyloxy-3′-hydroxy-3,4′-dimethoxydihydrostilbene (6).—Benzoylstilbene (4) (5.5 g, 0.012 mol) was hydrogenated in ethyl acetate (100 ml) over 10% palladium on carbon (1 g) at 20 °C for 16 h. Filtration, evaporation, and chromatography on dry silica, with ether–hexane (1 : 1) as eluant, gave the title *stilbene* (6) (4.3 g, 97%), m.p. 77—78 °C (Found: C, 73.0; H, 5.9. $C_{23}H_{22}O_5$ requires C, 73.0; H, 5.85%), $\nu_{max.}$ 1 725 cm^{-1}; ^{1}H n.m.r.: δ 8.20 (m, 2 H, $PhCO_2$), 7.57 (m, 3 H, $PhCO_2$), 6.83—6.63 (m, 6 H, Ar), 5.61 (s, 1 H, OH), 3.88 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), and 2.88 (s, 4 H, CH_2CH_2).

Dimethylprop-2-ynyl Ether (7) *of the Dihydrostilbene* (6). Dihydrostilbene (6) (378 mg, 1 mmol) in dry acetone (3 ml)

was refluxed and stirred under nitrogen for 22 h with potassium carbonate (150 mg, 1.1 mmol), potassium iodide (100 mg, 0.6 mmol), 18-crown-6 (10 mg), and 3-chloro-3-methylbutyne (1 ml, 10 mmol). Water was added to the cooled solution which was then just acidified with hydrochloric acid. Extraction of the reaction mixture with ether, and washing, drying, and evaporation of the extract gave an oil which was chromatographed on dry silica, with ether–hexane (1 : 1) as eluant; it gave the *dimethylprop-2-ynyl ether* (7) (109 mg, 24%) as a colourless oil (M^+, 444.1944. $C_{28}H_{28}O_5$ requires M, 444.1937), $\nu_{max.}$ ($CHCl_3$), 1 730 cm^{-1}; ^1H n.m.r.: δ 8.18 (m, 2 H, $PhCO_2$), 7.58 (m, 3 H, $PhCO_2$), 7.20 (s, 1 H, 2′-H), 6.83 (s, 2 H, 5′-H, 6′-H), 6.62 (m, 3 H, 2-H, 4-H, 6-H), 3.82 (s, 3 H, OMe), 2.89 (s, 4 H, CH_2CH_2), 2.50 (s, 1 H, C≡CH), and 1.66 (s, 6 H, *gem*-methyls).

Dimethylallyl Ether (8) *of the Dihydrostilbene* (6).—Dimethylprop-2-ynyl ether (7) (100 mg) was hydrogenated in ethyl acetate (20 ml) over Lindlar catalyst (30 mg) at 20 °C and atmospheric pressure. After 20 min the rate of hydrogen uptake had decreased considerably and rather less than 1 mol had been absorbed. The catalyst was filtered off and the solvent evaporated to give an almost colourless oil. The n.m.r. spectrum indicated that no discernible acetylene resonance remained, and that the product was the almost pure *dimethylallyl ether* (8) (M^+, 446. $C_{28}H_{30}O_5$ requires M, 446); ^1H n.m.r.: δ 8.16 (m, 2 H, $PhCO_2$), 7.53 (m, 3 H, $PhCO_2$), 6.81 (m, 3 H, 2′-H, 5′-H, 6′-H), 6.61 (br s, 3 H, 2-H, 4-H, 6-H), 6.12 (dd, 1 H, J 17, 9 Hz, C*H*=CH_2), 5.07 (d, 1 H, J 17 Hz, CH=C*H*$_2$), 5.03 (d, 1 H, J 9 Hz, CH=C*H*$_2$), 3.78 (s, 6 H, 2 × OMe), 2.84 (s, 4 H, CH_2CH_2), and 1.45 (s, 6 H, *gem*-methyls). It was used directly for the Claisen rearrangement.

Claisen Rearrangement of the Dimethylallyl Ether (8).—The ether (8) (80 mg) was heated to 150 °C for 1.25 h after which time t.l.c. indicated that no starting material remained and predominantly one compound had been formed. Chromatography on 20 × 20 cm silica plates, with ether–hexane (1 : 1) as eluant gave the *prenylated dihydrostilbene* (9) (40 mg, 50%), as an oil (M^+, 446.2088. $C_{28}H_{30}O_5$ requires M, 446.2093), $\nu_{max.}$ ($CHCl_3$) 1 735 cm^{-1}; ^1H n.m.r.: δ 8.22 (m, 2 H, $PhCO_2$), 7.60 (m, 3 H, $PhCO_2$), 6.71 (s, 5 H, Ar), 5.76 (s, 1 H, OH), 5.17 (br t, 1 H, J 7 Hz, CH=C), 3.88 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 3.44 (br d, 2 H, J 7 Hz, C*H*$_2$C=), 1.79 (s, 3 H, CH=CC*H*$_3$), and 1.67 (s, 3 H, CH=CC*H*$_3$).

Canniprene (10).—The prenylated dihydrostilbene (9) (26 mg) was hydrolysed when stirred with aqueous 10% sodium hydroxide (0.2 ml) containing 1 drop of ethanol at 85 °C for 1 h. After acidification and work-up *via* extraction with ether, the product was chromatographed on a 20 × 20 cm silica plate, with ether–hexane (2 : 1) as eluant. *Canniprene* (10) (18 mg, 90%), crystallised from ether–hexane, m.p. 111.5—112.5 °C (M^+, 342.1844. $C_{21}H_{26}O_4$ requires M, 342.1831). Its m.p. was undepressed on mixed m.p. with natural canniprene,[1] m.p. 112—113 °C. The i.r. (KBr) and n.m.r. spectra were virtually superimposable on those of the natural product.

