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

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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(5H)-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

Figure 1. Strigolactones 1–3 and some active analogues.

Scheme 1. Molecular Mechanism for Germination

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).

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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 *Orobancha 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. ¹H-NMR spectra (90 MHz) were recorded on a Varian EM 390 spectrometer, Varian Analytical Instruments (Houten, The Netherlands); 100 MHz and 400 MHz ¹H-NMR spectra were recorded on a Bruker AC 100 spectrometer and a Bruker AM-400 spectrometer, respectively (Me₄Si as internal standard), both from Bruker (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 P₂O₅. Diethyl ether was distilled from NaH. Hexane was distilled from CaH₂. 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(5*H*)-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 (SiO₂, hexane/ethyl acetate 2:1) to give 9 as a yellow oil in 80% yield: ¹H NMR (CDCl₃, 90 MHz) δ 6.2 (d, 1H, *J* = 6 Hz, =CH_a), 6.8 (d, 1H, *J* = 1 Hz, CHBr), 7.62 (dd, 1H, *J* = 6 Hz, *J* = 1 Hz, =CH_b).

5-Bromo-4-methoxy-3-methyl-2(5*H*)-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); ¹H NMR (CDCl₃, 90 MHz) δ 2.0 (s, 3H, CH₃), 4.1 (s, 3H, OCH₃), 6.6 (s, 1H, CHBr).

5-Bromo-4-phenyl-2(5*H*)-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: ¹H NMR (CDCl₃, 90 MHz) δ 6.4 (s, 1H, =CH), 7.2 (s, 1H, CHBr), 7.5 (m, 5H, arom H) (see Scheme 4).

3-Phenyl-2(5*H*)-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 ¹H-NMR analysis: ¹H NMR (CDCl₃ + few drops of D₂O, 100 MHz) δ 1.21–2.12 (m, 20H, 20 cyclohexyl H), 2.98 (m, 2H, 2 CHN), 3.82 (s, 3H, OCH₃), 6.41 (s, 1H, =CH), 7.36 (m, 5H, 5 arom 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 Et₃N·HCl was filtered off. A solution of NaBH₄ (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 (MgSO₄) 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). ¹H-NMR data were in agreement with those reported previously (Kayser and Morand, 1980).

5-Bromo-3-phenyl-2(5*H*)-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. ¹H-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 NH₄Cl 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 (MgSO₄), 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; ¹H NMR (CDCl₃, 90 MHz) δ 1.1 (t, *J* = 7.5 Hz, 3H, CH₃), 1.9 (m, 2H, CH₂), 2.2 (q, *J* = 7.5 Hz, 2H, CH₂CH₃), 4.2 (m, 2H, CH₂O), 7.2 (m, 5H, 5 arom H).

3-Ethyl-2(5*H*)-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 Na₂SO₃ (50 mL) was added, and the organic phase was successively washed with saturated NaHCO₃, water, and brine. Drying (MgSO₄) and concentration *in vacuo* afforded the crude sulfoxide in nearly quantitative yield. The residue was heated at reflux temperature in CCl₄ (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); ¹H NMR (CDCl₃, 90 MHz) δ 1.1 (t, *J* = 6 Hz, 3H, CH₃), 2.2 (m, 2H, CH₂CH₃), 4.7 (m, 2H, CH₂), 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); ¹H NMR (CDCl₃, 100 MHz) δ 1.85 (m, 3H, CH₃), 2.73 (dd, *J* = 2 Hz, ²*J* = 20 Hz, 1H, CH₂), 3.08 (dd, *J* = 6 Hz, ²*J* = 20 Hz, 1H, CH₂), 5.11 (m, 1H, CH=Br), 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 (MgSO₄), 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-dihydroisindol-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; ¹H NMR (CDCl₃, 100 MHz) δ 3.78 (s, 3H, OCH₃), 6.72 (br s, 1H, OCHO), 7.70–7.90 (m, 8H, 8 arom H), 7.97 (s, 1H, =CHO). Anal. Calcd for C₂₀H₁₃NO₇: 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-dihydroisindol-2-yl)-3-(5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (20). Coupling of 5-bromo-2(5H)-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 (SiO₂, 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; ¹H NMR (CDCl₃, 100 MHz) δ 3.78 (s, 3H, OCH₃), 6.33 (br s, 1H, OCHO), 6.37 (dm, *J* = 5 Hz, 1H, =CH_α), 7.34 (dm, *J* = 5 Hz, =CH_β), 7.72–7.96 (m, 5H, 4 arom H + =CHO); MS [EI, *m/z*, rel intensity (%)] 329 ([M]⁺, 1.5), 246 ([C₁₂H₈NO₅]⁺, 100), 83 ([C₆H₅O₂]⁺, 37.5). Analysis Calcd for C₁₈H₁₁NO₇: 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-dihydroisindol-2-yl)-3-(3-methyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (21). Coupling of 5-bromo-4-methyl-2(5H)-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 (SiO₂, hexane/ethyl acetate 1:1), followed by crystallization from 2-propanol to give **21** (200 mg, 12%) as white crystals: mp 170–173 °C; ¹H NMR (CDCl₃, 100 MHz) δ 2.11 (d, 3H, ⁴*J* = 1.4 Hz, CH₃), 3.79 (s, 3H, OCH₃), 5.99 (m, 1H, =CH), 6.08 (br s, 1H, OCHO), 7.72–7.96 (m, 5H, 4 arom H +

