A New Expedient Synthesis of 3-Methyl-2(5*H*)-furanone, the Common Substructure in Strigolactones, and Its Proposed Biosynthesis

Heetika Malik, Floris P. J. T. Rutjes,* Binne Zwanenburg*

Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands
Fax +31(24)3653393; E-mail: b.zwanenburg@science.ru.nl

Received 27 March 2010; revised 15 June 2010

Abstract: 3-Methyl-2(5*H*)-furanone is the common structural unit in natural and several synthetic strigolactones, which are germination stimulants for seeds of the parasitic weeds *Striga* and *Orobanche* spp. A simple, one-step, ring-closing metathesis of allyl methacrylate using an appropriate Grubbs catalyst gives this furanone in good yield. Acid-catalyzed condensation of glyoxal and methylmalonic acid gives 5-hydroxy-3-methyl-2(5*H*)-furanone, which is another synthon for the introduction of the furanone unit into strigolactones. In addition, a biosynthetic pathway is presented for the incorporation of the furanone unit into strigolactones, which is relevant in view of the current interest in the newly discovered biological functions of strigolactones.

Key words: ring-closing metathesis, Grubbs catalyst, allyl methacrylate, strigolactones, aldol condensation, biosynthesis

Strigolactones constitute a family of compounds which induce the germination of seeds of the parasitic weeds *Striga* and *Orobanche* spp. These weeds pose a great threat to food crops in third world countries and around the Mediterranean Sea.[1] Several germination stimulants have been isolated from root exudates of host plants (Figure 1).[2]

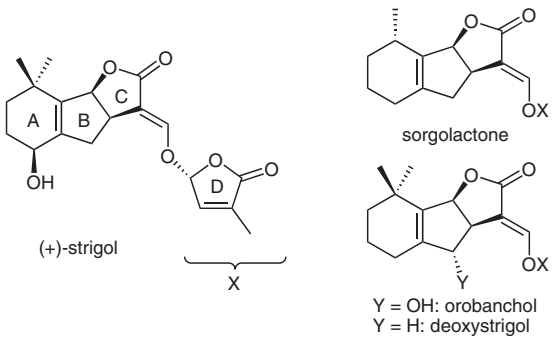


Figure 1 Naturally occurring strigolactones

In all of the strigolactones isolated from root exudates, the D-ring is the butenolide X (Figure 1). A series of synthetic analogues have been reported, e.g. nijmegen-1 and GR24 (Figure 2), all of them containing the same D-ring.[3] It has been demonstrated that this particular D-ring is essential for the germination activity.[3,4] The commonly used synthon for the D-ring in the synthesis of natural strigolactones and their synthetic analogues is 3-methyl-2(5*H*)-furanone (**1**). The preparation of this butenolide is not as easy as it seems. An early synthesis involved bromination and dehydrobromination of commercially available but expensive 3-methyl-2,3-dihydro-2(3*H*)-furanone, in 53% yield.[5] A four-step sequence starting from ethyl α-bromopropionate resulted in furanone **1** in 75% overall yield.[6] Citraconic anhydride (**2**) seemingly is a suitable starting material and reductive removal of the carbonyl group would give the desired compound **1**. Unfortunately, metal hydride reducing agents invariably lead to the 4-methyl-substituted butenolide.[7] This problem has been overcome by first converting citraconic anhydride into the Diels–Alder adduct of cyclopentadiene, then carrying out the reduction of the desired carbonyl group, followed by cycloreversion using flash-vacuum thermolysis.[8] Alternatively, the anhydride was first opened with dicyclohexylamine in a regiospecific manner, converted into the mixed anhydride and subsequently reduced to **1** in 80% yield.[9]

