N-Phthaloylglycine-Derived Strigol Analogues. Influence of the D-Ring on Seed Germination Activity of the Parasitic Weeds *Striga hermonthica* and *Orobanche crenata*

Jan Willem J. F. Thuring, Harry H. Bitter, Margreet M. de Kok, Gérard H. L. Nefkens, Annemiek M. D. A. van Riel, and Binne Zwanenburg*

NSR-Center for Molecular Structure, Design and Synthesis, Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Several strigol analogues with modifications in the D-ring were synthesized and assayed for germination stimulatory activity of seeds of *Striga hermonthica* and *Orobanche crenata*. All of these D-ring analogues are derived from *N*-phthaloylglycine as the common ABC-fragment. It was concluded that the correct structure of the 2(5*H*)-furanone D-ring is essential to retain full biological activity.

Keywords: *Striga; Orobanche; germination; strigol analogue*

INTRODUCTION

The extremely devastating parasitic weeds *Striga* and *Orobanche* cause severe reductions in food crop yield of several graminaceous and leguminous crops in tropical and semitropical areas of the eastern hemisphere (Musselman, 1987; Parker and Riches, 1993). An absolute requirement for the seeds of these parasitic weeds to germinate is exposure to a chemical substance, which is usually present in the root exudate of a potential host plant (Press *et al*., 1990; Butler, 1995). The first known naturally occurring germination stimulant, (+)-strigol (**1**; Figure 1), was isolated from the root exudate of the false host cotton (*Gossypium hirsutum* L.) (Cook *et al*., 1966, 1972). Recently, (+)-strigol (**1**) was also identified in the root exudates of the *Striga* host plants maize (*Zea mays* L.) and proso millet (*Panicum miliaceum* L.) (Siame *et al*., 1993). In addition, some structurally closely related "strigolactones" (Butler, 1995) have been identified in the root exudates of other *Striga* hosts, *viz*. sorgolactone (**2**) (Hauck *et al*., 1992) and alectrol (**3**) (Müller *et al*., 1992). An attractive control strategy for the eradication of infested fields is the concept of suicidal germination, *i.e.* introduction of a germination-stimulating agent into the soil to induce germination of the parasitic seeds in the absence of a host plant (Eplee, 1975).

However, strigolactones **1**−**3** are not suitable for weed control purposes, because their structures are too complicated to allow synthesis in an economically feasible manner. During the past 15 years several studies have been conducted to design synthetic analogues with the aim to obtain relatively simple compounds possessing high germination stimulatory activity being suitable as potential herbicides and to locate the bioactiphore, *i.e.* the part of the molecule, which is primarily responsible for the biological activity (Johnson *et al*., 1976, 1981; Vail *et al*., 1990; Bergmann *et al*., 1993; Zwanenburg *et al*., 1994). These studies have mainly been focused on the ABC-part of the strigolactones. It was concluded that there exists a relatively large degree of structural freedom in this part of the molecule to retain full biological activity. One of the most potent synthetic strigol analogues is GR24 (**4**), containing an aromatic A-ring (Johnson *et al*., 1976, 1981), the preparation of which is much easier than that of strigol (**1**) (Mangnus *et al*., 1992a). Further structure−bioactivity relationship studies revealed that the connecting enol ether unit is essential for stimulatory activity. This finding has led to the proposal of a molecular mechanism for germination (Scheme 1) in which the bioactiphoric CD-part plays a key role (Mangnus and Zwanenburg, 1992).

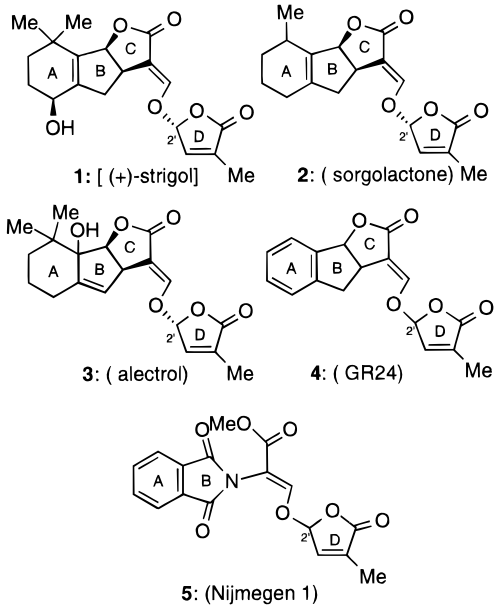
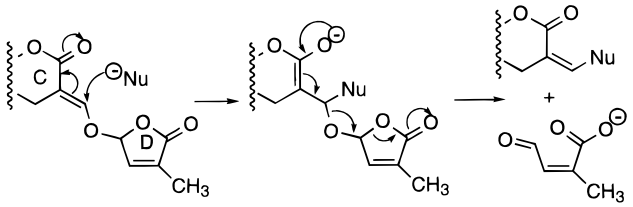


Figure 1. Strigolactones **1**−**3** and some active analogues.

Scheme 1. Molecular Mechanism for Germination



* Author to whom correspondence should be addressed (fax +31.24.3652929; e-mail zwanenb@sci.kun.nl).

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Thus far, relatively little attention has been paid to the influence of the structure of the D-ring. It was demonstrated that replacement of this 2(5*H*)-furanone moiety by other substituents leads to complete loss of bioactivity (Mangnus and Zwanenburg, 1992; Bergmann *et al*., 1993).

The present paper describes the influence of the structure of the D-ring on the germination stimulatory activity of *Striga hermonthica* (Del.) Benth. and *Orobanche crenata* Forsk. seeds. To make such an evaluation feasible, several five-membered ring analogues of the 3-methyl-2(5*H*)-furanone moiety, as is present in the strigolactones **1**−**3** and GR24 (**4**), were synthesized and subsequently coupled with a common ABC-fragment. We have selected Nijmegen 1 (**5**), derived from *N*-phthalimidoglycine, as the reference compound, the preparation of which has been reported recently (Nefkens *et al*., 1997a). It was demonstrated that **5** exhibits considerable activity as a germination stimulant. An important benefit of using **5** as the reference compound is that it contains an achiral ABC-fragment, which precludes the formation of a diastereomeric mixture after its coupling with a D-ring. Moreover, the preparation of **5** is simple, because readily available aldehyde **6** (Scheme 1) is used as the ABC-precursor.

