Synthesis of Sterically Hindered Stilbenes of Biological Importance

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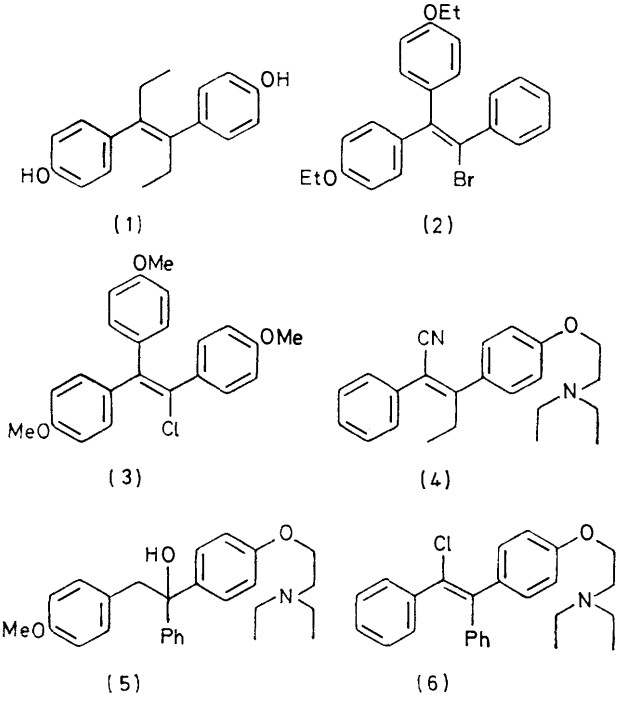
A series of (2-, 6-, α-)alkyl-substituted 4,4'-dimethoxystilbenes, of biological interest, have been synthesised by employing appropriate deoxybenzoins and benzylic phosphonium ylides as key intermediates.

3,5-Dimethylphenol was converted in six steps into the benzylphosphonium salt (11e) and the benzylphosphonate (11f). Condensations between (11e) and appropriate aryl carbonyl compounds led to mixtures of *Z*- and *E*-isomers of the stilbenes (21), (25), (33), (34), and (38). Forcing conditions were required to obtain the stilbenes (34) and (38) (yields >5%), which probably reflects steric limitations to the Wittig synthesis of these molecules. The secondary phosphonium salts (29), (35), and (37) were also synthesised, but whereas (29) reacted with the benzaldehyde (20) giving (25), no stilbene products were formed from similar condensations with (35) and (37). Attempts to prepare stilbenes from the phosphonate (11f) and aryl ketones instead led to chalcones [*e.g.* (31)]. The phenylacetic acid (11h) was prepared and used in the synthesis of deoxybenzoins (13) and (14) by appropriate Friedel–Crafts reactions. Grignard reactions with the deoxybenzoins led to intermediate tertiary alcohols, which were dehydrated to the corresponding stilbenes [*e.g.* (25), (34), and (38)]. The geometrical isomers of the stilbenes (21), (25), (34), and (38) were separated by chromatography and characterised.

The hexamethylstilbene (48), which represents the most sterically hindered (2-, 6-, α-)methyl-substituted stilbene, was synthesised from acetophenone (41) by intermolecular deoxygenation with the reagent from titanium trichloride and lithium aluminium hydride.

BIOLOGICAL interest in derivatives of (*E*)-stilbene stems from the work of Dodds and his co-workers, who observed that (*E*)-stilboestrol (1) exhibited the same hormonal activity as the natural female sex hormone 17β-oestradiol.[1] This observation initiated a burst of activity in stilbene chemistry, and several stilboestrol-type molecules were subsequently synthesised and found to display modified steroidal hormone-type activity.[2] Indeed a number of these molecules, *e.g.* (2) and (3), have found clinical application for the treatment of various conditions such as primary amenorrhoea, functional uterine bleeding, and the menopausal syndrome, and in the palliative treatment of carcinoma of the prostate and the breast.[3] Recent research has shown that several stilbenes exhibit antifertility activity (*i.e.* are anti-oestrogens),[4] and others, *e.g.* (4), lower serum cholesterol levels in the human male.[5] Some closely related structures, *e.g.* (5), also act as effective antifertility agents,[6] and paradoxically (6) is used clinically as a fertility agent.[7]

A number of attempts have been made to correlate molecular structure with oestrogenic activity amongst stilbene molecules (for extensive discussion see ref. 2). With regard to the ' geometrical requirements ' for the molecules at receptor binding sites, (α-)substitution of the ethylenic system in the stilbene structure is a prerequisite for maximum activity. α-Alkyl substituents [*cf.* stilboestrol (1)] introduce steric effects which twist the phenyl rings out of plane, leading to a molecule with overall molecular ' thickness '. Features of the concept of molecular ' thickness ' and its bearing on structure–activity relations amongst stilbene molecules have been



examined previously.[8,9] One conclusion emanating from these studies was that only those stilbenes which have both α- and α'-positions substituted display high biological (oestrogenic) activity. It was one of our con-

[1] E. C. Dodds, L. Golberg, W. Lawson, and R. Robinson, *Nature*, 1938, **141**, 247.

[2] For reviews see (*a*) U. V. Solmssen, *Chem. Rev.*, 1945, **37**, 481; (*b*) J. Grundy, *ibid.*, 1957, **57**, 281; (*c*) J. A. Hoggard, and J. Korman, ' Medicinal Chemistry,' vol. 2, Wiley, New York, 1956; (*d*) D. Lednicer in ' Contraception: The Chemical Control of Fertility,' ed. D. Lednicer, Dekker, New York, 1969.

[3] See ref. 2*d* and (*a*) C. Huggins and C. V. Hodges, *Cancer Res.*, 1941, **1**, 293; (*b*) *British Med. J.*, 1969, **3**, 285.

[4] See (*a*) D. J. Collins and J. J. Hobbs, *Austral. J. Chem.*, 1967, **20**, 1413; (*b*) E. R. Clark and A. M. McCracken, *J. Pharm. Pharmacol.*, 1971, **23**, 339.

[5] See (*a*) M. M. Gertler, P. B. Hudson, and H. Jost, *Geriatrics*, 1953, **8**, 500; (*b*) E. M. Russ, H. A. Eder, and D. P. Barr, *Amer. J. Med.*, 1951, **11**, 468; (*c*) M. L. Eilert, *Amer. Heart J.*, 1949, **38**, 472.

[6] (*a*) L. J. Lerner, F. J. Holthaus, and C. R. Thompson, *Endocrinology*, 1958, **63**, 295; (*b*) S. J. Segal and W. O. Nelson, *Proc. Soc. Exp. Biol. Med.*, 1958, **98**, 431.

[7] *Cf.* D. W. Cudmore and W. R. C. Tupper, *Fertility Sterility*, 1966, **17**, 363.

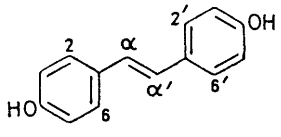
[8] M. Oki, *Bull. Chem. Soc. Japan*, 1952, **25**, 112; M. Oki and Y. Urushibara, *ibid.*, 1952, **25**, 109.

[9] W. H. Laarhoven, R. J. F. Nivard, and E. Havinga, *Experientia*, 1961, **17**, 214.

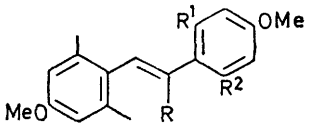
tentions that by suitable (2-, 6-, or α-)substitution of the 4,4′-dihydroxystilbene molecule (7) an appropriate geometrical configuration could be devised for maximum activity in molecules possessing only *one* α-alkyl substituent. In an examination of this proposal, this paper describes our studies of the development of synthetic routes to members of the stilbene series (8).

Although several synthetic routes to stilbenes,[10] and particularly to stilboestrol analogues,[11] have been described, the synthesis of molecules of the type (8) posed special problems because of the severe steric crowding of (2-, 6-, and α-) substituents. Routes subject to minimal steric limitations were required. In one approach we chose to employ deoxybenzoins [*e.g.* (14)] as key intermediates, and in a second we examined the use of benzylic phosphonium ylide intermediates. Both types of intermediate were synthesised from 3,5-dimethylphenol.

Bromination of 3,5-dimethylphenol with bromine in acetic acid at low temperatures led first to the bromophenol (9a), which was then methylated with dimethyl sulphate leading to the methyl ether (9b).[12] Reaction of (9b) with magnesium in the presence of ethyl bromide (' entrainment ' method [13]) followed by carboxylation of



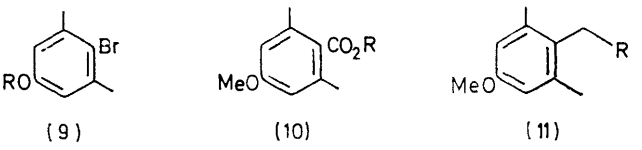
(7)



(8) R = alkyl; R^1, R^2 = H or alkyl.

the resulting Grignard reagent produced the benzoic acid (10a). Reduction of (10a) with lithium aluminium hydride gave the carbinol (11c) in only *ca.* 40% conversion, whereas reduction of the corresponding ester (10b) led to (11c) in *ca.* 90% overall yield from (10a). Esterification of the sterically hindered benzoic acid (10a) was best accomplished with dimethyl sulphate,[14] a method apparently not subject to steric limitations (*cf.* ref. 15).

