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# Strategies for the synthesis of canonical, non-canonical and analogues of strigolactones, and evaluation of their parasitic weed germination activity

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**Abstract** Strigolactones (SLs) are natural products with promising applications as agrochemicals to prevent infestation with parasitic weeds due to their ability to trigger seed germination. However, their use is still limited because of the low yields in which they are isolated from natural sources. As such, numerous studies have led to strategies for obtaining them, and various structural analogues, by organic synthesis. These analogues have focused attention on the study of SLs, as some of them are easier to synthesize and possess enhanced properties, such as the level of bioactivity. This review provides an overview of the synthesis of SLs, subsequently focusing on the production of analogues with the canonical structure. The germinating activity of the compounds is also described herein, with positive effects on different species of the problematic genera *Striga*, *Orobanche* and *Phelipanche* having been found. The highly active analogue GR24 is currently the most widely studied in the literature, and relevant structural-activity relationships have been proposed as a result of the study of derivatives functionalized in different positions. Analogues based on other natural SLs such as strigol and orobanchol have also been developed, as have some novel canonical SLs derived from eudesmanolide or guaianolide sesquiterpene lactones. This review aims to provide useful information for the development of bioactive compounds applicable in new generation herbicides, in an attempt to employ similar compounds to those produced naturally in ecosystems that provoke effective herbicide effects at low concentrations.

**Keywords** Natural product chemistry · Organic synthesis · Strigolactones · Analogues · GR24 · Parasitic weeds

## Introduction

Strigolactones (SLs) are a family of natural products synthesized by some plant species from carotenoids (López-Ráez et al. 2008). They have been studied since the second half of the twentieth century as activities of agronomical and pharmacological (Carrillo et al. 2019) interest have been discovered. Based on the structure of the molecule, SLs can be classified into two types.

The first type is canonical SLs. These molecules have a fused tricyclic scaffold (ABC-rings) with a fourth ring (D-ring) bonded to the C-ring, via an enol ether bond (highlighted in red in Fig. 1). The C-ring

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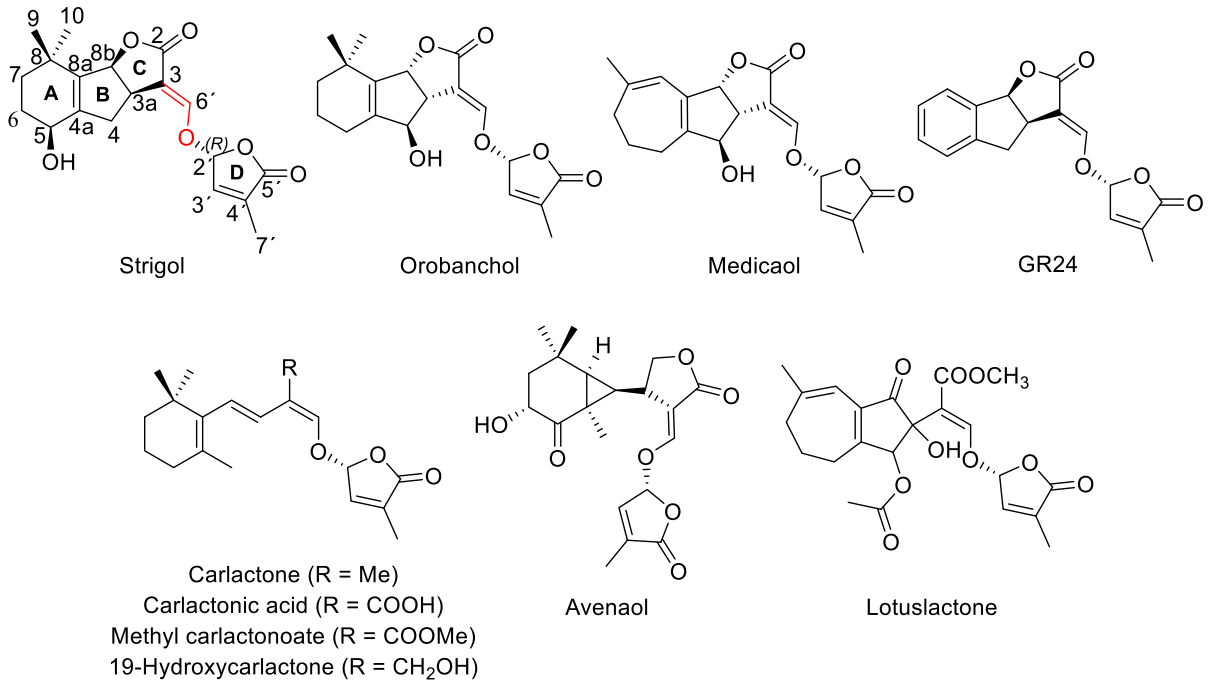



**Fig. 1** Examples of canonical (top) and non-canonical (bottom) SLs

must be a lactone and the D-ring a methyl furanone, whereas the AB-rings vary. Thus, this latter system can contain different functional groups and double bonds, and, in the case of the A-ring, different numbers of carbon atoms. To the best of our knowledge, a total of 23 canonical SLs have been identified and characterized to date, being 7β-hydroxy-5-deoxystrigol the most recent one (Yoneyama et al. 2018). As examples of the most representative, Fig. 1 shows the structures of strigol and orobanchol, together with medicaol and the synthetic GR24. One isomeric feature, namely the configuration of both 3a and 8b, which results in an upwards or backwards orientation of the C-ring, must be considered for canonical SLs. Indeed, some authors commonly classify SLs as being of the strigol or orobanchol type.

The second type comprises non-canonical SLs. The structure of these compounds is simpler than for their canonical counterparts, with carlactone being the most representative (Fig. 1). In comparison to canonical SLs, this second type lacks one or two rings of the ABC-system, or the fusion between them (see avenaol). The presence of a methyl furanone as the D-ring is mandatory.

Despite the structural differences between the two types, bioactivities of particular interest have been observed for both. This has been attributed to the maintenance of the D-ring in a conjugated system. One of the most relevant activities is stimulation of the germination of seeds of parasitic weeds, with SLs being considered, in terms of activity, as suitable phytochemicals for the control of several damaging species as part of the preventive strategy of suicidal germination. In addition, other agronomic applications are being studied for SLs, highlighting their use as biofertilizers to increase the colonization of crop roots with symbiotic arbuscular mycorrhizal fungi (AMF) (López-Ráez et al. 2017). The activity shown by the different structures of natural SLs on this kind of fungi, as well as on parasitic weeds, were recently reviewed by our research group (Soto-Cruz et al. 2021). Moreover, studies such as the conducted by Yoshimura et al. (2020) have proved certain benefits that the application of SLs could generate to crop plants. It particularly proved the effectiveness of some non-canonical SLs to accelerate the germination of corn seeds.

Nevertheless, the study and use of natural SLs in herbicides is limited to a large extent by the low yields

in which they are isolated from plant materials. Thus, some research groups have focused on their synthesis, providing routes involving many steps due to the complexity of their structures. One of the main handicaps is the selectivity of the reactions concerned as different chiral centers must be generated and activity is highly dependent on stereochemistry.

In order to simplify the production of canonical SLs, the design of more efficient routes that lead to simpler bioactive compounds have been published. This review will present an updated overview of the state of the art as regards the synthesis of canonical and non-canonical SLs, subsequently focusing on the synthesis of canonical SL analogues, which represent the most efficient strategy for obtaining canonical SLs on a multigram scale. The results from parasitic weed bioassays will also be presented from a structure–activity relationship perspective. All these points have been considered relevant to provide practical information for the commercial use of SLs that are the same as, or similar to, those produced naturally.

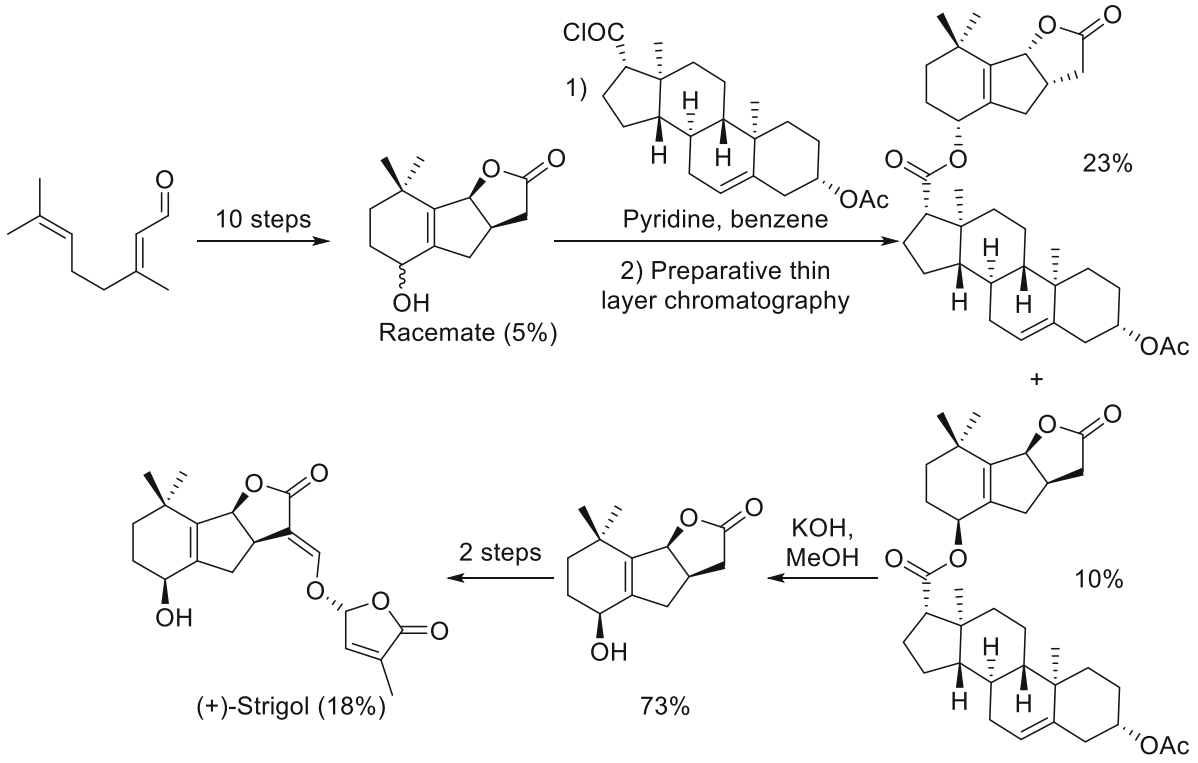
## Synthesis of natural canonical SLs

Several synthetic routes for natural strigolactones have been reported in the last few decades, with the access to single enantiomers and the implementation of scalable processes that allow gram-scale synthesis being a particular challenge for organic chemists. This is due to the high stereospecificity of the biological activity shown by SLs and the multiple chiral centers present in their structures. Almost all such strategies involve three key steps: synthesis of the ABC scaffold, functionalization of the A/B-ring, and attachment of the D-ring (Zwanenburg et al. 2016). The first syntheses of strigolactones required the separation of racemic mixtures by formation of the corresponding diastereomers and their purification by exhaustive chromatography. This process was improved with the development of chiral columns. However, in the last few years, the publication of enantioselective syntheses has increased in an effort to improve the maximum resolution yield of 50% obtained in this process. This progress can be exemplified with the case of strigol. The first synthetic approach to ( +)-strigol was reported in 1976 and involved the chiral auxiliary resolution shown in Scheme 1 (Heather et al. 1976).

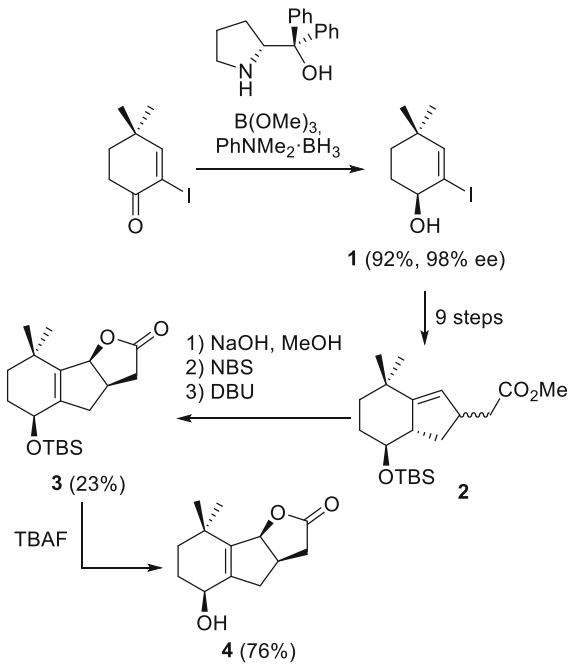
Subsequently, Samson et al. (1991) and Reizelman et al. (2000) employed chiral HPLC columns to isolate the single enantiomer of strigol. Hirayama and Mori (1999)reported the application of a chemoenzymatic method in the only gram-scale synthesis of canonical strigolactone reported to date. Finally, Takahashi et al. (2016) published the only enantioselective synthesis of the tricyclic core of ( +)-strigol reported to date (Scheme 2). Compound **1** was generated using a catalytic Corey–Bakshi–Shibata (CBS) reduction with excellent levels of enantiomeric excess. After a few steps, compound **2** was isolated in a reasonable yield, but with only moderate diastereoselectivity. The mixture of diastereomers was saponified, brominated and cyclized. Then, the bromine atom was eliminated to obtain **3** after a simple column chromatographic separation. As only the desired diastereomer was able to participate in the base-catalyzed elimination, compound **3** was obtained as a single stereoisomer. Removal of the protecting group gave the tricyclic core of ( +)-strigol.

The last step in strigolactone synthesis is commonly attachment of the D-ring. In the majority of cases this follows the same sequence, namely formylation of the ABC scaffold with (m)ethyl formate in the presence of an appropriate base and treatment of the enolate thus obtained with either chloro or bromo butenolide. A racemic D-ring is used and a mixture of two epimers is obtained in equal amounts. However, all strigolactones possess the *R*-configuration on this ring. To obtain the desired stereochemistry in the D-ring, Sugimoto et al. (1998) and Thuring et al. (1997a) employed a homochiral D-ring approach, although the subsequent retro-Diels–Alder reaction requires forcing conditions which may not be compatible with all target molecules. In addition, use of Trost's asymmetric allylic alkylation (Pd catalyzed) methodology to install the D-ring in a stereoselective manner has been described for the synthesis of strigolactones analogues (Bromhead et al. 2014) but, surprisingly, not for natural strigolactones.

The syntheses of natural strigolactones published prior to 2017 were reviewed by Bromhead and McErlean (2017) in that year. Subsequently, and to the best of our knowledge, only one enantioselective synthesis of (–)-solanacol has been published (Bromhead et al. 2018). In that article, authors synthesized (–)-solanacol using a dynamic kinetic resolution (DKR) in the stereo-defining step (Scheme 3). This synthesis

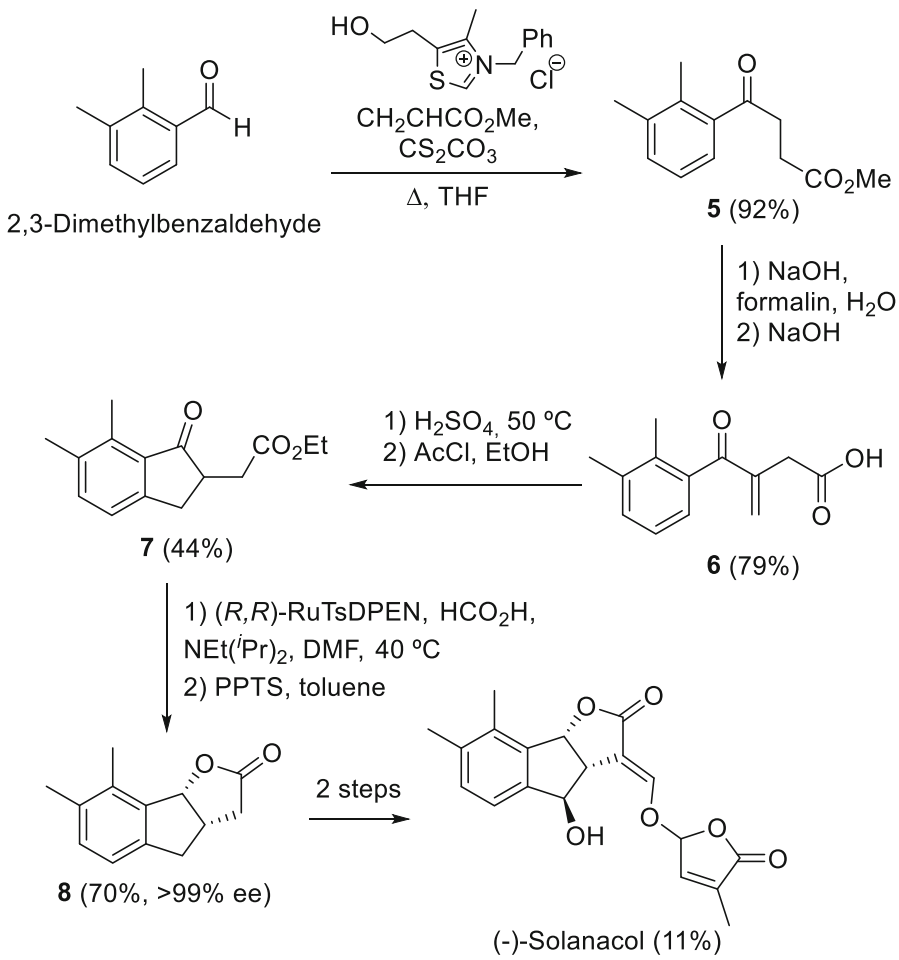



**Scheme 1** Heather's chiral auxiliary resolution strategy to isolate ( +)-strigol




**Scheme 2** Takahashi's enantioselective synthesis of the tricyclic core of ( +)-strigol (**4**)

starts with an intermolecular Stetter reaction between 2,3-dimethylbenzaldehyde and methyl acrylate to obtain the keto ester **5**. Aldol condensation of **5** with formalin and in situ saponification then leads to the formation of enone **6** in good overall yield. The next step is a Nazarov cyclization with sulfuric acid in a one-pot process to obtain the indanone **7**. The Nazarov reaction is used in different synthetic routes to form the cyclopentenone B or C ring of the target strigolactones (as will be seen throughout this review), so it is worth citing at this point the recent study by Nejrotti et al. (2020), in which this reaction was optimized through the use of natural deep eutectic solvents to provide alternative methods closer to the green chemistry principles. The tricyclic core of (–)-solanacol (**8**) is obtained by performing a Noyori asymmetric transfer hydrogenation with a DKR (Bromhead et al. 2018), thus providing excellent enantioselectivity (> 99% *ee*).




