JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Synthesis and Insecticidal Activity of Some Novel Fraxinellone-Based Esters

Yong Guo, Yuanyuan Yan, Xiang Yu, Yi Wang, Xiao-Yan Zhi, Ying Hu, and Hui Xu*

Laboratory of Pharmaceutical Design and Synthesis, College of Sciences, Northwest A&F University, Yangling 712100, Shannxi Province, People's Republic of China.

Supporting Information

ABSTRACT: In continuation of a program aimed at the discovery and development of natural products-based insecticidal agents, two series of novel fraxinellone-based esters were synthesized by modification at the C-4 or C-10 position of fraxinellone and evaluated for their insecticidal activity against the pre-third-instar larvae of *Mythimna separata* in vivo. An efficient method for the stereoselective synthesis of 4α-hydroxyfraxinellone from fraxinellonone was developed, and the steric configuration of **6h** was unambiguously confirmed by X-ray crystallography. Among 37 compounds, some derivatives displayed potent insecticidal activity; especially compounds **6h**, **6q**, **6t**, and **7q** showed more promising insecticidal activity than toosendanin, a commercial botanical insecticide derived from *Melia azedarach*. This suggested that introduction of the fluorine atom on the phenyl ring could lead to a more potent compound than one possessing chlorine or bromine. Meanwhile, introduction of the heterocyclic fragments at the C-4 or C-10 position of fraxinellone was essential for their insecticidal activity. This will pave the way for further design, structural modification, and development of fraxinellone as an insecticidal agent.

KEYWORDS: *fraxinellone, insecticidal activity, botanical insecticide, structural modification*

INTRODUCTION

Nowadays, the increasing application of synthetic chemical insecticides over the years has resulted in the development of resistance in insect pest populations and environmental problems. On the other hand, in many cases plants have a history of usage as folk remedies and are still used to kill or repel insects;[1] therefore, botanical insecticides have long been touted as attractive alternatives to synthetic chemical insecticides for pest management because botanicals reputedly pose little threat to the environment or to human health.[2] Some botanical insecticides such as nicotine, pyrethrum, and neem extracts are made by plants as defenses against insects.[3] The discovery of new insecticidal compounds from plant secondary metabolites and their use lead structures for further modification have been important approaches for the research and development of new pesticides.[3]

Fraxinellone (**1**, Figure 1), a well-known and significant naturally occurring degraded limonoid, has been successfully isolated and identified from many species of plants in Meliaceae and Rutaceae, including *Dictamnus angustifolius*,[4] *Fagaropsis glabra*,[5] *Melia azadarach*,[6,7] *Raulinoa echinata*,[8,9] and *Dictamnus dasycarpus*.[10,11] Liu et al. found compound **1** exhibited significant feeding deterrence against two stored-product insects, *Tribolium castaneum* Herbst and *Sitophilus zeamais* Motsch,[10] and showed effects on the growth and digestive physiology of Asian corn borer, *Ostrinia furnacalis* Guenee.[11] Lü et al. described that the poisoned insects usually exhibited typical stomach-poisoned symptoms (e.g., vomiting and diarrhea) after treatment by compound **1**, and compound **1** showed delayed insecticidal activity against *Mythimna separata*.[12] Although total synthesis of compound **1** has been reported,[13−15] to the best of our knowledge, little attention has been paid to structural modifications of **1** for use as insecticidal agents. Encouraged by the above-mentioned interesting results, and in continuation of our program aimed at the discovery and development of natural products-based insecticidal agents,[16−19] herein we designed and prepared two series of novel fraxinellone-based esters as insecticidal agents.

