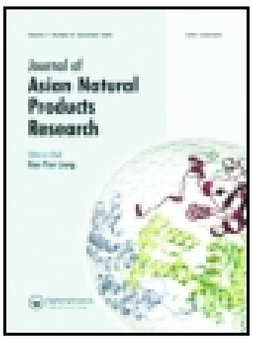


Journal of Asian Natural Products Research

ISSN: 1028-6020 (Print) 1477-2213 (Online) Journal homepage: https://www.tandfonline.com/loi/ganp20

Synthesis of novel 9*R/S*-acyloxy derivatives of cinchonidine and cinchonine as insecticidal agents

Zhi-Ping Che, Jin-Ming Yang, Song Zhang, Di Sun, Yue-E Tian, Sheng-Ming Liu, Xiao-Min Lin, Jia Jiang & Gen-Qiang Chen

To cite this article: Zhi-Ping Che, Jin-Ming Yang, Song Zhang, Di Sun, Yue-E Tian, Sheng-Ming Liu, Xiao-Min Lin, Jia Jiang & Gen-Qiang Chen (2020): Synthesis of novel 9*R/S*-acyloxy derivatives of cinchonidine and cinchonine as insecticidal agents, Journal of Asian Natural Products Research, DOI: 10.1080/10286020.2020.1729136

To link to this article: https://doi.org/10.1080/10286020.2020.1729136

JOURNAL OF ASIAN NATURAL PRODUCTS RESEARCH
https://doi.org/10.1080/10286020.2020.1729136

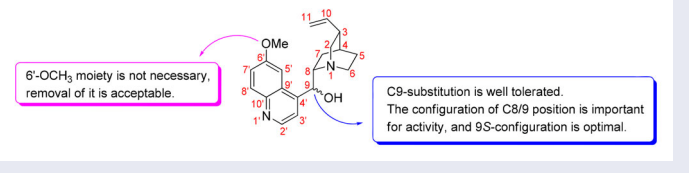
Synthesis of novel 9*R/S*-acyloxy derivatives of cinchonidine and cinchonine as insecticidal agents

Zhi-Ping Che, Jin-Ming Yang, Song Zhang, Di Sun, Yue-E Tian, Sheng-Ming Liu, Xiao-Min Lin, Jia Jiang and Gen-Qiang Chen

Laboratory of Pesticidal Design & Synthesis, Department of Plant Protection, College of Forestry, Henan University of Science and Technology, Luoyang 471023, China

ABSTRACT

Endeavor to discover biorational natural products-based insecticides, two series (27) of novel 9*R/S*-acyloxy derivatives of cinchonidine and cinchonine were prepared and assessed for their insecticidal activity against *Mythimna separata in vivo* by the leaf-dipping method at 1 mg/mL. Among all the compounds, especially derivatives **6l** and **6o** exhibited the best insecticidal activity with final mortality rates of 75.0% and 71.4%, respectively. Overall, a free 9-hydroxyl group is not a prerequisite for insecticidal activity and C9-substitution is well tolerated; the configuration of C8/9 position is important for insecticidal activity, and 9*S*-configuration is optimal; 6′-OCH_3 moiety is not necessary, removal of it is also acceptable.



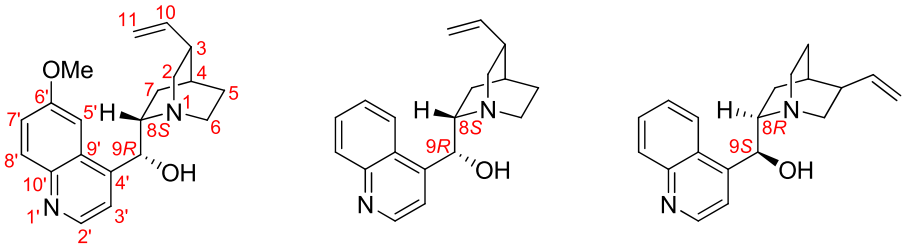
ARTICLE HISTORY
Received 22 November 2019
Accepted 9 February 2020

KEYWORDS
Cinchonidine; cinchonine; quinine analogues; acyloxy; insecticidal activity

1. Introduction

Oriental armyworm also known as *Mythimna separata* Walker (Lepidoptera: Noctuidae), is a gluttonous, omnivorous insect. Its larvae and adults can cause extensive damage to many crops, such as the larvae damage the leaves of the grass family (Gramineae), the adult is an important migratory pest in the world, and sometimes its outbreaks result in complete crop loss [1]. For example, *M. separata* intermittent outbreaks in China in 2012, about 4 million hectares of crops were completely loss [2]. Although, existing chemical insecticides were used to control *M. separate*, many problems have arisen, such as residue, resistance, and resurgence (3R) [3]. So how to solve these troubles has become a thorny problem in agriculture insect pest control. Fortunately, biopesticides, especially botanical insecticides (take it from the plant and

CONTACT Zhi-Ping Che zhipingche@163.com Laboratory of Pesticidal Design & Synthesis, Department of Plant Protection, College of Forestry, Henan University of Science and Technology, Luoyang 471023, China



1 **2** **3**

Figure 1. Chemical structures of quinine (**1**), cinchonidine (**2**), and cinchonine (**3**).