Reaction of (11c) with dry hydrogen bromide gave the benzyl bromide (11d), which on reaction with triphenylphosphine or triethyl phosphite led to the phosphonium salt (11e) or the phosphonate (11f), respectively. The deoxybenzoins (13) and (14) were synthesised *via* the acid chloride (12). Treatment of bromide (11d) with sodium cyanide in dimethyl sulphoxide led first to the nitrile (11g), which on hydrolysis with sodium hydroxide in hot

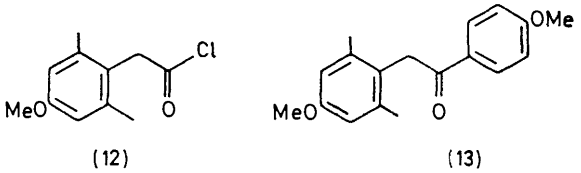


(9) (10) (11)

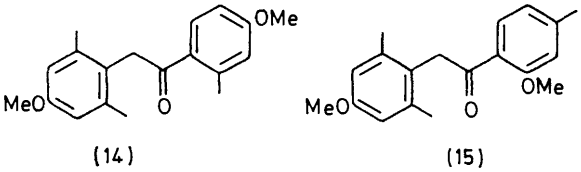
a; R = H b; R = Me c; R = OH d; R = Br e; R = $\overset{+}{P}Ph_3\bar{B}r$
f; R = PO(OEt)$_2$ g; R = CN h; R = CO_2H

aqueous ethylene glycol gave the phenylacetic acid (11h). The phenylacetic acid was converted cleanly into the acid chloride (12) with phosphorus pentachloride, and this in a Friedel–Crafts reaction with *p*-anisaldehyde, with tin(IV) chloride as Lewis acid, led to the *para*-oriented deoxybenzoin (13) exclusively. In a similar Friedel–Crafts reaction, the acid chloride (12) and 3-methylanisole produced a mixture of the trimethyldeoxybenzoins (14) and (15), which were separated by fractional crystallisation. During attempts to produce the isomeric deoxybenzoin (17) by a Friedel–Crafts reaction between 3,5-dimethylanisole and *p*-methoxyphenylacetyl chloride, only the *ortho*-oriented isomer (16) was obtained under several conditions.[16] The orientation of (16) followed from inspection of spectral data and comparison with those obtained for (13), and from comparison of the stilbene product (18), obtained from (16) by reduction and dehydration, with an authentic sample of the stilbene (21).

We next turned to the application of the deoxybenzoins (13) and (14) and the organophosphorus compounds (11e and f) in the synthesis of stilbenes (8). First we examined the synthesis of the least sterically hindered



(12) (13)



(14) (15)

member (21). Condensation between *p*-anisaldehyde and the ylide produced from the salt (11e) with methylsulphinylmethanide ion led (75%) to a 15 : 85 mixture of

[10] *E.g.* (*a*) D. A. Ballard and W. M. Dehn, *J. Amer. Chem. Soc.*, 1932, **54**, 3969; (*b*) E. C. Dodds, L. Golberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc.*, 1939, *A*, **127**, 140; (*c*) H. Meerwein, E. Buchner, and K. Van Emster, *J. prakt. Chem.*, 1939, **152**, 237; (*d*) A. L. Wilds and W. R. Biggerstaff, *J. Amer. Chem. Soc.*, 1945, **67**, 789; (*e*) R. E. Buckles and N. G. Wheeler, *Org. Synth.*, 1953, **33**, 88; (*f*) O. H. Wheeler and H. N. Pattle de Pabon, *J. Org. Chem.*, 1965, **30**, 1473.

[11] *E.g.* (*a*) ref. 2*b*; (*b*) F. V. Wessely, E. Kerschbaum, A. Kleedorfer, F. Prillinger, and E. Zajic, *Monatsh.*, 1940, **73**, 127; (*c*) R. L. Huang, *J. Chem. Soc.*, 1954, 2539; (*d*) S. H. Zaheer, B. Singh, B. Bhushan, P. M. Bhargava, I. K. Kacker, K. Ramachandran, V. D. N. Sastri, and N. S. Rao, *ibid.*, 1954, 3360; (*d*) W. H. Laarhoven, R. J. F. Nivard, and E. Havinga, *Rec. Trav. chim.*, 1961, **80**, 775.

[12] R. C. Fuson, J. Corse, and P. B. Welldon, *J. Amer. Chem. Soc.*, 1941, **63**, 2645.

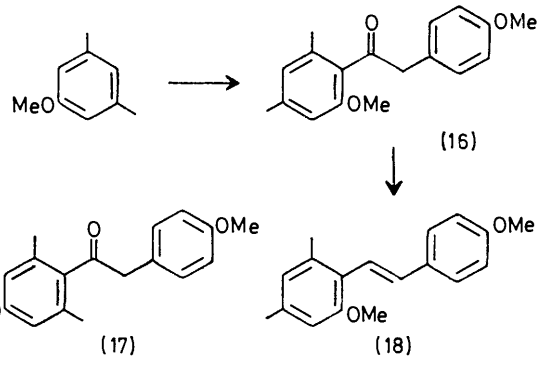
[13] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' vol. 1, Wiley, New York, 1967, p. 417.

[14] J. Grundy, B. G. James, and G. Pattenden, *Tetrahedron Letters*, 1972, 757.

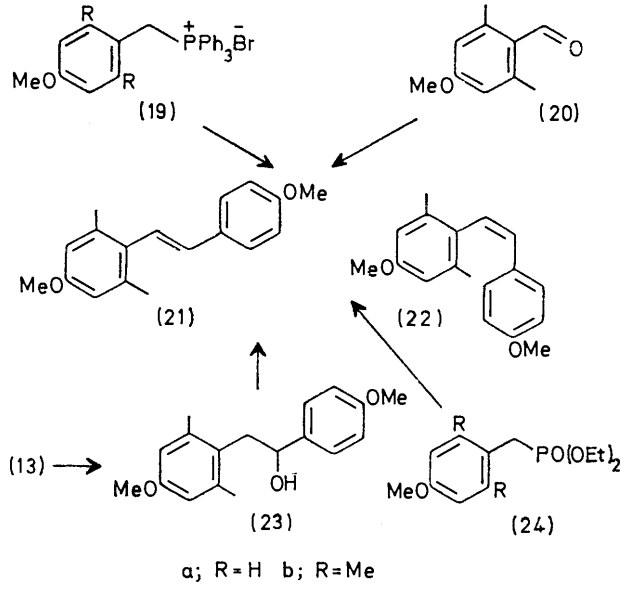
[15] See ' Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, p. 213.

[16] *Cf.* E. von Auwers and E. Borsche, *Ber.*, 1915, **48**, 1698.

Z- and *E*-isomers of the required stilbene (21). The *E*-isomer, a solid, m.p. 82°, was easily separated by



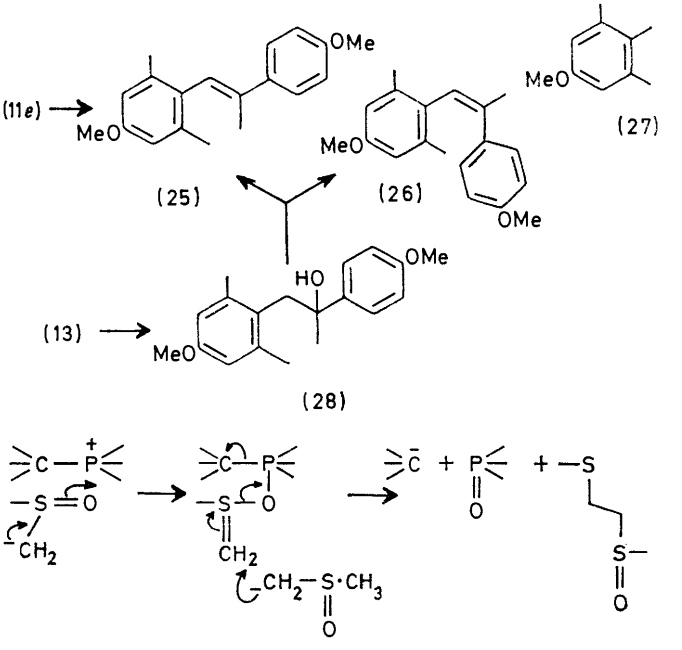
crystallisation, whereas the oily *Z*-isomer (22) was purified by g.l.c. The configurations assigned to the isomers followed largely from comparison of spectral data (see Experimental), and also from the observation that iodine-catalysed isomerisation of the *Z*-isomer produced quantitatively the *E*-isomer. Proton absorptions in the n.m.r. spectrum of the *Z*-isomer (22) were at higher τ values than corresponding absorptions in that of the *E*-isomer, reflecting mutual shielding of hydrogen atoms in the *Z*-isomer as a result of noncoplanarity of the phenyl rings. A similar proportion of *Z*- and *E*-isomers [(22) and (21)] was obtained when the ylide from the salt (19a) was treated with the hindered aldehyde (20). The aldehyde (20) was easily available from 3,5-dimethylphenol by use of the Gatterman–Adams procedure [17] followed by methylation, or alternatively from (11c) by



a; R = H b; R = Me

oxidation with manganese dioxide. Reactions between the anions from the phosphonates (24a and b) and the respective aldehydes were considerably more stereoselective than approaches *via* the ylides, and these reactions led almost entirely (>98%) to the *E*-stilbene. A less practical route to (21) was *via* the deoxybenzoin (13). Reduction of (13) with lithium aluminium hydride gave the carbinol (23), which on acid-catalysed dehydration with accompanying isomerisation led to (21) in relatively low overall yield.

Surprisingly, condensation between the ylide from (11e) and 4′-methoxyacetophenone under conditions similar to those described above gave an 85 : 15 mixture of (25) and (26) in only *ca.* 2% yield. The major product isolated was 3,4,5-trimethylanisole (27) (50%), the product of hydrolysis of the C–P bond in the salt (11e).



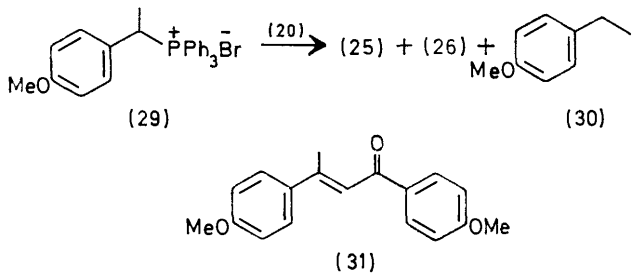
SCHEME

Several base–solvent systems and reaction conditions were investigated to optimise the yields of (25) from (11e), but at best, with sodium hydride in bis-(2-methoxyethyl) ether as medium and heating the ylide from (11e) with a 4 molar excess of 4′-methoxyacetophenone at 70 °C for 3 h, stilbene yields of ⩾30% were realised. It appears that in the synthesis of (25) from (11e), unprecedented steric or (less likely) electronic considerations preclude rapid olefin formation, and instead competitive salt hydrolysis predominates. Cleavage of the C–P bond in phosphonium salts in basic media is well known; [18] we envisage the hydrolysis of the C–P bond in (11e) in the methylsulphinylmethanide ion medium as shown in the Scheme. The most convenient route to (25) was found to be that from the deoxybenzoin (13). Reaction of (13) with methylmagnesium iodide led first to the tertiary alcohol (28), which on dehydration with glacial acetic acid containing iodine produced a crystalline mixture of *Z*- and *E*-isomers [(26) and (25),

[17] A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1862.

