ChemPubSoc Europe

DOI: 10.1002/ejoc.201600576

EurJOC European Journal of Organic Chemistry

Communication

Plant Hormone Synthesis

Strigolactone Analogues with a D-Ring Modified at C-2

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Abstract: Strigolactones (SLs) are important new plant hormones that receive much attention in current plant science. SLs are produced by many plants and are exuded by the root system. SLs are, amongst others, germination stimulants for seed of parasitic weeds. Naturally occurring SLs invariably contain three annelated rings, the ABC-scaffold, connected to a butenolide (the D-ring) via an enol ether unit. The synthesis of natural SLs requires many steps, therefore there is a continuous search for SL analogues with a simpler structure but with retention of bioactivity. In this study modified D-ring variants are investigated, especially analogues having a methyl group at C-2 instead of a hydrogen. For these analogues the ABC-scaffolds of GR24 and Nijmegen-1 were used. The coupling reaction proceeds profoundly better with chlorobutenolides than with the corresponding bromides. Bioassays reveal that the introduction an extra methyl at C-2 does not influence the germination activity, which is relevant for gaining insight in the mode of action of SLs.

Introduction

The agricultural food production in developing countries and the Mediterranean region suffers severely from the infestation of the parasitic weeds *Striga* and *Orobanche* sp.[1,2] Seeds of these parasitic weeds can germinate only when a chemical stimulant exuded by the roots of host plants, such as maize, sorghum and millet come into contact or are in close proximity. This process leads to the development of a radicle from the seeds which then attaches itself to the root of the host plant through haustorium formation, thus enabling the germinated seed to extract nutrients, water and salts from the host plant with the consequence that its growth and production of a crop is severely affected.[3] Yield losses up to 90 % have been reported.[2] The chemical stimulants that were found to be responsible for triggering the germination of *Striga* and *Orobanche* seeds are the naturally occurring germination stimulants, collectively termed strigolactones (SLs). The first SL, namely, strigol **1** was isolated as early as 1966 from the root exudate of cotton plants.[4a] Its detailed structure was established about

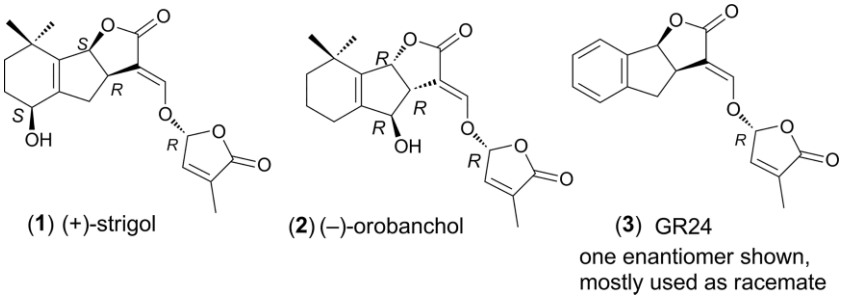

Figure 1. Structures of strigol, orobanchol and GR24.

20 years later.[4] Currently, a series of about 20 natural SLs have been isolated and characterized,[5–7] which are subdivided in two families, namely, one having the BC/2′ stereochemistry as in (+)-strigol (**1**) and the other one as in (–)-orobanchol (**2**) (Figure 1).

The control of parasitic weeds is extremely difficult due to the biological complexity of these weeds when coupled to their hosts, and hitherto no general method is available.[5–9] An exciting and appealing option is that of suicidal germination approach, which involves applying an exogenous SL to the soil in

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600576.

absence of a host resulting in the germination of the seeds, but due to lack of nutrients the germinated seeds will die. Natural SLs cannot be used for this approach as they have a too complex structure for a multigram synthesis.[10] Hence simpler SL analogues with an appreciable bioactivity are needed for this purpose. Thus a series of these simple SL analogues was designed and synthesized. Early examples of such SL analogues are the GR compounds, e.g. GR24 (Figure 1).[5,6,11] For a rational design of SL analogues a structure-activity relationship study provides valuable insight. Systematic simplification of SLs revealed that the bioactiphore resides in the CD part of the molecule (Figure 2).[6,7,12] In this model there is a considerable structural freedom in the A-part of the molecule.

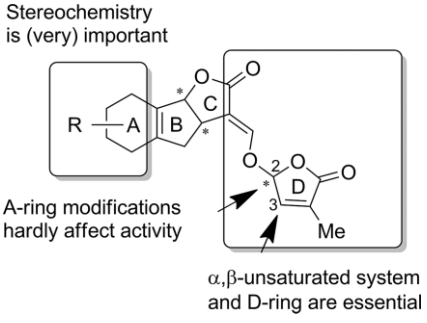


Figure 2. Model for designing SL analogues with germination activity.