**Scheme 3** Bromhead's enantioselective synthesis of the tricyclic core of (−)-solanacol (**8**)

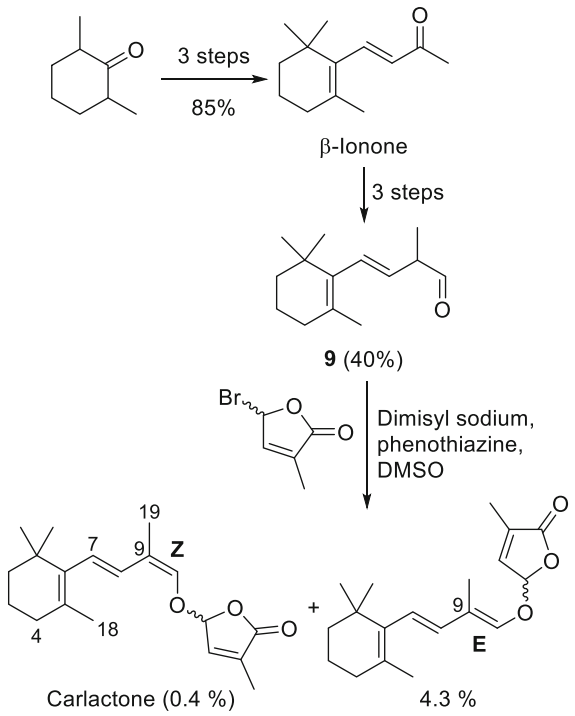
## Synthesis of non-canonical SL and analogues

The synthesis of a non-canonical strigolactone as a single enantiomer has not been reported to date. Carlactone and its analogues carlactonoic acid, methyl carlactonoate and 19-hydroxycarlactone (Fig. 1) were the first non-canonical SLs synthesized as racemates. As these SLs lack the B- and C-rings, steps to form the bicyclic and tricyclic scaffold are not necessary.

Carlactone is the most representative and, after it was first isolated in 2012 (Alder et al. 2012), Seto et al. (2014) published its synthesis using 2,6-dimethylcyclohexanone as starting material. This route can be divided into three parts (Scheme 4): functionalization of the ring (also including a conjugated side chain in substitution of the carbonyl group) to obtain β-ionone, the formation of an aldehyde at the end of the chain (product **9**), and introduction of the furanone ring. The two geometric isomers (*Z*/*E*) at C-9 of carlactone were obtained, but with a low yield for the last step (Scheme 5).

Mori et al. (2016) used the previous strategy to synthesize carlactonoic acid, methyl carlactonoate and 19-hydroxycarlactone (all functionalized at C-19). However, in the case of the former two, a later enantiomerically pure synthesis was published (four steps in 36% overall yield and three steps in 50% overall yield, respectively; Dieckmann et al. 2018). These syntheses are based on a Stille cross-coupling of a stannane of the A-ring precursor compound with **10** (this strategy will be detailed below for the synthesis of heliolactone; Scheme 6).

Two more hydroxylated analogues of carlactone were synthesized by Mori et al. (2016) by adapting the strategy shown in Scheme 4: at C-4, using α-ionone as starting material; and at C-18 using methyl 3,3-



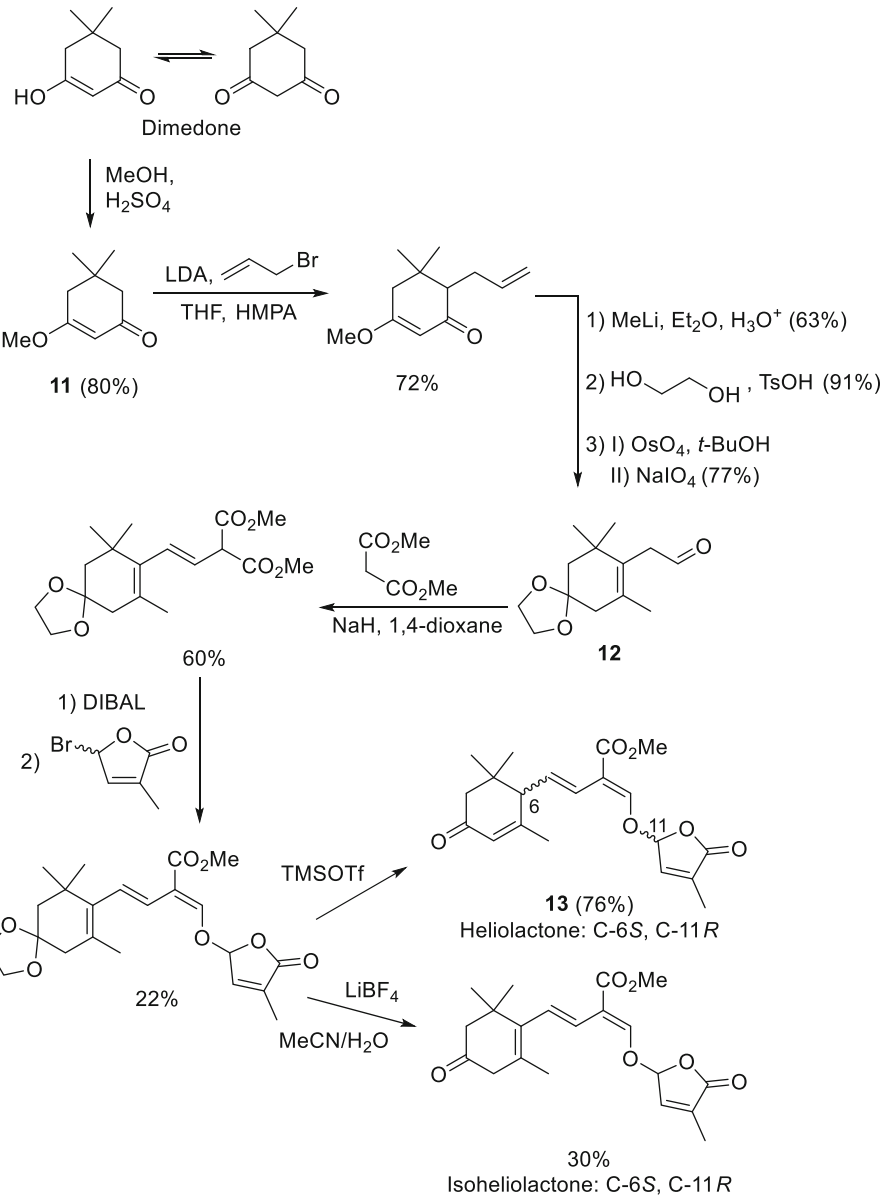

**Scheme 4** Synthesis of carlactone

dimethyl-2-oxocyclohexane-1-carboxylate as starting material. The yields for the furanone addition step were notoriously low, as mentioned previously for carlactone. These results highlight that the optimization or design of an alternative reaction would be a great opportunity to improve the synthesis of these products. Furthermore, the same study presented a set of new analogues synthesized in two steps (employing formyl Meldrum's acid as starting material), all of them with a distinctive ester at C-7. These analogies are therefore more closely related to canonical SL as the D-ring is connected via an enol ether bond. Different types of six-membered ring were used as the A-ring.

In the case of heliolactone, the recent synthetic procedure published by Yamamoto et al. (2020), which employs dimedone as starting material (Scheme 5), should be noted. The first intermediate (**11**) was obtained by the procedure of Yoshino et al. (2006), which is then allylated by reaction with LDA and allyl bromide. To introduce the butenolide ring, the new double bond must be oxidized to an aldehyde (**12**), which is then transformed into a diester by reaction with dimethyl malonate. These reactions require prior protection of the oxygenated function located at the ring. After butenolide addition, the final steps are deprotection and isomerization using a Lewis acid, with the best yield being obtained with TMSOTf. The product is a racemic and diastereomeric mixture of heliolactone (**13**), obtained in 2.6% overall yield. This yield could be significantly improved if the butenolide addition step was optimized, as its yield is much lower (22%) than those for the other steps (60–91%). If $LiBF_4$ is employed in the last step, the product obtained is the isomer isoheliolactone (1% overall yield) as migration of the double bond in the six-membered ring does not occur.

Alternative routes were recently reported by Yoshimura et al. (2019) (Scheme 6). The first steps are aimed at synthesizing a stannane (**14**) from 4-ketoisophorone, and the key step (route A in Scheme 6) is the subsequent Stille cross-coupling reaction with **10** and a palladium catalyst, which leads to selective formation of the C-11*R* epimers of isoheliolactone (**15**) and heliolactone (**16**) if **10** is used enantiomerically pure. This strategy was improved to selectively synthesize heliolactone (route B in Scheme 6) after the prior transformation of **14** into **17**, and subsequent HPLC purification using a chiral column. In the next steps, formation of the stannane of **17**, and subsequent Stille cross-coupling with **10** (both reactions including a Pd catalyst), leads to heliolactone. In addition, reaction of the pure (*S*) enantiomer of **14** with **10** also provided pure isoheliolactone. This study also afforded the C-12 methylated analogues of heliolactone and isoheliolactone. The stability of this methylated heliolactone was considered by the authors to be improved (in comparison with heliolactone) in acidic and mildly basic aqueous solutions, while the biological activities were retained. An alternative synthesis of **17** (and pure heliolactone) was published by Woo and McErlean (2019), which requires fewer steps and used ( ±)**18** as starting material. The first four steps allow addition of the iodine atom (oxidation of the carbonyl group to carboxylic acid, bonding to a phthalimide moiety, borylation and iodination), while the fifth step involves allylic oxidation to introduce the carbonyl group at the ring, thus resulting in **17**.

In a subsequent study, Yoshimura et al. (2020) treated the corresponding stannane (**20**, synthesized from **19** in good yield) with **10** to also obtain the non-canonical zealactone with selectivity at C-2′, although as a racemate at C-6 (Scheme 7). It should be noted that zealactone, also named methyl zealactonoate (Xie



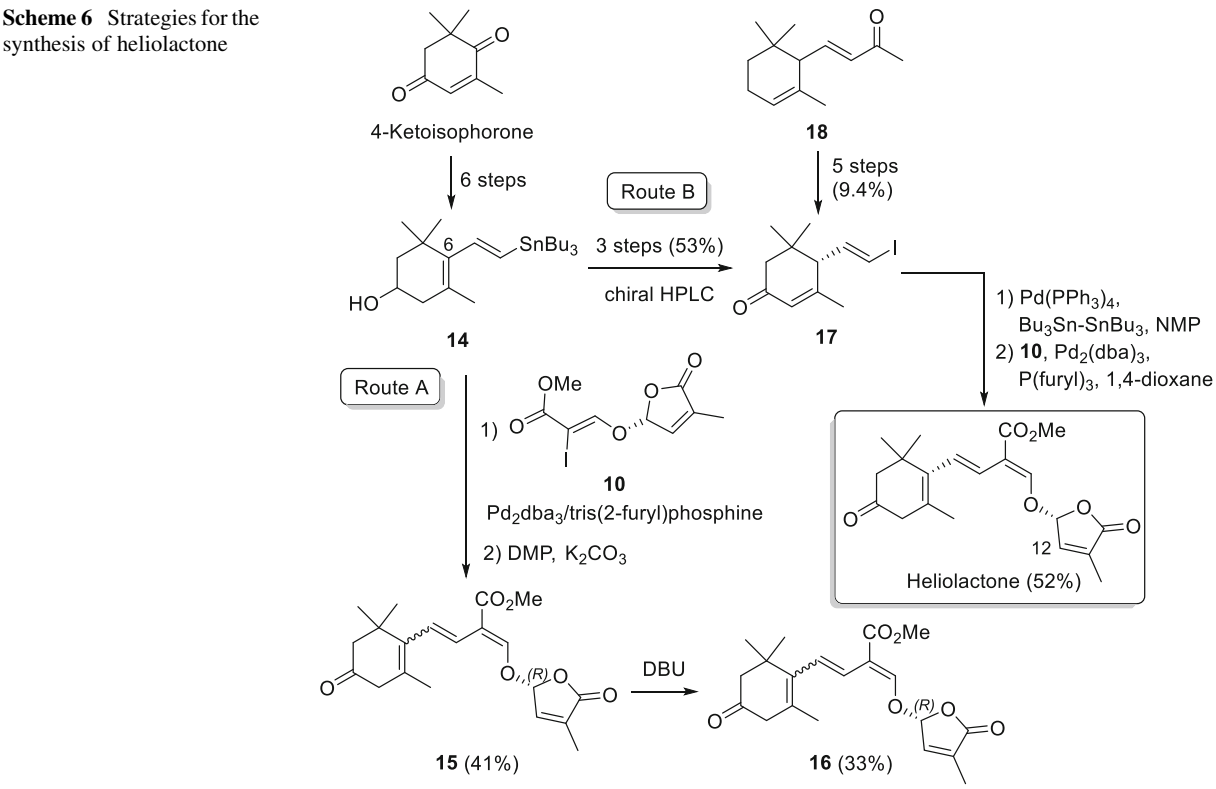

**Scheme 5** Synthesis of heliolactone (non-selective) and isoheliolactone

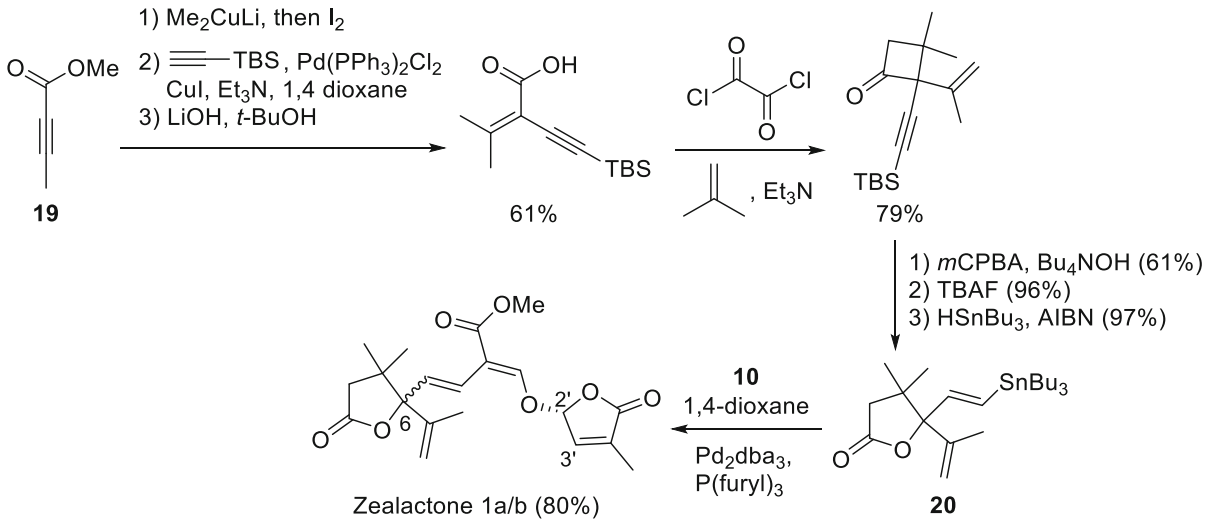
et al. 2017), is a natural product isolated from corn roots as a mixture of epimers at C-6, proving not to epimerize under the isolation conditions (Yoshimura et al. 2020). The overall yield of the route shown in Scheme 7 is 21%. Analogues methylated at C-2′ were also synthesized in this study.

With regard to the non-canonical SL avenaol (Fig. 1), a total synthesis of this compound has also been published (Scheme 8; Yasui et al. 2017). This synthesis is characterized by the complexity of forming the AB-ring system (11 steps from 2,2-dimethylpent-4-enal, with good and high yields for each step, always over 68%). This strategy paid particular attention to formation of the appropriate cyclopropane B-ring, which was achieved using the rhodium catalyst $Rh_2(OAc)_4$.

