The Preparation of Synthetic Analogues of Strigol

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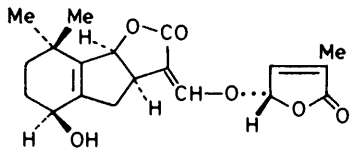
A range of analogues of the natural germination stimulant, strigol, for parasitic weeds of the genera *Striga* and *Orobanche*, has been prepared. Most of the products contain an α-formyl-γ-lactone (or α-formyl-γ-lactam) grouping attached through an enol-ether linkage to the 5-position of a but-2-enolide. Some have shown sufficiently high activities as to warrant large-scale field trials.

THE parastic weeds of the genera *Striga* and *Orobanche* directly affect the lives of more than 400 million people in Africa, India, and the Middle East by severely reducing yields of graminaceous and legume crops respectively.[1,2] *Striga lutea* (witchweed) was recognised in the U.S. (N. and S. Carolina) in 1956, since when extensive efforts have been made to eradicate it. The seeds of the parasites, known to be viable in the soil for up to twenty years, are generally dormant and germinate only when stimulated by a chemical exuded from the roots of the host crops.[3,4] The germinated parasite then attaches itself to the host root, drawing all its nutrients from the host, severely stunting it and reducing the potential crop yield, in extreme cases to nil. Our early experiments [3,4] on the purification of these chemicals established methods for assay techniques and bulk preparation of the stimulants from appropriate host plants. Chromatography, solvent extraction, and counter-current techniques were applied [5-8] to obtain concentrates of the natural factors but no compounds were isolated in the pure state. More than one active fraction appears to be present.[9] However, evidence was presented in favour of a lactone function in the biologically active molecules; later workers [10] favoured coumarin structures. The action of the stimulant also appeared to be enhanced by gibberellic acid.[11] In 1966, Cook and his co-workers [12] described the isolation of a crystalline compound, strigol, from the root exudates of cotton (*Gossypium hirsutum* L.) which was not itself parasitised by *Striga* spp. Nevertheless strigol was highly potent in causing the stimulation of *S. lutea*, and some years later the structure (1) was established by *X*-ray crystallography.[13] Soon after the announcement of the structure, synthetic routes to strigol were described by Raphael [14] (±-form) and by Sih [15] [natural (+)-isomer] and their colleagues, both using the coupling of the sodio-derivative of the hydroxymethylene-lactone (2) with the bromobutenolide (3; X = Br) as the final step. In addition to these syntheses, a simplified method involving Michael addition of dimethylpyruvic acid and 5-oxohept-6-enoic acid, to produce rings A and B of (2) was developed by Dolby and Hanson.[16] The product was then converted into (2) in several stages.

Meanwhile it was shown that ethylene [17-19] and ethylene precursors [20] were highly effective in causing germination of *Striga* spp., although, as we have shown, not of *Orobanche* spp. However, it is still uncertain whether treatment of field soil with ethylene gas will prove to be a useful economic proposition for many of the tropical countries where *Striga* control is needed. Introduction of chemical stimulants into the soil to germinate the parasite before planting the host is an attractive idea for *Striga* and *Orobanche* control, and once the structure of strigol had been established, we decided in 1972 to



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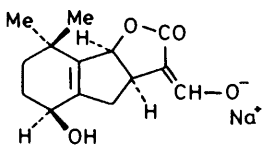

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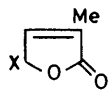
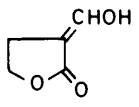


(3)

examine the properties of simpler structures containing either or both of the lactone rings. Thus 4-hydroxy-2-methylbut-2-en-4-olide (3; X = OH) (obtained by photochemical oxidation of 3-methyl-2-furoic acid [21,22]), as its methanesulphonate, and 2-hydroxymethylenebutan-4-olide (4) [23] as its sodio-derivative gave the bis-lactone (5; R = H) (*cf.* ref. 24). This contains two of the four rings of strigol and moreover, like strigol,[14,15] is the *E*-isomer on the basis of its n.m.r. spectrum.



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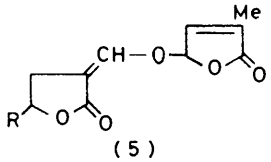

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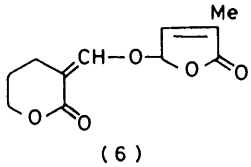
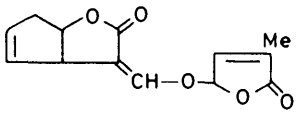


(6)

Solutions of the mono-lactones (3; X = OH) and (4) had little effect on seeds of *S. hermonthica* (Del.) Benth. but the bis-lactone (5; R = H) showed biological activity (preliminary communication, ref. 25) albeit at a low level. The activity was markedly increased, especially for *Striga* spp. when a 4-methyl group was introduced into the butyrolactone fragment, *i.e.* (5; R = Me), although when the extra carbon was introduced into the ring [compound (6)] only weak activity was observed. Because of the encouraging activities of (5; R = H, Me) we extended the syntheses to include a third ring of the strigol molecule, (7) in the first instance, which require the hydroxymethylene derivative (8) as a key intermediate. Fortunately the parent lactone of (8) is available as a prostaglandin intermediate;[26] it was converted into (8) by formylation, and then coupled with (3; X = O·SO_2Me) to give (7).



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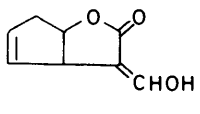
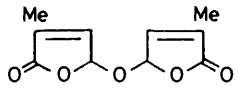


(8)

The bis-lactone (7) proved to be highly active, observable germination effects on both *S. hermonthica* and *S. asiatica* being obtained at concentrations of 10^{-10} mol l^{-1}. At higher concentrations, 10^{-5} mol l^{-1} and above, inhibitory effects were observed, a phenomenon common to many of the active synthetic products. The bis-lactone (7) has been used widely for an assessment of the utility of synthetic analogues of strigol for *Striga* control both in the laboratory and in the field. As a bonus, (7) was effective also for the germination of *Orobanche* spp. as well as for *Alectra vogellii*, a parasite of cowpea in many parts of Africa. In view of the potential of (7) for the commercial control of *Striga* and *Orobanche* spp. we have examined the preparation of its intermediates in more detail as well as the synthesis of a variety of related compounds.

The Butenolide Intermediates.—Both Raphael [14] and Sih [15] (*cf.* also ref. 24) in their syntheses of strigol used the 4-bromobutenolide (3; R = Br), which was obtained either by *N*-bromosuccinimide bromination of the parent butenolide (3; R = H) obtained by bromination and hydrolysis of various methylbutenoic acids,[27] particularly 2-methylbut-3-enoic acid,[28] or by conversion of (3; R = OH) [21,22] into (3; R = Br) by the action of carbon tetrabromide and triphenylphosphine.[15] In later work we have replaced the rather unstable methylsulphonate (3; R = O·SO_2Me) by the analogous chloro-derivative (3; R = Cl),[29] obtained from the 5-hydroxy-compound with thionyl chloride. A by-product from this reaction has been identified as the vinylogous anhydride (9).

However the literature preparations selected previously for the butenolides (3; R = H and OH) were lengthy, and other literature methods, *e.g.* refs. 27, 30, and 31, did not lend themselves to large scale preparations. We have therefore examined alternatives and for (3; R = H), we favour bromination and dehydrobromination of the commercially available 2-methylbuten-4-olide (10). A more lengthy but related method was described by Inayama *et al.*[32] who introduced a 2-ethoxycarbonyl and thence a 2-carboxy-group into (10) before brominative decarboxylation. We have shown that the extra steps are unnecessary.



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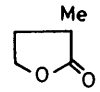
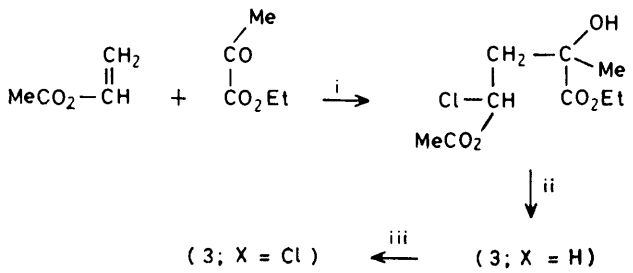


(10)

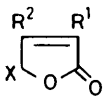
Two other syntheses of 2-methylbut-2-en-4-olides should be mentioned. We have shown that (3; X = Cl) can be obtained in a simple procedure from reaction of vinyl acetate and ethyl pyruvate in the presence of titanium tetrachloride followed by cyclisation and chlorination (Scheme 1). Aldol reactions of this type using aldehydes with pyruvic ester in the presence of amines are known,[33,34] although the yields quoted were lower, and titanium tetrachloride-catalysed reactions of silyl enol ethers from ketones with pyruvic ester have also been described.[35,36]



SCHEME 1 *Reagents*: i, $TiCl_4$; ii, EtOH–HCl, H_2O; iii, $SOCl_2$

Recently, details of a multi-stage synthesis of 4-hydroxy-2-methylbut-2-en-4-olide (3; X = OH) have appeared [37] in which crotonaldehyde is the starting product.