=CHO). Anal. Calcd for C₁₇H₁₃NO₇: 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-dihydroisindol-2-yl)acrylate (22). Coupling of 5-chloro-3,4-dimethyl-2(5H)-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 (SiO₂, 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; ¹H NMR (CDCl₃, 100 MHz) δ 1.85 (m, 3H, CH₃), 1.99 (m, 3H, CH₃), 3.78 (s, 3H, OCH₃), 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 ([C₁₂H₈NO₅]⁺, 57.9), 111 ([C₆H₇O₂]⁺, 100). Anal. Calcd for C₁₈H₁₅NO₇: 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-dihydroisindol-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(5H)-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 ¹H-NMR > 90%) was crystallized from 2-propanol to give **23** (1.16 g, 63%) as colorless crystals: mp 173 °C; ¹H NMR (CDCl₃, 100 MHz) δ 1.89 (d, ⁴*J* < 1 Hz, 3H, CH₃), 3.78 (s, 3H, OCH₃), 4.05 (s, 3H, =COCH₃), 6.00 (d, ⁴*J* < 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 ([C₁₂H₈NO₅]⁺, 5.2), 127 ([C₆H₇O₃]⁺, 100). Anal. Calcd for C₁₈H₁₅NO₈: 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-dihydroisindol-2-yl)-3-(4-ethyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (24) and Methyl 2-(1,3-Dioxo-1,3-dihydroisindol-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(5H)-furanone (**13a**) (8.9 mmol), according to the general procedure (see Scheme 3). Purification was accomplished by flash chromatography (SiO₂, 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; ¹H NMR (CDCl₃, 100 MHz) δ 1.17 (t, *J* = 7.4 Hz, 3H, CH₂CH₃), 2.35 (br q, *J* = 7.4 Hz, 2H, CH₂CH₃), 3.79 (s, 3H, OCH₃), 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 ([C₁₂H₈NO₅]⁺, 100), 111 ([C₆H₇O₂]⁺, 29). Anal. Calcd for C₁₈H₁₅NO₇: 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; ¹H NMR (CDCl₃, 100 MHz) δ 1.54 (d, *J* = 6.4 Hz, 3H, CH₃), 3.76 (s, 3H, OCH₃), 4.90 (m, 2H, OCH₂), 5.00 (m, 1H, CHCH₃), 7.67–7.97 (m, 6H, 4 arom H, =CH, =CHO). Anal. Calcd for C₁₈H₁₅NO₇: 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-dihydroisindol-2-yl)-3-(4-phenyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (25). Coupling of 5-bromo-3-phenyl-2(5H)-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 (SiO₂, 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; ¹H NMR (CDCl₃, 100 MHz) δ 3.79 (s, 3H, OCH₃), 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 ([C₁₂H₈NO₅]⁺, 81.7), 159 ([C₁₀H₇O₂]⁺, 100). Anal. Calcd for C₂₂H₁₅NO₇: 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-dihydroisindol-2-yl)-3-(3-phenyl-5-oxo-2,5-dihydrofuran-2-yloxy)acrylate (26). Coupling of 5-bromo-4-phenyl-2(5H)-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 (SiO₂, 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; ¹H NMR (CDCl₃, 100 MHz) δ 3.77 (s, 3H, OCH₃), 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 ([C₁₂H₈NO₅]⁺, 38.6), 159 ([C₁₀H₇O₂]⁺, 100). Anal. Calcd for C₂₂H₁₅NO₇: 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; ¹H NMR (CDCl₃, 100 MHz) δ 2.28–2.73 (m, 4H, 2 CH₂), 3.78 (s, 3H, OCH₃), 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 ([C₁₂H₉NO₅]⁺, 61), 85 ([C₄H₅O₂]⁺, 100). Anal. Calcd for C₁₆H₁₃NO₇: 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). ¹H-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; ¹H NMR (CDCl₃, 100 MHz) δ 1.83 (m, 3H, CH₃), 2.45 (dd, J = 2.1 Hz, ² J = 18.7 Hz, 1H, CH₂), 2.89 (dd, J = 6.1 Hz, ² J = 18.7 Hz, 1H, CH₂), 3.76 (s, 3H, OCH₃), 5.28 (m, 1H, OCHCH₂), 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 ([C₁₂H₉NO₅]⁺, 41.9), 95 ([C₆H₇O]⁺, 100). Anal. Calcd for C₁₈H₁₅NO₆: 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 (SiO₂, 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; ¹H NMR (CDCl₃, 100 MHz) δ 3.80 (s, 3H, OCH₃), 6.18 (s, 1H, OCHO), 7.73–7.97 (m, 5H, 4 arom H + =CHO); MS [EI, m/z , rel intensity (%)] 399 ([C₁₆H₉³⁵Cl³⁷CINO₇]⁺, 0.7), 397 ([C₁₆H₈³⁵Cl₂NO₇]⁺, 1.1), 368 ([C₁₅H₈³⁵Cl³⁷CINO₆]⁺, 1.0), 366 ([C₁₅H₈³⁵Cl₂NO₆]⁺, 1.6), 246 ([C₁₂H₈NO₅]⁺, 100), 153 ([C₄H³⁵Cl³⁷ClO₂]⁺, 9.2), 151 ([C₄H³⁵Cl₂O₂]⁺, 14.4). Anal. Calcd for C₁₆H₉Cl₂NO₆: 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

