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Stereoselective synthesis of 4α-acyloxy-2α/β-bromopodophyllotoxin derivatives as insecticidal agents

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ABSTRACT

To find new natural products-based insecticidal agents, and substantially extend our previous work, we have designed and stereoselectively synthesized 4α-acyloxy-2α/β-bromopodophyllotoxin derivatives from podophyllotoxin. Interestingly, 4α-acyloxy-2α-bromopicropodophyllotoxins were easily converted to a more rigid compound **14** by an intramolecular Friedel–Crafts alkylation reaction in the presence of $BF_3 \cdot Et_2O$ when the reaction time was prolonged to 4–18 h. Compounds **5g**, **6h**, **6i**, and **14** displayed the more promising and pronounced insecticidal activity than toosendanin, a commercial insecticide derived from *Melia azedarach*, against the pre-third-instar larvae of *Mythimna separata*.

1. Introduction

Podophyllotoxin (**1**, Fig. 1), a naturally occurring aryltetralin lignan, besides its use as the lead-compound for the preparation of potent anticancer drugs, such as etoposide, teniposide and etopophos,[1–6] has also received much research attention for its interesting insecticidal and antifungal activities.[7–13] More recently, we have studied stereoselective synthesis of 4α-acyloxy-2β-chloropodophyllotoxins (**2**, Fig. 1),[14] 4α-alkyloxy-2α-bromopicropodophyllotoxins (**3**, Fig. 1) and 4α-alkyloxy-2β-bromopodophyllotoxins (**4**, Fig. 1),[15] and found some compounds showed more potent insecticidal activity than toosendanin, a commercial insecticide derived from *Melia azedarach*. To find new natural products-based insecticidal agents, and substantially extend our above-mentioned work,[14,15] we herein further designed four series of 4α/β-acyloxy-2α/β-bromopodophyllotoxins (**5**, **5′**, **6**, and **6′**, Fig. 1), and investigated their insecticidal activity.

2. Results and discussion

Firstly, as depicted in Scheme 1, the 4-hydroxy group of **1** was protected by a tetrahydropyranyl (THP) group in the presence of phosphorus oxychloride ($POCl_3$) and dihydropyran (DHP) at rt for 3 h to give 4-*O*-tetrahydropyranylpodophyllotoxin (**7**) in a 90% yield.[16] Two stereoisomers, 2α-bromo-4-*O*-tetrahydropyranylpicropodophyllotoxin (**9**) and 2β-bromo-4-*O*-tetrahydropyranylpodophyllotoxin (**10**), were prepared by treatment of **7** with lithium diisopropylamide (LDA) at −78 °C in dry THF, via the intermediate **8**, followed by reaction with Br_2. Then hydrolysis of the THP group of **9** and **10** afforded 2α-bromopicropodophyllotoxin (**11**) and 2β-bromopodophyllotoxin (**12**), respectively.[15,17]

Secondly, as shown in Scheme 2, 4α-acyloxy-2α-bromopicropodophyllotoxins (**5a**–**i**) were smoothly obtained in 52–86% yields by reaction of **11** with carboxylic acids (**13a**–**i**) in the presence of *N*,*N′*-diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP). Similarly, **12** reacted with **13b**, **13h**, and **13i** in the presence of DIC and DMAP to afford 4α-acyloxy-2β-bromopodophyllotoxins (**6b**, **6h**, and **6i**) in 60–83% yields.

Thirdly, as shown in Scheme 3, when **11** reacted with **13f**, **13g** or **13i**, in the presence of $BF_3 \cdot Et_2O$ for 1–3 h, only 4α-acyloxy-2α-bromopicropodophyllotoxins (**5f**, **5g**, and **5i**) were obtained in 53–84% yields. On the contrary, the corresponding isomers, 4β-acyloxy-2α-bromopodophyllotoxins (**5′f**, **5′g**, and **5′i**) were not obtained at all. The assignment of configuration of C-4 position of **5a**–**i** (bearing *cis*-lactone) was according to our previous research results: if $J_{3,4} \approx 2.0$ Hz, it indicates that H-3 and H-4 is *trans* relationship, that is, the substituent on the C-4 position of picropodophyllotoxin is α configuration.[15] The $J_{3,4}$ values of H-4 of **5a**–**i** were 1.5–2.5 Hz, therefore, the substituents on the C-4 position of **5a**–**i** were α configuration.

The precise three-dimensional structural information of **5i** was further determined by X-ray crystallography as illustrated in