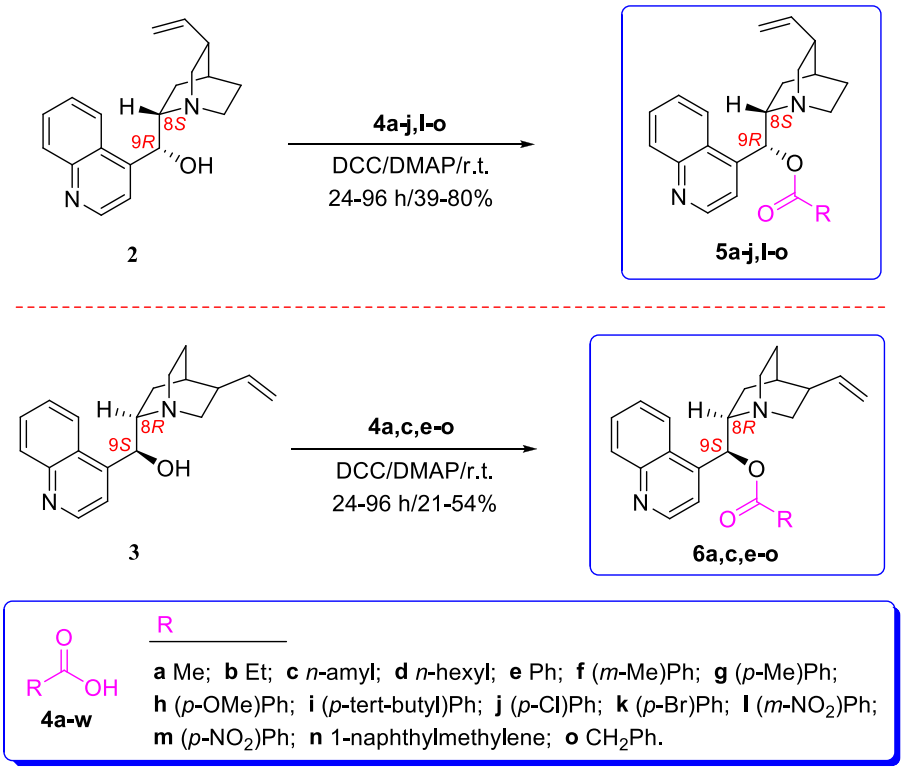
use it to the plant), are properly applied. According to the Change Advisory Board (CAB) scientific report, botanical insecticide has grown rapidly over the past three decades [4]. By 2014, the Environmental Protection Agency (EPA) of the United States data showed that about 69 botanical pesticides were registered and commercialized [5]. Nowadays, azadirachtin, rotenone, matrine, pyrethrins, and so forth, all are commercial botanical insecticides, which are made by plants as widely defenses against insect pests [6].

Cinchonidine (**2**, Figure 1) and cinchonine (**3**, Figure 1) are the analogue of quinine (**1**, Figure 1) and have similar biological activities to quinine. Quinine is the main alkaloids in the bark of cinchona tree as well as in plants in the same genus [7]. Strains of the human parasite *Plasmodium falciparum* resistant to the quinine and its analogs are widespread, and the prevalence of multiple types of drug-resistant *P. falciparum* strains has severely limited the use of quinines to treat malaria [8]. Besides its use as the lead compound for the preparation of catalysts and ligands which can effectively catalyze the reaction such as Michael/Mannich [9], Aza-Henry [10], cycloaddition [11], and asymmetric olefin isomerization [12], **1** has also exhibited numerous interesting insecticidal and antibacterial activities [13–16]. However, research on structure optimizations and structure–activity relationship (SAR) of 9*R*/*S*-acyloxy derivatives of cinchonidine and cinchonine as insecticidal agents has not yet been reported. Therefore, in this study, 27 novel 9*R*/*S*-acyloxy derivatives of cinchonidine and cinchonine were designed and semisynthesized, and used as insecticidal agents against the pre-third-instar larvae of *M. separata* Walker *in vivo* for the first time. Furthermore, the SAR of these compounds was also described.

2. Results and discussion

2.1. Chemistry

The synthetic route to prepare two series of novel 9*R*/*S*-acyloxy derivatives of cinchonidine and cinchonine (**5a–j,l–o** and **6a,c,e–o**) is depicted in Scheme 1. Target ester compounds **5a–j,l–o** and **6a,c,e–o** were smoothly obtained by reaction of **2** or **3** with the corresponding carboxylic acids (**4**) in the presence of DCC and DMAP [17–19]. The structures of all derivatives were well characterized by ^{1}H NMR, HRMS, and m.p.



Scheme 1. Route for the synthesis of 9*R*/*S*-acyloxy derivatives of cinchonidine and cinchonine **5a–j,l–o** and **6a,c,e–o**.

2.2. Insecticidal activity

The insecticidal activity of two series (27) of novel 9*R*/*S*-acyloxy derivatives of cinchonidine and cinchonine (**5a–j,l–o** and **6a,c,e–o**) against the pre-third-instar larvae of *M. separata* was assessed at 1 mg/mL by the leaf-dipping method. Toosendanin, a triterpenoid extracted and isolated from Meliaceae plants, is currently a commercial botanical insecticide, and was used as a positive control at a concentration of 1 mg/mL. As shown in Table 1, the corresponding corrected mortality rates (CMRs) caused by the parent and target compounds after 10 and 20 days were generally lower than those after 30 days. For example, the CMRs of **3** against *M. separata* after 10, 20, and 30 days were 20.0%, 44.8%, and 67.9%, respectively. That is, the CMRs of 30 days were more than 3 times of that of 10 days. Additionally, the symptoms of death of the tested *M. separata* during the whole process of growth were similar to our previous reports [17–19]: owing to feeding too many compounds coated leaves during the first 2 days, some larvae of the tested *M. separata* exhibited developmental abnormalities during three stages (larval, pupation, and adult emergence; Figures 2–4). Specifically, the larval stage was mainly manifested as wrinkled bodies caused by ecdysial stasis, and slim bodies attributed to antifeedant (Figure 2); even though the tested insects were normal in larval stage, deformed pupae or half-larva and half-pupae appeared in the pupation process (Figure 3); certainly, some of the tested

Table 1. Insecticidal activity of two series of 9*R/S*-acyloxy derivatives of cinchonidine and cinchonine (**5a–j,l–o** and **6a,c,e–o**) at 1 mg/mL against *M. separata*.

