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Synthesis of andrographolide-related esters as insecticidal and acaricidal agents

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ABSTRACT

In continuation of our program aimed at the development of natural product-based pesticidal agents, a series of andrographolide-related esters, such as 3,19-dialkyl(aryl)carbonyloxy andrographolide (**3a**–**g**), 3-alkyl(aryl)carbonyloxyandrographolide (**4a**–**g**), and 19-alkyl(aryl)carbonyloxyandrographolide (**5a**–**g**), were prepared. Their structures were well characterized by ^{1}H NMR, IR, optical rotation, HRMS and mp. Especially three-dimensional structures of compounds **3a**, **4g**, and **5g** were unambiguously confirmed by single-crystal X-ray diffraction. Compounds **3a** and **5a** exhibited good insecticidal and acaricidal activities against *Mythimna separata* and *Tetranychus cinnabarinus*. Their structure-activity relationships were also discussed.

Mythimna separata Walker (oriental armyworm) and *Tetranychus cinnabarinus* Boisduval (spider mite) are two typical and crop-threatening insect pests, and they are generally difficult to control.[1] For example, the intermittent outbreaks of 3rd-generation larvae of *M. separata* occurred in China, and about 4 million hectares of crops were heavily loss in 2012.[2] On the other hand, due to extensive and unreasonable application of synthetic agrochemicals for pest control, resistance in pest populations and negative impacts on human health and environment have simultaneously developed.[3–5] Therefore, the discovery of the potential alternatives to efficiently control insect pests is very necessary.[6–9]

Andrographolide (**1**, Fig. 1), a labdane diterpenoid isolated from *Andrographis paniculata*, exhibited a wide range of biological properties such as anti-inflammatory activity,[10,11] antimicrobial activity,[12,13] antitumor activity,[14–20] and anti-influenza virus activity,[21] and insecticidal activity.[22] Recently, by structural modifications of podophyllotoxin and deoxypodophyllotoxin, a series of ester derivatives of 2′(2′,6′)-(di)halogenopodophyllotoxins (**I**, Fig. 1), 2α-chloro-2′(2′,6′)-(di)halogenopicropodophyllotoxins (**II**, Fig. 1), 4′-demethoxy deoxypodophyllotoxin (**III**, Fig. 1) and 2′-chloro-4′-demethoxyepipodophyllotoxin (**IV**, Fig. 1) have been prepared, and some compounds showed more promising insecticidal activity than their precusors.[23–26] Moreover, we also prepared a series of ester derivatives of C7β-hydroxyobacunone (**V**, Fig. 1) and C7α-hydroxyobacunone (**VI**, Fig. 1), and two derivatives, C7α-propionyloxybacunone and C7β-(*n*)heptanoyloxybacunone, displayed more potent insecticidal activity than their precursor obacunone, and toosendanin.[27] Additionally, Liu et al. found that 14-deoxy-11,12-didehydroandrographolide (**2**, Fig. 1) exhibited the good antitumor activity against Eca 109 and CNE cell lines.[20] Based upon the above results, and in continuation of our program aimed at the development of natural-product-based pesticidal agents,[28,29] herein we wanted to synthesize a series of ester derivatives (**VII**, Fig. 1) of 14-deoxy-11,12-didehydroandrographolide (**2**, Fig. 1). Their insecticidal and acaricidal activities were tested against *Mythimna separata* and *Tetranychus cinnabarinus*.

As shown in Scheme 1, first, 14-deoxy-11,12-didehydroandrographolide (**2**) was prepared by reaction of andrographolide (**1**) with Al_2O_3-pyridine.[20] Then, in the presence of DMAP, although compound **2** reacted with 4 equiv. of acyl chlorides, besides the target diester derivatives (**VII**, Fig. 1), i. e., 3,19-dialkyl(aryl)carbonyloxy andrographolide (**3a**–**g**), the monoesters including 3-alkyl(aryl)carbonyloxyandrographolide (**4a**–**g**) and 19-alkyl(aryl)carbonyloxyandrographolide (**5a**–**g**), were also obtained. Their structures were well characterized by ^{1}H NMR, IR, optical rotation, HRMS and mp (see Supplementary data).