3-*Hydroxy*-4-*methoxytoluene*.—Zinc amalgam [from zinc (150 g) and mercuric chloride (60 ml of 5% solution)] was treated with concentrated hydrochloric acid (80 ml) and the mixture was heated to reflux. Isovanillin (15.2 g) in ethanol (45 ml) and concentrated hydrochloric acid (150 ml) was added dropwise during 75 min and the mixture was refluxed for a further 75 min. Work-up, finally by chromatography on a silica column with ether–hexane (1 : 1) as eluant, gave 3-hydroxy-4-methoxytoluene, m.p. 30—32 °C (lit.,[17] m.p. 32—33 °C) (7.0 g, 51%).

3-*Hydroxy*-4-*methoxy*-2-(3-*methylbut*-2-*enyl*)*toluene* (11).—The dimethylprop-2-ynyl ether was prepared (970 mg, 47%) from the above toluene (1.38 g) and 3-chloro-3-methylbutyne (1.2 g) by a procedure analogous to that given earlier. The acetylenic ether (250 mg) was semi-hydrogenated using Lindlar catalyst to give the *O*-dimethylallyl ether (150 mg, 60%) after chromatographic purification. The latter (100 mg) when heated at 150 °C for 2 h and then chromatographed on a dry silica column with ether–hexane (1 : 10) as eluant gave the *toluene* (11) as an oil (60 mg, 60%) (M^+, 206.1321. $C_{13}H_{18}O_2$ requires M, 206.1307), ^1H n.m.r.: δ 6.60 (s, 2 H, Ar), 5.68 (s, 1 H, OH), 5.10 (t, 1 H, J 6 Hz, C=CH), 3.82 (s, 3 H, OMe), 3.35 (d, 2 H, J 6 Hz, ArC*H*$_2$), 2.22 (s, 3 H, $ArCH_3$), and 1.76 and 1.66 (each s, 3 H, *gem*-Me_2). Treated with 1% BF_3–Et_2O in dichloromethane for 10 min the toluene (11) gave the chroman (12); this was identified on the basis of its ^1H n.m.r. spectrum: δ 6.66 (s, 2 H, Ar), 3.84 (s, 3 H, OMe), 2.62 (t, 2 H, J 7 Hz, $ArCH_2$), 2.17 (s, 3 H, $ArCH_2$), 1.82 (t, 2 H, J 7 Hz, $ArCH_2CH_2$), and 1.42 (s, 6 H, *gem*-Me_2).

Dimethylprop-2-*ynyl Ether of Isovanillin* (14).—Anhydrous potassium carbonate (5.6 g, 0.04 mol), potassium iodide (8.0 g, 0.048 mol), and 3-chloro-3-methylbutyne (8 ml, 0.8 mol) were added to isovanillin (6.0 g, 0.04 mol) in dry acetone (60 ml) and the mixture was refluxed for 65 h. The reaction mixture was cooled and acidified with dilute hydrochloric acid, and the product was extracted with ether. The extract was washed, dried, and evaporated to give an oil which was chromatographed on a wet silica column (50—100 mesh) with ether–hexane as eluant. Recrystallisation of the product from ether–hexane gave the *isovanillin ether* (14) (1.97 g, 23%), m.p. 51.5—52.5 °C (Found: C, 71.25; H, 6.4. $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47%), $\nu_{max.}$ (KBr)1 675 cm^{-1}; ^1H n.m.r.: δ 9.88 (s, 1 H, CHO), 7.97 (d, 1 H, J 2 Hz, Ar), 7.62 (dd, 1 H, J 2 and 9 Hz, Ar), 7.02 (d, 1 H, J 9 Hz, Ar), 3.98 (s, 3 H, OMe), 2.60 (s, 1 H, C≡CH), and 1.75 (s, 6 H, *gem*-methyls).

Dimethylallyl Ether of Isovanillin.—The acetylenic ether (14) (1.97 g, 0.009 mol) was hydrogenated in ethyl acetate (175 ml) over Lindlar catalyst (0.7 g) at 20 °C and atmospheric pressure. When 220 ml of hydrogen (*ca.* 1 mol) had been absorbed the reaction almost ceased. Work-up gave an oil (1.80 g, 91%), pure enough as judged by its n.m.r. spectrum for the next stage. A small sample was purified by chromatography on a dry silica column with ether–hexane (1 : 1) as eluant to give the *dimethylallyl ether* as a colourless oil (M^+, 220.1083. $C_{13}H_{16}O_3$ requires M, 220.1099), $\nu_{max.}$ (film) 1 685 cm^{-1}; ^1H n.m.r.: δ 9.80 (s, 1 H, CHO), 7.54 (m, 2 H, Ar), 6.95 (d, 1 H, J 9 Hz, Ar), 6.14 (dd, 1 H, J 18 and 10 Hz, C*H*=CH_2), 5.15 (d, 1 H, J 18 Hz, CH=C*H*$_2$), 5.11 (d, 1 H, J 10 Hz, CH=C*H*$_2$), 3.90 (s, 3 H, OMe), and 1.50 (s, 6 H, *gem*-methyls).

3-*Hydroxy*-4-*methoxy*-2-(3-*methylbut*-2-*enyl*)*benzaldehyde* (15).—The preceding dimethylallyl ether (1.8 g, 0.008 mol) was heated for 6 min at 135 °C and the product was purified on a dry silica column with ether–hexane (1 : 1) as eluant. Crystallisation gave the *isovanillin* (15) (1.55 g, 86%), m.p. 75—76 °C from ether–hexane (Found: C, 70.9; H, 7.6. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%), $\nu_{max.}$ (KBr) 1 660 cm^{-1}; ^1H n.m.r.: δ 10.05 (s, 1 H, CHO), 7.40 (d, 1 H, J 9 Hz, Ar), 6.80 (d, 1 H, J 9 Hz, Ar), 5.86 (s, 1 H, OH), 5.16 (br t, 1 H, C*H*=C), 3.95 (s, 3 H, OMe), 3.79 (d, 2 H, J 7 Hz, $ArCH_2$), 1.80 (s, 3 H, C*Me*$_2$), and 1.67 (s, 3 H, C*Me*$_2$).

