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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.

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 method[11] 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**.

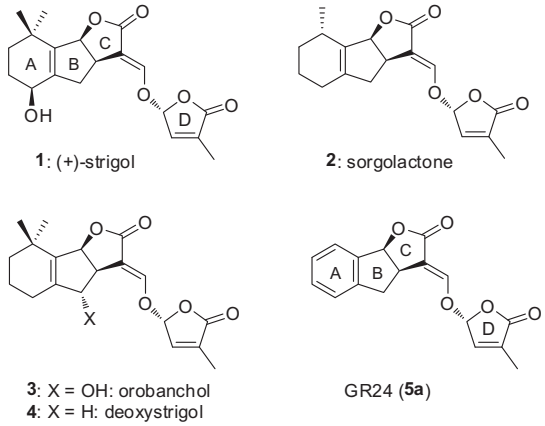

Figure 1. Naturally occurring strigolactones and synthetic analogue GR24.

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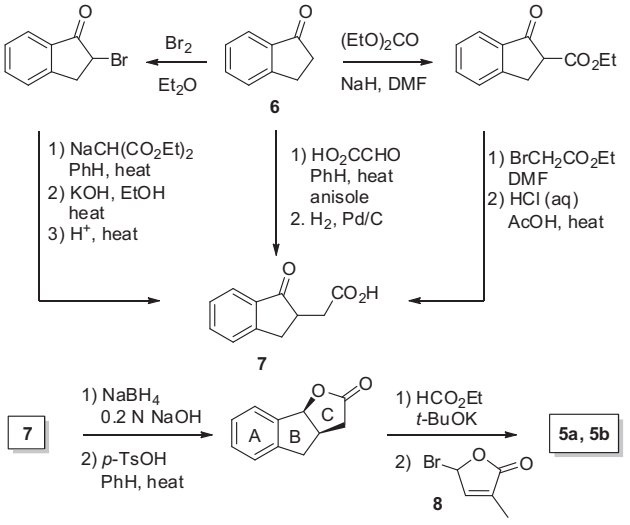
So far, a third method involving condensation of indan-1-one (**6**) with glyoxylic acid and subsequent removal of the double bond to give intermediate **7** via a two-step process is the easiest one.[9]



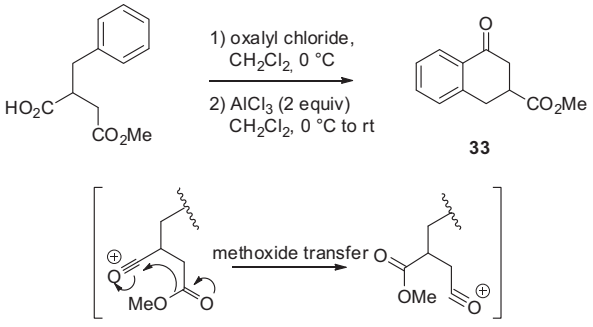
Scheme 1.

Reduction of the carbonyl group with $NaBH_4$ 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.

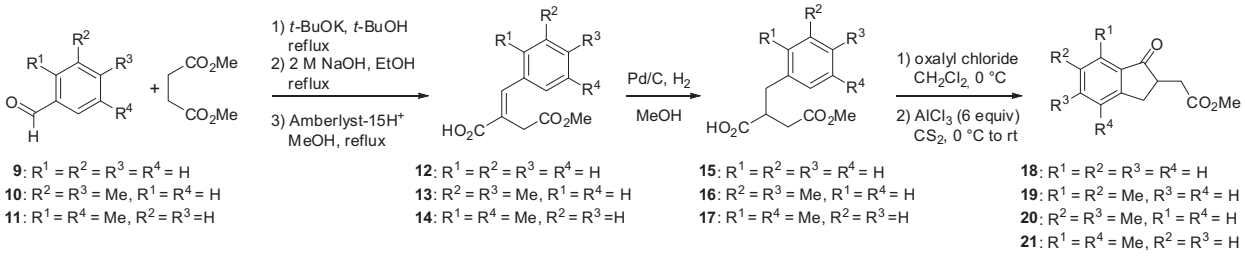
2. Results and discussion

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 $AlCl_3$ in CS_2 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 $AlCl_3$ (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

