JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Semisynthesis and Insecticidal Activity of Some Fraxinellone Derivatives Modified in the B Ring

Yong Guo, Huan Qu, Xiaoyan Zhi, Xiang Yu, Chun Yang, and Hui Xu*

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

Supporting Information

ABSTRACT: A series of novel fraxinellone derivatives modified at the C-1 or C-8 position in the B ring were prepared as insecticidal agents against the pre-third-instar larvae of oriental armyworm, *Mythimna separata* Walker at 1 mg/mL. Five key steric configurations of compounds **2**, **3**, and **8f,g,j** were further determined by single-crystal X-ray diffraction. It was found that the kinds and the amount of the reduction products of fraxinellone were related to the molar ratio between the reduction agent Red-Al and the substrate fraxinellone. Among all of the derivatives, compounds **2** and **8i,j,o** displayed more promising insecticidal activity than their precursors fraxinellone and toosendanin. The preliminary structure−activity relationships revealed that the lactone (B-ring) of fraxinellone contributed to the observed insecticidal activity; the double bond at the C-2 position of fraxinellone was not necessary for the insecticidal activity; conversion of the oxygen atom of carbonyl group on the lactone of fraxinellone to a sulfur one does not improve the insecticidal activity; introduction of electron-withdrawing groups on the phenyl ring of **8f**, to the benzoyloxy series, could result in more potent compounds.

KEYWORDS: *fraxinellone, B-ring modification, insecticidal activity, natural product-based insecticide, limonoid, reduction reaction*

INTRODUCTION

Lepidoptera are an important group of agricultural insect pests that can result in widespread and extensive economic damage on food and fiber crop plants, fruit trees, forests, and stored grains.[1] Oriental armyworm, *Mythimna separata* (Walker), a typical lepidopteran pest, undertakes a seasonal, long-distance, and multigeneration roundtrip migration between southern and northern China,[2] and intermittent outbreaks of its larvae at very high densities can lead to complete crop loss.[3] Meanwhile, the repeated use of synthetic agrochemicals to control lepidopteran pests over the years has produced risks in the development of resistance in lepidopteran pest populations and environmental problems.[4,5] Obviously, the development of new methods for lepidopteran pest management is still an important challenge for the world economy and health. It is well-known that due to plant secondary metabolites resulting from the interaction between plants and the environment (life and nonlife) during the long period of evolution in plants, the new agrochemicals originating from plant secondary metabolites can cause less or slower resistance development and lower environmental pollution.[6] Moreover, some new insecticidal agents originating from natural products usually give us an opportunity to discover the novel modes of action.[7−10] Therefore, research and development of new agrochemicals directly or indirectly originating from plant secondary metabolites have received much attention in recent years.[11−17]

Fraxinellone (**1**, Figure 1) was isolated as a degraded limonoid from many species of Meliaceae and Rutaceae plants.[18−20] Besides its interesting medicinal activities,[21−24] fraxinellone also showed insecticidal activities against some pest insects.[25,26] More recently, we have studied the insecticidal activity of fraxinellone-based esters[27] (**I** and **II**, Figure 1) and hydrazones[28] (**III** and **IV**, Figure 1) modified at the C-4 or C-10 position in the A ring of fraxinellone and found some compounds against *M. separata* displayed higher insecticidal activity than toosendanin, a commercial botanical insecticide isolated from *Melia azedarach*. Until now, little attention has been paid to the structural modification in the B ring of fraxinellone. Consequently, in the present paper we further designed a series of novel fraxinellone derivatives (**V** and **VI**, Figure 1) modified at the C-1 or C-8 position in the B ring of fraxinellone as insecticidal agents.

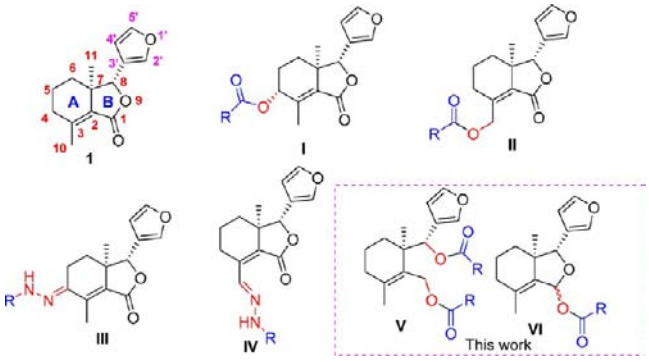


Figure 1. Chemical structures of fraxinellone (**1**) and its derivatives (**I**−**VI**).

Received: September 18, 2013
Revised: November 20, 2013
Accepted: November 21, 2013
Published: November 21, 2013

ACS Publications © 2013 American Chemical Society

MATERIALS AND METHODS

General. All reagents and solvents were commercially available or purified with standard methods before use. Melting points (mp) were recorded on an XT-4 digital melting point (mp) apparatus (Beijing Tech Instrument Co., Ltd., China) and were uncorrected. Infrared spectra (IR) were carried out on a Bruker TENSOR 27 spectrometer. Optical rotation was measured on a Rudolph Research Analytical Autopol III automatic polarimeter. ^{1}H NMR spectra were carried out in $CDCl_3$ on a Bruker Avance (400 or 500 MHz) spectrometer using tetramethylsilane (TMS) as the internal standard. HR-MS and ESI-MS were obtained on IonSpec 4.7 T FTMS and Bruker ESI-TRAP Esquire 6000 plus mass spectrometry instruments, respectively.

Typical Procedure for the Synthesis of Compounds ***2*****–*****4*****.** Commercial Red-Al solution (6 mmol, 1.68 mL, 70 wt % in toluene) was diluted with dry toluene (5 mL). To a solution of fraxinellone (2 mmol, 464 mg) in dry THF (15 mL) at −78 °C under N_2 was added dropwise the above diluted Red-Al solution for 15 min. Subsequently, the solution was allowed to warm slowly from −78 to 10 °C over about 24 h, at which time methanol (2.0 mL) and then saturated aq.ueous NH_4Cl (10 mL) were added. The reaction mixture was allowed to warm slowly to room temperature. The organic layer was separated, and the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography (200−300 mesh) eluting with petroleum ether/ethyl acetate (5:1, v/v) to afford **2** (29% yield), **3** (46% yield), and **4** (16% yield; very unstable).

Data for ***2****:* CAS Registry no. 1179343-59-9; white solid; mp 86−87 °C (lit.[29] mp not reported); $[\alpha]^{20}_D$ = −17 (*c* 4.7 mg/mL, $CHCl_3$); IR (cm^{-1}) 2963, 2928, 2870, 1757, 1260, 1161, 1018, 956, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 1.6 Hz, 1H, H-2′), 7.37 (t, *J* = 0.8 Hz, 1H, H-5′), 6.29 (d, *J* = 0.8 Hz, 1H, H-4′), 4.89 (s, 1H, H-8), 2.38 (d, *J* = 4.4 Hz, 1H, H-2), 1.57−1.78 (m, 5H, H-3, 4, 5), 1.41−1.51 (m, 1H, H-6), 1.30 (d, *J* = 7.2 Hz, 3H, H-10), 1.15−1.25 (m, 1H, H-6), 0.96 (s, 3H, H-11); MS (ESI) *m*/*z* (rel intensity) 234.9 ([M + H]$^+$, 100).

