Medicinal Plants of Southern Africa. Part 4.[1] Synthesis of Brackenin-like Molecules from 1,4-Dicarbonyl Precursors and by Oxidative Coupling. *X*-Ray Molecular Structure of Racemic-2,3-Dibenzyl-1,4-diphenylbutane-1,4-dione

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Oxidative coupling of appropriate trimethylsilyl enol ethers is shown to give 1,4-diaryl-1,4-diketones in acceptable yields. Subsequent dibenzylation of these intermediates affords compounds related to the naturally occuring brackenin (**1**). Examination of these products by ^{1}H n.m.r. and ^{13}C n.m.r. demonstrates that these techniques can be used for the determination of relative configurations without resorting to *X*-ray crystallography.

Brackenin (**1**), an unusual biflavonoid which consists of two α,α′-coupled dihydrochalcones, has previously been isolated by us from the bark of *Brackenridgea anguebarica*.[2,3] To date it is the only naturally occurring compound in this class. In this paper we describe two general procedures applicable to the synthesis of brackenin-like molecules.

In considering various alternatives for its synthesis we chose to regard brackenin simply as a substituted 1,4-dicarbonyl compound. Two basic approaches were then adopted:

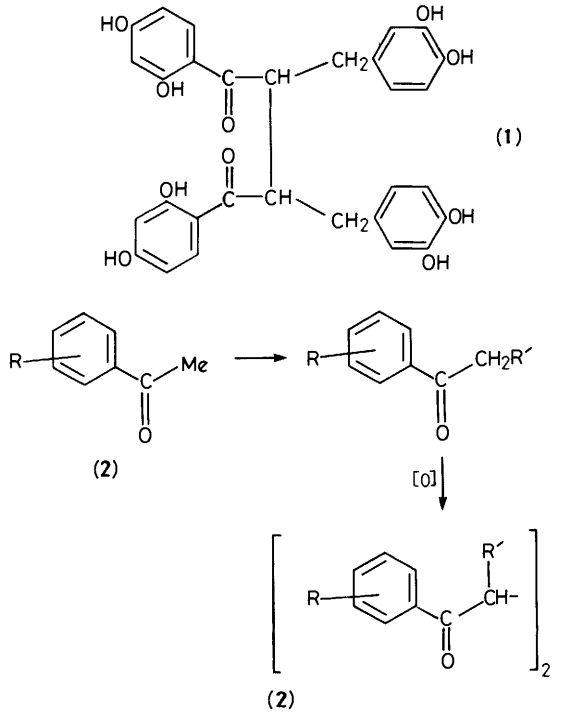
(i) A dimerisation procedure in which both carbonyl groups originated from the same precursor. Oxidative coupling is an obvious choice in this instance.

(ii) Transformation of suitable 1,4-dicarbonyl precursors to give the desired target molecule.

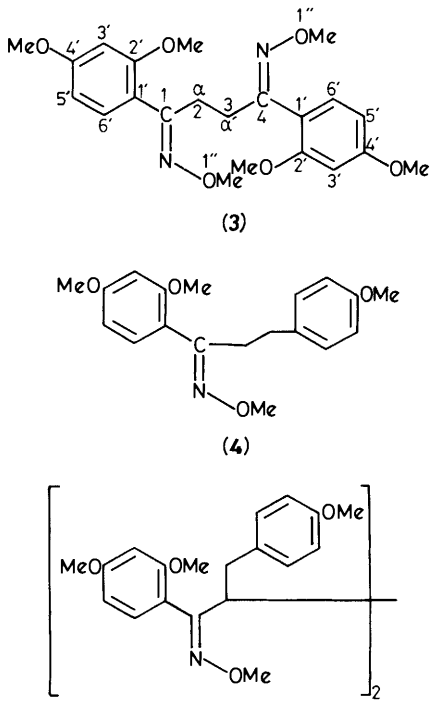
Oxidative Coupling.—The ready availability of acetophenones such as (**2**), their proven ability to undergo oxidative coupling, and the ease with which they can be converted into α-substituted carbonyls (Scheme 1) makes this an attractive route. A study of oxidative methods showed that silyl enol ethers[4] and *O*-methyl oximes[5] have been coupled successfully by this method. With the latter procedure we were able to produce the dioxime (**3**) in low (25%) yield. Our attempts to effect substitution at the α,α′-positions were not successful. When the α-substituent was introduced prior to coupling, as in substrate (**4**), the dimer (**5**) did not form.

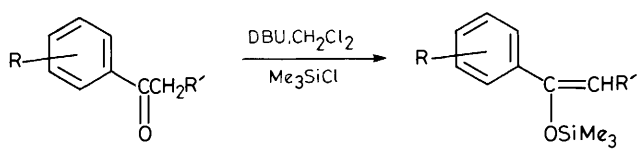
With the silyl enol ethers good results were achieved. A series of these ethers was prepared in near-quantitative yield using the method of Yamaguchi and co-workers[6] (Scheme 2). This procedure was found to be superior to that of House *et al.*[7] in which triethylamine in dimethylformamide (DMF) is used as base. For the silyl enol ether of propiophenone, (**7**) detailed spectral information was available.[8,9] From this we deduced that all the compounds prepared by us had the (*Z*)-configuration.

Using the silver(I) oxide procedure of Saegusa[4] the propiophenone derivative (**7**) was used as a model compound to study the oxidative coupling reaction. Coupling proceeded in good



Scheme 1. Oxidative coupling of an acetophenone derivative



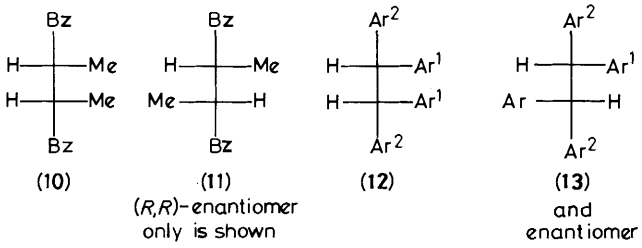


Silyl ether	Yield (%)
(**6**) R = R′ = H	97
(**7**) R = H, R′ = Me	94
(**8**) R = 2,4-(OMe)$_2$, R′ = $CH_2C_6H_4OMe$-4	96
(**9**) R = 2,4-(OMe)$_2$, R′ = H	94

Scheme 2. Formation of trimethylsilyl enol ethers

(70%) yield and resulted in an equal mixture of *meso* (**10**) and racemic (**11**) 1,4-diketones. Compound (**10**) was separated from its isomer (**11**) by column chromatography. Comparison of our spectroscopic data (^{1}H and ^{13}C n.m.r.) with those of Kobayashi[10] showed good agreement. The less polar product (**10**) had m.p. 98–99 °C while racemate (**11**) melted at 84–85 °C. By contrast, both Wolf[11] and Russell[12] had previously reported m.p. 67 °C for racemate (**11**) and we assume this was due to impurities in the samples.