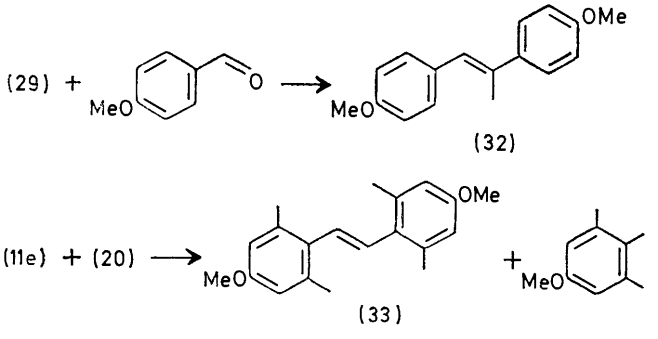
[18] J. R. Corfield, N. J. De'ath, and S. Trippett, *J. Chem. Soc.*, (*C*), 1971, 1930.

respectively], which were separated by fractional crystallisation. Iodine-catalysed isomerisation of the *Z*-isomer (26) gave further quantities of the *E*-isomer (25).

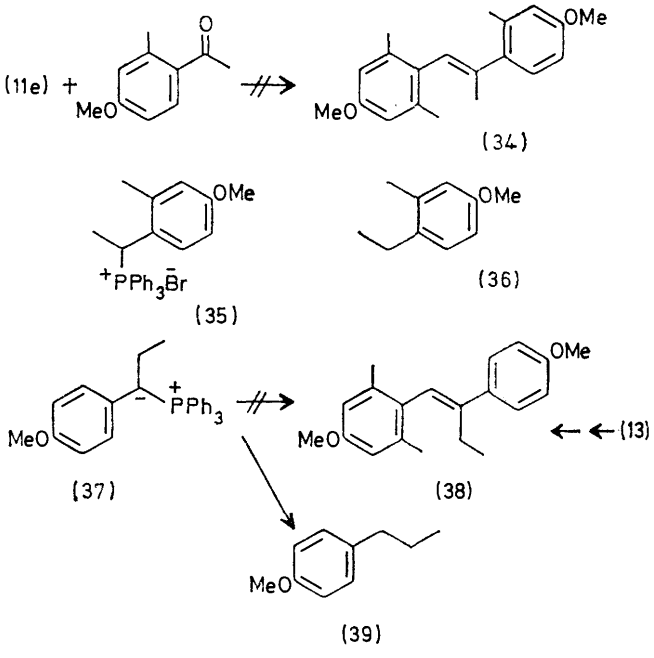


In another route to (25), the secondary phosphonium salt (29) was used. Reduction of 4′-methoxyacetophenone with lithium aluminium hydride led to the corresponding secondary alcohol, which on sequential reaction with hydrogen bromide and triphenylphosphine gave the salt (29). Condensation between (29) and the aldehyde (20), with methylsulphinylmethanide ion as base, produced a 45 : 55 mixture of (25) and (26) in *ca.* 20% yield, accompanied by 4-ethylanisole (30), the product of hydrolysis of (29). Attempts to prepare (25) from 4-methoxyacetophenone and the phosphonate ester (11f) were unsuccessful; instead only the chalcone (31) was isolated.

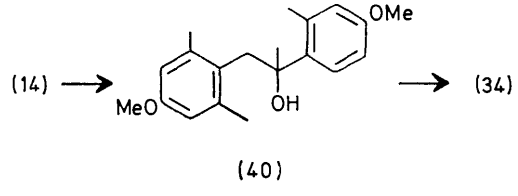
The low yields of stilbene products obtained from condensations involving the salt (11e) with *p*-methoxyacetophenone and the salt (29) with the aldehyde (20) were unexpected, and possibly reflect unprecedented steric limitations to the Wittig olefin synthesis within this series of stilbenes. In parallel studies, condensation between the salt (29) and *p*-anisaldehyde, under similar conditions, gave the stilbene (32) in 70% yield, and only *ca.* 7% of hydrolysis product (30). Similarly, whereas condensation between the salt (11e) and *p*-anisaldehyde led to the stilbene [(21)/(22)] as sole product in *ca.* 80% yield, reaction between (11e) and the hindered aldehyde (20) gave the stilbene (33) in only 28% yield, accompanied by (27) (30%). These limitations to the Wittig synthesis of hindered stilbenes were further reflected in attempts to prepare (34) and (38) *via* benzylic phosphonium ylide intermediates.



Condensations between the salt (11e) and 4′-methoxy-2′-methylacetophenone and between the salt (35) and the aldehyde (20), under the usual conditions (Me_2SO–$MeSO{\cdot}CH_2^-$; 25 °C) did not produce any of the stilbene product (34). In both instances only the products [(27) and (36), respectively] resulting from hydrolysis of the respective phosphonium salts were isolated. Similarly, attempts to synthesise the α-ethylstilbene (38) from the salts (11e) and (37) and the respective carbonyl compounds met with failure; once again only the hydrolysis products (27) and (39) were obtained. Even under the



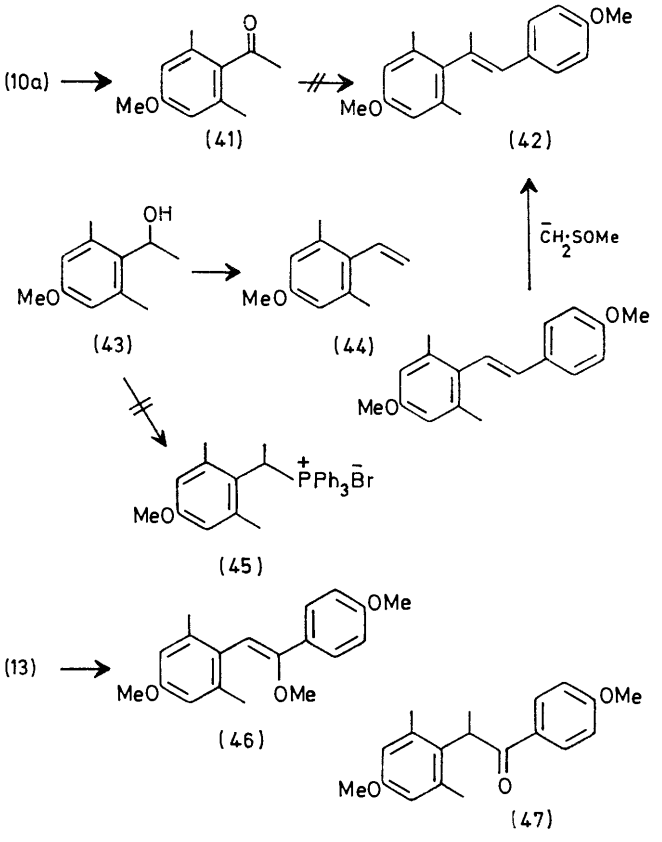
more forcing conditions [bis-(2-methoxyethyl) ether at 70 °C] found useful in enhancing the yield of (25) from



(11e), only *ca.* 5% yields of (34) and (38) from (11e) were realised. The most practical route to both (34) and (38) was that *via* the corresponding deoxybenzoins (14) and (13), respectively. Treatment of (14) with methylmagnesium iodide led to the tertiary alcohol (40), which on dehydration in acetic acid–phosphoric acid gave a 7 : 3 mixture of *E*- and *Z*-isomers of (34). The isomers were separated by fractional crystallisation, and their configurations followed from comparative spectral data (see Experimental section). In a similar Grignard reaction–dehydration sequence, the deoxybenzoin (13) was converted into the stilbene (38).

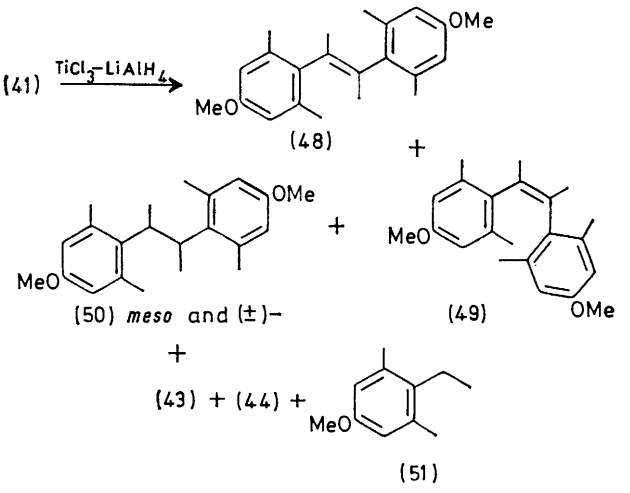
We next turned to the synthesis of the stilbene (42). Acetophenone (41) was first prepared from (10a) *via* the reaction of the corresponding acid chloride with dimethylcadmium reagent.[11d] All attempts to bring about

the reaction of the ketone with the Wittig reagent (19a) (and the tri-n-butyl analogue) and the phosphonate ester (24a), however, were unsuccessful; the starting ketone was recovered in either case. Similarly, attempts to prepare the secondary salt (45) from the ketone (41) were unsuccessful. Although reduction of (41) with lithium aluminium hydride led to the alcohol (43), treatment of the latter with dry hydrogen bromide gave only the styrene (44). Methylation of the anion produced from the deoxybenzoin (13) resulted in the methyl vinyl ether (46); none of the required ketone (47) [for elaboration to (42)] was detected. Ultimately (42) was synthesised

