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Natural products-based insecticidal agents 11. Synthesis and insecticidal activity of novel 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxin derivatives against *Mythimna separata* Walker in vivo

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ABSTRACT

In continuation of our program aimed at the discovery and development of natural products-based insecticidal agents, 14 novel 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxin derivatives were stereoselectively semisynthesized from podophyllotoxin, and preliminarily evaluated for their insecticidal activity against the pre-third-instar larvae of *Mythimna separata* Walker in vivo. Especially compounds **9c′** and **9g′** exhibited the most promising and pronounced insecticidal activity than toosendanin, a commercial insecticide derived from *Melia azedarach* at 1 mg/mL. Generally, it was preliminarily demonstrated that arylsulfonyloxy groups at the C-2 position of benzyloxy moiety and the length of the side chain on the benzenesulfonyloxy group of 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxins might be important for the insecticidal activity.

The routine use of a wide variety of synthetic pesticides in agriculture has now become an accepted practice, however, the application of those agrochemicals over the years has led to the development of resistance in insect pest populations and environmental problems.[1] Due to plant secondary metabolites resulting from the interaction between plants and environment (life and non-life) during the long period of evolution in plants, recently, the discovery of new insecticidal compounds from plant secondary metabolites, followed by using them as the lead-compounds for further modification has been one of the important ways for research and development of new pesticides.

Podophyllotoxin (**1**, Fig. 1), a naturally occurring aryltetralin lignan, besides its use as the lead-compund for the preparation of potent anticancer drugs,[2–4] has also drawn attention to its insecticidal activity,[5–7] and some research works on semisynthesis of podophyllotoxin derivatives as insecticidal agents have been carried out in recent years.[8,9]

More recently, the insecticidal activity of 4α-alkyloxy-2-chloropodophyllotoxins (**2**, Fig. 1)[10] has been studied in our research group, and some derivatives have showed the potent insecticidal activity. During investigation of structure–insecticidal activity relationships of **2**, 4α-benzyloxy-2-chloropodophyllotoxin (**3**, Fig. 1) exhibited the potent insecticidal activity. Meanwhile, arylsulfonyloxy was usually treated as the important functional fragment to design and prepare the bioactive molecules, which showed antithrombotic activity,[11] reduction in plasma and liver cholesterol accumulation,[12] and insecticidal activity.[13] In light of the above interesting results, and in continuation of our program aimed at the discovery and development of natural products-based insecticidal agents, we in present Letter wanted to prepare novel 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxin derivatives by introduction of arylsulfonyloxy group on the benzyloxy moiety of **3**, and investigate whether their insecticidal activity could be improved as compared with **3**.

As described in Scheme 1, fourteen novel 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxins (**9a–g** and **9a′–g′**) were semisynthesized from podophyllotoxin (**1**). Arylsulfonyloxybenzaldehyde derivatives (**4**) were readily afforded in 82–100% yields by

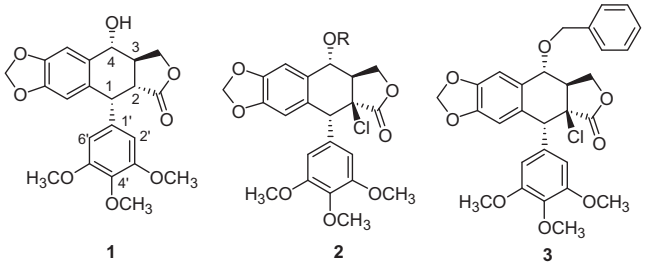

Figure 1. Chemical structures of podophyllotoxin (**1**), 4α-alkyloxy -2-chloropodophyllotoxins (**2**), and 4α-benzyloxy-2-chloropodophyllotoxin (**3**).