Using this model several new SL analogues with a high germination activity were designed, synthesized and subjected to bio-evaluation. Typical examples are Nijmegen-1 (**4**),[6,7,13] ketone derived analogue **5**[6,7,14] and keto-enol-derived SL analogue **6**[6,7,15] (Figure 3).

A successful suicidal germination was reported in 1976,[16] but this approach for weed control was abandoned, because of lack of funds and also because of the presumed instability of SL analogue under field conditions.[17–19] About 30 years later the method was successfully used in tobacco infested by *Orobanche*.[7,20] Some of the new SL analogues, e.g **5** and **6**, were evaluated in pot experiments and shown to be potential suicidal germinating agents.[21] Hence, suicidal germination is a realistic option and there is a need for identifying optimal germinating agents to be applied in an effective combat of parasitic weeds.[20]

The model shown in Figure 2 was further detailed by varying the substituents at the position 3 and 4 of the D-ring.[22] Replacing the hydrogen at C-2 of the D-ring with a methyl group was not investigated at that time as it was considered not to be relevant. However, now there is new information available about the mode of action of SLs, namely that the enzymatic detachment of the D-ring plays a key role in the molecular cascade leading to germination (Figure 4).[23] The question now arises whether a methyl at the C-2 position, indicated by an arrow in Figure 4, will affect this process. This paper addresses this problem and deals with the preparation of some SL analogues having a methyl group at C-2 of the D-ring and their bio-evaluation.

Results and Discussion

GR 24 and Nijmegen-1 were taken as the target molecule for the introduction of a methyl group at C-2 of the D-ring. The preparation of ABC-part of GR24 (**7**) and Sheehan aldehyde **10** was conveniently accomplished using literature procedures.[24,25] For the coupling of the D-ring, the general strategy[26] was followed, as outlined in Scheme 1. The required hydroxy and chlorobutenolides **9** and **12** were prepared as shown in Scheme 2[27] by condensation of pyruvic acid and with acetone and butenone, respectively. The scaffold **7** upon treatment with chlorobutenolides **9a** and **9b** gave the D-ring modified SL analogues **8a** and **8b**, respectively. In a similar manner, scaffold **10** was converted into analogues **11a** and **11b** in moderate yields which were not optimized in this stage.

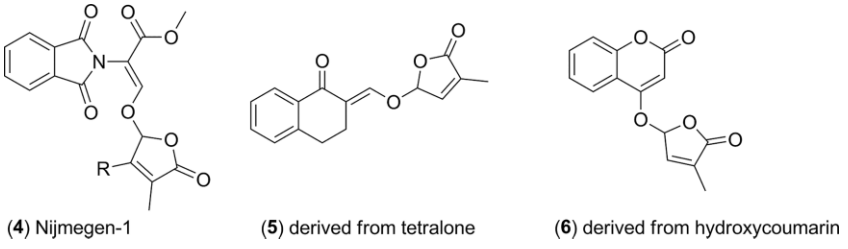


Figure 3. Some representative SL analogues with germinating activity.

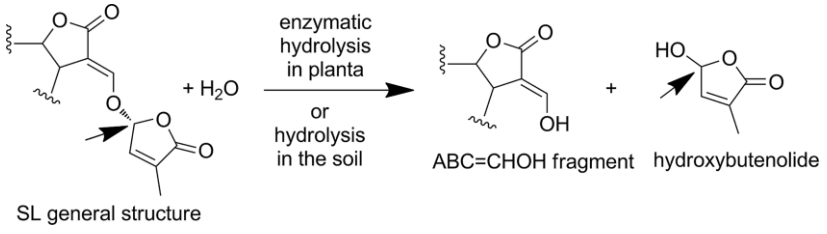
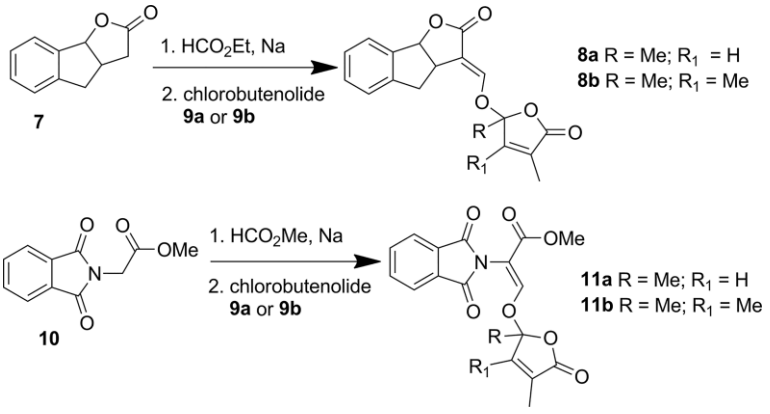
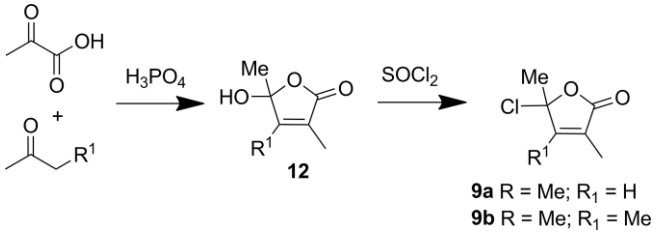