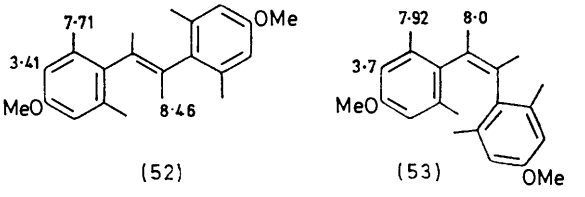


from (21) by methylation with methylsulphinylmethanide.[19]

The hexamethylstilbene (48) represents the most sterically hindered (2-, 6-, α-)methyl-substituted stilbene; its synthesis was therefore of considerable interest. From the studies above, routes based on either deoxybenzoin or benzylic phosphonium ylide intermediates were clearly not applicable. Accordingly, we examined intermolecular deoxygenation of the acetophenone (41) by the procedure delineated by McMurry and his co-workers,[20] using lower-valent titanium species. Heating a solution of acetophenone (41) (1 equiv.) in tetrahydrofuran with the reagent produced from addition of 1 equiv. of lithium aluminium hydride to 1 equiv. of titanium trichloride led to a complex mixture of products, from which the stilbene (48) could be separated in *ca.* 10% yield. The stilbene (48) was accompanied by the corresponding *Z*-stilbene (49), and also by racemic and *meso*-diphenylethanes (50), the styrene (44), the carbinol (43), and the ethylbenzene (51). The stilbenes (48) and



(49) and the diphenylethanes (50) were all crystalline, and were separated from each other by a combination of fractional crystallisation and preparative layer chromatography. ^{1}H N.m.r. data for the two stilbene isomers are summarised on formula (52) and (53). The aryl methyl protons and the aryl protons in the *Z*-isomer (49) resonate at higher field than the corresponding protons in the *E*-isomer; this is found for all the *ZE*-isomeric pairs [(21) and (22), (25) and (26), (34), and (38)] synthesised in the present study (see Experimental section). These data suggest that the *Z*-isomers adopt conformations in which the phenyl rings are face to face and the protons are shielded by the adjacent phenyl rings. The α-methyl substituents similarly show different chemical shifts ($\Delta\tau$ *ca.* 0.45) within the *ZE*-isomeric pairs (48) and (49), (25) and (26), and (34) and its isomer, which again reflect differential shielding by the neighbouring phenyl rings. The τ values of the α′-methyl groups in the *E*-stilbenes (25), (34), and (48) increase as the number of *ortho*(2′ or 6′)-methyl substituents increases [*viz.* τ 8.2 (25), 8.29 (34), and 8.46 (48)]. These data again reflect the differential shielding by adjacent phenyl rings, and provide a measure of the degree of ' twist ' about the substituted



2,6-dimethylphenyl rings and the olefinic units within these molecules.

In biological tests, the stilbenes (34) and (38) exhibited ' oestrogenic activity ' closely similar to that of 4,4′-di-

[19] B. G. James and G. Pattenden, *J.C.S. Perkin I*, 1974, 1195.
[20] J. E. McMurry, *Accounts Chem. Res.*, 1974, **7**, 281.

methoxy-α,α′-dimethylstilbene, which was *ca.* 5% as active as stilboestrol dimethyl ether.

EXPERIMENTAL

For general experimental details see ref. 19.

4-Methoxy-2,6-dimethylbenzoic Acid (10a).—A solution of 4-bromo-3,5-dimethylanisole (150 g, 0.7 mol) and ethyl bromide (153 g, 1.4 mol) in ether (420 ml) was added, during 2.5 h, to magnesium (51 g) at such a rate as to maintain a gentle reflux. The mixture was boiled for 1 h, then cooled and poured on to powdered solid carbon dioxide. The mixture was left for 12 h, and was then treated with ice–dilute hydrochloric acid, and extracted with ether (4 × 500 ml). The combined extracts were washed with sodium carbonate solution, and the aqueous phase was filtered into 30% sulphuric acid. The precipitate was collected, washed, dried, and crystallised from aqueous ethanol to give the acid (117 g, 93%), m.p. 147° (lit.,[12] 144°), $\lambda_{max.}$ (EtOH) 248 nm (4 500), $\nu_{max.}$ (Nujol) 1 680, 1 603, 1 575, 853, and 835 cm^{-1}, τ 3.35 (2 H), 6.28 (OMe), and 7.56 (2 × :CMe) (Found: C, 66.6; H, 6.6. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.7%).

Methyl 4-Methoxy-2,6-dimethylbenzoate (10b).—The ester was prepared (97%) from 4-methoxy-2,6-dimethylbenzoic acid with dimethyl sulphate and anhydrous potassium carbonate in hot acetone; [14] it showed b.p. 98—100° at 0.1 mmHg; m.p. 54—55° (lit.,[21] 56.5°), $\lambda_{max.}$ (EtOH) 250 (6 000) and 282 nm (1 000), $\nu_{max.}$ (Nujol) 1 730, 1 600, 1 490, 1 350, 1 270, 890, 850, and 820 cm^{-1}, τ 3.45 (2 H), 6.13 (OCH_3), 6.25 (OCH_3), and 7.74 (2 × :CMe), *m/e* 194.

4-Methoxy-2,6-dimethylbenzyl Alcohol (11c).—A solution of methyl 4-methoxy-2,6-dimethylbenzoate (48.5 g) in ether (200 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (10 g), in ether, at such a rate that a gentle reflux was maintained. The mixture was heated for 2.5 h, and then cooled in ice, and the excess of lithium aluminium hydride was destroyed by careful addition of water. The mixture was treated with dilute hydrochloric acid, and the ether layer was then separated, washed with water and sodium carbonate solution, and evaporated to leave the alcohol (39 g, 94%) as a solid, m.p. 71° (lit.,[22] 71°); $\nu_{max.}$ (Nujol) 3 300 and 1 295 cm^{-1}; τ 3.45 (2 H), 5.46 (2 H), 6.24 (OCH_3), 7.63 (2 × :C·CH_3), and 7.98 (OH); *m/e* 166. The alcohol eliminated water on attempted distillation to produce the corresponding *ether*, m.p. 70—71°, $\lambda_{max.}$ (EtOH) 283 (1 070) and 274 nm (1 040); $\nu_{max.}$ (Nujol) 1 602, 1 585, 1 146, 846, and 830 cm^{-1}; τ 3.3 (4 H), 5.46 (2 × CH_2O), 6.24 (2 × OCH_3), and 7.63 (4 × :C·CH_3) (Found: C, 76.5; H, 8.4. $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.3%).

(4-Methoxy-2,6-dimethylbenzyl)triphenylphosphonium Bromide (11e).—Dry hydrogen bromide gas was passed into a cooled (0—2 °C) solution of 4-methoxy-2,6-dimethylbenzyl alcohol [17] (7 g) in benzene (100 ml) until the solution was saturated (*ca.* 0.75 h). The aqueous layer was separated and the benzene solution was then evaporated *in vacuo*. More dry benzene was added, and the solution was once more evaporated to leave the bromide as a pale yellow oil.

A solution of the bromide and triphenylphosphine (12.8 g) in benzene (100 ml) was boiled under reflux for 2 h. The solid which separated was filtered off, and then washed thoroughly with dry ether. Crystallisation from methylene chloride–ethyl acetate gave the *salt* (17.6 g, 83%), m.p. 212—214°, $\nu_{max.}$ (Nujol) 1 605, 1 585, 750, 740, 720, and 690 cm^{-1}, τ 2.1—2.6 (15 H), 3.52 (2 H), 4.97 (d, *J* 13 Hz, CH_2P^+), 6.25 (OCH_3), and 8.19 (2 × :C·CH_3) (Found: C, 68.3; H, 6.2. $C_{28}H_{28}BrOP$ requires C, 68.4; H, 5.7%).

Diethyl 4-Methoxy-2,6-dimethylbenzylphosphonate (11f).—Triethyl phosphite (30 g) was added to 4-methoxy-2,6-dimethylbenzyl bromide [from 4-methoxy-2,6-dimethylbenzyl alcohol (33.2 g)] and the mixture was then gently warmed on a steam-bath to produce a homogeneous solution. The mixture was added dropwise to triethyl phosphite (15 g) at 120 °C (oil-bath) over 0.3 h, and the temperature was then maintained at 120—140 °C for 2.5 h. After cooling, the solution was distilled to give the *phosphonate* (52.6 g, 92%) as an oil, b.p. 184—187° at 0.4 mmHg, n_D^{23} 1.5103, $\lambda_{max.}$ (EtOH) 230 (12 280), 275 (1 430), and 283 nm (1 500), $\nu_{max.}$ (film) 1 610, 1 590, 1 490, 1 250, 1 150, 1 055, 1 029, 965, 840, and 810 cm^{-1}; τ 3.52 (2 H), 6.23 q (*J* 7 Hz, 2 × CH_2·CH_3), 6.38 (OCH_3), 7.1 (d, *J* 22 Hz, CH_2·PO), 7.7 (2 × :C·CH_3), and 8.88 (t, *J* 7 Hz, 2 × CH_2·CH_3), *m/e* 286 (a satisfactory elemental analysis was not obtained).

4-Methoxy-2,6-dimethylphenylacetonitrile (11g).—A solution of 4-methoxy-2,6-dimethylbenzyl bromide [from 4-methoxy-2,6-dimethylbenzyl alcohol (25 g)] in dry dimethyl sulphoxide (55 ml) was added, during 1 h, to a stirred slurry of sodium cyanide (12 g) in dimethyl sulphoxide (55 ml) at such a rate that the temperature did not exceed 48 °C. The mixture was kept at 45—50 °C for 0.25 h, then at 25 °C for a further 0.5 h, and was then poured into water (200 ml). The precipitate was extracted into ether, and the extracts were then washed with concentrated hydrochloric acid and water, dried, and evaporated. Distillation of the residue gave the *nitrile* (20 g, 80%), b.p. 120—125° at 1.5 mmHg, as a solid, m.p. 65—66°, $\lambda_{max.}$ (EtOH) 274 (1 130) and 282 nm (1 160); $\nu_{max.}$ (Nujol) 2 243, 1 603, 1 585, 878, and 845 cm^{-1}; τ 3.34 (2 H), 6.22 (OMe), 6.41 (CH_2), and 7.62 (2 × CMe) (Found: C, 74.9; H, 7.7; N, 7.5%; *m/e* 175. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%; *M*, 175).