MATERIALS AND METHODS

Nomenclature. The AUTONOM 1.0 program, provided by the Beilstein Institute and Springer Verlag, Weinheim, Germany, was used.

Synthesis. *General Remarks*. IR spectra were recorded on Perkin-Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra (90 MHz) were recorded on a Varian EM 390 spectrometer, Varian Analytical Instruments (Houten, The Netherlands); 100 MHz and 400 MHz ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer and a Bruker AM-400 spectrometer, respectively (Me_4Si as internal standard), both from Brucker (Wissembourg, France). All coupling constants are given as ^3J in hertz, unless indicated otherwise. For mass spectra a double-focusing VG7070E mass spectrometer was used. GC/MS spectra were run on a Varian Saturn 2 GC/MS ion-trap system. Separation was carried out on a fused-silica capillary column (DB-5, 0.25 μm film thickness, 30 m × 0.25 mm). Helium was used as carrier gas, and electron impact (EI) was used as ionization mode. GLC was conducted with a Hewlett-Packard (Avondale, PA) HP 5890 gas chromatograph, using a capillary column (25 m) of HP-1 and nitrogen (2 mL/min, 0.5 atm) as the carrier gas. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. Elemental analyses were performed at the Department of Micro-analysis 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. Tetrahydrofuran was distilled from lithium aluminum hydride just before use. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on Merck precoated 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 atm, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was carried out, using Merck Kieselgel 60.

Nijmegen 1 (**5**) was prepared as reported previously (Nefkens *et al*., 1997a). 2(5*H*)-Furanone (**9a**) (Takano and Ogasawara, 1973), 3-bromophthalide (**8**) (Koten and Sauer, 1973), 5-bromo-4-methyl-2(5*H*)-furanone (**10**) (Johnson *et al*., 1981), and 5-chloro-3,5-dimethyl-2(5*H*)-furanone (**11**) (Canévet and Graff, 1978) were prepared following literature procedures (see Scheme 2).

*5-Bromo-2(5H)-furanone (**9**).* 2(5*H*)-Furanone (**9a**) was brominated with *N*-bromosuccinimide according to the procedure of MacAlpine *et al*. (1976). The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 2:1) to give **9** as a yellow oil in 80% yield: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.2 (d, 1H, J = 6 Hz, =C$\underline{H}_\alpha$), 6.8 (d, 1H, J = 1 Hz, C$\underline{H}$Br), 7.62 (dd, 1H, J = 6 Hz, J = 1 Hz, =C$\underline{H}_\beta$).

*5-Bromo-4-methoxy-3-methyl-2(5H)-furanone (**12**).* 4-Methoxy-3-methyl-2(5*H*)-furanone (**12a**) (6.04 g, 47 mmol) was brominated according to the procedure of MacAlpine *et al*. (1976). The crude product was purified by distillation to give **12** as a yellow oil in 55% yield: bp 110−120 °C (3 mmHg); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.0 (s, 3H, C$\underline{H}_3$), 4.1 (s, 3H, OC$\underline{H}_3$), 6.6 (s, 1H, C$\underline{H}$Br).

*5-Bromo-4-phenyl-2(5H)-furanone (**15**).* Precursor **15a** was prepared in 21% yield by reduction of phenylmaleic anhydride **34a** with lithium aluminum hydride according to the procedure of Kayser and Morand (1980). Bromination of **15a** with *N*-bromosuccinimide (NBS) following the procedure of MacAlpine *et al*. (1976) afforded **15** (Steyn *et al*., 1965) in quantitative yield and was used in the coupling reaction without further purification: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.4 (s, 1H, =C$\underline{H}$), 7.2 (s, 1H, C$\underline{H}$Br), 7.5 (m, 5H, arom $\underline{H}$) (see Scheme 4).

*3-Phenyl-2(5H)-furanone (**14a**).* Phenylmaleic anhydride **34a** was prepared according to the method of Miller *et al*. (1949). To a solution of **34a** (3.24 g, 19.0 mmol) in methanol (15 mL) was gradually added dicyclohexylamine (DCA; 3.78 g, 21.0 mmol) with stirring at 0 °C. After 1 h, the precipitate of the DCA-salt **35a** was removed by filtration and washed with small portions of cold methanol to give 5.44 g (76%) of **35a** as one single regioisomer according to ^{1}H-NMR analysis: ^{1}H NMR ($CDCl_3$ + few drops of D_2O, 100 MHz) δ 1.21−2.12 (m, 20H, 20 cyclohexyl $\underline{H}$), 2.98 (m, 2H, 2 C$\underline{H}$N), 3.82 (s, 3H, OC$\underline{H}_3$), 6.41 (s, 1H, =C$\underline{H}$), 7.36 (m, 5H, 5 arom $\underline{H}$).

A solution of DCA-salt **35a** (5.44 g, 14.0 mmol) in THF (10 mL) was treated with trifluoroacetic acid (TFA; 1.71 g, 15.0 mmol) at 0 °C. The TFA-DCA salt was removed by filtration. Triethylamine (1.4 g, 14 mmol) at 0 °C was gradually added to the filtrate. The temperature was lowered to −30 °C, and then ethyl chloroformate (1.6 g, 14 mmol) was added. The temperature was kept at −30 °C for 1 h, after which time the precipitate of $Et_3N{\cdot}HCl$ was filtered off. A solution of $NaBH_4$ (0.98 g, 26 mmol) in water (10 mL) was slowly added to the filtrate at 0 °C under vigorous stirring. The reaction mixture was stirred overnight at room temperature. The salts were removed by filtration and washed with diethyl ether. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to give **14a** as a greenish solid. Purification by recrystallization (two times) from hexane/benzene gave **14a** (0.54 g, 24%) as colorless plates: mp 85 °C (lit. 89 °C; Swain *et al*., 1944). ^{1}H-NMR data were in agreement with those reported previously (Kayser and Morand, 1980).

