# Synthesis and biological evaluation of strigol analogues modified in the enol ether part

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**Several analogues of strigol, which is a germination stimulant for seeds of the parasitic weeds *Striga* and *Orobanche*, have been prepared. Structural modifications are introduced in the vinyl ether part and include: i, analogues containing an endocyclic vinyl ether double bond, using tetronic acids as precursors; ii, geometrical isomerization of the vinyl ether double bond; and iii, analogues containing a methyl substituent on the vinyl ether double bond. During coupling reactions to give compounds belonging to the last-mentioned class, undesired *C*-alkylation occurs, which can be minimized by choosing the appropriate reaction conditions. Bioassays reveal that the analogues prepared exhibit considerable activity in the stimulation of seed germination of *Striga hermonthica* and *Orobanche crenata*.**

## Introduction

Parasitic weeds of the genera *Striga* and *Orobanche* cause severe damage to graminaceous and leguminous crops in tropical and sub-tropical regions.[1,2] These parasitic species generally obtain their water, minerals and/or energy from a host plant. A unique feature of these parasitic angiosperms is that they require a specific chemical signal produced by the host root to stimulate germination of their seeds. Root exudates of different *Striga* hosts contain highly potent germination stimulants, *viz*. strigol,[3–5] sorgolactone[6] and alectrol[7] (Fig. 1). This class of compounds are collectively named as strigolactones.[8]

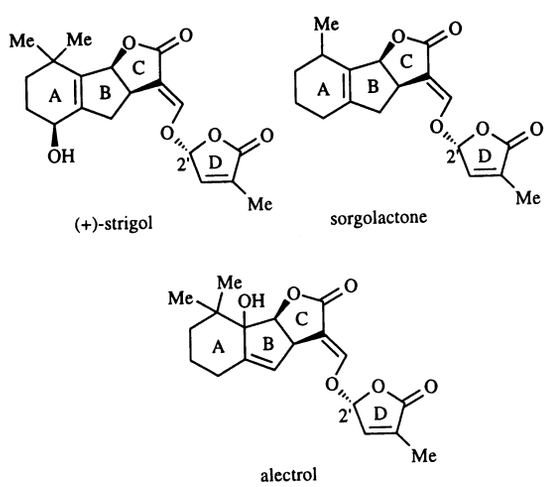
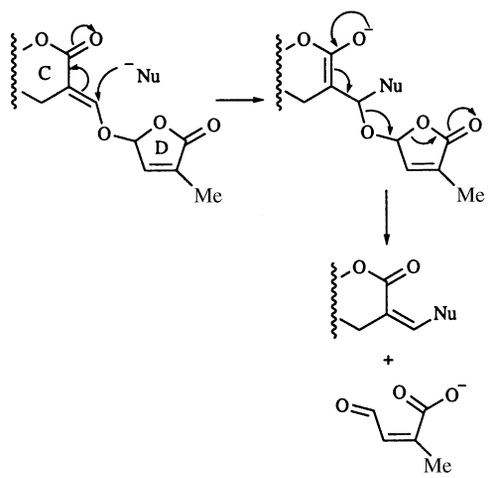



**Fig. 1**

Extensive structure–activity studies of analogues of strigolactones revealed that the bioactiphore resides in the CD-part of the molecule.[9–12] One of the most potent synthetic strigol analogues is GR24,[13,14] whose half-maximal activity is at $10^{-9}$ M for seeds of *Striga hermonthica* (Del.) Benth. Recently, a tentative molecular mechanism, which accounts for the germination stimulatory activity of strigol and its (synthetic) analogues was proposed (Scheme 1).[15]

The enol ether unit plays a crucial role in this mechanism, since it enables the D-ring to be eliminated as shown. Reduction of this moiety[15] or replacing the oxygen atom by a methylene function[16] results in complete loss of bioactivity.



**Scheme 1**

The aim of the present paper is to study the influence of structural modifications in the enol ether part on the induction of germination of seeds of *Striga hermonthica* and *Orobanche crenata* Forsk. These modifications can be divided into three classes (Fig. 2): i, analogues possessing an endocyclic enol ether double bond instead of an exocyclic double bond, *viz*. as in structures **1a–c**; ii, methyl substitution on the enol ether double bond of the strigol analogues **2a–4a**[11,12] resulting in analogues **2b–4b** and iii, geometric isomers of the enol ether double bond (*cf*. compounds **4a** and **5**).

## Results and discussion

### Synthesis

**Tetronic acid derived ABC-analogues.** ABC-strigol analogues **1a–c** contain a β-tetronic acid moiety, which is coupled to a furan-2(5*H*)-one fragment (Scheme 2). The chemistry of β-tetronic acids [4-hydroxyfuran-2(5*H*)-ones, $pK_a \approx 2$–4] has been reviewed.[17,18] Tetronic acids **6a–c** were obtained by standard procedures. Unsubstituted **6a** is commerically available, **6b** was prepared in a one-pot synthesis by bromination of ethyl 2-methylacetoacetate to give the 2-bromo derivative,[19] which rearranged in the presence of hydrobromic acid to the corresponding 4-bromo derivative and, when subsequently heated,

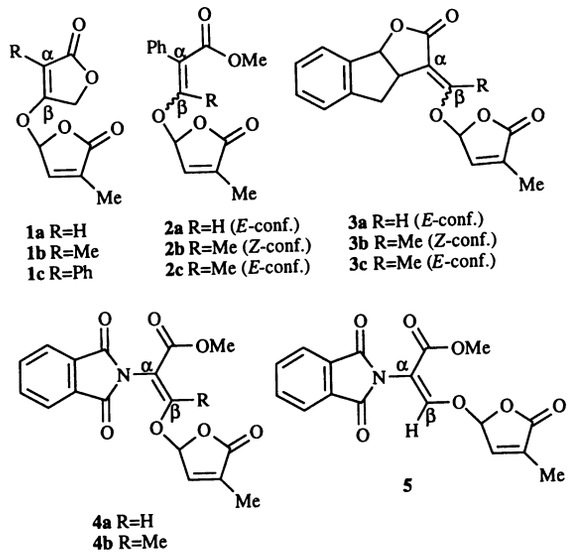
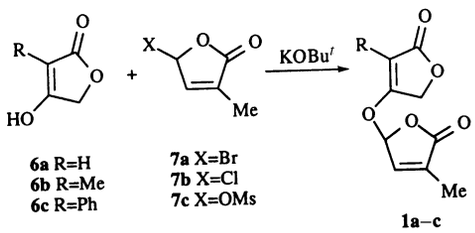






**Fig. 2**




**Scheme 2**

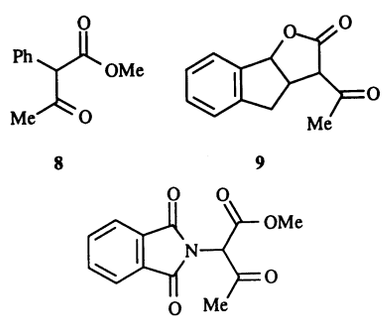



**Fig. 3**

gave 2-methyltetronic acid **6b**.[20] 3-Phenyl derivative **6c** was prepared *via* an internal Claisen condensation of methoxycarbonylmethyl phenylacetate.[21]

Coupling of **6a–c** with **7a**,[22] using potassium *tert*-butoxide as the base in DMF, smoothly gave **1a–c**, which could readily be purified by crystallization without chromatography. The formation of *O*-alkylated compounds **1a–c** was established by $^{13}C$ NMR and $^{1}H$ NMR spectral analysis. No indication of *C*-alkylation was observed.

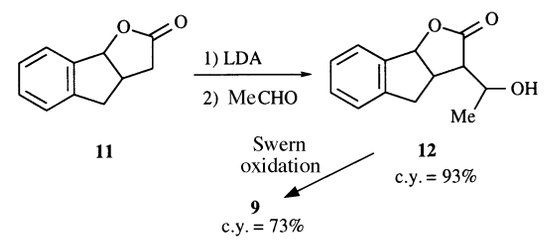
**Methyl substituted analogues 2b–4b.** The preparation of **2b–4b** was attempted in a similar manner as described for the synthesis of the demethyl analogues **2a–4a**[12,22,23] from the precursors **8–10** (Fig. 3) and 5-bromofuran-2(5*H*)-one **7a**.

