Synthetic Approaches towards 4-Ylidenebutenolides and 4-Ylidenetetronic Acids. Regioselective Nucleophilic Additions to Unsymmetrically Substituted Maleic Anhydrides

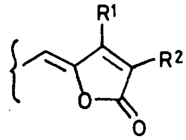
By **David W. Knight** and **Gerald Pattenden,*** Department of Chemistry, The University, Nottingham NG7 2RD

The application of unsymmetrically substituted maleic anhydrides in the synthesis of but-2-enolides, 4-hydroxybut-2-enolides, 4-ylidenebut-2-enolides, and 4-ylidenetetronic acid derivatives is examined. Reduction of 2-methylmaleic anhydride with metal hydride agents leads to a mixture of but-2-enolides (8a) and (8b), and 4-hydroxybut-2-enolides (7a) and (7b) corresponding to *ca.* 88% regioselective hydride ion attack at the more hindered (C-1) carbonyl function in the anhydride. Similar reductions of methoxy-substituted anhydrides (13) and (16) were completely regioselective and led to tetronic acid and 4-hydroxytetronic acid products resulting from hydride ion attack at only C-1 in the anhydrides.

Condensation of the phosphorane (22a) with 2-methylmaleic anhydride produced largely the *E*-ylidenebutenolide (23), accompanied by smaller amounts of the *Z*-butenolides (24) and (25); similar condensations with the anhydrides (16a) and (16b) were totally regioselective and produced *Z,E*-mixtures of ylidenetetronic acids corresponding to attack at C-1 in the anhydrides. The addition of ethylmagnesium bromide to 2-methylmaleic anhydride, followed by dehydration of the intermediate carbinol, led to a 3 : 2 mixture of the ylidenebut-2-enolides (39) and (40), whereas the corresponding reaction with the 2-methoxy-anhydride (16b) was more selective producing only (41).

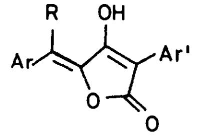
These studies have provided a basis for the development of syntheses of the ' pulvinone,' ' pulvinic acid, ' and ' multicolic acid ' groups of natural pigments.

4-Ylidenebutenolides (1) and 4-ylidenetetronic acids (2) are widely distributed in nature, and many display interesting biological properties.[1] In earlier publications we have outlined the application of 4-phosphoranylidenebutenolide intermediates in the synthesis of these molecules.[2] The necessary phosphonium salt precursors for these studies were conveniently prepared *via* allylic bromination of but-2-enolides or by halogenation of 4-hydroxybut-2-enolides. The availability of a number of unsymmetrically substituted maleic anhydrides suggested a new approach to these, and related synthons for the synthesis of (1) and (2), based on regioselective nucleophilic additions to the anhydrides. When we began our investigations of this approach, it had been shown that both phthalic anhydride[3] and 2-methylmaleic anhydride[4] condense smoothly with phosphoranes of the type $Ph_3P{=}CH{\cdot}COR$, providing a useful direct route to certain 4-ylidenebutenolides. In this paper we describe the results of a more general study of the regioselectivities of additions of hydride ion and carbanion nucleophiles to unsymmetrically substituted maleic anhydrides.[5] A novel dichotomy in the reactivity of 2-methylmaleic anhydride toward these nucleophiles is observed, and the studies have provided flexible routes to tetronic acid precursors used in the total synthesis of natural pulvinone and pulvinic acid pigments, (3) and (4) respectively, found in lichen and higher fungi, and to the carbon skeleton present in multicolic acid (5a) and related metabolites (5b, c) isolated from *Penicillium multicolor* (see following papers).



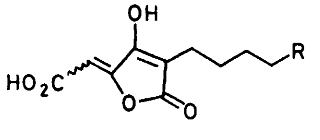
(1) R¹ = R² = H, alkyl, *etc.*,

(2) R¹ = OH; R² = H, alkyl *etc.*,



(3) R = H

(4) R = CO_2H



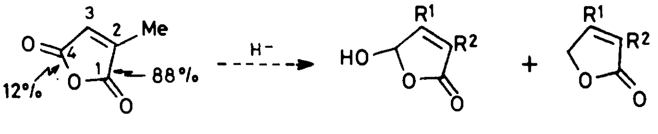
(5)

a; R = CH_2OH

b; R = CO_2H

c; R = Me

We first examined the regioselectivity during reductions of unsymmetrically substituted maleic anhydrides using metal hydride reducing agents. Treatment of 2-methylmaleic anhydride (6) with lithium tri-t-butoxyaluminium hydride (LITBAL) at —30 °C led (*ca.* 60%) to a mixture of but-2-enolide and 4-hydroxybut-2-enolide products (7—8a, b) resulting from hydride ion attack at both carbonyl functions in the anhydride. The 4-hydroxybutenolides (7a) and (7b) were separated by a combination of fractional distillation and preparative-layer chromatography, and were fully characterised by comparison with authentic specimens.[6,7] The butenolides (8a) and (8b) were only difficultly resolved in chromatography, and their structures followed from comparison between spectral data recorded for mixtures of the two and those of authentic samples synthesised by independent routes. Inspection of ^1H n.m.r. spectral

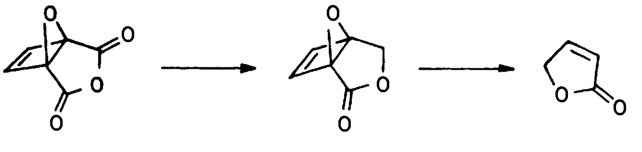


(6) (7) (8)

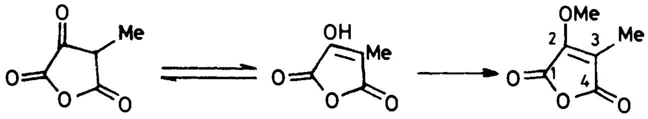
a; R¹ = Me; R² = H

b; R¹ = H ; R² = Me

data of crude reaction mixtures showed that the butenolides (8a) and (8b), and the 4-hydroxy-derivatives (7a) and (7b) were produced in the approximate proportions 35 : 3 : 53 : 9, showing that attack by hydride ion was approximately 88% selective at the more hindered (C-1) carbonyl function in the anhydride; this ratio was not altered when lithium aluminium hydride (LAH) was used in place of LITBAL. Attempts to reduce maleic anhydride itself to but-2-enolide (11) with LAH or LITBAL were unsuccessful, and instead only polymeric material resulted. This problem was circumvented by first preparing the corresponding Diels–Alder adduct (9) with furan. Reduction of (9) with LAH then led to the lactone (10), accompanied by smaller amounts of the 4-hydroxy-derivative, which by retro Diels–Alder reaction gave the required but-2-enolide (11). This route to (11) was also reported by Takano and Ogasawara[8] while our own work was in progress.