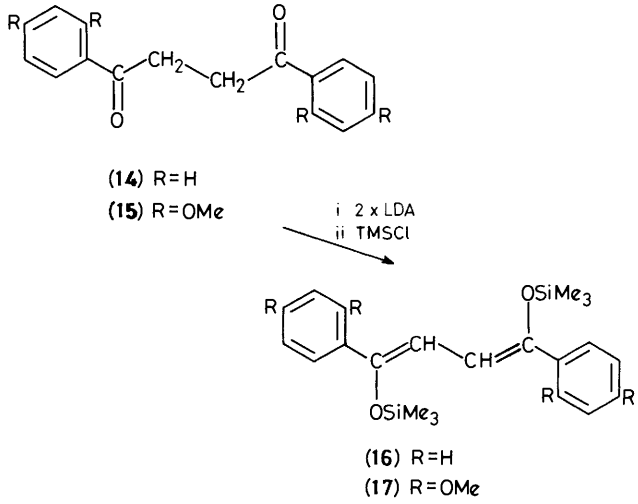
Following the above, compound (**8**), a substituted dihydrochalcone, was also coupled to afford a mixture of *meso* (**12**) and racemic (**13**) 1,4-diketone derivatives in 38% yield. A bulky substituent at the α-position clearly reduces the yield, an observation recorded earlier by Saegusa.[4] ^{1}H N.m.r. analysis of



Ar^1 = $CH_2C_6H_4OMe$-4, Ar^2 = $COC_6H_3(OMe)_2$-2,4, Bz = COPh

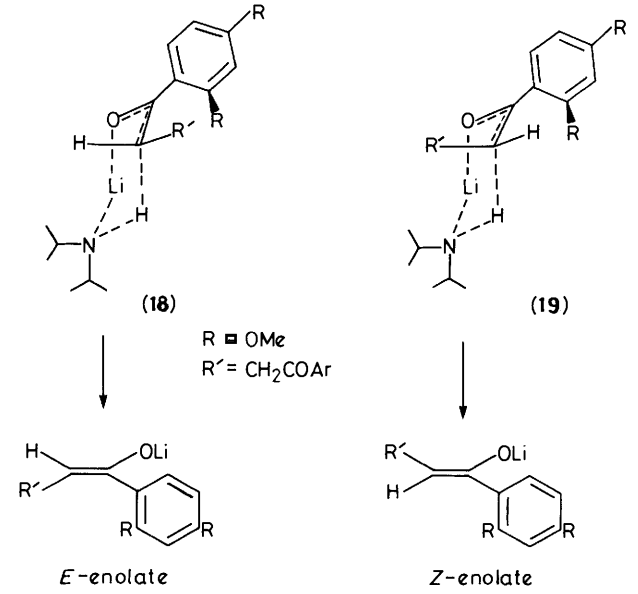
the mixture indicated a 1 : 1 ratio of isomers. Repeated separation followed by fractional crystallisation eventually afforded the pure racemic diastereoisomer (**13**) which could then be characterised. The use of Li enolates[13] in place of trimethyl silyl enol ethers proved to be unsatisfactory.

Structure and Reactivity of 1,4-*Dicarbonyl Compounds.*—A logical synthesis of brackenin (**1**) and related compounds could involve initial preparation of a 1,4-diketone unsubstituted at the α,α′-positions, followed by appropriate alkylation at these positions. Our review of the literature revealed good coverage on enolates of 1,3-dicarbonyls[14] and 1,4-diesters,[15] but, with the exception of Ireland's work,[16] very little information on the reactivity of 1,4-diketone enolates. The two 1,4-diketones (**14**) and (**15**) were prepared by oxidative coupling (above) from the trimethylsilyl enol ether of acetophenone, (**6**), and of 2,4-dimethoxyacetophenone (**9**), respectively. In order to study their enolisation behaviour lithium di-isopropylamide (LDA) (2 mol equiv.) was added to each followed by trimethylsilyl chloride (TMSCl) to trap the enolate. In this way excellent yields of the crystalline bis-enol ethers (**16**) and (**17**) were obtained. ^{1}H N.m.r. spectra of these products showed them to be pure geometrical isomers having either an (*E*,*E*) or (*Z*,*Z*)-configuration. This contrasts with the findings of Rathke[15] and of Yamamoto[17] on diethyl succinate enolate. Both these groups of researchers state that at least two geometrical isomers were present in the corresponding products.



Ireland[16] has demonstrated the remarkable effect which hexamethylphosphoric triamide (HMPTA) has in controlling the geometry of an enolate. When the diketones (**14**) and (**15**) were treated under Ireland's[16] reaction conditions favouring (*Z*)enolates (LDA, HMPTA–THF) (THF = tetrahydrofuran), the *same two* enolates (**16**) and (**17**) were isolated. At −78 °C and at 15 °C, with both LDA and lithium tetramethylpiperidine (LTMP) in THF and THF–HMPTA, the *same* geometrical isomer was produced in very reaction.

Our inability to produce *both* geometric isomers made the assignment of configuration to compounds (**16**) and (**17**) very difficult since the usual ^{13}C n.m.r. method[9] could not be used. However, consideration of the transition states postulated by Ireland[16] enabled us to reach a definite conclusion. In the transition state (**18**) non-bonded interactions are clearly larger than in (**19**) (Scheme 3). This situation would favour formation of the (*Z*)-enolate when co-ordinating HMPTA was present. It is suggested that even in THF, where strong keto oxygen and lithium cation interaction occurs, the steric bulk of the phenyl ring would be dominant. Consequently we believe that only one



Scheme 3. Possible transition states for enolate formation

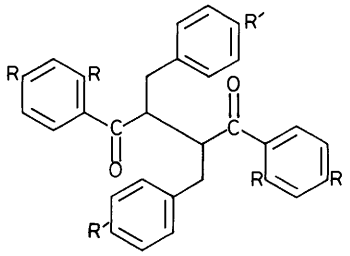
Table 1. Ratio of *threo* and *erythro* isomers resulting from dibenzylation

Erythro (*meso*) *isomers*	*Threo* (racemic) isomers	Ratio
(**20a**)	(**20b**)	20:80
(**21a**)	(**21b**)	30:70
(**22a**)	(**22b**)	40:60

enolate is generated and that dienolates (**16**) and (**17**) both have the (*Z*,*Z*)-geometry.