	Corrected mortality rate (%)[a]		
Compounds	10 days	20 days	30 days
1	10.0 ± 0	17.2 ± 0	32.1 ± 4.7
2	13.3 ± 4.7	27.6 ± 0	50.0 ± 4.7
5a	6.7 ± 9.4	20.7 ± 4.7	42.9 ± 4.7
5b	26.7 ± 4.7	48.3 ± 0	50.0 ± 4.7
5c	13.3 ± 4.7	17.2 ± 0	28.6 ± 4.7
5d	16.7 ± 4.7	27.6 ± 8.2	39.3 ± 4.7
5e	23.3 ± 4.7	44.8 ± 4.7	50.0 ± 4.7
5f	10.0 ± 8.2	10.3 ± 4.7	39.3 ± 9.4
5g	10.0 ± 0	13.8 ± 4.7	32.1 ± 4.7
5h	3.3 ± 4.7	17.2 ± 0	28.6 ± 4.7
5i	20.0 ± 0	27.6 ± 0	53.6 ± 4.7
5j	20.0 ± 0	44.8 ± 9.4	53.6 ± 4.7
5l	16.7 ± 4.7	34.5 ± 4.7	60.7 ± 4.7
5m	26.7 ± 9.4	37.9 ± 0	39.3 ± 4.7
5n	6.7 ± 0	17.2 ± 0	46.4 ± 8.2
5o	20.0 ± 8.2	34.5 ± 4.7	53.6 ± 4.7
3	20.0 ± 0	44.8 ± 9.4	67.9 ± 0
6a	26.7 ± 4.7	31.0 ± 4.7	50.0 ± 4.7
6c	16.7 ± 4.7	20.7 ± 4.7	42.9 ± 4.7
6e	23.3 ± 9.4	37.9 ± 0	57.1 ± 0
6f	23.3 ± 4.7	27.6 ± 0	53.6 ± 9.4
6g	13.3 ± 4.7	34.5 ± 4.7	42.9 ± 4.7
6h	26.7 ± 4.7	31.0 ± 4.7	39.3 ± 4.7
6i	26.7 ± 9.4	31.0 ± 4.7	64.3 ± 4.7
6j	23.3 ± 4.7	34.5 ± 4.7	64.3 ± 4.7
6k	10.0 ± 0	31.0 ± 4.7	35.7 ± 0
6l	26.7 ± 4.7	44.8 ± 9.4	75.0 ± 4.7
6m	23.3 ± 4.7	44.8 ± 4.7	53.6 ± 4.7
6n	16.7 ± 4.7	34.5 ± 4.7	60.7 ± 4.7
6o	23.3 ± 4.7	58.6 ± 0	71.4 ± 4.7
Toosendanin	10.0 ± 0	31.0 ± 4.7	50.0 ± 4.7
Blank control	0 ± 0	3.3 ± 4.7	6.7 ± 4.7

[a]Values are means ± *SD* of three replicate.

insects can reach the adult stage, but there were malformed moths, such as imperfect wing or half-pupae and half moth (Figure 4). On the other hand, Table 1 shows 17 compounds have equal to or higher insecticidal activity than the botanical insecticide toosendanin. Seven compounds, **5l**, **3**, **6i**, **6j**, **6l**, **6n**, and **6o** displayed more potent insecticidal activity with the final mortality rates (FMRs) $\geq$60%. Especially 2 derivatives (**6l** and **6o**) exhibited the best insecticidal activity with FMRs of 75.0% and 71.4%, respectively.

At the same time, some interesting and valuable views are obtained by analyzing the structure–activity relationships (SAR). Overall, as described in Figure 5 (1) a free 9-hydroxyl group is not a prerequisite for insecticidal activity, and C9-substitution is well tolerated. The bioassay results indicated that introduction of acyloxy groups at the C9 position on **2** and **3** could significantly affect the insecticidal activity. For example, the FMRs of **2** and **3** were 50.0% and 67.9%, respectively. Simultaneously, the FMRs of the corresponding esterification products **5l** and **6l** were 60.7% and 75.0%, respectively. (2) 6'-OCH_3 moiety is not necessary, and removal of it is also acceptable (e.g. 32.1% for **1** vs. 50.0% for **2** and 67.9% for **3**). (3) The configuration of C8/9 position is important for insecticidal activity, and 9*S*-configuration is optimal

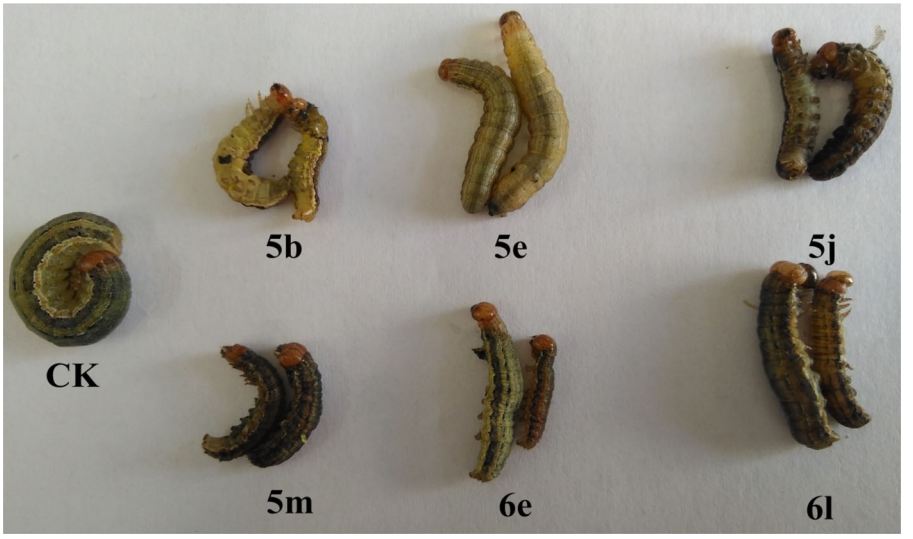


Figure 2. The representative abnormal larvae pictures of **5b**, **5e**, **5j**, **5m**, **6e**, and **6l** during the larval period (**CK**: blank control group).

Figure 3. The representative malformed pupae pictures of **5b**, **5e**, **5j**, **5l**, **6g**, and **6m** during the pupation period (**CK**: blank control group).