*5-Bromo-3-phenyl-2(5H)-furanone (**14**).* Compound **14a** was brominated with NBS following the procedure of MacAlpine *et al*. (1976). The reaction was stopped after 80% conversion (unfortunately, the reaction did not go to completion) to give a mixture of **14**/**14a** (4:1), which was used in the coupling reaction without further purification. ^{1}H-NMR data of **14** were in complete agreement with those reported previously (Edgar *et al*., 1978).

*3-Ethyl-3-phenylsulfanyldihydrofuran-2-one (**31**).* To a cooled solution (−78 °C) of freshly prepared lithium diisopropylamide (5.7 mmol) in tetrahydrofuran (THF; 20 mL) was gradually added a solution of 3-phenylsulfanyldihydrofuran-2-one (**30**) (1.0 g, 5.2 mmol), prepared according to the procedure of Iwai *et al*. (1977), in THF (10 mL) (see Scheme 3). After 15 min of stirring at −78 °C, ethyl iodide (2.0 g, 14 mmol) was added and the reaction mixture was stirred overnight at room temperature. Saturated NH_4Cl was added and THF was removed *in vacuo*. The residue was extracted with ethyl acetate (three times). The combined extracts were washed with water (two times), dried ($MgSO_4$), and concentrated *in vacuo* to give **31** (0.68 g, 60%) as an oil, which was used in the next reaction without further purification: purity 95% according to GC; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.1 (t, J = 7.5 Hz, 3H, C$\underline{H}_3$), 1.9 (m, 2H, C$\underline{H}_2$), 2.2 (q, J = 7.5 Hz, 2H, C$\underline{H}_2$CH$_3$), 4.2 (m, 2H, C$\underline{H}_2$O), 7.2 (m, 5H, 5 arom $\underline{H}$).

*3-Ethyl-2(5H)-furanone (**13a**).* A solution of **31** (8.3 g, 37.4 mmol) in dichloromethane (50 mL) at 0 °C was treated with

80% *m*-chloroperbenzoic acid (*m*CPBA; 7.7 g, 45 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at 0 °C for 1 h. Then a saturated solution of Na_2SO_3 (50 mL) was added, and the organic phase was successively washed with saturated $NaHCO_3$, water, and brine. Drying ($MgSO_4$) and concentration *in vacuo* afforded the crude sulfoxide in nearly quantitative yield. The residue was heated at reflux temperature in CCl_4 (50 mL) for 1 h. The solvent was removed under reduced pressure, and the residue was purified by distillation to give **13a** (1.5 g, 40%) as a colorless oil: bp 42 °C (0.1 mmHg); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.1 (t, J = 6 Hz, 3H, CH_3), 2.2 (m, 2H, CH_2CH_3), 4.7 (m, 2H, CH_2), 7.0 (m, 1H, =CH).

*Bromination of 3-Ethyl-2(5H)-furanone (**13a**).* Compound **13a** (1.0 g, 8.9 mmol) was brominated with NBS according to the procedure of MacAlpine *et al*. (1976). A mixture of mainly **13** and **32** in an equimolar ratio was isolated in quantitative yield, which could not be separated. This mixture was used in the coupling reaction (*vide infra*).

*4-Bromo-2-methylcyclopent-2-enone (**18**).* 2-Methylcyclopent-2-enone (**18a**) was prepared as described by Gassman and Pascone (1973). The bromination reaction was performed similarly as reported by DePuy *et al*. (1964) starting from **18a** (4.20 g, 43.8 mmol): yield 5.51 g (72%) of **18** after distillation; bp 52−55 °C (0.25 mmHg); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.85 (m, 3H, CH_3), 2.73 (dd, J = 2 Hz, ^2J = 20 Hz, 1H, CH_2), 3.08 (dd, J = 6 Hz, ^2J = 20 Hz, 1H, CH_2), 5.11 (m, 1H, CHBr), 7.32 (m, 1H, =CH).