Data for ***3****:* CAS Registry No. 16191-54-1; white solid; mp 41−43 °C (lit.[30] mp not reported); $[\alpha]^{20}_D$ = 15 (*c* 4.3 mg/mL, $CHCl_3$); IR (cm^{-1}) 3343, 2928, 2871, 1163, 1020, 984, 874, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.2 Hz, 2H, H-2′, 5′), 6.40 (t, *J* = 1.2 Hz, 1H, H-4′), 4.76 (br s, 1H, H-8), 4.29 (d, *J* = 11.6 Hz, 1H, H-1), 4.09 (d, *J* = 11.6 Hz, 1H, H-1), 3.47, (s, 2H, −OH), 2.06−2.10 (m, 2H, H-4), 1.79 (s, 3H, H-10), 1.67−1.73 (m, 1H, H-5), 1.50−1.54 (m, 1H, H-5), 1.40−1.46 (m, 1H, H-6), 1.16−1.24 (m, 1H, H-6), 1.05 (s, 3H, H-11); MS (ESI) *m*/*z* (rel intensity) 259.21 ([M + H]$^+$, 100); HRMS *m*/*z* calcd for $C_{14}H_{20}O_3Na$ ([M + Na]$^+$) 259.1305, found 259.1312.

Synthesis of Compound ***5****:* To a solution of **1** (116.0 mg, 0.5 mmol) in toluene (10 mL) was added Lawesson's reagent (404.5 mg, 1 mmol). Then the mixture was refluxed for 12 h. When the reaction was complete, checked by TLC analysis, the solvent was evaporated, and the crude product was purified by PTLC to give **5**: yellow solid; yield 54%; mp 137−139 °C; $[\alpha]^{20}_D$ = −11 (*c* 4.2 mg/mL, $CHCl_3$); IR (cm^{-1}) 2933, 2922, 2872, 1642, 1414, 1293, 1104, 919, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 0.8 Hz, 1H, H-2′), 7.44 (t, *J* = 2.0 Hz, 1H, H-5′), 6.39 (d, *J* = 1.2 Hz, 1H, H-4′), 5.06 (s, 1H, H-8), 2.31−2.37 (m, 4H, H-4, 10), 2.13−2.24 (m, 1H, H-4), 1.70−1.86 (m, 3H, H-5, 6), 1.44−1.51 (m, 1H, H-6), 0.89 (s, 3H, H-11); MS (ESI) *m*/*z* (rel intensity) 249.01 ([M + H]$^+$, 100); HRMS *m*/*z* calcd for $C_{14}H_{16}O_2SNa$ ([M + Na]$^+$) 271.0763, found 271.0753.

General Procedure for the Synthesis of ***6a*****–*****m*** *and* ***7a*****–*****n*****.** A mixture of the corresponding acids RCO_2H (0.7 mmol), diisopropylcarbodiimide (DIC, 0.7 mmol), 4-dimethylaminopyridine (DMAP, 0.07 mmol), and **3** (0.35 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature. When the reaction was complete according to TLC analysis, the mixture was diluted by CH_2Cl_2 (30 mL), washed by aqueous HCl (0.1 mol/L, 15 mL), 5% aqueous $NaHCO_3$ (15 mL), and brine (15 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by PTLC to give the pure target products **6a**−**m** and **7a**−**n**. The example data of **6a**−**d** and **7a**−**d** are shown as follows, whereas data of **6e**−**m** and **7e**−**n** can be found in the Supporting Information.

Data for ***6a****:* colorless liquid; yield 29%; $[\alpha]^{20}_D$ = 9 (*c* 4.6 mg/mL, $CHCl_3$); IR (cm^{-1}) 3030, 2936, 2871, 1731, 1250, 1146, 969, 723; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.31 (m, 11H, Ph-H and H-2′), 7.05 (s, 1H, H-5′), 6.10 (s, 1H, H-4′), 5.87 (s, 1H, H-8), 4.74 (d, *J* = 12.0 Hz, H-1), 4.61 (d, *J* = 12.0 Hz, H-1), 3.60 (s, 2H, $-CH_2C_6H_5$), 3.58 (s, 2H, $-CH_2C_6H_5$), 1.92−1.97 (m, 2H, H-4), 1.57 (s, 3H, H-10), 1.44−1.52 (m, 3H, H-5, 6), 1.24−1.29 (m, 1H, H-6), 0.96 (s, 3H, H-11); HRMS *m*/*z* calcd for $C_{30}H_{32}O_5Na$ ([M + Na]$^+$) 495.2142, found 495.2151.

Data for ***6b****:* colorless liquid; yield 35%; $[\alpha]^{20}_D$ = 10 (*c* 3.8 mg/mL, $CHCl_3$); IR (cm^{-1}) 2937, 2872, 1731, 1509, 1223, 1152, 1027, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.26 (m, 5H, Ph-H and H-2′, 5′), 7.09 (s, 1H, Ph-H), 6.96−7.02 (m, 4H, Ph-H), 6.10 (d, *J* = 1.2 Hz, 1H, H-4′), 5.87 (s, 1H, H-8), 4.73 (d, *J* = 12.0 Hz, 1H, H-1), 4.60 (d, *J* = 12.0 Hz, 1H, H-1), 3.58 (s, 2H, $-CH_2C_6H_5F$), 3.55 (s, 2H, $-CH_2C_6H_5F$), 1.90−2.01 (m, 2H, H-4), 1.58 (s, 3H, H-10), 1.44−1.55 (m, 3H, H-5, 6), 1.23−1.29 (m, 1H, H-6), 0.96 (s, 3H, H-11); HRMS *m*/*z* calcd for $C_{30}H_{30}O_5F_2Na$ ([M + Na]$^+$) 531.1954, found 531.1946.

Data for ***6c****:* colorless liquid; yield 42%; $[\alpha]^{20}_D$ = 6 (*c* 4.8 mg/mL, $CHCl_3$); IR (cm^{-1}) 2936, 2872, 1731, 1250, 1154, 1091, 806, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.30 (m, 5H, Ph-H and H-2′, 5′), 7.18−7.20 (m, 4H, Ph-H), 7.10 (s, 1H, Ph-H), 6.11 (d, *J* = 1.2 Hz, 1H, H-4′), 5.87 (s, 1H, H-8), 4.73 (d, *J* = 12.4 Hz, 1H, H-1), 4.60 (d, *J* = 12.4 Hz, 1H, H-1), 3.57 (s, 2H, $-CH_2C_6H_5Cl$), 3.54 (s, 2H, $-CH_2C_6H_5Cl$), 1.91−2.01 (m, 2H, H-4), 1.59 (s, 3H, H-10), 1.44−1.56 (m, 3H, H-5, 6), 1.23−1.30 (m, 1H, H-6), 0.97 (s, 3H, H-11); HRMS *m*/*z* calcd for $C_{30}H_{30}O_5Cl_2Na$ ([M + Na]$^+$) 563.1363, found 563.1389.

Data for ***6d****:* colorless liquid; yield 37%; $[\alpha]^{20}_D$ = 5 (*c* 4.9 mg/mL, $CHCl_3$); IR (cm^{-1}) 2935, 2870, 1731, 1488, 1249, 1155, 1012, 801, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.45 (m, 4H, Ph-H and H-2′, 5′), 7.26−7.27 (m, 1H, Ph-H), 7.10−7.14 (m, 5H, Ph-H), 6.11 (d, *J* = 0.8 Hz, 1H, H-4′), 5.86 (s, 1H, H-8), 4.73 (d, *J* = 12.4 Hz, 1H, H-1), 4.60 (d, *J* = 12.0 Hz, 1H, H-1), 3.56 (s, 2H, $-CH_2C_6H_5Br$), 3.53 (s, 2H, $-CH_2C_6H_5Br$), 1.91−2.02 (m, 2H, H-4), 1.59 (s, 3H, H-10), 1.45−1.56 (m, 3H, H-5, 6), 1.25−1.30 (m, 1H, H-6), 0.97 (s, 3H, H-11); HRMS *m*/*z* calcd for $C_{30}H_{30}O_5Br_2Na$ ([M + Na]$^+$) 651.0352, found 651.0367.