In the course of our work, we have prepared a number of 2- and 3-substituted butenolides for assessment, and, as before, the syntheses have been directed either at 4-hydroxy- or 4-unsubstituted derivatives, both of which are readily transformed to the 4-halogeno-compounds required for the subsequent coupling reactions. The butenolides have been prepared by reported methods [sometimes with modifications (see Experimental section)] *e.g.* (11; R^1 = Ph, R^2 = H, X = OH) and (11; R^1 = R^2 = Ph, X = OH) by oxidative irradiation of 3-phenyl- and 3,4-diphenyl-2-furoic acid [38] respectively. Progressive introduction of phenyl groups caused a marked acceleration in the rate of the oxidative rearrangement.



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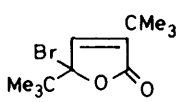
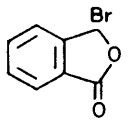


(12)

In contrast, the photochemical oxidation of 3-t-butylfuran-2-carboxylic acid failed to yield the butenolide (11; $R^1 = CMe_3$, $R^2 = H$, X = OH). However the related compound (11; $R^1 = CMe_3$, $R^2 = X = H$) was prepared by the borohydride reduction of t-butylmaleic anhydride, and bromination of the product with *N*-bromosuccinimide gave the 4-bromo-derivative (11; $R^1 = CMe_3$, $R^2 = H$, X = Br). Borohydride reduction of citraconic anhydride, on the other hand, gave the 3-methylbutenolide (11; $R^1 = X = H$, $R^2 = Me$) with small quantities of (11; $R^1 = Me$, $R^2 = X = H$) and (11; $R^1 = H$, $R^2 = Me$, X = OH) as by-products. Reasons for the preferential reduction of the more hindered carbonyl group in this case have been discussed previously.[37,39]

2,4-Di-t-butylbut-2-en-4-olide (11; $R^1 = X = CMe_3$, $R^2 = H$) was obtained by alkaline oxygenation of 2,4-di-t-butylcatechol,[40] and it was converted into the bromo-derivative (12) with *N*-bromosuccinimide. Finally 3-bromophthalide (13) from the bromination of phthalide was used as an example of a condensed butenolide.

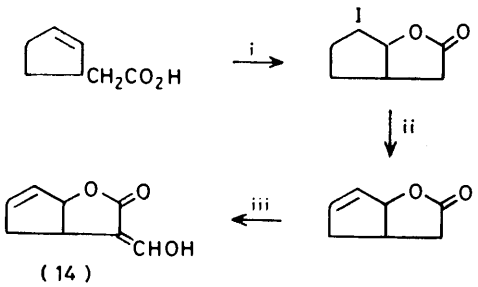


(13)

Each of these 4-halogenobut-2-en-4-olides was condensed with the sodio-derivative (8) to provide a range of strigol analogues. Germinating activity on seeds of *Striga* and *Orobanche* spp. was observed only with derivatives of the monosubstituted but-2-en-4-olides, 3-methyl-, and 2-t-butyl- [both of the same order as (7)] and 2-phenyl- [10% of activity of (7)]. The 3-methylbut-2-en-4-olide derivative, isomeric with (7), was attractive because of its ease of preparation and its apparent increased stability to alkali, but further biological tests both in the laboratory and in the field have indicated that the original compound (7) is somewhat more active.

The α-Formyl-lactone Intermediates.—Reference has been made to the preparation of some α-formyl-lactones, especially (8), and their condensation with 4-halogenobut-2-en-4-olides to produce strigol analogues. An isomer of (8), (14), which contains the double bond in the same relative position as in strigol has been prepared by the route shown in Scheme 2 from cyclopent-2-enylacetic acid [41] to (14). Subsequent condensation with (3; X = Cl) gave the strigol analogue (15), isomeric with (7). The product was highly effective in causing the germination of the seeds of *Striga* and *Orobanche* spp., particularly the latter, but it proved to be appreciably less stable than (7) towards light, heat, and alkali, and its application has therefore been limited.

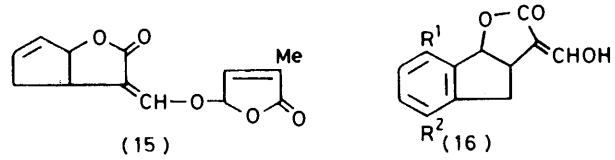
We have examined the substitution of the 4,4-dimethylcyclohex-2-enol ring of strigol (1) by an aromatic ring, *e.g.* (8; $R^1 = R^2 = H$) which required the intermediate (16; $R^1 = R^2 = H$). This was obtained from 1-oxoindan-2-ylacetic acid [42] by reduction, lactonisation,[43] and formylation. We prefer this route to that of House *et al.*,[43] whereby 3-benzoylbutan-4-olide is subjected to rearrangement using sulphuric acid, but which in our hands, has given unsatisfactory yields. After condensation with the butenolide (3; X = Cl, Br), the strigol



(14)

SCHEME 2 *Reagents*: i, NaOI; ii, DBU; iii, HCO_2Et–NaOEt

analogue (17; $R^1 = R^2 = H$) was obtained and this proved to be the most active synthetic compound for the germination of the seeds of *Striga* and *Orobanche* spp. In addition it is appreciably more stable to both light and alkali than (7) or (15). In a recent publication,[44] Cook



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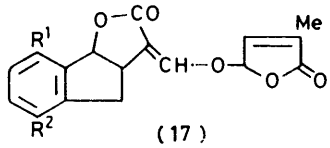

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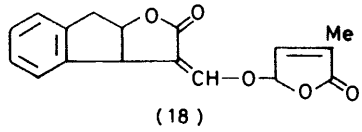
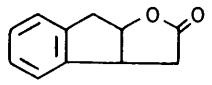


(18)

et al. described the preparation of the lactone (17; $R^1 = Me$, $R^2 = OH$) using a Fries rearrangement of 6-methyldihydrocoumarin as the initial step. However addition of the 2-carboxymethyl group to the 4-hydroxy-7-methylindan-1-one so obtained required special conditions for formation of the appropriate carbanion because of interference by the phenolic group, and gave a moderate yield of the product in contrast to the parent series (above). Formylation to give (16; $R^1 = Me$, $R^2 = OH$) and coupling with 4-bromo-2-methylbut-2-en-4-olide (3; X = Br) gave the *E*-isomer (17; $R^1 = Me$, $R^2 = OH$) which was claimed to have 2% of the biological activity of natural strigol.

We have also prepared (18), isomeric with (17; $R^1 = R^2 = H$), from indene through 2-bromoindan-1-ol which, with sodiomalonic ester, unexpectedly gave the 2-

hydroxy-1-malonic ester derivative (n.m.r. spectrum), in contrast to a literature statement.[45,cf.43] The reaction presumably involves the intermediate formation of the 1,2-oxide. The malonic ester was then hydrolysed, decarboxylated, and reduced to give the lactone (19), and this by the standard sequence of reactions was converted into the strigol analogue (18). This isomer proved to be less biologically active than (17; $R^1 = R^2 = H$).



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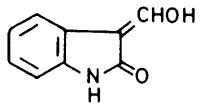

(20)

In another variation of the α-formyl-lactone fragment we have examined products derived from 3-hydroxymethyleneindolin-2-one (20), and its *N*-methyl, 5-nitro-, and *N*-methyl-5-nitro-derivatives, using the method of Wenkert *et al.*[46] for formylation of the indolinones. All the 3-hydroxymethyleneindolinones were condensed with the butenolide (3; X = Br) and with 3-bromophthalide (13) to give analogues of strigol, but in no cases was biological activity observed comparable with that of strigol or the bis-lactones (7) and (17). It had been expected that the substitution of lactam for lactone in these compounds would lead to increased alkaline stability as is required for many *Orobanche*-infested soils where the pH can rise as high as 8.5—9.

The stereochemistry of strigol was established by *X*-ray crystallography.[13] In the synthetic products the natural *E*-isomers appear to be favoured and are normally produced almost exclusively. The *Z*-isomers, if required, can be formed by irradiation of the *E*-isomers. Each geometric isomer can exist in two diastereoisomeric forms, which can be separated by chromatography [compounds (7) and (17)] and each can be resolved into individual optical isomers.

Full details of the biological activities of the compounds synthesised will be given elsewhere, but the activities of the bis-lactones (7) and (17; $R^1 = R^2 = H$) have been sufficiently encouraging as to warrant field trials for *Striga hermonthica* in Nigeria, Sudan, and India and for *Orobanche crenata* in Syria and Lebanon.