Dibenzylation of 1,4-*Dicarbonyl Compounds.*—A considerable number of 1,4-dicarbonyl substrates have been dialkylated *via* their vicinal dienolates. They include disuccinimides,[18] *N*-substituted dicarboxamides,[19] and diesters.[15] In our experience diethyl succinate was readily dibenzylated at the α,α′-positions, but subsequent conversion of the diester into the desired diketone was not successful, largely, as a result of the insolubility of the intermediate dilithium salt.[20]

Dibenzylation of the 1,4-diketones (**14**) (from acetophenone) and (**15**) [from (**9**)] using the method of Rathke[15] and Pohmakotr *et al.*[21] afforded good yields if the reaction was conducted at room temperature in the presence of HMPTA. At −78 °C, with or without a polar aprotic cosolvent, monosubstituted products only were isolated. The disubstituted products (**20**), (**21**), and (**22**) prepared as above from (**14**) and

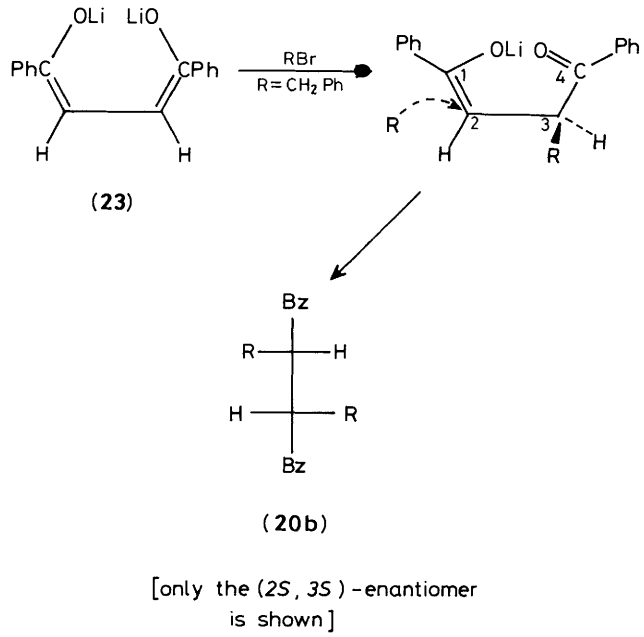


(**20**) R=R′=H
(**21**) R=H, R′=OMe
(**22**) R=R′=OMe

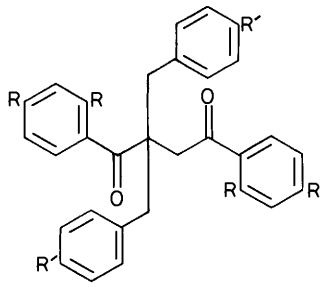
(**15**) were accompanied by low concentrations (5—10%) of 2,2-dibenzylated derivatives (**24**). Separation of the diastereoisomeric mixtures (**20a**) and (**20b**), (**21a**) and (**21b**), and (**22a**) and (**22b**) was achieved by multiple development of preparative t.l.c. (p.l.c.) plates using a low-polarity solvent followed by crystallisation. In this way all the diastereoisomers with the exception of (**22a**) (less polar isomer) were isolated in pure form. Diastereoisomeric excesses (d.e.) were determined with the chiral shift reagent Eu(fod)$_3$* (Table 1).

Rationalisation of Diastereoselectivity.—Earlier on we presented arguments in favour of a (*Z*,*Z*)-configuration for the symmetrical enol ethers (**16**) and (**17**). It seems reasonable to assume that the Li-dienolate (**23**) would also have a (*Z*,*Z*)-configuration. The observed stereoselectivities (Table 1) may then be rationalised by the process shown in Scheme 4. The resultant *threo* isomer[22] (**20b**) is shown. *X*-Ray crystallographic examination of compound (**20b**) confirmed the *threo* assignment (Figure).

Comparison of the spectroscopic data for (**20b**) and those of the corresponding *erythro* isomer with those of the other dibenzylated products (**21**) and (**22**) indicated that the major isomer in each of the reactions was the *threo* isomer [*i.e.* (2*R*,3*R*) and (2*S*,3*S*)]. Similar *threo* selectivity has been observed by Snieckus[18] for *N*,*N*′-dimethyl- and -diethyl-succinamide.



Scheme 4. Formation of *threo* isomer from dienolate



(**24**)

Formation of 2,2-*Dibenzylated* 1,4-*Diketones as By-products.*—During dibenzylation of the 1,4-diketones described above, low concentrations (5—10%) of 2,2-dialkylated (**24**) products were consistently obtained and their mode of formation was of interest to us. Our attempts to convert any one of the three 2,3-dibenzylated 1,4-diketones (**20**), (**21**), and (**22**) into the corresponding 2,2-dibenzylated derivative with the aid of base (K_2CO_3 or LDA) were not successful, thus eliminating (1,2)-sigmatropic rearrangement as a possible mechanism.[23]

Use of N.m.r. Spectroscopy to Establish the Relative Configurations of Brackenin-like Molecules.—We have previously reported ^{1}H and ^{13}C n.m.r. data for brackenin (**1**) and its derivatives.[3] The synthesis of both diastereoisomers of analogues of this compound has highlighted useful chemical-shift differences which can be of assistance in assigning relative configurations without having to resort to sophisticated *X*-ray techniques.

The non-equivalent benzylic hydrogens (5_a-H and H_b-H) in compounds (**20**), (**21**), and (**22**) resonate between δ 2.7—3.3 and they display pronounced shift differences between diastereoisomers. This was even more marked in the ^{13}C n.m.r. spectra carbons (Table 2). The C-5 hydrogens of the racemic mixture resonated to low field relative to those of the *meso* compound.

* Europium(III)tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-dionate).

This trend was reversed and was also more marked in the ^{13}C n.m.r. spectra where the signal for C-5 of the *meso* compound was always deshielded relative to that of the racemate. Since we had established the stereochemistry of compound (**20b**) from *X*-ray crystallography it was now possible to assign relative configurations to products (**21**) and (**22**) by analogy.

That the spectroscopic correlation outlined above is a general one was supported from examination of the data available on naturally occurring brackenin (**1**).[3,24] *X*-Ray crystallography had shown it to be the *meso* compound. The ^1H n.m.r. spectra of brackenin, its tetramethyl ether, and the hexa-acetate all had the 5-H resonances between δ 2.7—3.0. The simple correlation between stereochemistry and chemical shift of the 5-protons and 5-carbons is also applicable to the simpler 1,4-diketones (**25**), (**10**), and (**11**) (Table 3).

It should be noted that Sudgen has previously reported the synthesis of dione (**20**) by photochemical dimerisation of α,β-unsaturated ketones. If the ^1H n.m.r. data quoted by Sugden[25] are compared with our findings there is little doubt that his figures are erroneous and, in fact, refer to starting material. This casts doubt on the claim that compound (**20**) has been synthesized previously.