The β-keto ester **8** was prepared by condensation of methyl phenylacetate and methyl acetate following a modified literature procedure,[24] using KOBu$^t$ as the base in THF. It was essential to keep the reaction mixture at −78 °C to avoid complete self-condensation of methyl phenylacetate. Pure **8** was obtained in a moderate yield (39%) after distillation. Precursors **9** and **10** could not be obtained in satisfactory yields by direct condensation of the tricyclic lactone **11** and phthaloyl glycine methyl

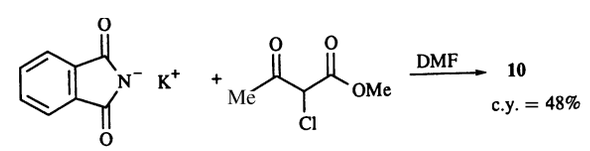
**Table 1** Results of coupling reactions of compounds **8–10** and **7a**

| Entry | Precursor | Base | Solvent | Ratio *O*:*C* [a] | Ratio of diast.[b] | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **10** | KOBu$^t$ | DMF | 2:3 | 6:1 | 67 |
| 2 | **9** | KOBu$^t$ | DMF | *C*-alk. | 2:1 | 40 |
| 3 | **8** | KOBu$^t$ | DMF | *C*-alk. | 1:1 | 65 |
| 4 | **8** | KOBu$^t$ [d] | THF | 3:7 | 1:1 | 61 |
| 5 | **8** | KOBu$^t$ [d] | Toluene | 7:3 | 1:1 | 69 |
| 6 | **8** | DCA | DMF | *C*-alk. | 1:1 | 30[e] |
| 7 | **8** | $Ag_2O$ | $CH_3CN$ | 3:4 | 2:1 | 50 |
| 8 | **10** | KOBu$^t$ [d] | THF | | | NR[f] |
| 9 | **10** | KOBu$^t$ [d] | Toluene | | | NR[f] |
| 10 | **9** | KOBu$^t$ [d] | Toluene | 1:2 | 3:1 | 55 |

[a] Ratio of *O*-alkylated products **2b–4b** and the corresponding *C*-alkylated products **13–15** as determined by $^{1}H$ NMR analysis of the crude reaction mixtures. [b] Diastereoisomeric ratio of the *C*-alkylated products **13–15**. [c] Combined yield of *C*- and *O*-alkylated products. [d] Addition of 0.5 equiv. 18-crown-6. [e] Ratio **13**:**8** in crude reaction mixture. [f] No reaction.




**Scheme 3**




**Scheme 4**

ester, respectively, with methyl acetate. Therefore alternative routes were devised. Compound **9** was synthesized in two steps by condensation with acetaldehyde to give **12**, followed by Swern oxidation (Scheme 3).[25]

For the synthesis of **10** a different route had to be followed, *viz*. Gabriel condensation[26] of potassium phthalimide with methyl α-chloroacetoacetate,[27] which gave **10** in a moderate yield (Scheme 4). Purification of **10** was complicated by the presence of small amounts of phthalimide, which could only be removed by repeated crystallization.

**Coupling of 8–10 with 7a.** Compounds **8–10** were subjected to standard coupling conditions (KOBu$^t$, DMF) with 5-bromofuran-2(5*H*)-one **7a** (*vide supra*). However, under these conditions almost exclusive formation of *C*-alkylated products **13–15** (Fig. 4) as mixtures of diastereoisomers was observed (substrate **10** is an exception). Relevant data are collected in Table 1 (entries 1–3).

The structure of compounds **13–15** was primarily established by $^{13}C$ NMR analysis and based on the signals between $\delta$ 195.2 and 202.5, which are characteristic for a ketone function.

To further explore the influence of the reaction conditions on the product distribution, **8** was selected as a model substrate (entries 3–7, Table 1). A decrease in the polarity of the solvent, *viz*. DMF > THF > toluene, resulted in a substantial increase of the *O*:*C* alkylation ratio (entries 3–5, Table 1). In the two last-mentioned solvents the addition of 18-crown-6 was essential for a successful reaction as it enhanced the solubility of the potassium enolate considerably. These results are in contrast with our expectations.[28] An increase in the polarity of an aprotic solvent should decrease the $S_N2$-character of the transition

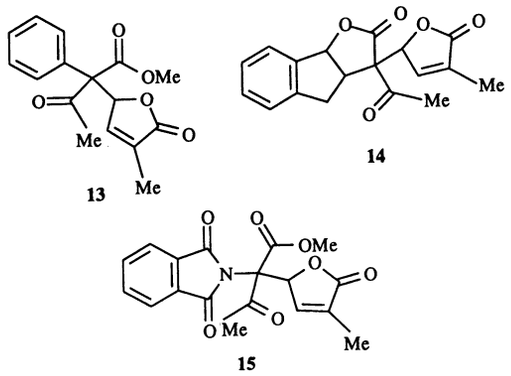
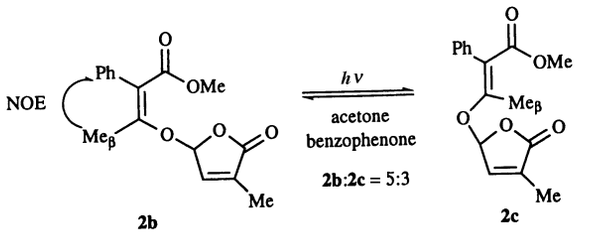



**Fig. 4**

state, which makes attack of the more electronegative oxygen atom of the ambident nucleophile more likely as is indicated by the HSAB principle.[29] Also the use of the bulky dicyclohexylammonium enolate (entry 6, Table 1) failed to result in significant *O*-alkylation. Apparently, solvation of this bulky cation is not very effective. Instead, it undergoes strong complexation with the enolate and, as a consequence, attack of the less electronegative atom is favoured. The use of $Ag^+$ as the cation was considered, since it specifically helps in removing the leaving group. This makes the transition state more $S_N1$-like, which indeed was reflected in the product distribution (entry 7, Table 1). The results collected in Table 1 apparently cannot be explained solely by electronic factors and steric factors should be considered as well. $S_N2$ Reactivity is usually associated with steric effects,[30] which implies that attack of the enolate oxygen in an $S_N2$-like transition state is favoured over attack by the highly branched α-carbon atom of the enolates **8**–**10**. This may explain the relatively high *O*:*C* alkylation ratio when the reaction was carried out in an apolar solvent (entry 5, Table 1). It was attempted to increase the *O*:*C* alkylation ratio further by using harder electrophiles, *e.g.* the chlorofuranone **7b** and methylsulfonyloxyfuranone **7c**. Surprisingly, **8** did not react under these conditions. When the reactions were carried out in DMF or toluene in the presence of 18-crown-6, **8** was recovered almost quantitatively. Attempts to enhance *O*-alkylation of **10** with the bromofuranone **7a** in THF and toluene (entries 8 and 9, Table 1) failed, which is most likely due to the poor solubility of its potassium enolate even in the presence of 18-crown-6. Application of the optimal conditions for *O*-alkylation, found for **8**, gave access to the GR24-analogues **3b**, although *C*-alkylation was the predominant reaction (entry 10, Table 1). These results indicate that the nature of the β-keto ester also plays a determining role in the ratio of *O*- and *C*-alkylation. Under similar reaction conditions the *O*:*C* alkylation ratio increases in the order **9** < **8** < **10**. The relatively strong tendency of **10** to undergo *O*-alkylation agrees with its presence in the enol form in $CDCl_3$. The relative stabilities of the enol and keto tautomers may reflect the relative activation energies leading to *O*- and *C*-alkylation.

**Assignment of *E*/*Z*-geometry to compounds 2b–4b.** Compounds **2b**–**4b** were subjected to 2D-NOESY NMR analysis in order to determine unambiguously the correct geometry at the vinyl ether double bond. However, for **4b** this analysis failed to provide sufficient information to assign its configuration and therefore an X-ray diffraction analysis was undertaken. The crystal structure[31] clearly showed the *Z*-configuration as is depicted in Fig. 2. Analysis of the NOESY data of **2b** reveals the *Z*-configuration, as was deduced from the observed NOE cross-peak between the β-methyl and phenyl groups (Scheme 5).