Figure 4. Hydrolysis of SLs in planta or in soil.



Scheme 1. Synthesis of GR24 and Nijmegen-1 modified at C-2 of the D-ring.



Scheme 2. Synthesis of chlorobutenolides.

The geometry of the enolic double bond in these analogues could not be deduced unambiguously from the NMR spectra. Therefore, an X-ray diffraction analysis was performed for analogue **11b** (Figure 5).

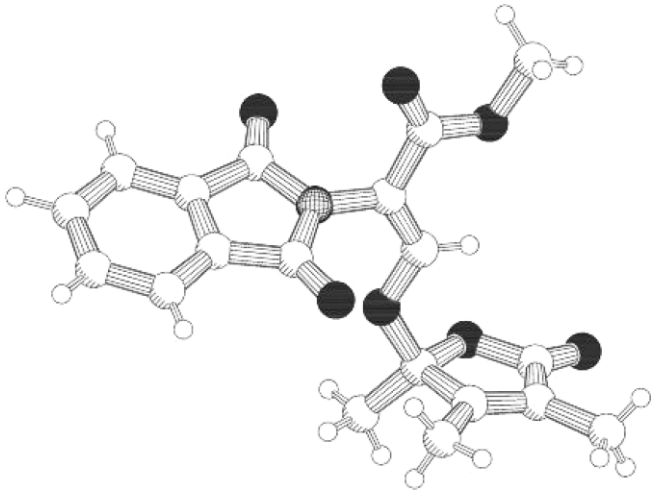


Figure 5. PLUTON generated drawing of X-ray structure of SL analogue **11b**.

In the literature there is only one mention[28] of a compound having a methyl group at C-2 of the D-ring, namely the compound **8b**. It was prepared in a different manner, namely from a hydroxybutenolide obtained by reaction of methyllithium with 2,3-dimethylmaleic anhydride[29] followed by treatment with thionyl chloride[30] and subsequent coupling[28] with the enolate derived from the ABC scaffold **7**. Our Scheme 2 is at least as convenient. An observation of great practical importance is that the coupling of the an enolate with a chlorobutenolide proceeds in most cases highly satisfactory, in contrast to the coupling with the corresponding bromo butenolide which often is problematic. For instance, for the synthesis of SL analogue **5** derived from tetralone the coupling with bromobutenolide could not be realized, whereas with the chlorobutenolide the product formation took place smoothly. In actual practice we now convert the bromide into the chloride by treatment with lithium chloride in dimethylformamide in order to ensure a successful coupling reaction.

Bio-Assays

The newly prepared SL analogues were bio-assayed using seeds of *S. hermonthica* and *O. cernua*. The results are summarized in bar diagrams shown in Figure 6 and Figure 7 (see also the Supporting Information). The bio-data reveal that the biological potency of the newly synthesized SL analogues with a D-ring substituted at C-2 is comparable to, or somewhat lower than, that of natural isomers of GR24 (**3**) and Nijmegen 1 (**4**). Therefore, this study suggests that structural changes in the D-ring moiety of GR 24 and Nijmegen-1 can be used as an alternative strategy to procure these materials in a rather economical manner, because the synthesis of hydroxybutenolide modified at C-2 (**9a** and **9b**) can be obtained from very cheap starting materials, namely pyruvic acid, acetone or 2-butanone using simple and short reaction pathways. In addition, the coupling with the chlorobutenolides is advantageous.