*Coupling of Chloro- and Bromofuranones **8**−**15** and **17** with Sheehan Aldehyde **6** (General Procedure).* To a solution of Sheehan aldehyde **6** (10 mmol) in dimethylformamide (DMF; 50 mL) was added potassium *tert*-butoxide (11 mmol) in a nitrogen atmosphere. The mixture was cooled to −60 °C, and a solution of the chloro- or bromofuranone **8**−**15** or **17** (11 mmol) in DMF (10 mL) was added with stirring. Stirring was continued for 18 h at room temperature. Then, DMF was removed *in vacuo* and the residue was dissolved in a mixture of water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (three times), and the combined organic extracts were washed with water (two times), dried ($MgSO_4$), and concentrated *in vacuo*. The crude coupling products **19**−**26** and **28** were further purified by flash chromatography and/or crystallization.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(3-oxo-1,3-dihydroisobenzofuran-1-yloxy)acrylate (**19**).* Coupling of 3-bromophthalide (**8**) with Sheehan aldehyde **6** (2.5 g, 10 mmol) was carried out as described in the general procedure. The crude product was purified by crystallization from 2-propanol to give **19** (2.1 g, 55%) as white crystals: mp 156−160 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 3.78 (s, 3H, OCH_3), 6.72 (br s, 1H, OCHO), 7.70−7.90 (m, 8H, 8 arom H), 7.97 (s, 1H, =CHO). Anal. Calcd for $C_{20}H_{13}NO_7$: C, 63.33; H, 3.45; N, 3.69. Found: C, 62.92; H, 3.43; N, 3.64.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (**20**).* Coupling of 5-bromo-2(5*H*)-furanone (**9**) with Sheehan aldehyde **6** (2.5 g, 10 mmol) was carried out as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) to give **20** (1.2 g, 37%) as a white solid. An analytical sample was obtained by crystallization from 2-propanol: mp 146−148 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 3.78 (s, 3H, OCH_3), 6.33 (br s, 1H, OCHO), 6.37 (dm, J = 5 Hz, 1H, $=CH_\alpha$), 7.34 (dm, J = 5 Hz, $=CH_\beta$), 7.72−7.96 (m, 5H, 4 arom H + =CHO); MS [EI, *m/z*, rel intensity (%)] 329 ([M]$^+$, 1.5), 246 ([$C_{12}H_8NO_5$]$^+$, 100), 83 ([$C_4H_3O_2$]$^+$, 37.5). Analysis Calcd for $C_{16}H_{11}NO_7$: C, 58.36; H, 3.36; N, 4.25. Found: C, 58.77; H, 3.34; N, 4.30.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(3-methyl-5-oxo-2,5-dihydrpfuran-2-yloxy)acrylate (**21**).* Coupling of 5-bromo-4-methyl-2(5*H*)-furanone (**10**) with Sheehan aldehyde **6** (1.23 g, 5.00 mmol) was carried out as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1), followed by crystallization from 2-propanol to give **21** (200 mg, 12%) as white crystals: mp 170−173 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.11 (d, 3H, ^4J = 1.4 Hz, CH_3), 3.79 (s, 3H, OCH_3), 5.99 (m, 1H, =CH), 6.08 (br s, 1H, OCHO), 7.72−7.96 (m, 5H, 4 arom H + =CHO). Anal. Calcd for $C_{17}H_{13}NO_7$: C, 59.48; H, 3.82; N, 4.08. Found: C, 59.32; H, 3.83; N, 4.04.

*Methyl 3-(3,4-Dimethyl-5-oxo-2,5-dihydrofuran-2-yloxy)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)acrylate (**22**).* Coupling of 5-chloro-3,4-dimethyl-2(5*H*)-furanone (**11**) with Sheehan aldehyde **6** (1.24 g, 5.00 mmol) was carried out as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:2) to give **22** (1.75 g, 95%) as a slightly yellow solid. An analytical sample was obtained by crystallization from diisopropyl ether/ethyl acetate: mp 155−157 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.85 (m, 3H, CH_3), 1.99 (m, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.02 (br s, 1H, OCHO), 7.92 (m, 5H, 4 arom H + =CHO); MS [EI, *m/z*, rel intensity (%)] 357 ([M]$^+$, 1.8), 246 ([$C_{12}H_8NO_5$]$^+$, 57.9), 111 ([$C_6H_7O_2$]$^+$, 100). Anal. Calcd for $C_{18}H_{15}NO_7$: C, 60.51; H, 4.23; N, 3.92. Found: C, 60.55; H, 4.16; N, 3.85.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(3-methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (**23**).* Coupling of 5-bromo-4-methoxy-3-methyl-2(5*H*)-furanone (**12**) with Sheehan aldehyde **6** (1.20 g, 4.90 mmol) was carried out as described in the general procedure. The crude product (1.55 g, 85%, purity according to ^{1}H-NMR > 90%) was crystallized from 2-propanol to give **23** (1.16 g, 63%) as colorless crystals: mp 173 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.89 (d, ^4J < 1 Hz, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.05 (s, 3H, $=COCH_3$), 6.00 (d, ^4J < 1 Hz, 1H, OCHO), 7.78 (s, 1H, =CHO), 7.73−7.97 (m, 4H, 4 arom H); MS [EI, *m/z*, rel intensity (%)] 373 ([M]$^+$, 0.9), 246 ([$C_{12}H_8NO_5$]$^+$, 5.2), 127 ([$C_6H_7O_3$]$^+$, 100). Anal. Calcd for $C_{18}H_{15}NO_8$: C, 57.91; H, 4.05; N, 3.75. Found: C, 58.07; H, 4.04; N, 3.76.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-ethyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (**24**) and Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-[1-(2-oxo-2,5-dihydrofuran-3-yl)ethoxy]acrylate (**33**).* Sheehan aldehyde **6** (1.1 g, 4.5 mmol) was treated with the crude mixture, obtained from bromination of 3-ethyl-2(5*H*)-furanone (**13a**) (8.9 mmol), according to the general procedure (see Scheme 3). Purification was accomplished by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) to give coupling products **24** (250 mg, 16%) and **33** (370 mg, 23%) as white solids. Analytical samples of **24** and **33** were obtained by crystallization from ethanol and *n*-butyl acetate, respectively.

*Compound **24**:* mp 164 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.17 (t, J = 7.4 Hz, 3H, CH_2CH_3), 2.35 (br q, J = 7.4 Hz, 2H, CH_2CH_3), 3.79 (s, 3H, OCH_3), 6.21 (m, 1H, OCHO), 6.86 (m, 1H, =CH), 7.78 (s, 1H, =CHO), 7.72−7.95 (m, 4H, 4 arom H); MS [EI, *m/z*, rel intensity (%)] 357 ([M]$^+$, 2.1), 246 ([$C_{12}H_8NO_5$]$^+$, 100), 111 ([$C_6H_7O_2$]$^+$, 29). Anal. Calcd for $C_{18}H_{15}NO_7$: C, 60.51; H, 4.23; N, 3.92. Found: C, 60.26; H, 4.22; N, 3.91.

