Tetrahedron Letters 53 (2012) 4514–4517

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel approach toward the synthesis of strigolactones through intramolecular [2+2] cycloaddition of ketenes and ketene-iminiums to olefins. Application to the asymmetric synthesis of GR-24

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ARTICLE INFO

Article history:
Received 26 April 2012
Revised 30 May 2012
Accepted 4 June 2012
Available online 12 June 2012

Keywords:
Strigolactones
Cycloaddition
Ketene
Ketene-iminium
Seed germination inducer

ABSTRACT

An intramolecular [2+2] cycloaddition of ketenes and ketene-iminium was developed for the preparation of GR-24, a synthetic analogue of the family of strigolactone plant hormones. Excellent levels of regioselectivity and of chiral induction were obtained using a bulky chiral amine for the formation of the cyclobutanone and a subsequent regioselective Baeyer–Villiger afforded the tricyclic lactone core of (+)-GR-24.

Strigolactones are a family of plant secondary metabolites whose first member strigol was isolated in 1966 from the root exudates of cotton and identified as the germination inducer for the parasitic weeds of *Striga* and *Orobanchae* species.[1] Since then, more than 14 other strigolactones have been isolated from root exudates of mono- and dicotyledonous plants.[2] However, until recently the various roles played by the strigolactones in plants remained uncovered and their importance as phytohormones became clear only in the last few years. In 2005, strigolactones have been shown to be the messenger that triggers symbiosis with arbuscular mycorrhizal (AM) fungi, which helps plants to adapt to environmental changes.[3] Moreover, in 2008, strigolactones were shown to inhibit shoot branching and act as the key phytohormone influencing plant architecture.[4] Possibly, many additional functions of the strigolactones as phytohormones remain to be uncovered.

Strigolactones are present only in very low concentration in plants and their isolation remains very challenging and time consuming. In order to investigate the roles of these new phytohormones and their precise mode of action, an efficient synthesis of strigolactones is required. Due to the relative complexity of strigol, organic chemists have been interested in developing simplified analogues of strigol. Thus, Johnson et al. reported the preparation of GR-24 **6**, which retained very potent biological activity and is still considered as the standard for synthetic strigolactones.[5] Later, Zwanenburg et al. developed synthetic analogues of strigolactones to understand their structure–activity relationship and possibly identify their putative receptors in plants.[6] Although improved by Zwanenburg,[7] the current synthesis of GR-24 is not fully satisfactory and not very flexible for the preparation of various analogues. Therefore, we have developed a short, efficient, and flexible stereoselective synthesis of GR-24, in which the tricyclic core structure is obtained by [2+2] intramolecular cycloaddition of a ketene or a ketene-iminium into an olefin followed by a Baeyer–Villiger oxidation (Scheme 1).[8]

The ketene approach was first investigated and the precursor for the cycloaddition was easily prepared from methyl 2-iodoacetic acetate **8** via a Stille coupling with the desired allyl stannane (Scheme 2). The desired acid precursor **10** was obtained in good yield after saponification of ester **9** (81% over 3 steps). Reaction with Ghosez' reagent and subsequent treatment of the acid chloride with triethylamine generate the ketene, which undergoes a [2+2] cycloaddition to give cyclobutanone **5**.[9] The easy formation of ketene **3** and its ability to undergo the desired [2+2] cycloaddition into cyclobutanone **5** were confirmed, as the acid chloride has reacted after only 5 min at 0 °C. However, the yield of the cyclobutanone **5** was disappointing, probably due to competitive side reactions such as dimerization of the ketene (Table 1, entry 1).

In order to minimize this side reaction and favor the intramolecular [2+2] cycloaddition, the ketene has to be generated in low concentration, by a slow addition of the triethylamine to the acid chloride **1** (Table 1, entry 2). The formation of cyclobutanone **5**