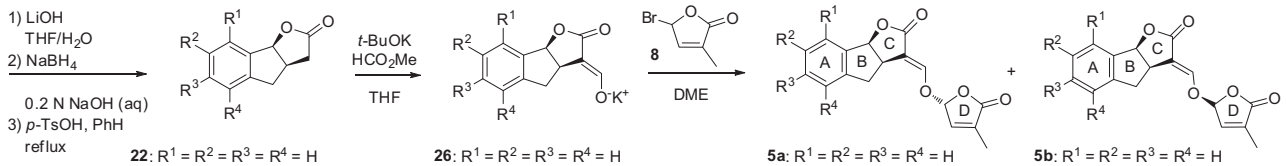


9: $R^1=R^2=R^3=R^4=H$
10: $R^2=R^3=Me$, $R^1=R^4=H$
11: $R^1=R^4=Me$, $R^2=R^3=H$

12: $R^1=R^2=R^3=R^4=H$
13: $R^2=R^3=Me$, $R^1=R^4=H$
14: $R^1=R^4=Me$, $R^2=R^3=H$

15: $R^1=R^2=R^3=R^4=H$
16: $R^2=R^3=Me$, $R^1=R^4=H$
17: $R^1=R^4=Me$, $R^2=R^3=H$

18: $R^1=R^2=R^3=R^4=H$
19: $R^1=R^2=Me$, $R^3=R^4=H$
20: $R^2=R^3=Me$, $R^1=R^4=H$
21: $R^1=R^4=Me$, $R^2=R^3=H$



22: $R^1=R^2=R^3=R^4=H$
23: $R^1=R^2=Me$, $R^3=R^4=H$
24: $R^2=R^3=Me$, $R^1=R^4=H$
25: $R^1=R^4=Me$, $R^2=R^3=H$

26: $R^1=R^2=R^3=R^4=H$
27: $R^1=R^2=Me$, $R^3=R^4=H$
28: $R^2=R^3=Me$, $R^1=R^4=H$
29: $R^1=R^4=Me$, $R^2=R^3=H$

5a: $R^1=R^2=R^3=R^4=H$
30a: $R^1=R^2=Me$, $R^3=R^4=H$
31a: $R^2=R^3=Me$, $R^1=R^4=H$
32a: $R^1=R^4=Me$, $R^2=R^3=H$

5b: $R^1=R^2=R^3=R^4=H$
30b: $R^1=R^2=Me$, $R^3=R^4=H$
31b: $R^2=R^3=Me$, $R^1=R^4=H$
32b: $R^1=R^4=Me$, $R^2=R^3=H$

Scheme 2.

into the faster moving diastereomer **5a** and slower moving diastereomer **5b** (Scheme 2).[11]

Originally, we performed the hydrogenation of the olefinic bond in **12** in an asymmetric manner with the rhodium complex Rh $(COD)_2BF_4$ in combination with a (*S*)-BINOL isopropoxy-substituted phosphite ligand. This catalytic hydrogenation gave the reduced product **15** in excellent chemical and optical yield (ee 97%). After Friedel–Crafts ring closure, reduction and lactonization the ABC-lactone **22** would then have been obtained in optically active form. Disappointingly, during the Friedel–Crafts ring closure the chiral integrity was almost entirely lost (ee 16%). Apparently, under the Friedel–Crafts conditions, the acid chloride undergoes racemization prior to the cyclization, most probably via a ketene type intermediate.

After having established the optimal conditions for the synthesis of GR24, 3,4- and 2,5-dimethylbenzaldehydes were subjected to this sequence of events. 3,4-Dimethylbenzaldehyde produced a mixture of the Friedel–Crafts ring-closed products **19** and **20**. They were separated by column chromatography and converted into ABC-lactones **23** and **24**. In contrast, 2,5-dimethylbenzaldehyde can proceed only in one way in the Friedel–Crafts cyclization to give the ABC-lactone **25**. ABC-lactones **23**–**25** were then coupled with the D-ring as described before. The resulting mixtures of diastereomers were separated by column chromatography to give the faster moving diastereomers **30a**, **31a**, **32a** and the slower moving diastereomers **30b**, **31b**, **32b**, respectively.

The six dimethyl-substituted GR24 analogues were tested for germination activity on seeds of the parasitic weed *Striga hermonthica*. The results of these bioassays, which are shown in Figure 2, reveal that dimethyl substitution lowers the activity. The diastereomers having the relative configuration of the C- and D-ring as in the natural strigolactones [3a(*R**),8a(*R**),2′(*R**)], exhibit as expected, a higher activity than the diastereomers with the epi-2′-configuration [3a(*R**),8a(*R**),2′(*S**)]. The highest activity for all six analogues is at a concentration 10 times higher than the general standard germinating agent GR24, which has the natural relative CD relationship [3a(*R**),8a(*R**),2′(*R**)]. The dose-response of stimulant GR24 shows a lower activity at the highest concentration. This in agreement with the general observation, that the dose response curves of stimulants have a bell shape with a maximum.[9] In the case of GR24 this maximum is clearly visible. For the dimethyl-substituted analogues the maximum is at a higher concentration than for GR24, but due to solubility problems higher concentration than 33 μM could not be biassayed.

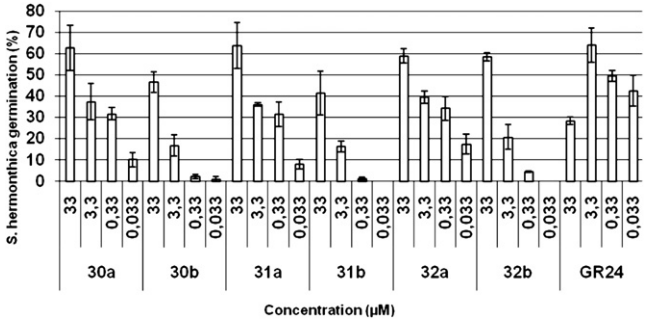


Figure 2. Bioassay: germination activity towards seeds of *S. hermonthica*.