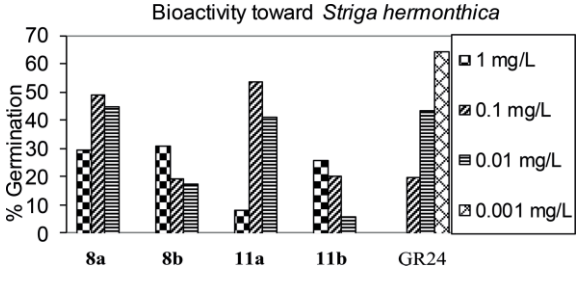


Figure 6. Bar diagram representation of percentages of the germinated seeds of *S. hermonthica* after exposure to various concentrations of compounds **8a**, **8b**, **11a**, **11b** and GR 24 (**3**) as a positive control.

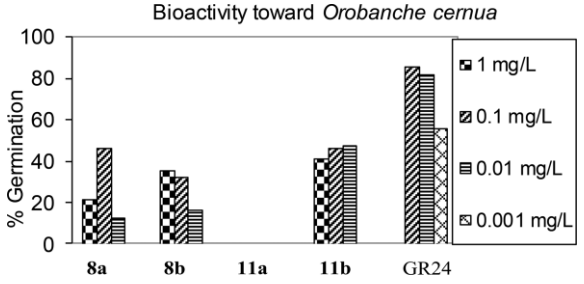


Figure 7. Bar diagram representation of percentages of the germinated seeds of *O. cernua* after exposure to various concentrations of compounds **8a**, **8b**, **11a**, **11b** and GR 24 (**3**) as a positive control.

Conclusions

The SL analogues having either the GR 24 or Nijmegen-1 basic skeleton and modified D-rings were readily obtainable by coupling with the appropriate chloro-butenolides modified at C-2. The yields were not optimized in this stage. The biological data reveal that the bioactivity is hardly affected by the methyl substituents at C-2. The coupling protocols with the butenolides shown in Scheme 2 can be added to the arsenal of methods for preparing a large variety of SL analogues.

It should be noted that the new SL analogues **8a**, **8b**, **11a** and **11b** having a methyl group at C-2 of the D-ring, are racemates. Compounds **8** consists of mixtures of two racemic diastereoisomers. Detailed conclusion on the influence of the C2-methyl group in the D-ring on the germination stimulating activity can only be drawn when the respective enantiopure single diastereomers and enantiomers of these analogues are tested. However, for the purpose of obtaining simple and cheap suicidal germination stimulants for use in the field, the procurement of these compounds as racemates is satisfactory.

The results of the bioassays are relevant for the understanding of the mode of action of SLs.[23]

Experimental Section

General Remarks: IR spectra were recorded using a Perkin–Elmer 298 infrared spectrophotometer and a Bio-Rad FTS-25 instrument. ^{1}H-NMR spectra were recorded on a Bruker AC 100 spectrometer (100 MHz), AC 300 (300 MHz), and a Bruker AM-400 (400 MHz), respectively, using Me_4Si (TMS) as the internal standard. ^{13}C-NMR spectra were recorded on a Bruker AC 300 (operating at 75 MHz) and AM 400 (operating at 100 MHz) spectrometers with $CDCl_3$ (δ = 77.0 ppm), [D_6]acetone (29.206 and 206 ppm) as standards. Melting points were determined with a Reichert Thermopan microscope and are uncorrected. Elemental analyses were conducted on a Carlo–Erba instruments CHNSO EA 1108 elemental analyzer. Mass spectra were recorded using a double focussing VG 7070E mass spectrometer in the mode indicated, or a Varian Saturn 2 GC–MS ion-trap system. GC–MS separations were carried out on a fused-silica capillary column (DB-5, 30 m × 0.25 mm) and helium was used as the carrier gas. GLC was conducted with a Hewlet–Packard HP 5890 gas chromatograph using a capillary column (25 m) HP-1 with nitrogen (2 mL/min, 0.5 atm) as the carrier gas. Thin-layer chromatography (TLC) was carried out on Merck pre-coated silica gel 60 F_{254} plates (0.25 mm) using the eluents indicated. Spots were visualized using a UV lamp, or with a potassium dichromate spray (prepared from 7.5 g of $K_2Cr_2O_7$ in 250 mL of H_2O containing 12.5 mL 1 M H_2SO_4) followed by heating at 140 °C. Column chromatography was performed on silica gel (Kieselgel, Merck) using eluents indicated. All solvents were dried under standard conditions.