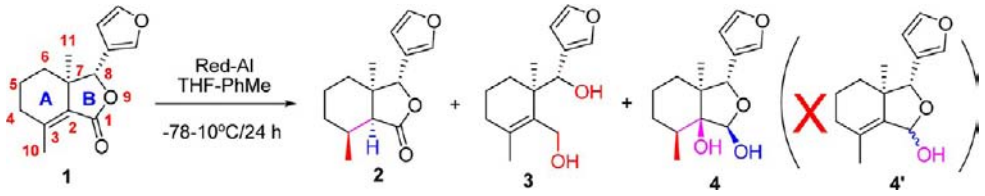
Data for ***7a****:* colorless liquid; yield 34%; $[\alpha]^{20}_D$ = 7 (*c* 3.3 mg/mL, $CHCl_3$); IR (cm^{-1}) 3485, 2933, 2870, 1726, 1257, 1159, 1022, 874, 726; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.33 (m, 7H, Ph-H and H-2′, 5′), 6.32 (d, *J* = 1.0 Hz, 1H, H-4′), 4.81 (d, *J* = 12.0 Hz, H-1), 4.69−4.72 (m, 2H, H-1 and H-8), 3.59 (s, 2H, $-CH_2C_6H_5$), 1.98−2.01 (m, 2H, H-4), 1.89 (s, 1H, −OH), 1.64 (s, 3H, H-10), 1.51−1.57 (m, 3H, H-5, 6), 1.26−1.32 (m, 1H, H-6), 1.07 (s, 3H, H-11); HRMS *m*/*z* calcd for $C_{22}H_{26}O_4Na$ ([M + Na]$^+$) 377.1723, found 377.1725.

Data for ***7b****:* colorless liquid; yield 40%; $[\alpha]^{20}_D$ = 6 (*c* 2.4 mg/mL, $CHCl_3$); IR (cm^{-1}) 3486, 2933, 2871, 1724, 1606, 1510, 1223, 1155, 1021, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 2.0 Hz, 1H, H-2′), 7.30 (d, *J* = 0.8 Hz, 1H, H-5′), 7.20−7.23 (m, 2H, Ph-H), 6.96−7.01 (m, 2H, Ph-H), 6.32 (d, *J* = 1.2 Hz, 1H, H-4′), 4.81 (d, *J* = 12.4 Hz, 1H, H-1), 4.70−4.73 (m, 2H, H-1, 8), 3.56 (s, 2H, $-CH_2C_6H_5F$), 1.99−2.06 (m, 2H, H-4) 1.93 (s, 1H, −OH), 1.64 (s, 3H, H-10), 1.48−1.59 (m, 3H, H-5, 6), 1.26−1.33 (m, 1H, H-6), 1.07 (s, 3H, H-11); HRMS *m*/*z* calcd for $C_{22}H_{25}O_4FNa$ ([M + Na]$^+$) 395.1629, found 395.1631.

Data for ***7c****:* colorless liquid; yield 46%; $[\alpha]^{20}_D$ = 10 (*c* 4.4 mg/mL, $CHCl_3$); IR (cm^{-1}) 3494, 2933, 2870, 2828, 1725, 1492, 1160, 1017, 805, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.34 (m, 4H, Ph-H and H-2′, H-5′), 7.18 (d, *J* = 8.4 Hz, 2H, Ph-H), 6.32 (d, *J* = 0.8 Hz, 1H, H-4′), 4.82 (d, *J* = 12.0 Hz, 1H, H-1), 4.70−4.73 (m, 2H, H-1, 8), 3.56 (s, 2H, $-CH_2C_6H_5Cl$), 1.99−2.03 (m, 2H, H-4) 1.89 (s, 1H, −OH), 1.64 (s, 3H, H-10), 1.52−1.60 (m, 3H, H-5, 6), 1.26−1.33 (m, 1H, H-6), 1.07 (s, 3H, H-11); HRMS *m*/*z* calcd for $C_{22}H_{25}O_4ClNa$ ([M + Na]$^+$) 411.1334, found 411.1334.

Data for ***7d****:* colorless liquid; yield 38%; $[\alpha]^{20}_D$ = 12 (*c* 2.4 mg/mL, $CHCl_3$); IR (cm^{-1}) 3493, 2931, 2870, 2827, 1725, 1488, 1253, 1159,

Table 1. Investigation of Reduction of Fraxinellone (1) in the Presence of Red-Al Reagent



	amount (mmol)			isolated yield (%)			
entry	1	Red-Al	molar ratio of Red-Al/1	2	3	4	recovery rate of 1 (%)
1	2	2	1:1			4	81
2	2	3	1.5:1			6	78
3	2	4	2:1	20	32	8	17
4	2	5	2.5:1	28	40	15	
5	2	6	3:1	29	46	16	

1013, 802, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H, Ph-H), 7.33 (t, J = 1.6 Hz, 1H, H-2′), 7.30 (s, 1H, H-5′), 7.12 (d, J = 8.4 Hz, 2H, Ph-H), 6.32 (d, J = 0.8 Hz, 1H, H-4′), 4.82 (d, J = 12.0 Hz, 1H, H-1), 4.70−4.74 (m, 2H, H-1, 8), 3.54 (s, 2H, $-CH_2C_6H_5Br$), 1.99−2.06 (m, 2H, H-4), 1.88 (s, 1H, −OH), 1.64 (s, 3H, H-10), 1.52−1.60 (m, 3H, H-5, 6), 1.25−1.33 (m, 1H, H-6), 1.07 (s, 3H, H-11); HRMS m/z calcd for $C_{22}H_{25}O_4BrNa$ ([M + Na]$^+$) 455.0828, found 455.0820.

General Procedure for the Synthesis of ***8a,e−k,o.*** A mixture of the corresponding acids RCO_2H (0.28 mmol), diisopropylcarbodiimide (DIC, 0.28 mmol), 4-dimethylaminopyridine (DMAP, 0.04 mmol), and **4** (0.2 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature. When the reaction was complete according to TLC analysis, the mixture was diluted by CH_2Cl_2 (30 mL), washed by aqueous HCl (0.1 mol/L, 15 mL), 5% aqueous $NaHCO_3$ (15 mL), and brine (15 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by PTLC to give the pure target products **8a,e−k,o**. The example data of **8a,e−g** are shown as follows, whereas data of **8h−k,o** can be found in the Supporting Information.

Data for ***8a:*** white solid; yield 55%; mp 86−87 °C; $[\alpha]^{20}_D$ = −19 (c 3.7 mg/mL, $CHCl_3$); IR (cm^{-1}) 3514, 2961, 2926, 2854, 1728, 1456, 1259, 1140, 1009, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.37 (m, 7H, Ph-H and H-2′,5′), 6.26 (d, J = 0.8 Hz, 1H, H-4′), 6.19 (s, 1H, H-8), 5.39 (s, 1H, H-2), 3.71 (s, 2H, $-CH_2C_6H_5$), 2.23 (s, 1H, −OH), 1.85−1.95 (m, 2H, H-4), 1.34−1.55 (m, 4H, H-3,5,6), 1.09−1.14 (m, 1H, H-6), 0.80 (s, 3H, H-11), 0.45 (d, J = 6.8 Hz, 3H, H-10); HRMS m/z calcd for $C_{22}H_{26}O_5Na$ ([M + Na]$^+$) 393.1673, found 393.1675.