(e.g. **1** and **2** vs. **3**). In general, The insecticidal activities of 9*S*-acyloxycinchonine derivatives are generally higher than that of 9*R*-acyloxycinchonidine derivatives (e.g. **5a,c,e–j,l–o** vs. **6a,c,e–j,l–o**). This further demonstrated that 9*S*-configuration of analogs of quinine was important for obtaining the most potent derivatives.

Interestingly, the tested experiments indicated that for the *n*-alkyloyloxy series derivatives, the appropriate chain length of R was very significant for their insecticidal activity. For example, the FMRs of **5a–d** and **6a,c** were 42.9%/50.0%/28.6%39.3%, and 50.0%/42.9%, respectively. In addition, when the methyl or nitro group was introduced at the meta-position (e.g. **5f**, **5l**, **6f**, and **6l**) on the phenyl ring, the insecticidal

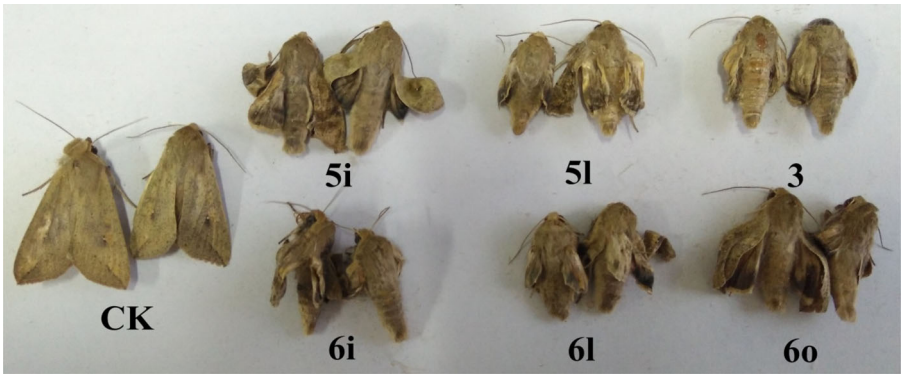


Figure 4. The representative malformed moth pictures of **5i**, **5l**, **3**, **6i**, **6l**, and **6o** during the emergence period (**CK**: blank control group).

activity was more potent than the para-position (e.g. **5g**, **5m**, **6g**, and **6m**). For example, the FMRs of **5f**, **5l**, **6f**, **6l** and **5g**, **5m**, **6g**, **6m** were 39.3%/60.7%/53.6%/75.0% and 32.1%/39.3%/42.9%/53.6%, respectively. To **5g–i** and **6g–i**, introduction of the *p*-tert-butylphenyloyloxy group (e.g. **5i** and **6i**) at the hydroxyl position of **2** and **3** could lead to more potent compounds than possessing *p*-methylphenyloyloxy (e.g. **5g** and **6g**) and *p*-methoxylphenyloyloxy (e.g. **5h** and **6h**) groups. For example, the FMRs of **5g–i** and **6g–i** were 32.1%/28.6%/53.6% and 42.9%/39.3%/64.3%, respectively. Similarly, when the chlorine atom (**6j**) was introduced at the para-position on the phenyl ring, the insecticidal activity was bettter than the bromine atom (**6k**) at the same position on the phenyl ring (64.3% for **6j** vs. 35.7% for **6k**). In addition, when R = benzylidene, the corresponding derivatives (e.g. **5o** and **6o**) were more active than that of R = 1-naphthylmethylene (e.g. **5n** and **6n**). For example, the FMRs of **5n,o** and **6n,o** were 46.4%/53.6% and 60.7%/71.4%, respectively.

3. Experimental

3.1. General experimental procedures

Optical rotation was measured on Rudolph Research Analytical Autopol III automatic polarimeter (Hackettstown, New Jersey, America). Proton nuclear magnetic resonance (^{1}H NMR) spectra was carried out with a Bruker Avance III 400 MHz instrument (Bruker Daltonik, Bremen, Germany) in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as the internal standard. High resolution mass spectrometry (HRMS) was determined on an IonSpec 4.7T FTMS instrument (Tesla, Lake Forest, CA, USA). Melting points (m.p.) of all compounds were detected on a digital melting point apparatus (Beijing Tech Instrument Co., Ltd.), and are uncorrected. As shown in Figure 1, quinine (**1**), cinchonidine (**2**), and cinchonine (**3**) were purchased from Wuhan Yuancheng Technology Development Co., Ltd. (Hubei, China). *N*,*N*'-Dicyclohexylcarbodiimide (DCC), 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and the corresponding acids RCOOH were ordered online from Aladdin Chemistry Co., Ltd. (Shanghai, China). Anhydrous methanol, dry ethyl acetate, petroleum ether, and dichloromethane were analytical grade, and obtained from Beichen Fangzheng

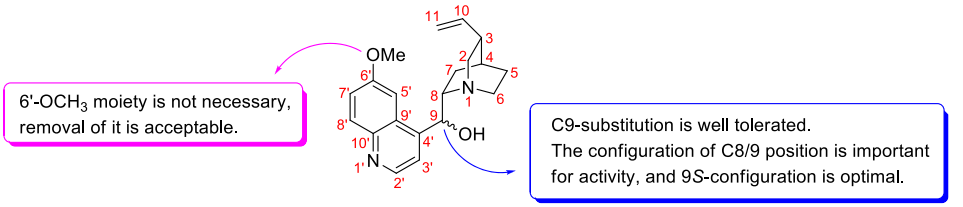


Figure 5. Brief description of structure–insecticidal activity relationships of quinine derivatives.

Reagent Factory (Tianjin, China). Detected thin layer chromatography (TLC) was performed with silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd., Qingdao, China). Silica gel column chromatography (CC) was performed with silica gel 200–300 mesh (Qingdao Haiyang Chemical Co., Ltd., Qingdao, China).