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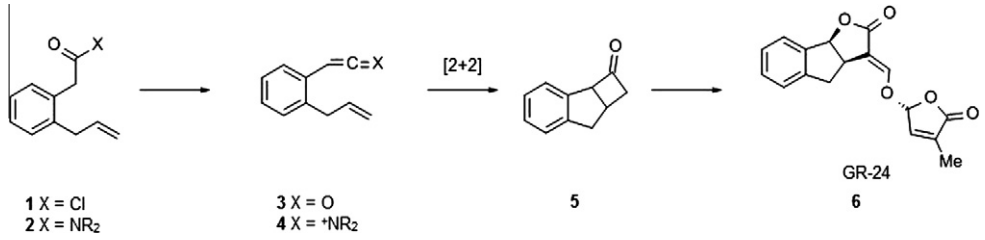
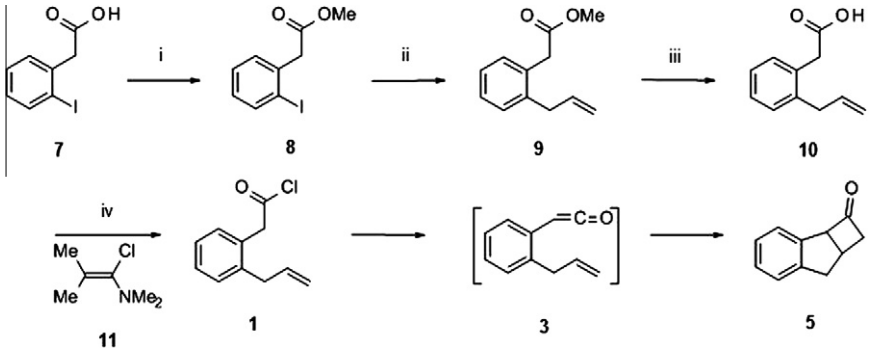
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.013



Scheme 1. Retrosynthetic analysis of GR-24 via [2+2] cycloaddition.



Scheme 2. Intramolecular ketene cycloaddition. Reagents and conditions: (i) MeOH, H_2SO_4, 0 °C, 2 h, quant.; (ii) allylstannane (1.2 equiv), $Pd(PPh_3)_4$ (5%), toluene, reflux, 16 h, 65%; (iii) LiOH (1.1 equiv), aq THF, rt, 5 h, quant.; (iv) **11** (1.2 equiv), CH_2Cl_2, 0 °C; then NEt_3 (1.5 equiv).

Table 1
Cycloaddition of ketene **3**

Entry	*T* (°C)	[C] (M)	Addition of Et_3N	Yield of **5** (%)
1	0 to rt	0.02	1 min at 0 °C	7
2	0	0.02	4 h at 0 °C	18
3	40	0.02	4 h at 40 °C	65
4	40	0.05	4 h at 40 °C	48

was improved, thought still not satisfactory. Gratefully, higher temperatures favor the intramolecular cycloaddition of the ketene on the C=C bond and when the triethylamine was slowly added to a refluxing solution of the acid chloride **1**, the corresponding cyclobutanone **5** was obtained in 65% yield (Table 1, entry 3).

These encouraging results still needed improvement to allow a practical approach to GR-24. In particular, the high dilution required for the reaction (0.02 M) was not suitable for large scale synthesis. Unfortunately, attempts to increase the concentration decreased already the yield rather significantly (Table 1, entry 4).

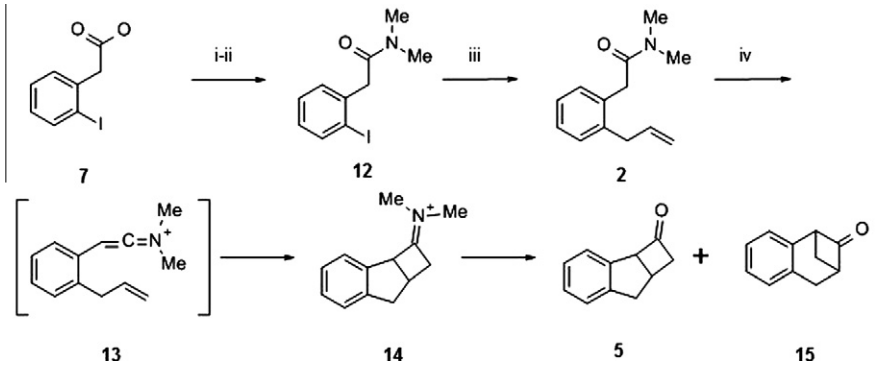
Therefore, we decided to turn our attention to the cycloaddition of ketene-iminiums as they are known to be more reactive than the corresponding ketenes and that they do not undergo dimerization.[8a,g,h] Ketene-iminiums are readily accessible from the corresponding secondary amide according to the method developed by Ghosez.[10] Thus, 2-iodo-phenyl acetic acid **7** was converted into dimethylamide **12** in quantitative yield. Then, a Stille coupling with allylstannane or a Suzuki coupling with allyl pinacol boronate in the presence of CsF afforded olefin **2** in good yields (Scheme 3).