3-Benzyloxy-4-methoxy-2-(3-methylbut-2-enyl)benzaldehyde (16).—The isovanillin (15) (1.55 g, 0.007 mol) in dry acetone (50 ml) containing anhydrous potassium carbonate (1.2 g, 0.0087 mol) and potassium iodide (0.3 g, 0.0018 mol) was stirred and treated dropwise with benzyl chloride (1.3 ml, 0.01 mol) in dry acetone (12 ml). The mixture was stirred and refluxed (16 h) and then worked up to give, after chromatography on a dry silica column with ether–hexane (1 : 1) as eluant, the 3-O-*benzylated isovanillin* (16) (1.82 g, 83%) as an oil (Found: M^+, 310.1577. $C_{20}H_{22}O_3$ requires M, 310.1569), $\nu_{max.}$ (film) 1 685 cm^{-1}; ^1H n.m.r.: δ 10.09 (s, 1 H, CHO), 7.67 (d, 1 H, *J* 8 Hz, Ar), 7.40 (m, 5 H, CH_2Ph), 6.90 (d, 1 H, *J* 8 Hz, Ar), 5.07 (br t, 1 H, *J* 6 Hz, CH=C), 4.98 (s, 2 H, CH_2Ph), 3.96 (s, 3 H, OMe), 3.76 (d, 2 H, *J* 6 Hz, CH_2CH=C), 1.70 (s, 3 H, =CMe_2), and 1.65 (s, 3 H, =CMe_2).

5-Benzyloxy-3-methoxybenzyl Bromide.—Methyl 5-benzyloxy-3-methoxybenzoate [18] (14 g, 0.05 mol) in dry ether (90 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (4.8 g, 0.13 mol) in ether (180 ml) at such a rate as to allow it to continue refluxing. Stirring and refluxing was continued for 90 min after which water and then dilute hydrochloric acid were added to the ice-cooled reaction mixture. Isolation in the usual way gave 5-benzyloxy-3-methoxybenzyl alcohol (12.0 g, 96%). Its n.m.r. spectrum was in agreement with that recorded in the literature: [18] it was used without further purification.

Phosphorus tribromide (7.5 ml, 0.068 mol) in dry benzene (30 ml) was added to 5-benzyloxy-3-methoxybenzyl alcohol (12.0 g, 0.05 mol) in benzene (170 ml) whilst the solution was stirred at 5 °C. Stirring was continued at this temperature for 10 min and then at 20 °C for 4 h. The reaction mixture was worked up with a hydrogen carbonate, wash to give 5-benzyloxy-3-methoxybenzyl bromide [10a] as an oil (15.0 g, 99%) which crystallised when set aside. The product was used immediately for formation of the phosphonium salt below.

5-Benzyloxy-3-methoxybenzyltriphenylphosphonium Bromide.—The above bromide (15 g, 0.049 mol) and triphenylphosphine (18.0 g, 0.069 mol) were stirred and refluxed in dry benzene (100 ml). On cooling, the white product was removed by filtration. The filtrate was concentrated to half volume and refluxed for a further 16 h to give a second crop of product. The combined material was washed thoroughly with benzene and dried *in vacuo* to give the title phosphonium salt [10a] (24.8 g, 89%), m.p. 199.5—201 °C (Found: C, 69.7; H, 5.3. Calc. for $C_{33}H_{30}BrO_2P$: C, 69.70; H, 5.3%). The ^1H n.m.r. spectrum confirmed the structure.

3′,5-Dibenzyloxy-3,4′-dimethoxy-2′-(3-methylbut-2-enyl)-stilbene (17).—n-Butyl-lithium (2.2 ml; 1.4M solution in hexane) was added dropwise to a stirred suspension of 5-benzyloxy-3-methoxybenzyltriphenylphosphonium bromide (1.7 g, 0.003 mol) in dry tetrahydrofuran (40 ml) under nitrogen, and the orange-red solution was stirred (20 min). A solution of the aldehyde (16) (850 mg, 0.027 mol) in dry tetrahydrofuran (10 ml) was added gradually and the mixture was stirred (1½ h). The reaction mixture was added to ammonium chloride solution and extracted twice with ether. The aqueous phase was just acidified with hydrochloric acid and again twice extracted with ether. After being washed with aqueous ammonium chloride and water, the combined extracts were dried, evaporated, and chromatographed on a dry silica column with ether–hexane (1 : 2) as eluant to give a *cis–trans* mixture of the *stilbene* (17) (900 mg, 63%) as an oil (M^+, 520.2624. $C_{35}H_{36}O_4$ requires M, 520.2613).

Canniprene (10) via *Sodium in Butanol Reduction*.—The stilbene (17) (730 mg, 0.0014 mol) in n-butanol was stirred under nitrogen and heated to 95 °C (bath). Sodium (4 g, 0.17 mol) was added rapidly in small pieces so that the butanol refluxed. When all the sodium had dissolved the solution was cooled, water was added, and the mixture was extracted with ether. The aqueous layer was acidified with dilute hydrochloric acid and extracted three times with ether. The ether extracts were washed, dried and evaporated and the crude product was purified on a dry silica column with ether–hexane (1 : 2) as eluant to give *canniprene* (10) (220 mg, 46%), m.p. and mixed m.p. with natural material, and with the above synthetic specimen, 111—112 °C (from ether–hexane) (Found: C, 73.6; H, 8.0. $C_{21}H_{26}O_4$ requires C, 73.66; H, 7.65%).

Dissolving-metal Reductions of 3′-Benzyloxy-5-benzoyloxy-3,4′-dimethoxystilbene (4).—A stirred suspension of stilbene (4) (200 mg) in n-butanol (20 ml; dried over molecular sieve) was heated in an oil-bath at 110 °C under nitrogen and sodium (1.5 g) was added in pieces to maintain reflux. Work-up as above gave an oil (100 mg, 85%) which crystallised and was identical (n.m.r. comparison) with the specimen of 3′,5-dihydroxy-3,4′-dimethoxydihydrostilbene (5) described below.