EXPERIMENTAL

I.r. spectra were measured for solutions in chloroform with a Perkin-Elmer 577 spectrophotometer. N.m.r. spectra were recorded with Varian EM-360 or Perkin-Elmer R32 spectrometers for $CDCl_3$ solutions (unless otherwise stated), using tetramethylsilane as internal reference. Mass spectra were determined with an AEI MS-30 instrument. For t.l.c., Kieselgel PF-254 (Merck) was used. Unless otherwise stated, light petroleum refers to the fraction of b.p. 60—80 °C.

Butenolides.—*4-Hydroxy-2-methylbut-2-en-4-olide* (3; X = OH). Prepared from 3-methyl-2-furoic acid by irradiation in the presence of oxygen.[21,22] The corresponding *O*-methanesulphonate formed crystals, m.p. 65—67 °C (from light petroleum) or it could be purified by sublimation at 80 °C and 0.02 mmHg.

4-Chloro-2-methylbut-2-en-4-olide (3; X = Cl). (*i*) A solution of 4-hydroxy-2-methylbut-2-en-olide[21,22] (40.0 g) in glyme (125 ml) was added dropwise to a stirred mixture of thionyl chloride (75.0 g) and anhydrous sodium carbonate (18.6 g) over 3 h. The mixture was maintained at 40 °C during this period and was then heated at 80 °C for 1 h. It was cooled, filtered, and the solvent removed *in vacuo* to give the *chlorobutenolide* (3; X = Cl) which was distilled at 60 °C and 2 mmHg to give an oil (39.1 g, 84%) (Found: C, 45.4; H, 3.8. $C_5H_5ClO_2$ requires C, 45.3; H, 3.8%), $\nu_{max.}$ 3 100m, 1 785s, and 1 660 cm^{-1}; δ 1.97 (3 H, m), 6.50 (1 H, m), and 7.05 (1 H, m). The residue from the distillation was crystallised from chloroform–light petroleum, when it formed crystals of the anhydride (9), m.p. 159—161 °C (Found: C, 57.5; H, 4.6. $C_{11}H_{10}O_2$ requires C, 57.1; H, 4.75%); $\nu_{max.}$ 3 100, 1 775, and 1 666 cm^{-1}; δ 1.95 (6 H, m), 6.18 (2 H, m), and 6.84 (2 H, m); *m/e* 181 (*M* − CHO) and 166 (*M* − 44).

(*ii*) Titanium tetrachloride (8.1 g, 43 mmol; freshly distilled) in dichloromethane (60 ml; dried over molecular sieves) was cooled and stirred in an ice-bath and then a solution of ethyl pyruvate (4.94 g, 43 mmol) and vinyl acetate (3.66 g, 43 mmol) in dry methylene dichloride (30 ml) was added dropwise over 2 h to the cooled and stirred mixture. Stirring was continued for another 2 h at 0 °C. Water (40 ml) was then added, the layers were separated, and the aqueous layer was extracted with further methylene dichloride (2 × 30 ml). The combined methylene dichloride extract was washed with water (30 ml), dried over sodium sulphate, and evaporated to give an oil (7.50 g), δ 1.40 (s, tertiary Me), 6.63(m), and 2.00 and 2.08 (diastereoisomeric acetates).

The crude colourless oil so obtained (7.12 g) was dissolved in absolute ethanol (80 ml), concentrated hydrochloric acid (4 ml) was added, and the mixture was heated under reflux for 4 h. Water (100 ml) was then added, the ethanol was removed by distillation and the remainder heated under reflux for a further 45 min. The reaction mixture was then extracted with ethyl acetate (3 × 50 ml) and the extract was dried over sodium sulphate and evaporated. The product was a yellow-brown gum (2.39 g), δ 1.90 (vinyl Me) and 6.00 and 6.38 (2m, 1 proton each). This was heated with thionyl chloride (20 ml) under reflux for 1 h and then the excess of reagent removed by distillation. The residue was distilled under reduced pressure to give a colourless mobile oil (1.4 g), b.p. 62 °C at 2 mmHg, identical with the product from the previous experiment.

2-Methylbut-2-en-4-olide (3; X = H). Bromine (168 g) was added to a well stirred, cooled (ice-bath) mixture of 3-methylbutanolide (10) (100 g) and red phosphorus (11.6 g) over 30 min. The mixture was then heated to 70 °C, and additional bromine (168 g) was added over 30 min. The temperature was then raised to 80 °C and the mixture held at that temperature for 3 h. Air was then blown into the cooled reaction product until the excess of bromine and hydrogen bromide were removed.

The aerated reaction mixture was then heated to 80 °C on an oil-bath, and water (20 ml) was added cautiously with stirring. On cessation of the reaction (which took *ca.* 30 min), additional water (300 ml) was added and the mixture was heated under reflux vigorously for 4 h. The product was cooled, water (50 ml) was added, and the aqueous layer was saturated with sodium chloride and extracted with

methylene chloride (4 × 100 ml). The combined extracts were dried (sodium sulphate) and the solvent was removed under reduced pressure. The resulting dark red residue was distilled under reduced pressure to afford 2-methylbut-2-en-4-olide (3; X = H) (52 g, 53%), b.p. 52 °C at 1.5 mmHg, 82 °C at 7 mmHg, and 97—98 °C at 20 mmHg (lit.,[28] 97—98.6 °C at 20 mmHg).

4-Bromo-2-methylbut-2-en-4-olide (3; X = Br). The bromide was prepared from the foregoing 2-methylbut-2-en-4-olide by the method of Raphael *et al.*[14]

3-Methylbut-2-en-4-olide (11; R^1 = X = H, R^2 = Me). A mixture of sodium borohydride (6.8 g, 1.178 mol) in tetrahydrofuran (80 ml; dried over $LiAlH_4$) was stirred under nitrogen and cooled (ice). Citraconic anhydride (20 g, 0.178 mol) in dry tetrahydrofuran (100 ml) was added over 10 min and the mixture was stirred at 0 °C for 45 min, warmed to room temperature, and then stirred for a further 45 min. It was then cooled to 0 °C and 6M-hydrochloric acid (80 ml) was added slowly with stirring and the mixture then allowed to warm to room temperature with continued stirring. It was then concentrated *in vacuo*, diluted with water (150 ml), and extracted with diethyl ether (2 × 100 ml) to remove the minor products, 2-methylbut-2-en-4-olide (0.9 g, 5%) (above) and 4-hydroxy-3-methylbut-2-en-4-olide (1.0 g, 5%), *m/e* 114 (M^+), 99 ($M^+ - CH_3$), and 86 ($M^+ - CO$); $\nu_{max.}$ 3 320 (OH) and 1 765 (CO) cm^{-1}; δ 5.95 (s, 1 H), 5.80 (m, 1 H), 5.50br (s, 1 H), and 2.10 (t, 3 H). The aqueous layer was extracted with ethyl acetate (3 × 100 ml) and the combined extracts were washed and dried. Removal of the solvent gave *3-methylbut-2-en-4-olide* (11; R^1 = X = H, R^2 = Me) (6.5 g, 43%) which was further purified by distillation, b.p. 60—64 °C at 3.5 mmHg (Found: C, 61.05; H, 6.15. $C_5H_6O_2$ requires C, 61.2; H, 6.1%), *m/e* 98 (M^+) and 69; δ 5.79 (m, 1 H), 4.72 (m, 2 H), and 2.11 (m, 3 H); $\nu_{max.}$(neat), 1 780 and 1 750 cm^{-1}.

3-Methylbut-2-en-4-olide was converted into its 4-bromo-derivative using *N*-bromosuccinimide.[47]

4-Hydroxy-2-phenylbut-2-en-4-olide (11; R^1 = Ph, R^2 = H, X = OH). Methyl 3-phenyl-2-furoate [48] was hydrolysed to the corresponding acid [colourless crystals, m.p. 143—145 °C (from water)]. The acid (1 g, 5.3 mmol) and eosin (10 mg, 1%) were dissolved in ethanol (50 ml) and irradiated with a 150-W bulb while bubbling in a stream of oxygen with stirring. The reaction was followed by t.l.c. (10% ethyl acetate–ether as eluant) and after *ca.* 37 h the reaction was complete. In order to hydrolyse the hemiacetal formed in the reaction, the alcohol was removed *in vacuo*, distilled water (100 ml) was added, and the reaction mixture was heated under reflux for 24 h under dry nitrogen. After this period, the hot reaction mixture was filtered (sintered funnel) and on cooling, the filtrate deposited colourless crystals. After recrystallisation from ethyl acetate (× 3) the *product* (0.9 g, 95%) had m.p. 131 °C (Found: C, 68.4; H, 4.55. $C_{10}H_8O_3$ requires C, 68.2; H, 4.55%); *m/e* 176.148 (M^+), 103, and 77 (C_6H_5); $\nu_{max.}$ 3 500—3 000br, 1 770s, 1 120s, and 950m cm^{-1}.