In order to obtain additional support for this assignment, **2b** was photoisomerized in acetone in the presence of benzophenone, to give a mixture of **2b** and **2c** (Scheme 5). The β-methyl group in **2c** displayed an 0.7 ppm downfield shift in the




**Scheme 5**

$^1$H NMR spectrum as compared to the corresponding methyl group in **2b** and showed *no* NOE contact with the phenyl group. This NOESY experiment was performed using a mixture of **2b** and **2c**, since we were unable to separate these compounds by chromatography. A correct interpretation could, nevertheless, readily be achieved, since the corresponding relevant proton signals of **2b** and **2c** could clearly be distinguished. Similarly, based on the observed relevant NOE contacts as is depicted in Fig. 5, the correct structure of **3b** is the *Z* configuration as shown (Fig. 5).

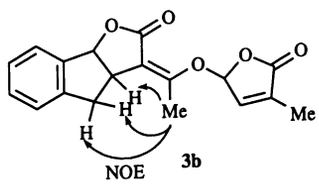



**Fig. 5**

Thus, the observed NOE contacts strongly disfavour the possibility of the alternative isomers, *viz*. **2c** and **3c**, as the products of the coupling reactions (Table 1). The stereochemical outcome of the reactions to give the *Z*-isomers **2b** and **3b** is quite unexpected, since the corresponding demethyl derivatives **2a** and **3a** are exclusively obtained in an *E*-selective fashion.[12,22] This behaviour cannot be explained as yet.

**Photoisomerization of 4a.** Isomerization of the enol ether double bond of compound **4a** was achieved by irradiation with UV light in toluene in the presence of benzophenone as sensitizer. Similar conditions, using another strigol analogue, were reported earlier,[32] but no data of the effect on the bioactivity were given. In our hands, a 1:1 mixture of **4a** and **5** was formed. Evidence for the isomerization was obtained by the upfield shift (0.8 ppm) of the β-proton of **5** in the $^1$H NMR spectrum as compared to the same proton of **4a**.

## Biological evaluation

The germination stimulatory activity of phthalimidoglycine derived strigol analogues **4a,b** and **5**, and tetronic acid derivatives **1a**–**c** was assayed using seeds of *Striga hermonthica* and *Orobanche crenata*. In each bioassay, GR24 **3a** (as an 1:1 mixture of diastereoisomers) at an optimal concentration (0.01 mg $l^{-1}$ for *Striga hermonthica* and 1 mg $l^{-1}$ for *Orobanche crenata*) was included as a positive control. This enables a comparison between results obtained in different test series. The reference test is important, since the response of seeds of parasitic weeds, in particular of *Striga hermonthica*, varies considerably from test to test. The germination percentages are collected in Tables 2 and 3.

The activity of both diastereoisomers of GR24 analogues **3b** was assessed and compared with that of GR24 **3a** at the concentrations 1 mg $l^{-1}$ and 0.1 mg $l^{-1}$, using seeds of *Orobanche crenata*, the results of which are collated in Table 4. All new compounds **1a**–**c**, **3b**, **4a**–**b** and **5** were tested as racemates. This is allowed, as we have shown for GR24 that the antipode of the

**Table 2** Germination stimulatory activity of strigol analogues **1**, **4** and **5** towards seeds of *Orobanche crenata* [a]

| | | % Germination ± S.E. | | | |
|---|---|---|---|---|---|
| Entry | Compd. | 2 mg $l^{-1}$ | 1 mg $l^{-1}$ | 0.01 mg $l^{-1}$ | **3a** 1 mg $l^{-1}$ [b] |
| 1 | **4a** | 58.3 ± 1.3 | 41.2 ± 1.4 | 0.0 ± 0.0 [c] | 67.2 ± 1.0 |
| 2 | **4b** | | 47.7 ± 4.5 | 1.3 ± 0.8 [c] | 76.1 ± 1.2 |
| 3 | **5** | 46.7 ± 3.5 | 32.6 ± 9.5 | 0.0 ± 0.0 [c] | 67.2 ± 1.0 |
| 4 | **1a** | | 47.4 ± 4.7 | 0.5 ± 0.3 [c] | 73.7 ± 1.2 |
| 5 | **1b** | | 34.6 ± 2.2 | 1.6 ± 0.8 [c] | 68.2 ± 1.3 |
| 6 | **1c** | | 29.3 ± 0.3 | 0.8 ± 0.4 [c] | 68.2 ± 1.3 |

[a] Activities are indicated as germination percentages after treatment of the seeds with test solutions at 2 mg $l^{-1}$, 1 mg $l^{-1}$ and 0.01 mg $l^{-1}$. Germination percentages given are the mean ± S.E. of two replicate tests. [b] Mean germination percentages ± S.E. obtained by treatment of the seeds with GR24 **3a** (1 mg $l^{-1}$) in the same bioassay (1 : 1 mixture of diastereoisomers). [c] Values are not significantly different from germination percentages obtained in the control (without stimulant).

**Table 3** Germination stimulatory activity of strigol analogues **1**, **4** and **5** towards seeds of *Striga hermonthica* [a]

| | | % Germination ± S.E. | | |
|---|---|---|---|---|
| Entry | Compd. | 1 mg $l^{-1}$ | 0.01 mg $l^{-1}$ | **3a** 0.01 mg $l^{-1}$ [b] |
| 1 | **4a** | 40.3 ± 1.7 | 4.1 ± 0.9 [c] | 52.5 ± 12.5 |
| 2 | **4b** | 36.5 ± 0.3 | 29.5 ± 4.7 | 48.9 ± 1.5 |
| 3 | **5** | 44.1 ± 1.6 | 3.1 ± 0.9 [c] | 78.3 ± 0.5 |
| 4 | **1a** | 29.6 ± 2.4 | 8.5 ± 0.7 [c] | 47.5 ± 2.2 |
| 5 | **1b** | 45.9 ± 7.9 | 14.5 ± 1.2 | 51.7 ± 4.2 |
| 6 | **1c** | 62.7 ± 7.7 | 15.6 ± 2.3 | 75.8 ± 2.5 |

[a] Activities are indicated as germination percentages after treatment of the seeds with test solutions at 1 mg $l^{-1}$ and 0.01 mg $l^{-1}$. Germination percentages given are the mean ± S.E. of two replicate tests. [b] Mean germination percentages ± S.E. obtained by treatment of the seeds with GR24 **3a** (0.01 mg $l^{-1}$) in the same bioassay (1 : 1 mixture of diastereoisomers). [c] Values are not significantly different from germination percentages obtained in the control (without stimulant).

**Table 4** Germination stimulatory activity of GR24 **3a** and **3b** towards seeds of *Orobanche crenata* [a]

| | | | % Germination ± S.E. | |
|---|---|---|---|---|
| | Entry | Compd. | 1 mg $l^{-1}$ | 0.1 mg $l^{-1}$ |
| | 1 | **3a** [b] | 59.0 ± 6.7 | 43.6 ± 2.9 |
| | 2 | **3b** [c] | 23.1 ± 6.8 | 5.7 ± 5.3 |
| | 3 | **3b** [d] | 14.5 ± 4.1 | 3.3 ± 0.4 |

[a] Activities are indicated as germination percentages after treatment of the seeds with test solutions at 1 mg $l^{-1}$ and 0.01 mg $l^{-1}$. Germination percentages given are the mean ± S.E. of two replicate tests. [b] Tested as a 1 : 1 mixture of diastereoisomers. [c] Fast-moving diastereoisomer as indicated by its chromatographic behaviour on TLC. [d] Slow-moving diastereoisomer as indicated by its chromatographic behaviour on TLC.

biologically most active stereoisomer does not contribute significantly to the stimulatory activity.[33]