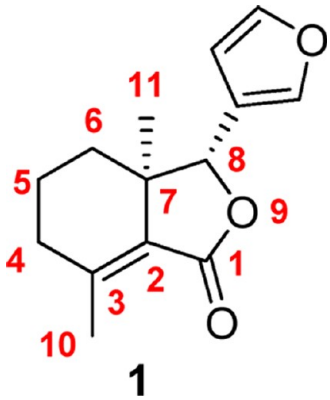


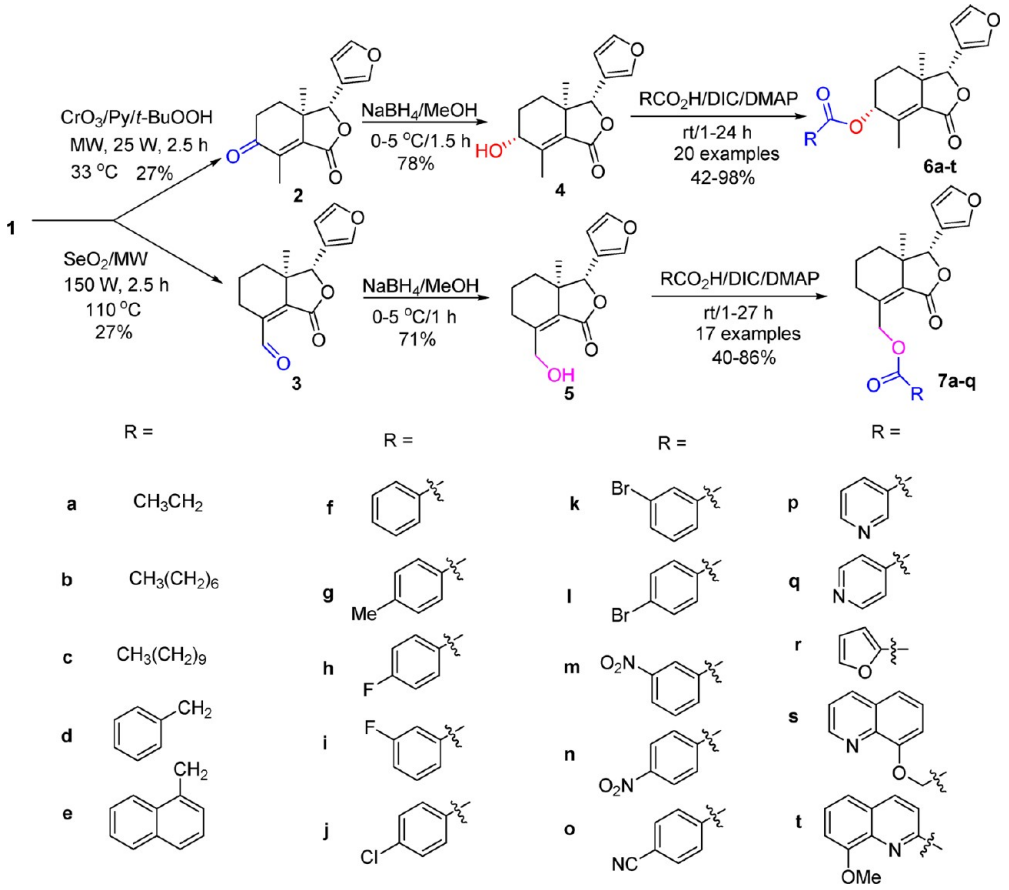
Figure 1. Chemical structure of fraxinellone (**1**).

MATERIALS AND METHODS

General. All reagents and solvents were of reagent grade or purified according to standard methods before use. Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points were

Received: April 23, 2012
Revised: June 22, 2012
Accepted: June 22, 2012
Published: June 22, 2012

Scheme 1. Synthetic Route for the Preparation of 6a−t and 7a−q



determined on a digital melting-point apparatus and were uncorrected. Infrared spectra (IR) were recorded on a Bruker TENSOR 27 spectrometer. Optical rotation was measured on Rudolph Research Analytical Autopol III automatic polarimeter. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance III 500 MHz instrument in $CDCl_3$ (^1H at 500 MHz and ^{13}C at 125 MHz) using tetramethylsilane (TMS) as the internal standard. High-resolution mass spectra (HR-MS) and electrospray ion trap mass spectrometry (ESI-MS) were carried out with an IonSpec 4.7 T FTMS instrument and an Agilent 1100 LC/MSD SL instrument, respectively. Microwave irradiation was performed in a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC, USA).

Fraxinellone was isolated from *D. dasycarpus* as a white solid in 0.118% yield, and its purity was >99% as measured with reverse phase high-performance liquid chromatography (RP-HPLC). R_f = 0.62 (petroleum ether/acetone = 5:1); mp 113−115 °C; IR cm^{-1} 3148, 3130, 2930, 1741, 1671, 1607, 1503, 1202, 1022, 949, 870, 812; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.47 (m, 2H, H-2′, 5′), 6.35 (s, 1H, H-4′), 4.88 (s, 1H, H-8), 2.16−2.31 (m, 2H, H-7), 2.13 (s, 3H, H-10), 1.44−1.86 (m, 4H, H-5, 6), 0.85 (s, 3H, H-11); MS (ESI), *m*/*z* (%) 233.05 ([M + H]$^+$, 58).

