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Asymmetric Construction of Cyclobutanes via Direct Vinylogous Michael Addition/Cyclization of β,γ-Unsaturated Amides

Yuzhen Chen, Yichen Wang, Shuzhong Wang, Yan-Yan Ma, Deng-Gao Zhao, Ruoting Zhan, and Huicai Huang*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02488 Read Online

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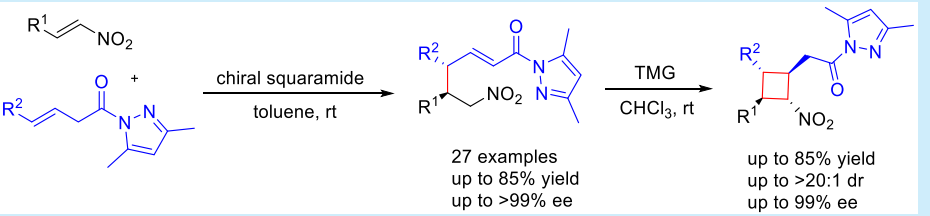


ABSTRACT: The construction of cyclobutanes has attracted much attention because of its unique four-membered ring skeleton. Herein, we report the highly enantioselective direct vinylogous Michael reaction of β,γ-unsaturated pyrazole amides and nitroolefin using a squaramide catalyst. Cyclobutane derivatives were obtained by subsequent cyclization in good yields (up to 85%) with excellent enantioselectivities (up to 99% ee). Importantly, the large-scale reaction experiment confirmed the reliability of the vinylogous reaction. Furthermore, the synthetic utility of the vinylogous adducts and cyclobutane derivatives has been realized.

Natural products containing a cyclobutane skeleton are widely distributed, and many of them have significant biological activities such as anticancer and antibacterial activity.[1] For example, a series of alkaloid pipercyclobutanamides containing a four-membered ring were isolated from the branches of the pepper. The dipiperamide A has been identified to have potent activity of cytochrome P450 (CYP) 3A4, an important enzyme in the body (Figure 1).[1c]

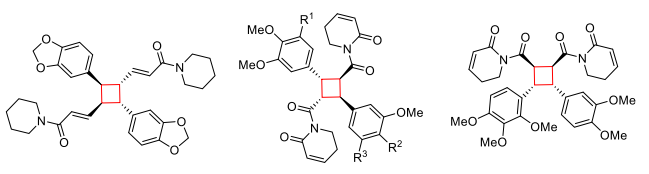


Figure 1. Natural products containing chiral cyclobutane units.

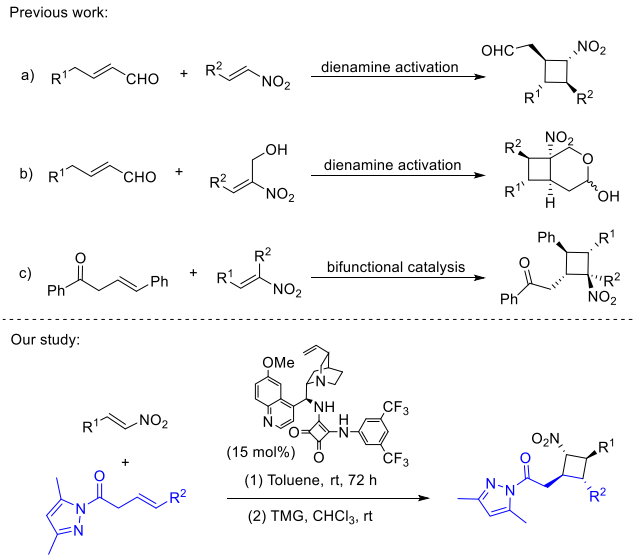
Cyclobutane is a highly strained skeleton, and stereoselective transformations involving this interesting molecule are mainly in the field of photocatalysis[2] and metal catalysis.[3] There are a few examples of the organocatalytic synthesis of chiral cyclobutane derivatives.[4] In 2007, the Ishihara group reported the first organocatalytic enantioselective [2 + 2] cycloaddition reaction of olefins and α-acyloxyacroleins to obtain cyclobutane derivatives through iminium catalysis.[5] It is noteworthy that several groups discovered cyclobutane intermediates in the Michael reaction of aldehydes with nitroolefins.[6] Furthermore, the strategy of the organocatalytic vinylogous Michael reaction[7] was used in the construction of cyclobutanes. In 2012, Jørgensen's group used a bifunctional catalyst that simultaneously activates aldehydes and nitroolefins through the formation of dienamines and hydrogen bonding to give cyclobutane products (Scheme 1a).[8] Subsequently, Vicario and co-workers reported a [2 + 2] annulation/hemiacetal reaction of α-hydroxymethylnitroolefin and α,β-unsaturated aldehyde by cooperative dienamine/hydrogen-bonding catalysis (Scheme 1b).[9] Recently, Hong's group reported a highly enantioselective [2 + 2] annulation of allyl ketones and α-substituent nitroalkenes for the synthesis of cyclobutane derivatives under bifunctional catalysis (Scheme 1c).[10]