The compounds **9a** and **9b** were prepared by previously described procedures.[27,28]

3-{(*E*)-1-[(2,4-Dimethyl-5-oxo-2,5-dihydro-2-furanyl)oxy]-methylidene}-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (8a): A stirred solution of the tricyclic lactone **7** (562. 2 mg, 3.23 mmol) in ethyl formate (20 mL) was treated with small pieces of metallic sodium (81.7 mg, 3.55 mmol) whilst being maintained under a stream of nitrogen. After 1.5 h the mixture was concentrated in vacuo and anhydrous DMF (10 mL) was added to the residue. Then the DMF solution was cooled (0 °C) and treated dropwise with a solution of the chlorobutenolide **9a** (710.0 mg, 4.85 mmol) in anhydrous DMF (5 mL). The mixture was allowed to reach room temperature and then set aside for 24 h. The mixture was concentrated in vacuo, the residue was treated with water (50 mL) and ethyl acetate (30 mL), the separated aqueous layer was extracted with ethyl acetate (2 × 20 mL), the combined organic layers were washed with water, dried ($MgSO_4$) and then concentrated in vacuo. The resultant crude material was purified by column chromatography (hexane/ethyl acetate, 1:1, v/v) to give a mixture of unchanged compounds **7** and **9a** (125.8 mg) and the desired compound **8a** (514.8 mg, 51 %), m.p. 200–202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51–7.27 (m, 4 H, ArH + =CHO), 6.88 (s, 1 H, CH=), 5.96 (d, J = 7.9 Hz, 1 H, H8b), 3.96–3.91 (m, 1 H, H3a), 3.45 (dd, $J_{4,3a,trans}$ = 9.3, ^2J = 16.9 Hz, 1 H, H4), 3.18 (dd, $J_{4,3a,cis}$ = 3.1, ^2J = 16.9 Hz, 1 H, H4), 2.02 (s, 3 H, CH_3), 1.82 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.4, 169.7, 147.6, 144.9, 142.6, 138.8, 134.9, 130.0, 127.4, 126.4, 125.2, 113.1, 106.3, 85.8, 38.8, 37.3, 23.8, 10.6 ppm. MS [EI: *m*/zel. intensity (%)]: 313 ([M + 1]$^+$, 0.4); 312 ([M]$^+$, 0.4); 202 ([M$^+$ + 1 – 111], [$C_{12}H_9O_3$]$^+$, 39.6); 111 ([M$^+$ – 201], [$C_6H_7O_2$]$^+$, 100). HRMS/EI: *m*/*z* calcd. for $C_{18}H_{16}O_5$: Exact mass found: 312.099773 (100 % abundance). It should be noted that the product obtained consists of a mixture of two racemic diastereoisomers.

3-{(*E*)-1-[(2,3,4-Trimethyl-5-oxo-2,5-dihydro-2-furanyl)oxy]-methylidene}-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (8b): A stirred solution of tricyclic lactone **7** (417.0 mg, 2.40 mmol) in ethyl formate (20 mL), while maintained under nitrogen, was treated with small pieces of metallic sodium (60.6 mg, 2.64 mmol) and then set aside for 2 h. The mixture was concentrated in vacuo and anhydrous DMF (10 mL) added to the residue. The thus obtained solution was cooled (–40 °C) and treated dropwise with a solution of chlorobutenolide **9b** (512.1 mg, 3.12 mmol) in anhydrous DMF (5 mL). The mixture was then processed in the manner described above to afford a mixture of unchanged compounds **7** and **9b** (66.4 mg) and the desired compound **8b** (377.4 mg, 48 %) after column chromatography (hexane/ethyl acetate, 1:1, v/v), m.p. 213-217 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.50–7.16 (m, 4 H, ArH + =CHO), 5.96 (d, J = 7.9 Hz, 1 H, H8b), 3.95–3.92 (m, 1 H, H3a), 3.42 (dd, $J_{4,3a,trans}$ = 9.3, ^2J = 16.9 Hz, 1 H, H4), 3.20 (dd, $J_{4,3a,cis}$ = 3.1, ^2J = 16.9 Hz, 1 H, H4), 1.98 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.3, 169.8, 155.3, 147.4, 142.6, 138.8, 130.0, 127.9, 126.4, 125.2, 113.3, 107.5, 85.8, 38.8, 37.3, 22.5, 10.6, 8.7 ppm. MS [FAB *m*/*z*, rel. intensity (%)]: 349 ([M$^+$ + Na$^+$], 23.0), 327 ([M + 1]$^+$, 62.5); 203 ([M$^+$ – 123], 38.1); 201 ([M$^+$-125], [$C_{12}H_9O_3$]$^+$, 4.9); 125 ([M$^+$ – 201], [$C_7H_9O_2$]$^+$, 100). $C_{19}H_{18}O_5$ (326.35): calcd. C 69.93, H 5.56; found C 69.64, H 5.59. Note that product **8b** is a mixture of racemic diastereoisomers.