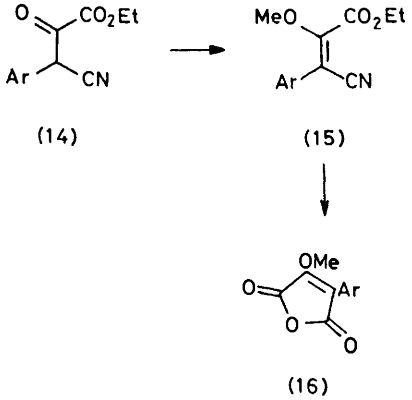


(9) (10) (11)



(12) (13)

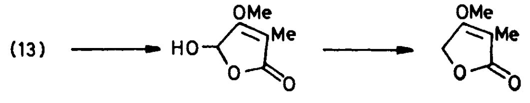
We next examined the regioselectivity of reduction of 2-methoxy-3-methyl- (13) and 2-methoxy-3-aryl- (16) maleic anhydrides with metal hydrides. The anhydride (13) was easily available *via* methylation (Me_2SO_4–K_2CO_3) of the oxo-anhydride (12)[9] produced from condensation between ethyl propionate and diethyl oxalate in the presence of base. The aryl-anhydrides (16) were most conveniently synthesised from the corresponding phenylacetonitriles following condensations with diethyl oxalate [to pyruvate (14)], methylation [to (15)], and treatment of the latter with acid.[10] Reduction of the methoxy-anhydrides (13) and (16a, b) with the metal hydride reducing agents above, under several conditions, produced mixtures of but-2-enolide and hydroxybut-2-enolides resulting from hydride ion attack at only the carbonyl functions adjacent to the methoxy-groups in the anhydrides. Thus, reduction of the anhydride (13) with LITBAL led (*ca.* 70%) to a 7 : 3 mixture of (17) and (18) whereas anhydrides (16a) and (16b) were reduced (by either LAH or LITBAL) to 2 : 1 mixtures of (19) and (20). Each of the 4-hydroxybut-2-enolides (17) (19a) and (19b) could be reduced further to the butenolides (18), (20a), and (20b) respectively, using alkaline sodium borohydride.[11] Small amounts ($<5\%$) of the arylbut-2-enolides (21),[12] lacking a 3-OMe substituent, were also found amongst the products of reduction of (19) and the corresponding anhydrides (16).



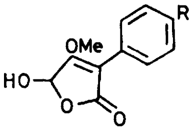
(14) (15) (16)

a; Ar = Ph
b; Ar = 4-MeOC_6H_4

The structure assigned to the butenolide (18) followed from comparison with an authentic sample prepared from 2-methylacetoacetate.[2] The regioselectivities of the reductions of the arylmethoxymaleic anhydrides (16) could not be established unambiguously from spectral data, and neither were we able to develop a satisfactory alternative synthetic route to the butenolide (20) along similar lines to those used to synthesise (18) from 2-methylacetoacetate.[13] We ultimately established the selectivity of hydride ion attack in these anhydrides from *X*-ray measurements on the hydroxybutenolide prepared from (16a). These measurements established structure (19a) for the hydroxybutenolide and hence (20a) for the butenolide obtained from the same reduction. Structures (19b) and (20b) followed for the reduction products of the corresponding 4-methoxyphenylmaleic anhydride (16b) by close comparison of spectral data.



(13) (17) (18)



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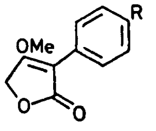

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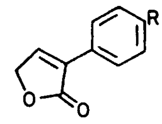
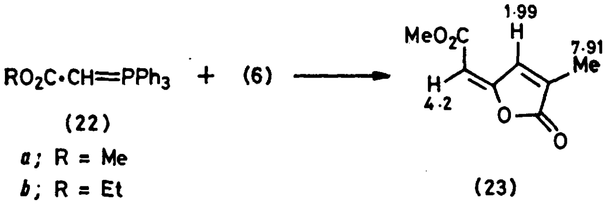


(21)

a; R = H
b; R = OMe

We next investigated the regioselectivity of condensation reactions between the stabilised phosphorane (22) and the anhydrides (6), (13), and (16). In the case of 2-methylmaleic anhydride, the reaction took a different steric course to the corresponding hydride ion reduction, and led largely to the ylidenebutenolide (23) resulting from nucleophilic addition to C-4 in the anhydride. Condensations with the methoxy-substituted anhydrides (13) and (16) were totally regioselective, and produced *Z*,*E*-mixtures of ylidenetetronic acids corresponding to attack only at C-1 in the anhydrides; our previous assignments [5] of these structures are thus revised.

The reaction between 2-methylmaleic anhydride and the phosphorane (22a) produced largely the *E*-butenolide (23) accompanied by smaller amounts of the *Z*-butenolides (24) and (25); the regioselectivity of this reaction, which has been previously examined,[14] corresponds to approximately 90% in favour of carbanion attack at C-1 in the anhydride. Massy-Westropp and co-workers, in contemporaneous studies,[14] assigned structure (23) to the major product of this reaction on the basis of differential olefinic proton coupling constants in its ^{1}H n.m.r. spectrum. This method is satisfactory only when both geometrical isomers of the two positional isomers [*e.g.* (24) and (25)] are available for comparison, but caution must be exercised since erroneous conclusions can be made using this method. We established structure (23) following catalytic hydrogenation to the tetrahydro-derivative (26) and comparison with an authentic sample of the isomeric butanolide (28) prepared from 3-nitro-*p*-cresol. Thus hydrogenation of (23) over Adams catalyst led to largely one diastereoisomer (by ^{1}H n.m.r. and ^{13}C n.m.r.) of the butanolide (26). This butanolide showed different spectroscopic properties (i.r., ^{1}H n.m.r., ^{13}C n.m.r.) to those of the isomeric butanolide (28) obtained by hydrogenation of the butenolide (27) [15] prepared by acid treatment of 3-nitro-*p*-cresol, followed by esterification. The *E*-geometry assigned to (23) followed from comparison of ^{1}H n.m.r. shift data with the corresponding *Z*-isomer (24) (vinylic-H *cis*- to butenolide oxygen deshielded).[2]