Compared with unsaturated aldehydes or ketones,[7] β,γ-unsaturated amides with potential enolization were less explored as active nucleophiles in the vinylogous reaction.[11] In previous work, we investigated a dienolate-mediated asymmetric inverse-electron-demand oxa-Diels–Alder reaction of β,γ-unsaturated pyrazole amides with β,γ-unsaturated α-ketoesters.[12] Subsequently, a regiodivergent vinylogous cyclization reaction of β,γ-unsaturated pyrazole amides was demonstraed.[13] Furthermore, pyrazole as a good leaving group can be easily derivatized to esters, amides, and alcohols under simple conditions.[14] Inspired

Received: July 27, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02488
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Vinylogous Reaction of Nitroolefin Access to Enantioenriched Cyclobutanes

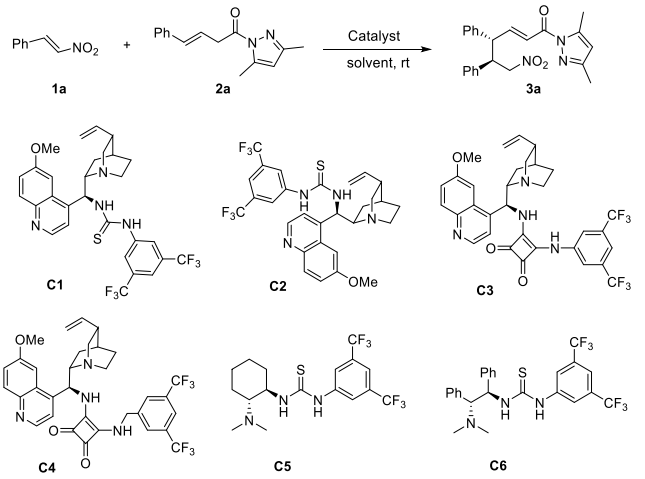


by the above work on synthesizing cyclobutane derivatives, we envision that a direct vinylogous Michael addition/cyclization of β,γ-unsaturated pyrazole amides can be used for the construction of cyclobutanes. Herein, we report a direct vinylogous Michael reaction of β,γ-unsaturated pyrazole amides with nitroalkenes by employing a squaramide organocatalyst and further study the vinylogous Michael products to construct chiral cyclobutane compounds with excellent stereoselectivities.

Our screening started with *trans*-nitrostyrene **1a** and β,γ-unsaturated pyrazole amide **2a** in the presence of 10 mol % of bifunctional organocatalysts (Table 1, entries 1−6). With cinchona-alkaloid-derived thioureas **C1** and **C2** as catalysts, the direct vinylogous Michael reaction proceeded smoothly, affording **3a** with high enantioselectivity but in a low yield (95% ee and −90% ee, entries 1 and 2). Compared to those of the thiourea catalyst, quinine-derived squaramide catalyst[15] **C3** has a better yield and enantioselectivity (entry 3). Encouraged by the results, we used squaramide catalyst **C4** for this reaction, but no improvement of yield was found (entry 4). The reaction was also carried out with Takemoto's catalyst **C5** and tertiary amine thiourea **C6**; unfortunately, lower yields were afforded (42 and 15%, entries 5 and 6). Then more reaction media were investigated with catalyst **C3**. Among the different kinds of solvents (entries 7−10), toluene was an effective solvent considering the yield and enantioselectivity of **3a**. Subsequently, the yield was increased to 81% while the reaction was carried out using 1.5 equiv of **2a** (entry 11). Further optimization of the reaction parameters, such as increasing the amount of catalyst and prolonging the time, could increase the yield to 85% while maintaining the enantioselectivity (entry 12). In other pyrazole amide groups, neither pyrazole nor diphenylpyrazole can obtain a single pure product.[12,13]

