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Original article

Synthesis and fungicidal activity study of novel daphneolone analogs with 2,6-dimethylmorpholine

Gao-Fei Xu [a], Xin-Ling Yang [a], Peng Lei [a], Xi-li Liu [b], Xue-Bo Zhang [a], Yun Ling [a,*]

[a] Department of Applied Chemistry, College of Science, China Agricultural University, Beijing 100193, China
[b] Department of Plant Pathology, College of Agronomy and Biotechnology, China Agricultural University, Beijing 100193, China

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ABSTRACT

A series of novel daphneolone analogs was designed and synthesized on the basis of natural product 1,5-diphenyl-2-penten-1-one (**I**) from *Stellera chamaejasme* L. as lead compound, whereby 2,6-dimethylmorpholine moiety was introduced to replace 1-phenyl group. Their structures were confirmed by IR, ^{1}H NMR, and HRMS (ESI) or elemental analysis, ^{13}C NMR for some representative compounds. The two isomers of target compounds were separated and identified by NOESY technique and chemical method. All of the synthesized compounds have been evaluated for anti-plant pathogenic fungi activities. The results showed that some compounds exhibited moderate to good antifungal activities against tested fungi at the concentration of 50 mg/L. Among them, compound **7d**, with a 4-bromine-substituted phenyl group and *cis*-2,6-dimethylmorpholine moiety, displayed best activity with an EC_{50} of 23.87 μmol/L against *Valsa mali*, superior to lead compound **I**. In addition, preliminary structure–activity relationship analysis indicated that, between two isomers of target compounds, the antifungal activities of the isomer with *cis*-2,6-dimethylmorpholine were better than the *trans*-isomer.

1. Introduction

Natural products (NPs) continue to play a highly significant role in the drug discovery and development process [1]. Natural products and their analogs, derivatives account for almost half of the 877 approved drugs all over the world from 1981 to 2010 [2]. In fact, exploring a range of natural product sources is also an important means to identify and develop novel lead compounds and agrochemicals against a range of insect pest and plant diseases in the recent decades. 1,5-Diphenyl-2-penten-1-one (**I**) and 1,5-diphenylpentan-1-one (**II**) (Fig. 1) were first isolated from *Stellera chamaejasme* L. (Thymelaeaceae, used in Chinese traditional medicine) in 2001 [3]. Laboratory bioassay showed that these two compounds had strong contact activity and very good antifeedant activity against *Aphis gossypii* and *Schizaphis graminum*. Moreover, compound **I** exhibited the similar effects on ATP-ase found in the three membranes amongst which the plasma membrane Ca^{2+}-Mg^{2+}-ATPase is the primary target [4,5]. After that, various analogs with different bioactivities were synthesized by Hou's group [6–8]. Our team is also devoted to the structural modification of **I** and **II** in the previous study. We found, beside insecticidal activity, compounds **I**, **II** and their analogs also have antifungal activities [9–12], which indicated that they could be an interesting lead structure of fungicide.

In continuation of our earlier interest in this field, here it was planned to synthesize new analogs by introducing 2,6-dimethylmorpholine moiety, a functional group of commercial fungicide fenpropimorph, tridemorph, dodemorph, *etc.*, to replace one side phenyl group of compound **I**, with expectation to obtain the new products with simple structure and better antifungal activities. The two isomers of target compounds were separated and identified by NOESY technique and chemical method. Their antifungal activities against six plant pathogenic fungi were evaluated for the first time. It is expected that the results of this study might be valuable for the discovery of new molecules as agrochemicals.

2. Experimental

^{1}H NMR spectra were collected on Bruker AM-300 (300 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with a KBr disk. High resolution mass

* Corresponding author.
E-mail address: lyun@cau.edu.cn (Y. Ling).

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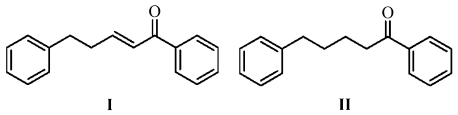


Fig. 1. The chemical structure of compounds **I** and **II**, originally isolated from *Stellera chamaejasme* L.

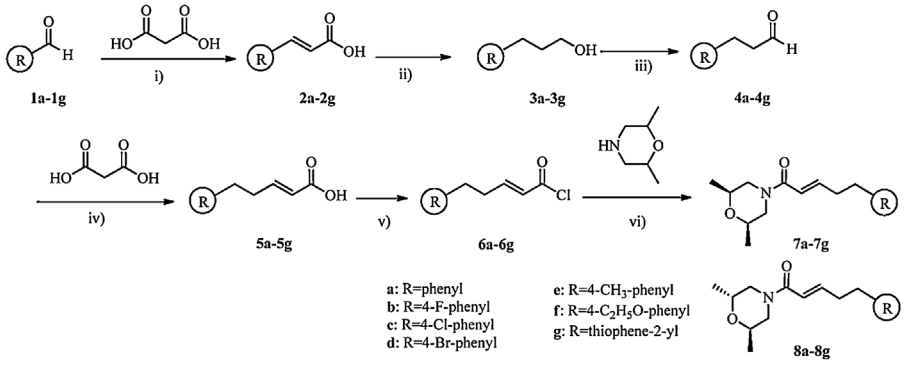
spectrometry (HRMS) data were recorded on an FTICR-MS Varian 7.0 T FTICR-MS instrument. Elemental analysis was determined on an ST-Carloerba. Co elemental analyser. All the reagents were obtained commercially and used without further purification. Column chromatography purification was carried out by using silica gel.