3. Concluding remarks

The sequence of events depicted in Scheme 2, which is based on the Stobbe condensation is suitable for the multigram syntheses of the ABC-lactones **22**–**25**. The route is particularly convenient for GR24, which is the general standard in bioassays of the germination of seeds of parasitic weeds. The method also allows the synthesis of dimethyl substituted A-ring analogues of GR24 by starting from appropriately substituted dimethyl benzaldehydes. Hence, 7,8-dimethyl, 5,8-dimethyl and 6,7-dimethyl compounds **30**–**32** were prepared starting from 3,4-dimethylbenzaldehyde and 2,5-dimethylbenzaldehyde, respectively. The bioassays reveal that dimethyl substitution lowers the germination activity. Earlier we demonstrated that A-ring substitution has some but not a dramatic influence on the bioactivity.[8] Methyl substitution can in principle be used for fine-tuning the activity of GR24 analogues. The bioassays reveal that GR24 has a potency of about ten times higher than the dimethyl analogues. However, a word of caution is in place, because the response to seeds of other *Striga* species may show a different relative behaviour. The dimethyl GR24 analogues are of particular interest because of the occurrence of the natural stimulant solanocol,[18] which is proposed to have a 5,8-dimethyl substituted aromatic ring. Recently it is shown that this structural assignment is not correct. Solanocol has methyl substituents at the 7- and 8-position.[19]

It is also of importance to note that strigolactones are currently in the focus of interest due to the newly discovered bioactivities of these compounds. It was found that some natural strigolactones, as well as GR24, are the branching factor of arbuscular mycorrhizal (AM) fungi.[20,21] Moreover, these compounds are active as inhibitor of shoot branching and bud outgrowth.[22,23] It is generally believed that strigolactones constitute a new type of plant hormones.[24] The synthetic strigolactone GR24 plays an important role in advancing the knowledge in this exciting field.

4. Experimental section

4.1. General remarks

All glass apparatus were oven dried prior to use. Solvents were distilled from appropriate drying agents prior to use and stored under nitrogen. Standard syringe techniques were applied for the transfer of dry solvents and air or moisture-sensitive reagents. All chemicals were obtained from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. Coupling constants are reported as *J*-values in hertz. Multiplicities are reported as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet) in ^{1}H NMR. Reactions were monitored using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F_{254}) with the indicated solvent mixture. Detection was performed with UV-light, and/or by charring at ~150 °C after dipping in to a solution of either 2% anisaldehyde in ethanol/H_2SO_4 or $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) or $KMnO_4$. Melting points were determined with a Buchi melting point B-545. High resolution mass spectra were recorded on a JEOL AccuTOF (ESI), or a MAT900 (EI, CI, and ESI). Column chromatography was performed over silica gel (0.035–0.070 mm) using freshly distilled solvents. Air and moisture sensitive reactions were carried out under an inert atmosphere of dry nitrogen or argon.

*4.1.1. Methyl (E)-2-benzylidenesuccinate (**12**)*[15]. To a refluxing suspension of *t*-BuOK (12.4 g, 111 mmol) in *t*-BuOH (80 mL) was carefully added a solution of dimethyl succinate (18.0 g, 120 mmol) and benzaldehyde **1** (10.0 g, 92.4 mmol) in *t*-BuOH (80 mL). The reaction mixture was stirred at reflux temperature for 18 h, after which the solvent was removed under vacuum. The residue was dissolved in 1 M HCl (80 mL) and this solution was extracted with EtOAc (3×80 mL). The organic layers were dried (Na_2SO_4) and concentrated. The resulting monoacid was dissolved and EtOH (40 mL) and aqueous NaOH (2 M, 80 mL) were added. The resultant mixture was stirred at reflux temperature for 1 h, followed by evaporation of

most of the EtOH under reduced pressure. Extra H_2O (80 mL) was added and the mixture was washed with EtOAc (3×80 mL). Next, the aqueous layer was acidified (pH ~ 1) with 2 M HCl, extracted with EtOAc (2×80 mL) and the organic layers were dried (Na_2SO_4) and concentrated. The resulting diacid was dissolved in MeOH (100 mL), Amberlyst-15H$^+$ (4.20 g) was added and the reaction mixture was heated under reflux for 16 h. The mixture was filtered over Celite and concentrated under vacuum, resulting in crude ester **12**. The product was recrystallized from toluene/*n*-heptane, yielding ester **12** as a white solid. The overall yield was 9.15 g (45%). Analytical data were in agreement with those reported in the literature.[15,25] FTIR (solid) cm^{-1}: 2941, 1735, 1670, 1631. ^1H NMR (300 MHz, $CDCl_3$): δ 12.34 (s, 1H), 8.03 (s, 1H), 7.38 (br s, 5H), 3.74 (s, 3H), 3.57 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6 (s), 171.0 (s), 143.8 (d), 134.1 (s), 128.7 (2×d), 128.2 (3×d), 124.7 (s), 51.8 (q), 32.7 (t).

Compounds **13** and **14** were prepared by following the same procedure.