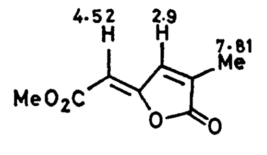


(22)

a; R = Me

b; R = Et

(23)



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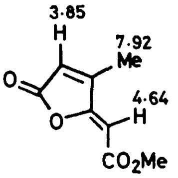

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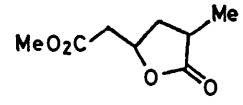
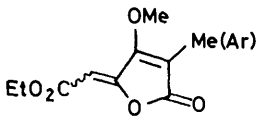


(26)

(27) (28)

Reactions between the methoxy-substituted anhydrides (13) and (16) and the phosphorane (22b) led to *Z*,*E*-mixtures of the corresponding C-1-derivatives [*viz.* (29)], from which the *Z*-isomers were separated as crystalline compounds; the *E*-isomers were oils which isomerised to the *Z*-isomers when set aside at room temperature. Assignment of structure amongst this class of compound was made difficult by the general paucity of suitable model systems, and this feature led us earlier to assign the alternative [*viz.* (30)] incorrect structures to the ylidenetetronic acids.



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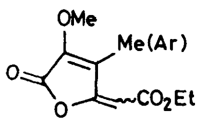
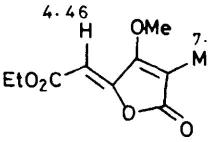
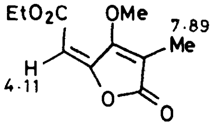


(30)

Comparative ^{1}H n.m.r. spectral data [see formulae (31) and (32)], and isomerisation studies, of the isomeric butenolides produced from the anhydride (13), permitted an unambiguous assignment of *Z*- and *E*-geometry to the molecules, but did not provide any clue as to the site of attack by the phosphorane on the anhydride. Comparison between the ^{13}C n.m.r. spectral



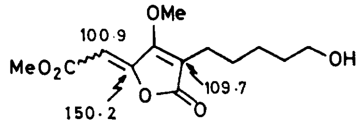
Z-(31)



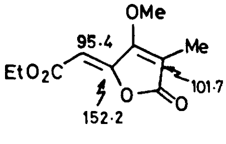
E-(32)

data of the crystalline *Z*-isomer with those of the permethylated derivative of multicolic acid (5a) ex. *P. multicolor*,[16] emphasised considerable differences, particularly between the chemical shifts of the olefinic carbons [see formulae (33) and (34)] and these data earlier led us to assign structure (30) to the ylidenetetronic acid. We ultimately resolved the problem by *X*-ray measurements on the *Z*-isomer, and these showed conclusively that the isomer had the alternative structure (31). This fortuitous result suggested a simple and attractive synthetic route to the carbon skeleton present in multicolic acid (5a) and the related metabolites (5b) and (5c), which is described in an accompanying paper.

The orientation shown in (35a) for the product resulting from condensation between (22b), and the methoxyphenyl-substituted anhydride (16) was also established from *X*-ray measurements on the crystalline *Z*-ylidenetetronic acid (36). Compounds (35a) and also the ylidenetetronic acids (35b) produced from similar condensations with $MeCO{\cdot}CH{=}PPh_3$, exhibited closely comparable ^1H n.m.r. data, suggesting that they all possessed structures corresponding to exclusive attack by the phosphoranes at C-1 in the anhydrides.



(33)



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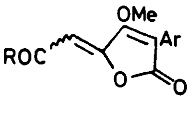
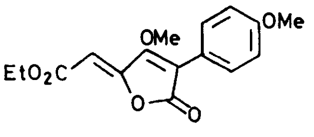


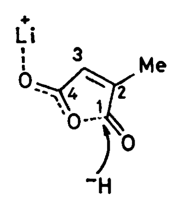


(35) Ar = Ph or 4-OMeC_6H_4-
a; R = OEt
b; R = Me

Z-(36)

The steric and electronic effects of substituents at C-2 and C-3, play complementary roles in determining the regioselectivity of the nucleophilic additions to the anhydrides (6), (13), and (16). The addition of the phosphorane (22) to 2-methylmaleic anhydride would appear to be controlled largely by steric factors since the less hindered carbonyl function is attacked preferentially. In similar reactions with the methoxy-substituted anhydrides (13) and (16) the reactivities of the C-4 carbonyl functions towards nucleophilic attack are reduced considerably as a result of electron release from the OMe-group, through the ' vinylogous ester ' systems. Irreversible decomposition of the intermediate betaines to products is presumably more rapid than reversible formation of starting materials, in these cases, which accounts for the observation that only those olefin products resulting from attack at C-1 in the anhydrides are found.

The selective hydride ion addition to the more hindered (C-1) carbonyl function in 2-methylmaleic anhydride can be rationalised by invoking initial formation of a cationic complex [*viz.* (37)] between the reducing agent and the less hindered (C-4) carbonyl oxygen in the anhydride. This makes C-4 less accessible towards attack, and hydride ion addition takes place preferentially at C-1. The regioselective reductions of methoxy-substituted anhydrides (13) and (16) can be accommodated by an intramolecular four-centre mechanism involving intermediate formation of an oxonium ion [*e.g.* (38)].



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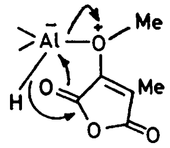
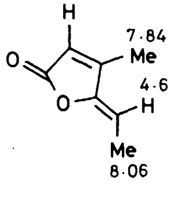


(38)

In an extension of our studies, we also briefly examined the specificities of the reactions between maleic anhydrides and Grignard reagents.[17] Treatment of 2-methylmaleic anhydride, at −70 °C, with ethylmagnesium bromide led to a mixture of carbinols, which was dehydrated by distillation from fused potassium hydrogen sulphate producing a 3 : 2 mixture of isomeric ylidenebutenolides. The butenolides were separated by chromatography, and attempts to interconvert them by thermal, photochemical, and catalytic isomerisation procedures were unsuccessful. We therefore concluded that they were positional, rather than π-geometrical isomers. This supposition was reinforced on inspection of their ^1H n.m.r. spectral data, which also suggested that each isomer assumed the preferred *Z*-configuration. Comparison with other ^1H n.m.r. data for isomeric butenolides in this paper, led us to assign structures (39) and (40) to the major and minor *Z*-butenolides respectively.