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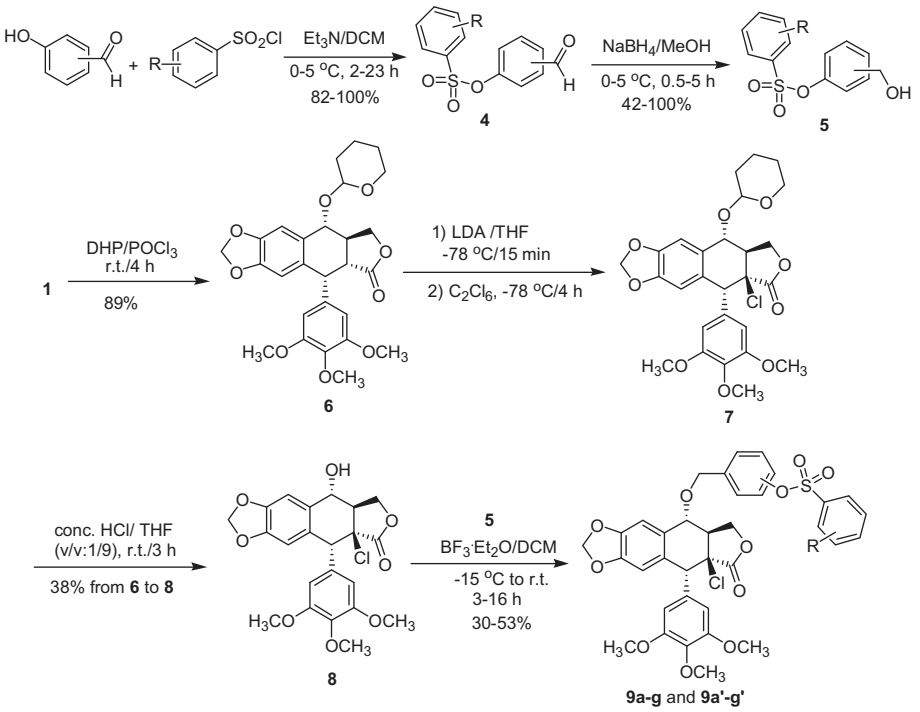


Scheme 1. The synthetic route of 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxins (**9a**–**g** and **99a′–g′**).

reaction of *o*-hydroxybenzaldehyde or *p*-hydroxybenzaldehyde with arylsulfonyl chlorides in the presence of triethylamine (Et_3N). Then reduction of **4** in the presence of $NaBH_4$ to give arylsulfonyloxybenzyl alcohols (**5**) in 42–100% yields. Subsequently, the 4-hydroxy group of **1** was firstly protected by a tetrahydropyranyl (THP) group in the presence of phosphorus oxychloride ($POCl_3$) and dihydropyran (DHP) at room temperature to give 4-*O*-tetrahydropyranylpodophyllotoxin (**6**) in a 89% yield.[14] 2β-Chloro-4-*O*-tetrahydropyranylpodophyllotoxin (**7**) was then prepared by treatment of **6** with lithium diisopropylamide (LDA) at −78 °C in dry THF, followed by the stereoselective reaction with hexachloroethane. Next, hydrolysis of the THP group of **7** gave 2β-chloropodophyllotoxin (**8**).[15] Finally, 14 novel 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxins (**9a**–**g** and **9a′–g′**) were stereoselectively obtained in 30–53% yields by reaction of **8** with **5** in the presence of BF_3·Et2O. The structures of all target compounds were well characterized by ^1H NMR, HRMS, optical rotation, mp, and MS (see Supplementary data).

The assignment of configuration of the arylsulfonyloxybenzyloxy groups at the C-4 position of **9a**–**g** and **9a′–g′** was based on $J_{3,4}$ coupling constants. The C-4β-substituted compounds have a $J_{3,4}$ ≈4.0 Hz due to a *cis* relationship between H-3 and H-4. If $J_{3,4} \geqslant 10.0$ Hz, it indicates that H-3 and H-4 is *trans* relationship, and the substituent on the C-4 position of podophyllotoxin is α configuration.[16] For example, the $J_{3,4}$ values of H-4 of **9a**–**g** and **9a′–g′** were between 9.0 and 9.6 Hz, therefore, the arylsulfonyloxybenzyloxy groups on the C-4 position of **9a**–**g** and **9a′–g′** were α configuration (see Supplementary data).