4-Chloro-2-phenylbut-2-en-4-olide (11; R^1 = Ph, R^2 = H, X = Cl). The foregoing hydroxy-compound (3.4 g, 2 mmol) in dry glyme (15 ml) was added slowly with stirring to a warm (60—80 °C) solution of redistilled thionyl chloride (4.4 g, 2.7 ml) and anhydrous sodium carbonate (1 g) in dry glyme (50 ml). After addition was complete, further thionyl chloride (2 ml) was added and the reaction mixture was then heated under reflux for 24 h. The resulting solution was filtered and the precipitate was washed with a small amount of dry ether. After removing the solvent *in vacuo*, the residual oil was extracted with methylene chloride (100 ml), washed with water (2 × 100 ml), sodium hydrogencarbonate solution (2 × 100 ml), and saturated salt solution (100 ml), and dried over sodium sulphate. After filtration and removal of the solvent *in vacuo*, the residue was sublimed under high vacuum when crystals were obtained. Recrystallization from toluene–light petroleum (b.p. 40—60 °C) gave *crystals* (3.6 g, 97%), m.p. 72—73 °C. Alternatively, the compound can be purified by column chromatography using silica gel with chloroform as eluant (Found: C, 61.7; H, 3.6. $C_{10}H_7ClO_2$ requires C, 61.7; H, 3.6%); *m/e* 194 (M^+), 159 (M − Cl), 103, and 77 (C_6H_5); δ(CCl_4) 6.5 (d, 1 H), 7.3 (m, 5 H), and 7.7 (d, 1 H).

4-Hydroxy-2,3-diphenylbut-2-en-4-olide (11; R^1 = R^2 = Ph, X = OH). 3,4-Diphenyl-2-furoic acid [38] (4 g, 1.5 mmol) and eosin (40 mg) were dissolved in ethanol (300 ml) and irradiated as described for the 3-phenyl derivative for 12 h. T.l.c. showed formation of only one product. The solvent was removed *in vacuo* and the solid residue was extracted with methylene chloride (100 ml). The extract was washed repeatedly with water to remove the eosin and then dried. After filtration and removal of the solvent *in vacuo*, the residue was sublimed under high vacuum when off-white crystals were obtained. Crystallization (× 3) from ether–light petroleum (b.p. 40—60 °C) gave colourless crystals (3.4 g, 89%), m.p. 143—144 °C, of *5-hydroxy-3,4-diphenylbut-2-en-4-olide* (11; R^1 = R^2 = Ph, X = OH) (Found: C, 76.3; H, 4.6. $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.75%); *m/e* 252 (M^+), 179, 178, and 77 (C_6H_5); $\nu_{max.}$ 3 300w, 1 760s, 1 730s, and 1 380s.

4-Chloro-2,3-diphenylbut-2-en-4-olide (11; R^1 = R^2 = Ph, X = Cl). Prepared from the foregoing 5-hydroxy-compound (1 g) by reaction with thionyl chloride as described above for the 3-phenyl derivative, the product was purified by high-vacuum sublimation and then crystallisation (× 3) from chloroform–pentane, when it was obtained as *crystals* (1 g, 93%); m.p. 147—149 °C (Found: C, 71.0; H, 4.2. $C_{16}H_{11}ClO_2$ requires C, 70.95; H, 4.05%); *m/e* 270 (M^+) and 235 (M^+ − Cl); $\nu_{max.}$(Nujol; CsI prism) 1 770s, 1 460s, 1 380m, and 700s (C–Cl stretching); $\nu_{max.}$(Nujol; NaCl prism) 1 770s, 1 380m, 1 020m, and 770m.

2-t-Butylbut-2-en-4-olide (11; R^1 = CMe_3, R^2 = X = H). t-Butylmaleic anhydride [49] (0.4 g, 2.6 mmol; also obtained from the acid t-butyl ester [49] by heating with acetic anhydride under reflux) was dissolved in dry tetrahydrofuran (25 ml) and added quickly with stirring to lithium tri-t-butoxyaluminium hydride (1.32 g, 5.2 mmol) in dry tetrahydrofuran (25 ml) at room temperature, the reaction mixture being kept under dry nitrogen. The mixture was then heated to reflux (oil-bath) for 1 h, cooled (ice-bath), and saturated aqueous ammonium sulphate (10 ml) was added dropwise with stirring at 0 °C. The thick, colourless precipitate was filtered off through a sintered funnel and washed with a few ml of dry THF. Water (50 ml) was added to the filtrate, the solvent was removed *in vacuo* and the residue was extracted with ethyl acetate (2 × 50 ml). The organic layer was separated and the aqueous layer was acidified with 2M-hydrochloric acid and extracted with fresh ethyl acetate (2 × 50 ml), and the combined extracts were washed with water (200 ml) and 10% salt solution and dried. After removal of the solvent *in vacuo*, t.l.c. (30% ethyl acetate–chloroform as eluant) showed the presence of three products which were separated by chromatography on

silica gel using chloroform for elution. The major product, the required lactone (40%), was eluted first and was followed by the 3-t-butyl isomer (20%) and t-butylbutan-4-olide (mixed isomers). Removal of the solvent from the fraction containing the major product and sublimation of the residue under high vacuum gave *2-t-butylbut-2-en-4-olide* (11; $R^1 = CMe_3$, $R^2 = X = H$) as crystals (Found: C, 68.6; H, 8.85. $C_8H_{12}O_2$ requires C, 68.55; H, 8.55%); *m/e* 141 ($M^+ + 1$), 140 (M^+), and 128; $\nu_{max.}$(Nujol) 2 960m, 1 750s, 1 480w, 1 360m, and 1 140m; δ 7.1 (t, 1 H), 4.7 (d, 2 H), and 1.2 (s, 9 H).

Variation of the experimental conditions for this reduction, including the use of lithium aluminium hydride and sodium borohydride, failed to increase the yield of the desired product. 4-Bromo-2-t-butylbut-2-en-4-olide (11; $R^1 = CMe_3$, $R^2 = H$, $X = Br$) was obtained from 2-t-butylbut-2-en-4-olide (0.85 g, 5.36 mmol), *N*-bromosuccinimide (2 g, 11.24 mmol), and benzoyl peroxide (10 mg) in CCl_4 (25 ml) under nitrogen. The reaction mixture was heated to reflux for 3.5 h when t.l.c. showed reaction to be complete. The mixture was cooled to 0 °C in an ice-bath, filtered quickly through a sintered funnel, and the precipitated succinimide was washed with a few ml of ice-cold CCl_4. The solvent was removed *in vacuo* without heating. The product was an unstable oil which must be stored at −20 °C; δ(CCl_4) 7.2 (d, 1 H), 6.8 (d, 1 H), and 1.3 (s, 9 H) (Found: *m/e*, 219.217. $C_8H_{11}BrO_2$ requires *M*, 219.079).

4-Bromo-2,4-di-t-butylbut-2-en-4-olide (12). 2,4-Di-t-butylbut-2-enolide [40] (0.41 g, 2.9 mmol) in carbon tetrachloride (40 ml) containing *N*-bromosuccinimide (0.85 g) and benzoyl peroxide (10 mg) was heated under reflux for 12 h under nitrogen, after which period t.l.c. showed essentially complete reaction. The red solution was cooled (ice), filtered, and the precipitated succinimide was washed with a few ml of cold carbon tetrachloride. The solvent was evaporated off *in vacuo* and the colourless residue was purified by crystallisation from iso-octane when it formed colourless crystals (0.5 g, 85%), m.p. 85—87 °C. The product could also be purified by chromatography on silica gel with chloroform for elution (Found: C, 52.35; H, 7.0. $C_{12}H_{19}BrO_2$ requires C, 52.35; H, 6.9%); *m/e* 278, 276, 274, and 195 ($M^+ - Br$); $\nu_{max.}$ 3 520w, 3 080m, 2 960s, 1 760s, 1 625m, and 1 470m; δ 6.6 (s, 1 H), 1.15 (s, 9 H), and 0.8 (s, 9 H).

Sodio-derivatives of α-Hydroxymethylene-lactones.—These were obtained by condensation of the lactones with ethyl formate and in many cases the sodio-derivatives were used directly for further condensation without isolation of the free α-hydroxymethylene derivatives. Examples include 2-hydroxymethylenebutan-4-olide [23] (4) (95%), and by similar methods 2-hydroxymethylene-4-methylbutan-4-olide and 2-hydroxymethylenepentan-5-olide.