In addition to the natural non-canonical SLs, it is worth highlighting at this point other synthetic derivatives that simplify the canonical structures. That is, they lack their A- or B-rings, maintaining the

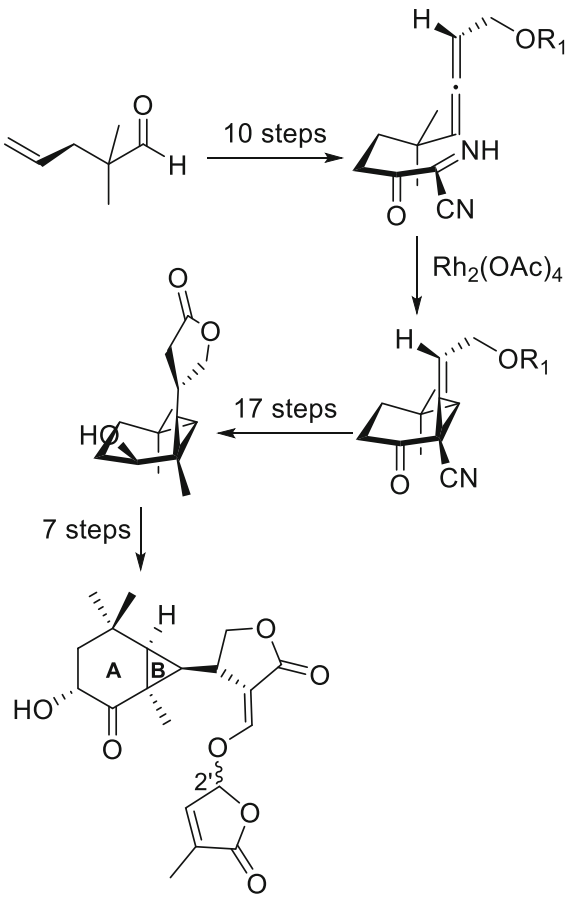
**Scheme 6** Strategies for the synthesis of heliolactone




**Scheme 7** Synthesis of zealactone as a mixture of epimers at C-6

moiety formed by the CD-rings and the enol ether bond. This moiety corresponds with the bioactiphore, the part that is primarily responsible for the bioactivity of the molecule (Zwanenburg et al. 2016). Some examples of bioactive compounds belonging to this type of derivatives (proven to be active as parasitic germination or branching arbuscular mycorrhizal fungi stimulators) are shown in Fig. 2 (Hýlová et al. 2019; Kondo et al. 2007; Lumbroso et al. 2016; Zwanenburg et al. 2016, 2009).




**Scheme 8** Total synthesis of avenaol (C-2′*R*)

With special emphasis, compounds MP1, MP3, MP13 and MP26 have shown promising results in the germination of the problematic parasitic weed *Striga hermonthica*, including in greenhouse and field trials through suicidal germination strategy (Jamil et al. 2019; Kountche et al. 2019). MP3 can be synthetized from methyl phenylacetate, and MP1 by nitrification of MP3 (Jamil et al. 2018), whereas MP13 could be obtained from 3-dimethylamino-2-methyl-2-propenal, and MP26 by reaction of MP13 with methyl (triphenylphosphoranylidene) acetate (Scheme 9; Jamil et al. 2019).

## Analogues of canonical strigolactones

The synthesis of SL analogues and mimics represents the most efficient method for obtaining compounds related to canonical SLs on a multigram scale. Among these synthetic compounds, those with optimal bioactivity, stability and solubility could be the best candidates for use as agrochemicals to prevent parasitic weeds. The following sections will present a brief summary of the synthesis of canonical SL analogues, focusing on the main characteristics, complexity and yield of the routes. In addition, the activity of compounds in germination bioassays (if carried out) will be discussed from a structure–activity perspective.

From a structural point of view, SL analogues are molecules which, in comparison to natural canonical SLs, present a lactone group as the C-ring and a methyl furanone as the D-ring, both linked via an enol ether bond. Analogues differ in terms of the presence of new structural features like alternative A- or B-rings, or functional groups.

Analogues are typically obtained by total or partial synthesis, using accessible molecules as starting material (usually commercially obtained, but also isolated from natural sources). In comparison to total synthesis strategies, partial synthesis allows the process to start with molecules related to the structure of the target compounds, thereby significantly reducing the number of steps. This point is highly important, as the majority of synthetic routes are focused on construction of the tricyclic scaffold (ABC-rings) of SLs. As intermediate compounds in the synthesis usually present different chiral or reaction centers, analogue synthesis is usually non-selective. This can be interpreted in two ways: positive, as analogues with alternative isomeric features can be obtained; or negative, as lower yields are obtained for the synthesis of a single analogue. C-2′ is a common chiral center in all SLs and analogues, and it must be noted that the study of its configuration requires experiments other than NMR spectroscopy, namely circular dichroism and computational calculations.

### GR24 family

The most widely studied SL analogue, known as GR24, was first synthesized and evaluated in a bioassay by Johnson et al. (1981). Since then, this phenolic analogue has been the subject of numerous studies due to its bioactivities in the fields of medicine (for example, GR24 was recently proposed as promising drug to control Alzheimer's disease; Kurt et al. 2020) or agriculture (as a herbicide). Eliciting the

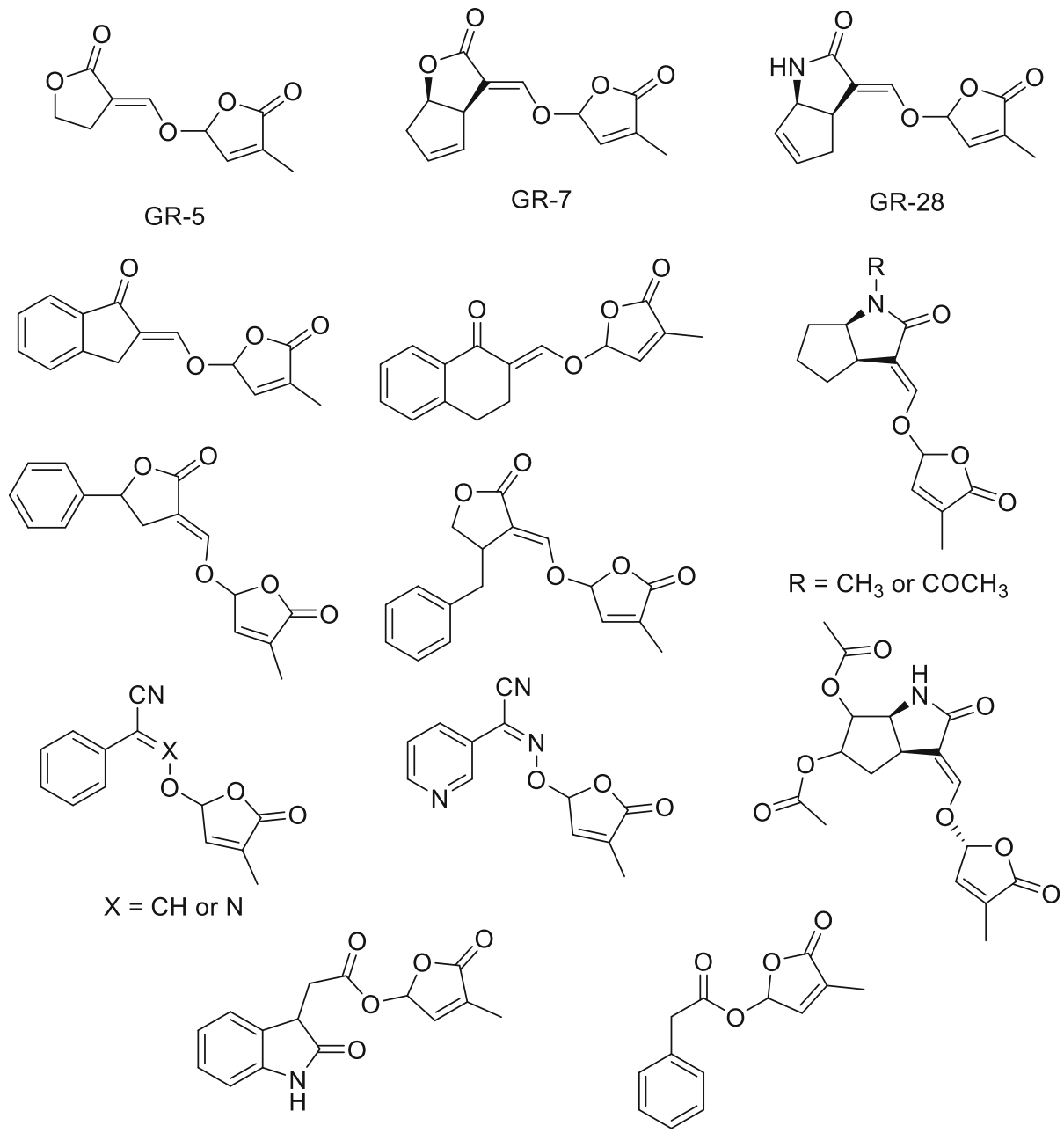
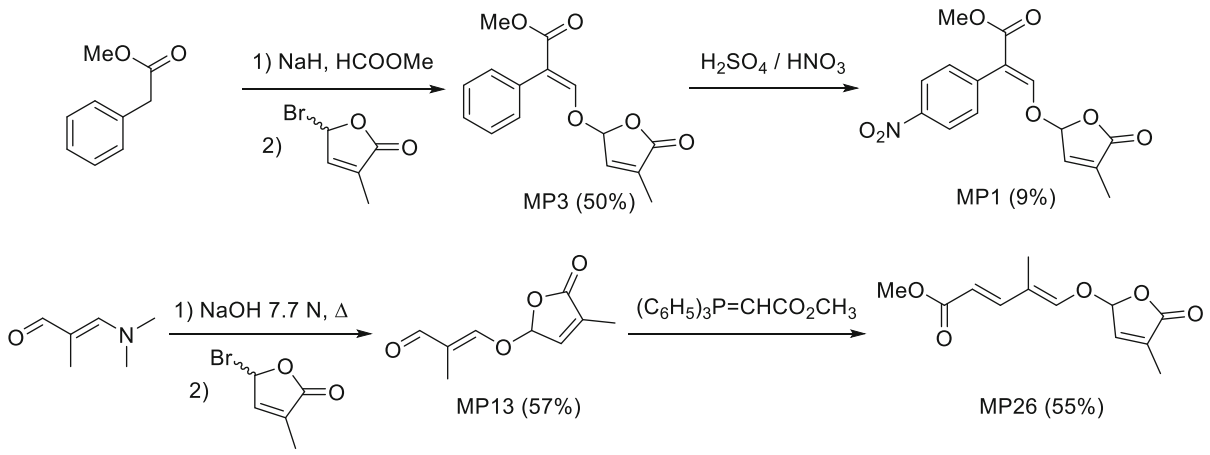



**Fig. 2** Examples of synthetic bioactive compounds based on simplified structures of SLs

germination of parasitic weed seeds is one of the most widely studied applications, thus making it a promising herbicide for the preventive strategy of suicidal germination. In fact, GR24 is commonly used, as a C-2′ racemate, in germination bioassays as standard positive control, due to its ability to germinate different species of the problematic genera *Striga*, *Orobanche* and *Phelipanche*.

Malik et al. (2010) reported that all synthetic routes published until 2010 employed the commercial bycyclic compound indan-1-one as starting material. The synthetic route to this compound was optimized to four steps, with an overall yield of 44% (route A in




**Scheme 9** Synthesis of bioactive compounds of the MP family

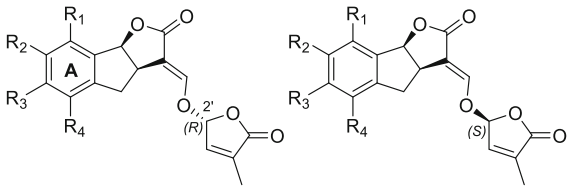
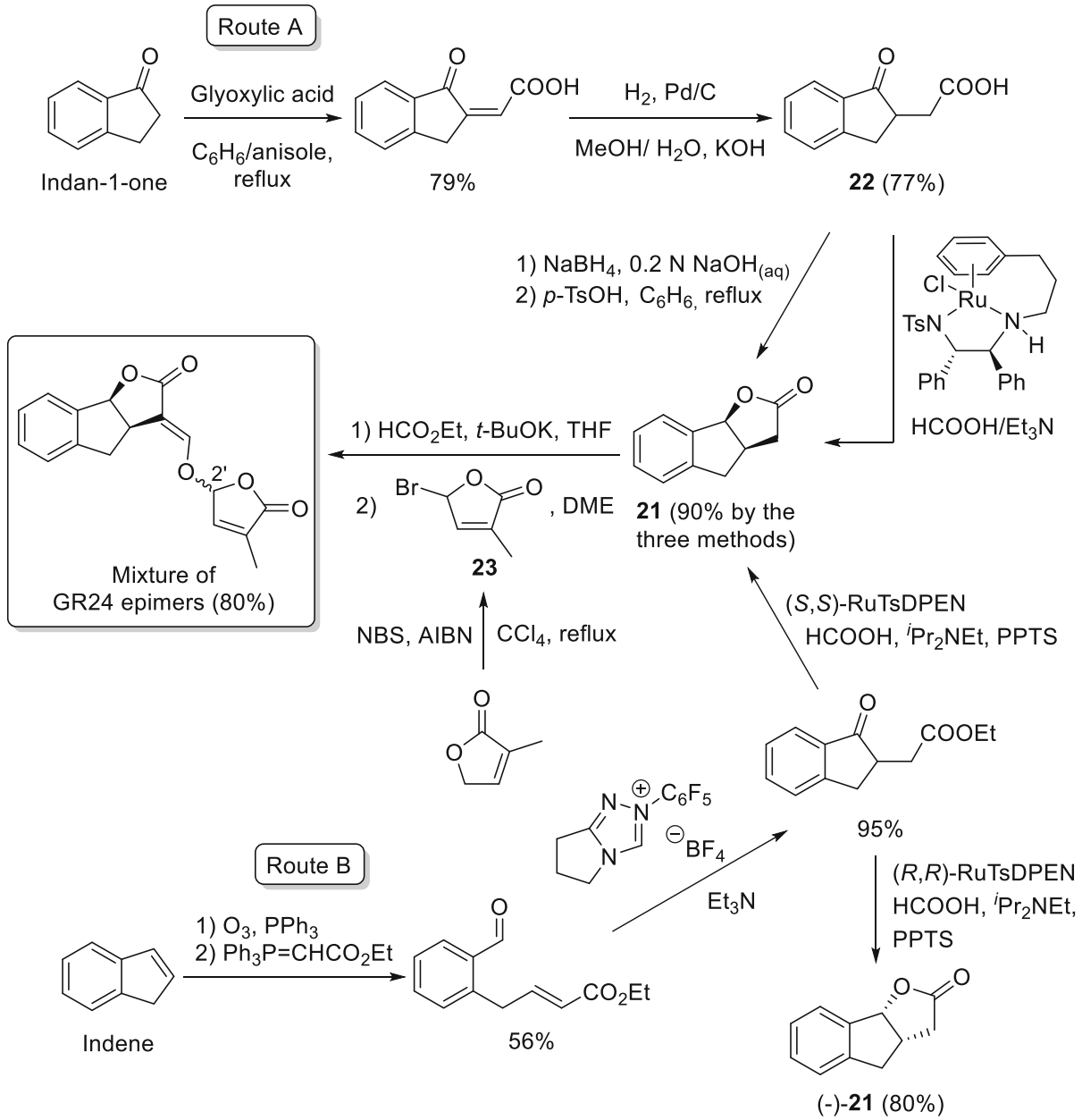



**Fig. 3** GR24 analogues methylated at the A-ring

Scheme 10), in which the first three steps concern enantioselective formation of the tricyclic scaffold (**21**) (Wigchert et al. 1999; Malik et al. 2010). The first step introduces a carboxylic acid group into an exocyclic position of the indanone, with the double bond being reduced in the second step to obtain **22**. The third step involves the use of $NaBH_4$ to reduce the carbonyl group to an alcohol, followed by treatment of the crude product with acid to form a new lactone group, thus giving the tricyclic molecule **21**. Efforts to optimize the synthesis of GR24 in the literature have focused on the efficient construction of this intermediate. Indeed, synthesis of this lactone accounts for most of the steps in the synthetic routes developed to obtain any analogue. One recent example is the attempt by Xiong et al. 2019 to simplify the last step to obtain **21**. This compound was synthesized in 90% yield by treating **22** with a Ru(II) catalyst (Scheme 10) in the presence of the azeotropic mixture HCOOH/$Et_3N$ as hydrogen source and solvent. The main benefit arising from use of this catalyst is its possible application with different substrates, as subsequently confirmed by authors by the high yield synthesis of the tricyclic scaffold using different derivatives of intermediate **22** (characterized by a halogen atom in the A-ring, or containing a cyclohexane or cycloheptane as the B-ring, amongst others). Once **21** has been obtained, the common final step is an initial formylation under basic conditions to form an enolate, which subsequently acts as a nucleophile in a nucleophilic substitution reaction with compound **23** (a brominated or chlorinated butenolide ring) to form the strigolactone-type product GR24. Pospíšil (2021) recently published some procedures for the attachment of **23** to phenols or carboxylic acids, which could be useful for the development of new SL analogues or mimics.