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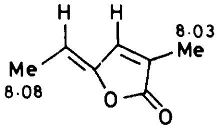
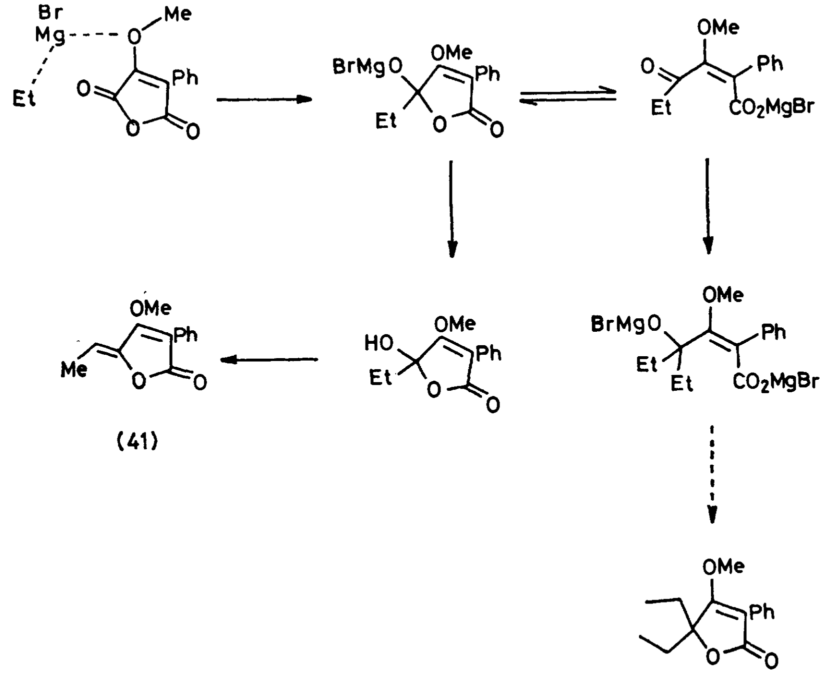


(40)

By contrast, the Grignard reaction between ethyl magnesium bromide and anhydride (16a), followed by dehydration of the intermediate carbinol, led to a single ylidenetetronic acid. The establishment of a structure to this tetronic acid was difficult. Its electronic absorption spectrum ($\lambda_{max.}$ 271 nm) indicated a 1-phenylpenta-1,3-diene chromophore, and the chemical shift of the vinylic-H in its ^1H n.m.r. spectrum (τ 4.48) suggested a *Z*-geometry. By analogy with the related phosphorane and hydride ion additions to (16), it seems most likely that the structure of this ylidenebutenolide is best represented by (41). Interestingly, the reaction between (16a) and an excess of ethylmagnesium bromide, led to an additional product, formulated as (42), resulting from the addition of two moles of Grignard reagent; this product presumably arises as shown in the scheme [*cf.* hydride ion additions to (16)].



(41)

(42)

The present studies thus established the utility of unsymmetrically substituted (methyl-, phenyl-, and methoxy-) maleic anhydrides for the controlled syntheses of the corresponding but-2-enolides, 4-hydroxybutenolides, and 4-ylidenetetronic acids. The extensions of these studies towards the total synthesis of natural pulvinones, natural pulvinic acids, and multicolanic acid are described in the accompanying papers.

EXPERIMENTAL

For general experimental details see ref. 2. ^{13}C N.m.r. spectra were recorded on a JEOL-PS-100 spectrometer, in $CDCl_3$ as solvent.

2-*Methoxy*-3-*methylmaleic Anhydride* (3-*Methoxy*-4-*methylfuran*-2,5-*dione*) (13).—Dimethyl sulphate (13 g) was added during 0.5 h to a stirred solution of 2-methyl-3-oxosuccinic anhydride (13 g)[9] in dry acetone (200 ml) containing anhydrous potassium carbonate (16 g), maintained under gentle reflux. The mixture was heated under reflux for 2 h, then cooled, and filtered. Evaporation of the acetone left a residue which crystallised from benzene to give the *anhydride* (9.4 g, 65%) as colourless plates, m.p. 44.5—45 °C, $\lambda_{max.}(CHCl_3)$ 285 (5 800) nm; $\nu_{max.}$(KBr) 1 876, 1 775, 1 676 cm^{-1}; τ 5.74 (O*Me*) and 7.93 (:C*Me*) (Found: C, 50.4; H, 4.2. $C_6H_6O_4$ requires C, 50.7; H, 4.2%).

Ethyl (3-*Cyano*-2-*methoxy*)*cinnamate* (*Ethyl* 3-*Cyano*-2-*methoxy*-3-*phenylprop*-2-*enoate*) (15a).—Condensation of phenylacetonitrile with diethyl oxalate, by the method of Hill,[18] led to ethyl (3-cyano-3-phenyl)pyruvate (14a), m.p. 129—130 °C (lit.,[19] m.p. 130 °C), τ 2.2—2.4 (m, 2 H), 2.5—2.75 (m, 3 H), 5.6 (q, *J* 7.5, C*H*$_2$CH$_3$), 8.6 (t, *J* 7.5, CH$_2$C*H*$_3$). Methylation with dimethyl sulphate, in the usual manner, then gave the cinnamate (15a), b.p. 123—124 °C/0.15 mmHg, n_D^{23} 1.549 8 (lit.,[20] b.p. 128 °C/0.4 mmHg, n_D^{21} 1.550 9), $\nu_{max.}$ 2 200, 1 730, 1 608 cm^{-1}; τ 2.2—2.4 (m, 2 H), 2.5—2.7 (m, 3 H), 5.56 (q, *J* 7.5, C*H*$_2$CH$_3$), 6.19 (O*Me*), and 8.58 (t, *J* 7.5, CH$_2$C*H*$_3$).