*Synthesis of Fraxinellonone (**2**).* To a mixture of CrO_3 (40 mg, 0.4 mmol), pyridine (0.074 mL, 0.8 mmol), and 70% aqueous *t*-BuOOH (0.55 mL, 4 mmol) in dried dichloromethane (DCM, 3 mL) was added compound **1** (92.8 mg, 0.4 mmol). Then the above mixture was reacted at 33 °C for 2.5 h using a microwave reactor at 25 W. When the reaction was complete as checked by TLC analysis, the mixture was diluted by DCM (40 mL), washed by saturated $NaHSO_3$ (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by PTLC to afford **2** in a 27% yield as a white solid. R_f = 0.30 (petroleum ether/ethyl acetate = 5:1); mp 141−143 °C; $[\alpha]^{23}_D$ = −39 (*c* 3.0 mg/mL, acetone); IR cm^{-1} (KBr) 3138, 2950, 2928, 1754, 1672, 1214, 1146, 877, 773; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H, H-2′), 7.49 (s, 1H, H-5′), 6.36 (s, 1H, H-4′), 5.11 (s, 1H, H-8), 2.62−2.64 (m, 2H, H-5), 2.18 (s, 3H, H-10), 2.14−2.21 (m, 1H, H-6a), 2.06−2.09 (m, 1H, H-6b), 1.08 (s, 3H, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.01, 168.62, 145.17, 144.00, 140.12, 139.46, 119.27, 108.28, 82.82, 43.92, 32.92, 31.97, 18.91, 10.07; MS (ESI), *m*/*z* (%) 244.94 ([M − H]$^+$, 100).

*Synthesis of 3-Formylfraxinellone (**3**).* A mixture of fraxinellone (**1**, 92.8 mg, 0.4 mmol) and selenium dioxide (88.8 mg, 0.8 mmol) in 1,4-dioxane (3 mL) was reacted at 110 °C for 2.5 h using a microwave reactor at 150 W. After the mixture had cooled to room temperature, the solvent was removed and the residue was dissolved in DCM and filtered. The filtrate was concentrated in vacuo and purified by PTLC to give **3** in 27% yield as a white solid. R_f = 0.26 (petroleum ether/ethyl acetate = 5:1); mp 118−120 °C; $[\alpha]^{23}_D$ = −50 (*c* 3.3 mg/mL, acetone); IR cm^{-1} (KBr) 3125, 2990, 2975, 1754, 1680, 1193, 1156, 873, 692; ^1H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1H, H-10), 7.52 (s, 1H, H-2′), 7.49 (s, 1H, H-5′), 6.37 (s, 1H, H-4′), 5.13 (s, 1H, H-8), 2.60−2.65 (m, 1H, H-4a), 2.24−2.32 (m, 1H, H-4b), 1.98−2.00 (m, 1H, H-5a), 1.87−1.90 (m, 1H, H-6a), 1.70−1.72 (m, 1H, H-5b), 1.47−1.53 (m, 1H, H-6b), 1.01 (s, 3H, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.25, 167.46, 145.86, 143.89, 140.06, 119.45, 108.30, 83.70, 44.52, 30.42, 21.90, 20.11, 17.06; HRMS (ESI), calcd for $C_{14}H_{15}O_4$ ([M + H]$^+$), 247.0965; found, 247.0963.

*Synthesis of 4α-Hydroxyfraxinellone (**4**).* To a stirred solution of fraxinellonone (**2**, 1 mmol, 246.3 mg) in methanol at 0−5 °C was slowly added $NaBH_4$ (2 mmol, 75.7 mg). After the addition, the reaction mixture was stirred at 0−5 °C for 1.5 h. The solvent was removed, and the residue was dissolved in DCM (50 mL). The mixture was then washed by brine (20 mL), and the organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by PTLC to give 4α-hydroxyfraxinellone (**4**) as a white solid in 78% yield. Mp 112−114 °C; $[\alpha]^{20}_D$ = 16 (*c* 3.2 mg/mL, $CHCl_3$); IR cm^{-1} 3435, 2941, 2861,

