



A new efficient synthesis of GR24 and dimethyl A-ring analogues, germinating agents for seeds of the parasitic weeds *Striga* and *Orobanche* spp.

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ABSTRACT

An efficient and high yielding preparation for the synthetic germination stimulant GR24 (**5**) and its A-ring dimethyl-substituted analogues **30–32** has been described. The first step involves a Stobbe condensation of benzaldehydes **9–11** with dimethyl succinate. Subsequent transposition of the ester and reduction of the double bond provides the building blocks **15–17** for an intramolecular Friedel–Crafts acylation. ABC-lactones **22–25** are prepared from γ -keto esters **18–21** by saponification, subsequent reduction with sodium borohydride followed by acid-catalyzed lactonization. Coupling of the lactones with the D-ring is accomplished by formylation and subsequent treatment with bromobutenolide **8** to give GR24 and its dimethyl analogues. Bioassays with *Striga hermonthica* seeds reveal that the dimethyl analogues are slightly less active than GR24 itself.

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1. Introduction

Parasitic weeds of the genera *Striga* and *Orobanche* cause immense damage to food crops, such as maize, sorghum, millet and rice, especially in third world countries.¹ Germination of the seeds of these parasites is induced by stimulant molecules present in the root exudates of the host plants that are attacked. The first stimulant was isolated from cotton roots as early as 1966.² At present several stimulants, collectively called strigolactones, have been reported.³ Representative examples, are strigol (**1**), sorgolactone (**2**), orobanchol (**3**) and 5-deoxystrigol (**4**), which are pictured in Figure 1.

Isolation and identification of germination stimulants is extremely difficult due to the minute amounts present in the root exudates (estimated production of stimulant per plant is 15 pg per day).⁴ As the natural stimulants are difficult to obtain and their total synthesis is very elaborate,^{5,6} synthetic analogues with simpler structures have been prepared.^{7,8} The aromatic A-ring analogue GR24 (**5**) is a successful example as it has a very high germinating activity (10^{-10} – 10^{-12} mol/L). GR24 is currently widely used as the standard germination agent as a positive control in bioassays of seeds of parasitic weeds.^{8–10}

The known syntheses of GR24 all use indan-1-one (**6**) as the starting material (Scheme 1). The first route^{7b} involves α -bromination, followed by reaction with sodium malonic ester, subsequent hydrolysis and decarboxylation to give the key intermediate **7**. This route suffers from α -dibromination especially on large scale. In the second improved method¹¹ an ethoxycarbonyl is introduced to enhance the α -CH activity. This is followed by direct alkylation with bromoacetate, hydrolysis and decarboxylation, again leading to the intermediate **7**.

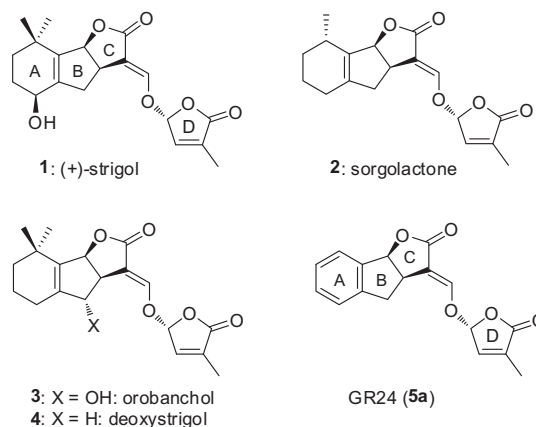
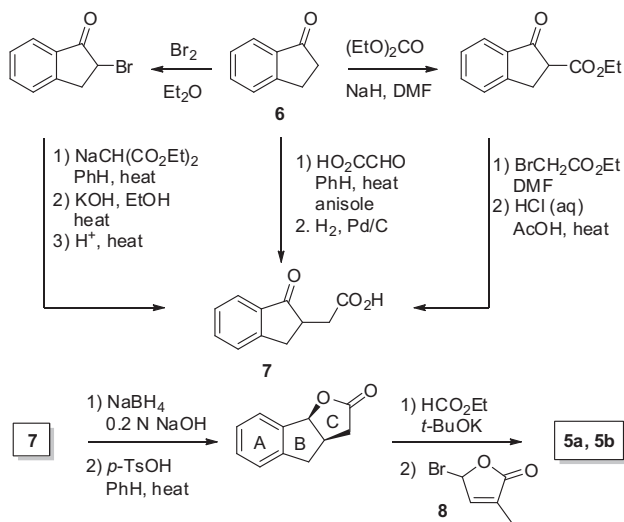


Figure 1. Naturally occurring strigolactones and synthetic analogue GR24.

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So far, a third method involving condensation of indan-1-one (**6**) with glyoxylic acid and subsequent removal of the double bond to give intermediate **7** via a two-step process is the easiest one.⁹



Scheme 1.

