Bioorganic & Medicinal Chemistry Letters 20 (2010) 5009–5012

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Natural products-based insecticidal agents 7. Semisynthesis and insecticidal activity of novel 4α-alkyloxy-2-chloropodophyllotoxin derivatives against *Mythimna separata* Walker in vivo

Hui Xu *, Xiao Xiao, Qing-tian Wang

Laboratory of Pharmaceutical Design and Synthesis, College of Sciences, Northwest A&F University, Yangling 712100, China

ARTICLE INFO

Article history:
Received 5 May 2010
Revised 19 June 2010
Accepted 13 July 2010
Available online 16 July 2010

Keywords:
Alkyloxy
Podophyllotoxin
2-Chloropodophyllotoxin
Semisynthesis
Insecticidal activity

ABSTRACT

In continuation of our program aimed at the discovery and development of natural products-based insecticidal agents, 16 novel 4α-alkyloxy-2-chloropodophyllotoxin derivatives were semisynthesized from podophyllotoxin, and preliminarily evaluated for their insecticidal activity against the pre-third-instar larvae of *Mythimna separata* Walker in vivo. Among all the tested derivatives, especially compounds **4b**, **4e**, **4g**, and **4p** exhibited more promising and pronounced insecticidal activity than toosendanin, a commercial insecticide derived from *Melia azedarach*. Generally, it was obviously demonstrated that the length of straight-chain or branched-chain alkyloxy, and heteroatom-containing cycloalkyloxy at the C-4 position of 2-chloropodophyllotoxin were very important for the insecticidal activity.

The routine use of a wide variety of synthetic insecticides in agriculture has now become an accepted practice, however, the application of those chemicals over the years has led to the development of resistance in insect pest populations and environmental problems. Meanwhile, plant secondary metabolites result from the interaction between plants and environment (life and non-life) during the long period of evolution in plants. Consequently, the discovery and development of new insecticidal compounds from plant secondary metabolites, followed by using them as the lead-compounds for further modification has recently been one of the important ways for the research and development of new pesticides. Podophyllotoxin (**1**, Fig. 1), a naturally occurring aryltetralin lignan, besides its use as the lead-compound for the preparation of potent anticancer drugs,[1] also exhibited the interesting insecticidal activity.[2–4]

More recently, the insecticidal activity of 4β-benzenesulfonamides of podophyllotoxin,[5] 4′-aromatic esters/substituted benzenesulfonates of 4-deoxypodophyllotoxin,[6,7] and 4α-acyloxy-2-

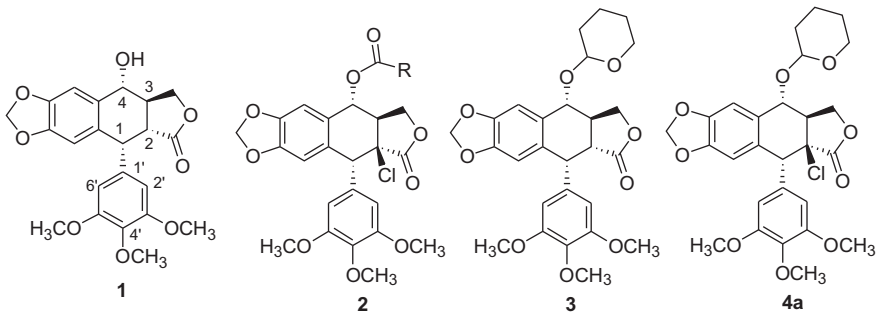


Figure 1. Chemical structures of podophyllotoxin (**1**), 4α-acyloxy-2-chloropodophyllotoxins (**2**), 4-*O*-tetrahydropyranylpodophyllotoxin (**3**), and 2-chloro-4-*O*-tetrahydropyranylpodophyllotoxin (**4a**).

* Corresponding author. Tel./fax: +86 29 87091952.
E-mail address: orgxuhui@nwsuaf.edu.cn (H. Xu).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.07.050

chloropodophyllotoxins (**2**, Fig. 1)[8] 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**, interestingly, 2-chloro-4-*O*-tetrahydropyranylpodophyllotoxin (**4a**, Fig. 1), an intermediate of **2**, exhibited more potent insecticidal activity than 4-*O*-tetrahydropyranylpodophyllotoxin (**3**, Fig. 1) and toosendanin, a commercial insecticide derived from *Melia azedarach*.[8] That is, introduction of chlorine atom at the 2β position of **3** led to the more potent compound **4a**. This encouraging result, therefore, prompted us in present Letter to further study other 4-alkyloxy derivatives of 2-chloropodophyllotoxin as insecticidal agents.