Upon treatment with triflic anhydride in the presence of a base such as collidine, the ketene-iminium **13** is formed and undergoes intramolecular cycloaddition. After hydrolysis of the cyclobutanone iminium **14**, the cyclobutanone **5** is isolated in excellent yield (82%). However, the desired product **5** resulting from the expected 'head-to-head' [2+2] intramolecular cycloaddition is contaminated by the formation of the 'head-to-tail' regioisomer **15** (Table 2, entry 1).

The superiority of the approach using the ketene-iminium compared to the previous one with the corresponding ketene is clearly demonstrated as the reaction could be carried out at reasonable concentration in high yield (Table 2, entry 2). The formation of regioisomer **15** is independent of the conditions of the reaction and is rather unexpected because mono-alkyl-substituted olefins are reported to react preferentially at the terminal position of the C=C bond.[8a,g,h] We postulated that the formation of **15** could arise from the very high reactivity of the ketene-iminium. Sterically, the approach of the ketene-iminium with the terminal carbon atom should be favored. Moreover, the largest coefficient in the HOMO of the olefin is on the terminal carbon atom. However, in the HOMO of the C=C bond, the difference between the size of the coefficients might be reduced because of the electron withdrawing character of the phenyl ring. In addition, we speculated that increasing the bulk of the amide could decrease the reactivity of the ketene-iminium and increase the steric repulsion in the 'head-to-tail' cyclization, improving the regioselectivity of the cycloaddition. Both di-benzyl and di-isopropyl amides were prepared and submitted to the conditions of the cycloaddition. Gratefully, cyclobutanone **5** was still formed in good yield and with almost complete control of the regioselectivity in the case of the very bulky diisopropyl amide **17**. [15]. Longer reaction times were required both for the cycloaddition and for the hydrolysis of the resulting iminium (Scheme 4).

With cyclobutanone **5** in hand, we then moved to the completion of the synthesis of GR-24. Baeyer–Villiger oxidation of **5** with hydrogen peroxide proceeded with complete regiocontrol and lactone **18** was formed in very high yield (90%) (Scheme 5). Lactone **18** is deprotonated with *t*BuOK and acylated with methyl formate, before being alkylated with the freshly prepared bromobutenolide **19**. The two diastereoisomers of GR-24 (±) **20** and (±) **21** were easily separated by column chromatography (Scheme 5).

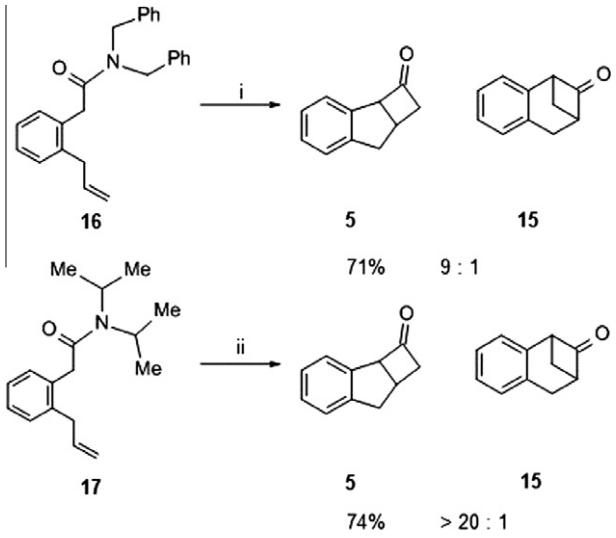
An additional advantage of using ketene-iminium for intramolecular cycloaddition reaction is that the corresponding cyclobutanone can be obtained, after hydrolysis of the iminium salt, with very high enantiomeric excess using an optically pure amine with C-2 symmetry.[11] Therefore, we applied this methodology to the asymmetric synthesis of (+)-GR-24 ((+)-**20**). Indeed, the isomer (+)-**20** is by far the most potent isomer among the 4 isomers of