Under this optimized condition, we explored the scope of the different substituted nitroalkenes **1**; the results are summarized in Scheme 2. To our delight, all tested nitroalkene substrates could be smoothly converted to the corresponding products (**3a**−**3r**) with excellent stereoselectivities (94−99% ee and >20:1 dr). For instance, with electron-donating and electron-withdrawing groups (such as halogen, methoxy, methyl, trifluoromethyl, and nitro groups) at the *para*- or *meta*-positions,

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**C1**	CH_2Cl_2	12	41	>20:1	95
2	**C2**	CH_2Cl_2	12	19	>20:1	−90
3	**C3**	CH_2Cl_2	12	80	>20:1	94
4	**C4**	CH_2Cl_2	12	51	>20:1	94
5	**C5**	CH_2Cl_2	12	42	>20:1	−95
6	**C6**	CH_2Cl_2	48	15	>20:1	−92
7	**C3**	$CHCl_3$	24	55	>20:1	93
8	**C3**	$PhCF_3$	24	66	>20:1	96
9	**C3**	CH_3CN	24	58	>20:1	98
10	**C3**	toluene	24	72	>20:1	98
11[e]	**C3**	toluene	60	81	>20:1	98
12[f]	**C3**	toluene	72	85	>20:1	98

[a]Unless otherwise noted, the reactions were performed with 1.0 equiv of **1a** (0.10 mmol), 1.2 equiv of **2a** (0.12 mmol), and catalyst **C** (10 mol %) in 1.0 mL of solvent at rt. [b]Yield of the isolated product. [c]The dr was determined by ^{1}H NMR analysis of the crude product. [d]Determined by chiral HPLC analysis. [e]The reaction was carried out using 1.5 equiv of **2a** (0.15 mmol). [f]Catalyst **C3** (15 mol %) and **2a** (0.15 mmol) were used in the reaction.

nitroalkenes were converted into desired products **3a**−**3g** and **3h**−**3i** in good yields (57−85%) with excellent enantioselectivities (94−99% ee). In the *ortho*-position of aromatic rings, halogen-substituted products **3j**−**3l** were obtained in good yields (76−82%) with excellent enantioselectivities (95−97% ee); the yield decreased slightly for the substrate with a methoxy substituent on the phenyl moiety, but product **3m** still maintained excellent stereoselectivity (98% ee, >20:1 dr). Moreover, the double substituent could also be suitable, and product **3n** was afforded in 70% yield with high enantioselectivity (94% ee). The naphthyl **1o** was also compatible under standard reaction conditions, generating the desired product in moderate yield (51%). It is noteworthy that aromatic heterocycle-substituted nitroalkenes (such as thiophene and furan) were also proven to be suitable substrates, and the corresponding products **3p** and **3q** were afforded with good yields (72 and 78%) and excellent enantioselectivities (>99% ee). A phenethyl-substituted nitroalkene **1r** reacted with **2a** to access product **3r** with excellent enantioselectivity (98% ee) but in lower yield.

In the course of further studies, the scope of various β,γ-unsaturated pyrazole amides was evaluated (Scheme 3). Satisfyingly, the reaction proceeded smoothly to obtain products **4** whether there was an electron-donating or electron-with-