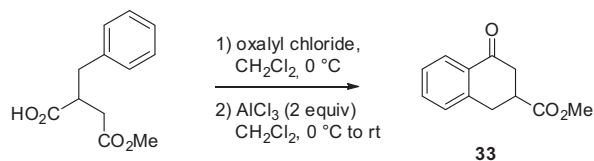
Reduction of the carbonyl group with NaBH₄ and acid-catalyzed lactonization leads to the ABC-skeleton of GR24.^{11,12} Coupling of this skeleton is accomplished by formylation with ethyl formate and subsequent treatment with bromobutenolide **8** as shown in Scheme 1.¹¹ The indanone route was also followed for the preparation of 6- and 8-methyl GR24. The required substituted indanones were obtained from an appropriate methyl-substituted benzyl chloride using the malonic ester synthesis.¹³ 8-Methyl-5-hydroxy GR24 was also reported by first making the appropriately substituted indanone from 6-methyl dihydrocoumarin.¹⁴

This paper deals with a new practical and atom efficient synthesis of the important germination stimulant GR24 and some of its A-ring dimethyl-substituted analogues.

2. Results and discussion

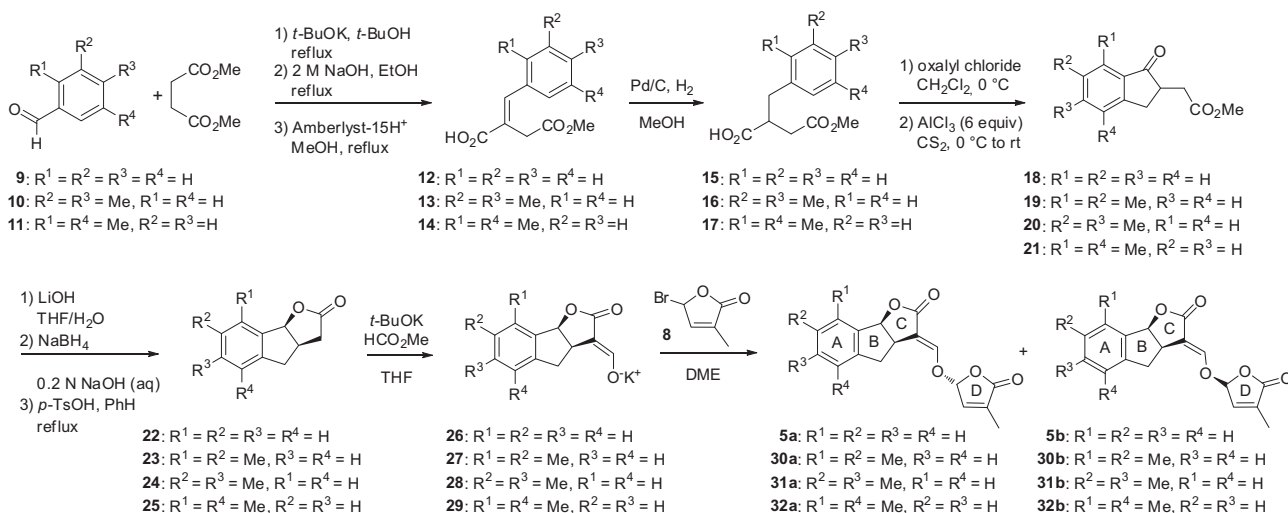
The new approach to the preparation of the key intermediate **7** makes use of the Stobbe condensation^{15–17} of benzaldehyde **9** with dimethyl succinate (Scheme 2). The Stobbe product, which is a half

ester, contains all the carbon atoms required for the construction of the key intermediate. Transposition of the ester was readily achieved by saponification to the corresponding diacid, which on treatment with Amberlyst-15H⁺ catalyst in methanol resulted in a selective esterification to the alternative monoester **12**. Catalytic hydrogenation gave the precursor **15** for the Friedel–Crafts ring closure to the key intermediate **7**. It should be noted that the Friedel–Crafts cyclization was not as straightforward as was expected. After careful experimentation, the optimum conditions, namely 6 equiv AlCl₃ in CS₂ at low temperature, gave the desired five-membered ring product **18** in good overall yield. Compound **18** is the methyl ester of key intermediate **7**. Surprisingly, with a smaller amount of AlCl₃ (2 equiv) in dichloromethane as the solvent the six-membered ring lactone **33** was exclusively obtained in good yield. Unexpectedly, under these conditions, prior to the Friedel–Crafts ring closure, a remarkable transposition of functionalities took place leading to the exclusive formation the six-membered ring product **33** (Scheme 3). Most likely, this transposition occurs through methoxide transfer to an acylium ion as is pictured in Scheme 3.



Scheme 3.

Conversion of the γ -ketoester **18** into the ABC-lactone **22** of GR24 was accomplished by first saponification into the keto acid, then reduction with sodium borohydride, followed by acid-catalyzed lactonization of the crude reduction product.^{11,12} Coupling of building block **22** and the D-ring was accomplished in a one-pot two-step process, i.e., first formylation of **22** with *t*-BuOK as the base and then without isolating the potassium enolate **26**, treatment with bromobutenolide **8**. The resulting mixture of diastereomers **5a** and **5b** was separated by column chromatography



Scheme 2.

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