3.2. General procedure for the synthesis of 9R/S-acyloxy derivatives of cinchonidine and cinchonine 5a–j,l–o and 6a,c,e–o

A mixture of **2** or **3** (0.50 mmol), the corresponding acids RCOOH (0.60 mmol), DCC (0.60 mmol), DMAP (0.1 mmol) in dry dichloromethane (15 mL) was stirred at room temperature. When the reaction was completed, and checked by TLC, the mixture was filtered to remove urea from the reaction, and the filtrate was diluted by dichloromethane (45 mL). Subsequently, the diluted organic phase was washed by saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by CC to give the pure 9*R*/*S*-acyloxy derivatives of cinchonidine and cinchonine **5a–j,l–o** and **6a,c,e–o** [17–19]. The data of target compounds are shown as follows.

3.2.1. Data for 5a

Yield = 39%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −28 (*c* 3.8 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Refs. [20–22].

3.2.2. Data for 5b

Yield = 80%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −19 (*c* 3.1 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [21].

3.2.3. Data for 5c

Yield = 42%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −7 (*c* 3.7 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [22].

3.2.4. Data for 5d

Yield = 54%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −3 (*c* 4.3 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (d, J = 4.4 Hz, 1H), 8.25 (dd, J = 8.4, 1.2 Hz, 1H), 8.13 (dd, J = 8.4, 1.2 Hz, 1H), 7.69–7.73 (m, 1H), 7.57–7.61 (m, 1H), 7.39 (d, J = 4.8 Hz, 1H),

6.54 (d, $J = 7.6$ Hz, 1H), 5.79–5.87 (m, 1H), 4.98–5.03 (m, 2H), 3.40 (q, $J = 8.0$ Hz, 1H), 3.08–3.16 (m, 1H), 3.06 (dd, $J = 14.0$, 10.0 Hz, 1H), 2.55–2.67 (m, 2H), 2.34–2.38 (m, 2H), 2.27 (s, 1H), 1.84–1.92 (m, 2H), 1.69–1.77 (m, 1H), 1.49–1.62 (m, 4H), 1.21–1.27 (m, 6H), 0.82–0.86 (m, 3H). HRESIMS: *m/z* 407.2695 $[M + H]^+$ (calcd for $C_{26}H_{35}N_2O_2$, 407.2693).

3.2.5. Data for 5e

Yield = 44%, Pale yellow solid, m.p. 67–69 °C; $[\alpha]_D^{20}$ +103 (*c* 3.6 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [23].

3.2.6. Data for 5f

Yield = 52%, Pale yellow solid, m.p. 36–38 °C; $[\alpha]_D^{20}$ +116 (*c* 3.1 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (d, $J = 4.4$ Hz, 1H), 8.33 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.14 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.88–7.91 (m, 2 H), 7.70–7.75 (m, 1H), 7.61–7.65 (m, 1H), 7.47 (d, $J = 4.4$ Hz, 1H), 7.34–7.41 (m, 2H), 6.80 (d, $J = 6.4$ Hz, 1H), 5.80–5.89 (m, 1H), 4.98–5.04 (m, 2H), 3.52 (q, $J = 8.0$ Hz, 1H), 3.18–3.26 (m, 1H), 3.11 (dd, $J = 14.0$, 10.0 Hz, 1H), 2.61–2.71 (m, 2H), 2.41 (s, 3H), 2.29 (s, 1H), 1.88–1.98 (m, 2H), 1.69–1.82 (m, 2H), 1.54–1.6 (m, 1H). HRESIMS: *m/z* 413.2222 $[M + H]^+$ (calcd for $C_{27}H_{29}N_2O_2$, 413.2224).

3.2.7. Data for 5g

Yield = 60%, Pale yellow oily liquid; $[\alpha]_D^{20}$ +81 (*c* 4.1 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [23].

3.2.8. Data for 5h

Yield = 46%, Pale yellow solid, m.p. 63–65 °C; $[\alpha]_D^{20}$ +123 (*c* 3.8 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [24].

3.2.9. Data for 5i

Yield = 58%, White solid, m.p. 68–70 °C; $[\alpha]_D^{20}$ +86 (*c* 4.5 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, $J = 4.8$ Hz, 1H), 8.14 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.14 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.02–8.05 (m, 2H), 7.70–7.75 (m, 1H), 7.61–7.65 (m, 1H), 7.48–7.51 (m, 2H), 7.46 (d, $J = 4.8$ Hz, 1H), 6.83 (d, $J = 6.0$ Hz, 1H), 5.78–5.87 (m, 1H), 4.97–5.04 (m, 2H), 3.45–3.51 (m, 1H), 3.20–3.28 (m, 1H), 3.13 (dd, $J = 14.0$, 10.0 Hz, 1H), 2.64–2.74 (m, 2H), 2.31 (s, 1H), 1.87–1.95 (m, 2H), 1.73–1.85 (m, 2H), 1.55–1.62 (m, 1H), 1.34 (s, 9H). HRESIMS: *m/z* 455.2699 $[M + H]^+$ (calcd for $C_{30}H_{35}N_2O_2$, 455.2693).

3.2.10. Data for 5j

Yield = 47%, White solid, m.p. 131–133 °C; $[\alpha]_D^{20}$ +125 (*c* 4.4 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (d, $J = 4.8$ Hz, 1H), 8.31 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.14 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.02 (d, $J = 8.4$ Hz, 2H), 7.75 (t, $J = 7.6$ Hz, 1H), 7.65 (t,

$J = 7.6$ Hz, 1H), 7.43–7.45 (m, 3H), 6.78 (d, $J = 7.2$ Hz, 1H), 5.80–5.89 (m, 1H), 4.99–5.04 (m, 2H), 3.53 (q, $J = 8.0$ Hz, 1H), 3.14–3.22 (m, 1H), 3.09 (dd, $J = 14.0$, 10.0 Hz, 1H), 2.60–2.71 (m, 2H), 2.30 (s, 1H), 1.88–1.99 (m, 2H), 1.72–1.79 (m, 1H), 1.64–1.69 (m, 1H), 1.54–1.61 (m, 1H). HRESIMS: *m/z* 433.1678 $[M + H]^+$ (calcd for $C_{26}H_{26}ClN_2O_2$, 433.1677).