Data for ***8e:*** white solid; yield 53%; mp 98−99 °C; $[\alpha]^{20}_D$ = −29 (c 3.0 mg/mL, $CHCl_3$); IR (cm^{-1}) 3560, 2959, 2922, 2870, 1745, 1461, 1250, 1006, 793; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H, Nap-H), 7.85 (d, J = 8.8 Hz, 1H, Nap-H), 7.79−7.81 (m, 1H, Nap-H), 7.48−7.58 (m, 2H, Nap-H), 7.42−7.44 (m, 2H, Nap-H and H-2′), 7.35−7.36 (m, 2H, Nap-H and H-5′), 6.25 (d, J = 0.8 Hz, 1H, H-4′), 6.09 (s, 1H, H-8), 5.35 (s, 1H, H-2), 4.12−4.22 (m, 2H, $-CH_2C_{10}H_7$), 1.93 (s, 1H, −OH), 1.67−1.84 (m, 2H, H-4), 1.42−1.45 (m, 2H, H-3, 5), 1.18−1.23 (m, 2H, H-5, 6), 1.03−1.08 (m, 1H, H-6), 0.73 (s, 3H, H-11), −0.07 (d, J = 6.4 Hz, 3H, H-10); HRMS m/z calcd for $C_{26}H_{28}O_5Na$ ([M + Na]$^+$) 443.1829, found 443.1828.

Data for ***8f:*** white solid; yield 70%; mp 106−108 °C; $[\alpha]^{20}_D$ = −16 (c 3.5 mg/mL, $CHCl_3$); IR (cm^{-1}) 3619, 2959, 2928, 1731, 1397, 1222, 1094, 993; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H, Ph-H), 7.58−7.62 (m, 1H, Ph-H), 7.45−7.49 (m, 2H, Ph-H), 7.42 (s, 1H, H-2′), 7.37 (t, J = 1.6 Hz, 1H, H-5′), 6.47 (s, 1H, H-8), 6.31 (d, J = 0.8 Hz, 1H, H-4′), 5.50 (s, 1H, H-2), 2.59 (s, 1H, −OH), 1.99−2.07 (m, 2H, H-4), 1.46−1.62 (m, 4H, H-3, 5, 6), 1.17−1.22 (m, 1H, H-6), 0.90 (s, 3H, H-11), 0.84 (d, J = 6.4 Hz, 3H, H-10); HRMS m/z calcd for $C_{21}H_{24}O_5Na$ ([M + Na]$^+$) 379.1516, found 379.1518.

Data for ***8g:*** white solid; yield 42%; mp 135−137 °C; $[\alpha]^{20}_D$ = −12 (c 3.0 mg/mL, $CHCl_3$); IR (cm^{-1}) 3575, 2956, 2936, 2873, 1718, 1611, 1277, 1014, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 2H, Ph-H), 7.41 (s, 1H, H-2′), 7.37 (t, J = 1.6 Hz, 1H, H-5′), 7.25−7.27 (m, 2H, Ph-H), 6.46 (s, 1H, H-8), 6.30 (d, J = 1.2 Hz, 1H, H-4′), 5.49 (s, 1H, H-2), 2.60 (s, 1H, −OH), 2.42 (s, 3H, $-CH_3$), 2.01−2.06 (m, 2H, H-4), 1.45−1.62 (m, 4H, H-3, 5, 6), 1.17−1.21 (m, 1H, H-6), 0.89 (s, 3H, H-11), 0.82 (d, J = 6.8 Hz, 3H, H-10); HRMS m/z calcd for $C_{22}H_{26}O_5Na$ ([M + Na]$^+$) 393.1673, found 393.1673.

Biological Assay. The insecticidal activity of compounds **1−3**, **5**, **6a−m**, **7a−n**, and **8a,e−k,o** against oriental armyworm (*M. separata* Walker) was tested according to the previously reported leaf-dipping method.[31] For each compound, 30 pre-third-instar larvae (10 larvae per group) were used. Acetone solutions of compounds **1−3**, **5**, **6a−m**, **7a−n**, and **8a,e−k,o** were prepared at the concentration of 1 mg/mL. Toosendanin (supplied by Research and Development Center of Biorational Pesticide, Northwest A&F University, Shaanxi province, China) was used as the positive control at 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 blank control group. Several treated leaves were kept in each dish (10 larvae were raised in each dish), which was then placed in a conditioned room (25 ± 2 °C, 65−80% relative humidity (RH), 12 h/12 h (light/dark) photoperiod). If the treated leaves were consumed, additional treated leaves were added to the corresponding dish. After 48 h, untreated fresh leaves were added to all dishes until adult emergence. The corrected mortality rates were assessed by the formula

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

where T is the mortality rate in the group treated with the tested compounds and C is the mortality rate in the blank control group (T and C were expressed as percentages).

RESULTS AND DISCUSSION

Synthesis. As described in Table 1, reduction of fraxinellone (**1**) in the presence of Red-Al reagent was first investigated. When the molar ratio of Red-Al/**1** was 1:1 or 1.5:1 at −78 to 10 °C for 24 h, besides the starting material **1**, only compound **4** (stereoselective reduction of the carbonyl group and the double bond at the C-1 and C-2 positions of **1**, respectively) was obtained in 4 and 6% yields, respectively (entries 1 and 2). Interestingly, when the molar ratio of Red-Al/**1** was increased to 2:1, products **2** (20% yield, stereoselective reduction of the double bond at the C-2 position of **1**), **3** (32% yield, lactone ring-opened, followed by reduction of carbonyl group of **1**), and **4** (8% yield) were all afforded (entry 3). When the molar ratio of Red-Al/**1** was increased to 2.5:1, products **2**, **3**, and **4** were obtained in 28, 40, and 15% yields, respectively (entry 4). If the molar ratio of Red-Al/**1** was further increased to 3:1, the yields of **2**, **3**, and **4** were 29, 46, and 16%, respectively (entry 5). However, the target intermediate **4′** (reduction of the carbonyl group at the C-1

position of **1**) was not produced at all. Obviously, the kinds and amounts of reduction products were related to the molar ratio of Red-Al/**1**. The steric configurations of **2** and **3** were determined by X-ray crystallography as illustrated in Figures 2

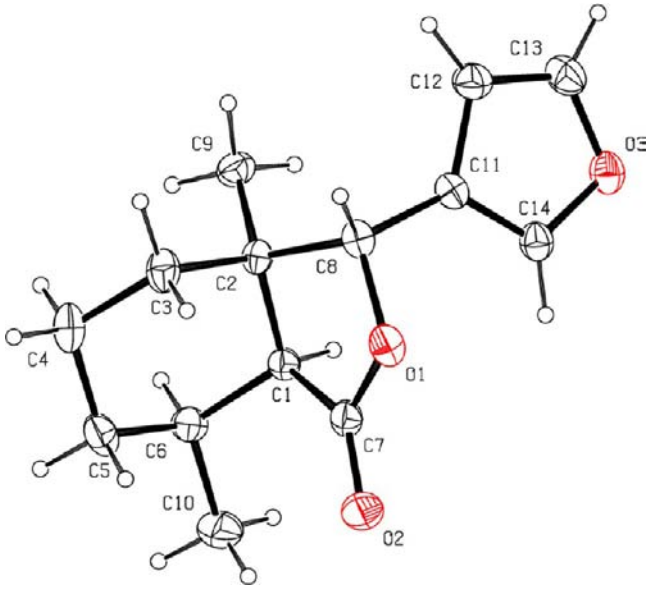


Figure 2. X-ray crystal structure of **2**.