Compounds **1**, **4** and **5** stimulate germination of both types of seeds at 1 mg $l^{-1}$. These compounds were virtually inactive with respect to seed germination of *Orobanche crenata* at a concentration of 0.01 mg $l^{-1}$. It should be noted that in this assay GR24 **3a** was also only moderately active at this concentration. A modest stimulatory activity of tetronic acid derivatives **1b–c** at 0.01 mg $l^{-1}$ (*Striga hermonthica*) was observed (entries 5–6, Table 3), whereas methyl substituted analogue **4b** stimulates germination considerably at this concentration (entry 2, Table 3). Comparison of the germination percentages of compounds **4a,b** at the lower concentration (entries 1–2, Table 3) indicates that a methyl substituent at the enol ether moiety is beneficial for the bioactivity. None of the isomeric *C*-alkylated analogues **13** and **15** exerted any stimulatory effect (data not shown). The data presented indicate that there can be a considerable degree of structural freedom at the enol ether function without the bioactivity being affected appreciably. These results can be summarized as follows: i, the *E/Z*-geometry of the enol ether double bond is not essential to retain stimulatory activity (*cf.* entries 1 and 3, Tables 2 and 3); ii, the presence of a small substituent at $C_\beta$ has no negative effect on the bioactivity (entries 2, 4–6, Tables 2 and 3); iii, on the other hand, double-bond isomerization including the relatively bulky ABC-part such as in **3b** (Table 4) leads to a substantial loss of bioactivity.

The activity of the tetronic acid analogue **1c** is comparable to that of the closely related compound **2a**.[12] Tetronic acid analogue **1a** only contains the essential structural features,[15] *viz*. the α,β-unsaturated enol ether moiety, which allows an addition-elimination mechanism (Scheme 1) and the 3-methylfuran-2(5*H*)-one fragment. Analogues **1**, **2b–4b** and **5** were designed in such a manner that the essence of the molecular mechanism (Scheme 1) is retained. These results are in full accord with the finding of complete loss of germination activity when the connecting unit was modified, *viz*. reduction of the olefinic bond[15] or replacement of the oxygen atom by a methylene function,[16] and thus the results described above provide a further substantiation of the proposed molecular mechanism. It may thus be concluded that, in order to retain germination stimulatory activity, the presence of the enol ether moiety is more important than the spatial arrangement.

## Experimental

### Synthesis

**General remarks.** $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC 100 (100 MHz) or a Bruker AM-400 (400 MHz) spectrometer ($Me_4Si$ as internal standard). All coupling constants are given as $^3J$ in Hz, unless indicated otherwise. IR Spectra were determined on a Perkin-Elmer 298 spectrophotometer. For mass spectra a double focussing VG7070E mass spectrometer was used. Melting points were determined using a Reichert thermopan microscope. Elemental analyses were performed at the Department of Microanalysis of this laboratory.

Solvents were dried using the following methods. Dichloromethane was distilled from $P_2O_5$. Diethyl ether was distilled from NaH. Hexane was distilled from $CaH_2$. Ethyl acetate was distilled from $K_2CO_3$. Tetrahydrofuran was distilled from $LiAlH_4$ just before use. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on Merck pre-coated silica gel 60 F254 plates (0.25 mm) using the eluents indicated. Spots were visualized with UV or using a molybdate spray. 'Flash' chromatography was carried out at a pressure of *ca*. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was carried out, using Merck Kieselgel 60. Irradiations were carried out using a Hanau TQ150 high-pressure mercury-vapour lamp (150 W), equipped with a Pyrex filter.

3,3a,4,8b-Tetrahydroindeno[1,2-*b*]furan-2-one **11**[22] and 5-bromo-3-methylfuran-2(5*H*)-one **7a**[22] were prepared following published methods.

#### 4-Hydroxy-3-phenylfuran-2(5*H*)-one 6c

This compound was prepared similarly as described previously,[21] starting from methoxycarbonylmethyl phenylacetate (0.1 mol) and potassium *tert*-butoxide (0.11 mol) in *tert*-butyl alcohol (200 ml). Work-up and recrystallization from ethanol gave analytically pure **6c** (6.8 g, 50%), having spectroscopic data identical with those reported previously.[21] The starting methoxycarbonylmethyl phenylacetate was obtained as follows. To a cooled (0 °C) solution of phenylacetic acid (13.6 g, 100 mmol) and methyl hydroxyacetate (9.00 g, 100 mmol) in THF (150 ml) were added dicyclohexylcarbodiimide (DCC; 21 g, 0.10 mol) and a catalytic amount of 4-dimethylaminopyridine

(DMAP). The mixture was allowed to warm to room temperature and then stirred overnight at room temperature. After this it was concentrated by removal of THF *in vacuo* and to the residue was added diisopropyl ether (150 ml). The precipitate of dicyclohexylurea (DCU) was filtered off and the filtrate was concentrated *in vacuo* to give methoxycarbonylmethyl phenylacetate as an oil in quantitative yield. This was sufficiently pure for use in the next reaction; $\delta_H$(100 MHz; $CDCl_3$) 3.74 (5 H, s, $OCH_3$ + PhC$H_2$), 4.63 (2 H, s, $OCH_2$) and 7.31 (5 H, s, Ph).

**Coupling of 4-hydroxyfuran-2(5*H*)-ones 6a–c with 5-bromo-3-methylfuran-2(5*H*)-one 7a: general procedure**

To a solution of 4-hydroxyfuran-2(5*H*)-one **6a–c** (10 mmol) in DMF (40 ml) was added potassium *tert*-butoxide (11 mmol) under a nitrogen atmosphere. The mixture was cooled to −60 °C and a solution of **7a** (11 mmol) in DMF (10 ml) was added to it with stirring. Stirring was continued for 18 h at room temperature after which the DMF was removed *in vacuo* and the residue was dissolved in a mixture of water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (2×) and the combined organic extracts were washed with sat. aqueous $NH_4Cl$ and water, dried ($MgSO_4$) and concentrated *in vacuo* to give **1a–c** as solids.

**3-Methyl-5-(5-oxo-2,5-dihydrofuran-3-yloxy)furan-2(5*H*)-one 1a**

Following the general procedure, 4-hydroxyfuran-2(5*H*)-one **6a** (1.0 g, 10 mmol) gave after work-up compound **1a** (1.5 g, 76%) as a yellow solid. An analytically pure sample was obtained by repeated recrystallization from ethanol to give **1a** as white crystals, mp 128 °C (from EtOH) (Found: C, 55.09; H, 4.09. $C_9H_8O_5$ requires C, 55.12; H, 4.11); $\delta_H$(100 MHz; $CDCl_3$) 2.05 (3 H, m, $CH_3$), 4.70 and 4.71 (2 H, 2 s, $CH_2$), 5.50 (1 H, m, =CH C-ring), 6.27 (1 H, m, OCHO) and 7.00 (1 H, m, =CH D-ring); $\delta_C$(25.2 MHz; $CDCl_3$) 10.6 (q, $CH_3$), 67.5 (t, $CH_2$), 93.3 (d, OCHO), 98.5 (d, =CH C-ring), 135.5 (s, =*C*$CH_3$), 140.4 (d, =CH D-ring), 169.9 (s, =CO), 172.1 (s, C=O) and 175.8 (s, C=O); *m/z* 197 ($M^+$ + 1, 3.1%) and 97 (100, $C_5H_5O_2$).

**3-Methyl-5-(4-methyl-5-oxo-2,5-dihydrofuran-3-yloxy)furan-2(5*H*)-one 1b**

Following the general procedure, 4-hydroxy-3-methylfuran-2(5*H*)-one **6b** (1.1 g, 10 mmol) gave after work-up compound **1b** (1.7 g, 82%) as a yellow solid. An analytically pure sample was obtained by recrystallization from ethanol to give **1b** as white crystals, mp 108–110 °C (from EtOH) (Found: C, 56.70; H, 4.64. $C_{10}H_{10}O_5$ requires C, 56.08; H, 4.71); $\delta_H$(100 MHz; $CDCl_3$) 1.85 (3 H, m, $CH_3$ C-ring), 2.04 (3 H, m, $CH_3$ D-ring), 4.79 (2 H, m, $CH_2$), 6.29 (1 H, m, OCHO) and 7.00 (1 H, m, =CH); $\delta_C$(25.2 MHz; $CDCl_3$) 6.8 (q, $CH_3$), 10.4 (q, $CH_3$), 65.8 (t, $CH_2$), 97.1 (d, O*C*HO), 103.3 (s, =*C*–$CH_3$ C-ring), 135.2 (s, =*C*–$CH_3$ D-ring), 140.9 (d, =CH), 168.0 (s, =CO), 169.9 (s, C=O) and 173.8 (s, C=O); *m/z* 210 ($M^+$, 3.1%) and 97 (100, $C_5H_5O_2$).