3.2.11. Data for 5l

Yield = 55%, Yellow solid, m.p. 66–68 °C; $[\alpha]_D^{20}$ +151 (*c* 3.3 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.89–8.91 (m, 2H), 8.43–8.46 (m, 1H), 8.36–8.39 (m, 1H), 8.33 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.16 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.72–7.77 (m, 1H), 7.64–7.70 (m, 2H), 7.49 (d, $J = 4.8$ Hz, 1H), 6.83 (d, $J = 7.2$ Hz, 1H), 5.83–5.92 (m, 1H), 5.01–5.06 (m, 2H), 3.54–3.60 (m, 1H), 3.14–3.22 (m, 1H), 3.10 (dd, $J = 14.0$, 10.0 Hz, 1H), 2.62–2.72 (m, 2H), 2.29–2.33 (m, 1H), 2.02–2.04 (m, 1H), 1.91–1.93 (m, 1H), 1.74–1.82 (m, 1H), 1.57–1.68 (m, 2H). HRESIMS: *m/z* 444.1921 $[M + H]^+$ (calcd for $C_{26}H_{26}N_3O_4$, 444.1918).

3.2.12. Data for 5m

Yield = 42%, Yellow oily liquid; $[\alpha]_D^{20}$ +113 (*c* 3.5 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [25].

3.2.13. Data for 5n

Yield = 55%, Pale yellow solid, m.p. 50–51 °C; $[\alpha]_D^{20}$ −33 (*c* 5.0 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.66 (d, $J = 4.4$ Hz, 1H), 8.03–8.09 (m, 2H), 7.86–7.89 (m, 2H), 7.84 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.65–7.69 (m, 1H), 7.47–7.51 (m, 2H), 7.40–7.44 (m, 3H), 6.95 (d, $J = 4.8$ Hz, 1H), 6.51 (d, $J = 6.4$ Hz, 1H), 5.63–5.71 (m, 1H), 4.89–4.94 (m, 2H), 4.13 (s, 2H), 3.13–3.19 (m, 1H), 2.98 (dd, $J = 14.0$, 10.0 Hz, 1H), 2.82–2.90 (m, 1H), 2.43–2.53 (m, 2H), 2.14–2.20 (m, 1H), 1.65–1.68 (m, 1H), 1.50–1.57 (m, 1H), 1.30–1.36 (m, 2H), 1.22–1.28 (m, 1H). HRESIMS: *m/z* 463.2383 $[M + H]^+$ (calcd for $C_{31}H_{31}N_2O_2$, 463.2380).

3.2.14. Data for 5o

Yield = 56%, White oily liquid; $[\alpha]_D^{20}$ − 20 (*c* 3.9 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, $J = 4.8$ Hz, 1H), 8.18 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.13 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.69–7.73 (m, 1H), 7.55–7.59 (m, 1H), 7.23–7.25 (m, 3H), 6.96–7.01 (m, 1H), 6.82–6.86 (m, 2H), 6.63 (d, $J = 7.2$ Hz, 1H), 5.75–5.84 (m, 1H), 4.97–5.01 (m, 2H), 4.68 (d, $J = 5.2$ Hz, 2H), 3.37 (q, $J = 8.0$ Hz, 1H), 2.97–3.07 (m, 2H), 2.52–2.62 (m, 2H), 2.25 (s, 1H), 1.79–1.85 (m, 2H), 1.64–1.72 (m, 1H), 1.42–1.55 (m, 2H). HRESIMS: *m/z* 413.2225 $[M + H]^+$ (calcd for $C_{27}H_{29}N_2O_2$, 413.2224).

3.2.15. Data for 6a

Yield = 21%, Pale yellow oily liquid; $[\alpha]_D^{20}$ +89 (*c* 3.1 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Refs. [21,22].

3.2.16. Data for 6c

Yield = 39%, Pale yellow oily liquid; $[\alpha]_D^{20}$ +72 (*c* 3.9 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [22].

3.2.17. Data for 6e

Yield = 54%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −14 (*c* 4.2 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [23].

3.2.18. Data for 6f

Yield = 46%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −12 (*c* 3.1 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (d, J = 4.8 Hz, 1H), 8.31 (dd, J = 8.4, 1.2 Hz, 1H), 8.14 (dd, J = 8.4, 1.2 Hz, 1H), 7.88–7.90 (m, 2H), 7.70–7.74 (m, 1H), 7.61–7.65 (m, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.32–7.41 (m, 2H), 6.81 (d, J = 6.8 Hz, 1H), 6.00–6.09 (m, 1H), 5.06–5.14 (m, 2H), 3.46 (q, J = 8.4 Hz, 1H), 2.90–3.04 (m, 2H), 2.80–2.87 (m, 1H), 2.69–2.77 (m, 1H), 2.41 (s, 3H), 2.25–2.32 (m, 1H), 1.96–2.03 (m, 1H), 1.84–1.88 (m, 1H), 1.54–1.66 (m, 3H). HRESIMS: *m/z* 413.2228 $[M+H]^+$ (calcd for $C_{27}H_{29}N_2O_2$, 413.2224).

3.2.19. Data for 6g

Yield = 39%, Pale yellow solid, m.p. 161–163 °C; $[\alpha]_D^{20}$ −45 (*c* 4.7 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, J = 4.8 Hz, 1H), 8.31 (dd, J = 8.4, 1.2 Hz, 1H), 8.13 (dd, J = 8.4, 1.2 Hz, 1H), 7.96–7.99 (m, 2H), 7.69–7.73 (m, 1H), 7.60–7.64 (m, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.24–7.27 (m, 2H), 6.78 (d, J = 7.2 Hz, 1H), 5.99–6.07 (m, 1H), 5.06–5.13 (m, 2H), 3.46 (q, J = 8.4 Hz, 1H), 2.89–3.03 (m, 2H), 2.68–2.85 (m, 2H), 2.41 (s, 3H,), 2.24–2.31 (m, 1H), 1.94–2.00 (m, 1H), 1.85 (s, 1H), 1.54–1.67 (m, 3H). HRESIMS: *m/z* 413.2226 $[M+H]^+$ (calcd for $C_{27}H_{29}N_2O_2$, 413.2224).