dx.doi.org/10.1021/jf301734h | J. Agric. Food Chem. 2012, 60, 7016−7021

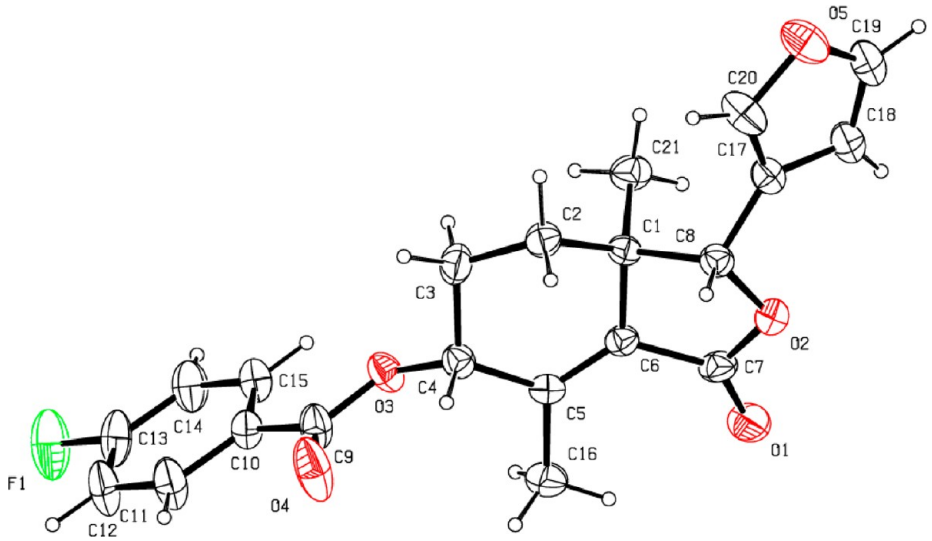


Figure 2. X-ray crystal structure of **6h**.

1743, 1667, 1501, 1204, 1024, 980; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H, H-2′), 7.44 (s, 1H, H-5′), 6.32 (s, 1H, H-4′), 4.91 (s, 1H, H-8), 4.24 (t, J = 8.5 Hz, 1H, H-4), 2.19−2.25 (m, 4H, H-5a, 10), 1.72−1.82 (m, 4H, H-5b, 6, −OH), 0.95 (s, 3H, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.42, 148.27, 143.61, 139.84, 130.02, 120.03, 108.37, 83.15, 71.64, 43.58, 31.39, 28.61, 20.40, 14.21; ESI-MS, m/z 271.0 ([M + Na]$^+$, 100).

*Synthesis of 10-Hydroxyfraxinellone (**5**).* To a stirred solution of 3-formylfraxinellone (**3**, 1 mmol, 246.3 mg) in methanol at 0−5 °C was slowly added $NaBH_4$ (2 mmol, 75.7 mg). The reaction mixture was stirred at 0−5 °C for 1 h. The solvent was removed, and the residue was dissolved in DCM (50 mL). The mixture was then washed by brine (20 mL), and the organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by PTLC to give 10-hydroxyfraxinellone (**5**) as a colorless liquid in 71% yield. $[\alpha]^{20}_D$ = −29 (c 3.0 mg/mL, $CHCl_3$); IR cm^{-1} 3416, 2940, 2874, 1748, 1670, 1503, 1264, 1198, 1055, 1003, 875; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H, H-2′), 7.46 (s, 1H, H-5′), 6.35 (s, 1H, H-4′), 5.01 (s, 1H, H-8), 4.50 (d, J = 14.0 Hz, 1H, H-10a), 4.25 (d, J = 14.0 Hz, 1H, H-10b), 2.44−2.50 (m, 1H, H-4a), 2.21−2.29 (m, 1H, H-4b), 1.89−1.92 (m, 1H, H-5a), 1.74−1.83 (m, 2H, H-5b, 6a), 1.44−1.49 (m, 1H, H-6b), 0.90 (s, 3H, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.84, 152.48, 143.65, 139.87, 129.86, 120.07, 108.45, 84.66, 62.54, 43.26, 31.13, 28.50, 20.47, 17.82; ESI-MS, m/z 271.0 ([M + Na]$^+$, 100).

*General Procedure for the Synthesis of Fraxinellone-Based Esters **6a−t** and **7a−q**.* A mixture of the corresponding acids RCO_2H (0.28 mmol), diisopropylcarbodiimide (DIC, 0.28 mmol), 4-dimethylaminopyridine (DMAP, 0.04 mmol), and **4** or **5** (0.2 mmol) in dried DCM (10 mL) was stirred at room temperature. When the reaction was complete according to TLC analysis, the mixture was diluted by DCM (40 mL), washed by aqueous HCl (0.1 mol/L, 20 mL), 5% $NaHCO_3$ (20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by PTLC to give the pure target products **6a−t** and **7a−q**. The data of **6a−t** and **7a−q** can be found in the Supporting Information.