In order to obtain precise three-dimensional structural information and absolute configuration of **9a**–**g** and **9a′–g′**, the single-crystal structure of **9f′** was further confirmed by X-ray crystallography as illustrated in Figure 2.[17] It was clearly demonstrated that 2-chloro and 4-(2-(*m*-nitrobenzenesulfonyloxy))benzyloxy groups of **9f′** adopted the β and α configuration, respectively.

As shown in Table 1, the insecticidal activity of **9a**–**g** and **99a′–g′** against the pre-third-instar larvae of *Mythimna separata* Walker in vivo was screened by the leaf-dipping method at the concentration of 1 mg/mL. Compound **3**, and toosendanin, a commercial insecticide derived from *Melia azedarach*, were used as positive controls at 1 mg/mL (see Supplementary data).

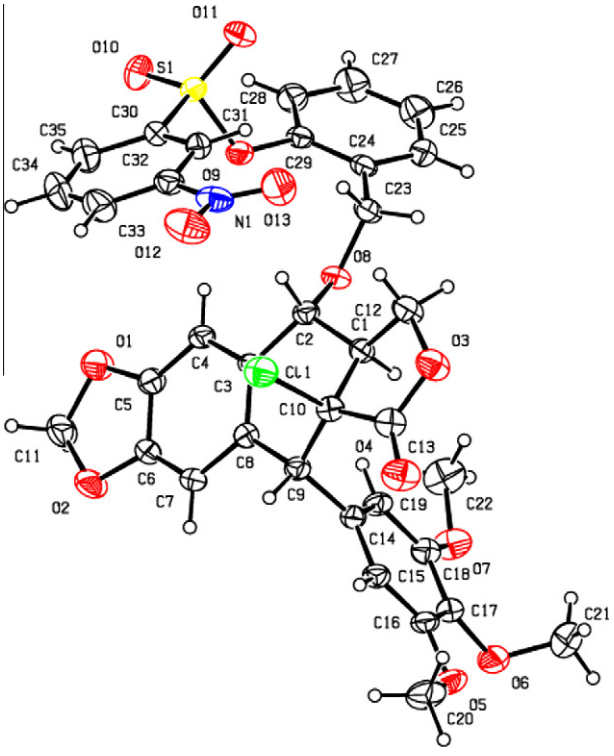
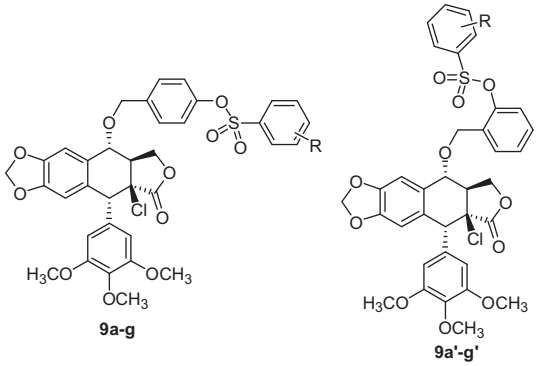


Figure 2. The X-ray crystallography of compound **9f′**.

The corrected mortality rates of *M. separata* caused by **9a**–**g** and **9a′–g′** with the advance of time were outlined in Figure 3. The corresponding mortality rates after 35 d were far higher than those after 10 and 20 d. That is, these compounds, in a time-dependent

Table 1
Insecticidal activity of novel 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxins (**9a**–**g** and **9a′–g′**) against *M. separata* at 1 mg/mL