2-*Methoxy*-3-*phenylmaleic Anhydride* (3-*Methoxy*-4-*phenylfuran*-2,5-*dione*) (16a).—A solution of ethyl (3-cyano-2-methoxy)cinnamate (11.2 g) in glacial acetic acid (120 ml) and water (80 ml) was treated dropwise with concentrated sulphuric acid (100 ml) to maintain a temperature $<$105 °C. The mixture was then cooled and diluted with water (250 ml) and extracted with ether (3 × 100 ml). The ether extracts were washed with 2N-KOH, and the aqueous extracts were then acidified with dilute H_2SO_4 and extracted with ether. Evaporation of the dried ether extracts left a residue which crystallised from methanol giving the anhydride (7.5, 83%), as pale yellow needles, m.p. 112—113 °C (lit.,[10] m.p. 115—116 °C), $\lambda_{max.}(CHCl_3)$ 342 nm, $\nu_{max.}$(KBr) 1 834, 1 764, and 1 636 cm^{-1}, τ 1.95—2.15 (m, 2 H), 2.5—2.65 (m, 3H), and 5.67 (O*Me*) (Found: C, 64.6; H, 4.1. Calc. for $C_{11}H_8O_4$: C, 64.7; H, 3.9%).

2-*Methoxy*-3-(4-*methoxyphenyl*)*maleic Anhydride* (3-*Methoxy*-4-p-*methoxyphenylfuran*-2,5-*dione*) (16b).—The anhydride was prepared (85%) from 4-methoxyphenylacetonitrile in an identical manner to that described for 2-methoxy-3-phenylmaleic anhydride. The intermediate ethyl 3-cyano-3-(4-methoxyphenyl)pyruvate showed m.p. 95—95.5 °C (lit.,[21] m.p. 94 °C), τ 2.16 (d, *J* 9, 2 H), 2.5br (s, O*H*), 3.08 (d, *J* 9, 2 H), 5.54 (q, *J* 7.5, OC*H*$_2$CH$_3$), 6.22 (OC*H*$_3$), 8.57 (t, *J* 7.5, OCH$_2$C*H*$_3$), and the intermediate ethyl (3-cyano-2-methoxyphenyl)-4-methoxycinnamate had b.p. 174 °C/0.1 mmHg, $\nu_{max.}$ (film) 2 220, 1 720, 1 602, and 834 cm^{-1}; τ 2.32 (d, *J* 9, 2 H), 3.11 (d, *J* 9, 2 H), 5.57 (q, *J* 7, OCH_2CH_3), 6.19 [:C(CO)·OCH_3], 6.23 ($PhOCH_3$), and 8.60 (*J* 7, OCH_2CH_3). The anhydride (16b) crystallised from methanol as bright yellow needles, m.p. 139.5—140 °C (lit.,[10] m.p. 140—142 °C), $\lambda_{max.}$($CHCl_3$) 378 nm; $\nu_{max.}$(KBr) 1 822, 1 756, 1 630, and 840 cm^{-1}.

Reduction of Maleic Anhydrides: General Procedure.—A suspension of lithium tri-t-butoxyaluminium hydride (1 equiv.) in glyme (2 ml per mmol of reagent) was added dropwise to a stirred solution of the anhydride (1 equiv.) in glyme (1 ml per mmol) maintained at −30 °C under nitrogen. The mixture was stirred at −30 °C for 1 h, and then at 25 °C for 12 h. The mixture was cooled to 0 °C, then diluted with dilute sulphuric acid, and extracted with ether. Evaporation of the dried ether extracts left a residue from which the but-2-enolide and 4-hydroxybut-2-enolide products were separated, and purified by chromatography on silica gel.

Sodium borohydride (10 equiv.) was added portionwise to a stirred solution of the 4-hydroxybut-2-enolide (1 equiv.) in water (10 ml per mmol) containing sodium hydroxide (12 equiv.). The mixture was stirred at 25 °C for 16 h, diluted with water, then acidified carefully with dilute hydrochloric acid and extracted with ether. Evaporation of the dried ether extracts left a residue, which was chromatographed or crystallised to give the but-2-enolide (yields 70—90%).

Reduction of 2-*Methylmaleic Anhydride.*—By the general procedure, reduction of the anhydride produced (*ca.* 50%) a mixture of the lactones (8a) and (8b), and the lactols (7b) and (7a) present in the approximate proportions 35 : 3 : 9 : 53 (by integration of appropriate ^{1}H n.m.r. resonances). Fractional distillation gave a fraction (b.p. 137—141 °C/1 mmHg) containing only the lactols (7a) and (7b) which were separated by chromatography in chloroform–ethyl acetate–acetic acid (5 : 4 : 1). Both lactols displayed identical physical and spectroscopic properties to those published previously.[6,7]

Reduction of 2-*Methoxy*-3-*methylmaleic Anhydride.*—By the general procedure, reduction of the anhydride, followed by chromatography in chloroform–methanol (10 : 1) gave (*a*) 3-methoxy-2-methylbut-2-enolide [4-methoxy-3-methylfuran-2(5*H*)-one] (18) (24%) (eluted first) an oil, identical (t.l.c., i.r., ^{1}H n.m.r.) with an authentic sample prepared from 2-methylacetoacetate,[2] and (*b*) 4-hydroxy-3-methoxy-2-methylbut-2-enolide (17) [5-hydroxy-4-methoxy-3-methylfuran-2(5*H*)-one] (45%) (eluted second), which crystallised from benzene as colourless needles, m.p. 93 °C, $\nu_{max.}$(KBr) 3 315, 1 750, 1 733, and 1 686 cm^{-1}; τ 3.8 (O*H*), 4.04 (C*H*.OH), 5.93 (OMe), and 8.21 (:C*Me*) (Found: C, 50.2; H, 5.8. $C_6H_8O_4$ requires C, 50.0; H, 5.6%).

Reduction of 2-*Methoxy*-3-*phenylmaleic Anhydride* (16a).—By the general procedure, reduction of the anhydride (2 g), followed by chromatography in chloroform–ethyl acetate (4 : 1) gave: (*a*) 3-methoxy-2-phenylbut-2-enolide [4-methoxy-3-phenylfuran-2(5*H*)-one] (20a) (0.4 g) (eluted first) which crystallised from methanol as colourless rods, m.p. 124—124.5 °C, $\lambda_{max.}$($CHCl_3$) 262 nm; $\nu_{max.}$(KBr) 1 742, 1 645 cm^{-1}; τ 2.0—2.25 (m, 2 H), 2.4—2.8 (m, 3 H), 5.24 (CH_2), and 6.12 (O*Me*) (Found: C, 69.3; H, 5.2. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.2%), and (*b*) 4-hydroxy-3-methoxy-2-phenylbut-2-enolide [5-hydroxy-4-methoxy-3-phenylfuran-2(5*H*)-one] (19a) (0.87 g) (eluted second) which crystallised from ethyl acetate as cubes, m.p. 133—134 °C, $\lambda_{max.}$(EtOH) 267 nm, $\nu_{max.}$(KBr) 3 270, 1 715, and 1 646 cm^{-1}; τ [$(CD_3)_2CO$] 1.98—2.2 (m, 2 H), 2.45—2.8 (m, 3 H), 3.0 (O*H*), 3.66 (C*H*·OH), and 5.86 (O*Me*) (Found: C, 64.0; H, 5.2. $C_{11}H_{10}O_4$ requires C, 64.0; H, 4.9%).