Biological Assay. The insecticidal activity of **6a−t** and **7a−q** against the pre-third-instar larvae of *M. separata* Walker was assessed by leaf-dipping method as described previously.[20] For each compound, 30 larvae (10 larvae per group) were used. Acetone solutions of **6a−t**, **7a−q**, and toosendanin (used as a positive control) were prepared at the concentration of 1 mg/mL. Fresh wheat leaves were dipped into the corresponding solution for 3 s, then taken out, and dried in a room. Leaves treated with acetone alone were used as a control group. Several treated leaves were kept in each dish, where every 10 larvae were raised. If the treated leaves were consumed, the corresponding ones were added to the dish. After 48 h, untreated fresh leaves were added to the all of the dishes until adult emergence. The experiment was carried out at 25 ± 2 °C and a relative humidity (RH) of 65−80% and on 12 h/12 h (light/dark) photoperiod. The insecticidal activity of the tested compounds against the pre-third-instar larvae of *M. separata* was calculated with the formula

$$\text{corrected mortality rate } (\%) = (T - C) \times 100/(1 - C)$$

where T is the mortality rate in the treated group expressed as a percentage and C is the mortality rate in the untreated group expressed as a percentage.

RESULTS AND DISCUSSION

Synthesis. As shown in Scheme 1, two key intermediates, fraxinellonone (**2**) and 3-formylfraxinellone (**3**) were first synthesized in 27% yields from compound **1** by regioselectively allylic oxidation in the presence of chromium trioxide or selenium dioxide under microwave irradiation. Then reduction of **2** and **3** in the presence of $NaBH_4$ afforded **4** and **5**, respectively. Finally, two series of novel fraxinellone-based esters (**6a−t** and **7a−q**) were smoothly obtained by reaction of **4** or **5** with the corresponding carboxylic acids in the presence of DIC and DMAP. The steric configuration of **6h** was unambiguously confirmed by X-ray crystallography as illustrated in Figure 2. Crystallographic data (excluding structure factors) for the structures of **6h** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 876475. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax, +44 (0)1223 336033; or e-mail, deposit@ccdc.cam.ac.uk]. This suggested that the 4-fluorobenzoyloxy group of **6h** adopted an α configuration; that is, the configuration of 4-hydroxy of **4** was also α. Therefore, in this paper we describe an efficient method for the stereoselective synthesis of **4** from **2** simply by the reducing agent $NaBH_4$.

Insecticidal Activity. The insecticidal activity of **6a−t** and **7a−q** against the pre-third-instar larvae of *M. separata* in vivo was tested by the leaf-dipping method at the concentration of 1 mg/mL. Toosendanin, a commercial insecticide derived from *M. azedarach*, was used as the positive control and supplied by the Research and Development Center of Biorational Pesticide, Northwest A&F University, Shannxi province, China. Leaves treated with acetone alone were used as a blank control group.

As depicted in Table 1, the corresponding mortality rates after 35 days were generally higher than those after 10 and 25 days as

Table 1. Insecticidal Activity of 6a−t and 7a−q against *M. separata* on Leaves Treated with a Concentration of 1 mg/mL[a]