Methyl (*Z*)-3-[(2,4-dimethyl-5-oxo-2,5-dihydro-2-furanyl)oxy]-2-(1,3-dioxo-1*H*-2-isoindolyl)-2-propenoate (11a) (2′-Me-Nijmegen-1): A stirred and cooled (–60 °C) solution of Sheehan aldehyde **10** (400.0 mg, 1.62 mmol) in anhydrous DMF (10 mL), while maintained under nitrogen, was treated with potassium *tert*-butoxide (199.7 mg, 1.78 mmol), followed by a solution of chlorobutenolide **9a** (261.0 mg, 1.78 mmol) in anhydrous DMF (5 mL). The mixture was allowed to attain room temperature and set aside for 24 h, and processed in the same manner as described above to afford compound **11a** (286.7 mg, 50 %) after column chromatography (hexane/ethyl acetate, 1:1, v/v), m.p. 182–184 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.90–7.70 (m, 4 H, ArH + =CHO), 6.93 (s, 1 H, CH=), 3.76 (s, 3 H, OCH_3), 2.00 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.9, 166.1, 163.3, 150.5, 145.8, 134.2, 133.7, 132.2, 123.8, 106.6, 106.3, 52.3, 23.5, 10.5 ppm. MS/CI [*m/z*, rel. intensity (%)]: 375 ([$M^+ + NH_4^+$], 39.3). MS/EI [*m/z*, rel. intensity (%)]: 247 ([$M^+ + 1 - 111$], [$C_{12}H_8NO_5]^+$, 97.3); 246 ([$M^+ - 111$], [$C_{12}H_7NO_5]^+$, 14.6); 111 ([$M^+ - 246$], [$C_6H_7O_2]^+$, 100). $C_{18}H_{15}NO_7$ (357.32): calcd. C 60.51, H 4.23, N 3.92; found C 60.47, H 4.21, N 3.93.

Methyl (*Z*)-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-[(2,3,4-trimethyl-5-oxo-2,5-dihydro-2-furanyl)oxy]-2-propenoate (11b) (2′,3′-Me$_2$-Nijmegen-1): A stirred and cooled (–40 °C) solution of Sheehan aldehyde **10** (716.9 mg, 2.90 mmol) in anhydrous DMF (10 mL), while maintained under nitrogen, was treated with potassium *tert*-butoxide (358.2 mg, 3.20 mmol), followed by a solution of chlorobutenolide **9b** (261.0 mg, 1.78 mmol) in anhydrous DMF (8 mL). The mixture was allowed to attain room temperature, set aside for 72 h, and processed as described above to afford the desired compound **11b** (360.2 mg, 34 %) after column chromatography (hexane/ethyl acetate, 1:1, v/v), m.p. 175–176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.91–7.60 (m, 4 H, ArH + =CHO), 3.75 (s, 3 H, OCH_3), 1.97 (s, 3 H, CH_3), 1.89 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.2, 166.1, 163.3, 156.9, 150.2, 134.2, 132.2, 126.8, 123.8, 107.7, 105.9, 52.3, 22.2, 10.5, 8.6 ppm. MS/FAB [*m/z*, rel. intensity (%)]: 394 ([$M^+ + Na^+$], 61.6), 372 ([$M^+ + 1$], 60.3), 371 ([$M]^+$, 13.2), 246 ([$M^+ - 125$], [$C_{12}H_8NO_5]^+$, 17.1); 125 ([M^+-246], [$C_7H_9O_2]^+$, 100). $C_{19}H_{17}NO_7$ (371.35): calcd. C 61.45, H 4.61, N 3.77; found C 61.17, H 4.47, N 3.71.

X-ray Diffraction Analysis of Compound 7: Crystals of **11b** suitable for X-ray diffraction studies were obtained by slow cooling of the solvent (isopropyl ether). A single crystal was mounted in air on a glass fibre. Intensity data were collected at room temperature. Crystal data are given in Table 1 in the Supporting Information.

Keywords: Natural products · Bioassays · Parasitic weeds · Strigolactone analogues · Structure–activity relationship

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Received: May 11, 2016
Published Online: June 27, 2016