3.2.20. Data for 6h

Yield = 53%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −31 (*c* 3.7 mg/mL, $CHCl_3$). Its spectroscopic characteristics of this compound were consistent with those previously reported in the Ref. [24].

3.2.21. Data for 6i

Yield = 50%, Pale yellow oily liquid; $[\alpha]_D^{20}$ −25 (*c* 3.3 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, J = 4.4 Hz, 1H), 8.32 (dd, J = 8.4, 1.2 Hz, 1H), 8.13 (dd, J = 8.4, 1.2 Hz, 1H), 8.01–8.04 (m, 2H), 7.69–7.74 (m, 1H), 7.60–7.64 (m, 1H), 7.45–7.49 (m, 3H), 6.79 (d, J = 7.2 Hz, 1H), 5.99–6.08 (m, 1H), 5.06–5.14 (m, 2H), 3.47 (q, J = 8.4 Hz, 1H), 2.91–3.04 (m, 2H), 2.69–2.85 (m, 2H), 2.32 (q, J = 8.4 Hz, 1H), 1.94–2.00 (m, 1H), 1.86 (s, 1H), 1.56–1.66 (m, 3H), 1.34 (s, 9H). HRESIMS: *m/z* 455.2695 $[M+H]^+$ (calcd for $C_{30}H_{35}N_2O_2$, 455.2693).

3.2.22. Data for 6j

Yield = 22%, Pale yellow solid, m.p. 157–159 °C; $[\alpha]_D^{20}$ −23 (*c* 3.3 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.88 (d, *J* = 4.4 Hz, 1H), 8.29 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.03 (t, *J* = 2.4 Hz, 1H), 8.01 (t, *J* = 2.4 Hz, 1H), 7.70–7.75 (m, 1H), 7.60–7.65 (m, 1H), 7.42–7.45 (m, 3H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.97–6.05 (m, 1H), 5.06–5.14 (m, 2H), 3.47 (q, *J* = 8.4 Hz, 1H), 2.89–3.00 (m, 2H), 2.68–2.79 (m, 2H), 2.25–2.32 (m, 1H), 1.85–1.96 (m, 2H), 1.55–1.68 (m, 3H). HRESIMS: *m/z* 433.1678 $[M+H]^+$ (calcd for $C_{26}H_{26}ClN_2O_2$, 433.1677).

3.2.23. Data for 6k

Yield = 36%, Pale yellow solid, m.p. 181–182 °C; $[\alpha]_D^{20}$ −44 (*c* 3.4 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.88 (d, *J* = 4.8 Hz, 1H), 8.29 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.92–7.95 (m, 2H), 7.70–7.74 (m, 1H), 7.58–7.64 (m, 3H), 7.44 (d, *J* = 4.4 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.96–6.05 (m, 1H), 5.06–5.14 (m, 2H), 3.47 (q, *J* = 8.4 Hz, 1H), 2.89–2.99 (m, 2H), 2.68–2.84 (m, 2H), 2.25–2.32 (m, 1H), 1.85–1.96 (m, 2H), 1.54–1.68 (m, 3H). HRESIMS: *m/z* 477.1177 $[M+H]^+$ (calcd for $C_{26}H_{26}BrN_2O_2$, 477.1172).

3.2.24. Data for 6l

Yield = 48%, Yellow oily liquid; $[\alpha]_D^{20}$ − 30 (*c* 3.5 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.92 (t, *J* = 2.0 Hz, 1H), 8.90 (d, *J* = 4.4 Hz, 1H), 8.43–8.46 (m, 1H), 8.36–8.39 (m, 1H), 8.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.72–7.76 (m, 1H), 7.63–7.69 (m, 2H), 7.48 (d, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.00–6.09 (m, 1H), 5.07–5.16 (m, 2H), 3.54 (q, *J* = 8.4 Hz, 1H), 2.96 (dd, *J* = 8.8, 1.2 Hz, 2H), 2.80–2.86 (m, 1H), 2.69–2.76 (m, 1H), 2.26–2.34 (m, 1H), 1.88–1.98 (m, 2H), 1.68–1.73 (m, 1H), 1.56–1.64 (m, 2H). HRESIMS: *m/z* 444.1919 $[M+H]^+$ (calcd for $C_{26}H_{26}N_3O_4$, 444.1918).

3.2.25. Data for 6m

Yield = 32%, Yellow solid, m.p. 203–204 °C; $[\alpha]_D^{20}$ −29 (*c* 3.2 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.90 (d, *J* = 4.8 Hz, 1H), 8.23–8.32 (m, 5H), 8.15 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.72–7.76 (m, 1H),7.62–7.66 (m, 1H), 7.46 (d, *J* = 4.4 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.96–6.05 (m, 1H), 5.07–5.16 (m, 2H), 3.52 (q, *J* = 8.4 Hz, 1H), 2.95 (d, *J* = 8.8 Hz, 2H), 2.68–2.85 (m, 2H), 2.26–2.34 (m, 1H), 1.87–1.93 (m, 2H), 1.65–1.72 (m, 1H), 1.56–1.62 (m, 2H). HRESIMS: *m/z* 444.1923 $[M+H]^+$ (calcd for $C_{26}H_{26}N_3O_4$, 444.1918).

3.2.26. Data for 6n

Yield = 32%, Pale yellow oily liquid; $[\alpha]_D^{20}$ +88 (*c* 3.3 mg/mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.59 (d, *J* = 4.8 Hz, 1H), 8.07 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.02 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.81–7.83 (m, 2H), 7.63–7.67 (m, 1H), 7.36–7.49 (m, 5H), 6.88 (d, *J* = 4.4 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 1H), 5.82–5.91 (m, 1H), 5.02–5.10 (m, 2H), 4.12 (s, 2H), 3.16 (q, *J* = 8.4 Hz, 1H), 2.80–2.83 (m, 2H), 2.58–2.68 (m, 2H), 2.15–2.66 (m, 1H), 1.66–1.70 (m, 1H), 1.54–1.61 (m, 1H),

1.41–1.46 (m, 2H), 1.18–1.25 (m, 1H). HRESIMS: *m/z* 463.2387 $[M+H]^+$ (calcd for $C_{31}H_{31}N_2O_2$, 463.2380).