Sodio-derivative of 3-hydroxymethylene-3,3a,6,6a-tetrahydrocyclopenta[b]furan-2-one (8). Sodium (8.64 g) and dry methanol (3 ml) were added to dry ether (300 ml) and the mixture was stirred at room temperature for 3 h. 3,3a,6,6a-Tetrahydrocyclopenta[*b*]furan-2-one [26] (45 g) and ethyl formate (30 6 g) in ether (100 ml) was added dropwise with stirring over 2 h, with vigorous stirring and cooling (ice). The mixture was stirred for a further 1 h and then cooled to −20 °C for 24 h. The precipitated sodium salt (54 g, 86%) was separated quickly, washed with dry ether (100 ml), and dried *in vacuo* at 40 °C.

The sodio-derivative (4 g) was dissolved in water (2 ml), cooled in ice, and 2N-hydrochloric acid was added until the solution had pH 1. The crystallised material was separated (3.1 g) and recrystallised from methylene chloride–light petroleum when it formed colourless *crystals*, m.p. 107—110 °C (Found: C, 63.05; H, 5.4. $C_8H_8O_3$ requires C, 63.15; H, 5.25%).

Sodio-derivative of 3-hydroxymethylene-3,3a,4,6a-tetrahydrocyclopenta[b]furan-2-one (14). Hypoiodous acid was added to cyclopent-2-enylacetic acid by the method of Fissekis and Markert [41] to give 6-iodo-3,3a,4,5,6,6a-hexahydrocyclopenta[*b*]furan-2-one. The iodo-lactone (22.66 g) and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (13.69 g) in anhydrous tetrahydrofuran (200 ml) was stirred at 50 °C for 2 h and heated under reflux for 90 min. It was then cooled to room temperature, diluted with water (100 ml), and extracted with dichloromethane (3 × 60 ml). The combined organic extracts were shaken with saturated salt solution, dried, filtered, and concentrated to give *3,3a,4,6a-tetrahydrocyclopenta[b]furan-2-one*, b.p. 69 °C at 0.4 mmHg (Found: C, 68.1; H, 6.5. $C_7H_8O_2$ requires C, 67.57; H, 6.45%). The corresponding formyl derivative (14) was obtained by condensation with ethyl formate by the usual procedure.

Sodio-derivative of 3-hydroxymethylene-3,3a,8,8a-tetrahydroindeno[2,1-b]furan-2-one [*4-hydroxymethylene derivative of* (19)]. 2-Carboxymethylindan-1-one was prepared from 2-bromoindan-1-one by the malonic ester route,[42] and then reduced with sodium borohydride to *trans*-2-carboxymethylindan-1-ol and cyclised with sulphuric acid to the *cis*-lactone (19), which formed colourless needles, m.p. 64—65 °C (from ether–light petroleum) (lit.,[43] 65—66 °C). Formylation with ethyl formate then produced the required intermediate.

Sodio-derivative of 3-hydroxymethylene-3,3a,4,8b-tetrahydroindeno[1,2-b]furan-2-one (16; $R^1 = R^2 = H$). Sodium (0.46 g) was added in small pieces to a stirred solution of diethyl malonate (3.2 g) in 1,2-dimethoxymethane (15 ml) at room temperature and the mixture was stirred for 3 h. The resulting solution was treated with a solution of *trans*-2-bromoindan-1-ol (2.13 g) in 1,2-dimethoxyethane (12 ml) and the mixture was stirred at room temperature overnight. It was then heated under reflux for 1 h, cooled, and evaporated to dryness.

The mixture of crude diester and excess of diethyl malonate was saponified by boiling with 2M-sodium hydroxide (60 ml) for 1.5 h. The resulting solution was cooled, washed with ethyl acetate (30 ml × 2), acidified with 6M-hydrochloric acid, and saturated with salt. Continuous extraction with diethyl ether for 24 h followed by removal of the solvent gave a solid, m.p. 116—118 °C (from benzene–ethanol).

The hydroxy-diacid was decarboxylated by heating (oil-bath) to *ca.* 130 °C with stirring under nitrogen for 1 h. The resulting oil solidified on cooling and was crystallized from benzene–hexane, m.p. 130—132 °C (Found: C, 68.6; H, 6.25. $C_{11}H_{12}O_3$ requires C, 68.75; H, 6.25%). The n.m.r. spectrum of the compound clearly showed it to be *trans*-2-hydroxyindan-1-ylacetic acid; double irradiation studies at 200 MHz showed the presence of the grouping $-CH_2-CH-CH-CH_2-$, inconsistent with the previous structural assignment.[45]

A solution of the hydroxy-acid (2.5 g) in 65% concentrated sulphuric acid in acetic acid (10 ml) was kept at room temperature for 24 h. It was then poured onto cracked ice (300 g) and the aqueous solution was extracted with dichloromethane (4 × 60 ml). The combined organic extract was

washed with water (2 × 100 ml) followed by 5% sodium hydrogencarbonate (2 × 50 ml) and then saturated salt solution (30 ml). After drying over sodium sulphate, the organic solution was filtered and evaporated to give an oil which slowly crystallized. Recrystallization from dichloromethane–hexane gave 3,3a,4,8b-*tetrahydroindeno*[1,2-b]-*furan*-2-*one* as needles, m.p. 73—74 °C (Found: C, 75.85; H, 5.75. $C_{11}H_{10}O_2$ requires C, 75.8; H, 5.7%).

Sodium (0.23 g) was added to a solution of the foregoing lactone (1.74 g) in a mixture of ethyl formate (1.11 g) and ether (20 ml) and the mixture was stirred at room temperature for 18 h. The light-tan sodio-enolate salt [sodio-derivative of (16)] was filtered off, washed quickly with a small amount of diethyl ether, and dried overnight in a desiccator.

3-*Hydroxymethyleneindolin*-2-*ones*.—3-Hydroxymethyleneindolin-2-one (20) was prepared by the method of Wenkert *et al.*[46] and 3-hydroxymethylene-1-methylindolin-2-one by that of Julian *et al.*,[50] by condensation of the indolinones with ethyl formate. By similar methods, 5-nitroindolin-2-one gave 3-*hydroxymethylene*-5-*nitroindolin*-2-*one* as yellow crystals, m.p. 194—195 °C (decomp.); *m/e* 206 (M^+), 189 (M^+ − OH), 160 (M^+ − NO_2), 132, and 104; $\nu_{max.}$(Nujol) 3 120 (NH), 1 705, 1 650 (CO), 1 615 (CO), 1 510, and 1 340 (NO_2) cm^{-1}. Likewise, 1-methyl-5-nitroindolin-2-one gave 3-*hydroxymethylene*-1-*methyl*-5-*nitroindolin*-2-*one* as yellow crystals, m.p. 166—168 °C (decomp.); *m/e* 220 (M^+), 203 (M^+ − OH), and 174 (M^+ − NO_2); $\nu_{max.}$(Nujol) 3 520—3 340br, 1 715, 1 690, 1 650 (CO), 1 510, 1 370, and 1 340 (NO_2) cm^{-1}.

Preparation of Strigol Analogues.—(a) *From* 2-*hydroxymethylenebutan*-4-*olide* (4). (i) *With* 2-*methyl*-4-*methylsulphonyloxybut*-2-*en*-4-*olide* (3; X = OSO_2Me). The methanesulphonate (19.04 g) was dissolved in 1,2-dimethoxyethane (200 ml), the sodium salt of the formyllactone (15 g) was added, and the mixture was stirred at room temperature for 24 h. It was then filtered, the residue was washed, and the combined filtrate and washings evaporated. The residue was dissolved in methylene chloride (20 ml) and diethyl ether was added carefully, when the colourless product slowly crystallised. It was separated and washed with diethyl ether. 2-*Methyl*-4-(2-*oxotetrahydrofuran*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* (5; R = H) (12 g, 60%) had m.p. 92—94 °C (Found: C, 57.05; H, 4.7. $C_{10}H_{10}O_5$ requires C, 57.15; H, 4.75%).

(ii) *With* 3-*bromophthalide* (13). By a similar method, 3-bromophthalide and the sodio-derivative of the formyllactone gave 3-(2-*oxotetrahydrofuran*-3-*ylidenemethoxy*)-*phthalide* as needles (from methylene chloride–diethyl ether), m.p. 186—189 °C (Found: C, 63.45; H, 4.15. $C_{13}H_{10}O_5$ requires C, 63.4; H, 4.05%).