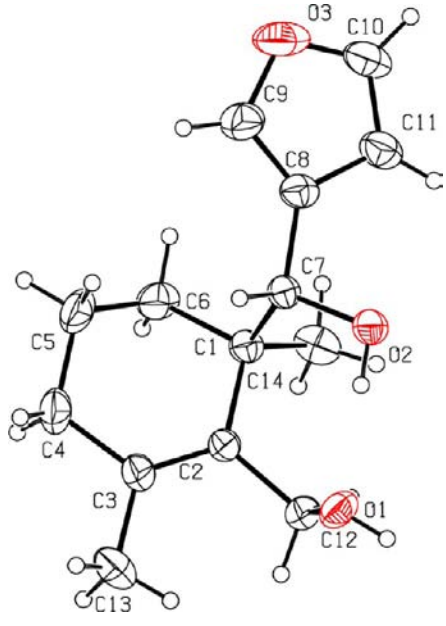


Figure 3. X-ray crystal structure of **3**.

and 3. As described in Figure 2, the hydrogen atom at the C-2 position and the methyl group at the C-3 position of compound **2** were clearly present in α and β configuration, respectively. As shown in Figure 3, the methyl group at the C-7 position and the furanyl ring at the C-8 position of compound **3** were all present in α configuration. The steric configuration of **4** was determined according to the X-ray crystallography structures of its esters (see Figures 5−7).

Then compound **5** was obtained in 54% yield by reaction of **1** with Lawesson's reagent.[32] Subsequently, as shown in Scheme 1, when **3** reacted with 2 equiv of carboxylic acids in the presence of DIC and DMAP, besides the target diacylation products **6a−m** (**V**, Figure 1), monoacylation products **7a−n** were also obtained. The evidence for the position of monoacylation of **7a−n** was demonstrated by ^{1}H NMR spectra. For example, as depicted in the partial ^{1}H NMR spectra of compounds **3** (a), **7i** (b), and **6i** (c) (Figure 4), the chemical shifts of two protons of H-1 and the proton of H-8 of **3** were 4.096/4.296, and 4.763 ppm, respectively. When **3** reacted with 4-cyanobenzoic acid in the presence of DIC and DMAP to monoacylation product **7i** and dioacylation product **6i**, the chemical shifts of two protons of H-1 and the proton of H-8 of **6i** were 4.899/5.045 and 6.277 ppm, respectively, whereas the chemical shifts of two protons of H-1 and the proton of H-8 of **7i** were 5.015/5.095 and 4.84 ppm, respectively. On the basis of the above-mentioned results, it was suggested that monoacylation of **7i** was at the C-1 position. Similarly, monoacylation at the C-1 position of other products **7a−h,j−n** was also determined by ^{1}H NMR spectra data. Finally, when **4** reacted with 1.4 equiv of carboxylic acids in the presence of DIC and DMAP, only monoacylation products **8a,e−k,o** were regioselectively afforded because the steric hindrance of the C2-hydroxy group of **4** was bigger than that of C1-hydroxy group. For the intermediate **4**′ was, the target products **VI** (Figure 1) were not prepared. The steric configurations of **8f,g,j** were unambiguously confirmed by X-ray crystallography as illustrated in Figures 5−7. It demonstrated that the C1-acyloxy groups and C2-hydroxy groups of **8f,g,j** all adopted β configuration; that is, the configuration of two hydroxy groups at the C-1 and C-2 positions of **4** was also β. The structures of all target compounds were well characterized by ^{1}H NMR, HRMS, optical rotation, IR, and mp. Crystallographic data (excluding structure factors) for the structures of **2**, **3**, and **8f,g,j** have been deposited at the Cambridge Crystallographic Data Centre with Data CCDC 951814-951818, respectively. These data can be obtained free of charge from CCDC [fax +44 (0)1223 336033 or e-mail deposit@ccdc.cam.ac.uk].

Insecticidal Activity. As shown in Table 2, the insecticidal activity of **1−3**, **5**, **6a−m**, **7a−n**, and **8a,e−k,o** against the pre-third-instar larvae of *M. separata* in vivo, tested by the leaf-dipping method at the concentration of 1 mg/mL, was expressed as the mortality rate. Toosendanin was used as the positive control, and leaves treated with acetone alone were used as a blank control group. As shown in Lü's and our previous papers,[26−28] the mortality rates of these tested compounds against *M. separata* after 35 days were often higher than those after 10 and 20 days (Table 2). Obviously, these tested compounds, as opposed to other quick-acting conventional neurotoxic insecticides such as organophosphates, carbamates, and pyrethroids, exhibited delayed insecticidal activity. Additionally, the symptoms of the larvae of *M. separata* treated by the above tested compounds were observed. First, a majority of larvae of the treated groups generally died with slim and wrinkled bodies during the larval period (Figure 8). Second, many larvae also molted to malformed pupae or died in the treated groups during the stage of pupation (Figure 9). Third, some malformed moths of the treated groups appeared with imperfect wings during the emergence period (Figure 10). On the basis of the above symptoms, it was suggested that these derivatives might display an antimolting hormone effect.[27,28] Compounds **2** and **8i,j,o** exhibited more pronounced

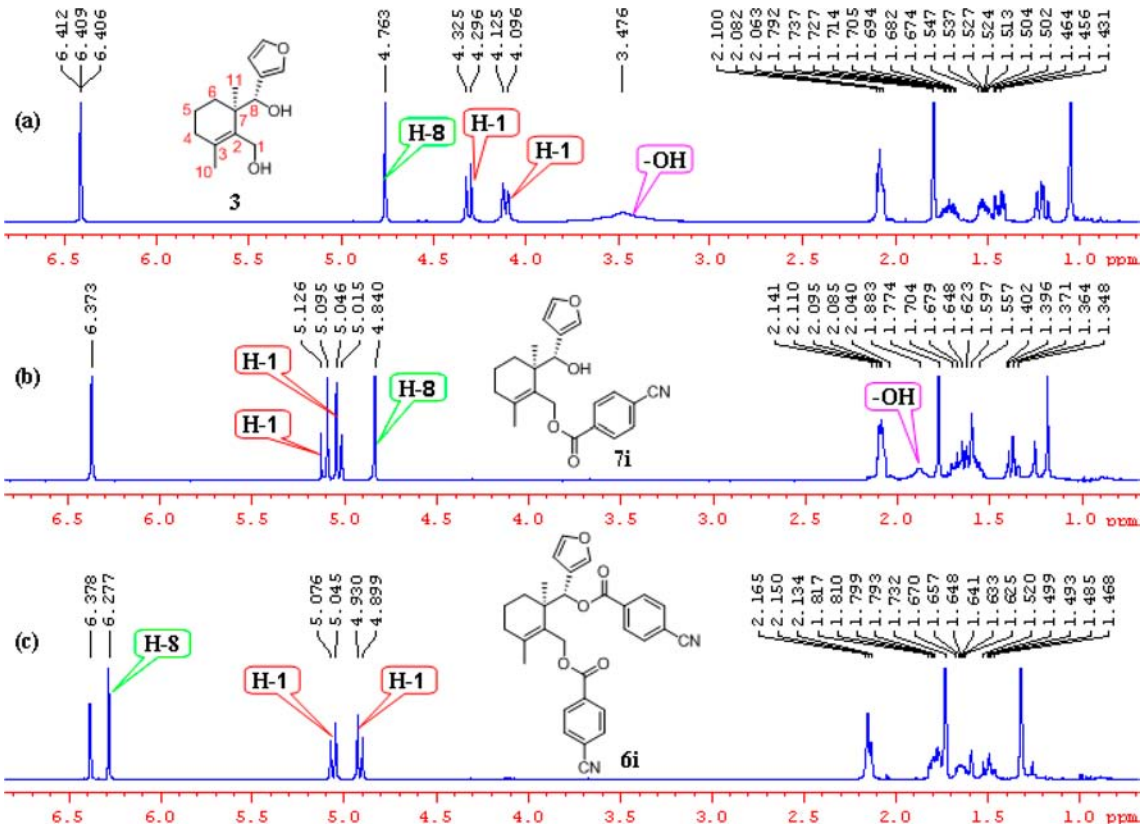


Figure 4. Partial ^{1}H NMR spectra of **3** (a), **7i** (b), and **6i** (c).