Reagent **23** is unstable and must be synthesized immediately prior to use. It can be easily obtained in a radical-substitution reaction catalyzed by AIBN, although **23** can also be synthesized via more complex routes requiring up to six steps (Mangnus et al. 1992).

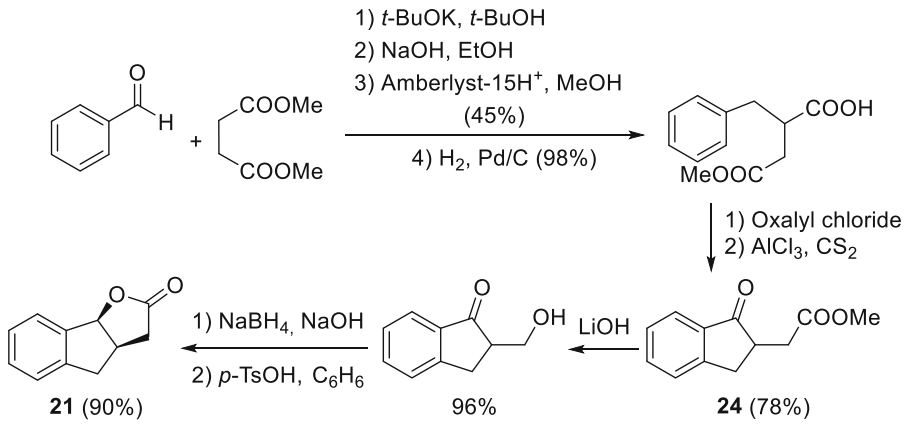
An alternative route to synthesize **21** was published in 2014 (route B in Scheme 10; Bromhead et al. 2014). This synthesis is based on opening of the cyclopentane ring in the indene (starting material) to form an aldehyde, which forms the carbonyl group after subsequent cyclization. The selective formation of **21** (> 99% after recrystallization) was accomplished using Noyori's (*S*,*S*)-RuTsDPEN catalyst in the next step. Similarly, if the (*R*,*R*)- RuTsDPEN catalyst is used, (–)-**21** is generated, thus allowing isolation of the corresponding (–)-GR-24 isomers after addition of the D-ring (**23**).




**Scheme 10** Synthesis of GR24 (C-2′*R*) from indan-1-one (route A) and indene (route B)

Another relevant route to synthesize **21** (Malik et al. 2010), which differs in the use of benzaldehyde as starting material, is shown in Scheme 11. This preparation starts with a Stobbe condensation of benzaldehyde with dimethyl succinate to obtain an ester intermediate, which forms the bicyclic product **24** after hydrogenation and a Friedel–Crafts transposition with oxalyl choride. Finally, the tricyclic scaffold is obtained by saponification of **24** with LiOH and subsequent reduction and acid-catalyzed lactonization reactions.

The overall yield is 30%, which is lower than that achieved following the routes shown in Scheme 10 (55% for route A, and 48% for route B) due to the 45% yield of the Stobbe condensation step. Despite this decrease in overall yield, one advantage of the route



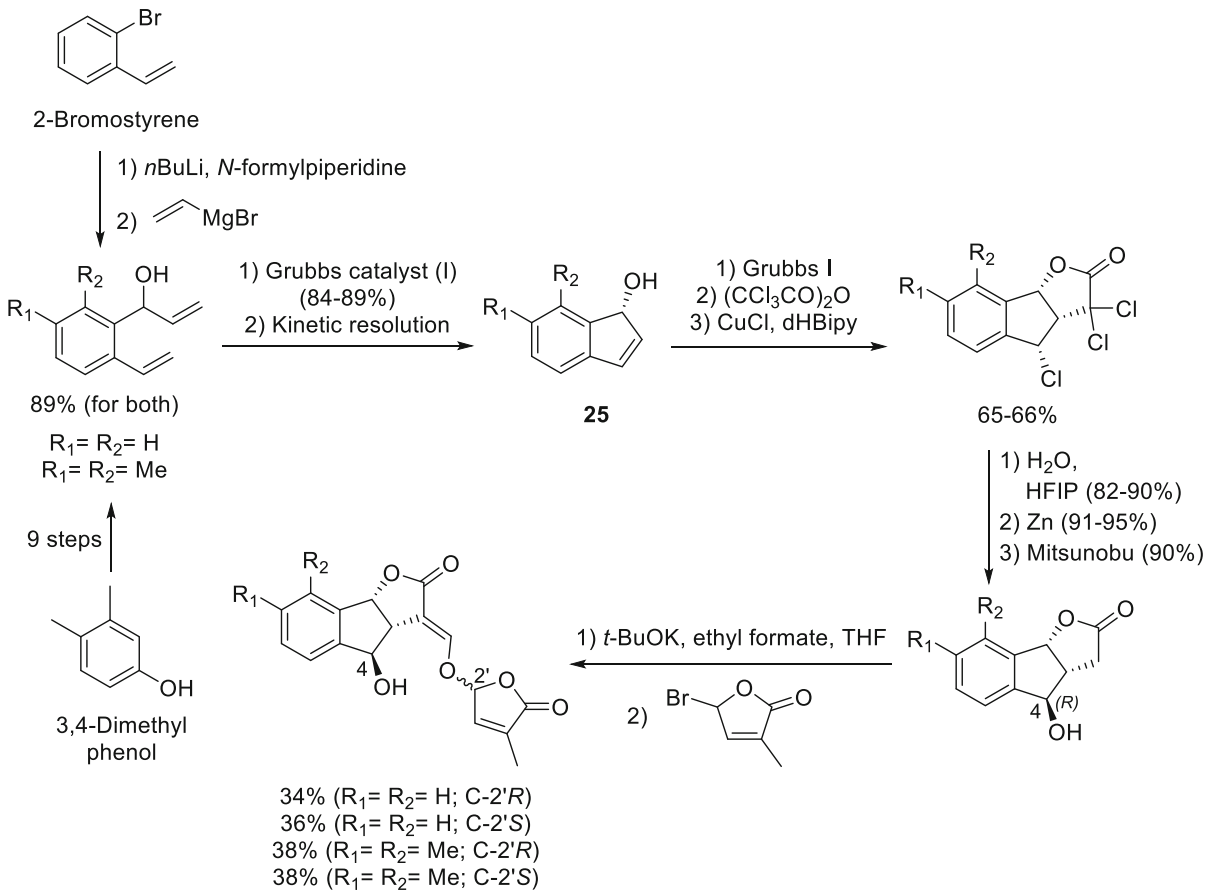

**Scheme 11** Synthesis of the GR24 scaffold (**21**) from benzaldehyde

depicted in Scheme 11 is the possibility to obtain new GR24 analogues differing in the A-ring (Fig. 2) when methylated benzaldehyde derivatives are used as starting material (Malik et al. 2010). Epimeric compounds at C-2′ were also obtained, and the evaluation of all these compounds in bioassays allowed the influence of the C-2′ configuration on the activity to be evaluated. Thus, all analogues germinated *S. hermonthica*, with maximum germination percentages of around 60% at the highest concentration tested ($3.3{\cdot}10^{-5}$ M). It could therefore be concluded that the configuration C-2′*R*, similar to that of natural SL, is better than C-2′*S* as regards obtaining higher levels of activity. This preference has been observed in different studies. With regard to substituents at the A-ring, the presence of H atoms or methyl groups did not have a marked influence on the activity.

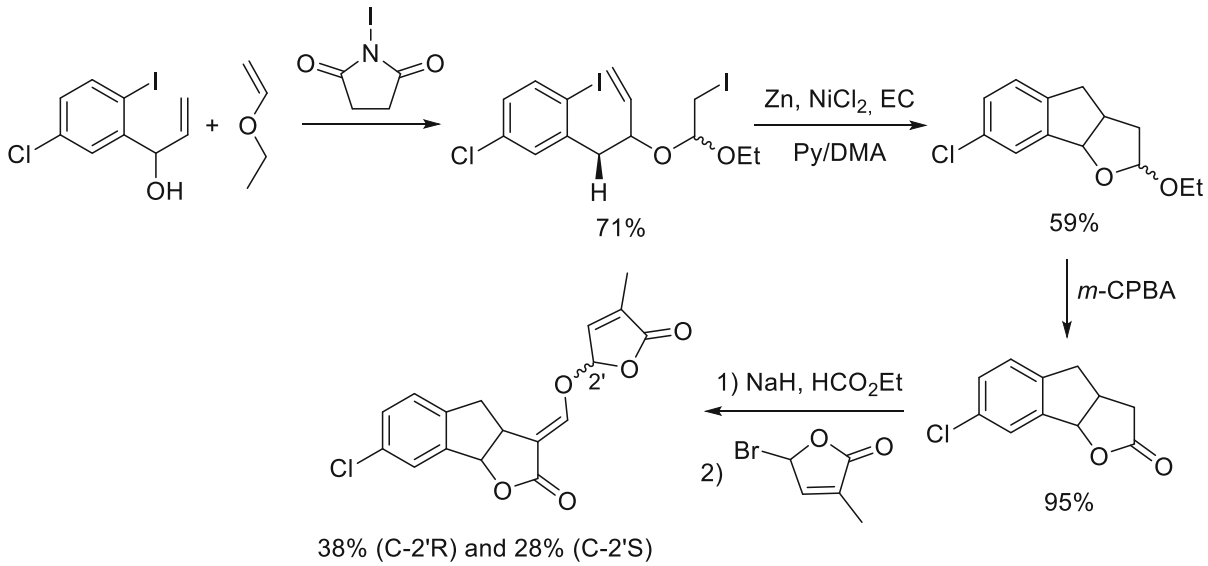
The synthesis of GR24 derivatives methylated at the A-ring is also feasible using the strategy of Chen et al. (2013) (Scheme 12), which also allows different substituents (OH, F or OAcyl) to be introduced at C-4. Moreover, enantiomerically pure analogues (including GR24) can be obtained as a kinetic resolution is applied. The starting material is commercial 2-bromostyrene, or 3,4-dimethylphenol for methylated analogues. Both compounds form the corresponding bicyclic intermediate **25** via a two- or nine-step route that concludes with a ring-closing metathesis (RCM) using the Grubbs ruthenium catalyst I. After enzymatic kinetic resolution (using *Candida antarctica* lipase), the tricylic scaffold is obtained in three steps: RCM, trichloroacetylation and atom-transfer radical cyclization with copper(I) coordinated to dHbipy. Prior to butenolide ring addition, the hydroxyl group is incorporated at C-4 by nucleophilic substitution (an additional Mitsunobu reaction is required to invert the configuration of C-4*S* products), and dechlorination of the C-ring with Zn is then carried out.

Xiao et al. (2017) published a strategy to obtain the GR24 scaffold (**21**) by nickel-promoted reductive cyclization of the acetal of *o*-iodophenyl allyl alcohol. This reaction was also used to obtain GR24 analogues chlorinated at the A-ring, as shown in Scheme 13. The vinyl alcohol reacts initially with ethyl vinyl ether and NIS (or NBS) to form the acetal, which is transformed into the tricyclic intermediate by nickel-promoted reductive cyclization and subsequent oxidation with *m*-CPBA. This strategy appears to be suitable for obtaining new analogues with new functionalities at the A-ring as synthetic derivatives of *o*-iodobenzaldehyde can be employed as starting material.

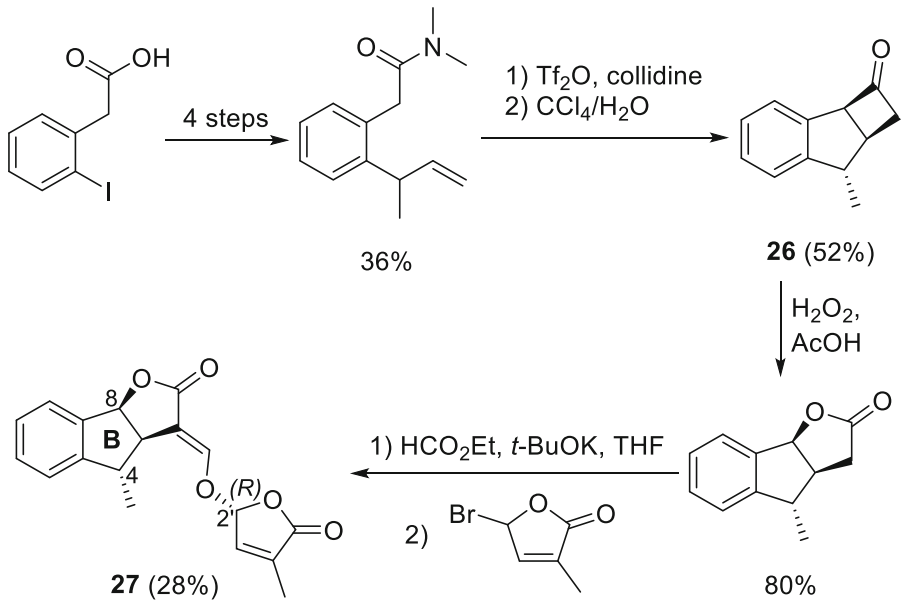
Lachia et al. (2014b) published several strategies for synthesizing up to thirteen GR24 analogues with different substituents at the B-ring. These were then tested on *O. cumana* seeds, and those with an C-2′*R* configuration were found to be more active than their respective C-2′*S* epimers, especially at lower doses (a C-2′*R* analogue can show 79% of activity, with no effects for the C-2′*S* epimer). This structure–activity relationship coincides with that previously mentioned for *S. hermonthica*. Some of the analogues reported contain a methyl group at C-4 (and therefore more similar to natural SL) or C-8. The starting material for their synthesis is 2-iodophenyl acid, and intramolecular [2 + 2] cycloaddition is used to form the first tricyclic system (**26**), which is




**Scheme 12** Synthesis of enantiomerically pure GR24 analogues (HFIP = hexafluoroisopropanol)



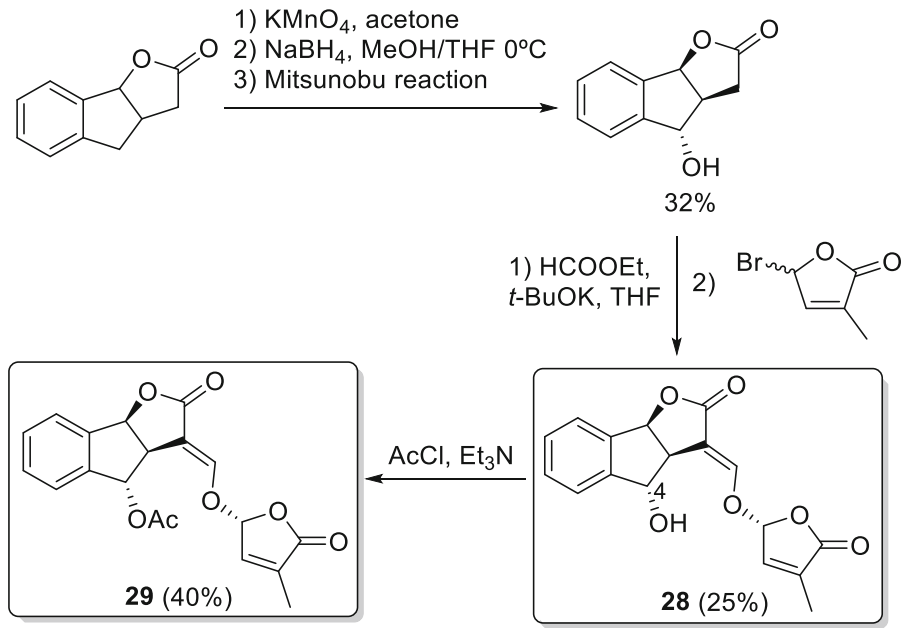

**Scheme 13** Synthesis of chlorinated GR24




**Scheme 14** Synthesis of a GR24 analogue methylated at C-4 (**27**)

transformed into the scaffold related to **21** via a subsequent Baeyer–Villiger oxidation catalyzed by $H_2O_2$. As an example, Scheme 14 shows the synthesis of analogue **27** (overall yield of 4.2%).