A similar reduction of compound (4) (100 mg) by sodium (0.7 g) in refluxing ethanol (20 ml) was worked up and chromatographed on 20 × 20 cm silica plates eluting twice with ether–hexane (1 : 1). Three bands were noted but the most polar contained the major material (60 mg). The latter was separated further by chromatography on 20 × 20 cm silica plates, with 2% methanol in chloroform as eluant. Two main bands were observed each *ca.* 20 mg. The less polar was identified (n.m.r.) as the debenzoylated stilbene (3): the more polar was (n.m.r.) the dihydrostilbene (5).

Magnesium (1 g) was added in portions to a stirred suspension of stilbene (4) (100 mg) in dry methanol (20 ml), heated under nitrogen by an oil-bath (75 °C). After the first addition, stirring was stopped, and a crystal of iodine was added to initiate reaction. Stirring was continued and the remainder of the magnesium added during 15 min, the flask being removed from the bath as the reaction became too vigorous. After addition of the magnesium the flask was returned to the bath and stirred for 2 h. Work-up by acidification (HCl) and ether extraction gave an oil (50 mg, 65%) shown by its n.m.r. spectrum to be the dihydrostilbene derived from structure (3), *i.e.* double bond reduced, benzoyl cleaved, benzyl retained; ^1H n.m.r.: δ 7.45—7.15 (m, 5 H, CH_2Ph), 6.80—6.60 (m, 3 H, Ar), 6.22 (br s, 3 H, Ar), 5.06 (s, 2 H, CH_2Ph), 3.82 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), and 2.74 (s, 4 H, CH_2CH_2).

Reduction of *trans*-stilbene itself (100 mg, 0.000 55 mol),[19] in dry methanol (20 ml) with magnesium (1 g, 0.04 mol) by the above method gave dihydrostilbene (90 mg, 89%) as a white solid identified by its n.m.r. spectrum. Reduction of *trans*-stilbene (0.48 g, 0.0026 mol) in dry ethanol at 70 °C (under nitrogen) by sodium (3 g, 0.13 mol) gave a solid product (0.47 g, 97%) shown by n.m.r. spectroscopy to be a mixture of dihydrostilbene and unreduced stilbene (2 : 1).

Deuteriated Alcohol (19).—Sodium borodeuteride (22 mg) was added to a solution of the aldehyde (18) (105 mg) in methanol (3 ml) and the mixture was stirred at 20 °C for 1 h. Acidification and extraction with ether gave the *deuterio-alcohol* (19) (95 mg, 90%), m.p. 45—46 °C (M^+, 313. $C_{20}H_{23}DO_3$ requires M, 313), ^1H n.m.r.: δ 7.40—7.15 (m, 5 H, CH_2Ph), 6.94 (d, 1 H, *J* 8 Hz, Ar), 6.64 (d, 1 H, *J* 8 Hz, Ar),

4.88 (m, 3 H, CH_2Ph and CH=C·), 4.45 (br s, 1 H, CHDOH), 3.76 (s, 3 H, OMe), 3.35 (d, 2 H, *J* 8 Hz, CH_2CH=), 1.96 (s, 1 H, OH), and 1.65 and 1.60 (each s, 3 H, CMe_2).

A specimen of *undeuteriated* (19) made in the same way (89%), had m.p. 46—47 °C (M^+, 312.1717. $C_{20}H_{24}O_3$ requires *M*, 312.1725): the n.m.r. spectrum was closely similar to the above except that *two* protons resonated at δ 4.46.

Deuteriated Aldehyde (20).—The alcohol (19) (95 mg) dissolved in dry dichloromethane (10 ml) was stirred with manganese dioxide (950 mg) for 16 h at 20 °C. Filtration and evaporation gave the *deuteriated aldehyde* (20) as a colourless oil (76 mg, 80%), (M^+, 311. $C_{20}H_{21}DO_3$ requires *M*, 311), $\nu_{max.}$ (film) 1 665 cm^{-1}. The ^1H n.m.r. spectrum was as for (16) above except for the low intensity of the aldehyde proton signal at δ 10.09 (*ca.* 1/10 H).

Deuteriated Canniprene (21).—Wittig reaction, as described above, between the deuteriated aldehyde (20) (90 mg) and the ylide (13), made from the phosphonium bromide (200 mg) in tetrahydrofuran (5 ml) using n-butyl-lithium (0.25 ml; 1.4M), gave the *cis*/*trans*-isomers of deuteriated-(17) (84 mg, 56%). The latter was reduced as before without further purification to give *deuteriated canniprene* (21) (33 mg, 60%), m.p. 108—110 °C (M^+, 343. $C_{21}H_{25}DO_4$ requires 343). The i.r. and ^1H n.m.r. spectra were closely similar to those for canniprene except that the signals at δ 2.81 due to the bridge methylenes integrated for 3, not 4, protons. From the mass spectral peak intensities at *m/e* 343 and 342 the sample was estimated to have *ca.* 85% of one deuterium atom. ^2H N.m.r.: one broadened signal at δ 2.84.

Hydrogenation and Deprotection of 4-p-*Bromophenacyloxystilbene* (27).—The title compound was made by refluxing 4-hydroxystilbene (100 mg, 0.5 mmol), potassium carbonate (70 mg, 0.5 mmol), and *p*-bromophenacyl bromide (140 mg, 0.5 mmol) in dry acetone (4 ml) for 4 h. 4-p-*Bromophenacyloxystilbene* (110 mg, 55%) had m.p. 140—142 °C (M^+, 392.0419. $C_{22}H_{17}BrO_2$ requires *M*, 392.0412). Hydrogenation of the latter (30 mg) over 5% palladium on carbon (5 mg) in ethyl acetate (10 mg) at 20 °C for 2 h at atmospheric pressure smoothly gave the dihydrostilbene (30 mg) as an oil identified by its ^1H n.m.r. spectrum: δ 7.86 (d, 2 H, *J* 8 Hz), 7.62 (d, 2 H, *J* 8 Hz), 7.50—6.80 (m, 9 H), 5.18 (s, 2 H), and 2.88 (s, 4 H, CH_2CH_2). Prolongation of the hydrogenation (16 h) gave evidence of partial cleavage of the *p*-bromophenacyl residue.