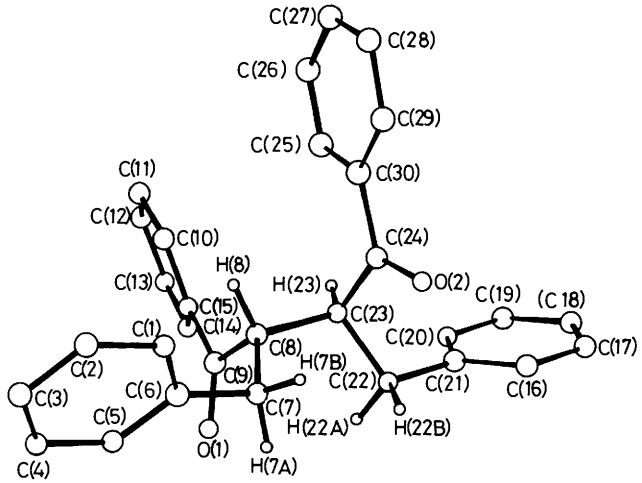
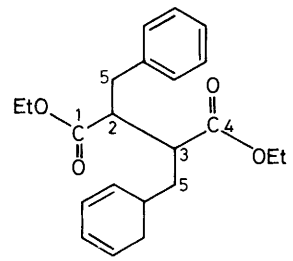


Figure. Solid-state *X*-ray molecular structure of compound (**20b**)

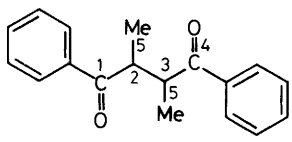
Table 2. Benzylic hydrogen and carbon chemical shifts (p.p.m.) for brackenin-like diastereoisomers

Diastereo-isomer	(20) 5-H_2	(20) C-5	(21) 5_a-H	(21) 5_b-H	(21) C-5	(22) 5_a-H	(22) 5_b-H	(22) C-5
Less polar (*meso*)	2.69—3.11	37.9	2.77	3.02	35.5	2.71	2.87	37.1
More polar (racemic)	3.06—3.31	35.7	2.75	3.11	31.9	3.08	3.14	34.8

Table 3. Determination of relative configuration by use of proton and carbon chemical shifts (p.p.m.)



(**25a**), (**25b**)



(**10**), (**11**)

Diastereo-isomer	(25) 5-H_2	(25) C-5	(10), (11) 5-H_2	(10), (11) C-5	Predicted stereo-chemistry
Less polar	1.08	36.6	*a*	16.6	*meso*
More polar	1.24[b]	35.5[b]	*a*	15.1	racemic

[a] Shown by Perry *et al.* (C. W. Perry, M. V. Calnins, and K. H. Deitcher, *J. Org. Chem.*, 1972, **37**, 4371) to be the racemic diastereoisomer. [b] Unresolved at 80 MHz.

Experimental

M.p.s were measured on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded using Perkin-Elmer 283, 457, and 1420 spectrophotometers. N.m.r. spectra were recorded on the following instruments: Varian FT 80A, Bruker WM 300, and Bruker WM 500. Solvents are indicated in the text. Low-resolution mass spectra were obtained on a Hewlett Packard 5988A spectrometer and high-resolution ones on a Varian MAT 212 instrument. For chemical ionisation methane was used as ionising gas at a pressure of 0.9 Torr. Light petroleum refers to the fraction with b.p. 30—40 °C.

(E,E)-*Bis*-(2,4-*dimethoxyphenyl*)*butane*-1,4-*dione Bis*-[*O*-*methyl Oxime*) (**3**).—The monomer for this reaction (*E*)-1-(2,4-dimethoxyphenyl)ethanone *O*-methyl oxime, was prepared from 2,4-dimethoxyacetophenone using the procedure of Hjeds.[26] This oxime (2 g, 9.6 mmol) was dissolved in dry THF under nitrogen, and the solution was cooled to −65 °C. To this was added dropwise 1.44M BuLi (7.3 ml, 10.6 mmol) and the mixture was stirred for 0.5 h at −65 °C. A solution of iodine (2.9 g, 11.5 mmol) in dry THF (8 ml) was added slowly and the temperature was maintained at −65 °C for a further 0.5 h. The mixture was quenched with water, and extracted with ether, and the extract was washed with sodium thiosulphate and dried ($MgSO_4$). Removal of the solvent yielded an oil, which was chromatographed on a silica gel column with light petroleum–ethyl acetate (3:1) as eluant. From the most polar fraction were obtained cream crystals of the *title compound* (0.5 g, 25%), m.p. 122 °C (light petroleum–ethyl acetate) (Found: C, 63.3; H, 6.9; N, 6.7. $C_{22}H_{28}N_2O_6$ requires C, 63.4; H, 6.8; N, 6.7%); $\nu_{max.}(CH_2Cl_2)$ 1 610 cm^{-1} (C=N and C=C); δ_H(80 MHz; $CDCl_3$) 2.80 (4 H, s, 2-, 3-H_2), 3.75 and 3.77 (both 6 H, s, OMe), 3.87 (6 H, s, 1″-H), 6.34—6.48 (4 H, m, 3′-, 5′-H), and 7.10 (2 H, d, *J* 8.9 Hz, 6′-H); δ_C(20 MHz; $CDCl_3$) 25.36 (t, C-2, -3), 55.17, 55.33 (both q, OMe), 61.46 (q, C-1″), 98.53 (d, C-3′), 104.26 (d, C-5′), 118.56 (s, C-′1), 130.92 (d, C-6′), and 158.60, 159.49, and 161.54 (all s, C-1, -2′, -4, -4′); *m/z* (e.i.) 416 (M^+, 69%), 385 (100), 353 (49), 339 (90), 222 (41), 190 (67), and 163 (61).

The *O*-methyl oxime derivative (**4**), obtained by benzylation of 2′,4,4′-trimethoxydihydrochalcone using the procedure described above, failed to undergo oxidative coupling.

Preparation of Trimethylsilyl Enol Ethers (**6**)—(**9**).—For all these the following general procedure[6] was employed: ketone (60 mmol) and TMSCl (8.4 ml, 66 mmol) were dissolved in dry dichloromethane (80 ml) in a suitable round-bottom flask fitted with a condenser ($CaCl_2$ drying-tube) and septum inlet. 1,8-Diazabicycloundec-7-ene (DBU) (10.8 ml, 72 mmol), previously dried over calcium hydride, was added dropwise and the stirred reaction mixture was refluxed overnight. Work-up of the mixture afforded an oily residue, which was redissolved in light petroleum, filtered (to remove DBU hydrochloride), and then

finally distilled immediately prior to use. These enol ethers were all oils and were characterised by means of ^1H and ^{13}C n.m.r. spectroscopy and mass spectrometry.