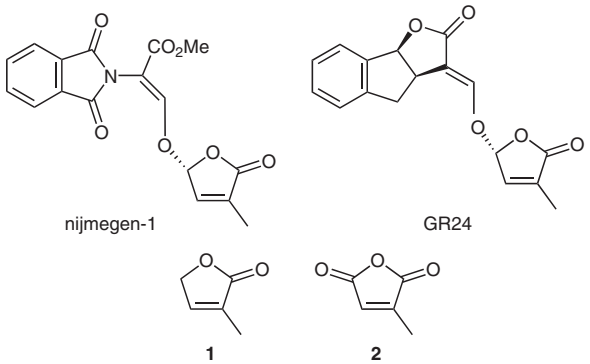
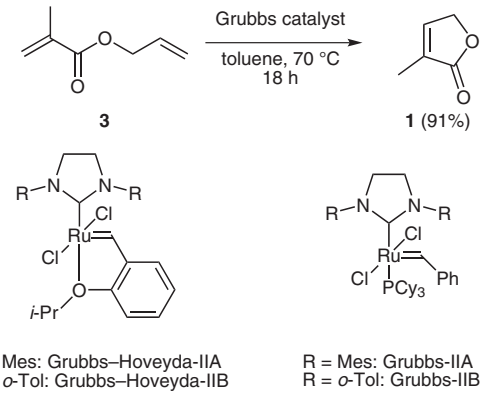


Figure 2 Synthetic strigolactones and D-ring precursors

In this paper we describe an expedient one-step synthesis of furanone **1**. Readily available allyl methacrylate (**3**) underwent a smooth ring-closing metathesis (RCM) in 91% yield using a recently developed Grubbs catalyst.[10] The choice of the catalyst, however, appeared to be crucial. It should be emphasized that the RCM could be accomplished smoothly in high yield only with catalyst Grubbs–Hoveyda-IIB (Scheme 1). In contrast, with catalyst Grubbs–Hoveyda-IIA, RCM to furanone **1** took place only to a minor extent. Interestingly, with catalysts Grubbs-IIA and -IIB, the reaction did not result in any product formation. One of the known limitations of RCM is the restricted tolerance of steric congestion on or around the reactive olefin moiety. Catalysts Grubbs-IIA and -IIB

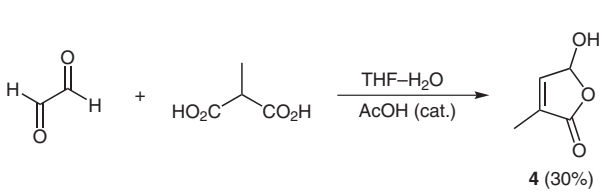
SYNTHESIS 2010, No. 19, pp 3271–3273
Advanced online publication: 30.07.2010
DOI: 10.1055/s-0030-1257911; Art ID: T07610SS

are especially sensitive to steric hinderance, although exceptions are known. A notable example is a RCM of an acrylate with catalyst Grubbs-I employing high catalyst concentration.[11] Catalyst Grubbs–Hoveyda-IIB gives the best performance with sterically hindered olefins.[10] This new RCM method for the preparation of furanone **1** is very attractive as it combines the use of an inexpensive starting material with a high yielding, single-step operation.



Scheme 1 One-step synthesis of 3-methyl-2(5*H*)-furanone (**1**)

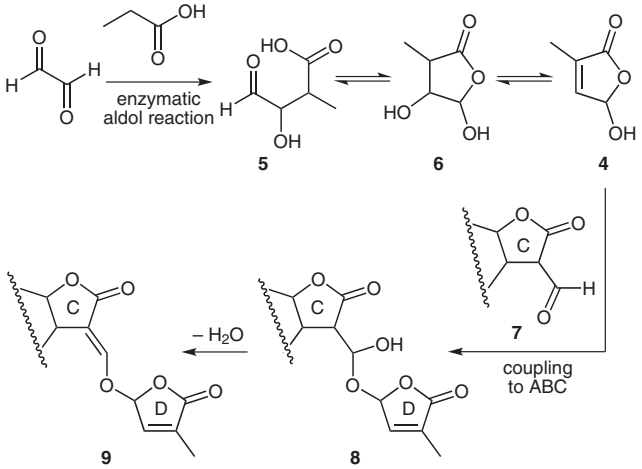
An alternative synthon for the introduction of the D-ring is 5-hydroxy-3-methyl-2(5*H*)-furanone (**4**). This compound has previously been prepared in a multistep process from crotonal using *p*-toluenesulfinic acid as a synthetic auxiliary[7] and by photooxygenation of 3-methylfuroic acid.[12] We found that the hydroxy-substituted butenolide **4** can simply be obtained by an acid-catalyzed aldol-type condensation of glyoxal with methylmalonic acid, albeit in moderate yield (Scheme 2). In a water–toluene mixture as the reaction medium and in the presence of acetic acid, the yield ranged between 5–20% depending on the quality of the glyoxal solution. By replacing toluene with tetrahydrofuran, the yield was improved to 30%.