*4.1.2. (E)-2-(3,4-Dimethylbenzylidene)-4-methoxy-4-oxobutanoic acid (**13**).* Yield 44%, mp 107–107.5 °C, FTIR (solid) cm^{-1}: 2962, 1739, 1661, 1627. ^1H NMR (300 MHz, $CDCl_3$): δ 11.92 (s, 1H), 7.98 (s, 1H), 7.12–7.18 (m, 3H), 3.75 (s, 3H), 3.60 (s, 2H), 2.28 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8 (s), 171.1 (s), 144.0 (d), 137.9 (s), 136.5 (s), 131.7 (s), 130.2 (d), 129.5 (d), 126.3 (d), 123.6 (s), 51.7 (q), 32.7 (t), 19.3 (q), 19.2 (q). HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_4$ (M+Na)$^+$: 271.09463, found: 271.09243.

*4.1.3. (E)-2-(2,5-Dimethylbenzylidene)-4-methoxy-4-oxobutanoic acid (**14**).* Yield 43%, mp 107.5–108 °C, FTIR (solid) cm^{-1}: 2958, 1726, 1679, 1627. ^1H NMR (300 MHz, $CDCl_3$): δ 11.78 (s, 1H), 7.06 (s, 1H), 7.12–7.05 (m, 2H), 6.99 (s, 1H), 3.72 (s, 3H), 3.42 (s, 2H), 2.30 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9 (s), 171.0 (s), 143.6 (d), 134.9 (s), 133.3 (s), 133.0 (s), 129.6 (d), 129.3 (d), 128.2 (d), 125.3 (s), 51.6 (q), 32.6 (t), 20.5 (q), 18.8 (q). HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_4$ (M+Na)$^+$: 271.09463, found: 271.09258.

*4.1.4. 2-Benzyl-4-methoxy-4-oxobutanoic acid (**15**).* To a solution of acid **12** (5.00 g, 22.5 mmol) in methanol (80 mL) Pd/C (0.45 g) was added under nitrogen. It was stirred under the same atmosphere for 10 min, followed by stirring for 18 h at room temperature under hydrogen, then it was filtrated over Celite. Removal of solvent under vacuum gave acid **15** (4.90 g, 98%) as a viscous oil. Analytical data were in agreement with those reported in literature.[15,26] FTIR (liquid film) cm^{-1}: 2958, 1735, 1709. ^1H NMR (300 MHz, $CDCl_3$): δ 11.17 (s, 1H), 7.32–7.17 (m, 5H), 3.64 (s, 3H), 3.23–3.11 (m, 2H), 2.83–2.75 (m, 1H), 2.70–2.62 (m, 1H), 2.42 (dd, 1H, *J*=17.1, 4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6 (s), 171.8 (s), 137.3 (s), 128.5 (2×d), 128.1 (2×d), 126.3 (d), 51.4 (q), 42.3 (d), 36.8 (t), 33.9 (t).

Similarly, acids **16** and **17** were prepared from **13** and **14**, respectively.

*4.1.5. 2-(3,4-Dimethylbenzyl)-4-methoxy-4-oxobutanoic acid (**16**).* Yield 98%, colourless viscous oil, FTIR (liquid film) cm^{-1}: 2945, 1735, 1705. ^1H NMR (300 MHz, $CDCl_3$): δ 11.30 (s, 1H), 7.06–7.03 (d, 1H, *J*=7.5 Hz), 6.94–6.89 (m, 2H), 3.64 (s, 3H), 3.18–3.05 (m, 2H), 2.72–2.59 (m, 2H), 2.40 (dd, 1H, *J*=16.8, 4.5 Hz), 2.22 (d, 6H, *J*=2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.2 (s), 171.9 (s), 136.2 (s), 134.7 (s), 134.5 (s), 129.8 (d), 129.3 (d), 125.9 (d), 51.3 (q), 42.4 (d), 36.5 (t), 33.9 (t), 19.2 (q), 18.8 (q). HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_4$ (M+Na)$^+$: 273.11028, found: 273.10814.

*4.1.6. 2-(2,5-Dimethylbenzyl)-4-methoxy-4-oxobutanoic acid (**17**).* Yield 98%, colourless viscous oil, FTIR (liquid film) cm^{-1}: 2958, 1739, 1705. ^1H NMR (300 MHz, $CDCl_3$): δ 11.24 (s, 1H), 7.05–7.02 (m, 1H), 6.96–6.88 (m, 2H), 3.63 (s, 3H), 3.02–3.18 (m, 2H), 2.76–2.63 (m, 2H), 2.42 (dd, 1H, *J*=17.1, 4.5 Hz), 2.29 and 2.28 (2×s, 2×3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0 (s), 171.9 (s), 135.5 (s), 134.9 (s), 132.7 (s), 130.1 (2×d), 127.2 (d), 51.3 (q), 41.3 (d), 34.4 (t), 34.0 (t), 20.4 (q), 18.3 (q). HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_4$ (M+Na)$^+$: 273.11028, found: 273.10814.