*Compound **33**:* mp 162−164 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.54 (d, J = 6.4 Hz, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.90 (m, 2H, OCH_2), 5.00 (m, 1H, $CHCH_3$), 7.67−7.97 (m, 6H, 4 arom H, =CH, =CHO). Anal. Calcd for $C_{18}H_{15}NO_7$: C, 60.51; H, 4.23; N, 3.92. Found: C, 60.26; H, 4.20; N, 4.17.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-phenyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (**25**).* Coupling of 5-bromo-3-phenyl-2(5*H*)-furanone (**14**) with Sheehan aldehyde **6** (358 mg, 1.45 mmol) was carried out as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) to give **25** (122 mg, 21%) as a white solid. An analytical sample was obtained by crystallization from 2-propanol: mp 171−172 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 3.79 (s, 3H, OCH_3), 6.33 (d, J = 1.6 Hz, 1H, OCHO), 7.35−7.46 (m, 4H, 3 arom H + =CH), 7.70−7.95 (m, 6H, 6 arom H), 7.98 (s, 1H, =CHO); MS [EI, *m/z*, rel intensity (%)] 405 ([M]$^+$, 1.7), 246 ([$C_{12}H_8NO_5$]$^+$, 81.7), 159 ([$C_{10}H_7O_2$]$^+$, 100). Anal. Calcd for $C_{22}H_{15}NO_7$: C, 65.19; H, 3.73; N, 3.46. Found: C, 64.84; H, 3.79; N, 3.46.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(3-phenyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (**26**).* Coupling of 5-bromo-4-phenyl-2(5*H*)-furanone (**15**) (Steyn *et al*., 1965) with Sheehan aldehyde **6** (598 mg, 2.42 mmol) was carried out as described in the general procedure. The crude product was purified by flash chromatography (SiO_2, hexane/ethyl acetate 2:1) to give **26** (262 mg, 27%) as a white solid. Analytically pure **26** was obtained by crystallization from 2-propanol: mp 142−144 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 3.77 (s, 3H, OCH_3), 6.51 (s, 1H,

OCHO)*, 6.61 (s, 1H, =CH)*, 7.50 (m, 5H, 5 arom H), 7.78 (m, 4H, 4 arom H), 8.04 (s, 1H, =CHO) (* indicates signals may be interchanged); MS [EI, *m/z*, rel intensity (%)] 405 ([M]$^+$, 1.0), 246 ([$C_{12}H_8NO_5$]$^+$, 38.6), 159 ([$C_{10}H_7O_2$]$^+$, 100). Anal. Calcd for $C_{22}H_{15}NO_7$: C, 65.19; H, 3.73; N, 3.46. Found: C, 64.9; H, 3.62; N, 3.51.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(5-oxotetrahydrofuran-2-yloxy)acrylate (**28**).* Coupling of 5-chloro-γ-butyrolactone (**17**) with Sheehan aldehyde **6** (1.62 g, 6.56 mmol) was carried out as described in the general procedure. The crude product was purified by recrystallization from 2-propanol to give **28** (1.07 g, 49%) as colorless crystals. Analytically pure **28** was obtained by repeated crystallization from 2-propanol: mp 162−164 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 2.28−2.73 (m, 4H, 2 CH_2), 3.78 (s, 3H, OCH_3), 5.97 (m, 1H, OCHO), 7.72−7.97 (m, 5H, 4 arom H + =CHO); MS [CI, *m/z*, rel intensity (%)] 332 ([M + 1]$^+$, 2.2), 247 ([$C_{12}H_9NO_5$]$^+$, 61), 85 ([$C_4H_5O_2$]$^+$, 100). Anal. Calcd for $C_{16}H_{13}NO_7$: C, 58.01; H, 3.96; N, 4.23. Found: C, 57.88; H, 3.85; N, 4.23.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(3-methyl-4-oxocyclopent-2-enyloxy)acrylate (**29**).* This compound was prepared in a similar way as described for the synthesis of furanones **19**−**26**, starting from Sheehan aldehyde **6** (1.62 g, 6.56 mmol) and 4-bromo-2-methylcyclopent-2-enone (**18**) (1.15 g, 6.56 mmol). ^{1}H-NMR analysis of the crude product (2.1 g) revealed the presence of an equimolar ratio of **29** and cyclopentadienone dimers. Trituration (diisopropyl ether) provided a solid (1.4 g), consisting of unreacted **6** and coupling product **29**. Crystallization from diisopropyl ether/ethyl acetate afforded analytically pure **29** (325 mg, 15%) as colorless crystals: mp 183−184 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.83 (m, 3H, CH_3), 2.45 (dd, J = 2.1 Hz, ^2J = 18.7 Hz, 1H, CH_2), 2.89 (dd, J = 6.1 Hz, ^2J = 18.7 Hz, 1H, CH_2), 3.76 (s, 3H, OCH_3), 5.28 (m, 1H, $OCHCH_2$), 7.18 (m, 1H, =CH), 7.70−7.95 (m, 5H, 4 arom H + =CHO); MS [EI, *m/z*, rel intensity (%)] 341 ([M]$^+$, 3.2), 247 ([$C_{12}H_9NO_5$]$^+$, 41.9), 95 ([C_6H_7O]$^+$, 100). Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.21; H, 4.28; N, 4.13.

*Methyl 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-[1-(2-oxo-2,5-dihydrofuran-3-yl)ethoxy]acrylate (**27**).* To a cooled (−5 °C) solution of Sheehan aldehyde **6** (2.5 g, 10 mmol) and mucochloric acid **16** (1.7 g, 10 mmol) in THF (10 mL) in the presence of a catalytic amount of dimethylaminopyridine (DMAP) was added dicyclohexylcarbodiimide (DCC; 2.2 g, 10 mmol). A precipitate of dicyclohexylurea (DCU) gradually formed. After 18 h of stirring at room temperature, the precipitate was removed by filtration. The residue was concentrated *in vacuo*. Purification by flash chromatography (SiO_2, hexane/ethyl acetate 1:1) afforded **27** (1.4 g, 35%) as a white solid. An analytical sample was obtained by crystallization from acetic acid: mp 157 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 3.80 (s, 3H, OCH_3), 6.18 (s, 1H, OCHO), 7.73−7.97 (m, 5H, 4 arom H + =CHO); MS [EI, *m/z*, rel intensity (%)] 399 ([$C_{16}H_9{}^{35}Cl^{37}ClNO_7$]$^+$, 0.7), 397 ([$C_{16}H_9{}^{35}Cl_2NO_7$]$^+$, 1.1), 368 ([$C_{15}H_6{}^{35}Cl^{37}ClNO_6$]$^+$, 1.0), 366 ([$C_{15}H_6{}^{35}Cl_2NO_6$]$^+$, 1.6), 246 ([$C_{12}H_8NO_5$]$^+$, 100), 153 ([$C_4H^{35}Cl^{37}ClO_2$]$^+$, 9.2), 151 ([$C_4H^{35}Cl_2O_2$]$^+$, 14.4). Anal. Calcd for $C_{16}H_9Cl_2NO_6$: C, 48.27; H, 2.28; N, 3.52. Found: C, 48.13; H, 2.26; N, 3.44.