Zinc (200 mg) was added to 4-*p*-bromophenacyloxydihydrostilbene (100 mg) in acetic acid (4 ml) and the mixture was stirred at 20 °C for 1 h. Work-up, and ^1H n.m.r. spectral examination of the product, showed complete removal of the protecting group (no signal at δ 5.18 due to OCH_2CO). Natural canniprene survived these conditions unchanged.

p-*Bromophenacyl Ether of Isovanillin*.—*p*-Bromophenacyl bromide (600 mg, 2.2 mmol) was added to a stirred mixture of isovanillin (300 mg, 2 mmol) and potassium carbonate (500 mg, 3.6 mmol) in dry acetone (10 ml), and the mixture was refluxed for 4 h.

Work-up, by extraction with ether, gave the p-*bromophenacyl ether of isovanillin* (400 mg, 57%), m.p. 131—132 °C from ethyl acetate (Found: C, 54.9; H, 3.75. $C_{16}H_{13}BrO_4$ requires C, 55.05; H, 3.75%), $\nu_{max.}$ ($CHCl_3$) 1 705 and 1 685 cm^{-1}.

3-*MEM-Ether of Isovanillin*.—Isovanillin (20 g, 0.13 mol) in dry dimethoxyethane (120 ml) was added to a stirred suspension of sodium hydride (50% in oil; 14 g, 0.29 mol) in dimethoxyethane (50 ml) at 0 °C under nitrogen. Stirring was continued (30 min) and then methoxyethoxymethyl chloride (16 ml, 0.13 mol) was added dropwise and the suspension was stirred for a further 2 h at 0 °C. Water was added to the mixture and the product was extracted with ether. Washing, drying, and evaporation gave two immiscible oils which were separated; the lower layer was then washed with hexane to give a colourless oil (25.2 g, 80%). (The upper layer was paraffin oil from sodium hydride suspension.) The 3-*methoxyethoxymethoxy*-4-*methoxybenzaldehyde* (M^+, 240.1025. $C_{12}H_{16}O_5$ requires *M*, 240.0998) was purified by distillation, b.p. 170 °C/0.2 mmHg; ^1H n.m.r.: δ 9.75 (s, 1 H, CHO), 7.62 (d, 1 H, *J* 2 Hz, 2-H), 7.47 (dd, 1 H, *J* 8 and 2 Hz, 6-H), 6.95 (d, 1 H, *J* 8 Hz, 5-H), 5.34 (s, 2 H, $ArOCH_2$), 3.96 (s, 3 H, $ArOCH_3$), 3.84 (m, 2 H, $OCH_2CH_2OCH_3$), and 3.53 (m, 2 H, $OCH_2CH_2OCH_3$), 3.37 (s, 3 H, CH_2OCH_3).

A mixture of the MEM-ether of isovanillin (40 mg) and the PBP-ether of isovanillin (58 mg) was stirred with anhydrous zinc bromide (200 mg) in dry dichloromethane (1 ml) for 4 h at 20 °C. Work-up and chromatography showed no MEM-ether of isovanillin remained. Isovanillin was present, and the PBP-ether of isovanillin was unchanged.

3-*MEM-Ether of* 4-*Methoxybenzyl Alcohol*.—The above aldehyde (11 g, 0.046 mol) in dry tetrahydrofuran (90 ml) was gradually added to a stirred suspension of lithium aluminium hydride (2.3 g, 0.06 mol) in tetrahydrofuran (110 ml), and the mixture was refluxed 2 h. Work-up gave 3-*methoxyethoxymethoxy*-4-*methoxybenzyl alcohol* (10.8 g, 97%) (M^+, 242.1163. $C_{12}H_{18}O_5$ requires *M*, 242.1154), ^1H n.m.r.: δ 7.13 (d, 1 H, *J* 2 Hz, 2-H), 6.92 (dd, 1 H, *J* 8 and 2 Hz, 6-H), 6.78 (d, 1 H, *J* 8 Hz, 5-H), 5.26 (s, 2 H, $ArOCH_2O$), 4.53 (s, 2 H, CH_2OH) 3.85 (s + m, 5 H, ArOMe and $OCH_2CH_2OCH_3$), 3.52 (m, 2 H, $OCH_2CH_2OCH_3$), 3.34 (s, 3 H, CH_2OCH_3), and 2.48 (br s, 1 H, D_2O exchg. OH).

5-p-*Bromophenacyloxy*-3-*methoxybenzyl Alcohol*.—5-Hydroxy-3-methoxybenzyl alcohol (2.8 g, 0.018 mol), dry potassium carbonate (7.5 g, 0.054 mol), and acetone (90 ml) were stirred and refluxed and *p*-bromophenacyl bromide (5.8 g, 0.021 mol) and 18-crown-6 (285 mg, 0.0011 mol) in dry acetone (90 ml) were gradually added. Stirring and refluxing was continued for 30 min after which the mixture was allowed to cool and then filtered. The filtrate was evaporated and the residue taken up in dichloromethane; the latter solution was then washed, dried, and evaporated to give 5-p-*bromophenacyloxy*-3-*methoxybenzyl alcohol* (4.7 g, 74%), m.p. 118—119 °C from ethyl acetate–hexane (Found: C, 54.65; H, 4.3%; M^+, 350.0170. $C_{16}H_{15}BrO_4$ requires C, 54.7; H, 4.3%; *M*, 350.0154), $\nu_{max.}$ (mull) 1 695 cm^{-1}; ^1H n.m.r.: δ 7.83 + 7.61 [2 × (d, 2 H, *J* 8 Hz), *p*-Br-C_6H_4CO], 6.54 (d, 2 H, *J* 2 Hz, 2-H and 6-H), 6.43 (d, 1 H, *J* 2 Hz, 4-H), 5.18 (s, 2 H, CH_2CO), 4.62 (s, 2 H, CH_2OH), 3.80 (s, 3 H, OCH_3), and 1.84 (br s, 1 H, D_2O exchg. OH).