Scheme 2 Synthesis of 5-hydroxy-3-methyl-2(5*H*)-furanone (**4**)

This aldol-type synthesis of butenolide **4** sheds some light on the biosynthesis of the D-ring and its coupling to the ABC skeleton in strigolactones. In a recent paper, a plausible biosynthesis of the ABC skeleton of natural strigolactones was described, but without any comment on the incorporation of the D-ring.[3,13]

The biosynthesis of the D-ring conceivably could proceed similar to the reaction shown in Scheme 2, starting with an enzymatic aldol-type condensation of glyoxal with propionic acid, of which methylmalonic acid is a synthetic equivalent. Glyoxal and propionic acid both are abundantly present in nature and their coupling could proceed as shown in Scheme 3. Formylation of the ABC skeleton produces the aldehyde **7**, which is in equilibrium with its enol form. Addition of the hydroxy substituent of **4** to **7** provides the hemiacetal **8**, which upon loss of water produces the D-ring-coupled product, i.e. the strigolactone **9**. Alternatively, one can envisage the initial formation of an oxonium ion from **4** which then reacts with the enol of **7** to give **9**. The stereochemistry at the 2′-position of the D-ring may be enzymatically controlled, however, natural strigolactones with a 2′-epimeric structure have been isolated.[2b]



Scheme 3 Proposed biosynthesis of the D-ring fragment

In summary, an expedient one-step synthesis of 3-methyl-2(5*H*)-furanone is described. This furanone is the substructure in natural and synthetic strigolactones, which are germination stimulants for seeds of the parasitic weeds *Striga* and *Orobanche* spp. Recently, it was discovered that natural strigolactones have two additional important biological functions.[14] They are the principal branching factor of *Arbuscular mycorrhizal* fungi and, most interestingly, are a new type of plant hormone that serves as a plant growth regulator. In view of these newly discovered functions of natural strigolactones and the synthetic analogue GR24, there is an increasing demand for these compounds. The furanone **1** is indispensable in their synthesis. We have also presented a simple preparation of the corresponding 5-hydroxyfuranone. In connection herewith, we have provided insight into the biosynthetic incorporation of the furanone into strigolactones.

All glass apparatus was oven dried prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrometer (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) using $CDCl_3$ as solvent. TMS (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR spectra. Reactions were monitored on silica gel TLC plates (Merck). Detection was performed with UV light and/or by charring at ~150 °C after dipping into a soln of either 2% anisaldehyde in EtOH–H_2SO_4 or $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) or $KMnO_4$. Column chromatography was performed over silica gel (0.035–0.070 mm) using freshly dis-

tilled solvents. Air- and moisture-sensitive reactions were carried out under an inert atmosphere of dry argon.

3-Methyl-2(5*H*)-furanone (1) via Ring-Closing Metathesis

Catalyst Grubbs–Hoveyda-IIB (45 mg, 5 mol%) was added to a soln of allyl methacrylate (200 mg, 1.58 mmol) in toluene (5 mL) and the reaction mixture was heated at 70 °C for 18 h. After completion of the reaction, the resultant mixture was chromatographed on a silica gel column (EtOAc–*n*-pentane, 1:3). Due to the volatile nature of the product, toluene was not removed from the reaction mixture prior to the chromatography.