Biological Activity. *Seeds.* Seeds of *Striga hermonthica* [from *Sorghum bicolor* (L.) Moench] and *Orobanche crenata* (from *Vicia faba* L.) were harvested in Sudan in 1987 and in Egypt in 1991, respectively, and were stored in the dark at room temperature until use in germination tests.

Preparation of Test Solutions. A compound to be tested was weighed out very accurately to the amount of 10 mg, dissolved in 10 mL of acetone p.a., and diluted with demineralized water to 100 mL. Aliquots of this stock solution were further diluted with water to obtain test solutions containing 1 and 0.01 mg/L test compound and 0.1 and 0.001% (v/v) acetone, respectively.

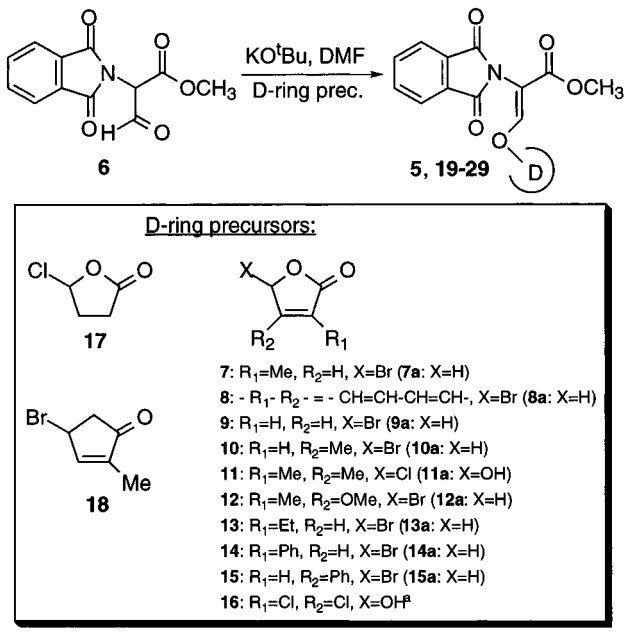
Bioassays. For surface sterilization seeds of *S. hermonthica* and *O. crenata* were exposed to an aqueous solution of sodium hypochlorite (2% active chlorine) for 5 min with agitation. The seeds were then thoroughly rinsed with water and dried overnight.

For conditioning the sterilized seeds were spread on glass fiber filter paper disks (8-mm diameter; approximately 30−70 seeds per disk) in Petri dishes, wetted with water, and stored in the dark for 14 days at 20 °C for *Orobanche* seeds and at 30 °C for *Striga* seeds. Then the conditioning water was 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 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 0.1 and 0.001% (v/v) acetone were used as negative control. Test solutions of the stimulant GR24 (concentrations of 1 and 0.01 mg/L) 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.

For full details of the bioassay, see Mangnus *et al.* (1992b).

Scheme 2. Coupling of D-Ring Precursors 7−18 with Aldehyde 6



a: Coupling conditions: DCC/DMAP in THF

RESULTS AND DISCUSSION

Synthesis. The final step in the synthesis of D-ring analogues **5** and **19**−**29** involves coupling (O-alkylation) of Sheehan aldehyde **6** with D-rings **7**−**18** (Scheme 2).

These coupling reactions involve nucleophilic substitution of the corresponding γ-bromo or γ-chloro derivatives **7**−**15** and **17**−**18**, according to the general procedure for the preparation of strigol and its analogues (Johnson *et al.*, 1981), using DMF as the solvent. This procedure provided the desired products in low to high yields (Table 1).

The D-ring precursors **7**−**15** and **17**−**18** were freshly prepared before use, because they are generally rather unstable. The poor stability of these compounds may account for some of the low yields of the desired products (Table 1), *e.g.* during several attempts to prepare carba D-ring analogue **29**. [Dimerization takes place by a Diels−Alder reaction of a cyclopentadienone intermediate which results upon dehydrobromination of **18** [*cf.* Baraldi *et al.* (1984, 198) and DePuy *et al.* (1964).]] Bischloro-substituted analogue **27** was prepared in an alternative manner, employing DCC-mediated coupling conditions in THF with commercially available mucochloric acid **16**. It was essential to carry out the reaction in the presence of a catalytic amount of DMAP, which enhanced the solubility of **16** considerably.

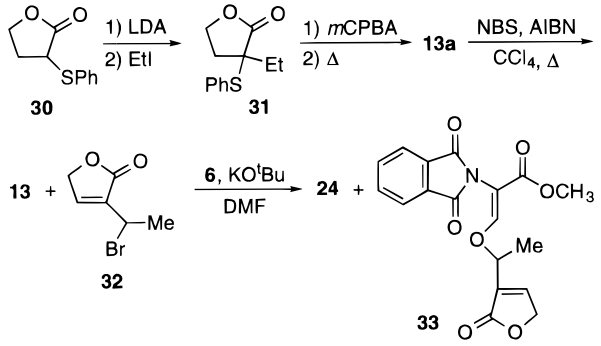
Preparation of D-Ring Precursors 7−18. All 5-bromo-2(5*H*)-furanones were prepared by radical initi-

Table 1. Yields of Coupling Reactions of 6 and D-Ring Precursors 7−18

entry	D-ring precursor	product	yield (%)
1	**7**	**5**	75
2	**8**	**19**	55[a]
3	**9**	**20**	37
4	**10**	**21**	12[a]
5	**11**	**22**	95
6	**12**	**23**	85
7	**13**	**24**	*b*
8	**14**	**25**	21
9	**15**	**26**	27
10	**16**	**27**	35
11	**17**	**28**	49[a]
12	**18**	**29**	15

[a] Yield after purification by recrystallization. [b] Not determined, see text.