*4.1.7. Methyl 2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetate (**18**).* To a solution of acid **15** (2.0 g, 9.01 mmol) in dry CH_2Cl_2 (30 mL) was added oxalyl chloride (1.37 g, 10.8 mmol). Two drops of dry DMF were added to initiate the reaction. The reaction mixture was stirred at room temperature for 1 h, after which the solvent was removed in vacuo. The resulting product was dissolved in carbon disulfide (20 mL) and then gradually added to a slurry of $AlCl_3$ (7.20 g, 54.1 mmol) in carbon disulfide (30 mL) at −30 °C. The reaction mixture was stirred at 0 °C for 4 h and then overnight at room temperature. Carbon disulfide was removed in vacuo and the resulting mixture was dissolved in CH_2Cl_2 (50 mL). Then, water (30 mL) was added dropwise to quench $AlCl_3$ followed by 1 M HCl (5 mL) leading to a clear solution. The product was extracted with CH_2Cl_2 (2×50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed over silica gel using EtOAc/*n*-heptane (2:8) to yield ketone **18** (1.40 g, 78%) as a white solid. Mp 144.3–144.8 °C, FTIR (solid) cm^{-1}: 1735, 1666. ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, 1H, *J*=7.5 Hz), 7.53–7.47 (m, 1H), 7.37 (d, 1H, *J*=7.5 Hz), 7.30–7.26 (m, 1H), 3.59 (s, 3H), 3.40–3.32 (m, 1H), 2.96–2.77 (m, 3H), 2.57–2.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0 (s), 171.8 (s), 152.7 (s), 135.7 (s), 134.3 (d), 126.9 (d), 126.0 (d), 123.3 (d), 51.2 (q), 43.0 (d), 34.3 (t), 32.4 (t). HRMS (ESI) *m/z* calcd for $C_{12}H_{12}O_3$ (M+Na)$^+$: 227.06841, found: 227.06719.

Carboxylic acids **16** and **17** were subjected to the same procedure. Compound **16** gave a mixture of Friedel–Crafts ring-closed products **19** and **20** in a ratio of 2:3 in 76% yield, which were separated by column chromatography into the faster moving product **19** and the slower moving product **20**. Compound **17** gave the Friedel–Crafts ring-closed ketone **21** as a single product.

*4.1.8. Methyl 2-(6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-2-yl) acetate (**19**).* Yield 31%, colourless viscous oil, FTIR (liquid film) cm^{-1}: 1739, 1700. ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 1H, *J*=7.5 Hz), 7.12 (d, 1H, *J*=7.5 Hz), 3.66 (s, 3H), 3.34–3.26 (m, 1H), 2.89–3.00 (m, 2H), 2.72 (dd, 1H, *J*=16.8, 4.8 Hz), 2.60–2.47 (m, 1H), 2.55 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3 (s), 172.2 (s), 151.0 (s), 136.9 (s), 135.8 (s), 135.4 (d), 133.0 (s), 122.7 (d), 51.2 (q), 43.8 (d), 34.6 (t), 31.4 (t), 18.4 (q), 13.1 (q). HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_3$ (M)$^+$: 233.11777, found: 233.11553.

*4.1.9. Methyl 2-(5,6-dimethyl-1-oxo-2,3-dihydro-1H-inden-2-yl) acetate (**20**).* Yield 45%, mp 72–72.5 °C, FTIR (solid) cm^{-1}: 1735, 1709. ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (s, 1H), 7.00 (s, 1H), 3.50 (s, 3H), 3.17–3.08 (m, 1H), 2.78–2.69 (m, 2H), 2.55 (dd, 1H, *J*=16.8, 3.9 Hz), 2.38–2.29 (m, 1H), 2.13 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3 (s), 171.8 (s), 150.7 (s), 144.3 (s), 135.6 (s), 133.7 (s), 126.5 (d), 123.4 (d), 51.0 (q), 43.1 (d), 34.3 (t), 31.9 (t), 20.0 (q), 19.0 (q). HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_3$ (M+Na)$^+$: 255.09971, found: 255.09720.

*4.1.10. Methyl 2-(4,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-2-yl) acetate (**21**).* Yield 74%, mp 87.3–87.8 °C, FTIR (solid) cm^{-1}: 1731, 1705. ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, 1H, *J*=7.5 Hz), 6.99 (d, 1H, *J*=7.5 Hz), 3.68 (s, 3H), 3.32–3.24 (m, 1H), 3.00–2.91 (m, 2H), 2.56 (s, 3H), 2.64 (dd, 1H, *J*=17.1, 4.5 Hz), 2.52–2.46 (m, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.2 (s), 172.2 (s), 152.2 (s), 135.6 (s), 134.2 (d), 132.8 (s), 132.1 (s), 128.9 (d), 51.3 (q), 43.2 (d), 34.2 (t), 31.0 (t), 17.4 (q), 16.9 (q). HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_3$ (M+Na)$^+$: 255.09971, found: 255.09960.