5-p-*Bromophenacyloxy*-3-*methoxybenzaldehyde* (22).—The above alcohol (3.5 g, 0.01 mol) was shaken at 20 °C for 50 min with active manganese dioxide (35 g) in dry dichloromethane (175 ml). Filtration of the mixture and evaporation of the filtrate gave the *aldehyde* (22) (1.75 g, 50%), m.p. 140—141 °C from ethyl acetate–hexane (Found: C, 55.0; H, 3.8%; M^+, 348.0015. $C_{16}H_{13}BrO_4$ requires C, 55.0; H, 3.75%; M^+, 347.9998), $\nu_{max.}$ (mull): 1 705 and 1 690 cm^{-1}; ^1H n.m.r.: δ 9.87 (s, 1 H, CHO), 7.85 and 7.62 [2 × (d, 2 H, *J* 8 Hz), *p*-BrC_6H_4CO], 7.01 (m, 2 H, 2-H, 6-H), 6.77 (m, 1 H, 4-H), and 3.87 (s, 3 H, OCH_3).

3-Methoxyethoxymethoxy-4-methoxybenzyltriphenylphosphonium Bromide.—Dimethyl sulphide (5.2 ml, 0.07 mol) was added dropwise by syringe to a suspension of *N*-bromosuccinimide (10.8 g, 0.06 mol) in dry dichloromethane (200 ml) during 3 min at 0 °C under a nitrogen atmosphere. The yellow solution was cooled to −20 °C and the 3-MEM-ether of 4-methoxybenzyl alcohol (9.7 g, 0.04 mol) in dry dichloromethane (20 ml) was added dropwise by syringe over 5 min. The reaction mixture was stirred at 0 °C (2 h) and then poured into ice–water; the mixture was then extracted with benzene. The benzene extracts were washed with brine, dried, and evaporated to give 3-MEM-4-methoxybenzyl bromide (10.8 g, 88%), used to form the phosphonium salt. The integrity of the sample was confirmed by ^{1}H n.m.r. spectroscopy.

The bromide (10.8 g, 0.035 mol) in dry benzene (100 ml) was treated with triphenylphosphine (11 g, 0.042 mol) and refluxed for 3 h. Cooling and filtration gave the title *phosphonium bromide* (16.7 g, 83%), m.p. 175—176 °C from isopropyl alcohol–ether (Found: C, 63.8; H, 5.65%; M^+, 566.1240. $C_{30}H_{32}BrO_4P$ requires C, 63.5; H, 5.7%; *M*, 566.1222), ^{1}H n.m.r.: δ 7.68 (m, 15 H, Ph_3), 6.89—6.52 (m, 3 H, 2-H, 5-H, 6-H), 5.15 (d, 2 H, *J* 13 Hz, CH_2P), 4.95 (s, 2 H, $ArOCH_2$), 3.80 (s, 3 H, $ArOCH_3$), 3.70 (m, 2 H, $OCH_2CH_2OCH_3$), 3.45 (m, 2 H, $OCH_2CH_2OCH_3$), and 3.35 (s, 3 H, $OCH_2CH_2OCH_3$).

5-p-Bromophenacyloxy-3,4′-dimethoxy-3′-methoxyethoxymethoxystilbene (24).—n-Butyl-lithium (1.56 molar in hexane; 3.2 ml, 5 mmol) was added dropwise to a stirred mixture of 3-methoxyethoxymethoxy-4-methoxybenzyltriphenyl phosphonium bromide (2.83 g, 5 mmol) in dry tetrahydrofuran and the mixture was stirred for 20 min. The red solution was added dropwise to the aldehyde (22) (1.75 g, 5 mmol) in dry tetrahydrofuran (30 ml) under nitrogen. After the mixture had been stirred for 40 min water was added to it and the product was extracted into ethyl acetate. The extract was washed with water and brine, dried, and evaporated to give an oil (4.5 g). This was chromatographed on dry silica with ether–hexane (3 : 1) as eluant, to give the *stilbene* (24) as a *cis–trans*-mixture (1.7 g, 61%), a colourless oil (M^+, 556.1099. $C_{28}H_{29}BrO_7$ requires *M*, 556.1097).

Dihydrostilbene (26).—The stilbene (24) (450 mg, 0.81 mmol) was hydrogenated at atmospheric pressure (20 °C) in ethyl acetate (5 ml) over 10% palladium on carbon for 2 h. The catalyst was filtered off and the filtrate was evaporated and chromatographed on a dry silica column with ether–hexane (3 : 1) as eluant to give one major product which was identified as *5-p-bromophenacyloxy-3,4′-dimethoxy-3′-hydroxydihydrostilbene* (26) (100 mg, 26%), m.p. 118—120.5 °C (M^+, 470.0713. $C_{24}H_{23}BrO_5$ requires *M*, 470.0729), $\nu_{max.}$ 1 695 cm^{-1}; ^{1}H n.m.r.: δ 7.81 + 7.57 [2 × (d, 2 H, *J* 8 Hz) *p*-BrC_6H_4CO], 6.68 (m, 3 H, Ar), 6.28 (m, 3 H, Ar), 5.50 (br s, 1 H, OH), 3.83 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), and 2.79 (s, 4 H, CH_2CH_2).