In light of the bioactivity with respect to *O. cumana*, the most promising analogues reported by Lachia et al. (2014b) included oxygenated groups at C-4 (hydroxy, methoxy, acetate or -OTBS), with the presence thereof increasing the germinating activity of the molecules by up to 20% in comparison to analogues methylated at C-4 or with no such substituent (GR24). The most active ones, with activities

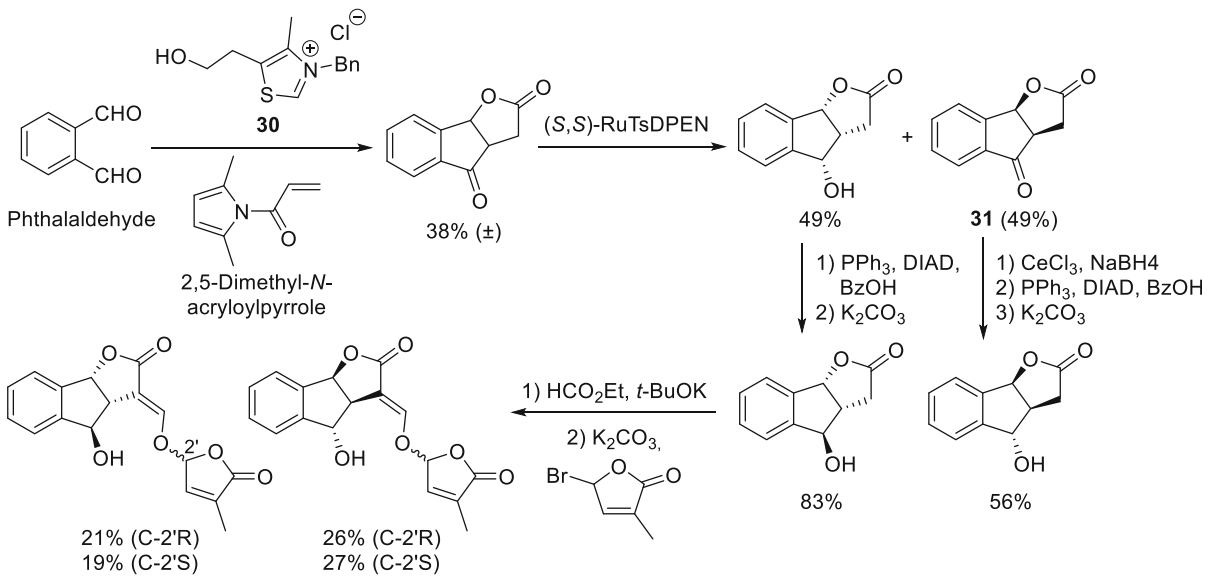



**Scheme 15** Synthesis of highly active oxygenated GR24 analogues

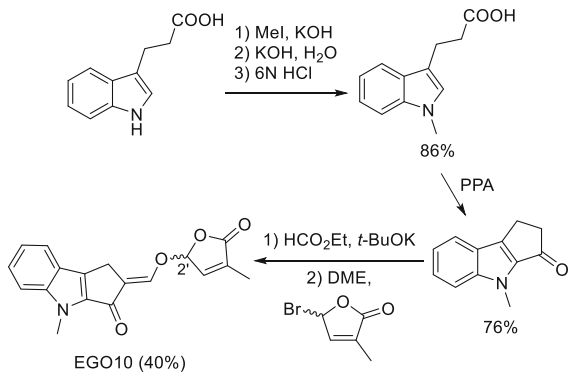
of 76–79% at the lowest dose tested (0.001 mg·l$^{-1}$), are shown in Scheme 15, together with the route for their synthesis from the tricyclic system. Given that this tricyclic intermediate can be synthesized in 55% yield following route A in Scheme 10, the global yield for synthesis of **28** is 4.4% (1.8% in the case of **29**). In a subsequent study, **28** showed activity in the germination of *S. hermonthica* (but only limited activity for *Striga gesnerioides*), and was found to be more active than the GR24 analogue epimer at C-4 (Ueno et al. 2015). Similarly, the study by Malik et al. (2011) presents the synthesis of similar analogues hydroxylated or acetylated at C-4, as well as others containing a ketone group. These analogues showed that hydroxylated analogues present higher activity when the hydroxyl group has a *trans* orientation with the C-ring, as is the case for product **27**. The high activity levels achieved by the analogues evaluated in this study for *O. ramosa* seeds, especially the acetyl and ketone derivatives with percentages of 60–100% in the range 0.033–3.3·10$^{-5}$ μM, should be noted.

Since more active analogues than GR24 could be synthesized, Morris and McErlean (2016) focused on optimization of the synthesis of 4-hydroxy-GR24 (**28**) in an effort to reduce the number of steps and avoid the formation of undesired stereoisomers. This study led to the route depicted in Scheme 16. The first step is perhaps the most innovative improvement as the tricyclic scaffold is obtained from a single reaction between phthalaldehyde, **30** and 2,5-dimethyl-*N*-acryloylpyrrole. As the 38% overall yield is the main disadvantage of this reaction, the search for more efficient conditions would represent a great achievement. The next step is formation of the hydroxyl group at the B-ring by hydrogenation in the presence of Noyori's (*S*,*S*)-RuTsDPEN catalyst. This step is also significant for resolving the racemate, as only the (−)-ketone stereoisomer is transformed. This is the key to obtaining up to four analogues in the final step. The unreacted (+)-ketone (**31**) is reduced to the alcohol via a Luche hydrogenation (using $CeCl_3$ and $NaBH_4$). Once the hydroxyl group is present in the target orientation (by Mitsunobu inversion with benzoic acid and subsequent hydrolysis with $K_2CO_3$), the butenolide is added as usual.

At this point it is interesting to mention some of the compounds in the so-called EGO family, the scaffold of which is related to that of GR24 and characterized by the presence of a tertiary amine at C-4 and no oxygen atom in the C-ring. Of these, EGO10 is the simplest as well as the most similar to GR24. This compound can be synthesized from commercial 3-(indol-3-yl)propanoic acid, in 26% overall yield, following a three-step strategy (Scheme 17; Prandi et al. 2011). Use of this molecule simplifies the route as it is a bicyclic compound with a carboxylic acid function, and therefore a precursor of the C-ring (formed by cyclization with polyphosphoric acid). In



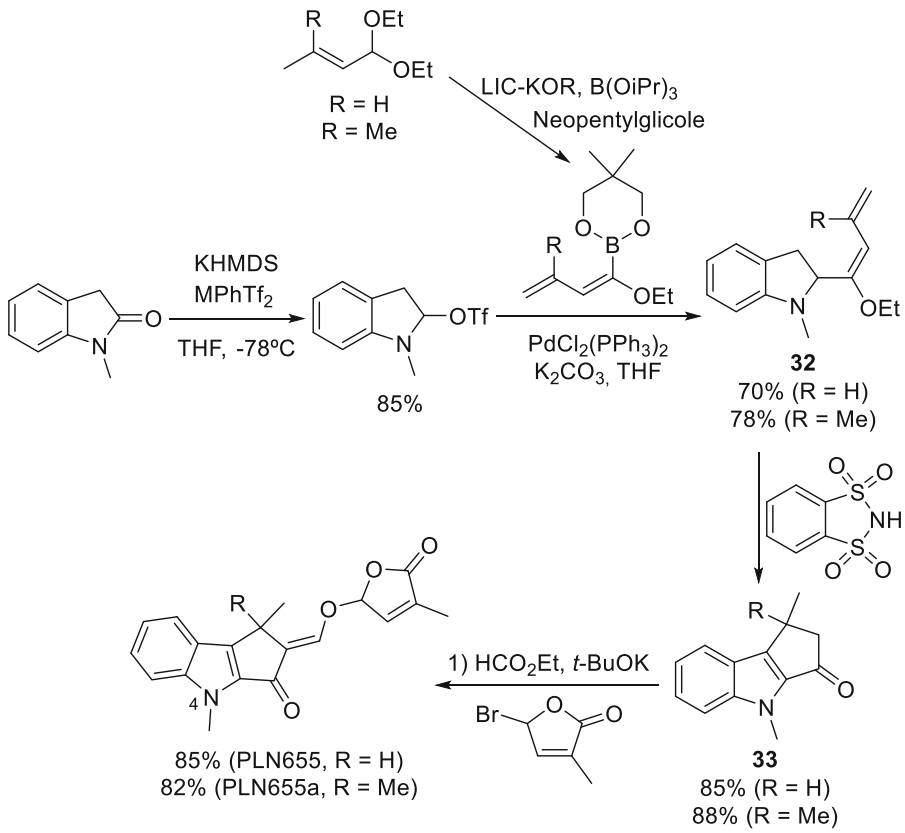

**Scheme 16** Improved synthesis of hydroxylated GR24 analogues



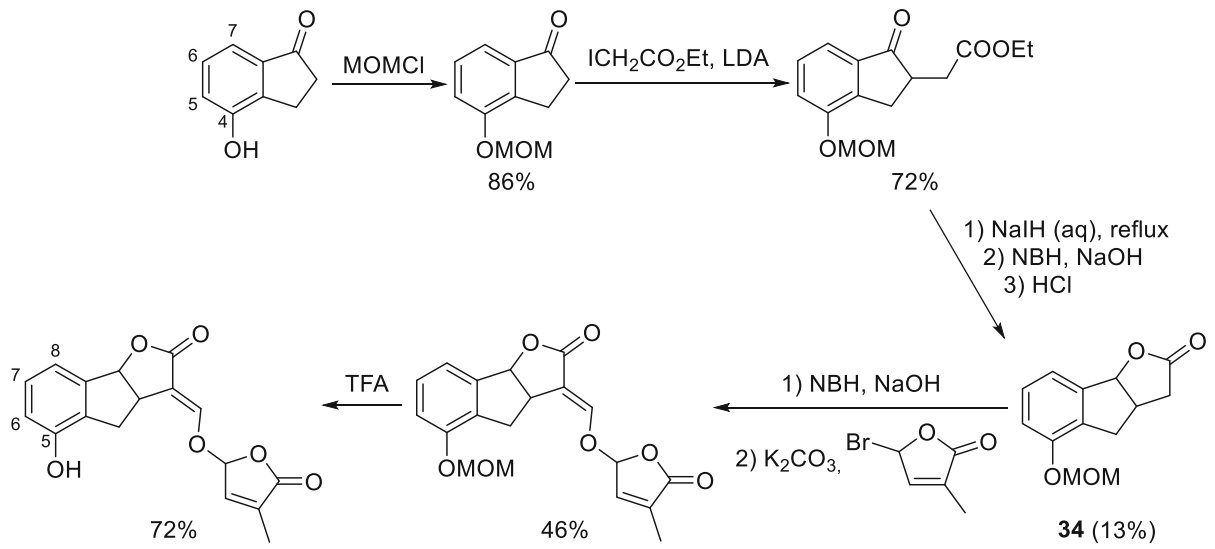

**Scheme 17** Synthesis of EGO10

bioassays, EGO10 induced the germination of *P. aegyptiaca* with high germination percentages (always up to 85%) in the range of 10–0.1 μM (Sanchez et al. 2018). A comparison of activity levels with GR24 showed that similar maximum response values were obtained, although the $EC_{50}$ is higher for EGO10 (Cohen et al. 2013). The study of Artuso et al. (2015) showed that the C-2′*R* configuration improves the activity of EGO10 for the germination of *P. aegyptiaca* to some extent, as occurs with the non-nitrogen-containing GR24 analogues.

Bhattacharya et al. (2009) previously reported two routes to obtain EGO derivatives methylated at the C-ring, which belong to the so-called ST series. The route with the best yield is shown in Scheme 18. The starting material is commercial 1-methylindolin-2-one, the ketone group of which is first transformed into an enol triflate. A subsequent Suzuki coupling with a dienyl boronate (previously synthesized from an α,β-unsaturated diethyl acetal) leads to the intermediate compounds (**32**), which undergo a Nazarov cyclization (catalyzed by the Brønsted acid *o*-benzenedisulfonimide) to form the triclyclic scaffold (**33**). After butenolide ring addition, the two analogues PLN655 and PLN655a were obtained in 43% and 48% overall yield respectively. The former, together with its non-nitrogen-containing derivative PLC655, which was also synthesized, were tested on *O. aegyptiaca* as




**Scheme 18** Synthesis of the ST analogues PLN655 and PLN655a



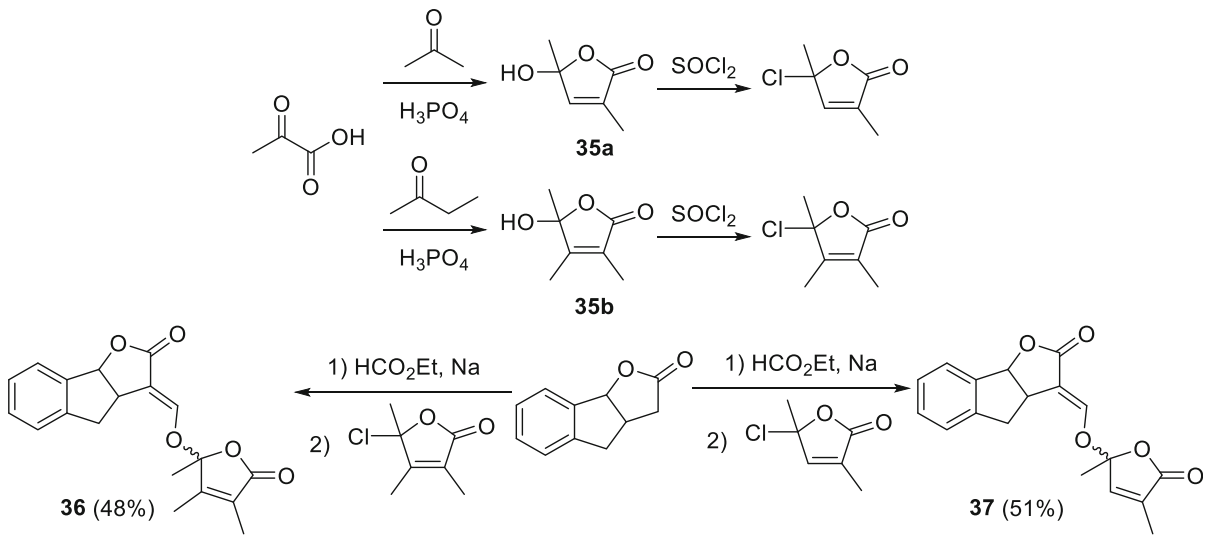

**Scheme 19** Synthesis of GR24 analogues with a hydroxyl group on the A-ring

racemates and their activity levels found to be higher than those for GR24: both were highly active at $10^{-4}$ and $10^{-6}$ M, with percentages of around 80–90%, and PLN655 retained this level down to $10^{-8}$ M.

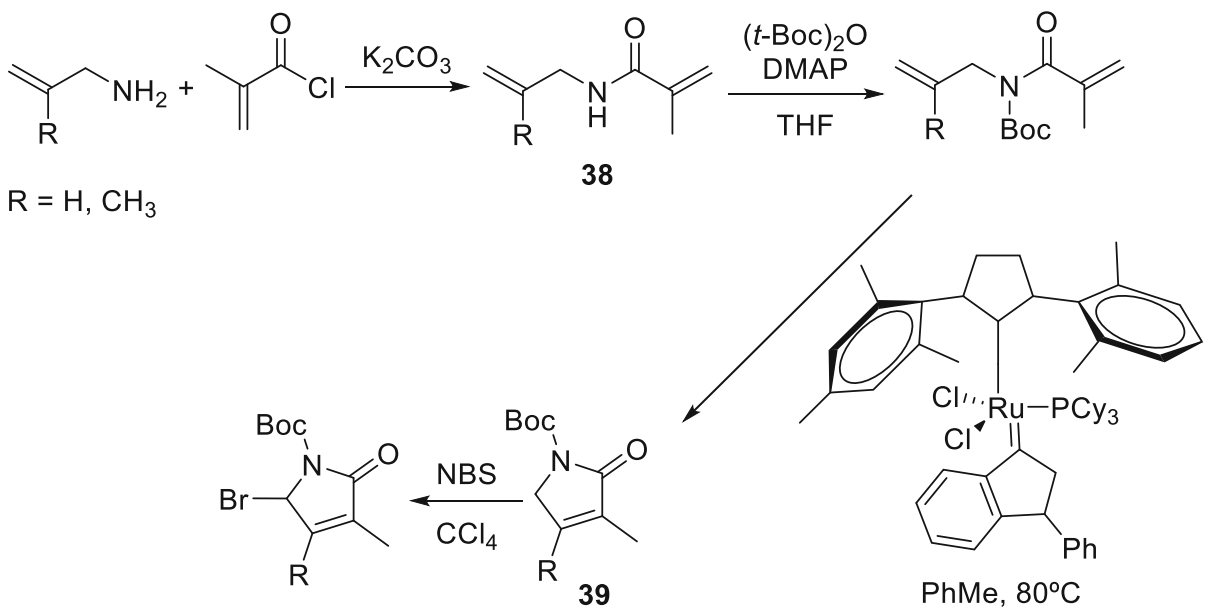
Ueno et al. (2015) synthesized the GR24 analogues monohydroxylated at each aromatic position of the A-ring (C-5, C-6, C-7 or C-8; Scheme 19). The starting materials in this case were four hydroxylated indan-1-one derivatives isolated from root exudates of hydroponically grown *Sorghum bicolor*. The synthesis of one of them is shown in Scheme 19 as an example. The synthesis starts with protection of the hydroxyl group by formation of an MOM ether. The yield for formation of the tricyclic scaffold (**34**) was much lower (13%) than for the other steps in this route (19%, 20% and 29% for the other starting materials), therefore optimization of these reactions could provide high-yielding synthetic routes. Analogues with similar and different isomeric features (C-ring geometry and C-2′ orientation) to GR24 were also obtained and evaluated in a bioassay. All analogues were active on *S. hermonthica* seeds, especially those with similar isomeric features to GR24, and analogues hydroxylated at C-7 and C-8 were significantly more active. With *Striga gesnerioides* seeds, only some analogues with a different C-ring geometry contrary to GR24 were active (below 20% at 10 or 0.1 μM), and the position of the hydroxyl group on the A-ring was not considered relevant.