Oxidative Coupling Procedure for the Preparation of the 1,4-*Diketones* (**10**), (**11**), (**12**), (**13**), (**14**), *and* (**15**).—The following general procedure[4] was employed. A heterogeneous mixture of trimethylsilyl enol ether (10 mmol), silver(I) oxide (2.5 g, 11.0 mmol), and dry dimethyl sulphoxide (DMSO) (6 ml) was heated for 6 h at 100 °C in a flask fitted with a $CaCl_2$ drying-tube. The reaction mixture was then cooled, diluted with chloroform, and filtered to remove metallic silver. Following concentration of the solution the residue was separated on a silica gel column with light petroleum–ethyl acetate (19:1) as eluant.

(2R,3S)-2,3-*Dimethyl*-1,4-*diphenylbutane*-1,4-*dione* (**10**) *and* (2R,3R)-*and* (2S,3S)-2,3-*dimethyl*-1,4-*diphenylbutane*-1,4-*dione* (**11**). Propiophenone trimethylsilyl enol ether (**7**) (2.1 g, 15.6 mmol) was oxidatively coupled as described above. Column chromatographic separation gave a 1:1 mixture of the 1,4-diketone diastereoisomers (**10**) and (**11**) (0.93 g, 70%). The less polar *meso* isomer had m.p. 102—104 °C (from ethyl acetate–pentane) (lit.,[10] 98—99 °C); δ_H (80 MHz; [$^2H_6$]acetone) 1.08 (6 H, d, *J* 6.5 Hz, 2-, 3-Me), 3.87—4.05 (2 H, m, 2-, 3-H), 7.40—7.61 (6 H, m, ArH), and 7.92—8.12 (4 H, m, ArH); δ_C(20 MHz; [$^2H_6$]acetone) 16.64 (q, Me), 43.31 (d, C-2, -3), 128.46 (d, C-3′, -5′), 129.03 (d, C-2′, -6′), 133.34 (d, C-4′), 137.37 (s, C-1′), and 202.89 (s, C-1, -4).

The more polar racemic diketone (**11**) had m.p. 82—84 °C (lit.,[10] 84—85 °C); $\nu_{max.}(CH_2Cl_2)$ 1 680 cm^{-1} (C=O); δ_H(80 MHz; [$^2H_6$]acetone) 1.24 (6 H, d, *J* 6.8 Hz, 2-, 3-Me), 3.76—3.99 (2 H, m, 2-, 3-H), 7.30—7.64 (6 H, m, ArH), and 7.80—8.03 (4 H, m, ArH); δ_C(20 MHz; [$^2H_6$]acetone) 15.12 (q, Me), 43.67 (d, C-2, -3), 128.51 (d, C-3′, -5′), 128.85 (d, C-2′, -6′), 133.03 (d, C-4′), 136.63 (s, C-1′), and 203.61 (s, C-1, -4); *m/z* (e.i.) 266 (M^+, 6%), 161 (5), 105 (100), 77 (42), and 56 (6).

(2R,3S)-1,4-*Bis*-(2,4-*dimethoxyphenyl*)-2,3-*bis*-(4-*methoxybenzyl*)*butane*-1,4-*dione* (**12**) *and* (2R,3R)- *and* (2S,3S)-1,4-*bis*-(2,4-*dimethoxyphenyl*)-2,3-*bis*-(4-*methoxybenzyl*)*butane*-1,4-*dione* (**13**). 2′,4,4′-Trimethoxydihydrochalcone trimethylsilyl enol ether (**8**) (3.7 g) was coupled at 100 °C using the standard method. Column chromatography on silica gel and light petroleum–ethyl acetate (7:3) effected separation of 2′,4,4′-trimethoxydihydrochalcone from the two 1,4-diketones (**12**) and (**13**) (1.0 g, 34%). Fractional crystallisation of the mixture gave the more polar *racemic isomer* (**13**) as white rods, m.p. 93—94 °C (from light petroleum–ethyl acetate; −10 °C) (Found: C, 72.5; H, 6.45. $C_{36}H_{38}O_8$ requires C, 72.2; H, 6.40%); $\nu_{max.}(CH_2Cl_2)$ 1 662 cm^{-1} (C=O); δ_H(80 MHz; $CDCl_3$) 2.75 (2 H, dd, *J* 6.4, 13.6 Hz, 5-H_a), 3.11 (2 H, dd, *J* 8.0, 13.6 Hz, 5-H_b), 3.45, 3.76, and 3.80 (all 6 H, s, OMe), 4.03—4.28 (2 H, m, 2-, 3-H), 6.29 (2 H, d, *J* 2.3 Hz, 3″-H), 6.44 (2 H, dd, *J* 2.3, 8.6 Hz, 5″-H), 6.68 (4 H, d, *J* 8.8 Hz, 3′-, 5′-H), 6.98 (4 H, d, *J* 8.8 Hz, 3′-, 5′-H), and 7.48 (2 H, d, *J* 8.6 Hz, 6″-H); δ_C(20 MHz; $CDCl_3$) 31.92 (t, C-5), 53.30 (d, C-2, -3), 55.12, 55.20, 55.48 (all q, OMe), 98.32 (d, C-3″), 104.81 (d, C-5″), 113.39 (d, C-3′, -5′), 122.03 (s, C-1″), 130.19 (d, C-2′, -6′), 132.52 (s, C-1′), 132.63 (d, C-6″), 157.67 (s, C-4′), 159.69 (s, C-2″), 163.73 (s, C-4″), and 202.31 (s, C-1, -4); *m/z* (e.i.) 598 (M^+, 0.1%), 580 (2), 300 (25), 299 (66), 165 (100), 135 (9), 134 (39), 122 (11), and 121 (37). The *meso* isomer (**12**), contaminated with (**2**) had m.p. 128 °C (lit.,[3] 86 °C).

1,4-*Diphenylbutane*-1,4-*dione* (**14**). Acetophenone trimethylsilyl enol ether (**6**) (1.98 g) was oxidatively coupled at 90 °C. Column chromatographic separation (as before) yielded the desired 1,4-diketone (**14**) (0.83 g, 70%), m.p. 145 °C (from ethyl acetate) (lit.,[27] 142—145 °C); $\nu_{max.}(CH_2Cl_2)$ 1 682 cm^{-1} (C=O); δ_H(80 MHz; $CDCl_3$) 3.44 (4 H, s, 2-, 3-H), 7.36—7.58 (6 H, m, ArH), and 7.96—8.09 (4 H, m, ArH); δ_C(20 MHz; $CDCl_3$) 32.72 (t, C-2, -3), 128.25 (d, C-3′, -5′), 128.73 (d, C-2′, -6′), 133.27 (d, C-4′), 136.95 (s, C-1′), and 198.79 (s, C-1, -4); *m/z* (e.i.) 238 (M^+, 8%), 133 (9), 105 (100), and 77 (58).