Reduction of 2-*Methoxy*-3-(4-*methoxyphenyl*)*maleic Anhydride* (16b).—By the general procedure, reduction of the anhydride (2.3 g), followed by chromatography in chloroform–methanol (95 : 5) gave: (*a*) 3-methoxy-2-(4-methoxyphenyl)but-2-enolide [4-methoxy-3-*p*-methoxyphenyl)furan-2(5*H*)-one] (20b) (0.5 g) (eluted first) which crystallised from methanol as colourless needles, m.p. 111.5—112 °C, $\lambda_{max.}$($CHCl_3$) 277 nm; $\nu_{max.}$(KBr) 1 726 and 1 637 cm^{-1}; τ[$(CD_3)_2CO$] 2.11 (d, *J* 9, 2 H), 3.08 (d, *J* 9, 2 H), 5.0 (CH_2), 5.94 (O*Me*), and 6.23 (ArO*Me*) (Found: C, 65.7; H, 5.6. $C_{12}H_{12}O_4$ requires C, 65.5; H, 5.5%), and (*b*) 4-hydroxy-3-methoxy-2-(4-methoxyphenyl)but-2-enolide [5-hydroxy-4-methoxy-3-*p*-methoxyphenyl)furan-2(5*H*)-one] (19b) (1.1 g) (eluted second), which crystallised from ethanol as pale yellow rhombs, m.p. 157.5—158 °C, $\lambda_{max.}$($CHCl_3$) 284 nm; $\nu_{max.}$(KBr) 3 270, 1 710, and 1 644 cm^{-1}; τ [$(CD_3)_2CO$] 2.13 (d, *J* 9, 2 H), 2.98 (O*H*), 3.06 (d, *J* 9, 2 H), 3.66 (C*H*·O), 5.82 (O*Me*), and 6.22 (ArOMe) (Found: C, 61.1; H, 5.3. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%).

Reduction of the anhydride (2.3 g) with lithium aluminium hydride in tetrahydrofuran at −70 °C for 1 h, followed at −30 °C for 1 h, also led to a mixture of the butenolide (20b) (0.58 g) and the 4-OH derivative (19b) (0.65 g).

Phosphorane Reactions with Maleic Anhydrides: General Procedure.—Solutions of the phosphoranes (1 equiv.) and anhydrides (1 equiv.) in chloroform [in the cases involving phosphorane (22)] or toluene (in the cases involving phosphorane, MeCO·CH=PPh_3) (5 ml per mmol of reactant) were heated under reflux for 16 h, in a nitrogen atmosphere. After cooling, the solutions were evaporated to dryness, and the residues were then chromatographed on silica gel to give isomerically pure ylidenebutenolides.

Reaction between the anhydride (6) *and the phosphorane* (22a). By the general procedure, reaction between the anhydride (0.22 g) and the phosphorane (0.67 g), followed by chromatography in chloroform gave (i) (E)-4-*methoxycarbonylmethylidene*-2-*methylbut*-2-*enolide* [(E)-5-*methoxycarbonylmethylidene*-3-*methylfuran*-2(5H)-*one*] (23) (0.26 g) (eluted first) which crystallised from methanol as colourless plates, m.p. 78—79 °C, $\lambda_{max.}$($CHCl_3$) 296 nm; $\nu_{max.}$($CHCl_3$) 1 768 and 1 650 cm^{-1}; τ 1.99 (m, MeC:C*H*), 4.2 (:C*H*·CO_2Me), 6.22 (OMe), and 7.91 (d, *J ca.* 1, :C*Me*) (Found: C, 56.9; H, 4.6; $C_8H_8O_4$ requires C, 57.1; H, 4.7%) and (ii) a mixture of *Z*-isomers of 2- and 3-methylbut-2-enolides (3- and 4-methylfuranones) (24) and (25) respectively (35 mg) (eluted second) which was not resolved, τ 2.9 (m, MeC:C*H*), 4.52 (C*H*·CO_2Me), 6.21 (OMe), 7.81 (:C*Me*) [for (24)] and τ 3.85 (m, MeC:C*H*), 4.64 (:C*H*·CO_2Me), 6.21 (OMe), and 7.92 (:C*Me*) [for (25)]. ^{1}H N.m.r. data on crude reaction products indicated that (23), (24), and (25) were present in the approximate proportions 87 : 7 : 6.

4-*Methoxycarbonylmethyl*-2-*methylbutanolide* [*Dihydro*-5-*methoxycarbonylmethyl*-3-*methylfuran*-2(5H)-*one*] (26).—A solution of 4-methoxycarbonylmethylidene-2-methylbut-2-enolide (0.1 g) in ethyl acetate (4 ml) was shaken in an atmosphere of hydrogen in the presence of Adams catalyst (0.05 g) until two mole equivalents of hydrogen were absorbed. The catalyst was filtered off and the filtrate was then evaporated to dryness. Chromatography of the residue on silica gel using chloroform as eluant gave largely one diastereoisomer of the butanolide as an oil (0.04 g), $\nu_{max.}$ 1 760 and 1 720 cm^{-1}; τ 5.2 (m, C*H*·O), 6.32 (O*Me*), 7.2—8.3 (m, 5 H), 8.8 (d, *J* 7, CH*Me*); δ 181.4 (5-ring CO), 173.9 (C:O), 74.1 (*C*H·O), 51.4 (O*C*H$_3$), 39.2 (*C*HMe), 34.0 (*C*H$_2$), 33.1 (*C*H$_2$), and 16.8 (CH*C*H$_3$) [diastereotopic carbons were also observed at δ 35.8, 37.1, 40.1, and at 15.1 (CH*C*H$_3$)]; *m/e* 172, $C_8H_{12}O_4$ *M* 172.