*4.1.11. (±)-3,3a,4,8b-Tetrahydro-2H-indeno[1,2b]furan-2-one (**22**).* A mixture of ketone **18** (1.40 g, 6.86 mmol) in THF/water (50:50)

(50 mL) and $LiOH \cdot H_2O$ (0.56 g, 13.7 mmol) was stirred for 16 h. Then, THF was evaporated and 1 M HCl (50 mL) was added. The product was extracted with EtOAc (2×100 mL). The organic layer was dried (Na_2SO_4) and concentrated to obtain the free keto acid derived from **18** as a white solid in 96% yield. Lactone **22** was prepared from the γ-keto acid obtained above by reduction with sodium borohydride followed by acid-catalyzed lactonization as described by House et al. in 90% yield.[12] Analytical data were in agreement with those reported in the literature.[12]

Lactones **23**–**25** were prepared following the same procedure.

*4.1.12. (±)-7,8-Dimethyl-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**23**).* Yield 87%, mp 74–74.5 °C, FTIR (solid) cm^{-1}: 1761, 1726. ^1H NMR (300 MHz, $CDCl_3$): δ 7.13 (d, 1H, *J*=7.6 Hz), 6.98 (d, 1H, *J*=7.6 Hz), 5.94 (d, 1H, *J*=6.9 Hz), 3.39–3.22 (m, 2H), 2.95–2.80 (m, 2H), 2.41 (dd, 1H, *J*=17.7, 4.5 Hz), 2.33 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6 (s), 139.8 (s), 137.2 (s), 135.3 (s), 134.6 (s), 131.3 (d), 121.7 (d), 87.0 (d), 37.6 (t), 36.6 (t), 35.5 (d), 18.9 (q), 15.1 (q). HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}O_2$ $(M+Na)^+$: 225.08915, found: 225.08829.

*4.1.13. (±)-6,7-Dimethyl-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**24**).* Yield 88%, mp 98–98.5 °C, FTIR (solid) cm^{-1}: 1718, 1696. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (s, 1H), 7.04 (s, 1H), 5.83 (d, 1H, *J*=6.9 Hz), 3.39–3.19 (m, 2H), 2.92–2.77 (m, 2H), 2.36 (dd, 1H, *J*=15.6, 5.4 Hz), 2.26 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5 (s), 139.5 (s), 138.3 (s), 135.9 (s), 135.6 (s), 126.5 (d), 125.7 (d), 87.3 (d), 37.1 (2×t), 35.3 (d), 19.5 (q), 19.2 (q). HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}O_2$ $(M+Na)^+$: 225.08915, found: 225.08965.

*4.1.14. (±)-5,8-Dimethyl-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**25**).* Yield 84%, mp 87.2–87.7 °C, FTIR (solid) cm^{-1}: 1752, 1692. ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, 1H, *J*=7.5 Hz), 6.99 (d, 1H, *J*=7.5 Hz), 5.95 (d, 1H, *J*=7.2 Hz), 3.41–3.31 (m, 1H), 3.29–3.18 (m, 1H), 2.98–2.89 (m, 1H), 2.77 (dd, 1H, *J*=16.5, 4.5 Hz), 2.44 (dd, 1H, *J*=16.5, 4.5 Hz), 2.38 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.4 (s), 141.1 (s), 136.6 (s), 133.4 (s), 131.2 (s), 130.3 (d), 128.3 (d), 87.2 (d), 36.9 (t), 36.0 (t), 35.6 (d), 18.3 (q), 17.6 (q). HRMS (ESI) *m*/*z* calcd for $C_{13}H_{14}O_2$ $(M+Na)^+$: 225.08915, found: 225.08896.

*4.1.15. 5-Bromo-3-methylfuran-2(5H)-one (**8**).* To 3-methylfuran-2(5*H*)-one (0.20 g, 2.06 mmol) in dry CCl_4 (20 mL) was added NBS (0.40 g, 2.26 mmol) and AIBN (5 mg) and the resulting reaction mixture was heated at reflux for 2 h while irradiating with a 250 W lamp. The mixture was cooled to 0 °C and the solid succinimide was filtered off. The solvent was removed in vacuo to give bromobutenolide **8**, which was used as such in the coupling step.

4.1.16. (3aR,8bS*,E)-3-(((R*)-4-Methyl-5-oxo-2,5-dihydrofuran-2-yl)oxymethylene)-3,3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan-2-one **5a** and its 2′S* diastereomer **5b**.* Potassium *tert*-butoxide (0.31 g, 2.75 mmol) was added in small portions to a solution of lactone **22** (0.40 g, 2.29 mmol) and methyl formate (0.30 mL, 3.44 mmol) in anhydrous THF (10 mL, freshly distilled) with stirring at 0 °C under nitrogen. Stirring was continued at room temperature until all lactone had reacted (monitored by TLC, EtOAc/*n*-heptane 3:7). THF was removed in vacuo. The resulting salt was used as such in the coupling with bromobutenolide **8**.

To a solution of formylated product **26** in DME (10 mL) under nitrogen was added a solution of bromobutenolide **8** in DME (5 mL). The reaction mixture was stirred overnight, DME was evaporated, diluted with water (15 mL) and extracted with EtOAc (3×20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The resulting diastereomeric mixture was purified by flash chromatography (SiO_2, EtOAc/*n*-heptane 1:1) to afford two partly separated diastereomeric products (**5a** and **5b**, 0.54 g, 80%). The faster moving diastereomer was crystallized from CH_2Cl_2/*n*-hexane to give GR24 (**5a**) as colourless crystals. The slower moving diastereomer was also crystallized from CH_2Cl_2/*n*-hexane to give GR24 isomer **5b** as colourless crystals. Analytical data were in agreement with those reported in the literature.[11]

GR24 analogues **30a**, **30b**, **31a**, **31b**, **32a** and **32b** were prepared by the same procedure.