Compounds	R	Corrected mortality rate (%)		
		10 d	20 d	35 d
9a	H	14.3 (±16.3)	30.8 (±16.3)	36.0 (±9.4)
9b	*p*-Me	17.9 (±9.4)	38.5 (±9.4)	40.0 (±14.1)
9c	*p*-Et	14.3 (±8.2)	38.5 (±4.7)	56.0 (±4.7)
9d	*p*-OMe	21.4 (±17.0)	34.6 (±4.7)	48.0 (±12.5)
9e	*p*-Cl	28.6 (±9.4)	38.5 (±8.2)	40.0 (±8.2)
9f	*m*-NO_2	14.3 (±16.3)	38.5 (±9.4)	52.0 (±0.0)
9g	3-NO_2,4-Cl	17.9 (±9.4)	26.9 (±12.5)	48.0 (±18.9)
9a′	H	7.1 (±12.5)	26.9 (±12.5)	40.0 (±8.2)
9b′	*p*-Me	21.4 (±9.4)	34.6 (±9.4)	52.0 (±8.2)
9c′	*p*-Et	35.7 (±8.2)	57.7 (±9.4)	68.0 (±4.7)
9d′	*p*-OMe	17.9 (±9.4)	34.6 (±4.7)	48.0 (±12.5)
9e′	*p*-Cl	7.1 (±4.7)	34.6 (±4.7)	48.0 (±9.4)
9f′	*m*-NO_2	10.7 (±4.7)	34.6 (±4.7)	36.0 (±4.7)
9g′	3-NO_2,4-Cl	25.0 (±8.2)	57.7 (±9.4)	72.0 (±4.7)
1	/	17.9 (±4.7)	23.1 (±9.4)	40.0 (±0.0)
3	/	10.7 (±17.0)	19.2 (±8.2)	52.0 (±0.0)
8	/	14.3 (±14.1)	15.4 (±9.4)	36.0 (±4.7)
Toosendanin	/	17.9 (±4.7)	34.6 (±4.7)	48.0 (±4.7)

manner as described in our previous Letter,[10,13] different from those conventional neurotoxic insecticides, such as organophosphates, carbamates, and pyrethroids, exhibited delayed insecticidal activity. For example, the corrected mortality rate of **9c** against *M. separata* after 10 d was only 14.3%, after 20 d the corresponding mortality rate was increased to 38.5%, but after 35 d the corresponding mortality rate was rapidly increased to 56% (Table 1). Meanwhile, the symptoms of the tested *M. separata* were also characterized by the same way as our previous Letters.[10,13] The pupation of the larvae and the adult emergence of *M. separata* were inhibited by these compounds, therefore, the period from the larvae to adulthood of *M. separata* was prolonged as compared with the blank control group. Due to feeding too much treated leaves during the first 48 h, some larvae died slowly with the slim and wrinkled bodies during the larval period (Fig. 4). Moreover, many larvae of the treated groups moulted to malformed pupae, which could not reach adulthood and died during the stage of pupation because they were not able to remove their pupal skin (Fig. 5). Malformed moths with imperfect wings were also appeared in the treated groups (Fig. 6).

Figure 4. The representative abnormal larvae pictures of **9c** (zjl-79), **9c′** (zjl-102), and **9g′** (zjl-107) during the larval period.

As depicted in Table 1, compounds **9c′** and **9g′** exhibited the most promising and pronounced insecticidal activity than toosendanin at 1 mg/mL. Through a comparative study on the relationship between the chemical structures of **9a**–**g** and **9a′–g′** and their insecticidal activity, some interesting results were also preliminarily concluded. To obtain more potent derivatives of 2β-chloropodophyllotoxin (**8**), the hydroxy group at the C-4 position of **8** should