3,3′,4′,5-Tetramethoxydihydrostilbene (30).—Wittig reaction using veratraldehyde (350 mg, 2.1 mmol) and 3,5-dimethoxytriphenylphosphonium bromide (1.0 g, 2 mmol), with sodium ethoxide (Na, 100 mg) as base gave, after chromatographic work-up [silica, elution with ether–hexane (2 : 3)], the expected *cis-trans*-stilbene (400 mg, 66%). Hydrogenation (10% Pd–C, EtOH) gave, after chromatography, dihydrostilbene (30) (50 mg, 50%), m.p. 55—56 °C (lit.,[20] m.p. 56.5—57.5 °C).

3′-Hydroxy-3,4′,5-trimethoxydihydrostilbene (31).—Wittig reaction using 3-benzyloxy-4-methoxybenzaldehyde (5 g, 0.021 mol) and 3,5-dimethoxytriphenylphosphonium bromide (10.8 g, 0.022 mol), with sodium ethoxide (Na, 1 g) as base, gave, after chromatographic work-up [silica, elution with ether–hexane (2 : 1)], *cis–trans*-3′-benzyloxy-3,4′,5-trimethoxystilbene (4.2 g, 51%). Hydrogenation (20 h, 20 °C, 760 mmHg), in ethyl acetate, gave, without chromatography, *3′-hydroxy-3,4′,5-trimethoxydihydrostilbene* (31) (2.7 g, 88%), m.p. 107—107.5 °C from methanol (Found: C, 70.75; H, 7.1%; M^+, 288. $C_{17}H_{20}O_4$ requires C, 70.8; H, 7.0%; *M*, 288), ^{1}H n.m.r. 6.28 (br s, 1 H, 2′-H), 6.72 (2 × d, 2 H, *J* 8 Hz, 5′-H and 6′-H), 6.36 (s, 3 H, 2-H, 4-H, 6-H), 5.58 (s, 1 H, D_2O exchg. OH), 3.88 (s, 3 H, OCH_3), 3.80 (s, 6 H, 2 × OCH_3), and 2.85 (s, 4 H, CH_2CH_2).

3′,5-Dihydroxy-3,4′-dimethoxydihydrostilbene (33).—Sodium (100 mg) was dissolved in dry ethanol (10 ml) with stirring under nitrogen. 3-Benzyloxy-4-methoxybenzaldehyde (190 mg, 0.79 mmol) was then added to the mixture with continued stirring to effect dissolution; this was followed by the addition of 5-benzyloxy-3-methoxybenzyltriphenylphosphonium bromide (400 mg, 0.70 mol). The reaction mixture was then stirred and refluxed for 18 h. Work-up followed by chromatography [silica, eluant ether–hexane (1 : 1)] gave the *cis–trans*-isomers of 3′,5-dibenzyloxy-3,4′-dimethoxystilbene (160 mg, 50%). The latter (160 mg) was hydrogenated [Pd–C (10 mg), ethyl acetate, 20 °C, 760 mmHg] to give the *dihydrostilbene* (33) (40 mg, 41%), m.p. 132—133 °C from ethyl acetate–hexane (M^+, 274.1221. $C_{16}H_{18}O_4$ requires *M*, 274.1205). It was identical (mixed m.p. and ^{1}H n.m.r. comparison) with the natural compound from *Cannabis*; ^{1} ^{13}C n.m.r. (CD_3COCD_3): δ 161.7 (s, C-3), 159.1 (s, C-5), 147.0 (s, C-3′/4′), 146.4 (s, C-3′/4′), 145.0 (s, C-1), 135.7 (s, C-1′), 120.0 (d, C-6′), 116.0 (d, C-2′), 112.3 (d, C-5′), 108.7 (d, C-6), 106.1 (d, C-2), 99.7 (d, C-4), 56.3 (q, OMe), 55.2 (q, OMe), 38.8 (t, C-7/7′), and 37.5 (t, C-7/7′).

5,4′-Dihydroxy-3,3′-dimethoxydihydrostilbene (34).—This compound was prepared as above using 4-benzyloxy-3-methoxybenzaldehyde (190 mg, 0.79 mmol) [the intermediate dibenzyloxy-stilbene was obtained in 47% yield (150 mg)]. It was similarly hydrogenated to yield the *dihydrostilbene* (34) as a colourless oil (50 mg, 55%) (M^+, 274.1222. $C_{16}H_{18}O_4$ requires *M*, 274.1205), ^{1}H n.m.r. (CD_3COCD_3): δ 6.81—6.61 (m, 4 H, one H D_2O exch., 2′-H, 5′-H, 6′-H, OH), 6.32—6.20 (m, 4 H, one H D_2O exch., 2-H, 4-H, 6-H, OH), 3.79 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), and 2.78 (s, 4 H, CH_2CH_2); ^{13}C n.m.r. (CD_3COCD_3): δ 161.3 (s, C-3), 158.6 (s, C-5), 147.8 (s, C-3′/4′), 144.9 (s, C-1 and C-3′/4′), 134.0 (s, C-1′), 121.3 (d, C-6′), 115.5 (d, C-5′), 112.8 (d, C-2′), 108.8 (d, C-6), 106.2 (d, C-2), 99.4 (d, C-4), 56.0 (q, OMe), 55.2 (q, OMe), 38.5 (t, C-7/7′), and 37.4 (t, C-7/7′).

4′,5-Dihydroxy-3-methoxydihydrostilbene (32).—The intermediate stilbene (2.7 g, 64%) was prepared as above using 4-benzyloxybenzaldehyde (3.0 g, 0.014 mol). A portion (200 mg) was hydrogenated and the product chromatographed to yield the title dihydrostilbene (32), m.p. 110 °C (lit.,[10b] m.p. 112.5—113.0 °C) (M^+, 244. Calc. for $C_{15}H_{16}O_3$: *M*, 244). It was identical with the natural material.