	corrected mortality rate (%)		
compd	10 days	25 days	35 days
1	20.7 ± 4.7	33.3 ± 0	44.4 ± 0
4	20.7 ± 4.7	37.0 ± 4.7	48.1 ± 4.7
5	10.3 ± 4.7	29.6 ± 4.7	40.7 ± 4.7
6a	20.7 ± 4.7	37.0 ± 4.7	44.4 ± 0
6b	10.3 ± 4.7	33.3 ± 8.2	48.1 ± 4.7
6c	20.7 ± 4.7	40.7 ± 4.7	48.1 ± 4.7
6d	31.0 ± 4.7	37.0 ± 4.7	44.4 ± 0
6e	10.3 ± 4.7	29.6 ± 4.7	51.9 ± 4.7
6f	41.4 ± 4.7	44.4 ± 0	44.4 ± 0
6g	24.1 ± 4.7	40.7 ± 4.7	40.7 ± 4.7
6h	24.1 ± 4.7	51.9 ± 4.7	63.0 ± 4.7
6i	24.1 ± 4.7	29.6 ± 4.7	44.4 ± 0
6j	20.7 ± 4.7	33.3 ± 8.2	40.7 ± 4.7
6k	20.7 ± 4.7	40.7 ± 4.7	44.4 ± 0
6l	24.1 ± 9.4	25.9 ± 4.7	37.0 ± 4.7
6m	10.3 ± 9.4	40.7 ± 4.7	48.1 ± 4.7
6n	27.6 ± 8.2	40.7 ± 4.7	51.9 ± 4.7
6o	20.7 ± 4.7	48.1 ± 4.7	55.6 ± 8.2
6p	20.7 ± 4.7	40.7 ± 4.7	55.6 ± 8.2
6q	24.1 ± 4.7	48.1 ± 4.7	66.7 ± 0
6r	31.0 ± 4.7	40.7 ± 4.7	51.9 ± 4.7
6s	13.8 ± 4.7	37.0 ± 4.7	51.9 ± 4.7
6t	20.7 ± 4.7	48.1 ± 4.7	63.0 ± 4.7
7a	17.2 ± 8.2	33.3 ± 0	40.7 ± 4.7
7b	6.9 ± 0	25.9 ± 4.7	33.3 ± 0
7c	27.6 ± 0	33.3 ± 8.2	37.0 ± 4.7
7d	27.6 ± 8.2	33.3 ± 8.2	44.4 ± 0
7e	20.7 ± 4.7	33.3 ± 8.2	48.1 ± 4.7
7f	17.2 ± 8.2	29.6 ± 4.7	29.6 ± 4.7
7g	17.2 ± 8.2	29.6 ± 4.7	29.6 ± 4.7
7h	10.3 ± 4.7	40.7 ± 4.7	51.9 ± 4.7
7i	24.1 ± 4.7	51.9 ± 4.7	55.6 ± 0
7j	6.9 ± 0	25.9 ± 4.7	40.7 ± 4.7
7k	13.8 ± 4.7	25.9 ± 4.7	33.3 ± 0
7l	24.1 ± 9.4	29.6 ± 4.7	33.3 ± 0
7m	24.1 ± 4.7	29.6 ± 4.7	44.4 ± 0
7n	13.8 ± 4.7	33.3 ± 0	40.7 ± 4.7
7o	6.9 ± 0	25.9 ± 4.7	44.4 ± 0
7p	27.6 ± 8.2	44.4 ± 8.2	51.9 ± 4.7
7q	24.1 ± 4.7	48.1 ± 4.7	59.3 ± 4.7
toosendanin	27.6 ± 8.2	33.3 ± 0	48.1 ± 4.7

[a]Values are the mean ± SD of three replicates.

Lü et al. reported;[12] therefore, these compounds, in a time-dependent manner, are different from conventional neurotoxic insecticides such as organophosphates, carbamates, and pyrethroids in exhibiting delayed insecticidal activity. Meanwhile, the symptoms of the tested *M. separata* were also characterized in the same way as in our previous papers.[16−19] Due to feeding too much treated leaves during the first 48 h, some larvae died slowly during the larval period (Figure 3). In the meantime, many larvae of the treated groups molted to malformed pupae and died during the stage of pupation (Figure 4). Malformed moths with imperfect wings also appeared in the

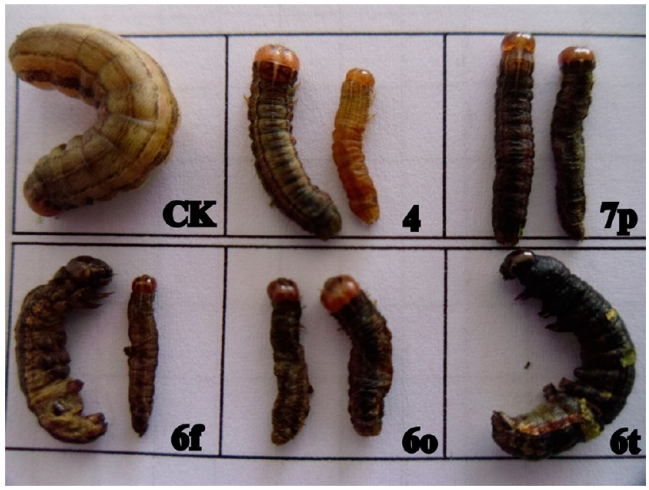


Figure 3. Representative abnormal larvae pictures of **4**, **6f**, **6o**, **6t**, and **7p** during the larval period (CK, blank control group).