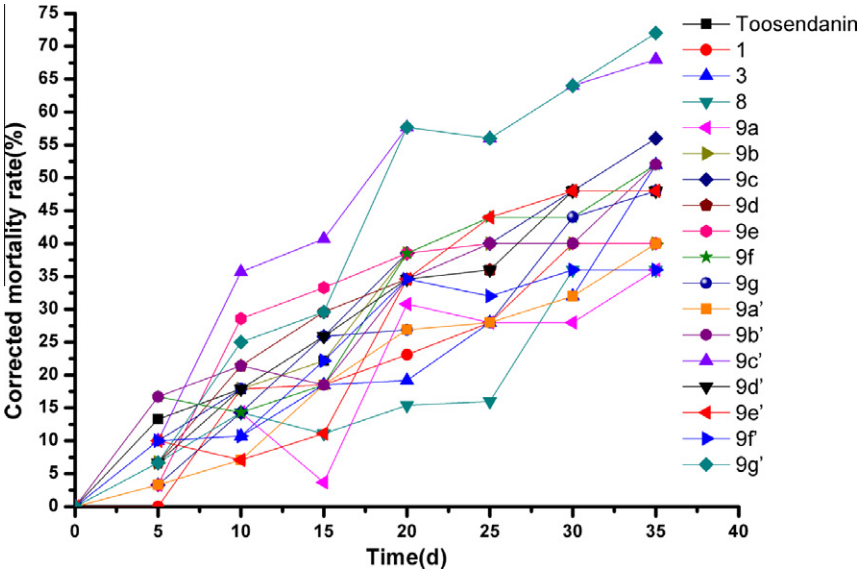


Figure 3. The corrected mortality rates of *M. separata* caused by **9a**–**g** and **99a′–g′** with the increase of time.

Figure 5. The representative malformed pupae pictures of **9a** (zjl-59), **9b** (zjl-62), **9f** (zjl-69), **9a′**(zjl-87), **9f′**(zjl-96), and **9g′** (zjl-107) during the pupation period.

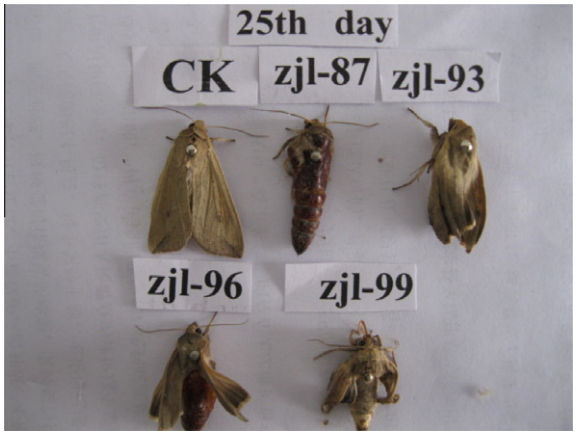


Figure 6. The representative malformed moth pictures of **9a′** (zjl-87), **9d′** (zjl-99), **9e′**(zjl-93), and **9f′** (zjl-96) during the emergence period.

not be free. For example, introduction of arylsulfonyloxybenzyloxy groups at the C-4 position of **8** via the ether bond, most of the corresponding compounds showed more potent insecticidal activity than **8**. Generally, introduction of arylsulfonyloxy groups at the C-2 position of benzyloxy moiety of **3** would lead to the more potent compounds than or comparable to those with the ones at the C-4 position (except **9f** and **9f′**). Especially when 4-ethylbenzenesulfonyloxy and 3-nitro-4-chlorobenzenesulfonyloxy groups were introduced at the C-2 position of benzyloxy moiety of **3**, respectively, the corresponding compounds **9c′** and **9g′** displayed more promising and pronounced insecticidal activity than **3**. Interestingly, the length of the side chain (when R = H, Me, and Et) on the benzenesulfonyloxy group of **9a–c** and **9a′–c′** was essential for the insecticidal activity. As the side chain on the benzenesulfonyloxy group was lengthened, the corresponding insecticidal activity was usually increased (**9a** vs **9b** vs **9c**; **9a′** vs **9b′** vs **9c′**). For example, the final mortality rates of **9a** and **9b** were 36% and 40%, respectively, while the final mortality rate of **9c** was 56%. The afore-mentioned results will prompt us to further investigate other benzenesulfonyloxy groups with different length of the side chain on the benzyloxy moiety of **3** as an insecticidal agent in future.

In conclusion, 14 novel 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxins (**9a**–**g** and **9a′–g′**) were stereoselectively semisynthesized and preliminarily evaluated their activity against the pre-third-instar larvae of *M. separata* in vivo at 1 mg/mL. Especially compounds **9c′** and **9g′** exhibited the most promising and pronounced insecticidal activity. In general, it preliminarily suggested that arylsulfonyloxy groups at the C-2 position of benzyloxy moiety and the length of the side chain on the benzenesulfonyloxy group of 4α-arylsulfonyloxybenzyloxy-2β-chloropodophyllotoxins might be important for the insecticidal activity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.07.075.

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17. Crystallographic data (excluding structure factors) for the structure of **9f** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 818540. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].