With regard to modifications on the D-ring, Mwakaboko and Zwanenburg (2016) focused on the introduction of methyl groups. The key to their success was the preparation of chlorobutenolides as precursors for the D-ring (instead of the brominated butenolide **23**; Scheme 20). This was carried out by condensation of pyruvic acid with acetone or 2-butanone to synthesize hydroxylated butenolides (**35**), and subsequent chlorination with $SOCl_2$. The final SL analogues (**36** and **37**) were tested on *S. hermonthica* and *O. cernua* seeds as racemates, with moderate activity being observed. Although these findings appeared to indicate a loss of activity when methyl groups are included in the D-ring, the authors state that firm conclusions can only be obtained after the evaluation of pure epimers.

Lombardi et al. (2017) also synthesized new alternative D-rings for subsequent introduction into **1**. The main aim of this study was to replace the butenolide with γ-lactams, thus forming GR24 derivatives containing this type of ring. The synthesis of brominated lactam rings (Scheme 21) starts with a condensation of allylamine or 2-methylallylamine (the latter to synthesize strigolactones containing a methylated D-ring) with methacryloyl chloride under basic conditions. The product (**38**) is an amide that must first be protected with $Boc_2O$ before subsequent cyclization catalyzed by the ruthenium catalyst catMETium-RF1. The resulting lactam (**39**) is then brominated with NBS.



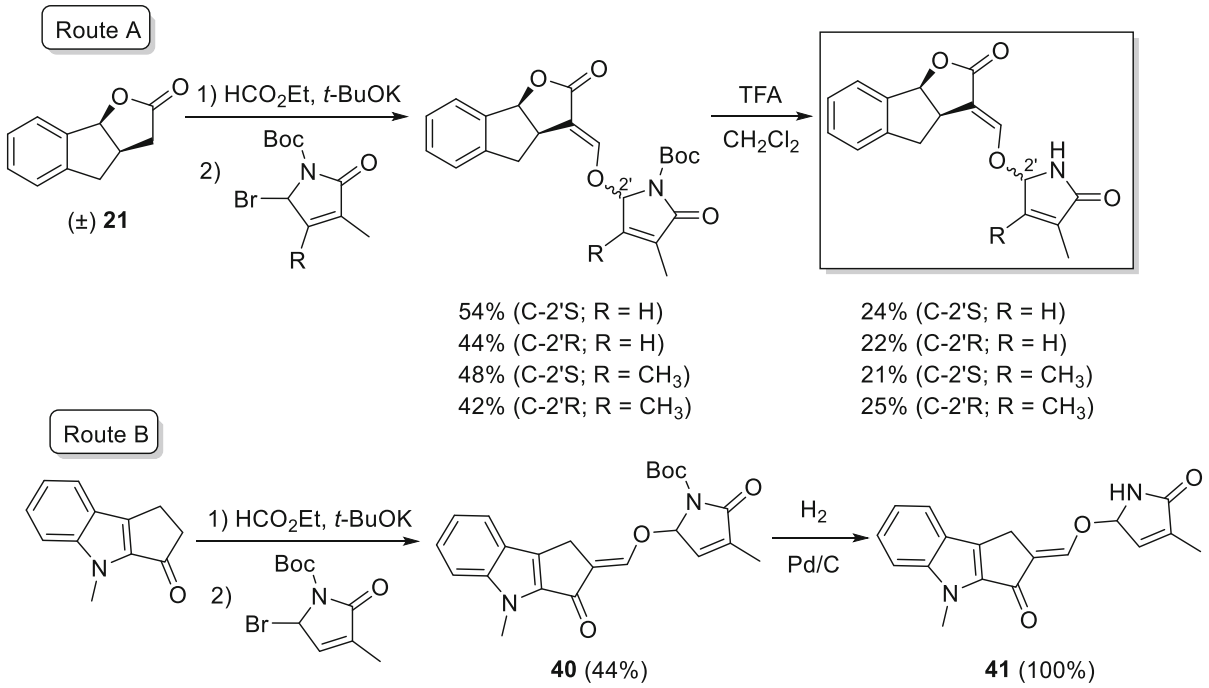

**Scheme 20** Synthesis of chlorobutenolides and GR24 analogues with methylated D-rings




**Scheme 21** Total synthesis of brominated lactam rings

Addition of the brominated lactams to **21** is carried out as usual, with very good yields (route A in Scheme 22). The final step corresponds to removal of the protecting group, with yields (21–25%) of around half those of the previous step.

Products with R = H were tested on *Phelipanche aegyptiaca*. All compounds were active at $10^{-5}$ M, with those with C-2′*S* exhibiting activities of more than 80% at this concentration. Similarly high percentages (around 75%) were obtained at $10^{-6}$ M, whereas the C-2′*R* epimers exhibited values of less than 35%. It must be noted that the C-2′*S* orientation of lactams is α for the butenolide ring, as in the SL with C-2′*R*, therefore the preference for the activity with this orientation also occurs in lactams. The high activity levels of C-2′*S* epimers were similar to those for GR24 at the same concentrations. In summary, the use of a lactam as the D-ring and the presence of a Boc



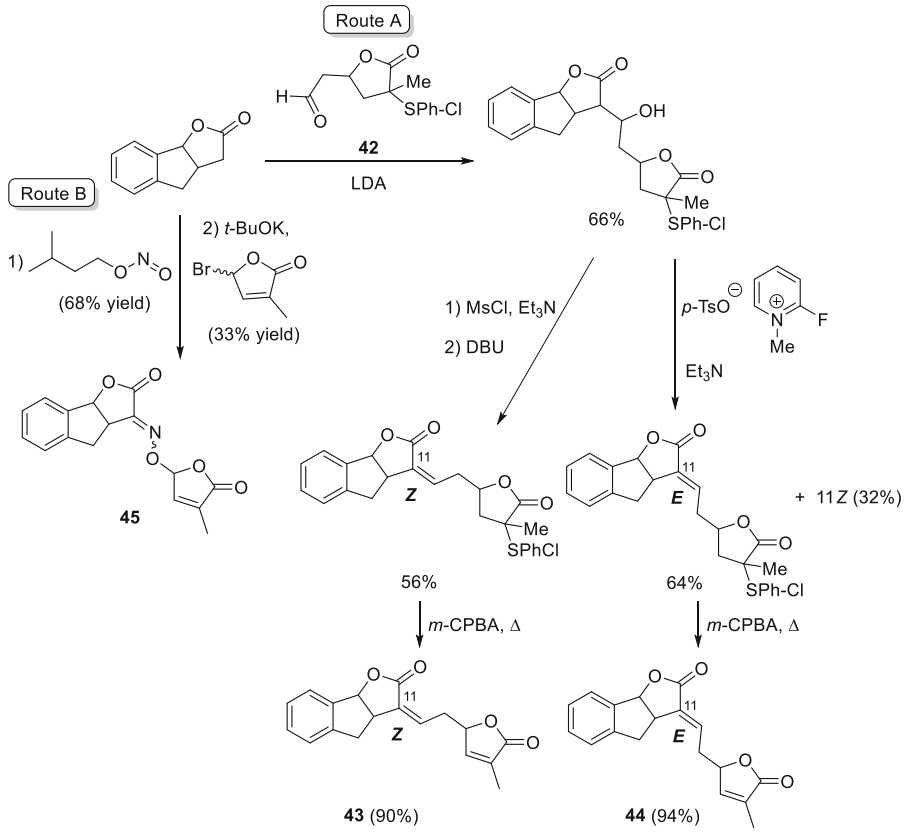

**Scheme 22** Final steps in the synthesis of GR24 analogues containing a lactam as D-ring

group in it does not result in a loss of activity at the highest concentrations if the configuration of the D-ring is C-2′*S*.

Products **40** and **41**, both lactams at the D-ring of EGO 10, were also synthesized by Lombardi et al. (2017) (route B in Scheme 22) and evaluated in a bioassay (Sanchez et al. 2018). These compounds showed poor activity for the germination of *P. aegyptiaca*, unlike the other strigolactams shown in Scheme 22, or EGO10 and PLN655.

With regard to the enol ether bond, different studies have shown that the modification thereof results in a loss of activity of the analogue for many parasitic weed species. Thus, Thuring et al. (1997b) synthesized the two geometric isomers (11*Z* for **43**, and 11*E* for **44**) of GR24 lacking the oxygen atom of the ether (route A in Scheme 23). The key was addition of the butenolide derivative **42** to the tricyclic GR24 scaffold. Different methods were employed to obtain each geometric isomer. Thus, 11*Z* was obtained by mesylation and subsequent elimination catalyzed by the base DBU, whereas 11*E* was obtained by reaction with 2-fluoro-1-methylpyridinium *p*-toluenesulfonate and $Et_3N$. The final step is elimination of the thioether protecting group. In bioassays, both analogues (**43** and **44**) were found to be inactive for the germination of *S. hermonthica* and *O. crenata*. On the other hand, Kondo et al. (2007) synthesized the imino derivative of GR24 at the enol ether bond, in which a nitrogen atom is found at the exocyclic position of the double bond (route B in Scheme 23). This product (**45**) is obtained by reaction of the tricyclic GR24 scaffold with isoamyl nitrite to form an oxime, and subsequent addition of the furanone ring. Compound **45** was tested in a bioassay as a possible mixture of geometric isomers, and found to be moderately active for *S. hermonthica* (28.3% at 10 μM) but inactive at the highest concentration tested (10 μM) for *S. gesneri-oides*, *O. minor* or *O. crenata*. These results show that some modifications to the enol ether bond do not provoke a total loss of activity for some parasitic species. This could be promising if this modification generated more stability and better solubility for the molecule, which would increase its suitability for use in herbicides.

The final GR24 derivatives presented herein are the promising strigolactams reported by Lachia et al. (2015), which contain an amide at the C-ring instead of the canonical ester. Two synthetic routes were reported to obtain the tricyclic scaffold (**46**;

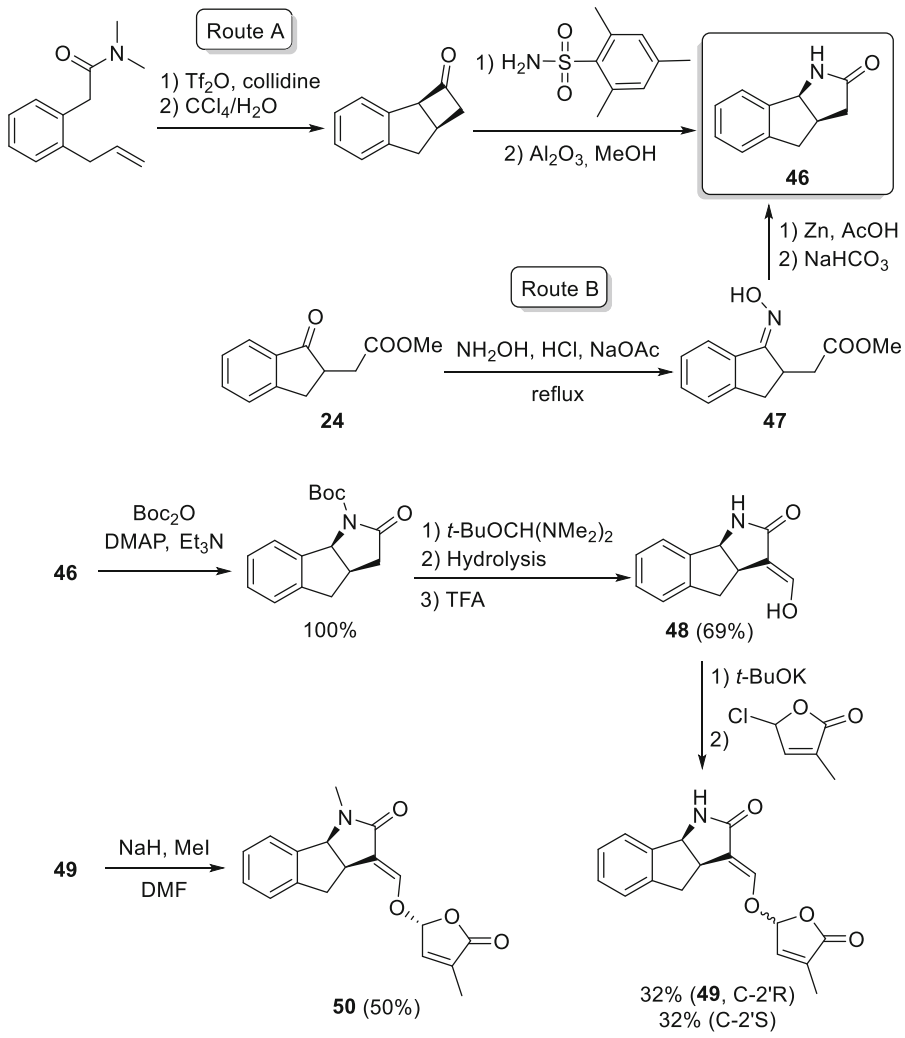



**Scheme 23** Synthesis of GR24 analogues with modifications at the enol ether

Scheme 24). The first (route A in Scheme 24) is related to the cycloaddition strategy previously shown in Scheme 14 to obtain **26**. The key step is the subsequent Beckman rearrangement catalyzed by 2,4,6-trimethylbenzenesulfonamide to obtain **46**. However, this reaction gave only a low yield (8%) of the desired product, therefore the second method (route B in Scheme 24) is clearly better in terms of overall yield (> 80%). Thus, starting from compound **24** (synthesized as shown in Scheme 11), a reductive amination is carried out to form an oxime (**47**), which is reduced to a lactam with Zn in the following step. Once **46** has been obtained, after protection of the amine with $Boc_2O$, the enol intermediate **48** is formed by formylation with Bredereck reagent and subsequent hydrolysis and removal of the protecting group with trifluoroacetic acid (TFA). The butenolide is added as usual to obtain strigolactam **49** and its C-2′ epimer. Compound **50** is obtained by methylation of **49** with NaH and MeI.

Recently, Ashida et al. (2020) reported the enantioselective synthesis of **49** using a nickel-catalyzed asymmetric cycloaddition. This study broadens the possibilities for the enantioselective synthesis of lactams and other compounds containing two contiguous stereogenic carbon centers.

Both **49** and **50** proved to be more active for the germination of *O. cumana* (82–93% activity in the range $10^{-1}$-$10^{-3}$ mg·$L^{-1}$) than GR24 (57–82% in the same range; Lachia et al. 2015). At lower concentrations, compound **49** stood out as 80% of activity was observed at $10^{-5}$ mg·$L^{-1}$, a concentration at which **26** or GR24 exhibited low percentages (3% and 19% respectively). The study of Lumbroso et al. (2016) also focused on the synthesis of strigolactams, specifically on the obtaining of simpler analogues possessing a bicyclic scaffold that lack of the canonical A-ring. They were based on the structure of GR-28 (Fig. 2). Showing different activity profiles, some of these compounds proved to be potent germination




**Scheme 24** Strategies to synthesize strigolactams at the C-ring

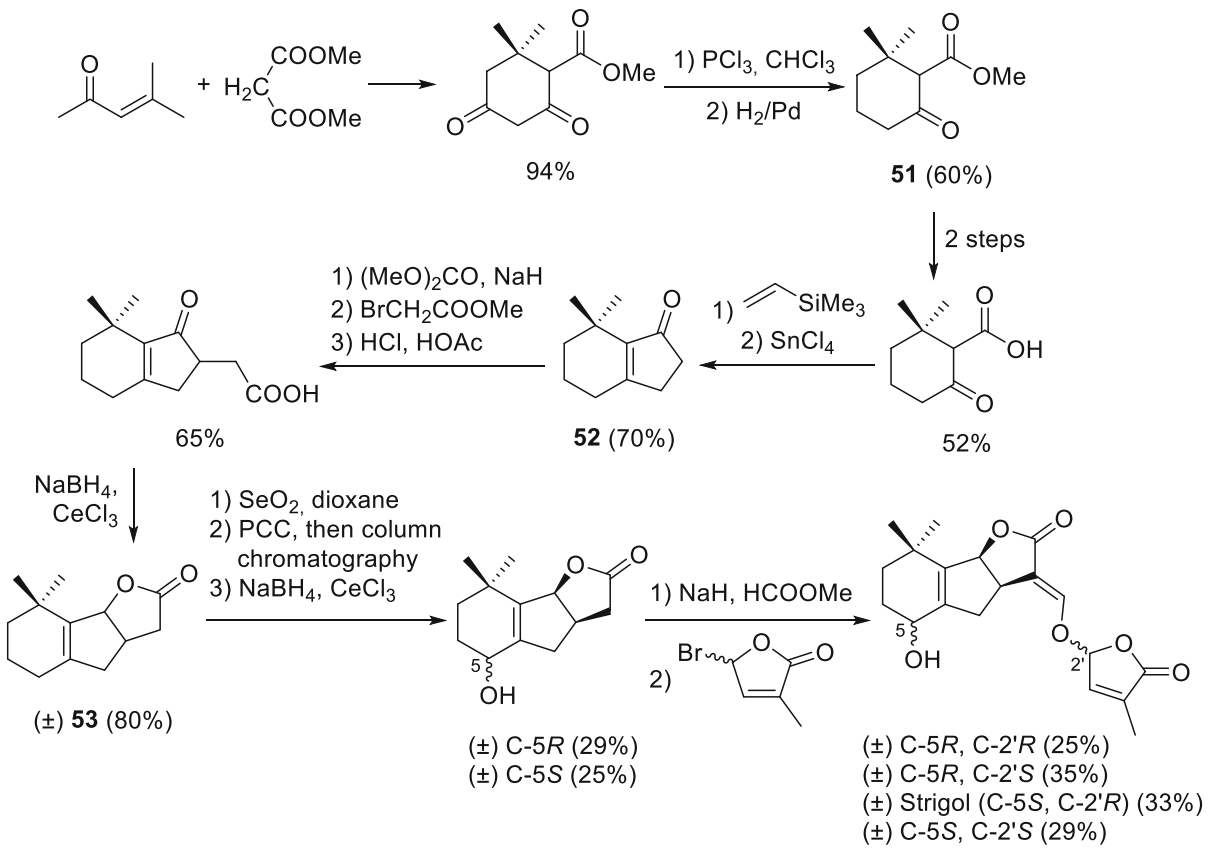
stimulants of *O. cumana*, reaching a maximum activity of 96% (0.01 mg·$L^{-1}$).