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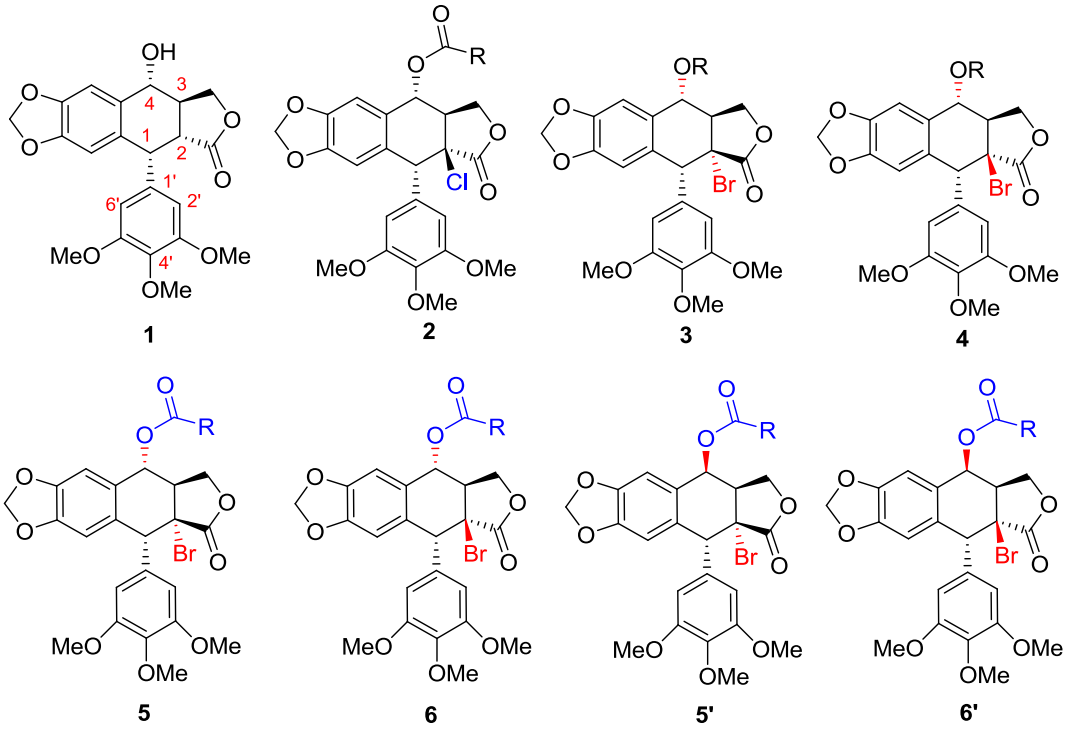
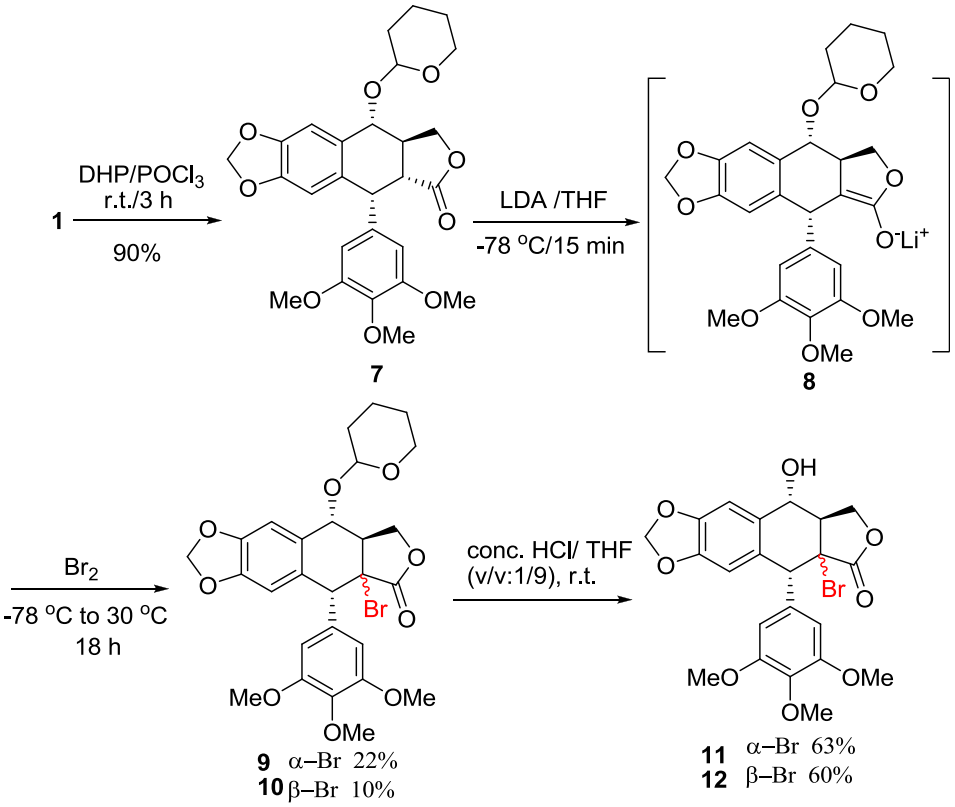


Fig. 1. Chemical structures of podophyllotoxin and its derivatives.



Scheme 1. Synthesis of isomers **11** and **12**.

Fig. 2.[18] It obviously suggested that 2-bromo and 4-naphthylacetoxy groups of **5i** all adopted α configuration. Based upon the X-ray crystallography of **5i**, if the acyloxy group on the C-4 position adopted β configuration, the big steric effects might be observed between the lactone (*endo*-configuration) and the acyloxy group. Consequently, the acyloxy groups on the C-4 position of **5f**, **5g**, and **5i** adopting α configuration was reasonable when **11** reacted with **13f**, **13g** or **13i**, in the presence of $BF_3 \cdot Et_2O$. Interestingly, when the reaction time was further prolonged (15 h for **5f**, 9 h for **5g**, and 10 h for **5i**), **5f**, **5g**, and **5i** were entirely converted to the