Figure 4. Representative malformed pupae pictures of **6e**, **6q**, **7c**, **7i**, and **7q** during the pupation period (CK, blank control group).

treated groups (Figure 5). Eighteen compounds exhibited insecticidal activity more pronounced than or comparable to

Figure 5. Representative malformed moth pictures of **6h**, **6o**, **6t**, **7e**, and **7q** during the emergence period (CK, blank control group).

dx.doi.org/10.1021/jf301734h | *J. Agric. Food Chem.* 2012, 60, 7016−7021

that of toosendanin. Especially compounds **6h**, **6q**, **6t**, and **7q** showed more promising insecticidal activity than toosendanin. Meanwhile, some interesting results of structure−activity relationships of **6a−t** and **7a−q** were also observed. The hydroxy at the C-4 or C-10 position of fraxinellone should not be free. For example, the final mortality rates of **4** and **5** were only 48.1 and 40.7%, respectively. In general, introduction of the fluorine atom on the phenyl ring could lead to a more potent compound than that possessing chlorine or bromine (**6h** vs **6j**, **6k**, and **6l**; **7h** and **7i** vs **7j**, **7k**, and **7l**). Introduction of the heterocyclic fragments at the C-4 or C-10 position of fraxinellone improved insecticidal activity. For example, the final mortality rates of **6p−t**, **7p**, and **7q** were 55.6, 66.7, 51.9, 51.9, 63, 51.9, and 59.3%, respectively. However, alkylacyloxy, benzoyloxy, *p*-methylbenzoyloxy, *m*-bromobenzoyloxy, or *p*-bromobenzoyloxy introduced at the C-10 position of fraxinellone in general decreased insecticidal activity (e.g., **7b**, **7c**, **7f**, **7g**, **7k**, and **7l**). Introduction of the ester groups at the C-4 position of fraxinellone usually afforded more potent compounds than those with the same groups at the C-10 position (e.g., **6m** vs **7m**; **6n** vs **7n**; **6o** vs **7o**). Interestingly, the proper chain length of alkylacyloxy was important to the speed of activity for 10 days. When the *n*-heptanoyloxy was introduced at the C-4 or C-10 position of fraxinellone to give **6b** and **7b**, the mortality rates of **6b** and **7b** against *M. separata* for 10 days were only 10.3 and 6.9%, respectively, whereas when the acetyloxy or *n*-decanoyloxy was introduced at the C-4 or C-10 position of fraxinellone to give **6a**, **6c**, **7a**, and **7c**, the mortality rates against *M. separata* for 10 days were 20.7, 20.7, 17.2, and 27.6%, respectively.

In conclusion, to improve the insecticidal activity of fraxinellone, 37 novel fraxinellone-based esters were synthesized by modification at the C-4 or C-10 position of fraxinellone and evaluated for their insecticidal activity against the pre-third-instar larvae of *M. separata* in vivo. Especially compounds **6h**, **6q**, **6t**, and **7q** showed more promising insecticidal activity than toosendanin. On the other hand, an efficient method for the stereoselective synthesis of 4α-hydroxyfraxinellone from fraxinellonone was developed. This suggested that introduction of the fluorine atom on the phenyl ring could lead to a more potent compound than that possessing chlorine or bromine, and introduction of the heterocyclic fragments at the C-4 or C-10 position of fraxinellone was essential for their insecticidal activity. This will pave the way for further design, structural modification, and development of fraxinellone as a botanical insecticidal agent.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR, ^{13}C NMR, HRMS, optical rotation, melting point, and IR data for the target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +86(0)29-87091952. Fax: +86(0)29-87091952. E-mail: orgxuhui@nwsuaf.edu.cn.

Funding

The present research was partly supported by National Natural Science Foundation of China (No. 31071737, 31171896), the Program for Changjiang Scholars and Innovative Research Team in University (IRT1035), and Special Funds of Central Colleges Basic Scientific Research Operating Expenses (QN2009045).

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Broussalis, A. M.; Ferraro, G. E.; Martino, V. S.; Pinzon, R.; Coussio, J. D.; Alvarez, J. C. Argentine plants as potential source of insecticidal compounds. *J. Ethnopharmacol.* **1999**, *67*, 219−223.

(2) Isman, M. B. Botanical insecticides, deterrents, and repellents in modern agriculture and an increasingly regulated world. *Annu. Rev. Entomol.* **2006**, *51*, 45−66.

(3) Dayan, F. E.; Cantrell, C. L.; Duke, S. O. Natural products in crop protection. *Bioorg. Med. Chem.* **2009**, *17*, 4022−4034.

(4) Hu, C. Q.; Han, J. W.; Zhao, J. G.; Song, G. Q.; Li, Y. H. Limonoids from *Dictamnus angustifolius*. *J. Integrative Plant Biol.* **1989**, *31*, 453−458.