1,4-*Bis*-(2,4-*dimethoxyphenyl*)*butane*-1,4-*dione* (**15**). 2,4-Dimethoxyacetophenone silyl enol ether (**9**) (2.5 g) was oxidatively coupled at 97 °C. Separation by column chromatography gave the 1,4-diketone (**15**) (1.2 g, 74%), m.p. 145 °C (from ethyl acetate–pentane; 0 °C) (lit.,[28] 148—150 °C); $\nu_{max.}(CH_2Cl_2)$ 1 667 cm^{-1} (C=O); δ_H(80 MHz; $CDCl_3$) 3.35 (2 H, s, 2-, 3-H), 3.83 and 3.88 (both 3 H, s, OMe), 6.45 (1 H, s, 3′-H), 6.50 (1 H, dd, *J* 2.3, 9.0 Hz, 5′-H), and 7.84 (1 H, d, *J* 9.0 Hz, 6′-H); δ_C(20 MHz; $CDCl_3$) 38.10 (t, C-2, -3), 55.39 (q, OMe), 98.22 (d, C-3′), 105.13 (d, C-5′), 120.96 (s, C-1′), 132.57 (d, C-6′), 160.90 (s, C-2′), 164.27 (s, C-4′), and 198.90 (s, C-1, -4); *m/z* (e.i.) 358 (M^+, 6%), 193 (6), 166 (10), 165 (100), 135 (3), 122 (8), 107 (5), and 77 (7).

General Procedure for Dibenzylation of 1,4-*Dicarbonyl Compounds*.—Dry di-isopropylamine (1.4 ml, 11.0 mmol) was added to a 250 ml flask cooled in an ice-bath, and placed under N_2. Butyl-lithium (7.45 ml, 10.8 mmol; 1.45M in hexane) was added dropwise during 5—10 min, and the mixture was stirred at ice-bath temperature for 10 min and at room temperature for 15 min. Excess of solvent was then removed under reduced pressure, the white residue (LDA) was dissolved in dry THF (20 ml), and the solution was cooled to −78 °C. The 1,4-dicarbonyl compound (5 mmol) was dissolved in dry THF (20 ml) and added to the LDA solution (kept at −78 °C) during 20 min. The mixture was stirred at this temperature for 1 h and then a solution of HMPTA (1.75 ml) in THF (1.75 ml) was added. Benzyl bromide (11.0 mmol) was added dropwise during 5 min. After 1 h at −78 °C the mixture was slowly warmed to room temperature and was stirred for a further 12 h. The solution was recooled to −78 °C, quenched with dil. hydrochloric acid, and extracted with chloroform. Concentration of the organic layer afforded a residue, which was purified by column chromatography (SiO_2). Separation of the diastereoisomers from the 2,2-dibenzylated by-product was achieved by repeated fractionation on a column with light petroleum–ethyl acetate as eluant.

(2R,3S)-2,3-*Dibenzyl*-1,4-*diphenylbutane*-1,4-*dione* (**20a**). 1,4-Diphenylbutane-1,4-dione (**14**) (1.9 g) was benzylated as described and subsequently separated [light petroleum–ethyl acetate (9:1)] into the less polar diastereoisomer (**20a**) and the more polar diastereoisomer (**20b**). Chiral shift reagent [Eu(fod)$_3$] indicated a ratio of 20:80. The meso *isomer* (**20a**) (0.34 g, 16%) crystallised as needles, m.p. 163 °C (from light petroleum–ethyl acetate) (Found: C, 86.3; H, 6.25. $C_{30}H_{26}O_2$ requires C, 86.1; H, 6.30%); $\nu_{max.}(CH_2Cl_2)$ 1 674 cm^{-1} (C=O); δ_H(80 MHz; $CDCl_3$) 2.69—3.11 (4 H, m, 2 × 5-H_2), 4.13—4.48 (2 H, m, 2-, 3-H), and 6.97—7.75 (20 H, m, ArH); δ_C(20 MHz; $CDCl_3$) 37.95 (t, C-5), 50.57 (d, C-2, -3), 126.34 (d, C-4′), 128.25, 128.39, and 129.09 (all d, ArH), 133.03 (d, C-4″), 138.39 (s, C-1′, -1″), and 203.52 (s, C-1, -4); *m/z* (e.i.) 418 (M^+, 3%), 400 (1), 210 (44), 209 (78), 105 (78), 105 (100), 91 (19), and 77 (34).

(2R,3R)- *and* (2S,3S)-2,3-*Dibenzyl*-1,4-*diphenylbutane*-1,4-*dione* (**20b**). The most polar fraction yielded the *racemic diastereoisomer* as white needles (1.33 g, 64%), m.p. 126.5 °C (from pentane–diethyl ether) (Found: C, 86.1; H, 6.1%); $\nu_{max.}(CH_2Cl_2)$ 1 679 cm^{-1} (C=O); δ_H(80 MHz; $CDCl_3$) 3.06—3.31 (4 H, m, 2 × 5-H_2), 4.04—4.35 (2 H, m, 2-, 3-H), and 6.91—7.73 (20 H, m, ArH); δ_C(20 MHz; $CDCl_3$) 35.73 (t, C-5), 50.09 (d, C-2, -3), 126.44 (d, C-4′), 128.30, 128.38, and 129.16 (all d, ArH), 132.75 (d, C-4″), 137.55 (s, C-1″), 138.57 (s, C-1′), and 203.30 (s, C-1, -4); *m/z* (c.i.) 419 (MH^+, 100%); *m/z* (e.i.) 210 (28), 209 (49), 105 (100), and 77 (37).