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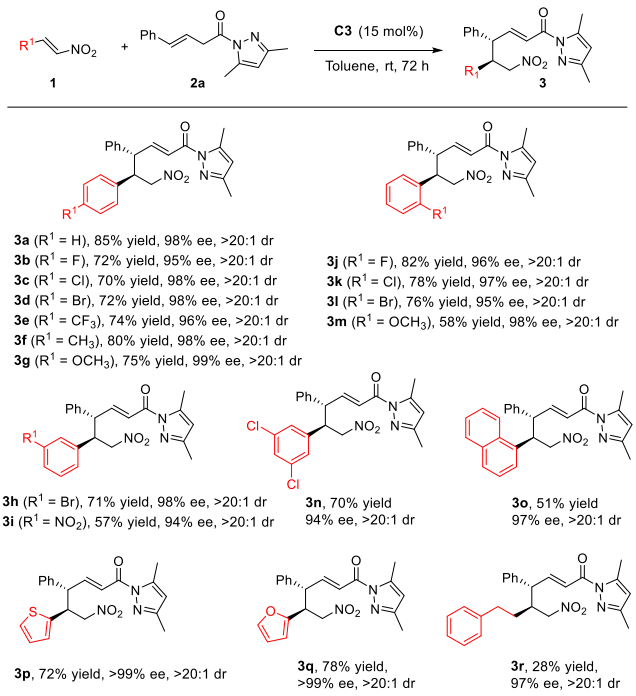
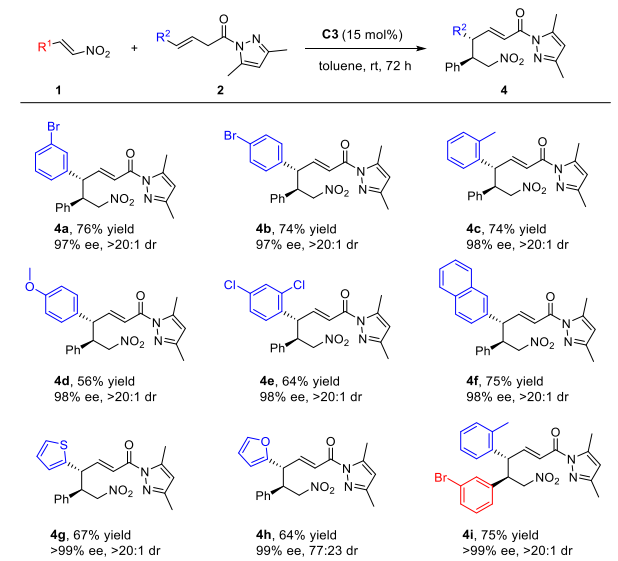
Scheme 2. Scope of Nitroalkenes[a]



[a]All reactions were carried out using **1** (0.20 mmol), **2a** (0.30 mmol), and catalyst **C3** (15 mol %) in toluene (2.0 mL) at rt for 72 h. Yield of the isolated product after flash column chromatography. The ee values were determined by HPLC analysis on a chiral column. The dr was determined by ^{1}H NMR analysis of the crude product.

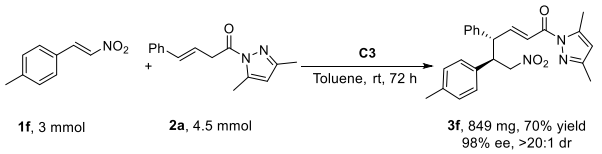
Scheme 3. Scope of *β,γ*-Unsaturated Pyrazole Amides[a]



[a]Unless otherwise noted, all reactions were carried out using 1.0 equiv of **1a** (0.20 mmol), 1.5 equiv of **2** (0.30 mmol), and catalyst **C3** (15 mol %) in 2.0 mL of toluene for 72 h. Yield of the isolated product after flash column chromatography. The ee values were determined by HPLC analysis on a chiral column. The dr was determined by ^{1}H NMR analysis of the crude product.

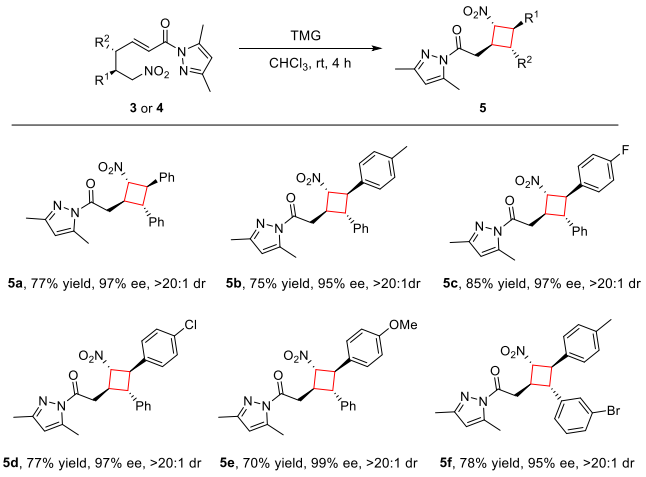
drawing substituent on the phenyl moiety. In view of the results, for different substituents at the *para*-, *meta*-, and *ortho*-positions or double substitution, the corresponding products **4a**−**4e** were obtained in moderate to good yields with high enantioselectivities (97−98% ee). In addition, 2-naphthyl and heteroaromatic allylic amides also gave the desired products **4f** and **4g** in moderate to good yields (67 and 75%) with excellent stereoselectivities (up to >99% ee), but the diastereoselectivity is poor for furyl-substituted product **4h**. Note that the *meta*-substituent on the phenyl of aromatic nitroalkene has almost no effect on the reaction (**4i**, >99% ee, >20:1 dr). Unfortunately, aliphatic-substituted *β,γ*-unsaturated pyrazole amides (methyl or benzyl) were not suitable in this reaction, and almost no product was observed. Meanwhile, a preparative-scale experiment was performed with (*E*)-1-methyl-4-(2-nitrovinyl)-benzene **1f** and *β,γ*-unsaturated pyrazole amide **2a**, and the direct vinylogous Michael reaction occurred smoothly to afford the corresponding product **3f** in 70% yield with 98% ee under the optimized condition (Scheme 4).