**3-Methyl-5-(4-phenyl-5-oxo-2,5-dihydrofuran-3-yloxy)furan-2(5*H*)-one 1c**

Following the general procedure, 4-hydroxy-3-phenylfuran-2(5*H*)-one **6c** (1.0 g, 5.7 mmol) gave after work-up compound **1c** (1.1 g, 68%) as a yellow solid. An analytically pure sample was obtained by recrystallization from ethanol to give **1c** as white crystals, mp 155–157 °C (from EtOH) (Found: C, 66.21; H, 4.34. $C_{15}H_{12}O_5$ requires C, 66.17; H, 4.44); $\delta_H$(100 MHz; $CDCl_3$) 2.04 (3 H, m, $CH_3$), 5.02 (2 H, AB, $J_{AB}$ 17, $CH_2$), 6.26 (1 H, m, OCHO), 7.03 (1 H, m, =CH), 7.37 (3 H, m, Ph) and 7.82 (2 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.3 (q, $CH_3$), 65.1 (t, $CH_2$), 97.3 (d, OCHO), 106.5 (s, =*C*–Ph), 127.8 (d, Ph), 128.1 (s, Ph), 128.3 (d, Ph), 128.4 (d, Ph), 135.5 (s, =*C*–$CH_3$), 140.9 (d, =CH), 168.6 (s, =CO), 169.8 (s, C=O) and 171.4 (s, C=O); *m/z* 272 ($M^+$, 2.4%), 176 (9.4, $C_{10}H_8O_3$) and 97 (100, $C_5H_5O_2$).

**Methyl 3-oxo-2-phenylbutyrate 8**

By a modified literature procedure,[24] a mixture of methyl phenylacetate (30.1 g, 200 mmol) and methyl acetate (30.0 g, 405 mmol) was gradually added to a cooled (−78 °C) solution of potassium *tert*-butoxide (24.7 g, 202 mmol) under a nitrogen atmosphere. The mixture was stirred for 2 h at the same temperature and then allowed to warm to room temperature. Stirring was continued for 18 h at room temperature and 1 h under reflux after which the mixture was cooled (0 °C) and neutralized with acetic acid (1 equiv.). The volatiles were removed *in vacuo* and the residue was dissolved in water and ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (3×) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the residue under reduced pressure gave **8** (14.9 g, 39%) as a colourless oil, which solidified with time. The physical properties were in agreement with those reported previously,[24] ratio keto:enol 2:1; $\delta_H$(100 MHz; $CDCl_3$) 1.84 (3 H, s, $CH_3$ enol), 2.17 (3 H, s, $CH_3$ keto), 3.67 (3 H, s, $OCH_3$ enol), 3.74 (3 H, s, $CH_3$ keto), 4.72 (1 H, s, CH keto), 7.35 (5 H, m, Ph) and 13.04 (1 H, br s, OH enol).

**Methyl 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-oxobutanoate 10**

To a cooled (−30 °C) solution of methyl 2-chloro-3-oxobutanoate (6.03 g, 40.1 mmol) in DMF (30 ml) was gradually added potassium phthalimide (8.15 g, 44.1 mmol). The mixture was stirred for 1 h at −20 to −30 °C after which stirring was continued for 18 h at room temperature. Insoluble salts were removed by filtration through Hyflo and the filtrate was poured into ice–water and the pH adjusted to 1–2 with 2 M HCl. A precipitate gently settled, and this was filtered off to afford a white solid (6.3 g), which consisted of **10** and phthalimide in a ratio 75:25 according to $^1$H NMR analysis. The residue was recrystallized from butyl acetate to give phthalimide as white crystals (1.32 g). The filtrate was concentrated *in vacuo* to give a solid (5.0 g, 48%), which contained almost pure **10** together with a trace amount of phthalimide. Analytically pure **10** (100% enol) was obtained by recrystallization thrice from propan-2-ol as pale yellow crystals, mp 126–127 °C (from propan-2-ol) (Found: C, 59.83; N, 5.23; H, 4.29. $C_{13}H_{11}NO_5$ requires C, 59.77; N, 5.36; H, 4.24); $\nu_{max}$(KBr)/cm$^{-1}$ 3200 (br, OH), 1722 (C=O, imide, ester) and 1668 (C=C, enol); $\delta_H$(100 MHz; $CDCl_3$) 1.95 (3 H, s, $CH_3$ enol), 3.71 (3 H, s, $OCH_3$), 7.87 (4 H, m, Ph) and 12.68 (1 H, br s, OH enol); *m/z* 261 ($M^+$, 31.4%), 219 (41.2, $C_{11}H_9O_4N$) and 132 (100, $C_8H_4O_2$).

**3-(1-Hydroxyethyl)-3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one 12**

A solution of the tricyclic lactone **11** (2.61 g, 15.0 mmol) in THF (25 ml) was added dropwise to a cooled (−78 °C) solution of freshly prepared lithium diisopropylamide (16.5 mmol) in THF (25 ml) under nitrogen. The reaction mixture was stirred for 15 min at the same temperature and then warmed to −40 °C. Freshly distilled acetaldehyde (1.27 ml, 22.7 mmol) was added *via* a syringe to the mixture and stirring was continued for 1 h at −40 °C. The reaction mixture was then warmed to 0 °C and stirred for 1 h. The mixture was quenched with 1 M HCl (65 ml), concentrated by removal of THF *in vacuo* and extracted with dichloromethane (3×). The combined organic layers were washed with water (2×), dried ($MgSO_4$) and concentrated. Purification by chromatography ($SiO_2$, eluent hexane–ethyl acetate, 2:1) afforded pure **12** (3.05 g, 93%); $R_f$ 0.20 (hexane–ethyl acetate, 2:1) as a white solid, consisting of two diastereoisomers in a 1:1 ratio according to capillary GC and $^1$H NMR analysis. For characterization purposes one diastereoisomer was obtained in a pure form by stirring in diisopropyl ether, filtration and recrystallization of the residue from hexane–ethyl acetate.

Diastereoisomer **12a**, mp 117–120 °C (from hexane–ethyl acetate) (Found: C, 70.65; H, 6.31. $C_{13}H_{14}O_3$ requires C, 71.54;

H, 6.47); $\nu_{max}$(KBr)/cm$^{-1}$ 3540 (br, OH) and 1750 (C=O, lactone); $\delta_H$(400 MHz; $CDCl_3$) 1.36 (3 H, d, *J* 6.5, $CH_3$), 2.10 (1 H, d, *J* 5.4, OH), 2.42 (1 H, dd, *J* 7.6, *J* 3.2, O=CCH), 2.92 (1 H, d, $^2J$ 16.2, $CH_2$), 3.36 (1 H, dd, $^2J$ 16.2, *J* 8.0, $CH_2$), 3.44 (1 H, m, $CH_2CH$), 4.42 (1 H, m, C*H*OH), 5.90 (1 H, d, *J* 7.7, PhC*H*), 7.28–7.37 (3 H, m, Ph) and 7.47 (1 H, d, *J* 7.3, Ph); $\delta_C$(25.2 MHz; $CDCl_3$, mixture of two diastereoisomers) 20.3, 20.9 (q, $CH_3$), 37.0, 37.7 (t, $CH_2$), 37.6, 40.6 (d, $CH_2CH$), 52.6, 54.1 [d, C(O)*C*H], 65.9, 68.0 (d, HCOH), 86.0, 86.3 (d, Ph*C*HO), 125.2, 125.3, 125.8, 125.9, 127.3, 127.4, 129.6, 129.7 (d, Ph), 138.5, 138.9, 141.4, 141.8 (s, Ph), 178.2 and 178.8 (s, C=O); *m/z* 218 ($M^+$, 75.7%), 201 (100, $C_{13}H_{13}O_2$), 128 (81.6, $C_{10}H_8$) and 115 (42.1, $C_9H_7$) [Found (HRMS/EI): *m/z* 218.0944 ± 0.0010. Calc. for $C_{13}H_{14}O_3$: 218.0943].