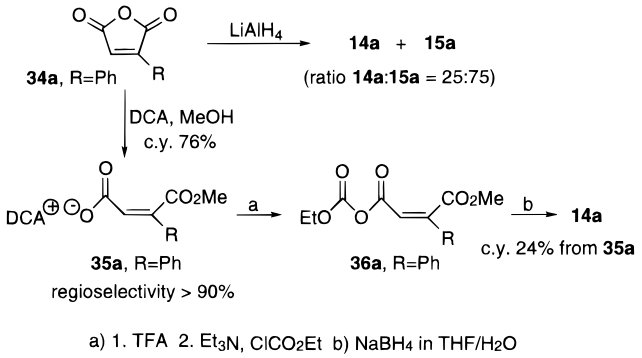
Scheme 3. Synthesis of D-Ring Analogues 24 and 33



ated allylic bromination of the parent 2(5*H*)-furanones (MacAlpine *et al.*, 1976). 5-Chloro-3,4-dimethyl-2(5*H*)-furanone (**11**) was prepared in three steps starting from propionaldehyde and ethyl pyruvate (Schreiber and Wermuth, 1965; Canévet and Graff, 1978). γ-Chloro-γ-butyrolactone (**17**) was obtained in one step by reaction of succinyl dichloride and tri-*n*-butyltin hydride (Kuivila, 1960). 4-Bromo-2-methyl-2-cyclopenten-1-one (**18**) was obtained upon bromination of 2-methyl-2-cyclopenten-1-one (Gassman and Pascone, 1973) with NBS (DePuy *et al.*, 1964). The preparation of 4-methoxy-3-methyl-2(5*H*)-furanone (**12a**) was accomplished by methylation with dimethyl sulfate of the parent 2-methyltetronic acid (Knight and Pattenden, 1975). The last-mentioned compound was prepared in a one-pot synthesis by bromination of ethyl 2-methylacetoacetate to give the 2-bromo derivative (Conrad, 1896), which rearranged in the presence of hydrobromic acid to the 4-bromo isomer, which on heating gave 2-methyltetronic acid (Reid *et al.*, 1950). The synthesis of 3-ethyl-2(5*H*)-furanone (**13a**) was carried out, using the concept outlined in Scheme 3.

The sequence of α-alkylation using methyl iodide (Iwai *et al.*, 1977) or α-condensation with simple aldehydes (Caldéron *et al.*, 1987) of phenylthio-γ-butyrolactone (**30**), followed by oxidation and thermal dehydrosulfenylation, is a simple route to 3-substituted 2(5*H*)-furanones. The scope, however, is rather limited. In our hands, quenching the lithio enolate of **30** with ethyl iodide gave **31** in 60% isolated yield, which upon oxidation with *m*CPBA and thermal elimination afforded **13a** in 40% yield after distillation. Compound **13a** has previously been prepared according to other methods, although no analytical data were reported (Martin and Moore, 1976; Khan and Paterson, 1982). Subsequent bromination with NBS in the presence of α,α′-azodiisobutyronitrile (AIBN) gave a mixture of mainly two monobrominated furanones **13** and **32** in an equimolar ratio (Scheme 3).

Scheme 4. Reduction of Phenylmaleic Anhydride 34a



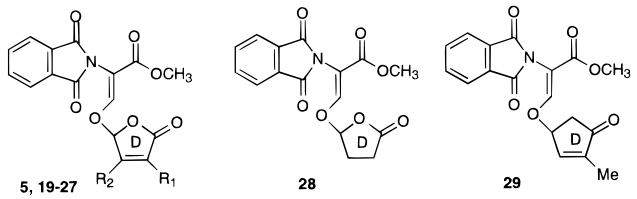
Regioisomers **13** and **32** could not be separated. Therefore, coupling with Sheehan aldehyde **6** was achieved using the crude mixture of **13** and **32** to provide **24** and **33** in 16% and 23% isolated yields, respectively.

The syntheses of 3- and 4-phenyl-substituted 2(5H)-furanones **14a** and **15a** were accomplished via reduction of maleic anhydride derivative **34a** (Scheme 4). Direct reduction of **34a** using $LiAlH_4$ afforded **15a** as the main regioisomer (Kayser and Morand, 1980). For the regioselective formation of **14a** a different procedure via DCA-salt **35a** (Scheme 4) had to be followed, the essence of which has been described (Nefkens *et al.*, 1997b) for the preparation of **7a** (Scheme 4, R = Me). The moderate overall yield of **14a** is most likely due to concomitant 1,4-reduction of **36a**, a problem that was also encountered during the reduction of **34a** using selectride reagents (Kayser *et al.*, 1986).

Biological Evaluation. The germination stimulatory activity of phthalimidoglycine-derived D-ring analogues **5**, **19**−**29**, and **33** was assayed using seeds of *S. hermonthica* and *O. crenata*. In each bioassay, GR24 (**4**) at an optimal concentration [0.01 mg/L [see Zwanenburg *et al.* (1994)] for *S. hermonthica* and 1 mg/L for *O. crenata*] was included as a positive control. The last-mentioned compound enables a comparison between results obtained in different test series. This is important, since the response of seeds of parasitic weeds, in particular of *S. hermonthica*, varies considerably from test to test. The germination percentages thus obtained are collected in Table 2.