The general synthetic scheme for representative compounds **7a–7g**, **8a–8g** is shown in Scheme 1. Substituted cinnamic acids **2** were prepared from substituted benzaldehyde **1** through knoevenagel reaction according to the method in the literature [13]. Compounds **2a–2g** were reduced by lithium aluminum hydride ($LiAlH_4$) to afford substituted phenylpropanol **3a–3g**. Next, compounds **3a–3g** were oxidized by PCC to afford substituted benzenepropanal **4**. (*E*)-5-(Substituted phenyl)pent-2-enoic acids **5** were obtained through the same process as compound **2**. The general procedure of compounds **2a–2g** to **5a–5g** is described in the Supporting information.

Target compounds **7a–7g** and **8a–8g** were prepared by the acylchloriration of compounds **5a–5g** followed by a condensation reaction with 2,6-dimethylmorpholine at the presence of triethylamine (TEA). The general procedure describe as below: To a stirred solution of compounds **5** (6 mmol) in chloroform, thionyl chloride (18 mmol) and one to two drop of *N*,*N*-dimethyl formamide (DMF) was added, the resulted mixture was refluxed for 1 h. Then the solvent and remaining thionyl chloride was removed under reduced pressure, the residue was dissolved in dichloromethane (DCM) to get the stock solution of **6** without further purification. The solution of **6** was dropped slowly into the solution of 2,6-dimethylmorpholine (6 mmol) and TEA (6.6 mmol) in DCM at 0 °C, the resulted mixture was stirred for 1 h. After the reaction completed, the mixture was washed with water. Organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Then the residue was separated by chromatography on silica-gel column (*n*-hexane:ethyl acetate = 4:1, v/v) to obtain the corresponding **7a–7g**, **8a–8g**.

3. Results and discussion

As shown in Scheme 1, the target compounds **7a–7g**, **8a–8g** were synthesized *via* six steps, including Knoevenagel reaction, reduction, oxidation, and amidation, with substituted benzaldehyde as starting material. Characterization data of all the target compounds are included in the Supporting information. The material 2,6-dimethylmorpholine we used in the last step was consisted of a mixture of *cis*-form and *trans*-form, due to the two methyl group could be on the same side or the different side of morpholine ring, namely *cis*-2,6-dimethylmorpholine and *trans*-2,6-dimethylmorpholine. Therefore we obtained our target compounds with two isomers (**7** and **8**) as well, which can be separated easily by silica-gel column but very complicated to be identified. Clear difference could be seen on the ^1H NMR spectra of two representative compounds **7f** and **8f** (Fig. 2). First, NOESY



Scheme 1. Synthetic route of title compounds. (i) piperidine, pyridine, 85 °C, 6 h; (ii) $LiAlH_4$, THF, reflux, 4 h; (iii) PCC, CH_2Cl_2, r.t. 1 h; (iv) piperidine, pyridine, 85 °C, 6 h; (v) $SOCl_2$, DMF, $CHCl_3$, reflux 1 h; (vi) TEA, CH_2Cl_2, r.t. 2 h.

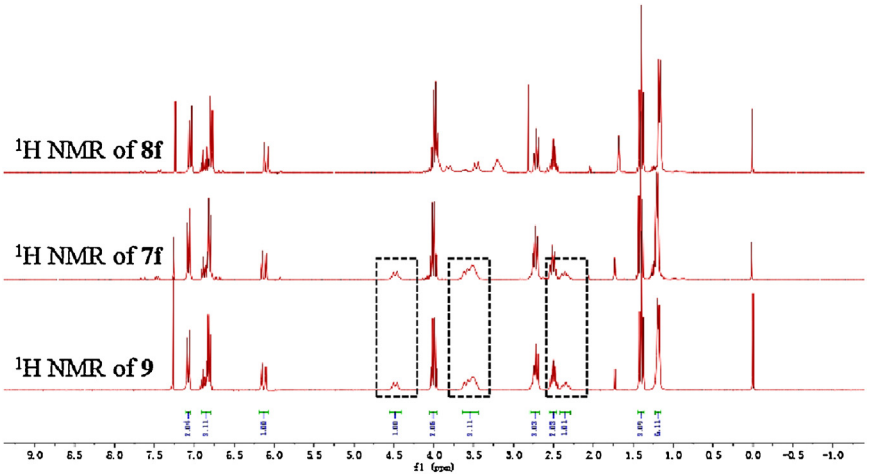


Fig. 2. The ^1H NMR spectra of compound **7f**, **8f** and **9.**