Diastereoisomer **12b** was obtained as a colourless oil, slightly contaminated with **12a** after being stirred in diisopropyl ether and concentration *in vacuo*. $R_f$ Value and mass data were the same as for **12a**.

### 3-Acetyl-3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one 9

To a stirred solution of distilled oxalyl chloride (1.92 g, 15.1 mmol) in dichloromethane (25 ml) was added DMSO (2.36 g, 30.3 mmol) at room temperature under nitrogen. The solution was cooled to −78 °C and then treated with a solution of **12** (3.00 g, 13.8 mmol) in dichloromethane (20 ml), added dropwise. Stirring was continued for 10 min at −78 °C after which a solution of triethylamine (6.96 g, 68.7 mmol) in dichloromethane was gradually added to it. After 5 min the reaction mixture was warmed to room temperature, quenched with 1 M HCl (30 ml) and extracted with dichloromethane (2×). The combined organic extracts were washed with water (1×) and dried ($MgSO_4$) to provide **9** (2.86 g, 96%) as a yellowish oil, which was sufficiently pure for further use. Ratio keto:enol tautomers 3:2 according to $^1$H NMR analysis; $R_f$ 0.30 (hexane–ethyl acetate, 4:1); $\delta_H$(400 MHz; $CDCl_3$) 2.04 (3 H, d, $CH_3$ enol), 2.40 (3 H, s, $CH_3$ keto), 2.85 (1 H, dd, *J* 3.3, $^2J$ 16.8, $CH_2$ keto), 3.02 (1 H, dd, *J* 3.4, $^2J$ 16.5, $CH_2$ enol), 3.35 (1 H, dd, *J* 8.6, $^2J$ 16.8, $CH_2$ keto), 3.49 (1 H, dd, *J* 8.7, $^2J$ 16.5, $CH_2$ enol), 3.56 [1 H, d, *J* 6.1, C*H*C(O)$CH_3$ keto], 3.84 (1 H, m, $CH_2CH$ keto), 3.91 (1 H, m, $CH_2CH$ enol), 5.91 (1 H, d, *J* 7.4, HCO keto), 5.97 (1 H, d, *J* 8.2, HCO enol), 7.26–7.47 (4 H, m, Ph) and 11.21 (1 H, br s, OH); *m/z* 216 ($M^+$, 11.3%), 174 (14.6, $C_{11}H_{10}O_2$), 129 (88.8, $C_{10}H_9$), 115 (20.3, $C_9H_7$) and 43 (100, $C_2H_3O$) [Found (HRMS/EI): *m/z* 216.0787 ± 0.0010. Calc. for $C_{13}H_{12}O_3$: 216.0786].

### Coupling of compounds 8–10 with 5-bromo-3-methylfuran-2(5*H*)-one 7a: general procedure

To a stirred solution of precursors **8**–**10** (2.50 mmol) in DMF (10 ml, procedure A) or toluene (10 ml, procedure B) was added potassium *tert*-butoxide (2.50 mmol) at room temperature under nitrogen; in procedure B this was followed by the addition of 18-crown-6 (1.25 mmol). The thus obtained solution was cooled to −65 °C (procedure A) or −78 °C (procedure B). A solution of **7a** (3.00 mmol) in DMF (3 ml, procedure A) or toluene (3 ml, procedure B) was gradually added to the reaction mixture which was then allowed to warm slowly to room temperature. Stirring was continued for 15 h after which the solvent was removed *in vacuo* and the residue was dissolved in sat. aqueous $NH_4Cl$ and ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (2×) and the combined organic extracts were washed with water (1×) and brine (1×), dried ($MgSO_4$) and concentrated *in vacuo*.

### Methyl 2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-oxo-2-phenylbutanoate 13

Following procedure A, **8** (269 mg, 1.38 mmol) gave a crude product with a ratio of diastereoisomers of 1:1, according to $^1$H NMR analysis. Purification by flash chromatography ($SiO_2$, eluent gradient hexane–ethyl acetate, 9:1, 6:1, 3:1) gave two diastereoisomers in a yield of 65%.

Diastereoisomer **13a**, $R_f$ 0.21 (hexane–ethyl acetate, 3:1): obtained as a white solid, mp 122–123 °C (from diisopropyl ether) (Found: C, 66.68; H, 5.61. $C_{16}H_{16}O_5$ requires C, 66.66; H, 5.59); $\nu_{max}$(KBr)/cm$^{-1}$ 1758 (C=O, lactone) and 1712 (C=O, ester, acetyl); $\delta_H$(100 MHz; $CDCl_3$) 1.59 (3 H, m, $=CCH_3$), 2.23 (3 H, s, $CH_3$), 3.90 (3 H, s, $OCH_3$), 5.85 (1 H, m, HCO), 6.94 (1 H, m, =CH) and 7.07–7.36 (5 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.2 (q, $CH_3$), 27.7 (q, $CH_3$), 53.4 (q, $OCH_3$), 72.1 (s, $CC_4$), 81.3 (d, HCO), 128.5, 128.6, (2 × d, Ph), 131.1 (s, Ph)*, 131.6 (s, $=CCH_3$)*, 146.8 (d, =CH), 166.0 (s, OC=O), 173.2 (s, OC=O) and 202.0 (s, O=$CCH_3$) (*: signals may be interchanged); *m/z* 288 ($M^+$, 1.7%), 246 (99.1, $C_{14}H_{14}O_4$), 191 (61.3, $C_{11}H_{11}O_3$), 187 (100, $C_{12}H_{11}O_2$), 97 (54.3, $C_5H_5O_2$) and 43 (70.9, $C_2H_3O$).

Diastereoisomer **13b**, $R_f$ 0.18 (hexane–ethyl acetate, 3:1): obtained as a colourless oil, purity according to capillary GC >99%; $\nu_{max}$(KBr)/cm$^{-1}$ 1772 (C=O, lactone) and 1722 and 1715 (C=O, ester, acetyl); $\delta_H$(100 MHz; $CDCl_3$) 1.69 (3 H, m, $=CCH_3$), 2.25 (3 H, s, $CH_3$), 3.84 (3 H, s, $OCH_3$), 5.89 (1 H, m, HCO) and 7.06–7.41 (6 H, m, Ph and =CH); $\delta_C$(25.2 MHz; $CDCl_3$) 10.5 (q, $CH_3$), 28.6 (q, $CH_3$), 53.1 (q, $OCH_3$), 71.5 (s, $CC\text{-}4_4$), 80.8 (d, H*C*O), 128.4, 128.5, 128.7 (3 × d, Ph), 131.7 (s, Ph)*, 132.7 (s, $=CCH_3$)*, 146.8 (d, =CH), 168.6 (s, OC=O), 173.2 (s, OC=O) and 201.3 (s, O=$CCH_3$) (*: signals may be interchanged); mass data were the same as for the diastereoisomer **13a** [Found (HRMS/EI): *m/z* 288.0997 ± 0.0014. Calc. for $C_{16}H_{16}O_5$: 288.0998].