The structure–activity relationships mentioned in this section are in accordance with the general lines provided by Mwakaboko and Zwanenburg (2011a): "for the germination activity, A-ring modifications affect to a minor extent, stereochemistry is important, and the enol ether bond and D-ring are essential."

All compounds discussed in this section are structurally based on GR24. This skeleton is the most common canonical SL analogue published in the literature, not only by studies on parasitic weeds, but also for its applicability to develop stimulators for the AMF growth and branching. As example of recent study, the results published by Borghi et al. (2021) showed the potential of GR24 and some analogues, including a strigolactam, for AMF branching promotion.

## Strigol, orobanchol and sorgomol families

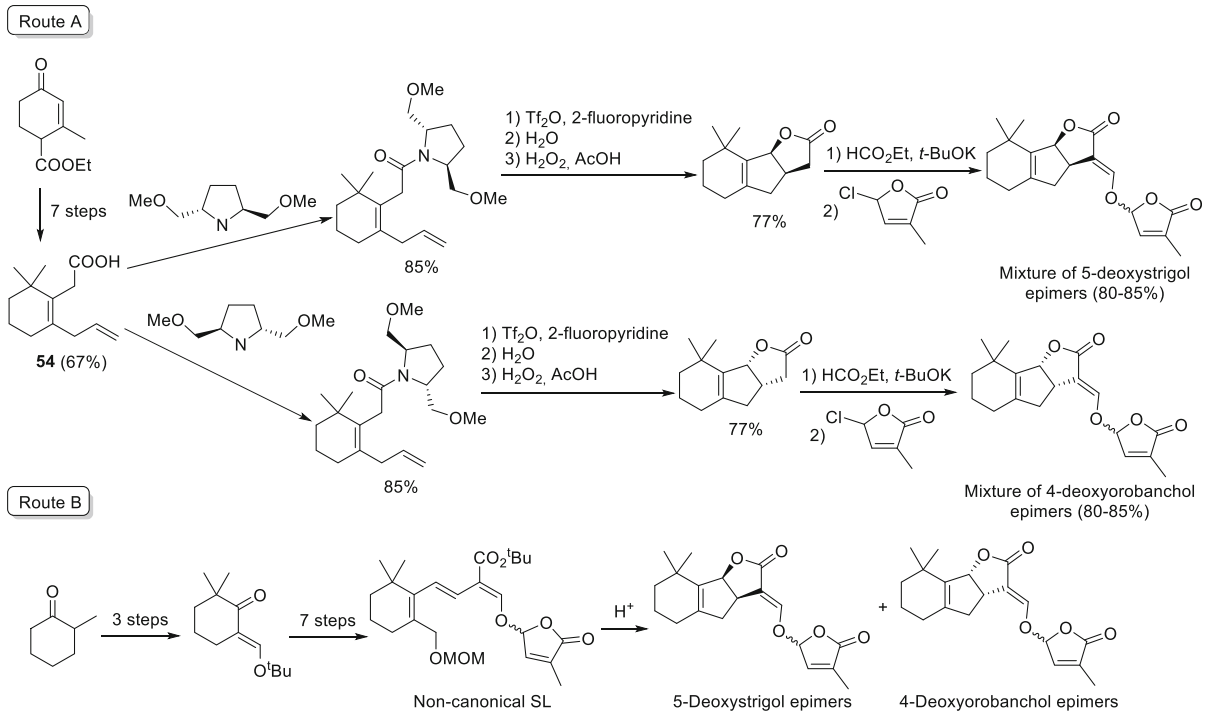
Strigol, the first strigolactone isolated and tested in a parasitic weed bioassay, has also been considered in different studies to synthesize structurally related analogues. The study by Reizelman et al. (2000) could be a good starting point in this regard since these authors reported the total synthesis of the eight stereoisomers of strigol (Scheme 25). The first steps correspond to the efficient three-steps methodology reported by Steiner and Willhalm (1952) to synthesize




**Scheme 25** Total synthesis of strigol and its stereoisomers

the intermediate **51**, which have been included in Scheme 25 to provide a complete synthetic route. The corresponding carboxylic acid of **51** was then synthesized to obtain the first bicyclic intermediate (**52**) by reaction with vinyl silane and a subsequent Nazarov reaction ($SnCl_4$-catalyzed cyclization). After insertion of a new carboxylic acid group, the tricyclic scaffold (**53**) was formed by a Luche reduction with $CeCl_3$ and $NaBH_4$. The next steps could be the most interesting for the design of new analogues since oxygenated functional groups are introduced at the A-ring using a strategy that also allows purification of the stereoisomers. To this end, a hydroxyl group is placed at C-5 by reaction with $SeO_2$, and then overoxidized to a ketone in order to form products more suitable for purification by column chromatography. The ketone is then reduced via a Luche reaction to obtain the target hydroxyl group at C-5. The resulting molecules are then formylated and bonded to the butenolide group. The diastereoisomers were resolved by cellulose triacetate HPLC.

5-Deoxystrigol is a natural SL similar to strigol but lacking the characteristic hydroxyl group. It was considered a SL analogue before its first isolation (Akiyama et al. 2005). Frischmuth et al. (1991) reported the first synthesis of 5-deoxystrigol together with other analogues based on functionalization at C-5 with hydroxyl or acetate groups. Alternative synthetic strategies were published later (Reizelman et al. 2000; Shoji et al. 2009), including the synthesis of 5-deoxystrigol together with its C-2′ epimer, and their C-ring stereoisomers (the latter, corresponding with analogues of orobanchol, namely 4-deoxyorobanchol), reported by Lachia et al. (2014a) (route A in Scheme 26). The first steps result in the acid **54**, which then forms an amide with (*S*,*S*)- or (*R*,*R*)-2,5-bis(methoxymethyl)pyrrolidine. The tricyclic system was prepared via an asymmetric intramolecular [2 + 2] cycloaddition of the ketene-iminium salts of the amides, catalyzed by $Tf_2O$ in the presence of 2-fluoropyridine as base. The butenolide ring is added as usual. We would like to recommend the review by



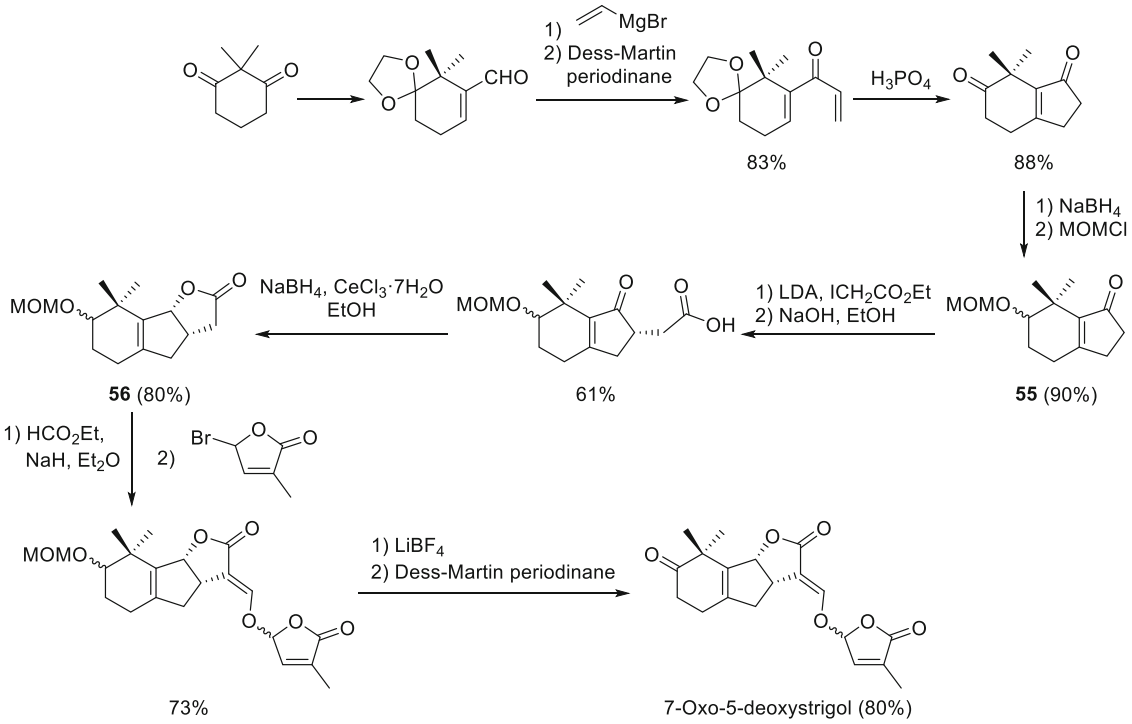

**Scheme 26** Strategies for the synthesis of 5-deoxystrigol and its stereoisomers

De Mesmaeker et al. (2019) to those who intend to obtain a more detailed background on this synthesis of 5-deoxystrigol and its stereoisomers.

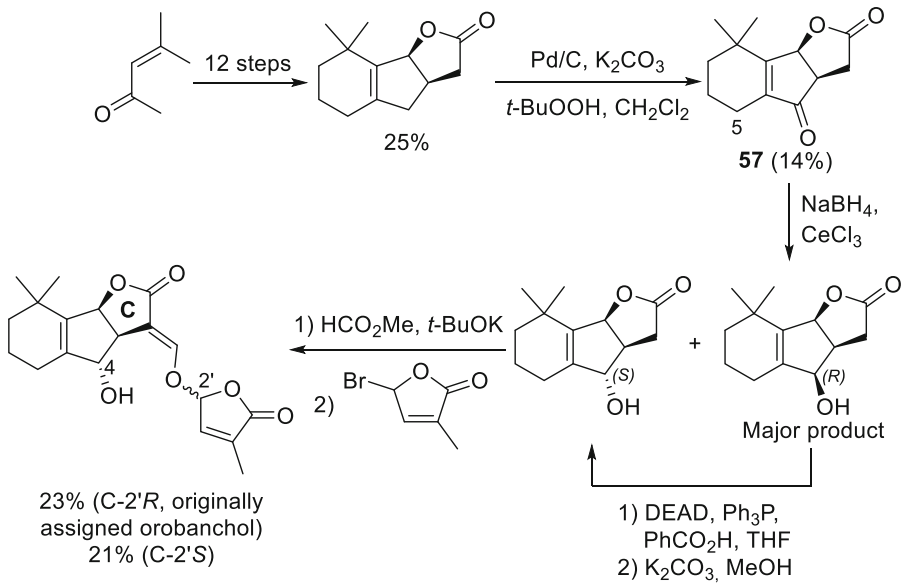
It is also worth highlighting the study recently published by Shiotani et al. (2021), which achieved the synthesis of 5-deoxystrigol as a racemate (therefore also obtaining 4-deoxyorobanchol) from a non-canonical SL structurally related to carlactone, by acid-mediated cascade cyclization (route B in Scheme 26). In a different study, Ueno et al. (2018)proved that 5-deoxystrigol acts like starting material for the natural synthesis in plants of the monohydroxylated SLs strigol and sorgomol. In the same way, some plants species synthetize orobanchol by bioconversion of 4-deoxyorobanchol, although other species would synthetize it from another compound.

Tanaka et al. (2013) reported a synthetic strategy to obtain the analogue 7-oxo-5-deoxystrigol in 11 steps from 2,2-dimethylcyclohexane-1,3-dione (Scheme 27). This route starts with protection of one of the ketone groups, which is then transformed into a dienone by way of Grignard and oxidation reactions. The bicyclic intermediate **55** is then obtained via a Nazarov cyclization catalyzed by $H_3PO_4$. After protection of the ketone group of the A-ring by formation of an MOM ether, the tricyclic scaffold (**56**) is formed. This requires the prior introduction of an acid group by reaction with the base LDA and $ICH_2CO_2Et$ (formation of an ester) and subsequent hydrolysis. The keto-acid group generated allows cyclization by way of a Luche reduction. The final steps correspond to introduction of the butenolide, removal of the MOM group by treatment with $LiBF_4$ and oxidation of the resulting hydroxyl group with Dess-Martin periodinane to form the ketone group at the A-ring. Although the overall yield for this synthesis is not available as the yield for the first step was not reported, it is noteworthy that the overall yield of the following steps is 19%.

With regard to orobanchol, it should be emphasized that until the correction of its structure in 2011, the total syntheses previously reported did not lead to orobanchol. The total synthesis of this originally assigned orobanchol molecule was for example published by (Zwanenburg et al. 2016), together with its 2′ epimer (Scheme 28), both as racemates. Mesityl oxide is used as starting material, and the ABC scaffold is obtained in 12 steps in 25% overall yield as a




**Scheme 27** Synthesis of 7-oxo-5-deoxystrigol




**Scheme 28** Total synthesis of racemates of originally assigned orobanchol and its 2' epimer

racemate. The following step is the formation of a ketone group at the B-ring to obtain **57** via allylic oxidation. This reaction was found to be low yielding (14%) as the major product (40%) is an undesired ketone at A-ring (C-5). On the other hand, this procedure employs reagents that reduce environmental impact, compared to the previously published methodology. A subsequent Luche reduction of **57** led

to the *cis* hydroxylated intermediate as major product, and a subsequent Mitsunobu inversion was then carried out to invert the configuration at C-4 by way of esterification of the hydroxyl group by treatment with diethyl azodicarboxylate (DEAD), and subsequent hydrolysis with $K_2CO_3$ (Matsui et al. 1999). These steps are similar to those previously described for the synthesis of hydroxylated derivatives of GR24 (see Scheme 16). Orobanchol and its epimer at C-2′ were obtained in similar yields after introduction of the butenolide ring.

Nomura et al. (2013) synthesized and purified all orobanchol stereoisomers (configuration at C-4 and C-2′; and enantiomers at the C-ring) from compound **57** by protecting the hydroxyl group with 2-trimethylsilylethoxymethyl (SEM) and subsequent deprotection using the strong acid TFA. In the bioassay, almost all orobanchol stereoisomers induced the germination of *S. hermonthica*, with orobanchol and its C-4' epimer being the most active (around 70% of activity at 1 µM). For *S. gesnerioides* seeds, only two of the stereoisomers were active (medium activity at 10 and 1 µM), namely the two C-2′ epimers of the C-4*R* and C-ring enantiomers of orobanchol.

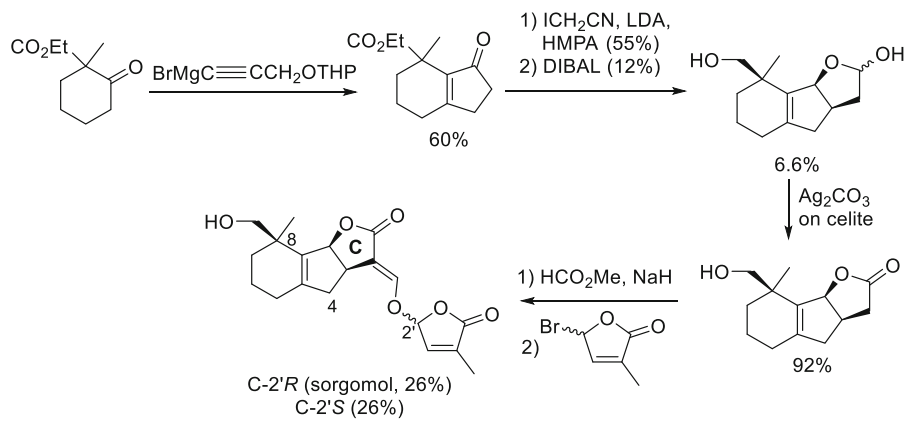
With regard to the strigolactone sorgomol, Kitahara et al. (2011) reported its synthesis from ethyl 2-oxocyclohexanecarboxylate (Scheme 29). The bicyclic intermediate is obtained first via a Nazarov cyclization using $BrMgC{\equiv}CCH_2OTHP$, then the tricyclic scaffold is formed in two steps. The second step is a reduction with diisobutylaluminium hydride (DIBAL), the low yield of which (12%) is the main disadvantage of this strategy. After oxidation of the hydroxyl group on the C-ring using $Ag_2CO_3$, the D-ring was added as usual. The overall yield for each 2′ epimer is 1%. Nomura et al. (2013) used this strategy to obtain the eight stereoisomers of sorgomol (configuration of C-8 and C-2′; and enantiomers at C-ring), which were isolated and evaluated in a bioassay in a similar manner to the orobanchol stereoisomers discussed in the previous paragraph. All were active for *S. hermonthica* seeds, although sorgomol was the most active. For *S. gesnerioides* seeds, only the C-ring enantiomer of sorgomol was significantly active, with around 35% activity at 1 µM.