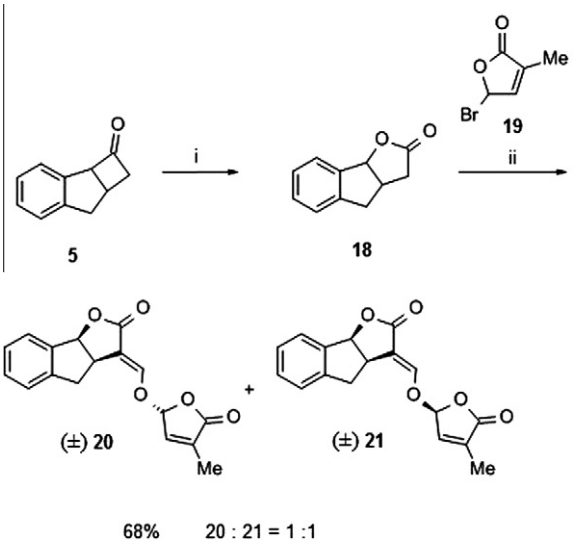
Scheme 3. Intramolecular ketene-iminium cycloaddition. Reagents and conditions: (i) oxalyl chloride (2 equiv), DMF (cat.), CH_2Cl_2; (ii) $NHMe_2$ (4 equiv), CH_2Cl_2, 0 °C, 99%; (iii) tributylallylstanane (1.5 equiv), $Pd(PPh_3)_4$ (3%), toluene, reflux, 16 h, 81%; or pinacol allylborane (1 equiv), CsF (1 equiv), $Pd(PPh_3)_4$ (5%), THF, reflux 4 h (76%); (iv) Tf_2O, collidine, CH_2Cl_2; then H_2O, 82%.

Table 2
Cycloaddition of ketene-iminium **13**

Entry	*T* (°C)	[C] (M)	Yield (%)	Selectivity 5:15
1	rt	0.05	82	7:1
2	rt	0.1	70	7:1
3	0	0.05	50	6:1
4	40	0.05	81	7:1



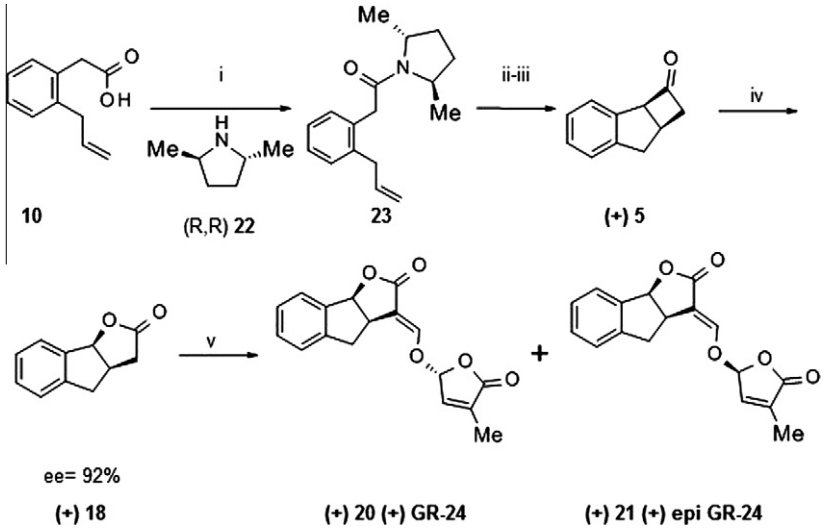
Scheme 4. Improved regioselectivity of the intramolecular [2+2] cycloaddition with bulky ketene-iminium. Reagents and conditions: (i) Tf_2O (1.1 equiv), collidine (1.2 equiv), 8 h; then CCl_4, water, reflux, 5 h, 71%; (ii) Tf_2O (1.1 equiv), collidine (1.2 equiv), 24 h; then CCl_4, water, reflux, 6 h, 74%;



Scheme 5. Synthesis of GR-24. Reagents and conditions: (i) H_2O_2 (3 equiv), AcOH, 0 °C, 3 h, 90%; (ii) *t*BuOK (1.2 equiv), HCO_2Et (3 equiv), THF, 0 °C, 3 h; then **19**, 0 °C, 3 h, 68% (mixture of diastereoisomers **20** and **21**).