(b) *From* 2-*hydroxymethylene*-4-*methylbutan*-4-*olide* [4-Me *derivative of* (4)]. (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide* (3; X = Cl). The sodio-salt (3 g) of the formyllactone was added quickly to a solution of the chloro-lactone (2.84 g) in dry tetrahydrofuran (50 ml) containing a few drops of hexamethylphosphoramide, at room temperature and with stirring. The solvent was removed *in vacuo* and the residue extracted with methylene chloride (50 ml) which was then washed with water, 10% aqueous sodium chloride, and dried. Removal of the solvent gave 2-*methyl*-4-(5-*methyl*-2-*oxotetrahydrofuran*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* (5; R = Me) as an oil and, for analysis, a sample was purified by preparative t.l.c. on silica using 2% ethyl acetate–chloroform for elution (Found: C, 58.4; H, 5.8. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%); *m/e* 224 (M^+), 151, and 128, $\nu_{max.}$ 3 250—3 700br, 2 960s, 2 920s, 1 725—1 795br, 1 720s, 1 440m, 1 380s, 1 325s, 1 170s, 1 050s, and 1 020s cm^{-1}, δ 7.5 (t, 1 H), 6.85 (m, 1 H), 6.1 (m, 1 H), 2.3—2.9 (m, 2 H), 1.98 (t, 3 H), and 1.4 (d, 3 H).

(ii) With 3-*bromophthalide*. The sodio-derivative (1.5 g) was treated with 3-bromophthalide (2.13 g) in 1,2-dimethoxyethane (25 ml) and worked up as above. 3-(5-*Methyl*-2-*oxotetrahydrofuran*-3-*ylidenemethoxy*)*phthalide* was obtained as crystals (1.95 g, 75%) (from ethyl acetate–light petroleum), m.p. 120—121 °C (Found: C, 65.05; H, 4.6. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.6%); *m/e* 260 (M^+), 188, 170, and 148; $\nu_{max.}$ 3 300—3 620br, 1 790s, 1 680s, 1 390s, 1 180s, and 960s cm^{-1}.

(c) *From* 2-*hydroxymethylenepentan*-5-*olide*. *With* 2-*methylsulphonyloxybut*-2-*en*-4-*olide*. The methanesulphonate (1.26 g) in 1,2-dimethoxyethane (20 ml) was treated with sodio-2-hydroxymethylenepentan-5-olide (1.5 g) and stirred at room temperature for 4 h. The mixture was poured into ice–water (100 ml) and extracted with dichloromethane (2 × 100 ml). The combined extracts were washed with water (2 × 50 ml) and dried, and the solvent was removed. The residue was dissolved in dichloromethane (1.5 ml), and diethyl ether (6 ml) was added carefully. 2-*Methyl*-4-(2-*oxotetrahydropyran*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* (6) (1.05 g, 71%) crystallised and was separated and washed with cold diethyl ether when it had m.p. 105—107 °C (Found: C, 58.85; H, 5.4. $C_{11}H_{12}O_5$ requires C, 58.95; H, 5.35%).

(d) *From* 3-*hydroxymethylene*-3,3a,6,6a-*tetrahydrocyclopenta*[b]*furan*-2-*one* (8). (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide*. A mixture of the sodio-derivative of the formyllactone (0.87 g) and the chlorobutenolide (0.67 g) in anhydrous glyme (10 ml) was stirred at room temperature for 24 h. The mixture was poured onto ice–water (50 ml) and extracted with chloroform (3 × 50 ml). The combined extracts were washed with saturated aqueous sodium chloride, dried, and evaporated to give a semi-crystalline residue (1.13 g) which was crystallised from methylene chloride–diethyl ether to give as a mixture of diastereoisomers, 2-*methyl*-4-(2-*oxo*-3,3a,6,6a-*tetrahydro*-2H-*cyclopenta*[b]-*furan*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* (7) (0.98 g, 80%), m.p. 128—130 °C, (Found: C, 62.95; H, 4.7. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.85%), $\nu_{max.}$ 1 790, 1 745, and 1 690 cm^{-1}; δ 2.0 (m, 3 H), 2.7 (m, 2 H), 4.1 (m, 1 H), 5.1 (m, 1 H), 5.6 (m, 2 H), 6.15 (m, 1 H), 6.85 (m, 1 H), and 7.4 (m, 1 H).

The product was subjected to chromatography on silica (activity III) using 20% ethyl acetate–diethyl ether for elution, when it was separated into fast- and slow-running isomers. Each was crystallised repeatedly from methylene chloride–hexane when the former had m.p. 163—164.5 °C (Found: C, 62.65; H, 4.75%) and the latter 180—182 °C (Found: C, 62.8; H, 4.75%).

(ii) *With* 3-*bromophthalide*. A mixture of the sodio-enolate (0.87 g) and 3-bromophthalide (1.07 g) in 1,2-dimethoxyethane (20 ml) was stirred at room temperature for 18 h and then diluted with ice–water (80 ml). The precipitate was collected and crystallised from dichloromethane–hexane to afford 4-(2-*oxo*-3,3a,6,6a-*tetrahydro*-2H-*cyclopenta*[b]*furan*-3-*ylidenemethoxy*)*phthalide* (1.48 g), m.p. 212—213 °C (Found: C, 67.6; H, 4.3. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.25%).

(iii) *With* 4-*bromo*-3-*methylbut*-2-*en*-4-*olide* (11; R^1 = H, R^2 = Me, X = Br). The sodio-enolate (2.24 g) in dry tetrahydrofuran (40 ml) at 0 °C was stirred under nitrogen

while a solution of the bromo-lactone (3 g) in tetrahydrofuran (10 ml) was added rapidly, and the mixture stirred overnight. Most of the solvent was removed *in vacuo*, and cold water (70 ml) was added to the residue. The mixture was extracted with dichloromethane (3 × 50 ml) and the combined extracts were washed and dried and the solvent was removed. The product was purified by chromatography on silica using chloroform–ethyl acetate (5 : 1 v/v) for elution. The main fraction was collected, and the solvent removed to give the product (mixed diastereoisomers) as a thick yellow oil (Found: *m/e*, 248.068 393. $C_{13}H_{12}O_5$ requires *M*, 248.068 467); δ 7.36 (m, 1 H), 6.02 (t, 1 H), 5.65 (m, 2 H), 5.26 (s, 1 H), 5.10 (m, 1 H), 4.10 (m, 1 H), 2.71 (m, 2 H), and 2.12 (m, 3 H). On standing, a solid product separated which was crystallised from methylene chloride–hexane to give 3-*methyl*-4-(2-*oxo*-3,3a,6,6a-*tetrahydro*-2H-*cyclopenta*[b]*furan*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide*, m.p. 199—200 °C (Found: C, 63.15; H, 4.75. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.85%); δ 6.80 (d, 1 H), 6.00 (m, 2 H), 5.70 (m, 1 H), 5.45 (m, 1 H), 5.05 (m, 1 H), 3.95 (m, 1 H), 2.90 (m, 2 H), and 2.15 (d, 3 H).

(iv) *With* 4-*chloro*-2-*phenylbut*-2-*en*-4-*olide* (11; R^1 = Ph, R^2 = H, X = Cl). Reaction of the sodio-enolate (0.49 g) with the chloro-lactone (0.49 g) in tetrahydrofuran (30 ml) at 70—75 °C with stirring for 24 h gave a product which was purified by t.l.c. on silica using 10% ethyl acetate–diethyl ether for elution. Removal of the solvent and extraction with dichloromethane gave a product which was further purified by chromatography on silica to afford 4-(2-*oxo*-3,3a,6,6a-*tetrahydro*-2H-*cyclopenta*[b]*furan*-3-*ylidene*-*methoxy*)-2-*phenylbut*-2-*en*-4-*olide* as yellow crystals (0.57 g, 74%), m.p. 122—125 °C (Found: C, 69.2; H, 4.8. $C_{18}H_{14}O_5$ requires C, 69.65; H, 4.5%); *m/e* 310 (M^+), 159, 103, and 77; $\nu_{max.}$ 1 760s, 1 700m, 1 490w, 1 440w, 1 335m, 1 170m, 1 100m, 1 090m, 930m, and 785m cm^{-1}; δ 7.8 (m, 1 H), 7.4 (m, 5 H), 6.3 (d, 1 H), 5.6 (s, 2 H), 5.1 (m, 2 H), 3.9—4.1 (m, 1 H), and 2.6 (m, 2 H).

(v) *With* 4-*chloro*-2,3-*diphenylbut*-2-*en*-4-*olide* (11; R^1 = R^2 = Ph, X = Cl). The sodio-enolate (0.17 g) was treated with the chloro-lactone (0.27 g) in dimethoxyethane under reflux with stirring for 24 h. The reaction mixture was worked up as above to give 4-(2-*oxo*-3,3a,6,6a-*tetrahydro*-2H-*cyclopenta*[b]*furan*-3-*ylidenemethoxy*)-2,3-*diphenylbut*-2-*en*-4-*olide* as a pale yellow solid (0.62 g, 64%) which was crystallised from ethyl acetate–light petroleum, m.p. 194—195 °C (Found: C, 74.7; H, 4.7. $C_{24}H_{18}O_6$ requires C, 74.6; H, 4.65%); *m/e* 358 ($M^+ - CO_2$), 252, 235, 169, and 168; $\nu_{max.}$ 1 780s, 1 740s, 1 680s, 1 490m, 1 440m, and 1 390m cm^{-1}; δ 7.75 (s, 1 H), 7.3 (s, 10 H), 6.48 (d, 1 H), 5.2—5.7 (m, 2 H), 4.7—5.2 (m, 1 H), 3.7—3.9 (m, 1 H), and 2.5—2.7 (m, 2 H).