To end this section, we suggest the design of synthetic routes to achieve sorgomol derivatives at C-4 via the introduction of oxygenated groups like hydroxyl or acetate. The resulting analogues could be more active for *S. hermonthica* germination as this structural improvement has been observed to be beneficial for GR24 and its hydroxylated analogue **5** described previously in this review.

## SL analogues based on sesquiterpene lactones

Sesquiterpene lactones are a large group of metabolites synthesized by plants (mostly the Astaraceae family). They have been studied for their medicinal or herbicidal properties, and some have been shown to be highly active at low concentrations. According to their structure, they can be classified into five subclasses (Moujir et al. 2020). All these compounds are bicyclic or tricyclic, and one of the rings is a lactone that is directly implicated in the bioactivities of these compounds.

The guaianolide and eudesmanolide subclasses will be highlighted herein as their structures have been used to synthesize canonical SL analogues. The synthetic routes involved are simpler, as the use of



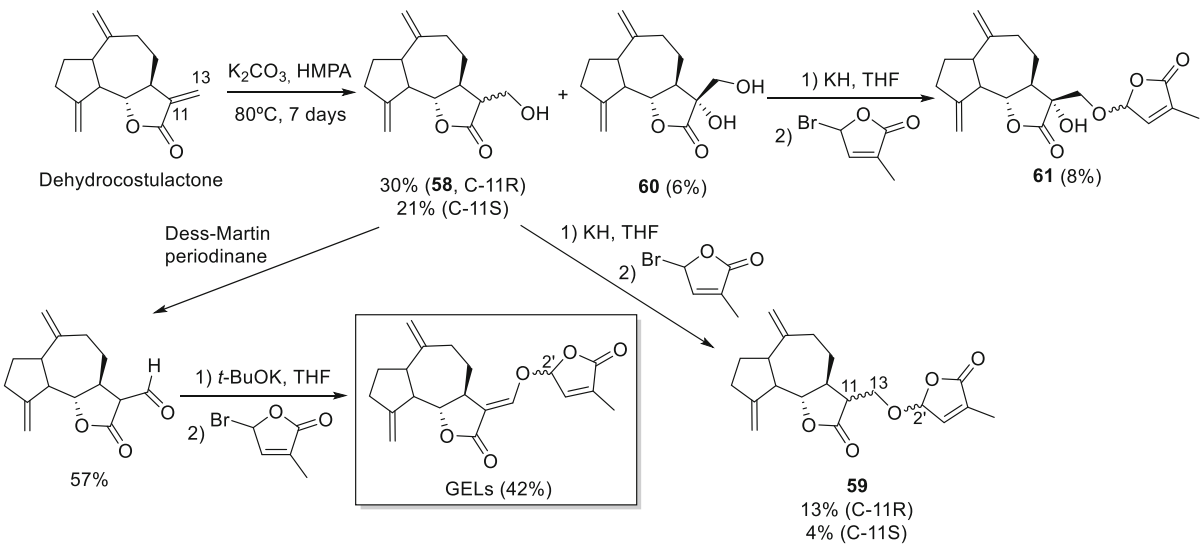

**Scheme 29** Synthesis of sorgomol and its 2' epimer

these tricyclic compounds, which already contain a lactone ring, as starting material avoids the large number of steps required to obtain the tricyclic scaffold of the analogues (like **21**). Thus, analogues can be synthesized via possible strategies that allow introduction of the butenolide ring via an enol ether bond in the lactone ring. From a practical point of view, the high-yielding synthesis is advantageous as some sesquiterpene lactones can be isolated on a multigram scale from natural sources. This is the case, for example, for dehydrocostulactone, a guaianolide-type lactone isolated from root extracts of *Saussurea costus*. Macías et al. (2009) reported a three-step synthesis of new analogues, known as guaianestrigolactones (GELs), derived from dehydrocostulactone (Scheme 30). The key step in this synthesis was the introduction of hydroxyl groups at the methylene of the lactone ring via a Michael addition with $K_2CO_3$, and the use of hexamethylphosphoramide as polar aprotic solvent. Monohydroxylated products were obtained in 51% yield (**58**), being then oxidized to the aldehyde by treatment with Dess-Martin periodinane. Finally, the butenolide ring was added to give an overall yield of 12%. This final step was also applied to **58** and **60** to synthesize GELs lacking an enol ether bond (11,13-dihydroGELs **59** and **61**, respectively).

The first step was improved by Cala et al. (2019), who reported a two-step procedure (Scheme 31) that reduces the reaction times significantly (from 7 to 2 days and 6 h), while also avoiding use of the toxic solvent HMPA and the formation of the dihydroxylated byproduct **60**. The first target intermediate was an ether at C-13, which was obtained by a Michael addition of the alkoxide of 4-methoxybenzyl alcohol (formed using the base 1,8-diazabicyclo[5.4.0]-undec-7-ene). The resulting ether (selective to C-11*R* configuration) is then oxidized using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to obtain the hydroxylated derivative **58**. The overall yield was 54%.

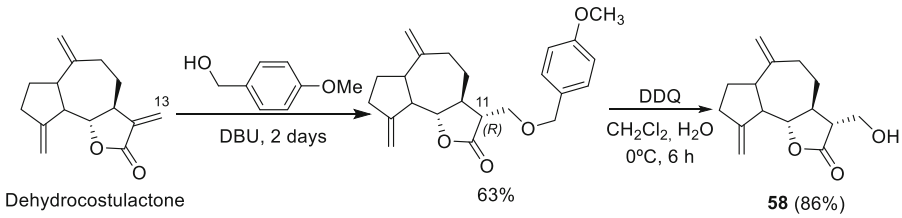
In the bioassay, the C-2′*R* GEL was found to be highly active for *O. cumana* (nearly 80% at 10 μM) and *Phelipanche ramosa* (60% at 10 and 1 μM, and 46% at 0.1 μM), whereas its C-2′*S* counterpart was somewhat less active (differences of 5–25%). Both epimers of **59**, which lack the enol ether, were also significantly active for *P. ramosa* (50–60% at 10 μM). With regard to *O. cumana*, the C-11*S* epimer stands out as an activity of 80% was observed at 10 μM and more than 60% was retained at the lowest dose tested (0.01 μM). Thus, the presence of the enol ether does not result in a loss of activity for the parasitic species evaluated, therefore the orientation of both C-2′ and C-11 must also be considered.

Recently, Zorrilla et al. (2020) selectively synthesized the C-11*R* epimers of **59** and isolated the epimers at C-2′. Both were tested in a bioassay, and significant activity was observed at 100 μM for *P. ramosa* (mean 83%) and *O. cumana* (53%). This activity was well retained at 10 μM, but only the C-2′R epimer was

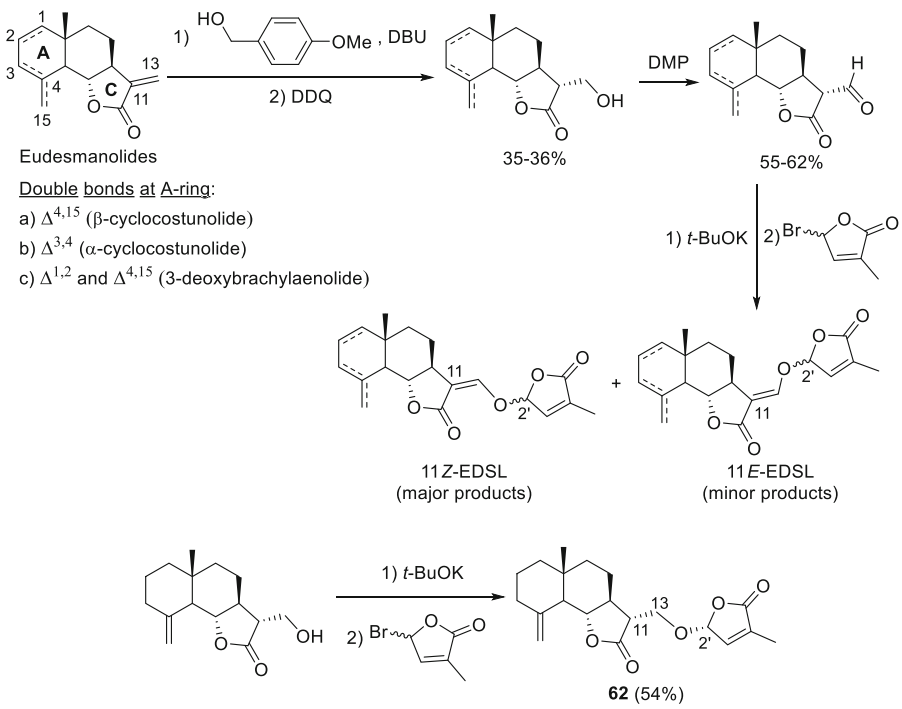



**Scheme 30** First synthesis reported for the synthesis of GEL and 11,13-dihydroGELs

**Scheme 31** Improved synthesis of the hydroxylated intermediate for the synthesis of GELs




**Scheme 32** Synthesis of canonical SL analogues based on eudesmanolides




significantly active for *P. ramosa* ($EC_{50}$ = 5.27 × $10^{-2}$ μM) at 1 μM or lower, thus highlighting the possibilities of this compound.

This same study also optimized the synthetic route shown in Schemes 30 and 31 for the synthesis of analogues based on eudesmanolides and thus obtain a new series of SL canonical analogues based on natural products, known as eudesmanestrigolactones (EDSLs). Three accessible eudesmanolides (α- and β-cyclocostunolide, and 3-deoxybrachylaenolide) were used as starting material. An important point of this strategy (Scheme 32) is the obtaining of SL analogues with both geometries of the enol ether bond (11*E* like natural SL, and 11*Z*) and configurations of C-2′ (*R* like natural SL, and *S*). Thus, up to four SL analogues could be obtained from each eudesmanolide, as well as 11,13-dihydroEDSLs like **62**. This synthetic procedure is relevant in the context of the synthesis of analogues, specifically analogues based on other sesquiterpene lactones, due to its potential applicability to each compound that contains a methylene-lactone group (C-ring).

All EDSLs were tested in parasitic seed bioassays, showing high activity profiles for the germination of *P. ramosa* and *O. cumana* even at the lowest concentrations tested, and medium activity for *O. crenata*. This activity was similar to, or even better than, that observed for GR24. EDSLs with the same isomeric features as natural SL (11*E* and C-2′*R*) were found to be remarkably active, and some EDSLs with alternative features achieved better results for some species. One of the main conclusions of the SAR study is that the double-bond system of the A-ring and the geometry of the enol ether have a marked influence on activity levels. Indeed, compound **62** (lacking the enol

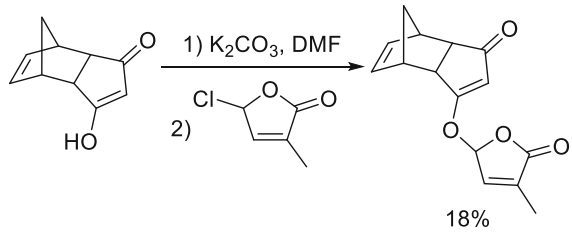
ether) was found to have no activity as regards *O. crenata* germination.

Since other sesquiterpene lactones, or sesquiterpenes of the guaiane- and eudesmane-type, can be isolated from natural sources (Cárdenas et al. 2020; Macías et al. 2013), the application or adaptation of the synthetic strategies shown in this review could provide new active analogues or mimics of strigolactones based on natural products.

## Other scaffolds for SL analogues

This final section presents the example of two products related to canonical analogues of SL that have not been as widely applied for the synthesis of analogues as the families mentioned previously.

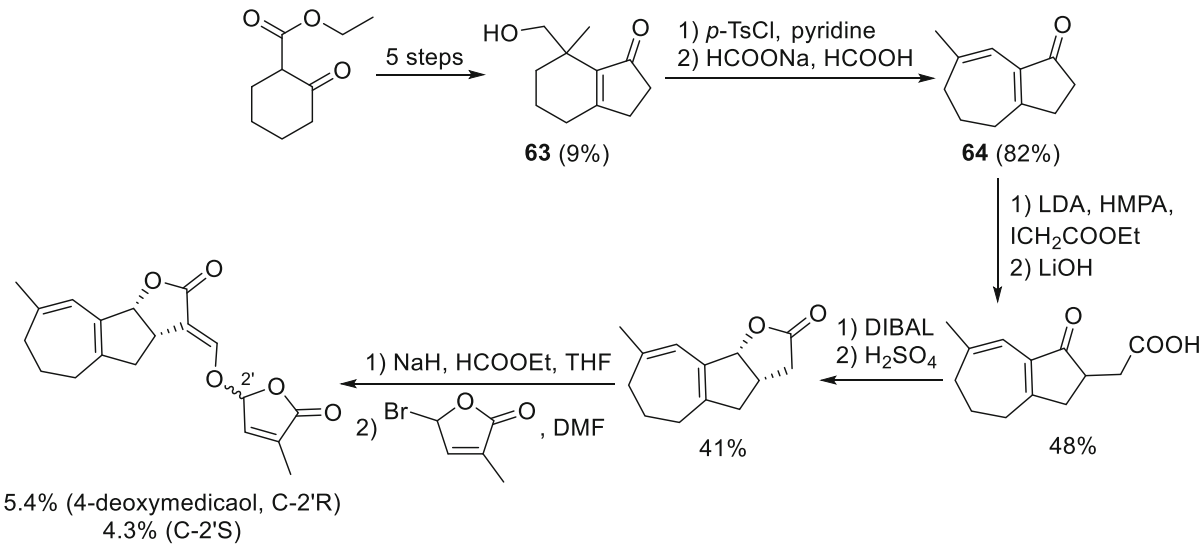
The first example is the total synthesis of 4-deoxymedicaol (analogue of the natural SL medicaol) and its C-2′ epimer, reported by Tokunaga et al. (2015) (Scheme 33). Overall yields of 0.08 and 0.06% were obtained, respectively. These low yields are reasonable as overall yields for the five-step synthesis of the bicyclic intermediate **63** from ethyl 2-oxocyclohexanecarboxylate, and addition of the butenolide ring in the final step, are between 4–9%. The high-yielding step involving expansion of the A-ring in **63** to a seven-membered ring (**64**) should be noted as similar reactions are not common in the synthesis of analogues. The tricyclic scaffold is then synthesized by forming a keto acid at the B-ring, followed by




**Scheme 34** Synthesis of an SL analogue based on a nobornene scaffold

treatment with DIBAL and acidification. 4-Deoxymedicaol was tested for the induction of hyphal branching of germinating spores of the arbuscular mycorrhizal fungus *Gigaspora margarita* rather than in a parasitic seed bioassay. Positive results were observed for both this compound and for medicaol.

The second example is provided by the study of Mwakaboko and Zwanenburg (2011b), in which different SL analogues of progressive structural complexity were synthesized. One of them is structurally comparable to canonical SL, although its structure is actually based on the nobornene system (Scheme 34), an unusual scaffold in the literature for the synthesis of analogues and mimics. A further distinctive feature is that the C- and D-rings are linked via an ether placed on a double bond on the C-ring rather than via an enol ether bond. In bioassays, this product germinated *S. hermonthica* (over 50% germination at 0.1 and 0.01 mg·$L^{-1}$) and *O. cernua* seeds (over 80% at




**Scheme 33** Synthesis of the analogue 4-deoxymedicaol

1 mg·L$^{-1}$ and around 55% at 0.1 mg·L$^{-1}$). As such, it may be of interest to develop related compounds containing nobornene scaffolds to perform more in-depth structure–activity studies.

## Conclusions

Strigolactone analogues are an alternative to the use of SL as agrochemicals given their improved activity levels and the more efficient methods available to synthesize them. Different synthetic strategies have been described, with most efforts focusing on construction of the main tricyclic scaffold in the final molecule. Although many of the steps in these routes have high yields, the use of at least one low-yielding step hinders the development of high-yielding routes, which is a particular disadvantage for routes involving a large number of steps. Thus, it is worth highlighting those routes that minimize the number of steps, principally by using a readily accessible bicyclic or tricyclic compound as starting material. In this regard, the synthesis of GR24 and some of the related analogues described in this review, as well as guaianestrigolactones (GELs) and eudesmanestrigolactones (EDSLs), are good examples.

With regard to the germination activity, recent advances in chromatography and the development of selective synthetic routes have led to the ability to evaluate pure SLs, thus demonstrating that the isomeric characteristics of these compounds could affect their activity levels. In the case of the GR24 family, the main relevance resides in the enol ether bridge and D-ring. However, these conclusions cannot be extrapolated to analogues containing other scaffolds, therefore more in-depth structure–activity relationship studies are required.

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### Decalration

**Conflicts of interest** The authors declare no conflict of interest or competing financial interest.



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