4-Methoxy-2,6-dimethylphenylacetic Acid (11 h).—A solution of 4-methoxy-2,6-dimethylphenylacetonitrile (33 g) and potassium hydroxide (75 g) in ethylene glycol (375 ml) and water (15 ml) was boiled under reflux for 30 h, then cooled and poured into water (200 ml). The solution was acidified with 50% sulphuric acid and then extracted with ether. The extracts were washed with sodium carbonate solution and the aqueous phase was separated and acidified with sulphuric acid. The precipitate was collected, then dried and crystallised from benzene to give the acid (35 g, 95%) as needles, m.p. 149—149.5° (lit.,[23] 138—139°); $\lambda_{max.}$ (EtOH) 276 (1 040) and 283.5 nm (1 100); $\nu_{max.}$ (Nujol) 3 440, 1 700, 1 603, 1 582, 955, 856, and 833 cm^{-1}; τ 1.76 (OH), 3.33 (2 H), 6.22 (OCH_3), 6.33 (CH_2), and 7.69 (2 × :C·CH_3) (Found: C, 68.1; H, 7.1%; *m/e*, 194. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3%; *M*, 194).

4,4′-Dimethoxy-2,6-dimethyldeoxybenzoin (13).—A solution of 4-methoxy-2,6-dimethylphenylacetic acid (9.7 g) in dry toluene (50 ml) and ether (50 ml) was treated in portions with phosphorus pentachloride (10.4 g) over 0.5 h. The solvents were then removed *in vacuo* to leave the acid chloride as a liquid, which was used immediately in the next stage.

Freshly distilled tin(IV) chloride (11.3 ml) in 1,2-dichloroethane (15 ml) was added, during 0.25 h, to a cooled

[21] M. L. Bender and M. C. Chen, *J. Amer. Chem. Soc.*, 1963, **85**, 37.

[22] A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 1949, 624.

[23] O. Dann, J. Lang, and H. Vohl, *Annalen*, 1960, **631**, 116.

(0—2 °C), stirred solution of the acid chloride and anisole (10.8 g) in dichloroethane (15 ml). The mixture was stirred for 0.5 h, then kept at 25 °C for 12 h, and poured on to ice–hydrochloric acid. The organic phase was separated and then washed with sodium carbonate solution and water. Evaporation, and crystallisation of the residue from glacial acetic acid gave the *ketone* (8.7 g, 62%) as needles, m.p. 152—153°; $\lambda_{max.}$ (EtOH) 273 nm (20 800); $\nu_{max.}$ (Nujol) 1 676, 1 598, 1 580, 1 570, 858, and 830 cm^{-1}; τ 1.88 (2 H, d, *J* 9 Hz), 2.99 (2 H, d, *J* 9 Hz), 3.3 (2 H), 5.72 (CH_2), 6.1 (OCH_3), 6.2 (OCH_3), and 7.8 (2 × :C·CH_3) (Found: C, 76.4; H, 7.1%; *m/e* 284. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%; *M*, 284).

4,4′-*Dimethoxy*-2,2′,6-*trimethyldeoxybenzoin* (14).—A mixture of isomeric deoxybenzoins was prepared from 4-methoxy-2,6-dimethylphenylacetic acid (9.7 g), *via* the acid chloride, and *m*-methoxytoluene (6.1 g), as described for (13). Fractional crystallisation from ether gave (i) 4,4′-*dimethoxy*-2,2′,6-*trimethyldeoxybenzoin* (4.9 g, 33%), as plates m.p. 105° (from ethanol), $\lambda_{max.}$ (EtOH) 270 nm (17 800); $\nu_{max.}$ (Nujol) 1 675, 1 610, 1 595, 1 570, 1 490, 1 000, 885, 842, and 815 cm^{-1}; τ 2.0 (1 H, d, *J* 9 Hz), 2.26 (1 H, d, *J* 9 Hz), 3.33 (3 H), 5.78 (CH_2), 6.15 (OCH_3), 6.22 (OCH_3), 7.48 (3 H), and 7.8 (6 H) (Found: C, 76.6; H, 7.05%; *m/e*, 298. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%; *M*, 298); and (ii) 2′,4-*dimethoxy*-2,6,4′-*trimethyldeoxybenzoin* (15) (2.9 g, 20%), m.p. 74—75°, $\lambda_{max.}$ (EtOH) 259 nm; $\nu_{max.}$ (Nujol) 1 665, 1 603, 1 565, 1 490, 1 250, 1 065, 855, and 810 cm^{-1}; τ 2.4 (d, *J* 9 Hz, 1 × aryl :CH), 3.12—3.22 (2 H, m), 3.4 (2 H), 5.72 (CH_2), 6.1 (OCH_3), 6.25 (OCH_3), 7.64 (:C·CH_3), and 7.82 (2 × :C·CH_3); *m/e* 298.

2,4′-*Dimethoxy*-4,6-*dimethyldeoxybenzoin* (16).—The deoxybenzoin was prepared (50%) from *p*-methoxyphenylacetic acid (8.3 g), *via* the acid chloride, and 3,5-xylenol methyl ether (7.2 g), as described for (13). It was purified by chromatography (silica gel; chloroform) and crystallised from methanol as *needles*, m.p. 69°, $\lambda_{max.}$ (EtOH) 283.5 (4 200), 277 (4 400), and 258sh nm (4 820); $\nu_{max.}$ (Nujol) 1 680 cm^{-1}, τ 2.83 (2 H, d, *J* 9 Hz), 3.16 (2 H, d, *J* 9 Hz), 3.41 (2 H), 6.0 (CH_2), 6.18 and 6.23 (2 × OCH_3), 7.7 (aryl 4-CH_3), and 8.0 (aryl 6-CH_3) (Found: C, 76.2; H, 7.2. $C_{18}H_{20}O_3$ requires C, 76.0; H, 7.1%).

(E)-2,4′-*Dimethoxy*-4,6-*dimethylstilbene* (18).—A solution of 2,4′-dimethoxy-4,6-dimethyldeoxybenzoin (2.9 g) in ether (20 ml) was added to a stirred suspension of lithium aluminium hydride (0.18 g) in ether (30 ml) at such a rate that a gentle reflux was maintained. The mixture was boiled for a further 1.5 h, then cooled in ice–water, and the excess of lithium aluminium hydride was destroyed by dropwise addition of water. 2N-Hydrochloric acid was added until two clear phases were produced, and the ether phase was then separated, washed (H_2O), and dried. Evaporation gave the intermediate secondary alcohol as an oil, $\nu_{max.}$ (film) 3 500 cm^{-1}, τ 2.8—3.4 (6 H, m), 5.1 (t, *J* 8 Hz, C*H*·CH_2), 6.2 and 6.3 (2 × OCH_3), 7.0 (d, *J* 8 Hz, CH·C*H*$_2$), 7.7 (aryl 4-CH_3), 7.7 (OH, D_2O exchanged), and 8.05 (aryl 6-CH_3), which was dehydrated without further purification.

A solution of the carbinol in butyric acid (10 ml) containing two drops of phosphoric acid was boiled under reflux for 1 h, then poured into water and extracted with ether (3 × 10 ml). Evaporation of the dried extracts followed by chromatography (silica gel; chloroform) and crystallisation gave the (E)-*stilbene* (1.8 g, 70%), m.p. 81° (from ethanol), τ 2.54 (2 H, d, *J* 9 Hz), 2.9 (2 H), 3.15 (2 H, d, *J* 9 Hz), 3.4 and 3.5 (2 H), 6.2 and 6.25 (2 × OCH_3), 7.6 (:C·CH_3), and 7.7 (:C·CH_3) (Found: C, 80.4; H, 7.6. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%).

Preparation of Stilbenes from Benzyltriphenylphosphonium Salts; General Procedure.—The phosphonium salt (0.01 mol) was added to a stirred solution of methylsulphinylmethanide ion [24] [from dimethyl sulphoxide with sodium hydride (0.01 mol)] in dimethyl sulphoxide (30 ml) at 25 °C under nitrogen. The mixture was stirred at 25 °C for 0.25 h and then treated during 5 min with the carbonyl compound (0.009 mol). After stirring at 25 °C for 1 h, the mixture was poured on to ice–water (200 ml) and extracted with ether (3 × 150 ml). Evaporation of the dried extracts left a residue which was chromatographed on silica gel to give the stilbene. Isomerically homogeneous samples of the *Z*- and *E*-stilbenes were then obtained by fractional crystallisation and/or preparative g.l.c. chromatography. Proportions of isomers were determined from g.l.c. data (Apiezon L; 220 °C).