4-*Methoxycarbonylmethyl*-3-*methylbutanolide* [*Dihydro*-5-*methoxycarbonylmethyl*-4-*methylfuran*-2(5H)-*one*] (28).—A solution of 4-methoxycarbonylmethyl-3-methylbut-2-enolide (0.1 g) [15] in ethyl acetate (3 ml) was treated with hydrogen as described above. Chromatography of the residue, as above, gave the butanolide (0.075 g), as an oily mixture of diastereoisomers, $\nu_{max.}$ 1 770 and 1 730 cm^{-1}; τ 5.1 and 5.55 (m, C*H*·O), 6.3 (O*Me*), 6.9—7.9 (m, 5 H), 8.8 and 8.95 (d, *J* 7, CH*Me*); δ 175.6 (5-ring CO), 170.3 (CO), 78.9 (*C*H·O), 52.0 (O*C*H$_3$), 37.0 (*C*H$_2$), 35.0 (*C*H$_2$), 32.6 (*C*HMe), and 14.1 (CH*C*H$_3$) [diastereotopic carbons were observed at δ 82.6 (*C*H·O), 35.7, 36.5, 38.6, and at 17.3 (CH*C*H$_3$)]; *m/e* 172.

Reaction between the anhydride (13) *and the phosphorane* (22b). By the general procedure, reaction between the anhydride (0.28 g) and the phosphorane (0.7 g) followed by chromatography in chloroform gave (i) (E)-4-*ethoxycarbonylmethylidene*-3-*methoxy*-2-*methylbut*-2-*en*-4-*olide* [(E)-5-*methoxycarbonylmethylidene*-4-*methoxy*-3-*methylfuran*-2(5H)-*one*] (32) (0.1 g) (eluted first), an oil, τ 4.11 (:C*H*CO$_2$Et), 5.76 (q, *J* 7, C*H*$_2$CH$_3$), 5.85 (O*Me*), 7.89 (:C*Me*), and 8.69 (t, *J* 7, CH$_2$C*H*$_3$), which isomerised rapidly to the corresponding *Z*-isomer, and (ii) (Z)-4-*ethoxycarbonylmethylidene*-3-*methoxy*-2-*methylbut*-2-*en*-4-*olide* [(Z)-5-*methoxycarbonylmethylidene*-4-*methoxy*-3-*methylfuran*-2(5H)-*one*] (31) (0.25 g) (eluted second) which crystallised from benzene–light petroleum (b.p. 80—90 °C) (1 : 1) as colourless needles, m.p. 66—67 °C, $\lambda_{max.}$(CHCl$_3$) 271 (ε 17 500) nm; $\nu_{max.}$(KBr) 1 790, 1 720, 1 678, and 1 645 cm^{-1}; τ 4.46 (:C*H*CO$_2$Et), 5.76 (q, *J* 7, C*H*$_2$CH$_3$), 5.81 (OMe), 7.90 (:C*Me*), and 8.71 (t, *J* 7, CH$_2$C*H*$_3$) (Found: C, 56.7; H, 5.9. $C_{10}H_{12}O_5$ requires C, 56.6; H, 5.7%).

Reaction between the anhydride (16a) *and the phosphorane* (22a). By the general procedure, reaction between the anhydride (0.41 g) and the phosphorane (0.64 g) followed by chromatography in chloroform gave (i) (*E*)-4-methoxycarbonylmethylidene-3-methoxy-2-phenylbut-2-en-4-olide [(*E*)-5-methoxycarbonylmethylidene-4-methoxy-3-phenylfuran-2(5*H*)-one] (35; R = OMe, Ar = Ph) (0.15 g) (eluted first), τ 2.6 (5 H), 4.01 (:CHCO$_2$Me), and 6.23 (2 × O*Me*) which isomerised rapidly to the corresponding *Z*-isomer, and (ii) (Z)-4-*methoxycarbonylmethylidene*-3-*methoxy*-2-*phenylbut*-2-*en*-4-*olide* [(Z)-5-*methoxycarbonylmethylidene*-4-*methoxy*-3-*phenylfuran*-2(5H)-*one*] (35; R = OMe, Ar = Ph) (0.3 g) (eluted second) which crystallised from methanol as colourless needles, m.p. 94—94.5 °C, $\lambda_{max.}$(EtOH) 268 and 307 nm; $\nu_{max.}$(KBr) 1 780, 1 706, 1 650, and 1 605 cm^{-1}; τ 2.59 (5 H), 4.29 (:C*H*·CO$_2$Me), and 6.23 (2 × O*Me*) (Found: C, 64.5; H, 4.8. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.6%).

(Z)-3-*Methoxy*-4-*methylcarbonylmethylidene*-2-*phenylbut*-2-*en*-4-*olide* [(Z)-4-*Methoxy*-5-*methylcarbonylmethylidene*-3-*phenylfuran*-2(5H)-*one*] (35b).—By the general procedure, reaction between the anhydride (16a) (0.41 g) and the phosphorane, MeCOCH=PPh$_3$ (0.64 g), followed by chromatography in chloroform gave the *butenolide* (0.25 g) which crystallised from methanol as almost colourless plates, m.p. 115 °C, $\lambda_{max.}$(CHCl$_3$) 275 and 315 nm; $\nu_{max.}$(KBr) 1 792, 1 699, 1 658, and 1 634 cm^{-1}; τ 2.61 (5 H), 4.2 (:C*H*COMe), 6.21 (O*Me*), and 7.5 (CO*Me*) (Found: C, 69.0; H, 5.1. $C_{14}H_{12}O_4$ requires C, 68.9; H, 4.9%).

Analysis of crude reaction products by ^{1}H n.m.r. spectroscopy suggested the presence of small amounts of the corresponding *E*-isomer [τ 3.85 (C*H*·COMe)].