Diastereomeric products **30a** and **30b** were obtained in 74% overall yield.

4.1.17. (3aR,8bS*,E)-7,8-Dimethyl-3-(((R)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)oxymethylene)-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**30a**).* Mp 180.8–181.2 °C, FTIR (solid) cm^{-1}: 1778, 1735, 1683. ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 1H, *J*=2.4 Hz), 7.12 (d, 1H, *J*=7.8 Hz), 6.97–6.93 (m, 2H), 6.15–6.13 (m, 1H), 5.99 (d, 1H, *J*=8.1 Hz), 3.95–3.87 (m, 1H), 3.38 (dd, 1H, *J*=16.5, 9.5 Hz), 3.03 (dd, 1H, *J*=16.5, 3.6 Hz), 2.32 (s, 3H), 2.25 (s, 3H), 2.01 (t, 3H, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0 (s), 169.8 (s), 150.3 (d), 140.6 (d), 139.7 (s), 137.3 (s), 135.3 (s), 135.2 (s), 134.7 (s), 131.4 (d), 121.5 (d), 113.2 (s), 100.1 (d), 85.4 (d), 38.2 (t), 37.0 (d), 19.1 (q), 15.2 (q), 10.2 (q). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}O_5$ $(M+Na)^+$: 349.10519, found: 349.10476.

4.1.18. (3aR,8bS*,E)-7,8-Dimethyl-3-(((S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)oxymethylene)-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**30b**).* Mp 190.9–191.4 °C, FTIR (solid) cm^{-1}: 1778, 1739, 1679. ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, 1H, *J*=2.7 Hz), 7.11 (d, 1H, *J*=7.5 Hz), 6.97–6.93 (m, 2H), 6.18–6.16 (m, 1H), 6.00 (d, 1H, *J*=7.8 Hz), 3.95–3.87 (m, 1H), 3.38 (dd, 1H, *J*=16.8, 9.6 Hz), 3.02 (dd, 1H, *J*=16.8, 3.6 Hz), 2.33 (s, 3H), 2.25 (s, 3H), 2.02 (t, 3H, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0 (s), 169.8 (s), 150.2 (d), 140.6 (d), 139.8 (s), 137.2 (s), 135.3 (s), 135.1 (s), 134.6 (s), 131.4 (d), 121.6 (d), 113.3 (s), 100.1 (d), 85.4 (d), 38.2 (t), 37.1 (d), 18.8 (q), 15.2 (q), 10.2 (q). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}O_5$ $(M+Na)^+$: 349.10519, found: 349.10543.

Diastereomeric products **31a** and **31b** were obtained in 76% overall yield.

4.1.19. (3aR,8bS*,E)-6,7-Dimethyl-3-(((R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)oxymethylene)-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**31a**).* Mp 233.8–234.3 °C, FTIR (solid) cm^{-1}: 1787, 1726, 1679. ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, 1H, *J*=2.7 Hz), 7.24 (s, 1H), 6.99 (s, 1H), 6.95 (t, 1H, *J*=1.5 Hz), 6.12 (t, 1H, *J*=1.5 Hz), 5.87 (d, 1H, *J*=7.5 Hz), 3.93–3.85 (m, 1H), 3.34 (dd, 1H, *J*=16.8, 9.3 Hz), 3.01 (dd, 1H, *J*=16.8, 3.1 Hz), 2.24 (s, 6H), 2.01 (t, 3H, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (s), 169.8 (s), 150.4 (d), 140.6 (d), 139.6 (s), 138.4 (s), 136.05 (s), 135.60 (s), 135.36 (s), 126.58 (d), 125.49 (d), 113.04 (s), 100.1 (d), 85.5 (d), 38.7 (t), 36.5 (d), 19.5 (q), 19.2 (q), 10.2 (q). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}O_5$ $(M+Na)^+$: 349.10519, found: 349.10503.

4.1.20. (3aR,8bS*,E)-6,7-Dimethyl-3-(((S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)oxymethylene)-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**31b**).* Mp 195.4–195.9 °C, FTIR (solid) cm^{-1}: 1769, 1748, 1674. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 1H, *J*=2.4 Hz), 7.24 (s, 1H), 6.99 (s, 1H), 6.96–6.94 (m, 1H), 6.18–6.16 (m, 1H), 5.88 (d, 1H, *J*=7.8 Hz), 3.93–3.85 (m, 1H), 3.33 (dd, 1H, *J*=16.8, 9.3 Hz), 3.00 (dd, 1H, *J*=16.8, 3.3 Hz), 2.24 (s, 6H), 2.02 (t, 3H, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (s), 169.8 (s), 150.4 (d), 140.6 (d), 139.7 (s), 138.4 (s), 135.9 (s), 135.5 (s), 135.3 (s), 126.5 (d), 125.5 (d), 113.1 (s), 100.2 (d), 85.5 (d), 38.6 (t), 36.5 (d), 19.5 (q), 19.2 (q), 10.2 (q). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}O_5$ $(M+Na)^+$: 349.10519, found: 349.10511.