GR-24 for seed germination induction.[12] The coupling of acid chloride **1** with the optically pure (*R*,*R*)-amine **22** results in low yield of the desired amide **23** due to the concomitant formation of ketene **3** as the side product. However, excellent yield of amide **23** is achieved using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) in the presence of 1-hydroxy-7-azabenzotriazole.[13] The intramolecular [2+2] cycloaddition of the optically pure ketene-iminium gave the corresponding cyclobutanone (+)-**5** in excellent yield and with a very good regioselectivity (13:1) (Scheme 6). The bulk of the (2*R*,5*R*)-2,5-dimethylpyrrolidine amide favors the approach of the central carbon of the ketene-iminium toward the terminal carbon atom of the olefin (vide supra). The cyclobutanone was oxidized to the corresponding lactone (+)-**18** in excellent yield and with very high enantiomeric excess (92% determined by chiral HPLC analysis). The level of chiral induction obtained with amine **22** is excellent and superior to the one observed with other chiral amines with C-2 symmetry.[14] Lactone (+)-**18** is further elaborated into (+)-**20**, the isomer of GR-24 having the same absolute stereochemistry as the natural strigolactones (Scheme 6).

In summary, we have reported here the use of intramolecular [2+2] cycloaddition of ketene and ketene-iminium for the short and efficient stereoselective synthesis of the core structure of the strigol analogue GR-24. Excellent regioselectivity was obtained for the ketene as well as for the ketene-iminium cycloadditions, provided that in the latter case bulky substituents are present on the nitrogen atom. Moreover, using large and optically pure substituents on the nitrogen atom of the ketene iminum, we obtained very high chiral induction for the formation of the desired cyclobutanone derivative with enantiomeric excess as high as 92%. The complete regioselectivity and the very high yield of the Baeyer–Villiger oxidation at the benzylic position contribute significantly to the overall efficiency of the synthesis allowing the broad evaluation of the biological performance of strigolactone derivatives not only in green houses but also in the field. This new methodology to synthesize strigolactones is currently successfully applied to the synthesis of the natural products and these results will be reported very soon, together with the biological activity of these compounds.



Scheme 6. Asymmetric synthesis of (+)-GR-24 (+)-**20**. Reagents and conditions: (i) EDCI (1.4 equiv), HOAt (1.4 equiv), Et_3N (3 equiv), DMF, 16 h, 93%; (ii) Tf_2O (1.1 equiv), collidine (1.2 equiv), CH_2Cl_2, rt, 6 h; (iii) CCl_4, H_2O, reflux 4 h, 68%; (iv) H_2O_2 (3 equiv), AcOH, 0 °C, 92%; (v) *t*BuOK (1.2 equiv), HCO_2Et (3 equiv), THF, 0 °C; then **19**, 20% of (+) **20** and 20% of (+) **21**.

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14. Reaction using bis(α-methylbenzyl)amine as a chiral auxiliary only led to the formation of the lactone (+)-**18** in only 44% ee.
15. *A typical procedure for the ketene-iminium cycloaddition*: To a solution of amide **17** (0.100 g, 0.386 mmol) in dichoromethane (10 mL) was added collidine (0.061 mL, 0.463 mmol) followed by triflic anhydride (0.072 mL, 0.424 mmol). The solution was stirred at room temperature for 24 h. The solvents were removed in vacuo and the residue was taken up in carbon tetrachloride (4 mL) and water (4 mL) and the biphasic mixture was stirred at 70 °C for 6 h. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography eluting with cyclohexane and ethyl acetate (20/1) to give 48 mg of colorless oil. ES: 159 (20%), 143 (100%); IR (liq.) cm^{-1}: 2921, 1777; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.36 (2H, m), 7.23–7.29 (2H, m), 4.65–4.80 (1H, m), 3.46 (1H, dd, *J* = 16.9, 8.1 Hz), 3.36 (1H, ddd, *J* = 18.0, 8.1, 4.8 Hz), 3.11–3.19 (1H, m) 3.08 (1H, d, *J* = 16.9 Hz), 2.88 (1H, ddd, *J* = 18.0, 5.9, 3.3 Hz).