3,3′,5,5′-Tetramethoxystilbene (35).—3,5-Dimethoxybenzyl bromide (4 g, 0.017 mol) in dry ether (20 ml) was added dropwise to magnesium (0.425 g, 0.017 g-atom) stirred in dry ether (5 ml) under nitrogen, a crystal of iodine being used to initiate reaction. After the mixture had been refluxed for 20 min, further bromide (4 g, 0.017 mol) in dry ether (20 ml)

was added, and the mixture was refluxed under nitrogen for 2 h. Work-up gave 3,3′,5,5′-tetramethoxystilbene (35) (5 g, 95%), m.p. 104.5—105.5 °C from ethyl acetate–hexane (lit.,[21] m.p. 102 °C); ^{1}H n.m.r.: δ 6.36 (s, 6 H), 3.80 (s, 12 H), and 2.87 (s, 4 H); ^{13}C n.m.r.: δ 160.8 (s, C-3, C-3′, C-5, C-5′), 144.1 (s, C-1, C-1′), 106.6 (d, C-2, C-2′, C-6, C-6′), 98.0 (d, C-4, C-4′), 55.1 (q, 4 × OMe), and 38.0 (t, 2 × CH_2).

4-Isopentyl-3,3′,5,5′-tetramethoxydihydrostilbene (36).—n-Butyl lithium (2M in hexane; 1 ml, 2 mmol) was added to an ice-cooled, stirred solution of 3,3′,5,5′-tetramethoxydihydrostilbene (604 mg, 2 mmol) in dry tetrahydrofuran (15 ml) under nitrogen. The solution was stirred at 0 °C for 5 min and then at 20 °C for 25 min. Isopentyl bromide (330 mg, 2.2 mmol) was added dropwise to the green solution, discharging the colour, and the solution was then stirred at 20 °C for 90 min. The mixture was poured into water and extracted with ether, the combined extracts were washed and dried and the solvent evaporated off. The product was chromatographed on 20 × 20 cm silica plates, with chloroform as eluant to give an oil (40 mg). Rechromatography in the same way using ether–hexane (1 : 3) as eluant split this into two components. The more polar was the *isopentyldihydrostilbene* (36) (21 mg), m.p. 34—35 °C (M^+, 372.2319. $C_{23}H_{32}O_4$ requires M, 372.2300), ^{1}H n.m.r.: δ 6.38 (br s, 5 H, Ar), 3.82 (s, 12 H, OMe), 2.90 (s, 4 H, CH_2-CH_2), 2.62 (br t, 2 H, J 7 Hz, benzylic CH_2 of side-chain), 1.68—1.24 (m, 3 H, side-chain CH_2CH), and 0.95 (d, 6 H, J 7 Hz, *gem*-Me_2).

Dimethylprop-2-ynyl Ether of 3′-Hydroxy-3,4′,5-trimethoxydihydrostilbene (38).—The dihydrostilbene (31) (1.8 g, 0.0063 mol) was refluxed under nitrogen for 48 h with potassium carbonate (2 g, 0.014 mol), potassium iodide (2 g, 0.012 mol), and 3-chloro-3-methylbutyne (1.3 g, 0.013 mol). Work-up and chromatography on a dry silica column, with ether–hexane (1 : 1) as eluant gave the *ether* (38) as a colourless oil (800 mg, 36%) (Found: M^+, 354.1841. $C_{22}H_{26}O_4$ requires M, 354.1831), $\nu_{max.}$ (film) 3 270 and 2 940 cm^{-1}; ^{1}H n.m.r.: δ 7.32 (s, 1 H, 2′-H), 6.88 (s, 2 H, 5′-H, 6′-H), 6.38 (s, 3 H, 2-H, 4-H, 6-H), 3.80 (s, 6 H, 2 × OMe), 3.74 (s, 3 H, 4′-OMe), 2.86 (s, 4 H, CH_2CH_2), 2.51 (s, 1 H, C≡CH), and 1.68 (s, 6 H, *gem*-Me_2).

5-(3,5-Dimethoxyphenylethyl)-8-methoxy-2,2-dimethyl-2H-chromen (39).—The above ether (38) (250 mg, 0.71 mmol) was dissolved in diethylaniline (4 ml; distilled from KOH) and heated to 218 °C for 2 h. The product was cooled, taken up in ether, and the solution washed with dilute sulphuric acid and water, dried, and evaporated. Chromatography on 20 × 20 cm silica plates, with ether–hexane (1 : 1) as eluant, gave the *chromen* (39) (140 mg, 56%), m.p. 70—71 °C from ether (Found: M^+, 354.1848. $C_{22}H_{26}O_4$ requires M, 354.1831), ^{1}H n.m.r.: δ 6.75 and 6.63 (ABq, 2 H, J 8 Hz, 7-H and 6-H), 6.52 (d, 1 H, J 10 Hz, chromen 4a-H), 6.37 (s, 3 H, 2′-H, 4′-H, 6′-H), 5.66 (d, 1 H, J 10 Hz, 8a-H), 3.87 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × OMe), 2.83 (s, 4 H, CH_2CH_2), 1.50 (s, 6 H, *gem*-Me_2).

5-(3,5-Dimethoxyphenylethyl)-3,4-dihydroxy-8-methoxy-2,2-dimethyl-2H-chroman (37).—The chromen (39) (40 mg, 0.11 mol) was hydrogenated over 5% Pd–C (10 mg) in ethyl acetate (5 ml) at atmospheric pressure. Work-up in the usual way followed by chromatography on a silica plate, with ether–hexane (1 : 1) as eluant, gave the *chroman* (37) (30 mg, 76%), m.p. 114—115 °C (Found: C, 73.8; H, 8.15%; M^+, 356.2012. $C_{22}H_{28}O_4$ requires C, 74.15; H, 7.9%; M, 356.1987). The m.p. was not depressed on admixture with the chroman methyl ether derived from canniprene, m.p. 113—114 °C: [1] i.r. and ^{1}H n.m.r. spectra were identical.

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