(5) Boustie, J.; Moulis, C.; Gleye, J.; Fouraste, I.; Servin, P.; Bon, M. A degraded limonoid from *Fagaropsis glabra*. *Phytochemistry* **1990**, *29*, 1699−1701.

(6) Nakatani, M.; Huang, R. C.; Okamura, H.; Iwagawa, T.; Tadera, K. Degraded limonoids from *Melia azedarach*. *Phytochemistry* **1998**, *49*, 1773−1776.

(7) Fukuyama, Y.; Nakaoka, M.; Yamamoto, T.; Takahashi, H.; Minami, H. Degraded and oxotane-bearing limonoids from the roots of *Melia azedarach*. *Chem. Pharm. Bull.* **2006**, *54*, 1219−1222.

(8) Biavatti, M. W.; Vieira, P. C.; da Silva, M. F. G. F.; Fernandes, J. B.; Albuquerque, S. Limonoids from the endemic Brazilian species *Raulinoa echinata*. *Z. Naturforsch.* **2001**, *56C*, 570−574.

(9) Biavatti, M. W.; Westerlon, R.; Vieira, P. C.; da Silva, M. F. G. F.; Fernandes, J. B.; Penaflor, M. F. G. V.; Bueno, O. C.; Ellena, J. Leaf-cutting ants toxicity of limonexic acid and degraded limonoids from *Raulinon echinata*. X-ray structure of epoxyfraxinellone. *J. Braz. Chem. Soc.* **2005**, *16*, 1443−1447.

(10) Liu, Z. L.; Xu, Y. J.; Wu, J.; Goh, S. H.; Ho, S. H. Feeding deterrents from *Dictamnus dasycarpus* Turcz against two stored-product insects. *J. Agric. Food Chem.* **2002**, *50*, 1447−1450.

(11) Liu, Z. L.; Ho, S. H.; Goh, S. H. Effect of fraxinellone on growth and digestive physiology of Asian corn borer, *Ostrinia furnacalis* Guenee. *Pestic. Biochem. Physiol.* **2008**, *91*, 122−127.

(12) Lü, M.; Wu, W. J.; Liu, H. X. Effects of fraxinellone on the midgut ultrastructural changes of *Mythimna separata* Walker. *Pestic. Biochem. Physiol.* **2010**, *98*, 263−268.

(13) Trudeau, S.; Morken, J. P. Short and efficient total synthesis of fraxinellone limonoids using the stereoselective Oshima-Utimoto reaction. *Org. Lett.* **2005**, *7*, 5465−5468.

(14) Okamura, H.; Yamauchi, K.; Miyawaki, K.; Iwagawa, T.; Nakatani, M. Synthesis and biological activities of degraded limonoids, (±)-fraxinellonone and its related compounds. *Tetrahedron Lett.* **1997**, *38*, 263−266.

(15) Fukuyama, Y.; Tokoroyama, T.; Kubota, T. Total synthesis of fraxinellone. *Tetrahedron Lett.* **1972**, *33*, 3401−3404.

(16) Xu, H.; Xiao, X. Natural products-based insecticidal agents 4. Semisynthesis and insecticidal activity of novel esters of 2-chloropodophyllotoxin against *Mythimna separata* Walker *in vivo*. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5415−5418.

(17) Xu, H.; Xiao, X.; Wang, Q. T. Natural products-based insecticidal agents 7. Semisynthesis and insecticidal activity of novel 4α-alkyloxy-2-chloropodophyllotoxin derivatives against *Mythimna separata* Walker *in vivo*. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5009−5012.

(18) Xu, H.; He, X. Q. Natural products-based insecticidal agents 6. Design, semisynthesis and insecticidal activity of novel monomethyl phthalate derivatives of podophyllotoxin against *Mythimna separata* Walker *in vivo*. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4503−4506.

(19) Xu, H.; Wang, Q. T.; Guo, Y. Stereoselective synthesis of 4α-alkyloxy-2-α/β-bromopodophyllotoxin derivatives as insecticidal agents. *Chem.—Eur. J.* **2011**, *17*, 8299−8303.

(20) Xu, H.; Wang, J. J.; Sun, H. J.; Lv, M.; Tian, X.; Yao, X. J.; Zhang, X. Semisynthesis and quantitative structure-activity relationship (QSAR) study of novel aromatic esters of 4′-demethyl-4-deoxypodophyllotoxin as insecticidal agents. *J. Agric. Food Chem.* **2009**, *57*, 7919–7923.