3.2.27. Data for 6o

Yield = 38%, Pale yellow oily liquid; $[\alpha]_D^{20}$ +162 (*c* 3.2 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, J = 4.4 Hz, 1H), 8.11–8.17 (m, 2H), 7.69–7.73 (m, 1H), 7.55–7.59 (m, 1H), 7.23–7.25 (m, 2H), 7.22 (d, J = 4.4 Hz, 1H), 6.97–7.01 (m, 1H), 6.83–6.86 (m, 2H), 6.66 (d, J = 7.6 Hz, 1H), 5.98–6.07 (m, 1H), 5.07–5.12 (m, 2H), 4.68 (d, J = 2.4 Hz, 2H), 3.34 (q, J = 8.4 Hz, 1H), 2.89 (d, J = 8.4 Hz, 2H), 2.64–2.79 (m, 2H), 2.22–2.28 (m, 1H), 1.77–1.80 (m, 2H), 1.47–1.55 (m, 3H). HRESIMS: *m/z* 413.2222 $[M+H]^+$ (calcd for $C_{27}H_{29}N_2O_2$, 413.2224).

3.3. Biological assay

The insecticidal activity of **1–3**, 9*R*/*S*-acyloxy derivatives of cinchonidine and cinchonine (**5a–j,l–o** and **6a,c,e–o**) and toosendanin (positive control) against *M. separate* (pre-third-instar larvae) was assessed at 1 mg/mL by the leaf-dipping method as reported previously [17–19].

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The present research was financially supported by the National Natural Science Foundation of China [Grant No. U1604105, 31901863].

References

[1] H.C. Sharma, D.J. Sullivan, and V.S. Bhatnagar, *Crop Prot.* **21**, 721 (2002).
[2] J. Zeng, Y. Jiang, and J. Liu, *Plant Prot.* **39**, 117 (2013).
[3] D.G. Heckel, *Science* **337**, 1612 (2012).
[4] M.B. Isman, *Annu. Rev. Entomol.* **51**, 45 (2006).
[5] X. Zhang, Z.Q. Ma, J.T. Feng, H. Wu, and L.R. Han, *Chin. J. Biol. Control* **31**, 685 (2015).
[6] F.E. Dayan, C.L. Cantrell, and S.O. Duke, *Bioorg. Med. Chem.* **17**, 4022 (2009).
[7] Z.P. Che, J.M. Yang, Y.E. Tian, S.M. Liu, J. Jiang, and G.Q. Chen, *Chem. Bull.* **81**, 792 (2018).
[8] C.A. Hrycyna, R.L. Summers, A.M. Lehane, M.M. Pires, H. Namanja, K. Bohn, J. Kuriakose, M. Ferdig, P.P. Henrich, D.A. Fidock, K. Kirk, J. Chmielewski, and R.E. Martin, *ACS Chem. Biol.* **9**, 722 (2014).
[9] R. Ding, B. Zheng, Y. Wang, and Y.G. Peng, *Org. Lett.* **17**, 4128 (2015).
[10] M.H. Li, N. Ji, T. Lan, W. He, and R. Liu, *RSC Adv.* **4**, 20346 (2014).
[11] T.P. Du, F. Du, Y.Q. Ning, and Y.G. Peng, *Org. Lett.* **17**, 1308 (2015).
[12] X.S. Xue, X. Li, A. Yu, C. Yang, C. Song, and J.P. Cheng, *J. Am. Chem. Soc.* **135**, 7462 (2013).
[13] D. Blades, and B.K. Mitchell, *Entomol. Exp. Appl.* **41**, 299 (1986).

[14] M.W. Chun, and L.M. Schoonhoven, *Entomol. Exp. Appl.* **16**, 343 (1973).
[15] P.B. Danielson, S.L. Gloor, R.T. Roush, and J.C. Fogleman, *Pestic. Biochem. Physilol.* **55**, 172 (1996).
[16] J.A. Wiles, A.S. Phadke, B.J. Bradbury, M.J. Pucci, J.A. Thanassi, and M. Deshpande, *J. Med. Chem.* **54**, 3418 (2011).
[17] Z.P. Che, Y.E. Tian, S.M. Liu, J. Jiang, M. Hu, and G.Q. Chen, *J. Asian Nat. Prod. Res.* **21**, 1028 (2019).
[18] Z.P. Che, J.M. Yang, X.J. Shan, Y.E. Tian, S.M. Liu, X.M. Lin, J. Jiang, M. Hu, and G.Q. Chen, *J. Asian Nat. Prod. Res.*
[19] Z.P. Che, Y.E. Tian, J.M. Yang, S.M. Liu, J. Jiang, M. Hu, and G.Q. Chen, *Nat. Prod. Commun.* **14**, 117 (2019).
[20] K. Maeda, T. Kurahashi, and S. Matsubara, *Eur. J. Org. Chem.* DOI: 10.1002/ejoc.201900834.
[21] T. Yamashita, H. Yasueda, Y. Miyauchi, and N. Nakamura, *B. Chem. Soc. Jpn.* **50**, 1532 (1977).
[22] T. Yamashita, H. Yasueda, N. Nakatani, and N. Nakamura, *B. Chem. Soc. Jpn.* **51**, 1183 (1978).
[23] A.E. Taggi, A.M. Hafez, H. Wack, B. Young, D. Ferraris, and T. Lectka, *J. Am. Chem. Soc.* **124**, 6626 (2002).
[24] A.K. Debnath, L. Radigan, and S. Jiang, *J. Med. Chem.* **42**, 3203 (1999).
[25] L. Li, Z.P. Zhang, X.X Zhu, A. Popa, and S.W. Wang, *Synlett* **12**, 1873 (2005).