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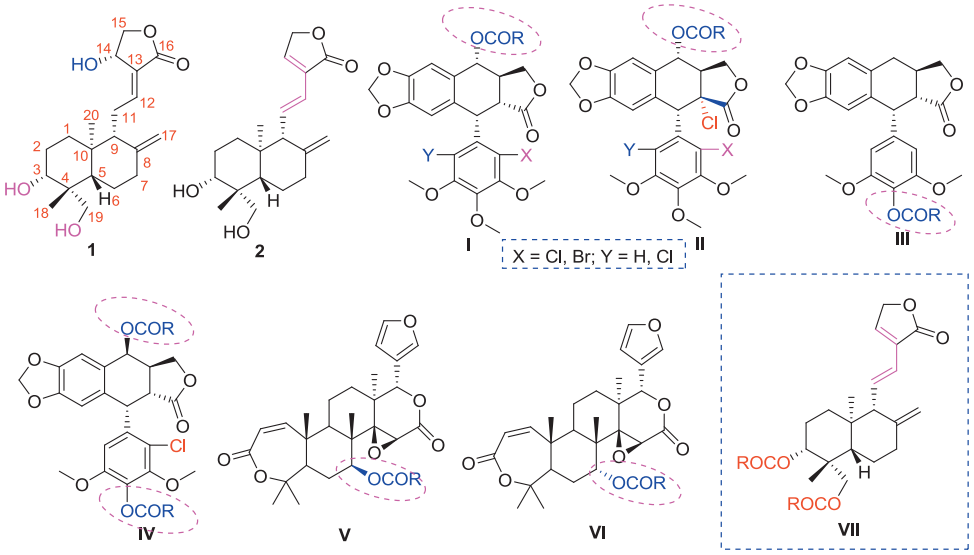
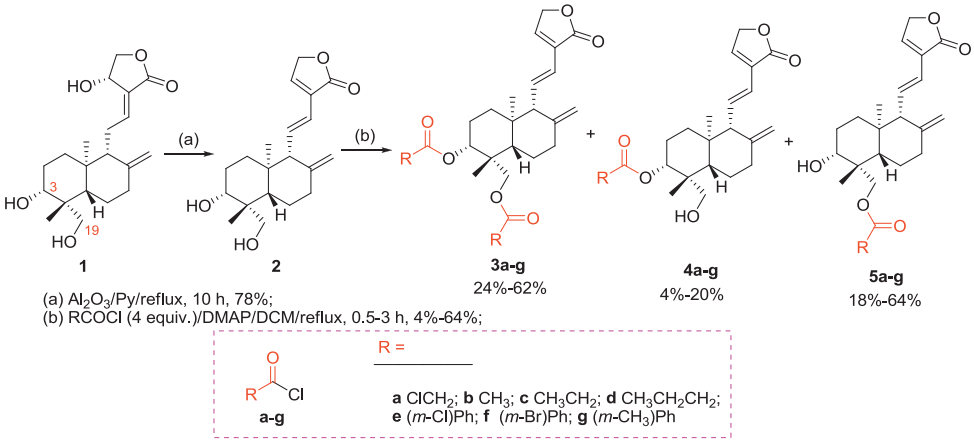


Fig. 1. The chemical structures of andrographolide (**1**), 14-deoxy-11,12-didehydroandrographolide (**2**), podophyllotoxin derivatives (**I**–**IV**), obacunone derivatives (**V** and **VI**), and target compounds (**VII**).



Scheme 1. Synthesis of andrographolide-related esters (**3a**–**g**, **4a**–**g**, and **5a**–**g**).

Assignment of the chemical structures for target compounds was based on their chemical shifts of H-3 and H-19. As shown in Table 1, the chemical shifts of H-3 and H-19 of compound **2** were at 3.49, 3.36, and 4.22 ppm, respectively. For 3,19-dialkyl(aryl)carbonyloxy andrographolide (**3a**–**g**), their chemical shifts of H-3 and H-19 (one proton) were at 4.62–4.99 ppm, and 4.16–4.54 ppm, respectively. To 3-alkyl(aryl)carbonyloxyandrographolide (**4a**–**g**), their chemical shifts of H-3 were obviously shifted from 3.49 ppm (**2**) to 4.68–4.96 ppm. To 19-alkyl(aryl)carbonyloxyandrographolide (**5a**–**g**), their chemical shifts of H-19 (one proton) were clearly shifted from 3.36 ppm (**2**) to 4.17–4.40 ppm. Moreover, the partial ^{1}H NMR spectra of compounds **2**, **3g**, **4g**, and **5g** were also described in Fig. 2.

The three-dimensional structures of compounds **3a**, **4g**, and **5g** were further confirmed by single-crystal X-ray diffraction. As shown in Fig. 3, two chloroacetyloxy groups were at the C-3 and C-19 positions of compound **3a**; the 3-methylbenzoyloxy group was at the C-3 position of compound **4g** (Fig. 4); and compound **5g** contained a 3-methylbenzoyloxy group at its C-19 position (Fig. 5). Crystallographic data (excluding structure factors) for the structures of compounds **3a**, **4g**, and **5g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1581148, 1581151, and 1581152, respectively. Copies of the data can be obtained, free of charge,

Table 1
Chemical shifts (ppm) of H-3 and H-19 of 14-deoxy-11,12-didehydroandrographolide (**2**), 3,19-dialkyl(aryl)carbonyloxy andrographolide (**3a**–**g**), 3-alkyl(aryl)carbonyloxyandrographolide (**4a**–**g**), and 19-alkyl(aryl)carbonyloxyandrographolide (**5a**–**g**) in $CDCl_3$.

Compound	R	δ_{H-3}	δ_{H-19}
2	/	3.49	3.36 4.22
3a	$ClCH_2$	4.72	4.25 4.54
4a		4.75	3.43 4.19
5a		3.37	4.24 4.53
3b	CH_3	4.62	4.16 4.39
4b		4.68	3.41 4.18
5b		3.34	4.17 4.36
3c	CH_3CH_2	4.63	4.22 4.35
4c		4.69	3.40 4.18
5c		3.33	4.17 4.37
3d	$CH_3CH_2CH_2$	4.62	4.23 4.32
4d		4.69	3.40 4.18
5d		3.33	4.17 4.37
3e	(*m*-Cl)C_6H_4	4.98	4.49 4.79
4e(		4.95	3.63 4.24
5e		3.40	4.39 4.65
3f	(*m*-Br)C_6H_4	4.99	4.48 4.79
4f		4.95	3.63 4.23
5f		3.40	4.39 4.65
3g	(*m*-CH_3)C_6H_4	4.97	4.54 4.73
4g		4.96	3.57 4.29
5g		3.40	4.40 4.61