(vi) *With* 4-*bromo*-2,3-*di*-*t*-*butylbut*-2-*en*-4-*olide* (12). Reaction of the sodio-enolate (0.18 g) with the bromo-lactone (0.28 g) in dry tetrahydrofuran under reflux with stirring for 24 h followed by treatment of the reaction mixture as in earlier condensations gave a pale brown solid which was crystallised from ethyl acetate–light petroleum to afford 4-(2-*oxo*-3,3a,6,6a-*tetrahydro*-2H-*cyclopenta*[b]*furan*-3-*ylidenemethoxy*)-2,3-*di*-*t*-*butylbut*-2-*en*-4-*olide* (0.28 g, 81%), m.p. 124—126 °C (Found: C, 69.85; H, 7.15. $C_{20}H_{26}O_5$ requires C, 69.4; H, 7.5%); *m/e* 346 (M^+) and 302 ($M^+ - CO_2$); $\nu_{max.}$ 3 090m, 2 960m, 1 780s, 1 770s, 1 750s, 1 660s, 1 480m, and 1 460m cm^{-1}; δ 7.0 (m, 1 H), 6.7 (s, 1 H), 5.7 (m, 2 H), 5.1 (m, 1 H), 4.1 (m, 1 H), 2.7 (m, 2 H), 1.18 (s, 9 H), and 0.98 (s, 9 H).

(e) *From* 3-*hydroxymethylene*-3a,6a-*dihydro*-4H-*cyclopenta*[b]*furan*-2(3H)-*one* (14). (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide*. The chloro-lactone (1.33 g) was added to a suspension of the sodio-enolate (1.74 g) in anhydrous 1,2-dimethoxyethane (20 ml) and the mixture stirred at 5 °C for 16 h. After dilution with water (20 ml), the product was extracted into dichloromethane, and after removal of solvent, it was obtained as a viscous oil which slowly solidified. Crystallisation from diethyl ether gave 2-*methyl*-4-(2-*oxo*-2,3,3a,6a-*tetrahydro*-4H-*cyclopenta*[b]*furan*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* as a mixture of diastereoisomers, m.p. 140—188 °C (Found: C, 62.8; H, 4.9. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.85%).

(ii) *With* 3-*bromophthalide*. Prepared similarly from the sodio-enolate (0.87 g) and 3-bromophthalide (1.07 g) in anhydrous 1,2-dimethoxyethane (20 ml) at room temperature for 18 h. 3-(2-*Oxo*-2,3,3a,6a-*tetrahydro*-4H-*cyclopenta*-[b]*furan*-3-*ylidenemethoxy*)*phthalide* crystallised from diethyl ether as a mixture of diastereoisomers, m.p. 178—200 °C (Found: C, 67.45; H, 4.3. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.25%).

(iii) *With* 4-*bromo*-3-*methylbut*-2-*en*-4-*olide*. Prepared from the sodio-enolate (10 g) and the bromo-lactone (13.5 g) in dry tetrahydrofuran (160 ml) at 0 °C for 6 h and room temperature for a further 14 h. The resulting mixture was treated as before followed by chromatography on silica when 3-*methyl*-4-(2-*oxo*-2,3,3a,6a-*tetrahydro*-4H-*cyclopenta*[b]-*furan*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* was obtained as plates (7 g, 49%), m.p. 167—168 °C [from chloroform–ethyl acetate (4 : 1 v/v)] (Found: C, 62.75; H, 4.65. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.85%); $\nu_{max.}$ 1 790, 1 740, 1 680, and 1 655 cm^{-1}; δ 7.55 (d, 1 H), 6.15—5.52 (m, 5 H), 3.72 (m, 1 H), 2.65 (m, 2 H), and 2.18 (m, 3 H).

(f) *From* 3-*hydroxymethylene*-3,3a,8,8a-*tetrahydroindeno*-[2,1-b]*furan*-2-*one* [4-*hydroxymethylene derivative of* (19)]. (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide*. The sodio-enolate (11.2 g) and the chloro-lactone (8 g) were stirred in dry 1,2-dimethoxyethane (150 ml) at room temperature for 19 h. Ice (40 g) was added and the mixture was extracted with chloroform. Removal of the solvent gave a colourless residue which, crystallised from dichloromethane–hexane, gave 2-*methyl*-4-(2-*oxo*-3,3a,8,8a-*tetrahydro*-2H-*indeno*[2,1-b]*furan*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide*, m.p. 116—124 °C (Found: C, 68.45; H, 5.05. $C_{17}H_{14}O_5$ requires C, 68.45; H, 4.7%) (11.1 g, 74.4%); *m/e* 298 (M^+), 201 (M − butenolide)$^+$, 184, 173, 155, and 97; $\nu_{max.}$ 1 793, 1 740, and 1 680 cm^{-1}.

(ii) *With* 4-*bromo*-3-*methylbut*-2-*en*-4-*olide*. Prepared similarly from the sodio-enolate (4 g) and the bromo-lactone (5 g) in dry tetrahydrofuran (100 ml) at room temperature overnight. Removal of the solvent followed by extraction with dichloromethane and crystallisation from methylene chloride–diethyl ether gave 3-*methyl*-4-(2-*oxo*-3,3a,8,8a-*tetrahydro*-2H-*indeno*[2,1-b]*furan*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide*, m.p. 188—189 °C (Found: C, 68.45; H, 5.05. $C_{17}H_{14}O_5$ requires C, 68.45; H, 4.7%); $\lambda_{max.}$ 226 and 238 nm (ε 27 390 and 25 470); $\nu_{max.}$ 1 795, 1 740, and 1 680 cm^{-1}; δ 7.55 (m, 1 H), 7.3 (m, 4 H), 6.1 (m, 3 H), 4.0 (m, 1 H), 3.3 (m, 1 H), and 2.2 (s, 3 H).

(iii) *With* 4-*chloro*-2-*phenylbut*-2-*en*-4-*olide*. The chloro-lactone (0.485 g) was dissolved with stirring in dry 1,2-dimethoxyethane (25 ml) and cooled to −50 °C. The sodio-enolate (0.81 g) was added, and the mixture was stirred overnight to attain room temperature and then heated under reflux for 3 h. It was then cooled, the solvent

was removed *in vacuo*, water (50 ml) was added, and the product was extracted into dichloromethane. The extract was washed, dried, and the solvent removed to yield a yellow amorphous solid which was purified by chromatography on silica gel using ethyl acetate for elution. Crystallisation from ethyl acetate gave 4-(2-*oxo*-3,3a,8,8a-*tetrahydro*-2H-*indeno*[2,1-b]*furan*-3-*ylidenemethoxy*)-2-*phenylbut*-2-*en*-4-*olide* as pale yellow prisms, m.p. 246 °C (Found: C, 72.65; H, 4.6. $C_{21}H_{16}O_5$ requires C, 72.4; H, 4.6%); $\nu_{max.}$ 1 790s, 1 770s, 1 740s, 1 680s, 1 380s, 1 350m, 1 180m, 1 060m, and 940m cm^{-1}. An n.m.r. spectrum was not obtained because of insolubility in the usual solvents. No parent ion was observed in the mass spectrum; *m/e* 147 and 189 represent loss of tricyclic lactone and butenolide fragments respectively.

(iv) *With* 3-*bromophthalide*. The bromophthalide (0.71 g) and the sodio-enolate (0.75 g) in dry 1,2-dimethoxyethane (10 ml) were stirred at room temperature for 19 h and then ice (20 g) was added. The precipitated solid was separated, washed, and dried to afford 3-(2-*oxo*-3,3a,8,8a-*tetrahydro*-2H-*indeno*[2,1-b]*furan*-3-*ylidenemethoxy*)*phthalide* (0.9 g, 8%), m.p. 163—173 °C (mixture of diastereoisomers); *m/e* 334 (M^+), 316, 201 (M^+ — butenolide), and 133; $\nu_{max.}$ 1 788, 1 740, and 1 680 cm^{-1}. A further quantity of product was obtained by extraction of the filtrate with chloroform.