The data in Table 2 reveal that most D-ring analogues exert little or no stimulatory effect. In particular, seeds of *O. crenata* are extremely sensitive toward structural modifications in the D-ring (Table 2B). Dimethyl-substituted 2(5*H*)-furanone analogue **22**, however, shows a considerable degree of biological activity and is at least as active as the parent compound **5** in the germination of seeds of *S. hermonthica*. However, its activity in the stimulation of *O. crenata* seed germination is only limited. Also α-ethyl 2(5*H*)-furanone derivative **24** gave significant stimulation of germination, particularly of seeds of *S. hermonthica*. Its isomeric counterpart **33** was completely inactive, as expected because the D-ring is not a suitable leaving group (see molecular mechanism, Scheme 1). For the same reason carba D-ring analogue **29** does not exert germination-inducing activity. A remarkable difference in activity was observed for β-methoxy-substituted 2(5*H*)-furanone analogue **23** and its β-methyl counterpart **22** (*cf.* entries 5 and 6, Table 2A), which, most likely, must be attributed to electronic factors. As a consequence, the inherent reactivity of the α,β-unsaturated carbonyl function present in the D-ring should be taken into consideration as a potential recognition site of a receptor protein.

Table 2. Germination Percentages for Seeds of *S. hermonthica* and *O. crenata* after Exposure to Aqueous Solutions of Strigol Analogues 5, 19−29, and 33 at Concentrations of 1 and 0.01 mg/L[a]



entry	compound	% germination ± SE		
		1 mg/L	0.01 mg/L	**4**[b]
		A. *S. hermonthica*		
1	**5**, R_1 = Me, R_2 = H	40.3 ± 1.7	4.1 ± 0.9[c]	52.5 ± 12.5
2	**19**, R_1, R_2 = −$(CH)_4$−	1.5 ± 0.4[c]	1.0 ± 0.0[c]	52.5 ± 12.5
3	**20**, R_1 = H, R_2 = H	13.1 ± 1.9	2.0 ± 0.0[c]	52.5 ± 12.5
4	**21**, R_1 = H, R_2 = Me	25.8 ± 5.1	9.6 ± 5.2[c]	52.5 ± 12.5
5	**22**, R_1 = Me, R_2 = Me	63.8 ± 6.8	5.8 ± 1.3[c]	62.5 ± 10.8
6	**23**, R_1 = Me, R_2 = OMe	12.0 ± 4.9	5.1 ± 0.8[c]	62.5 ± 10.8
7	**24**, R_1 = Et, R_2 = H	48.5 ± 2.7	9.3 ± 1.6[c]	59.5 ± 2.1
8	**25**, R_1 = Ph, R_2 = H	15.5 ± 2.8[d]	7.6 ± 0.5[c]	38.6 ± 10.3
9	**26**, R_1 = H, R_2 = Ph	8.0 ± 0.7[c]	8.3 ± 1.0[c]	45.3 ± 8.7
10	**27**, R_1 = Cl, R_2 = Cl	18.2 ± 5.3[d]	11.3 ± 1.9[d]	43.4 ± 1.9
11	**28**	6.7 ± 2.1[c]	7.3 ± 1.5[c]	42.0 ± 8.4
12	**29**	5.7 ± 1.2[c]	5.5 ± 1.0[c]	73.3 ± 1.5
13	**33**	7.3 ± 0.7[c]	10.8 ± 4.7[c]	59.5 ± 2.1
		B. *O. crenata*		
1	**5**[f]	34.2 ± 9.8	1.1 ± 0.6[e]	68.1 ± 8.3
2	**22**[g]	15.1 ± 1.3	0.0 ± 0.0[e]	66.1 ± 1.8
3	**24**	14.0 ± 0.9	0.0 ± 0.0[e]	63.8 ± 5.8
4	**19−21**, **23**, **25−29**, **33**	0−4.9[e]	0−0.8[e]	51.7−74.9

[a] Germination percentages given are the mean ± SE of two replicate tests. [b] Values are the mean germination percentages ± SE obtained by treatment of the seeds with GR24 **4** (*S. hermonthica*, 0.01 mg/L; *O. crenata*, 1 mg/mL) in the same bioassay. [c] Values are not significantly different from germination percentages obtained in the aqueous control. [d] Relatively high germination percentage in aqueous control; values are not significantly different. [e] Values are not significantly different from germination percentages obtained in the control (without stimulant). [f] Germination percentage 58.3 ± 1.3% at a concentration of 2 mg/L. [g] Germination percentage 14.5 ± 2.8% at a concentration of 2 mg/L.

Reduction of this highly reactive double bond (compound **28**) results in complete loss of activity. Strigol analogues containing 3-phenyl-, 4-phenyl-, and 3,4-dichloro-2(5*H*)-furanone moieties as D-ring have previously been assayed as germination stimulants (Hassanali, 1984). It was concluded that these compounds exhibit no stimulatory activity, although no data were provided. These results are confirmed here, using the related analogues **25**−**27**.

Concluding Remarks. Several D-ring analogues of strigol have been synthesized and assayed for germination stimulatory activity of seeds of *S. hermonthica* and *O. crenata*. It was found that the structure of the 2(5*H*)-furanone D-ring, which is present in all known strigolactones **1**−**3**, is very critical for the bioactivity. This finding suggests an essential role of the D-ring in the receptor interaction. From a practical point of view, replacement of the 3-methyl-2(5*H*)-furanone moiety by another D-ring is of considerable interest, as its preparation is a serious bottleneck in the large scale synthesis of GR24 and other strigol analogues. The slightly modified 3,4-dimethyl-2(5*H*)-furanone moiety is an attractive candidate for this purpose for the following reasons: First, the preparation of the corresponding 5-chloro synthon **11** can be readily performed in three steps from simple, cheap starting materials. Second, the coupling reaction with **11** proceeds in almost quantitative yield. Finally, the biological activity in the stimulation of *S. hermonthica* seeds is hardly affected by this replacement of the common D-ring by the dimethyl congener. The use of **22**, or an analogue containing a modified ABC-fragment, as a germination stimulant for the control of *S. hermonthica* needs serious consideration and deserves further (field) studies.

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