2,2-*Dibenzyl*-1,4-*diphenylbutane*-1,4-*dione* (**24**). The fraction of intermediate polarity yielded the 2,2-*disubstituted* 1,4-*dione derivative* (0.15 g, 7%), m.p. 156—157 °C (from light petroleum–

ethyl acetate) (Found: C, 86.3; H, 6.3. $C_{30}H_{26}O_2$ requires C, 86.1; H, 6.30%); $\nu_{max.}(CH_2Cl_2)$ 1 682 cm^{-1} (C=O); δ_H(300 MHz; $CDCl_3$) 3.26 (2 H, s, 3-H_2), 3.31 (2 H, d, *J* 13.4 Hz, 5-H_a), 3.45 (2 H, d, *J* 13.4 Hz, 5-H_b), and 7.08—7.74 (20 H, m, ArH); δ_C(75 MHz; $CDCl_3$) 41.95 (t, C-5), 44.26 (t, C-3), 55.06 (s, C-2), 126.73, 127.33, 127.66, 127.80, 128.31, 128.35, 130.13, 130.55, and 132.83, (all d, ArH), 137.03 (s, C-1′), 137.13 (s, C-1″), 140.51 (s, C-1″), 198.48 (s, C-4), and 208.24 (s, C-1); *m/z* (e.i.) 418 (M^+, 1%), 327 (12), 299 (17), 298 (18), 105 (100), 91 (16), and 77 (20).

(2R,3S)-2,3-*Bis*-(4-*methoxybenzyl*)-1,4-*diphenylbutane*-1,4-*dione* (**21a**). 1,4-Diphenylbutane-1,4-dione (**14**) (1.19 g) was treated with 4-methoxybenzyl bromide (1.6 ml) as described. Preliminary chromatography separated monobenzylated diketone (7%) from the more polar dibenzylated products. The diastereoisomeric ratio (d.r.) of the less polar isomer (**21a**): more polar isomer (**21b**) was 30:70. Column chromatography [light petroleum–ethyl acetate (8:2)] yielded the *crystalline dione derivative* (**21a**) (0.54 g, 23%), m.p. 143 °C (from light petroleum–ethyl acetate) (Found: C, 80.6; H, 6.30%; M^+, 478.2144. $C_{32}H_{30}O_4$ requires C, 80.3; H, 6.30%; *M*, 478.2143); $\nu_{max.}(CH_2Cl_2)$ 1 672 cm^{-1} (C=O); δ_H(300 MHz; $CDCl_3$) 2.71 (2 H, dd, *J* 3.5, 13.5 Hz, 5-H_a), 2.87 (2 H, dd, *J* 9.4, 13.5 Hz, 5-H_b), 3.64 (6 H, s, OMe), 4.20—4.29 (2 H, m, 2-, 3-H), 6.58 (4 H, d, *J* 8.8 Hz, 3′-, 5′-H), 6.86 (4 H, d, *J* 8.8 Hz, 2′-, 6′-H), and 7.27—7.72 (5 H, m, 2″-, 6″-H, 3″-, 5″-H, 4″-H); δ_C(20 MHz; $CDCl_3$) 37.05 (t, C-5), 50.59 (d, C-2, -3), 55.14 (q, OMe), 113.66 (d, C-3′, -5′), 128.32, 128.43, and 130.12 (all d, C-2′, 2″, 3″, 5″, 6′, 6″), 130.46 (s, C-1″), 133.00 (d, C-4″), 138.36 (s, C-1), 158.08 (s, C-4′), and 203.69 (s, C-1, -4); *m/z* (e.i.) 358 (5), 240 (24), 239 (59), 121 (100), 105 (60), and 77 (34).

(2R,3R)- *and* (2S,3S)-2,3-*Bis*-(4-*methoxybenzyl*)-1,4-*diphenylbutane*-1,4-*dione* (**21b**). The most polar fraction gave the *crystalline dione derivative* (**21b**) (1.26 g, 53%), m.p. 120 °C (from pentane–diethyl ether) (Found: C, 80.6; H, 6.25. $C_{32}H_{30}O_4$ requires C, 80.3; H, 6.30%); $\nu_{max.}(CH_2Cl_2)$ 1 680 cm^{-1} (C=O); δ_H(300 MHz; $CDCl_3$) 3.08 (2 H, dd, *J* 8.4, 13.8 Hz, 5-H_a), 3.14 (2 H, dd, *J* 4.2, 13.8 Hz, 5-H_b), 3.69 (6 H, s, OMe), 4.09—4.17 (2 H, m, 2-, 3-H), 6.66 (4 H, d, *J* 8.8 Hz, 3′-, 5′-H), 6.97 (4 H, d, *J* 8.8 Hz, 2′-, 6′-H), and 7.26—7.71 (5 H, m, 2″-, 6″-H, 3″-, 5″-H, 4″-H); δ_C(20 MHz; $CDCl_3$) 34.83 (t, C-5), 50.10 (d, C-2, -3), 55.13 (q, OMe), 113.81 (d, C-3′, -5′), 128.30 and 130.12 (all d, C-2′, 2″, 3″, 5″, 6′, 6″), 130.48 (s, C-1″), 132.67 (d, C-4″), 137.62 (s, C-1′), 158.18 (s, C-4′), and 203.54 (s, C-1, -4); *m/z* (e.i.) 478 (M^+, 1%), 140 (37), 239 (100), 238 (4), 121 (77), 105 (56), and 77 (40).

The fraction of intermediate polarity yielded 2,2-*bis*-(4-*methoxybenzyl*)-1,4-*diphenylbutane*-1,4-*dione* (0.22 g, 9%), m.p. 143 °C (from light petroleum–ethyl acetate) (Found: C, 80.5; H, 6.30. $C_{32}H_{30}O_4$ requires C, 80.3; H, 6.30%); $\nu_{max.}(CH_2Cl_2)$ 1 685 cm^{-1} (C=O): δ_H(80 MHz; $CDCl_3$) 3.24 (2 H, s, 3-H_2), 3.24 (2 H, d, *J* 13.8 Hz, 5-H_a), 3.40 (2 H, d, *J* 13.8 Hz, 5-H_b, 3.71 (6 H, s, OMe), 6.72 (4 H, d, *J* 8.8 Hz, 3‴-, 5‴-H), 7.01 (4 H, d, *J* 8.8 Hz, 2‴-, 6‴-H), 7.26—7.51 (6 H, m, 3′-, 3″-; 4′-, 4″-; 5′-, 5″-H), and 7.67—7.80 (4 H, m, 2′-, 2″-; 6′-, 6″-H); *m/z* (e.i.) 478 (M^+, 1%), 359 (9), 358 (31), 357 (15), 327 (8), 253 (9), 121 (100), 105 (92), and 77 (40).

(2R,3R)- *and* (2S,3S)-1,4-*Bis*-(2,4-*dimethoxyphenyl*)-2,3-*bis*-(4-*methoxybenzyl*)*butane*-1,4-*dione* (**22b**). 1,4-Bis-(2,4- dimethoxyphenyl)butane-1,4-dione (**15**) (1.79 g) was treated with 4-methoxybenzyl bromide (1.6 ml) as described. After removal of monobenzylated 1,4-dione (5%) a mixture of dibenzylated isomers (2.13 g, 71%) was isolated. The diastereoisomeric ratio of less polar (**22a**): more polar (**22b**) ester was 40:60. P.l.c. and multiple developments of the same plates, using light petroleum–ethyl acetate (8:2), resulted in isolation of the pure *racemic isomer* (**22b**) but the *meso* isomer (**22a**) could not be obtained pure. The physical and spectral properties for compound (**22b**) are the same as those listed for compound (**13**) obtained by oxidative coupling of the appropriate dihydrochalcone.