Z- and E-*Isomers of* 4,4′-*Dimethoxy*-2,6-*dimethylstilbene* [(22) *and* (21)].—(a) *From* (4-*methoxy*-2,6-*dimethylbenzyl*)-*triphenylphosphonium bromide* (11e). By the general procedure, the phosphonium salt with *p*-anisaldehyde produced (73%), after chromatography in benzene–ethyl acetate (97 : 3), an 85 : 15 mixture of *E*- and *Z*-isomers of the stilbene. Crystallisation from methanol gave the (E)-*stilbene*, m.p. 82°, $\lambda_{max.}$ 289 nm (22 800); $\nu_{max.}$ (Nujol) 1 610, 1 575, 1 510, 1 250, and 990 cm^{-1}; τ 2.59 (d, *J* 9 Hz, 2 × aryl :CH), 3.08 (d, *J* 17 Hz, α′-C:CH), 3.12 (d, *J* 9 Hz, 2 × aryl :CH), 3.38 (2 × aryl :CH), 3.54 (d, *J* 17 Hz, α-CH:C), 6.18 (OCH_3), 6.22 (OCH_3), and 7.67 (2 × aryl CH_3) (Found: C, 80.4; H, 7.6%; *m/e*, 268. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%; *M*, 268), and preparative g.l.c. (25% Apiezon L; 220 °C) of the mother liquors from the crystallisation gave the (Z)-*stilbene*, an oil, $\lambda_{max.}$ 271 nm (14 500), $\nu_{max.}$ (film) 2 825, 1 610, 1 580, 1 515, 1 255, and 720 cm^{-1}, τ 3.08 (d, *J* 9 Hz, 2 × aryl :CH), 3.38 (d, *J* 9 Hz, 2 × aryl :CH), 3.42 (2 × aryl :CH), 3.48 (d, *J* 12 Hz, α′-C:CH), 3.7 (d, *J* 12 Hz, α-HC:C), 6.25 (OCH_3), 6.32 (OCH_3), and 7.88 (2 × aryl CH_3) (Found: *m/e*, 268.1463. $C_{18}H_{20}O_2$ requires *M*, 268.1463).

(b) *From diethyl* (4-*methoxy*-2,6-*dimethylbenzyl*)*phosphonate* (11f). Solutions of the phosphonate (6.2 ml) in dimethylformamide (20 ml) and of *p*-anisaldehyde (2.2 g) in dimethylformamide (20 ml) were added simultaneously over 0.25 h to a stirred suspension of sodium hydride (0.6 g) in dimethylformamide (50 ml) under nitrogen, at 50 °C. The mixture was stirred at 70 °C for 1.5 h, then cooled to room temperature and diluted with water (200 ml). The stilbene (4.2 g, 77%) which precipitated was filtered off and then recrystallised from methanol to give the *E*-isomer, m.p. 81°, identical with that prepared by method (a). In another reaction the aqueous mixture was extracted with ether, to examine the *Z* : *E* ratio of stilbene formed in the condensation. Evaporation of the dried extracts, followed by g.l.c. analysis (Apiezon L; 220 °C) of the residue showed that the *Z*- and *E*-isomers were present in the ratio 1 : 49.

(c) *From diethyl* 4-*methoxybenzylphosphonate* (24a). The phosphonate[25] (3 g) and 4-methoxy-2,6-dimethylbenzaldehyde (1.9 g), treated in a similar manner to that described in (b), gave (70%) a 2 : 98 mixture of *Z*- and *E*-isomers of the stilbene.

(d) *From* (4-*methoxybenzyl*)*triphenylphosphonium bromide* (19a). By the general procedure, the phosphonium salt

[24] See T. Durst, *Adv. Org. Chem.*, 1969, **6**, 285.

[25] B. E. Ivanov and L. C. Valitova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1963, 1049.

with 4-methoxy-2,6-dimethylbenzaldehyde produced (84%) an 85 : 15 mixture of *E*- and *Z*-isomers of the stilbene.

(e) *From* 4,4′-*dimethoxy*-2,6-*dimethyldeoxybenzoin* (13). The deoxybenzoin (1 g) was added to a suspension of lithium aluminium hydride (0.2 g) in tetrahydrofuran (50 ml) and the mixture was boiled under reflux for 2 h, and then cooled. The excess of lithium aluminium hydride was destroyed by dropwise addition of water, and then dilute hydrochloric acid was added. The mixture was extracted with ether, and the extracts were dried and evaporated to leave the intermediate alcohol as an oil. The alcohol was dissolved in glacial acetic acid (20 ml) containing two drops of polyphosphoric acid, and the mixture was boiled under reflux for 1 h, and then poured onto water (100 ml) and extracted with ether (3 × 75 ml). Evaporation of the dried extracts gave a residue which was chromatographed (silica gel; benzene) to give a solid which was crystallised from methanol to give the *E*-stilbene (0.48 g, 50%), m.p. 80—82°, spectrally identical with that prepared by method (a).

1-(4-*Methoxyphenyl*)*ethyltriphenylphosphonium Bromide* (29).—Reduction of 4′-methoxyacetophenone with lithium aluminium hydride gave (85%) 1-(4-*methoxyphenyl*)*ethanol*, a liquid, b.p. 110—112° at 3.5 mmHg, n_D^{22} 1.5333; $\lambda_{max.}$ (EtOH) 255 (4 560), 275 (2 280), and 282 nm (1 976); $\nu_{max.}$ (film) 3 350 and 1 250 cm^{-1}; τ 2.92 (2 H, d, *J* 9 Hz), 3.33 (2 H, d, *J* 9 Hz), 5.4 (q, *J* 7 Hz, CH_3·C*H*), 6.18 (OH), 6.35 (OCH_3), and 8.68 (d, *J* 7 Hz, CH_3·CH) (Found: C, 71.0; H, 8.2%; *m/e*, 152. $C_9H_{12}O_2$ requires C, 71.0; H, 8.0%; *M*, 152).

A solution of the alcohol (15.2 g) in dry benzene (100 ml) was cooled (ice–water) and then saturated with dry hydrogen bromide gas (*ca.* 2 h). The aqueous layer was separated, and the benzene solution was then evaporated *in vacuo*. More dry benzene was added and the solution was once more evaporated to leave the bromide as an oil. A solution of the bromide in dry benzene (50 ml) was added dropwise over 0.3 h to a stirred solution of triphenylphosphine (30 g) in dry benzene. The solution was refluxed for 2 h, then cooled to room temperature, and the benzene was decanted from the clear glassy gum. Trituration of the gum with dry ether gave the *salt* (15.1 g, 32%), $\nu_{max.}$ (Nujol) 1 605, 1 590, 1 510, 1 255, 1 180, and 1 110 cm^{-1}; τ 2.0—2.5 (15 H, m), 2.8—3.4 (4 H, m), 5.75 (m, CH_3·C*H*), 6.3 (OCH_3), and 8.25 (dd, J_{PH} 19, J_{HH} 8 Hz, CH_3·CH), as a deliquescent, frothy solid, which was dried *in vacuo* and used without further purification.

(*E*)-4,4′-*Dimethoxy*-2,6,α′-*trimethylstilbene* (25).—(*a*) 4,4′-Dimethoxy-2,6-dimethyldeoxybenzoin (1.4 g) was added to a solution of methylmagnesium iodide [from magnesium (0.15 g) in ether (75 ml)]; the mixture was boiled for 2 h, then cooled, poured on to cold ammonium chloride solution and extracted with ether. Evaporation of the washed (H_2O) and dried extracts left the intermediate tertiary alcohol as an oil.

The alcohol was dissolved in glacial acetic acid (15 ml) containing a crystal of iodine and the mixture was boiled under reflux for 2 h, then diluted with water (75 ml), and extracted with ether. The ether phase was washed with sodium thiosulphate solution and water, then dried and evaporated. The residue was chromatographed (silica gel; benzene) and the stilbene fractions were evaporated and crystallised from ethanol to give the (E)-*stilbene* (0.45 g, 30%), m.p. 81—82°, $\lambda_{max.}$ (EtOH) 265 nm (17 700); $\nu_{max.}$ (Nujol) 1 605, 1 575, 1 515, 1 250, 850, and 825 cm^{-1}; τ 2.52 (d, *J* 9 Hz, 2 × aryl :CH), 3.1 (d, *J* 9 Hz, 2 × aryl :CH), 3.38 (C:C*H*), 3.38 (2 × aryl :CH), 6.2 (OCH_3), 6.23 (OCH_3), 7.82 (2 × aryl :C·CH_3), and 8.2 (CH_3·C:C–) (Found: C, 80.6; H, 7.7%; *m/e*, 282. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.8%; *M*, 282). The (*Z*)-stilbene (26), m.p. 69—71° (see following paper), was obtained by fractional crystallisation of the residues remaining after separation of the (*E*)-isomer.

(b) (*Z*)-4,4-Dimethoxy-2,6,α′-trimethylstilbene (1.3 g) [from above; and also from tributyl-(4-methoxy-2,6-dimethylbenzyl)phosphonium bromide; see accompanying paper] in glacial acetic acid (30 ml) containing iodine (0.12 g) was heated under reflux for 5 h, then cooled and washed with sodium thiosulphate solution. The mixture was then diluted with water (100 ml) and extracted with ether (3 × 75 ml). Evaporation of the dried extracts followed by chromatography and crystallisation gave the (*E*)-stilbene (0.7 g), m.p. 81—82°, identical with that prepared as in (*a*).

(*c*) *From* 1-(4-*methoxyphenyl*)*ethyltriphenylphosphonium bromide* (29). By the general procedure, the phosphonium salt with 4-methoxy-2,6-dimethylbenzaldehyde gave (20%) a 55 : 45 mixture of *E*- and *Z*-isomers of the stilbene. Fractional crystallisation from ethanol produced the *E*-stilbene, identical with that prepared in (*a*). 4-Ethylanisole (*ca.* 15%), n_D^{18} 1.5070, $\nu_{max.}$ (film) 2 830, 1 615, 1 585, and 1 515 cm^{-1}, τ 2.92 (2 H, d, *J* 9 Hz), 3.22 (2 H, d, *J* 9 Hz), 6.25 (OMe), 7.4 (q, *J* 7 Hz, CH_2·CH_3), and 8.82 (t, *J* 7, CH_2·CH_3), *m/e* 136.0888 ($C_9H_{12}O$), and triphenylphosphine (*ca.* 20%) were also isolated by chromatography.

(*d*) *From* (4-*methoxy*-2,6-*dimethylbenzyl*)*triphenylphosphonium bromide*. By the general procedure, the phosphonium salt with 4′-methoxyacetophenone gave (2%) an 85 : 15 mixture of *E*- and *Z*-isomers of the stilbene. 3,4,5-Trimethylanisole (48%) was also isolated by chromatography.