Yield: 140 mg (91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (s, 3 H), 4.73 (br s, 2 H), 7.12 (br s, 1 H).

The rest of the spectroscopic properties were as reported previously.[15]

5-Hydroxy-3-methyl-2(5*H*)-furanone (4)

A 40 wt % soln of aqueous glyoxal (1.85 g, 12.7 mmol), methylmalonic acid (1.00 g, ca. 8.5 mmol) and glacial AcOH (0.1 mL) in H_2O (5 mL) and THF (20 mL) was heated under reflux with stirring at 120 °C for 26 h. The progress of the reaction was monitored by TLC and ^{1}H NMR spectroscopy. After cooling, a small amount of the product was present in the THF layer. By excessive extraction of the aqueous layer with EtOAc an additional amount of product **4** was obtained, mixed with methylmalonic acid. After removal of solvents, the residue was triturated with CH_2Cl_2, then filtered, thereby leaving methylmalonic acid behind. Product **4** was then obtained as a white solid upon concentration; yield: 290 mg (30%). The spectroscopic properties were as reported previously.[7]

Acknowledgment

Financial support provided by Radboud University Nijmegen and Wageningen University is fully acknowledged.

References

(1) Parker, C. *Pest Manag. Sci.* **2009**, *65*, 453; and references cited therein.
(2) (a) Cook, C. E.; Whichard, L. P.; Wall, M. E.; Egley, G. H.; Coggon, P.; Luhan, P. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1972**, *94*, 6198. (b) Yoneyama, K.; Xie, X.; Yoneyama, K.; Takeuchi, Y. *Pest Manag. Sci.* **2009**, *65*, 467; and references cited therein.
(3) Zwanenburg, B.; Mwakaboko, A. S.; Reizelman, A.; Anilkumar, G.; Sethumadhavan, D. *Pest Manag. Sci.* **2009**, *65*, 478.
(4) Thuring, J. W. J. F.; Bitter, H. H.; de Kok, M. M. K.; Nefkens, G. H. L.; van Riel, A. M. D. A.; Zwanenburg, B. *J. Agric. Food Chem.* **1997**, *45*, 2273.
(5) Johnson, A. W.; Gowda, G.; Hassanali, A.; Knox, J.; Monaco, S.; Razawi, Z.; Roseberry, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1734.
(6) Mangnus, E. M.; Dommerholt, F. J.; de Jong, R. L. P.; Zwanenburg, B. *J. Agric. Food Chem.* **1992**, *40*, 1230.
(7) Cooper, G. K.; Dolby, L. J. *J. Org. Chem.* **1979**, *44*, 3414.
(8) Mangnus, E. M.; Zwanenburg, B. *Synth. Commun.* **1992**, *22*, 783.
(9) Nefkens, G. H. J.; Thuring, J. W. J. F.; Zwanenburg, B. *Synthesis* **1997**, 290.
(10) (a) Stewart, I. C.; Ung, T.; Plenev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589. (b) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45.
(11) Furstner, A.; Dierkes, T. *Org. Lett.* **2000**, *2*, 2463.
(12) Burness, D. M. *Org. Synth.* **1959**, *36*, 46.
(13) Rani, K.; Zwanenburg, B.; Sugimoto, Y.; Yoneyama, K.; Bouwmeester, H. J. *Plant Physiol. Biochem.* **2008**, *46*, 617.
(14) (a) Tsuchiya, Y.; McCourt, P. *Curr. Opin. Plant Biol.* **2009**, *12*, 556. (b) Bouwmeester, H. J.; Roux, C.; Lopez-Raez, J. A.; Bécard, G. *Trends Plant Sci.* **2007**, *12*, 224.
(15) Ichihara, A.; Nio, N.; Terayama, Y.; Kimura, R.; Sakamura, S. *Tetrahedron Lett.* **1979**, 3731.