Table 4. Fractional co-ordinates (× 10^4) for the atoms of 1,4-diketone (**20b**), with e.s.d.s in parentheses

Atom	*x*	*y*	*z*
C(1)	2 589(4)	3 500(4)	8 265(2)
C(2)	1 171(4)	4 003(4)	8 665(3)
C(3)	85(4)	5 401(4)	8 169(3)
C(4)	429(3)	6 300(4)	7 270(3)
C(5)	1 853(3)	5 800(3)	6 874(2)
C(6)	2 963(3)	4 388(3)	7 362(2)
C(7)	4 525(3)	3 820(4)	6 938(2)
C(8)	5 441(3)	4 348(3)	7 387(2)
C(9)	5 112(3)	6 006(3)	6 840(2)
O(1)	4 675(2)	6 597(2)	5 920(1)
C(10)	5 350(3)	6 589(3)	8 528(2)
C(11)	5 655(4)	7 421(4)	9 039(3)
C(12)	6 087(4)	8 493(4)	8 445(4)
C(13)	6 227(4)	8 749(4)	7 352(4)
C(14)	5 903(3)	7 942(3)	6 835(3)
C(15)	5 462(2)	6 846(3)	7 428(2)
C(16)	10 091(4)	1 023(3)	5 899(2)
C(17)	11 610(5)	406(5)	5 784(3)
C(18)	12 325(4)	1 217(7)	5 797(3)
C(19)	11 546(5)	2 670(6)	5 920(3)
C(20)	10 031(4)	3 289(4)	6 029(2)
C(21)	9 282(3)	2 478(3)	6 023(2)
C(22)	7 637(3)	3 164(3)	6 156(2)
C(23)	7 140(3)	3 374(3)	7 291(2)
C(24)	7 593(3)	1 849(3)	8 133(2)
O(2)	7 676(2)	752(2)	7 905(1)
C(25)	8 046(3)	2 854(3)	9 525(2)
C(26)	8 352(3)	2 686(4)	10 572(2)
C(27)	8 481(3)	1 393(4)	11 351(2)
C(28)	8 316(3)	282(4)	11 101(2)
C(29)	8 012(3)	441(3)	10 064(2)
C(30)	7 879(2)	1 742(3)	9 255(2)

Diethyl 2,3-*Dibenzylbutanedioate* (**25a**) *and* (**25b**). Diethyl succinate (1.40 ml) was benzylated by the usual procedure with benzyl bromide (1.3 ml). The oily residue obtained after work-up was chromatographed to yield an isomeric mixture of dibenzylated esters (1.42 g, 80%). The diastereoisomeric ratio of less polar ester (**25a**): more polar ester (**25b**) was 35:65. Both Rathke[15] and Pohmakotr[21] have prepared a mixture of these esters but no spectroscopic data were reported.

The less polar ester (**25a**) had m.p. 58 °C (from light petroleum–ethyl acetate); $\nu_{max.}(CH_2Cl_2)$ 1 734 cm^{-1} (C=O); δ_H(80 MHz; $CDCl_3$) 1.03 (6 H, t, *J* 7.1 Hz, Me), 2.80—3.03 (6 H, m, 2-, 3-, 5-H), 3.97 (4 H, q, *J* 7.2 Hz, OCH_2), and 7.06—7.22 (10 H, m, ArH); δ_C(20 MHz; $CDCl_3$) 13.97 (q, Me), 36.65 (t, C-5), 50.10 (d, C-2, -3), 60.39 (t, OCH_2), 126.49 (d, C-4′), 128.29 (d, C-2′, -6′), 128.89 (d, C-3′, -5′), 138.37 (s, C-1′), and 173.17 (s, C-1, -4); *m/z* (e.i.) 354 (M^+, 5%), 189 (21), 178 (50), 177 (94), 132 (16), 131 (46), and 91 (100).

The more polar diastereoisomer (**25b**) had m.p. 85 °C (from light petroleum–ethyl acetate); $\nu_{max.}(CH_2Cl_2)$ 1 738 cm^{-1} (C=O); δ_H(80 MHz; $CDCl_3$) 1.12 (6 H, t, *J* 7.1 Hz, Me), 2.81—3.08 (6 H, m, 2-, 3-, 5-H), 4.03 (4 H, q, *J* 7.2 Hz, OCH_2), and 6.99—7.31 (10 H, m, ArH); δ_C(20 MHz; $CDCl_3$) 14.03 (q, Me), 35.48 (t, C-5), 48.09 (d, C-2, -3), 60.51 (t, OCH_2), 124.62 (d, C-4′), 128.34 (d, C-1′, -6′), 128.90 (d, C-3′, -5′), 138.69 (s, C-1′), and 173.23 (s, C-1, -4); *m/z* (e.i.) 354 (M^+, 28%), 309 (18), 263 (15), 189 (47), 178 (47), 177 (100), 132.17 (17), and 91 (79).

Crystal Data for 2,3-*Dibenzyl*-1,4-*diphenylbutane*-1,4-*dione* (**20b**).—$C_{30}H_{26}O_2$, M^+, 418, triclinic, space group $P\bar{1}$, *a* = 10.272(3), *b* = 10.271(1), *c* = 13.0471(1) Å; α = 72.63(1), β = 81.61(2), γ = 62.00(2)°; *Z* = 2. Data were collected on a Nonius CAD-4 four-circle diffractometer with graphite-monochromated Mo-K_α radiation in the range $3 < \theta < 27°$. The

structure was solved by direct methods with the SHELLX-76 programme[29] using 2 704 L_p-corrected, but not absorption-corrected, reflections having $I > 4\sigma(I)$. All non-hydrogen atoms were assigned anisotropic temperature factors; the hydrogen atoms were located on the difference map and refined isotropically. Refinement of the atomic co-ordinates using least-squares techniques converged at $R = 0.0459$; fractional co-ordinates for non-hydrogen atoms are listed in Table 4. Fractional co-ordinates for the hydrogen atoms, and the anisotropic temperatures factors for the non-hydrogen atoms, and the intramolecular bond lengths and angles are available on request from the Crystallographic Data Centre, Cambridge.* A perspective view of the crystallographically numbered structure for molecule (**20b**) is given in the Figure.

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* See section 5.6.3 of Instructions for Authors, January issue.

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