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

a: Coupling conditions: DCC/DMAP in THF

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 μ L 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).

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).] Bishloro-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(5H)-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 dehydro-sulfonylation, 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(5*H*)-furanones 14a and 15a were accomplished via reduction of maleic anhydride derivative 34a (Scheme 4). Direct reduction of 34a using LiAlH₄ 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

5, 19-27

28

29

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

ACKNOWLEDGMENT

We thank Dr. A. G. T. Babiker and Dr. F. M. F. Zaitoun for supplying *Striga* and *Orobancha* seeds. We thank H. Amatdjais, P. van Galen, and A. Swolfs for conducting elemental analysis, mass, and 400 MHz ¹H-NMR measurements.

LITERATURE CITED

- Baraldi, G. P.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. Trapping of cyclopentadienone as a 4π component in Diels-Alder reactions with ethyl acrylate: A simple synthesis of (±)-sarkomycin. *J. Chem. Soc., Chem. Commun.* **1984**, 1049–1050.
- Baraldi, G. P.; Pollini, G. P.; Simoni, D.; Zanirato, V. A facile, efficient synthesis of 2-substituted-4-hydroxy-2-cyclopenten-1-ones. *Synthesis* **1986**, 781–782.
- Bergmann, C.; Wegmann, K.; Frischmuth, K.; Samson, E.; Kranz, A.; Weigelt, D.; Koll, P.; Welzel, P. Stimulation of *Orobancha crenata* seed germination by (+)-strigol and structural analogues. Dependence of constitution and configuration of the germination stimulants. *J. Plant Physiol.* **1993**, 142, 338–342 and references cited therein.
- Butler, L. G. Chemical communication between the parasitic weed *Striga* and its crop host. *ACS Symp. Ser.* **1995**, No. 582, 158–166.
- Calderón, A.; de March, P.; Font, J. Synthesis of 3-(1-hydroxy-alkyl)furan-2(5H)-ones: unexpected substitution reaction in allylic alcohols by bromine. *J. Org. Chem.* **1987**, 52, 4631–4633.
- Canévet, J. C.; Graff, Y. Réactions de Friedel-Crafts de dérivés aromatiques sur des composés dicarbonylés-1,4-éthyléniques-2,3. II Alkylations par quelques hydroxy-5 ou chloro-5 dihydro-2,5 furannones-2. Nouvelle méthode de synthèse des acides 1H-indènecarboxyliques-1. *Tetrahedron* **1978**, 34, 1935–1942.