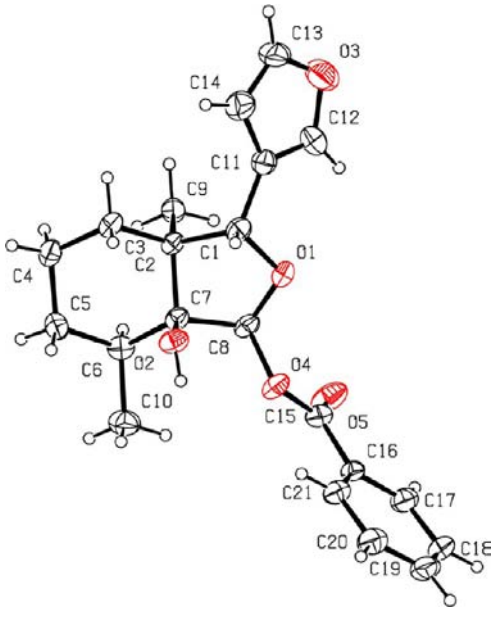


Figure 5. X-ray crystal structure of **8f**.

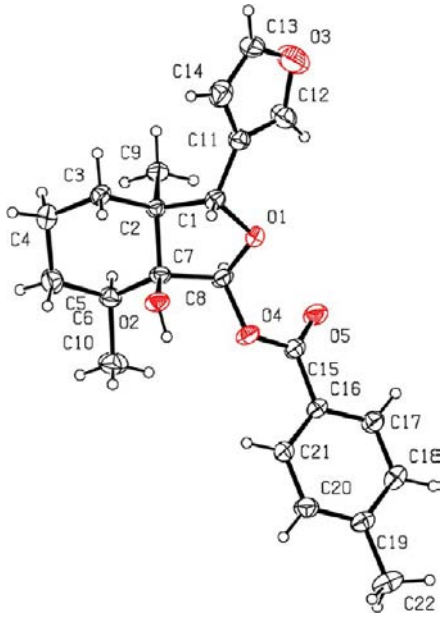


Figure 6. X-ray crystal structure of **8g**.

insecticidal activity than toosendanin. Especially compound **8i** showed the most promising insecticidal activity with a final mortality rate of 65.5%.

Meanwhile, some interesting results of structure−activity relationships of tested compounds were also observed: (1) The double bond at the C-2 position of **1** was not necessary for the insecticidal activity. For example, when the double bond at the C-2 position of **1** was reduced by Red-Al reagent to give **2**, the final mortality rate of **2** was increased to 58.6% compared to that of **1** (41.4%). (2) Substitution of the oxygen atom of the carbonyl group on the lactone of **1** by a sulfur one does not improve the insecticidal activity. For example, the final mortality rates of **1** and **5** were 41.4 and 34.5%, respectively. (3) The lactone (B ring) of **1** was important for the insecticidal activity. Once the lactone of **1** was opened, even if many functional groups (acyloxy) were introduced at the C-1 and C-8 positions of **1**, the insecticidal activity of the corresponding derivatives was not be improved (e.g., **3**, **6a**−**m**, and **7a**−**n**). (4)

dx.doi.org/10.1021/jf404195m | J. Agric. Food Chem. 2013, 61, 11937−11944

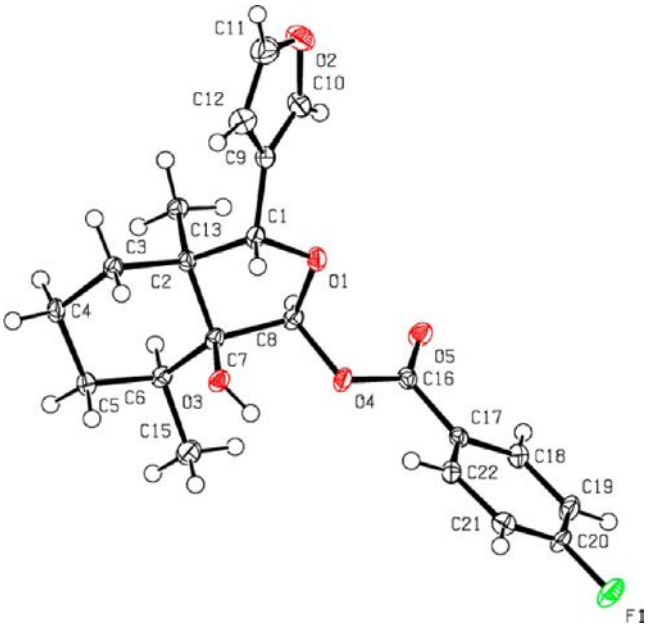


Figure 7. X-ray crystal structure of **8j**.

In general, in benzoyloxy series **8f–o**, introduction of electron-withdrawing groups on the phenyl ring of **8f** could lead to more potent compounds. For example, the final mortality rates of **8i** (containing the cyano on the phenyl ring), **8j** (containing a fluorine atom on the phenyl ring), and **8o** (containing a chlorine atom on the phenyl ring) were 65.5, 58.6, and 51.7%, respectively, whereas the final mortality rates of **8f** (containing the hydrogen atom on the phenyl ring), **8g** (containing the methyl group on the phenyl ring), and **8h** (containing the methoxy group on the phenyl ring) were 48.3, 41.4, and 44.8%, respectively.

In conclusion, a series of novel fraxinellone derivatives modified at the C-1 or C-8 position in the B ring of fraxinellone were synthesized and evaluated for their insecticidal activity against the pre-third-instar larvae of *M. separata* in vivo. Five key steric configurations of compounds **2**, **3**, and **8f,g,j** were unambiguously determined by single-crystal X-ray diffraction. It was found that the kinds and amount of the reduction products of fraxinellone were related to the molar ratio between the reduction agent Red-Al and the substrate fraxinellone. Especially compounds **2** and **8i,j,o** showed more promising insecticidal activity than their precursor fraxinellone and toosendanin. This suggested that the lactone (B ring) of

Scheme 1. Synthetic Route for the Preparation of Fraxinellone Derivatives 5, 6a–m, 7a–n, and 8a,e–k,o