Diastereomeric products **32a** and **32b** were obtained in 73% overall yield.

4.1.21. (3aR,8bS*,E)-5,8-Dimethyl-3-(((R*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)oxymethylene)-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**32a**).* Mp 179.3–179.8 °C, FTIR (solid) cm^{-1}: 1787, 1744, 1670. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, 1H, J=2.4 Hz), 7.07–7.04 (m, 1H), 7.00 (s, 1H), 6.98 (t, 1H, J=1.5 Hz), 6.18 (t, 1H, J=1.5 Hz), 5.99 (d, 1H, J=7.8 Hz), 3.97–3.89 (m, 1H), 3.34 (dd, 1H, J=16.8, 9.6 Hz), 2.93 (dd, 1H, J=16.8, 3.9 Hz), 2.40 (s, 3H), 2.19 (s, 3H), 2.04 (t, 3H, J=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (s), 169.6 (s), 150.0 (d), 141.0 (s), 140.4 (d), 136.0 (s), 135.6 (s), 133.5 (s), 131.0 (s), 130.4 (d), 128.2 (d), 113.4 (s), 100.0 (d), 85.2 (d), 37.7 (t), 36.6 (d), 17.8 (q), 17.5 (q), 10.3 (q). HRMS (ESI) m/z calcd for $C_{19}H_{18}O_5$ $(M+Na)^+$: 349.10519, found: 349.10352.

4.1.22. (3aR,8bS*,E)-5,8-Dimethyl-3-(((S*)-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)oxymethylene)-3,3a,4,8b-tetrahydro-2H-indeno[1,2b]furan-2-one (**32b**).* Mp 230.8–231.3 °C, FTIR (solid) cm^{-1}: 1778, 1731, 1674. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 1H, J=2.7 Hz), 7.05 (d, 1H, J=7.5 Hz), 6.99 (s, 1H), 6.97 (t, 1H, J=1.5 Hz), 6.19–6.18 (m, 1H), 5.99 (d, 1H, J=8.1 Hz), 3.96–3.88 (m, 1H), 3.32 (dd, 1H, J=17.1, 9.6 Hz), 2.92 (dd, 1H, J=17.1, 3.6 Hz), 2.39 (s, 3H), 2.18 (s, 3H), 2.03 (t, 3H, J=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0 (s), 169.8 (s), 150.2 (d), 141.2 (s), 140.5 (d), 136.5 (s), 135.4 (s), 133.4 (s), 131.2 (s), 130.4 (d), 128.2 (d), 113.4 (s), 100.2 (d), 85.5 (d), 37.6 (t), 36.6 (d), 18.1 (q), 17.7 (q), 10.3 (q). HRMS (ESI) m/z calcd for $C_{19}H_{18}O_5$ $(M+Na)^+$: 349.10519, found: 349.10392.

*4.1.23. Methyl 4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**33**).* To a solution of **15** (2.01 g, 9.01 mmol) in dry CH_2Cl_2 (40 mL) was added oxalyl chloride (1.37 g, 10.8 mmol). Two drops of dry DMF were added to initiate the reaction. The reaction mixture was stirred at room temperature for 1 h, after which the solvent was removed in vacuo. The resulting product was dissolved in CH_2Cl_2 (20 mL) and then gradually added to a slurry of $AlCl_3$ (2.40 g, 18.0 mmol) in CH_2Cl_2 (20 mL) at −30 °C. The reaction mixture was stirred at 0 °C for 4 h and then overnight at room temperature. The water (30 mL) was added dropwise to quench $AlCl_3$ followed by 1 M HCl (2 mL) to make the solution clear. The product was extracted with CH_2Cl_2 (2×50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The product was chromatographed over silica gel using EtOAc/*n*-heptane (2:8) to yield **33** (1.25 g, 74%) as a white solid. Mp 88.8–89.3 °C, FTIR (solid) cm^{-1}: 1726, 1679. ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, 1H, J=7.4 Hz), 7.43 (t, 1H, J=7.4 Hz), 7.28–7.20 (m, 2H), 3.65 (s, 3H), 3.15–3.08 (m, 3H), 2.91–2.70 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0 (s), 172.8 (s), 141.3 (s), 133.3 (d), 131.2 (s), 128.3 (d), 126.5 (d), 126.4 (d), 51.5 (q), 40.0 (d), 39.4 (t), 31.3 (t). HRMS (ESI) m/z calcd for $C_{12}H_{12}O_3$ $(M+Na)^+$: 227.06841, found: 227.06642.

4.2. Bioassay

The germination bioassay was conducted as reported earlier.[9–11,13] *S. hermonthica* seeds were conditioned and then incubated with stimulant solution. Four concentrations were used. The number of germinated seeds was counted under a microscope. All tests were carried out in triplicate. The bar diagram in Figure 2 shows the average values with the standard deviation.

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