An authentic sample of 3,4,5-*trimethylanisole*, m.p. 28°, b.p. 60° at 0.5 mmHg, $\lambda_{max.}$ (EtOH) 277 nm, $\nu_{max.}$ (film) 1 610, 1 590, 950, 850, and 835 cm^{-1}, τ 3.48 (2 H), 6.32 (OMe), 7.8 (2 × :CMe), and 7.95 (:CMe) (Found *m/e*, 150.1045. $C_{10}H_{14}O$ requires *M*, 150.1045), was obtained (62%) by treating the salt (11e) with methylsulphinylmethanide ion at 25 °C for 20 h, followed by extraction and chromatography (silica gel; benzene).

The reaction between the ylide obtained from the salt (11e) [with sodium hydride as base in bis-(2-methoxyethyl) ether] and 4′-methoxyacetophenone (4 molar excess) at 70 °C for 3 h led to a 9 : 1 mixture of the *E*- and *Z*-stilbenes in 30% overall yield based on phosphonium salt.

An attempted condensation between the phosphonate (11f) and 4′-methoxyacetophenone by using sodium hydride in dimethylformamide led instead to 4,4′-*dimethoxy*-β-*methylchalcone* (31) (25%), which crystallised from ethanol as pale yellow needles, m.p. 95° $\lambda_{max.}$ (EtOH) 325 nm (19 000); $\nu_{max.}$ (Nujol) 1 680, 1 645, 1 603, 1 580, 1 510, 1 250, 1 170, 830, and 810 cm^{-1}; τ 1.96 (d, *J* 9 Hz, 2 × aryl :CH), 2.4 (d, *J* 9 Hz, 2 × aryl :CH), 2.85 (O:C·CH:C), 3.0 (d, *J* 9 Hz, 4 × aryl :CH), 6.12 (2 × OCH_3), and 7.42 (C:C·CH_3) (Found: C, 76.5; H, 6.6%; *m/e*, 282. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%; *M*, 282). G.l.c. analysis of the crude product indicated that none of the expected α′-methylstilbene was formed.

(E)-4,4′-*Dimethoxy*-α-*methylstilbene* (32).—By the general procedure, 1-(4-methoxyphenyl)ethyltriphenylphosphonium bromide and *p*-anisaldehyde gave (70%) a mixture of isomers of the stilbene, from which the *E*-stilbene, m.p. 122—123° (lit.,[26] 124°), τ 2.55 (2 H, d, *J* 8 Hz), 2.71 (2 H, d,

[26] R. L. Huang, *J. Chem. Soc.*, 1954, 2539.

J 8 Hz), 3.11 (4 H, d, *J* 8 Hz), 3.3 (1 H), 6.2 (2 × OMe), and 7.75 (:CMe), *m/e* 254, was obtained by crystallisation. 4-Ethylanisole (7%) was also isolated by chromatography.

(E)-4,4′-*Dimethoxy*-2,2′,6,6′-*tetramethylstilbene* (33).—By the general procedure, the salt (11e) and 4-methoxy-2,6-dimethylbenzaldehyde gave (30%) the *E*-stilbene as needles, m.p. 183—184° (lit.,[11d] 181°); $\lambda_{max.}$ (EtOH) 273 nm (20 200); $\nu_{max.}$ (Nujol) 1 600, 1 485, 1 300, 1 150, 1 060, 985, and 850 cm^{-1}, τ 3.37 (4 × aryl :CH), 3.53 (2 × olefinic CH), 6.22 (2 × OCH_3), and 7.62 (4 × aryl :CH_3) (Found: C, 80.8; H, 8.4%; *m/e* 296. Calc. for $C_{20}H_{24}O_2$: C, 81.0; H, 8.2%; *M*, 296).

3,4,5-Trimethylanisole (0.46 g, 30%) was also isolated by chromatography.

1-(4-*Methoxy*-2-*methylphenyl*)*ethyltriphenylphosphonium Bromide* (35).—The salt was prepared (60% overall yield) from 4′-methoxy-2′-methylacetophenone as for the phosphonium salt (29), and obtained as a deliquescent solid, m.p. 85—88°, $\nu_{max.}$ (Nujol) 1 605, 1 500, and 1 115 cm^{-1}; τ 2.0—2.6 (16 H, m), 3.25—3.45 (2 H, m), 4.75 (dq, J_{PH} 20, J_{HH} 8 Hz, CH_3·C*H*), 6.2 (OMe), 8.05 (dd, J_{PH} 18, J_{HH} 8 Hz, CH_3·CH·P), and 8.05 (:CMe) (Found: C, 68.2; H, 5.4; Br, 16.3. $C_{28}H_{28}BrOP$ requires C, 68.2; H, 5.7; Br, 16.1%).

(E)-4,4′-*Dimethoxy*-2,2′,6,α′-*tetramethylstilbene* (34).—(*a*) 4,4′-Dimethoxy-2,2′,6-trimethyldeoxybenzoin (2.6 g) was added in portions over 10 min to a solution of methylmagnesium iodide [from magnesium (0.6 g)] in ether (50 ml). The ether was then slowly evaporated off and simultaneously replaced with dry benzene (30 ml). The resulting benzene solution was boiled under reflux for 3 h, then cooled and poured on to cold saturated ammonium chloride solution. The benzene layer was separated, and the aqueous phase was extracted with benzene (2 × 20 ml). The combined benzene solutions were dried and evaporated to leave the intermediate carbinol as an oil, $\nu_{max.}$ (Nujol) 3 400 cm^{-1}. A solution of this alcohol in glacial acetic acid (20 ml), containing three drops of phosphoric acid, was boiled under reflux for 3.5 h, and then poured on to ice–water and extracted with ether (3 × 50 ml). Evaporation of the dried extracts gave a solid, which was chromatographed (silica gel; benzene–ethyl acetate, 97 : 3) to give the *stilbene* (0.31 g, 20% based on deoxybenzoin consumed), as a 3 : 7 mixture of *Z*- and *E*-isomers (by n.m.r.). Recrystallisation from ethanol gave the (E)-*isomer* as needles, m.p. 58.5—59°, $\lambda_{max.}$ (EtOH) 235 (14 300) and 283 nm (4 440); $\nu_{max.}$ (Nujol) 1 610, 1 570, 1 500, 1 235, 1 065, 850, 815, and 800 cm^{-1}; τ 2.88 (d, *J* 9 Hz, aryl :CH), 3.1—3.6 (m, 4 × aryl :CH), 3.84 (olefinic :CH), 6.2 (2 × OCH_3), 7.6 (aryl :CCH_3), 7.72 (2 × aryl :CCH_3), and 8.29 (olefinic :CCH_3) (Found: C, 81.0; H, 8.1%; *m/e* 296.1777. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; *M*, 296.1776).

(*b*) A solution of (*Z*)-4,4′-dimethoxy-2,2′,6,α′-tetramethylstilbene (0.3 g) [prepared from tributyl-(4-methoxy-2,6-dimethylbenzyl)phosphonium bromide; see accompanying paper] in glacial acetic acid (15 ml), containing iodine (75 mg) was heated under reflux for 5 h, then cooled and washed with sodium thiosulphate solution. The mixture was then diluted with water (50 ml) and extracted with ether (3 × 50 ml). Evaporation of the dried extracts followed by chromatography and crystallisation gave the stilbene (0.18 g), m.p. 59—60°, identical with that prepared as in (*a*).

(*c*) By the general procedure, attempts were made to prepare the stilbene from 1-(4-methoxy-2-methylphenyl)-ethyltriphenylphosphonium bromide (35) and 4-methoxy-2,6-dimethylbenzaldehyde. The usual work-up led to 4-*ethyl*-3-*methylanisole* (20%), b.p. 54° at 0.5 mmHg, n_D^{18} 1.5158, $\lambda_{max.}$ (EtOH) 260 nm; $\nu_{max.}$ (film) 1 615, 1 585, 1 510, 1 060, and 825 cm^{-1}; τ 2.99 (1 H, d, *J* 9 Hz), 3.32 (1 H), 3.34 (1 H, d, *J* 9 Hz), 6.28 (OMe), 7.46 (q, *J* 8 Hz, CH_2·CH_3), 7.76 (:CMe), and 8.85 (t, *J* 8 Hz, CH_2·C*H*$_3$) (Found: *m/e* 150.1045. $C_{10}H_{14}O$ requires *M*, 150.1045) and triphenylphosphine (10%).

(*d*) By the general procedure, attempts were made to prepare the stilbene from 4-methoxy-2,6-dimethylbenzyltriphenylphosphonium bromide and 4′-methoxy-2′-methylacetophenone. The usual work-up led to 3,4,5-trimethylanisole (52%) only; g.l.c. analysis of crude products did not detect the required stilbene. Use of sodium hydride in bis-(2-methoxyethyl) ether, and heating the mixture at 70 °C for 3 h, led to the stilbene in *ca.* 5% overall yield.

1-(4-*Methoxyphenyl*)*propyltriphenylphosphonium Bromide* (37).—Reduction of 4′-methoxypropiophenone with lithium aluminium hydride gave (95%) 1-(4-*methoxyphenyl*)*propan*-1-*ol*, a liquid, b.p. 110° at 2 mmHg, n_D^{20} 1.5265; $\nu_{max.}$ (film) 3 360, 1 610, 1 575, 1 510, 1 250, 1 180, 1 040, and 835 cm^{-1}; τ 2.91 (2 H, d, *J* 9 Hz), 3.28 (2 H, d, *J* 9 Hz), 5.7 (t, *J* 7 Hz, C*H*·CH_2), 6.35 (OCH_3), 6.62 (OH, disappears on addition of D_2O), 8.4 (quint, *J* 7 Hz, CH·CH_2·CH_3), and 9.22 (t, *J* 7 Hz, CH_2·CH_3) (Found: C, 72.4; H, 8.8. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.5%).

The alcohol was converted into the salt (22% overall) in a manner identical to that described for the phosphonium salt (29). The salt, a deliquescent glassy powder showed $\nu_{max.}$ (Nujol) 1 610, 1 590, 1 520, 1 115, 1 000, 850, and 740 cm^{-1}; τ 1.9—2.7 (15 H, m), 2.9 (2 H, d, *J* 9 Hz), 3.25 (2 H, d, *J* 9 Hz), 4.15 (dd, *J* 14 and 10 Hz, CH_2·C*H*·P$^+$), 6.25 (OCH_3), 7.4—8.3 (m, CH·CH_2·CH_3), and 8.95 (t, *J* 7 Hz, CH_2·CH_3), and was used without further purification (a satisfactory analysis was not obtained).