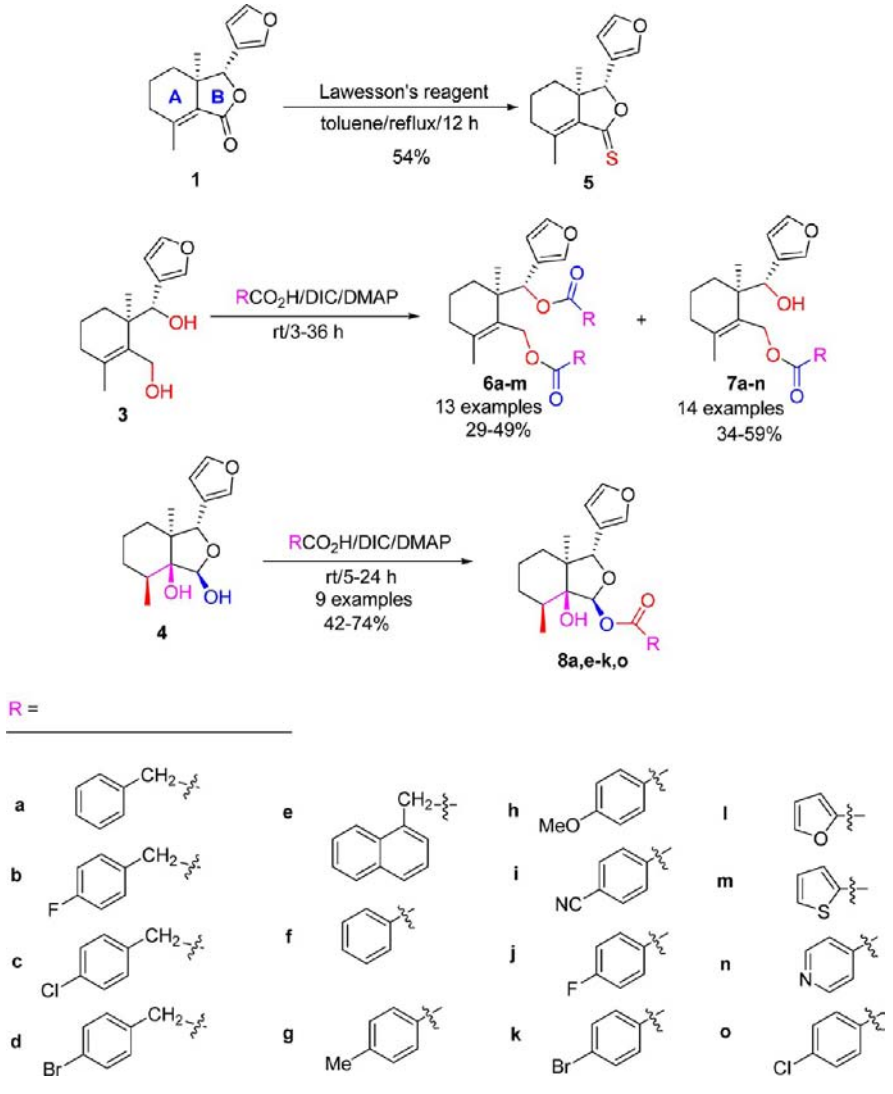


Table 2. Insecticidal Activity of Fraxinellone Derivatives 5, 6a−m, 7a−n, and 8a,e−k,o against *M. separata* on Leaves Treated at a Concentration of 1 mg/mL[a]

compd	corrected mortality rate (%)		
	10 days	20 days	35 days
1	6.7 ± 3.3	10.3 ± 3.3	41.4 ± 3.3
2	36.7 ± 3.3	44.8 ± 3.3	58.6 ± 5.8
3	3.3 ± 3.3	31.0 ± 3.3	41.4 ± 3.3
5	3.3 ± 3.3	6.9 ± 5.8	34.5 ± 3.3
6a	3.3 ± 3.3	3.4 ± 3.3	27.6 ± 0
6b	3.3 ± 3.3	6.9 ± 0	24.1 ± 3.3
6c	13.3 ± 3.3	17.2 ± 0	20.7 ± 3.3
6d	3.3 ± 3.3	6.9 ± 0	27.6 ± 0
6e	20.0 ± 0	17.2 ± 0	24.1 ± 3.3
6f	3.3 ± 3.3	10.3 ± 3.3	31.0 ± 3.3
6g	3.3 ± 3.3	13.8 ± 3.3	27.6 ± 0
6h	3.3 ± 3.3	6.9 ± 0	24.1 ± 3.3
6i	3.3 ± 3.3	6.9 ± 0	34.5 ± 3.3
6j	3.3 ± 3.3	17.2 ± 0	34.5 ± 3.3
6k	3.3 ± 3.3	17.2 ± 0	24.1 ± 3.3
6l	16.7 ± 3.3	17.2 ± 0	24.1 ± 3.3
6m	6.7 ± 3.3	17.2 ± 0	24.1 ± 3.3
7a	6.7 ± 3.3	17.2 ± 5.8	37.9 ± 0
7b	3.3 ± 3.3	10.3 ± 3.3	41.4 ± 3.3
7c	10.0 ± 0	17.2 ± 0	41.4 ± 3.3
7d	6.7 ± 3.3	20.7 ± 3.3	34.5 ± 3.3
7e	10.0 ± 0	27.6 ± 0	37.9 ± 0
7f	13.3 ± 3.3	37.9 ± 0	41.4 ± 3.3
7g	3.3 ± 3.3	17.2 ± 0	37.9 ± 0
7h	10.0 ± 0	31.0 ± 3.3	37.9 ± 0
7i	10.0 ± 0	13.8 ± 3.3	41.4 ± 3.3
7j	10.0 ± 5.8	20.7 ± 3.3	44.8 ± 3.3
7k	3.3 ± 3.3	17.2 ± 0	31.0 ± 3.3
7l	3.3 ± 3.3	17.2 ± 0	34.5 ± 3.3
7m	0 ± 0	13.8 ± 3.3	37.9 ± 0
7n	6.7 ± 6.7	24.1 ± 3.3	37.9 ± 0
8a	6.7 ± 3.3	17.2 ± 0	44.8 ± 3.3
8e	13.3 ± 3.3	10.3 ± 3.3	44.8 ± 3.3
8f	10.0 ± 5.8	24.1 ± 3.3	48.3 ± 0
8g	6.7 ± 6.7	13.8 ± 3.3	41.4 ± 3.3
8h	16.7 ± 3.3	24.1 ± 3.3	44.8 ± 3.3
8i	10.0 ± 5.8	13.8 ± 3.3	65.5 ± 3.3
8j	23.3 ± 3.3	31.0 ± 3.3	58.6 ± 0
8k	13.3 ± 3.3	17.2 ± 5.8	48.3 ± 0
8o	6.7 ± 3.3	17.2 ± 0	51.7 ± 3.3
toosendanin	3.3 ± 3.3	17.2 ± 5.8	48.3 ± 0

[a]Values are means ± SD of three replicate. The final mortality rate of the blank control group was 3.3%.

fraxinellone was important for the insecticidal activity; the double bond at the C-2 position of fraxinellone was not necessary for the insecticidal activity; conversion of the oxygen atom of carbonyl group on the lactone of fraxinellone to a sulfur one does not improve the insecticidal activity; introduction of the electron-withdrawing groups on the phenyl ring of **8f**, to the benzoyloxy series, could result in more potent compounds. This work will pave the way for further design, structural modification, and development of fraxinellone as botanical insecticidal agents.

Figure 8. Representative abnormal larva pictures of **2**, **7e,j,n**, and **8i,j,o** during the larval period (CK, blank control group).

Figure 9. Representative malformed pupa pictures of **6l**, **7e,f,j,n**, and **8j,8o** during the pupation period (CK, blank control group).

Figure 10. Representative malformed moth pictures of **3**, **7e,I,j,n**, and **8i,j** during the emergence period (CK, blank control group).

dx.doi.org/10.1021/jf404195m | *J. Agric. Food Chem.* 2013, 61, 11937−11944

■ ASSOCIATED CONTENT

Supporting Information

^{1}H 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

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

Funding

The present research was supported by the National Natural Science Foundation of China (No. 31171896) and Special Funds of Central Colleges Basic Scientific Research Operating Expenses (YQ2013008) to H.X.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Scoble, M. J. *The Lepidoptera: Form, Function and Diversity*, 2nd ed.; Oxford University Press: Oxford, UK, 1995; pp 4−5.

(2) Jiang, X. F.; Luo, L. Z.; Zhang, L.; Sappington, T. W.; Hu, Y. Regulation of migration in *Mythimna separata* (Walker) in China: a review integrating environmental, physiological, hormonal, genetic, and molecular factors. *Environ. Entomol.* **2011**, *40*, 516−533.

(3) Han, E.; Gatehouse, A. G. Genetics of precalling period in the oriental armyworm, *Mythimna separata* (Walker) (Lepidoptera: Noctuidae), and implications for migration. *Evolution* **1991**, *45*, 1502−1510.

(4) Heckel, D. G. Insecticide resistance after silent spring. *Science* **2012**, *337*, 1612−1614.

(5) Guillette, L. J., Jr.; Iguchi, T. Life in a contaminated world. *Science* **2012**, *337*, 1614−1615.