- Conrad, M. Über halogensubstituierte acetessigester. *Ber. Dtsch. Chem. Ges.* **1896**, 29, 1042–1048.
- Cook, C. E.; Whichard, L. P.; Turner, B.; Wall, M. E.; Egley, G. H. Germination of witchweed (*S. lutea* Lour.): isolation and properties of a potent stimulant. *Science* **1966**, 1189–1190.
- Cook, C. E.; Whichard, L. P.; Wall, M. E.; Egley, G. H.; Coggan, P.; Luhan, P. A.; McPhail, A. T. Germination stimulants II. The structure of strigol—a potent seed germination stimulant for witchweed (*Striga lutea* Lour.). *J. Am. Chem. Soc.* **1972**, 94, 6198–6199.
- DePuy, C. H.; Isaks, M.; Eilers, K. L.; Morris, G. F. The formation of cyclopentadienones. *J. Org. Chem.* **1964**, 29, 3503–3507 and references cited therein.
- Edgar, M. T.; Pettit, G. R.; Smith, T. H. Synthesis of 3-aryl-5-bromo-2(5H)-furanones. *J. Org. Chem.* **1978**, 43, 4115–4120.
- Eplee, R. E. Ethylene: a witchweed seed germination stimulant. *Weed Sci.* **1975**, 23, 433–436.
- Gassman, P. G.; Pascone, J. M. Synthesis and solvolysis of derivatives of 7-methyl-7-hydroxynorbornane and the epimeric 7-methyl-7-hydroxynorbornenes. *J. Am. Chem. Soc.* **1973**, 95, 7801–7813.
- Hassanali, A. Strigol analogues: synthetic achievements and prospects. In *Striga: Biology and Control*; Ayensu, E. S., Doggett, H., Keynes, K. D., Marton-Lefevre, J., Musselman, L. J., Parker, C., Peckering, A., Eds.; ICSU Press: Paris, 1984; pp 125–132.
- Hauck, C.; Müller, S.; Schildknecht, H. A germination stimulant for parasitic flowering plants from *Sorghum bicolor*, a genuine host plant. *J. Plant Physiol.* **1992**, 139, 474–478.
- Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. New method for synthesis of various types of substituted 2(5H)-furanones. *Bull. Chem. Soc. Jpn.* **1977**, 50, 242–247.
- Johnson, A. W.; Roseberry, G.; Parker, C. A novel approach to *Striga* and *Orobanch* control using synthetic germination stimulants. *Weed Res.* **1976**, 16, 223–227.
- Johnson, A. W.; Gowda, G.; Hassanali, A.; Knox, J.; Monaco, S.; Razawi, Z.; Roseberry, G. The preparation of synthetic analogues of strigol. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1734–1743.
- Kayser, M. M.; Morand, P. Regioselectivity of metal hydride reductions of unsymmetrically substituted cyclic anhydrides. Systems where “steric hindrance along the preferred reaction path” rationalization is not applicable. *Can. J. Chem.* **1980**, 58, 2484–2490.
- Kayser, M. M.; Breau, L.; Eliev, S.; Morand, P.; Ip, H. S. Regioselectivity control in metal hydride reductions of substituted maleic anhydrides. *Can. J. Chem.* **1986**, 64, 104–109.
- Khan, H. A.; Paterson, I. O-silylated enolate phenylthioalkylation: A synthesis of α,β -unsaturated 5- and 6-membered lactones. *Tetrahedron Lett.* **1982**, 23, 5083–5084.
- Knight, D. W.; Pattenden, G. 4-Phosphoranylidenebutenolide intermediates in the synthesis of 4-ylidenebutenolides and 4-ylidenetetrone acids. Synthesis of alkylidenephthalide constituents of celery odour and models for freelingyne. *J. Chem. Soc., Perkin Trans. 1* **1975**, 635–640.
- Knight, D. W.; Pattenden, G. Synthetic approaches towards 4-ylidenebutenolides and 4-ylidenetetrone acids. Regioselective nucleophilic additions to unsymmetrically substituted maleic anhydrides. *J. Chem. Soc., Perkin Trans. 1* **1979**, 62–69.
- Koten, I. A.; Sauer, R. J. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, pp 145–147.
- Kuivila, H. G. Reduction of phthalyl and succinyl dichloride with tri-*n*-butyltin hydride. Cyclization of γ -oxoacyl chlorides. *J. Org. Chem.* **1960**, 25, 284–285.
- MacAlpine, G. A.; Raphael, R. A.; Shaw, A.; Taylor, A. W.; Wild, H. J. Synthesis of the germination stimulant ($\pm$)-strigol. *J. Chem. Soc., Perkin Trans. 1* **1976**, 410–416.
- Mangnus, E. M.; Zwanenburg, B. Tentative molecular mechanism for germination stimulation of *Striga* and *Orobanch* seeds by strigol and its synthetic analogues. *J. Agric. Food Chem.* **1992**, 40, 1066–1070.