Reaction between the anhydride (16b) *and the phosphorane* (22b). By the general procedure, reaction between the anhydride (0.47 g) and the phosphorane (0.7 g), followed by chromatography in chloroform gave (i) (*E*)-4-ethoxycarbonylmethylidene-3-methoxy-2-(4-methoxyphenyl)but-2-en-4-olide [(*E*)-5-ethoxycarbonylmethylidene-4-methoxy-3-*p*-methoxyphenylfuran-2(5*H*)-one] (35a; Ar = 4-OMeC$_6$H$_4$) (0.09 g) (eluted first), τ 2.45 (d, *J* 9, 2 H), 3.04 (d, *J* 9, 2 H), 4.02 (C*H*·CO$_2$Et), 5.74 (q, *J* 7, C*H*$_2$CH$_3$), 6.19 (O*Me*), 6.22 (ArO*Me*), and 8.67 (t, *J* 7, CH$_2$C*H*$_3$) which isomerised rapidly to the corresponding *Z*-isomer, and (ii) (Z)-4-*ethoxycarbonylmethylidene*-3-*methoxy*-2-p-*methoxyphenylbut*-2-*en*-4-*olide* [(Z)-5-*ethoxycarbonylmethlidene*-4-*methoxy*-3-p-*methoxyphenylfuran*-2(5H)-*one*] (36) (0.35 g) (eluted second) which crystallised from ethanol as yellow needles, m.p. 104—105 °C; $\lambda_{max.}$(CHCl$_3$) 267 and 345 nm; $\nu_{max.}$(KBr) 1 780, 1 718, 1 662, and 1 604 cm^{-1}; τ 2.57 (d, *J* 9, 2 H), 3.08 (d, *J* 9, 2 H), 4.33 (:C*H*·CO$_2$Et), 5.75 (q, *J* 7, C*H*$_2$CH$_3$), 6.18 (O*Me*), 6.22 (ArO*Me*), and 8.69 (t, *J* 7, CH$_2$C*H*$_3$) (Found: C, 63.1; H, 5.3. $C_{16}H_{16}O_6$ requires C, 63.1; H, 5.3%).

(Z)-4-*Ethylidene*-2-(*and* 3-)*methylbut*-2-*enolides* [(Z)-5-*Ethylidene*-3-(*and* 4-)*methylfuran*-2(5H)-*ones*] (40) *and* (39).—A solution of ethylmagnesium bromide (from 1.06 g of Mg) in ether (40 ml) was added to a stirred solution of 2-methylmaleic anhydride (4.5 g) in ether (30 ml) at −70 °C. The mixture was stirred at −70 °C for 1 h, and then allowed to warm to −10 °C and diluted with iced hydrochloric acid. The ether extract was separated, and the aqueous solution was extracted with ether. Evaporation of the dried ether extracts left an oily mixture of carbinols, which was heated *in vacuo* with fused potassium hydrogen sulphate (10 g). The distillate (3.9 g), b.p. 80—100 °C/11 mmHg, was chromatographed in chloroform on silica gel to give: (i) (*Z*)-4-ethylidene-2-methylbut-2-enolide [(*Z*)-5-ethylidene-3-methylfuran-2(5*H*)-one] (40) (0.7 g), eluted first, as a pale yellow oil, $\lambda_{max.}$(EtOH) 275.5 nm; $\nu_{max.}$(film) 1 770, 1 676, and 1 628 cm^{-1}; τ 3.01 (m, C*H*:CMe), 4.84 (q, *J* 8, :C*H*Me), 8.03 (d, *J ca.* 1, CH:C*Me*), and 8.08 (d, *J* 8, *Me*CH:); *m/e* 124.053 3; $C_7H_8O_2$ requires *M* 124.052 4; and (ii) (*Z*)-4-ethylidene-3-methylbut-2-enolide [(*Z*)-5-ethylidene-4-methylfuran-2(5*H*)-one] (39) (0.9 g), eluted second, as a pale yellow oil, $\lambda_{max.}$(EtOH) 273 nm; $\nu_{max.}$(film) 1770, 1 685, and 1 617 cm^{-1}; τ 4.12 (m, C*H*:CMe), 4.6 (q, *J* 8, MeC*H*:), 7.84 (d, *J ca.* 1, CH:C*Me*), and 8.06 (d, *J* 8, *Me*CH:); *m/e* 124.053 0; and (iii) an unresolved mixture (*ca.* 2 g) of the two isomers.

(Z)-4-*Ethylidene*-3-*methoxy*-2-*phenylbut*-2-*enolide* [(Z)-5-*Ethylidene*-4-*methoxy*-3-*phenylfuran*-2(5H)-*one*] (41).—A solution of ethylmagnesium bromide (from 0.26 g of Mg) in ether (15 ml) was added to a stirred solution of 2-methoxy-3-phenylmaleic anhydride (2 g) in ether (15 ml) at −70 °C. The mixture was allowed to warm to room temperature, and then stirred at 25 °C for 18 h; it was then diluted with iced hydrochloric acid. The ether extract was separated and the aqueous solution was extracted with ether. Evaporation of the dried ether extracts left the carbinol as a viscous oil (1.9 g), τ 2.6—3.0 (5 H), 5.4 (O*H*), 6.2—6.6 (m, 5 H), and 8.25 (m, CH$_2$*Me*).

A solution of the carbinol (1 g) in glacial acetic acid (400 ml), acetic anhydride (200 ml), and conc. sulphuric acid (10 ml) was heated at 100 °C for 0.25 h, and then poured onto iced water and extracted with ether. Evaporation of the dried ether extracts, and chromatography of the residue in benzene on silica gel gave the *butenolide* (41) (0.5 g), a pale yellow oil, $\lambda_{max.}$(CHCl$_3$) 272 nm; $\nu_{max.}$(film) 1 762, 1 640, and 1 601 cm^{-1}; τ 2.7 (br, 5 H), 4.48 (q, *J* 7, :C*H*Me), 6.28 (O*Me*), 8.11 (d, *J* 7, :CH*Me*); *m/e* 216.078 3; $C_{13}H_{12}O_3$ requires *M*, 216.078 6.

Using an excess Grignard reagent resulted in the isolation of 4,4-diethyl-3-methoxy-2-phenylbut-2-enolide [5,5-diethyl-4-methoxy-3-phenylfuran-2(5*H*)-one] (42), $\nu_{max.}$(film) 1 740 and 1 660 cm^{-1}; τ 2.8 (5 H), 6.4 (O*Me*), 8.16 (q, *J* 7, C*H*$_2$Me), 9.12 (t, *J* 7, CH$_2$*Me*); *m/e* 246.127 4; $C_{15}H_{18}O_3$ requires *M* 246.125 6, in addition to the ylidenebutenolide.

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