(6) Xu, H. Comments to "Insecticide resistance after silent spring"; http://comments.sciencemag.org/content/10.1126/science.1226994, 2013.

(7) Lin, L.; Mulholland, N.; Wu, Q.; Beattie, D.; Huang, S.; Irwin, D.; Clough, J.; Gu, Y.; Yang, G. F. Synthesis and antifungal activity of novel sclerotiorin analogues. *J. Agric. Food Chem.* **2012**, *60*, 4480−4491.

(8) Zhang, M.; Mulholland, N.; Beattie, D.; Irwin, D.; Gu, Y. C.; Chen, Q.; Yang, G. F.; Clough, J. Synthesis and antifungal activity of 3-(1,3,4-oxadiazol-5-yl)-indoles and 3-(1,3,4-oxadiazol-5-yl)methyl-indoles. *Eur. J. Med. Chem.* **2013**, *63*, 22−32.

(9) Zhang, M.; Chen, Q.; Mulholland, N.; Beattie, D.; Irwin, D.; Gu, Y. C.; Yang, G. F.; Clough, J. Synthesis and fungicidal activity of novel pimprinine analogues. *Eur. J. Med. Chem.* **2012**, *53*, 283−291.

(10) Lin, L.; Mulholland, N.; Huang, S. W; Beattie, D.; Irwin, D.; Gu, Y. C.; Clough, J.; Wu, Q. Y.; Yang, G. F. Design, synthesis and fungicidal activity of novel sclerotiorin derivatives. *Chem. Biol. Drug Des.* **2012**, *80*, 682−692.

(11) Aissani, N.; Tedeschi, P.; Maietti, A.; Brandolini, V.; Garau, V. L.; Caboni, P. Nematicidal activity of allylisothiocyanate from Horseradish (*Armoracia rusticana*) roots against *Meloidogyne incognita*. *J. Agric. Food Chem.* **2013**, *61*, 4723−4727.

(12) Sousa, R. M. O. F.; Rosa, J. S.; Oliveira, L.; Cunha, A.; Fernandes-Ferreira, M. Activities of Apiaceae essential oils against armyworm, *Pseudaletia unipuncta* (Lepidoptera: Noctuidae). *J. Agric. Food Chem.* **2013**, *61*, 7661−7672.

(13) Jang, J. Y.; Yang, S. Y.; Kim, Y. C.; Lee, C. W.; Park, M. S.; Kim, J. C.; Kim, I. S. Identification of orfamide A as an insecticidal metabolite produced by *Pseudomonas protegens* F6. *J. Agric. Food Chem.* **2013**, *61*, 6786−6791.

(14) Jeon, J. H.; Yang, J. Y.; Chung, N.; Lee, H. S. Contact and fumigant toxicities of 3-methylphenol isolated from *Ostericum koreanum* and its derivatives against house dust mites. *J. Agric. Food Chem.* **2012**, *60*, 12349−12354.

(15) Yeom, H. J.; Kang, J. S.; Kim, G. H.; Park, I. K. Insecticidal and acetylcholine esterase inhibition activity of Apiaceae plant essential oils and their constituents against adults of German cockroach (*Blattella germanica*). *J. Agric. Food Chem.* **2012**, *60*, 7194−7203.

(16) Sajid, M.; Azim, M. K. Characterization of the nematicidal activity of natural honey. *J. Agric. Food Chem.* **2012**, *60*, 7428−7434.

(17) Munafo, J. P.; Gianfagna, T. J. Antifungal activity and fungal metabolism of steroidal glycosides of Easter lily (*Lilium longiflorum* Thunb.) by the plant pathogenic fungus, *Botrytis cinerea*. *J. Agric. Food Chem.* **2011**, *59*, 5945−5954.

(18) Wu, T. S.; Li, C. Y.; Leu, Y. L.; Hu, C. Q. Limonoids and alkaloids of the root bark of *Dictamnus angustifolius*. *Phytochemistry* **1999**, *50*, 509−512.

(19) D'Ambrosio, M.; Guerriero, A. Degraded limonoids from *Melia azedarach* and biogenetic implications. *Phytochemistry* **2002**, *60*, 419−424.

(20) Yoon, J. S.; Sung, S. H.; Kim, Y. C. Neuroprotective limonoids of root bark of *Dictamnus dasycarpus*. *J. Nat. Prod.* **2008**, *71*, 208−211.

(21) Jeong, G. S.; Byun, E.; Li, B.; Lee, D. S.; An, R. B.; Kim, Y. C. Neuroprotective effects of constituents of the root bark of *Dictamnus dasycarpus* in mouse hippocampal cells. *Arch. Pharm. Res.* **2010**, *33*, 1269−1275.

(22) Lee, C. S.; Won, C.; Yoo, H.; Yi, E. H.; Cho, Y.; Maeng, J. W.; Sung, S. H.; Ye, S. K.; Chung, M. H. Inhibition of double-stranded RNA-induced inducible nitric oxide synthase expression by fraxinellone and sauchinone in murine microglia. *Biol. Pharm. Bull.* **2009**, *32*, 1870−1874.

(23) Yoon, J. S.; Yang, H.; Kim, S. H.; Sung, S. H.; Kim, Y. C. Limonoids from *Dictamnus dasycarpus* protect against glutamate-induced toxicity in primary cultured rat cortical cells. *J. Mol. Neurosci.* **2010**, *42*, 9−16.

(24) Sun, Y.; Qin, Y.; Gong, F. Y.; Wu, X. F.; Hua, Z. C.; Chen, T.; Xu, Q. Selective triggering of apoptosis of concanavalin A-activated T cells by fraxinellone for the treatment of T-cell-dependent hepatitis in mice. *Biochem. Pharmacol.* **2009**, *77*, 1717−1724.

(25) Liu, Z. L.; Ho, S. H.; Goh, S. H. Modes of action of fraxinellone against the tobacco budworm *Heliothis virescens*. *Insect Sci.* **2009**, *16*, 147−155.

(26) Lü, M.; Wu, W. J.; Liu, H. X. Insecticidal and feeding deterrent effects of fraxinellone from *Dictamnus dasycarpus* against four major pests. *Molecules* **2013**, *18*, 2754−2762.

(27) Guo, Y.; Yan, Y.; Yu, X.; Wang, Y.; Xu, H. Synthesis and insecticidal activity of some novel fraxinellone-based esters. *J. Agric. Food Chem.* **2012**, *60*, 7016−7021.

(28) Guo, Y.; Yan, Y.; Yang, C.; Yu, X.; Zhi, X.; Xu, H. Regioselective synthesis of fraxinellone-based hydrazone derivatives as insecticidal agents. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5384−5387.

(29) Miyazawa, M.; Tsurumi, J.; Mori, K. Degraded limonoids, their preparations, insect antifeedants and compositions containing them, and insect control using the compositions. JP A 20090813, 2009.

(30) Zhao, W.; Wolfender, J.-L.; Hostettmann, K.; Xu, R.; Qin, G. Antifungal alkaloids and limonoid derivatives from *Dictamnus dasycarpus* Switz. *Phytochemistry* **1998**, *47*, 7−11.

(31) Wang, Y.; Shao, Y.; Wang, Y.; Fan, L.; Yu, X.; Zhi, X.; Yang, C.; Qu, H.; Yao, X.; Xu, H. Synthesis and quantitative structure-activity relationship (QSAR) study of novel isoxazoline and oxime derivatives of podophyllotoxin as insecticidal agents. *J. Agric. Food Chem.* **2012**, *60*, 8435−8443.

(32) Choi, M. G.; Kim, Y. H.; Namgoong, J. E.; Chang, S.-K. Hg^{2+}-selective chromogenic and fluorogenic chemodosimeter based on thiocoumarins. *Chem. Commun.* **2009**, 3560−3562.