Scheme 4. Preparative-Scale Synthesis



After obtaining the vinylogous Michael adducts, we further investigated the synthesis of cyclobutanes. Varieties of bases and solvents were used to investigate the screening of cyclization conditions (for more details, see the Supporting Information). Eventually, dealing with tetramethylguanidine in chloroform at room temperature for 4 h, intramolecular nitro-Michael cyclization reaction proceeded well and cyclobutane products **5a**−**5f** were obtained in good yields (70−85%) with excellent enantioselectivities (95−99% ee). As shown in Scheme 5, both the electron-donating and electron-withdrawing substituents with regard to vinylogous Michael products **3** and **4** were tolerated. The reaction was not affected by the position of substituents on the aromatic ring. The absolute configurations of

Scheme 5. Synthetic Cyclization[a]



[a]The reactions were carried out using 1.0 equiv of **3** (0.10 mmol) and 0.2 equiv of TMG (0.02 mmol) in 1.0 mL of $CHCl_3$. Yield of the isolated product after flash column chromatography. The ee values were determined by HPLC analysis on a chiral column. The dr was determined by ^{1}H NMR analysis of the crude product. TMG: 1,1,3,3-tetramethylguanidine.

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4i and **5c** were confirmed by an X-ray crystallography study (Figure 2).

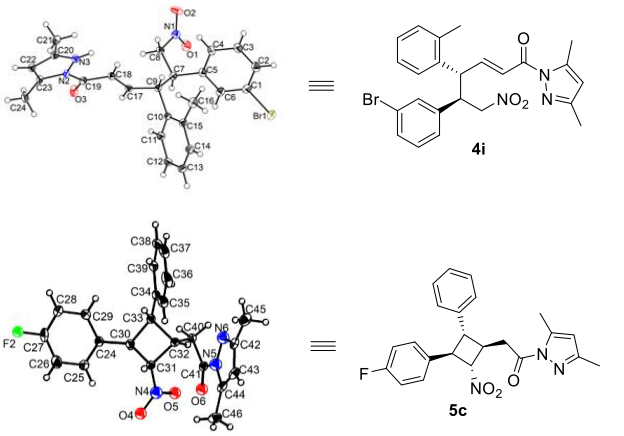

Figure 2. X-ray crystallographic structures of **4i** and **5c**.

Based on the above results, a possible catalytic transition state was proposed[10] in Figure 3. The dienolates were formed by β,γ-unsaturated amides **2** with catalyst **C3** through the α-position deprotonation. At the same time, nitroalkene was activated by squaramide hydrogen bonding. The conjugate addition of the enolized substrates **2** and the nitroalkenes **1** gave the vinylogous Michael addition products **3** or **4**, which were then subjected to intramolecular cyclization under the action of TMG to obtain the cyclobutane products **5**.

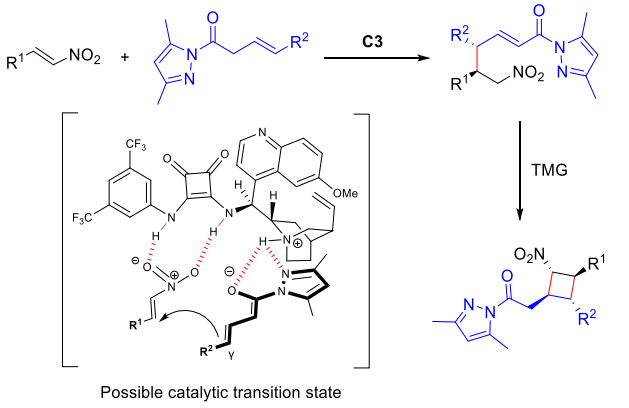

Figure 3. Synthesis of cyclobutanes.

As a good leaving group, 3,5-dimethylpyrazole could be substituted by nucleophiles simply and effectively (Figure 4). For example, alcoholysis of vinylogous Michael adduct **3f** and cyclobutane derivative **5b** with methanol gave ester products **6** and **7**, while retaining excellent enantioselectivitives (97 and 98% ee) and high yields (89 and 93%). Aminolysis of cyclobutane derivative **5a** with benzylamine gave amide **8** in high yield (86%) with retention of the stereochemistry (95% ee). In addition, after treatment of the *N*-acylpyrazole group with $NaBH_4$ in H_2O/THF, cyclobutane **5a** was reduced to the corresponding alcohol **9** in 72% yield and 98% ee.