Sixteen novel 4α-alkyloxy-2-chloropodophyllotoxin derivatives (**4b–q**) were synthesized from podophyllotoxin (**1**) as outlined in Scheme 1. The 4-OH 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 (**3**) in a 92% yield.[9] 2-Chloro-4-*O*-tetrahydropyranylpodophyllotoxin (**4a**) was then prepared by treatment of **3** with lithium diisopropylamide (LDA) at −78 °C in dry THF, followed by the stereoselective reaction with hexachloroethane. Subsequently, hydrolysis of the THP group of **4** afforded 2-chloropodophyllotoxin (**5**).[10] Finally, 16 novel 4α-alkyloxy-2-chloropodophyllotoxin derivatives (**4b–q**) were obtained in 13–78% yields by reaction of **5** with the corresponding alcohols in the presence of $BF_3{\cdot}Et_2O$. The structures of the target compounds were well characterized by ^1H NMR, HRMS, mp, and IR (see Supplementary data).

The assignment of configuration of C-4 position was based on $J_{3,4}$ coupling constants. The C-4β-substituted compounds have a $J_{3,4} \approx 4.0$ Hz due to a *cis* relationship between H-3 and H-4. If $J_{3,4} \geqq 10.0$ 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.[11] For example, the $J_{3,4}$ value of H-4 of **4d** was 9.2 Hz, therefore, the hydroxylethoxy group on the C-4 position of **4d** was α configuration.

In order to obtain precise three-dimensional structural information and absolute configuration of **4b–q**, the single-crystal structure of **4h** was determined by X-ray crystallography as illustrated in Figure 2.[12] It was clearly demonstrated that the 2-chloro and the 4-*n*-butoxy groups of **4h** adopted the β and α configuration, respectively.

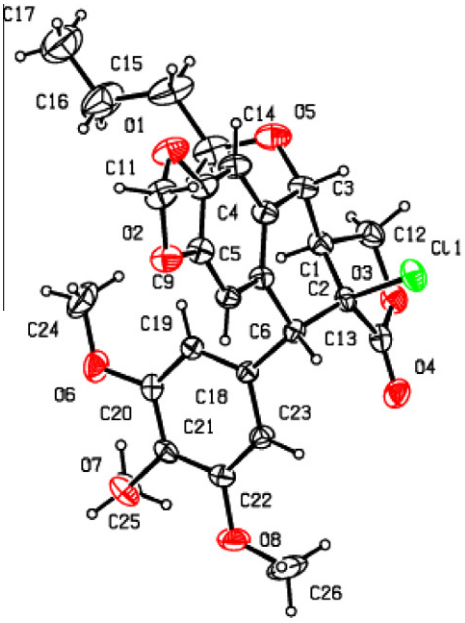
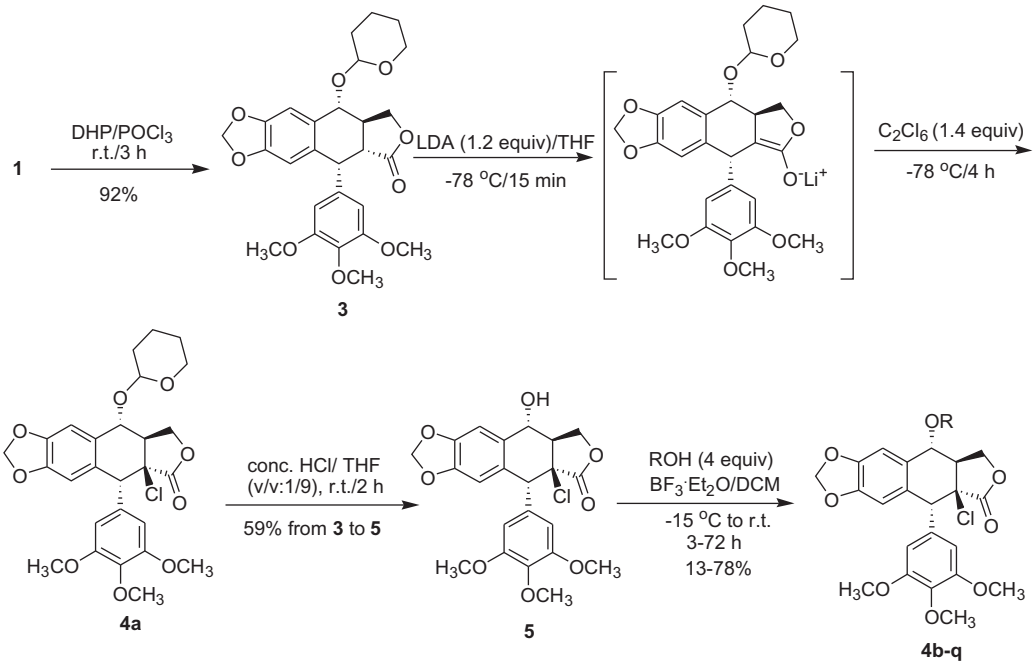


Figure 2. The X-ray crystallography of compound **4h**.

The insecticidal activity of **4b–q** 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 **4a**, and toosendanin, a commercial insecticide derived from *M. azedarach*, were used as positive controls.[8]

The corrected mortality rates of *M. separata* caused by **4b–q** with the advance of time were shown in Figure 3. The corresponding mortality rates after 35 d were far higher than those after 10 d and 20 d. That is, these compounds, different from those conven-



Scheme 1. The synthetic route of 4α-alkyloxy-2-chloropodophyllotoxins (**4b–q**).