### Methyl 3-(4-methyl-5-oxo-2,5-dihydrofuran-2-yloxy)-2-phenylbut-2-enoate 2b

This compound was prepared according to procedure B, starting from **8** (269 mg, 1.38 mmol). The ratio of isomers **13** and **2b** was 3:7, according to $^1$H NMR analysis. Purification by flash chromatography ($SiO_2$, eluent gradient hexane–ethyl acetate, 9:1, 6:1, 3:1) afforded pure diastereoisomer **13a** as a white solid and **2b** as a colourless oil, which was slightly contaminated with diastereoisomer **13b**. Total yield of **13b** and **2b** 69%, $R_f$ 0.18 (hexane–ethyl acetate, 3:1); $\nu_{max}$(KBr)/cm$^{-1}$ 1782 (C=O, lactone) and 1720 (C=O, ester); $\delta_H$(100 MHz; $CDCl_3$) 2.01 (6 H, m, 2 $CH_3$), 3.68 (3 H, s, $OCH_3$), 6.21 (1 H, m, OCHO), 7.05 (1 H, m, =CH) and 7.33 (5 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.5 (q, $CH_3$), 17.6 (q, $CH_3$), 51.8 (q, $OCH_3$), 99.9 (d, OCHO), 120.0 (s, $=CCO_2Me$), 127.7, 128.4, 129.6 (3 × d, Ph), 134.1 (s, Ph)*, 134.9 (s, $=CCH_3$)*, 142.7 (d, =CH), 158.0 (s, =CO), 166.8 (s, OC=O) and 171.4 (s, OC=O) (*: signals may be interchanged).

### 3-[1-(4-Methyl-5-oxo-2,5-dihydrofuran-2-yloxy)ethylidene]-3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one 3b and 3-acetyl-3-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3,3a,4,8b-tetrahydroindeno[1,2-*b*]furan-2-one 14

These compounds were prepared following procedure B, starting from **9** (568 mg, 2.63 mmol). The ratio of isomers **3b** and **14** in the crude reaction mixture was 1:2, according to $^1$H NMR analysis. Purification by flash chromatography ($SiO_2$, eluent gradient hexane–ethyl acetate, 6:1, 3:1 and 1:1) afforded three fractions containing *O*- and *C*-alkylated products.

Compound **14**, $R_f$ 0.18 (hexane–ethyl acetate, 3:1): obtained as a white solid (299 mg, 36%) as a mixture of two diastereoisomers (ratio 3:1). An analytically pure sample of the main diastereoisomer was obtained after recrystallization from hexane–ethyl acetate, mp 173–176 °C (from hexane–ethyl acetate) (Found: C, 69.29; H, 5.15. $C_{18}H_{16}O_5$ requires C, 69.22; H, 5.16); $\nu_{max}$(KBr)/cm$^{-1}$ 1760 (C=O, lactone) and 1695 (C=O, acetyl); $\delta_H$(400 MHz; $CDCl_3$) 1.84 (3 H, s, $CH_3$ D-ring), 2.02 (3 H, m, $CH_3$), 2.77 (1 H, dd, $^2J$ 17.1, *J* 2.9, $CH_2$), 2.97 (1 H, m, $CH_2CH$), 3.14 (1 H, dd, $^2J$ 17, *J* 8.8, $CH_2$), 5.35 (1 H, m, HCO), 5.94 (1 H, d, *J* 7.5, PhC*H*O), 7.20 (1 H, m, Ph), 7.35 (2 H, m, Ph), 7.46 (1 H, m, =CH) and 7.53 (1 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.9 (q, $CH_3$), 29.9 (q, $CH_3$), 33.4 (t, $CH_2$), 41.3 (d, $CH_2CH$), 66.0 (s, $CC_4$), 80.4 (d, HCO), 85.9 (d, HCO), 125.0,

126.1, 128.2, 130.4 (4 × d, Ph), 133.6 (s, Ph)*, 138.3 (s, Ph)*, 141.8 (s, =*C*$CH_3$)*, 145.5 (d, =CH), 172.4 (s, OC=O), 173.9 (s, OC=O) and 202.5 (s, O=*C*$CH_3$) (*: signals may be interchanged); *m/z* 313 ($M^+$ +1, 3.1%), 270 (8.3, $C_{16}H_{14}O_4$), 215 (20.2, $C_{13}H_{11}O_3$), 97 (5.5, $C_5H_5O_2$) and 43 (100, $C_2H_3O$).

Fast-moving diastereoisomer **3b**, $R_f$ 0.12 (hexane–ethyl acetate, 3:1): obtained as a yellow solid (88 mg, 11%), mp 144–148 °C (from hexane–ethyl acetate) (Found: C, 69.27; H, 5.14. $C_{18}H_{16}O_5$ requires C, 69.22; H, 5.16); $\nu_{max}(CCl_4)/cm^{-1}$ 1780 (C=O, lactone) and 1750 and 1725 (C=O, lactone); $\delta_H$(100 MHz; $CDCl_3$) 1.96 (3 H, m, $CH_3$ D-ring), 2.24 (3 H, d, $^5J$ 1.2, $CH_3$), 3.02 (1 H, dd, $^2J$ 16.4, *J* 4.0, $CH_2$), 3.58 (1 H, dd, $^2J$ 16.4, *J* 9.3, $CH_2$), 3.92 (1 H, m, $CH_2CH$), 5.86 (1 H, d, *J* 7.7, PhC*H*O), 6.15 (1 H, m, OCHO), 7.15 (1 H, m, =CH) and 7.29–7.54 (4 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.6 (q, $CH_3$), 20.2 (q, $CH_3$), 39.6 (t, $CH_2$), 40.7 (d, $CH_2CH$), 84.3 (d, HCO), 101.5 (d, O*C*HO), 114.9 [s, *C*=C(O)$CH_3$], 125.1, 126.5, 127.6, 130.2 (4 × d, Ph), 134.1 (s, Ph)*, 138.9 (s, Ph)*, 142.3 (s, =*C*$CH_3$)*, 143.1 (d, =CH), 163.0 (s, C=O)*, 167.6 (s, C=O)* and 171.5 [s, =*C*(O)$CH_3$]* (*: signals may be interchanged).

Slow-moving diastereoisomer **3b**, $R_f$ 0.05 (hexane–ethyl acetate, 3:1): obtained as a yellow solid (61 mg, 7%), mp 164–167 °C (from hexane–ethyl acetate) (Found: C, 69.39; H, 5.06. $C_{18}H_{16}O_5$ requires C, 69.22; H, 5.16); $\nu_{max}(CCl_4)/cm^{-1}$ 1780 (C=O, lactone) and 1750 and 1725 (C=O, lactone); $\delta_H$(400 MHz; $CDCl_3$) 1.97 (3 H, m, $CH_3$ D-ring), 2.25 (3 H, d, $^5J$ 1.2, $CH_3$), 3.05 (1 H, dd, $^2J$ 16.6, *J* 4.7, $CH_2$), 3.57 (1 H, dd, $^2J$ 16.6, *J* 9.5, $CH_2$), 3.93 (1 H, m, $CH_2CH$), 5.85 (1 H, d, *J* 7.8, PhC*H*O), 6.21 (1 H, m, OCHO), 7.15 (1 H, m, =CH), 7.25–7.38 (3 H, m, Ph) and 7.51 (1 H, d, *J* 7.5, Ph); *m/z* 312 ($M^+$, 0.23%), 215 (38.7, $C_{13}H_{11}O_3$) and 97 (100, $C_5H_5O_2$).

### Methyl 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-(4-methyl-5-oxo-2,5-dihydrofuran-2-yloxy)but-2-enoate 4b and methyl 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)-3-oxobutyrate 15

The reaction was carried out following procedure A, starting from **10** (0.63 g, 2.4 mmol). The ratio of isomers **4b** and **15** in the crude reaction mixture was 2:3, according to $^1$H NMR analysis. Purification by flash chromatography ($SiO_2$, eluent hexane–ethyl acetate, 1:1) gave **4b** and **15** (ratio of diastereoisomers **15a**:**15b**, 6:1) as pale yellow solids in a yield of 67%.

Diastereoisomers **15a** and **15b**: recrystallized from propan-2-ol to give analytically pure **15a** and **15b** (ratio 6:1) as white crystals, mp 181–183 °C (propan-2-ol) (Found: C, 60.44; N, 3.83; H, 4.14. $C_{18}H_{15}NO_7$ requires C, 60.51; N, 3.92; H, 4.23); $\nu_{max}$(KBr)/$cm^{-1}$ 1760 (C=O, lactone) and 1720 (C=O, imide, acetyl, ester); *m/z* 357 ($M^+$, 0.1%), 315 (58.1, $C_{16}H_{13}NO_6$), 260 (100, $C_{13}H_{10}NO_5$), 97 (7.0, $C_5H_5O_2$) and 43 (44.9, $C_2H_3O$).