- Mangnus, E. M.; Dommerholt, F. J.; de Jong, R. L. P.; Zwanenburg, B. Improved synthesis of strigol analogue GR24 and evaluation of the biological activity of its diastereomers. *J. Agric. Food Chem.* **1992a**, 40, 1230–1235.
- Mangnus, E. M.; Stommen, P. L. A.; Zwanenburg, B. A standardized bioassay for evaluation of potential germination stimulants for seeds of parasitic weeds. *J. Plant Growth Regul.* **1992b**, 11, 91–98.
- Martin, S. F.; Moore, D. R. A new approach to the synthesis of α -alkylidene- γ -butyrolactones and $\Delta^{\alpha,\beta}$ -butenolides. *Tetrahedron Lett.* **1976**, 17, 4459–4462.
- Miller, L. E.; Staley, H. B.; Mann, D. J. A preparation of phenyl maleic anhydride. *J. Am. Chem. Soc.* **1949**, 71, 374.
- Müller, S.; Hauck, C.; Schildknecht, H. Germination stimulants produced by *Vigna unguiculata* Walp cv Saunders Upright. *J. Plant Growth Regul.* **1992**, 11, 77–84.
- Musselman, L. J., Ed. *Parasitic Weeds in Agriculture. Vol. I. Striga*; CRC Press: Boca Raton, FL, 1987; 317 pp.
- Nefkens, G. H. L.; Thuring, J. W. J. F.; Beenackers, M. F. M.; Zwanenburg, B. Synthesis of a phthaloylglycine-derived strigol analogue and its germination stimulatory activity toward seeds of the parasitic weeds *Striga hermonthica* and *Orobanch crenata*. *J. Agric. Food Chem.* **1997a**, 45, 2273–2277.
- Nefkens, G. H. L.; Thuring, J. W. J. F.; Zwanenburg, B. A novel and convenient synthesis of 3-methyl-2(5H)-furanone. *Synthesis* **1997b**, 290.
- Parker, C.; Riches, C. R. *Parasitic Weeds of the World: Biology and Control*; CAB International Press: Wallingford, Oxon, U.K., 1993; 332 pp.
- Press, M. C.; Graves, J. D.; Stewart, G. R. Physiology of the interaction of angiosperm parasites and their higher plant hosts. *Plant, Cell Environ.* **1990**, 13, 91–104.
- Reid, E. B.; Fortenbaugh, R. B.; Patterson, H. R. The oxidation of tetrone acids. I. Structural criteria for the formation of 1,2-diketones. *J. Org. Chem.* **1950**, 15, 572–582.
- Schreiber, J.; Wermuth, C. G. Etude de la condensation de l'acide pyruvique avec les aldéhydes aliphatiques non substitués en α . I. Produits de condensation dont la chaîne carbonée est ramifiée: semialdéhydes méthyl-alcoyl maliques et semialdéhydes méthyl-alcoyl maléiques. *Bull. Soc. Chim. Fr.* **1965**, 32, 2242–2249.
- Siame, B. A.; Weerasuriya, Y.; Wood, K.; Ejeta, G.; Butler, L. G. Isolation of strigol, a germination stimulant for *Striga asiatica*, from host plants. *J. Agric. Food Chem.* **1993**, 41, 1486–1491.
- Steyn, P. S.; Conradie, W. J.; Garbers, C. F.; de Vries, M. J. Bromination of but-2-enolides with N-bromosuccinimide. *J. Chem. Soc.* **1965**, 3075–3079.
- Swain, G.; Todd, A. R.; Waring, W. S. The synthesis of some unsaturated γ -lactones. *J. Chem. Soc.* **1944**, 548–553.
- Takano, S.; Ogasawara, K. An improved synthesis of γ -crotonolactone (2-buten-4-olide). *Synthesis* **1973**, 42–43.
- Vail, S. L.; Dailey, O. D.; Blanchard, E. J.; Pepperman, A. B.; Riopel, J. L. Terpenoid precursors of strigol as seed germination stimulants of broomrape (*Orobanch ramosa*) and witchweed (*Striga asiatica*). *J. Plant Growth Regul.*, **1990**, 9, 77–83 and references cited therein.
- Zwanenburg, B.; Mangnus, E. M.; Thuring, J. W. J. F. Strigol analogues: design, synthesis and biological activity. In *Proceedings of the Third International Workshop on Orobanch and Related Striga Research*; Pieterse, A. H., Verkley, J. A. C., Ter Borg, S. J., Eds.; Royal Tropical Institute: Amsterdam, The Netherlands, 1994; pp 187–197 and references cited therein.

Received for review June 28, 1996. Revised manuscript received February 24, 1997. Accepted April 1, 1997.* These investigations were supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Research (NWO).

JF9604652

* Abstract published in *Advance ACS Abstracts*, May 15, 1997.