(E)-α′-*Ethyl*-4,4′-*dimethoxy*-2,6-*dimethylstilbene* (38).—(*a*) A Grignard reaction between 4,4′-dimethoxy-2,6-dimethyldeoxybenzoin (2 g) and ethylmagnesium iodide produced a tertiary alcohol which was dehydrated by heating for 1 h at 100—110 °C with a few crystals of iodine. The mixture was diluted with ether, then washed with sodium thiosulphate, dried, and evaporated. Chromatography (silica gel; benzene) and crystallisation gave the *stilbene* (25%) as needles, m.p. 67—68° (from methanol), $\lambda_{max.}$ (EtOH) 256 nm (16 900), $\nu_{max.}$ (Nujol) 1 603, 1 510, and 1 250 cm^{-1}, τ 2.62 (d, *J* 9 Hz, 2 × aryl :CH), 3.13 (d, *J* 9 Hz, 2 × aryl :CH), 3.42 (2 × aryl :CH), 3.65 (olefinic :CH), 6.23 (2 × OCH_3), 7.77 (q, *J* 7 Hz, CH_2·CH_3), 7.8 (2 × aryl :C·CH_3), and 9.22 (t, *J* 7 Hz, CH_2·CH_3) (Found: C, 80.9; H, 8.1. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%).

(*b*) Isomerisation of the corresponding (*Z*)-stilbene [prepared from tributyl-(4-methoxy-2,6-dimethylbenzyl)phosphonium bromide; see accompanying paper] gave the (*E*)-stilbene, m.p. 66—67°, identical with that prepared in (*a*).

(*c*) By the general procedure attempts were made to prepare the stilbene from 1-(4-methoxyphenyl)propyltriphenylphosphonium bromide (37) and 4-methoxy-2,6-dimethylbenzaldehyde. The usual work-up gave only 4-methoxypropylbenzene (20%), b.p. 100° at 10 mmHg; n_D^{22} 1.5072 (lit.,[27] b.p. 110° at 13 mmHg, n_D^{21} 1.5045); $\lambda_{max.}$ (EtOH) 279 nm; $\nu_{max.}$ (film) 2 885, 1 610, 1 590, 1 250, 1 040, and 800 cm^{-1}; τ 3.1 (d, *J* 9 Hz, 2 × aryl :CH), 3.29 (d, 2 × aryl :CH), 6.38 (OCH_3), 7.53 (t, *J* 8 Hz, CH_2·CH_2), 8.45 (sextet,

[27] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, 1965, vol. 5, p. 2797.

J 8 Hz, $CH_2{\cdot}CH_2{\cdot}CH_3$), and 9.12 (t, *J* 8 Hz, $CH_2{\cdot}CH_3$), *m/e* 150.1045 ($C_{10}H_{14}O$), and triphenylphosphine (15%).

4′-Methoxy-2′,6′-dimethylacetophenone (**41**).—The ketone, prepared as described previously (50%), showed b.p. 100—102° at 1 mmHg, m.p. 46—47° (lit.,[11d] 47°); $\nu_{max.}$ (Nujol) 1 690 cm^{-1}; τ 3.42 (2 × :CH), 6.26 (OMe), 7.59 (COMe), and 7.68 (2 × :CMe), *m/e* 178.

4-Methoxy-2,6-dimethylstyrene (**44**).—Reduction of 4′-methoxy-2′,6′-dimethylacetophenone with lithium aluminium hydride gave (70%) 1-(4-methoxy-2,6-dimethylphenyl)-ethanol, an oil, $\nu_{max.}$ 3 360 cm^{-1}; τ 3.5 (2 H), 4.75 (q, *J* 7 Hz, C*H*Me), 6.3 (OMe), 7.63 (2 × :CMe), and 8.5 (d, *J* 7 Hz, CH*Me*). The alcohol was treated with dry hydrogen bromide, and the resulting bromide was treated immediately with triphenylphosphine in benzene. Evaporation of the benzene and distillation of the residue gave the *styrene* (*ca.* 25% overall from the alcohol), b.p. 76—77° at 0.15 mmHg; τ 3.44 (dd, *J* 10 and 16 Hz, C*H*:CH_2), 3.5 (2 H), 4.6 (dd, *J* 1.5 and 10 Hz, CH:C*H*H), 4.87 (dd, *J* 1.5 and 16 Hz, CH:CH*H*), 6.44 (OMe), and 7.8 (2 × Me) (Found: *m/e*, 162.1040. $C_{11}H_{14}O$ requires *M*, 162.1045).

4,4′,α′-Trimethoxy-2,6-dimethylstilbene (**46**).—A solution of the anion produced from 4,4′-dimethoxy-2,6-dimethyldeoxybenzoin (1.5 g) and sodium hydride (0.2 g) in toluene (50 ml) was treated with methyl iodide (5 g) at 20 °C, and the resulting mixture was heated under reflux for 12 h. Evaporation of the toluene and chromatography of the residue on silica gel (benzene as eluant) gave (*a*) the stilbene (0.15 g) (eluted first) as a 3 : 2 mixture of *Z*- and *E*-isomers (by n.m.r.), τ 2.4—3.5 (6 H, m), 4.05 (:CH; *Z*-isomer), 4.46 (:CH; *E*-isomer), 6.15—6.3 (2 × OMe), 6.32 (:C·OMe; *E*-isomer), 6.65 (:C·OMe, *Z*-isomer), 7.72 (:CMe; *Z*-isomer), and 7.93 (:CMe; *E*-isomer), *m/e* 298, and (*b*) starting deoxybenzoin (0.66 g) (eluted second), identical with an authentic sample.

Z- and E-Isomers of 4,4′-Dimethoxy-2,2′,6,6′,α,α′-hexamethylstilbene [(**49**) *and* (**48**)].—4′-Methoxy-2′,6′-dimethylacetophenone (1.46 g) was introduced, all at once, to a stirred mixture of titanium trichloride (1.27 g) and lithium aluminium hydride (0.31 g) in tetrahydrofuran (150 ml) under nitrogen. The mixture was heated under reflux for 4 h, then cooled, diluted with water, and extracted with ether. Evaporation of the dried extracts left a solid (1.16 g) which was chromatographed on silica gel (chloroform as eluant) to give three fractions. Fraction (i) was a mixed fraction (0.6 g), a solid (eluted first) containing an isomeric mixture of stilbenes and diphenylethanes. Fractional crystallisation from ethanol produced two crystalline solids, m.p.s 175—177° (0.14 g) and 145—147° (0.12 g), and left an oily residue (0.2 g). G.l.c. analysis (Apiezon L; 220 °C) of each solid showed two peaks in the ratio 2 : 3. Preparative layer chromatography of the solid of m.p. 175—177° (3 : 1 cyclohexane–benzene as eluant) led to (a) the (E)-*stilbene* (40 mg) (eluted first), m.p. 208.5—209.5° (from ethanol), $\lambda_{max.}$ 239, 278, and 285 nm; $\nu_{max.}$ 1 608 and 1 580 cm^{-1}; τ 3.41 (4 H), 6.25 (2 × OMe), 7.71 (4 × aryl :CMe), and 8.46 (2 × :CMe) (Found: C, 81.0; H, 8.9%; *m/e*, 324.2075. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324.2089); and (b) (±)-2,3-*bis*-(*4-methoxy-2,6-dimethylphenyl*)*butane* (60 mg) (eluted second), m.p. 183—184° (from ethanol), τ 3.47 (4 H), 6.27 (2 × OMe), 7.47 (2 × Me), 7.6 (2 × Me), *ca.* 7.6 (q, *J* 7 Hz, C*H*Me), and 8.99 (d, *J* 7 Hz, CH*Me*) [Found: *m/e*, 326 and 163.1117 (base peak). $C_{22}H_{30}O_2$ requires *M*, 326. $C_{11}H_{15}O$ requires 163.1123]. Preparative layer chromatography of solid of m.p. 145—147° (1 : 1 cyclohexane–benzene as eluant) led to (a) meso-2,3-*bis*-(*4-methoxy-2,6-dimethylphenyl*)*butane* (20 mg) (eluted first), m.p. 142—143°, τ 3.68 (4 H, m), 6.38 (2 × OMe), 7.57 (2 × Me), *ca.* 7.67 (q, *J* 7 Hz, C*H*Me), 8.3 (2 × Me), and 8.6 (d, *J* 7 Hz, CH*Me*) [Found: *m/e*, 326 and 163.1117 (base peak)]; and (b) the (Z)-*stilbene* (20 mg) (eluted second), m.p. 154—155°, $\lambda_{max.}$ 239, 280, and 286 nm, $\nu_{max.}$ 1 600 cm^{-1}; τ 3.7 (4 H), 6.35 (2 × OMe), 7.92 (4 × aryl :CMe), and 8.0 (2 × :CMe) (Found: *m/e*, 324.2096. $C_{22}H_{28}O_2$ requires *M*, 324.2089). Spectroscopic analysis of the oily residue remaining after fractional crystallisation indicated that it was composed largely of a mixture of 1-ethyl-4-methoxy-2,6-dimethylethylbenzene (**51**), τ 3.48 (aryl :CH), 6.31 (OMe), 7.45 (q, *J* 7 Hz, $CH_2{\cdot}CH_3$), 7.73 (:CMe), and 8.94 (t, *J* 7 Hz, $\cdot CH_2CH_3$), *m/e* 164; and the styrene (**44**), *m/e* 162.1038 ($C_{11}H_{14}O$ requires *M*, 162.1045).

Fraction (ii) was the starting acetophenone (0.27 g) (eluted second), identical with an authentic sample. Fraction (iii) was 1-(4-methoxy-2,6-dimethylphenyl)ethanol (0.12 g) (eluted last), identical with an authentic sample.

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