Diastereoisomer **15a**, $R_f$ 0.32 (hexane–ethyl acetate, 1:1); $\delta_H$(100 MHz; $CDCl_3$) 1.75 (3 H, m, =CC*H*$_3$), 2.35 (3 H, s, $CH_3$), 3.92 (3 H, s, $OCH_3$), 6.20 (1 H, m, HCO), 7.15 (1 H, m, =CH) and 7.64 (4 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.5 (q, $CH_3$), 26.8 (q, $CH_3$), 54.1 (q, $OCH_3$), 73.3 (s, N*C*$C_3$), 80.6 (d, HCO), 124.0 (d, Ph), 130.8 (s, Ph)*, 131.4 (s, =*C*$CH_3$)*, 135.0 (d, Ph), 145.9 (d, =CH), 163.8 (s, OC=O), 166.9 (s, NC=O), 172.7 (s, OC=O) and 197.5 (s, O=*C*$CH_3$) (*: signals may be interchanged).

Diastereoisomer **15b**: $R_f$ 0.32 (hexane–ethyl acetate, 1:1); $\delta_H$(100 MHz; $CDCl_3$) 1.75 (3 H, m, =CC*H*$_3$), 2.39 (3 H, s, $CH_3$), 3.87 (3 H, s, $OCH_3$), 6.20 (1 H, m, HCO), 7.15 (1 H, m, =CH) and 7.64 (4 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.5 (q, $CH_3$), 26.7 (q, $CH_3$), 53.8 (q, $OCH_3$), 73.3 (s, N*C*$C_3$), 79.6 (d, HCO), 124.0 (d, Ph), 130.8 (s, Ph)*, 131.4 (s, =*C*$CH_3$)*, 135.0 (d, Ph), 146.2 (d, =CH), 163.8 (s, OC=O), 166.9 (s, NC=O), 172.7 (s, OC=O) and 195.2 (s, O=*C*$CH_3$) (*: signals may be interchanged).

Compound **4b**, $R_f$ 0.20 (hexane–ethyl acetate, 1:1), mp 195–196.5 °C (from propan-2-ol–dichloromethane) (Found: C, 60.78; N, 3.92; H, 4.15. $C_{18}H_{15}NO_7$ requires C, 60.51; N, 3.92; H, 4.23%); $\nu_{max}$(KBr)/$cm^{-1}$ 1774 (C=O, lactone), 1718 (C=O, ester), 1698 (C=O, imide) and 1638 (C=C, enol ether); $\delta_H$(100 MHz; $CDCl_3$) 1.89 (3 H, m, =CC*H*$_3$ D-ring), 2.82 (3 H, s, $CH_3$), 3.70 (3 H, s, $OCH_3$), 6.31 (1 H, m, OCHO), 6.71 (1 H, m, =CH) and 7.73–7.96 (4 H, m, Ph); $\delta_C$(25.2 MHz; $CDCl_3$) 10.6 (q, $CH_3$), 15.6 (q, $CH_3$), 52.2 (q, $OCH_3$), 96.5 (d, OCHO), 105.5 (s, =*C*$CO_2$Me), 123.5, 123.8 (2 × d, Ph), 132.1 (s, Ph)*, 134.2 (d, Ph), 134.7 (s, =*C*$CH_3$)*, 141.7 (d, =CH), 164.0 (s, =CO), 165.8 (s, NC=O), 166.6 (s, OC=O), 170.5 (s, OC=O) (*: signals may be interchanged); *m/z* 357 ($M^+$, 0.4%), 260 (100, $C_{13}H_{10}NO_5$) and 97 (21.7, $C_5H_5O_2$).

### Irradiation of (*Z*)-methyl 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-(4-methyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate 4a

This reaction was carried out in a similar way to that described by MacAlpine *et al.*[32] A solution of the *Z*-isomer **4a** (500 mg, 1.46 mmol) in dry toluene (200 ml) was irradiated for a few hours in the presence of benzophenone (200 mg). The solution was concentrated *in vacuo* and subsequently passed through a short column of silica to remove benzophenone. A 1:1 mixture of **5** and **4a** in quantitative yield was thus obtained, the two compounds having identical $R_f$ values on TLC (eluent: hexane–ethyl acetate, 1:1). The crude mixture was triturated with ethyl acetate, from which only the *E*-isomer **5** was precipitated. Analytically pure **5** (175 mg, 35%) was obtained by recrystallization from propan-2-ol as white crystals, mp 197–200 °C (from propan-2-ol) (Found: C, 59.34; N, 4.10; H, 3.76. $C_{17}H_{13}NO_7$ requires C, 59.48; N, 4.08; H, 3.82%); $\delta_H$(100 MHz; $CDCl_3$) 2.04 (3 H, m, $CH_3$), 3.74 (3 H, s, $OCH_3$), 6.22 (1 H, br s, OCHO), 7.07 (1 H, br s, =CH), 7.10 (1 H, s, =CHO) and 7.72–7.97 (4 H, m, Ph).

### Irradiation of (*Z*)-methyl 3-(4-methyl-5-oxo-2,5-dihydrofuran-2-yloxy)-2-phenylbut-2-enoate 2b

A solution of the *Z*-isomer **2b** (194 mg, 0.67 mmol), slightly contaminated with **13**, in acetone (10 ml) was irradiated for 30 min in the presence of benzophenone (31 mg, 0.17 mmol). The solution was concentrated *in vacuo* and subsequently passed through a short column of silica (eluent dichloromethane) to remove benzophenone. An inseparable mixture of **2b** and **2c** (ratio 5:3) in almost quantitative yield was thus obtained as a colourless oil, the two compounds having identical $R_f$ values on TLC using several eluents. Relevant $^1$H NMR data (400 MHz, $CDCl_3$) of **2c**: $\delta_H$ 1.86 (3 H, m, $CH_3$ D-ring), 2.56 (3 H, s, $CH_3$), 3.68 (3 H, s, $OCH_3$), 6.05 (1 H, br s, OCHO) and 6.45 (1 H, br s, =CH).

### Biological activity

**Seeds.** Seeds of *Striga hermonthica* [from *Sorghum bicolor* (L.) Moench] and *Orobanche crenata* (from *Vicia faba* L.) were harvested in Burkina Faso in 1994 and in Egypt in 1991, respectively, and were stored in the dark at room temperature until used in germination tests. Bioassays were carried out essentially following the procedure of Mangnus *et al.*[34] with minor modifications.

**Preparation of test solutions.** A compound to be tested (2.5 mg) was weighed out very accurately, dissolved in acetone p.a. (5 ml) and diluted with demineralized water to 25 ml. Aliquots of this stock solution were further diluted with water to obtain test solutions containing 2, 1, 0.1 and 0.01 mg $l^{-1}$ test compound and 0.4, 0.2, 0.02 and 0.002% (v/v) acetone, respectively.

**Bioassays.** For surface sterilization, seeds of *Striga hermonthica* and *Orobanche crenata* were exposed to aqueous sodium hypochlorite (2% active chlorine) for 5 min with agitation. The seeds were then thoroughly rinsed with water and dried overnight. For conditioning the sterilized seeds were spread on glass fibre filter paper disks (8-mm diameter; approximately 30–70 seeds per disk) in Petri dishes, moistened with water and stored in the dark for 14 days at 20 °C for *Orobanche* seeds and at 30 °C for *Striga* seeds. The conditioning water was then removed and replaced by 100 μl of test solution per disk. After incubation for 24 h (*Striga*) and 5 days (*Orobanche*) in the dark

at the indicated temperatures, the germination percentage was determined under a microscope. Seeds were considered to be germinated if the radical protruded through the seed coat. In each test series aqueous solutions with 0.2, 0.02 and 0.002% (v/v) acetone were used as negative control. Test solutions of the stimulant GR24 as a 1:1 mixture of diastereoisomers (concentrations of 1 and 0.01 mg $l^{-1}$) were used as positive controls. All tests were performed in duplicate and in each test the germination percentages were determined on 12 disks per treatment.

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