(g) *From* 3-*hydroxymethylene*-3,3a,4,8b-*tetrahydroindeno*-[1,2-b]*furan*-2-*one* (16; $R^1 = R^2 = H$). (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide*. The chloro-lactone (0.66 g) and the sodio-enolate (1.12 g) were stirred in dry 1,2-dimethoxyethane (20 ml) at room temperature for 16 h, when the mixture was diluted with water (50 ml) and extracted with chloroform (3 × 60 ml). The extract was washed and dried, and the solvent removed to give a pale brown solid which was crystallised from chloroform–diethyl ether to give 2-*methyl*-4-(2-*oxo*-2,3,3a,8b-*tetrahydro*-4H-*indeno*[1,2-b]*furan*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* as colourless crystals, m.p. 200—214 °C (Found: C, 68.45; H, 4.85. $C_{17}H_{14}O_5$ requires C, 68.45; H, 4.7%). The product was a mixture of diastereoisomers which was separated by chromatography on silica (activity III) using 2% ethyl acetate–diethyl ether for elution. The ' slow ' isomer after isolation had m.p. 205 °C, and the ' fast ' isomer, m.p. 119—120 °C.

(ii) *With* 3-*bromophthalide*. The bromophthalide (0.7 g) was treated with the sodio-enolate (0.75 g) in dry 1,2-dimethoxyethane (15 ml) as above and the reaction product poured onto ice (50 g). The solid which separated was removed and dried and a further quantity obtained by extraction of the filtrate with chloroform (3 × 30 ml) and removal of solvent from the dried extract. Crystallisation of the product from dichloromethane–hexane gave 3-(2-*oxo*-2,3,3a,8b-*tetrahydro*-4H-*indeno*[1,2-b]*furan*-3-*ylidene*-*methoxy*)*phthalide*, m.p. 161—168 °C (mixture of diastereoisomers) (Found: C, 71.55; H, 4.3. $C_{20}H_{14}O_5$ requires C, 71.85; H, 4.2%).

(h) *From* 3-*hydroxymethyleneindolin*-2-*one* (20). (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide*. The chloro-lactone (305 mg) was added to a solution of 3-hydroxymethyleneindolin-2-one [47] (332 mg) and potassium carbonate (290 mg) in hexamethylphosphoramide (2 ml) with stirring under nitrogen. Stirring was continued for 18 h at room temperature when the reaction mixture was poured into ice–water (70 ml) and extracted with ethyl acetate (3 × 40 ml). The combined extracts were washed and dried and the solvent was removed. A small amount of chloroform was added to the residue and crystallisation was induced by the addition of diethyl ether and cooling. The yellow-brown product (100 mg, 19%) was separated and a further quantity (50 mg) obtained by cautious addition of diethyl ether to the mother-liquor. Vacuum sublimation afforded 2-*methyl*-4-(2-*oxo*-*indolin*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide*, m.p. 96—98 °C (Found: C, 65.25; H, 4.7; N, 5.4. $C_{14}H_{11}NO_4$ requires C, 65.35; H, 4.3; N, 5.45%); *m/e* 257 (M^+), 229 (M — CO), 161 (M — butenolide), 132 (hydroxymethyleneindolinone fragment), and 97 (butenolide fragment); $\nu_{max.}$ 1 775, 1 700, and *ca.* 3 300br.

(ii) *With* 3-*bromophthalide*. Prepared from 3-bromophthalide (490 mg) and 3-hydroxymethyleneindolin-2-one (322 mg) by a similar method. After dilution of the reaction mixture with water, the products were extracted with dichloromethane (3 × 50 ml). The extract was washed and dried, and the solvent removed to give a red oily residue which was dissolved in a little chloroform–diethyl ether (1 : 1 v/v) and then treated with light petroleum (b.p. 40—60 °C) until the solution was just cloudy. It was then cooled at 0 °C overnight. 3-(2-*Oxoindolin*-3-*ylidenemethoxy*)-*phthalide* was obtained as red crystals (200 mg) which were recrystallised from dichloromethane–light petroleum, m.p. 112—115 °C (Found: C, 69.45; H, 4.05; N, 5.05. $C_{17}H_{11}NO_4$ requires C, 69.6; H, 3.75; N, 4.8%); *m/e* 293 (M^+) and 133 (phthalidyl fragment); $\nu_{max.}$ 1 775, 1 710, and 3 170br.

(i) *From* 3-*hydroxymethylene*-1-*methylindolin*-2-*one*. (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide*. The chloro-lactone (332 mg) and the potassio-enolate [from the hydroxymethylene-1-methylindolin-2-one (332 mg)] were reacted by the method described above for the indolin-2-one derivative. After removal of the ethyl acetate, a thick yellow oil was obtained which was dissolved in a little dichloromethane–diethyl ether followed by light petroleum and cooling as before. 2-*Methyl*-4-(1-*methyl*-2-*oxoindolin*-3-*ylidene*-*methoxy*)*but*-2-*en*-4-*olide* (43%) was crystallised twice from dichloromethane–pentane to afford yellow prisms, m.p. 136—137 °C (Found: C, 66.35; H, 5.05; N, 5.1. $C_{15}H_{13}NO_4$ requires C, 66.4; H, 4.8; N, 5.15%); *m/e* 271 (M^+), 174 (M^+ — butenolide fragment), 146, and 97 (butenolide); $\nu_{max.}$ 1 780, 1 715, 1 665, and 1 615 cm^{-1}.

(ii) *With* 3-*bromophthalide*. Prepared by the usual method by reaction of bromophthalide (533 mg) and the potassio-enolate [from the indolinone (322 mg)]. After removal of the ethyl acetate, a yellow viscous oil was obtained which slowly crystallised at 0 °C after the addition of a little 1 : 1 v/v dichloromethane–diethyl ether. The crystalline product (80 mg) was separated and a further quantity (120 mg) obtained by addition of light petroleum to the mother-liquor. 3-(1-*Methyl*-2-*oxoindolin*-3-*ylidene*-*methoxy*)*phthalide* crystallised from dichloromethane–light petroleum as pale yellow prisms, m.p. 73—74 °C (Found: C, 70.3; H, 4.6; N, 4.05. $C_{18}H_{13}NO_4$ requires C, 70.35; H, 4.25; N, 4.55%); *m/e* 307 (M^+), 149 (3-oxyphthalide fragment), and 133 (phthalidyl fragment); $\nu_{max.}$ 1 782, 1 760, 1 670, and 1 610 cm^{-1}.

(j) *From* 3-*hydroxymethylene*-5-*nitroindolin*-2-*one*. (i) *With* 4-*chloro*-2-*methylbut*-2-*en*-4-*olide*. The condensation was carried out by the usual method from the chloro-lactone (310 mg) and the potassio-enolate [from the indolinone (322 mg)]. After removal of the ethyl acetate, the residual dark oil on treatment with a little 1 : 1 v/v dichloromethane–diethyl ether crystallised to afford 2-*methyl*-4-(5-*nitro*-2-*oxoindolin*-3-*ylidenemethoxy*)*but*-2-*en*-4-*olide* (180 mg, 38%), m.p. 185—187 °C (from aqueous dimethyl sulphoxide) (Found: C, 55.55; H, 3.65; N, 9.15. $C_{14}H_{10}N_2O_5$ requires

C, 55.65; H, 3.3; N, 9.25%); *m/e* 302 (M^+), 274 (M^+ — CO), 256 (M^+ — NO_2), 205, 189, 178, 160, 113, and 97; $\nu_{max.}$ 3 400, 3 300, 1 770, 1 715, 1 615, 1 515, 1 370, and 1 330 cm^{-1}.

(ii) *With 3-bromophthalide.* Reaction of 3-bromophthalide (498 mg) and the indolinone (322 mg) as in the previous experiment yielded *3-(5-nitro-2-oxoindolin-3-ylidenemethoxy)but-2-en-4-olide* (150 mg, 28%) as brown crystals, m.p. 245—247 °C (from acetone–diethyl ether) (Found: C, 59.75; H, 3.5; N, 8.15. $C_{17}H_{10}N_2O_6$ requires C, 60.35; H, 2.95; N, 8.3%); *m/e* 310 (M^+ — CO), 292 (M^+ — NO_2), 205, 189, 177, 149, and 133; $\nu_{max.}$ 3 340br, 1 770, 1 730, 1 610, 1 510, 1 370, and 1 345 cm^{-1}.

(k) *From 3-hydroxymethylene-1-methyl-5-nitroindolin-2-one. With 4-chloro-2-methylbut-2-en-4-olide.* Prepared by the standard method from the chloro-lactone (265 mg) and the indolinone (322 mg), *2-methyl-4-(1-methyl-5-nitro-2-oxoindolin-3-ylidenemethoxy)but-2-en-4-olide* (170 mg, 37%) was obtained as brown crystals, m.p. 240—242 °C (decomp.) (from acetone–diethyl ether) (Found: C, 56.45; H, 3.9; N, 8.95. $C_{15}H_{12}N_2O_6$ requires C, 56.95; H, 3.8; N, 8.85%); *m/e* 301 (M^+ — CH_3), 286 (M^+ — $2CH_3$), 270 (M^+ — NO_2), 192, 146, and 97; $\nu_{max.}$ 1 770, 1 715, 1 510, 1 370, and 1 330 cm^{-1}.

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