In summary, not only have we reported a direct vinylogous Michael reaction between β,γ-unsaturated pyrazole amides and nitroolefins but we have also developed a new strategy for construction of cyclobutanes. The desired vinylogous Michael products and cyclobutanes were afforded in moderate to good yields with excellent stereoselectivities. Importantly, this method of asymmetric vinylogous Michael reaction and subsequent cyclization will be a useful contribution to chemical synthesis. Further biological activity evaluation of these compounds is being carried out in our laboratory.

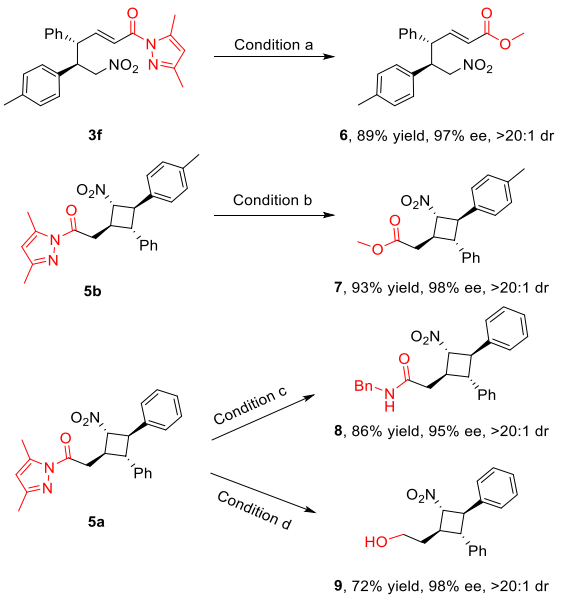

Figure 4. Transformation of products. Reaction conditions: (a) MeOH, 60 °C, 60 h; (b) MeOH, 60 °C, 48 h; (c) $BnNH_2$, THF, 50 °C, 5 h; (d) $NaBH_4$, THF/H_2O, 0 °C to rt, 2 h.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02488.

Experimental procedures and spectroscopic data for adduct compounds (PDF)

Accession Codes

CCDC 1971730 and 1971733 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Huicai Huang − *Research Center of Chinese Herbal Resource Science and Engineering, Key Laboratory of Chinese Medicinal Resource from Lingnan, Ministry of Education, Guangzhou University of Chinese Medicine, Guangzhou 510006, China;* orcid.org/0000-0002-8813-1499; Email: huanghc@gzucm.edu.cn

Authors

Yuzhen Chen − *Research Center of Chinese Herbal Resource Science and Engineering, Key Laboratory of Chinese Medicinal Resource from Lingnan, Ministry of Education, Guangzhou University of Chinese Medicine, Guangzhou 510006, China*

Yichen Wang − *Research Center of Chinese Herbal Resource Science and Engineering, Key Laboratory of Chinese Medicinal*

https://dx.doi.org/10.1021/acs.orglett.0c02488
Org. Lett. XXXX, XXX, XXX−XXX

Resource from Lingnan, Ministry of Education, Guangzhou University of Chinese Medicine, Guangzhou 510006, China

Shuzhong Wang − *Research Center of Chinese Herbal Resource Science and Engineering, Key Laboratory of Chinese Medicinal Resource from Lingnan, Ministry of Education, Guangzhou University of Chinese Medicine, Guangzhou 510006, China*

Yan-Yan Ma − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Deng-Gao Zhao − *School of Biotechnology and Health Sciences, Wuyi University, Jiangmen 529020, China*

Ruoting Zhan − *Research Center of Chinese Herbal Resource Science and Engineering, Key Laboratory of Chinese Medicinal Resource from Lingnan, Ministry of Education, Guangzhou University of Chinese Medicine, Guangzhou 510006, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02488

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Guangzhou University of Chinese Medicine, Pearl River Talents Recruitment Program of Guangdong Province (2017GC010361), Department of Education of Guangdong Province (2016KCXTD015), and Jiangmen Program for Innovative Research Team (2018630100180019806).

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https://dx.doi.org/10.1021/acs.orglett.0c02488
Org. Lett. XXXX, XXX, XXX−XXX