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Synthesis and cytotoxicity of oleanolic acid trisaccharide saponins

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ABSTRACT

An array of oleanolic acid-type saponins based on β-hederin has been synthesized in a linear or one-pot manner. The cell viability assays indicate that synthetic saponins show antiproliferation activities in three cancer cell lines with IC_{50} values of 2.4–15.1 μM and hederacolchiside A_1 being the most potent. The results demonstrate that the type of terminal monosaccharides and linkage position have apparent effects on cytotoxicities and selectivities of these saponins against cancer cell lines tested. This study is helpful for future development of more potent anticancer leads.

1. Introduction

Saponins are a vast group of naturally occurring plant glycosides, characterized by their strong foam-forming properties in aqueous solution. Saponins show diverse biological effects including anti-tumor [1,2], anti-inflamatory, anti-diabetic and anti-fungal functions [3]. They are also the key ingredients of traditional Chinese medicines and other folk medicines worldwide. Among them, oleanane-type saponins such as β-hederin, hederacolchiside A_1 (HA_1) from Ivy [4], and other memebers from *Pulsatilla chinensis* [5] and *Anemone flaccida* [6] have drawn considerable attention due to their strong anti-tumor activities. Because of micro-heterogenecity and limited amounts of saponins from natural sources, natural saponins can't meet the current needs for biological evaluation. Thus, total synthesis of complex saponins has beenan active field [7–15], and has witnessed a significant progress over the past few decades.

Studies on structure-activity relationship of bioactive natural products are crucial steps for discovering new lead compounds. In recent years, we have been devoted to discovering pharmacologically anticancer agents. A diverse range of oleanane-type saponins has been identified from various traditional Chinese medicines, including *Pulsatilla chinensis* [16,17] and *Patrinia scabiosaefolia* Fisch. [18,19] Previous studies on synthesis [20,21] and isolation [7–9] have revealed that β-hederin and hederacolchiside A_1 are potential antitumor agents. Herein we report synthesis and cytotoxiticity evaluation of a family of saponins based on β-hederin (**1**–**11**, Fig. 1), which can help future development of more promising anticancer agents.

2. Results and discussion

2.1. Chemistry

Based on the structures of β-hederin, saponins **1**–**11** can be classified into two types. The first class constitutes β-hederin (**1**) and its advanced analogues (**2**–**7**) featuring the different monosaccharide at 4-OH of the arabinosyl unit. The second class is composed of saponins **8**–**11** with sugar chain extension at 3-OH of the rhanmosyl moiety of β-hederin. The syntheses of saponins **1**–**4** have been accomplished using a linear strategy by Cheng's group

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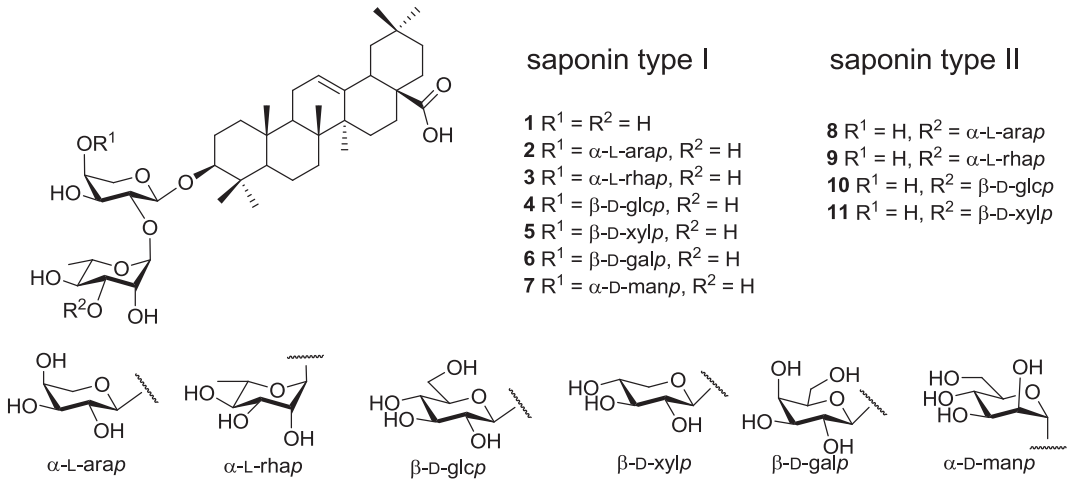
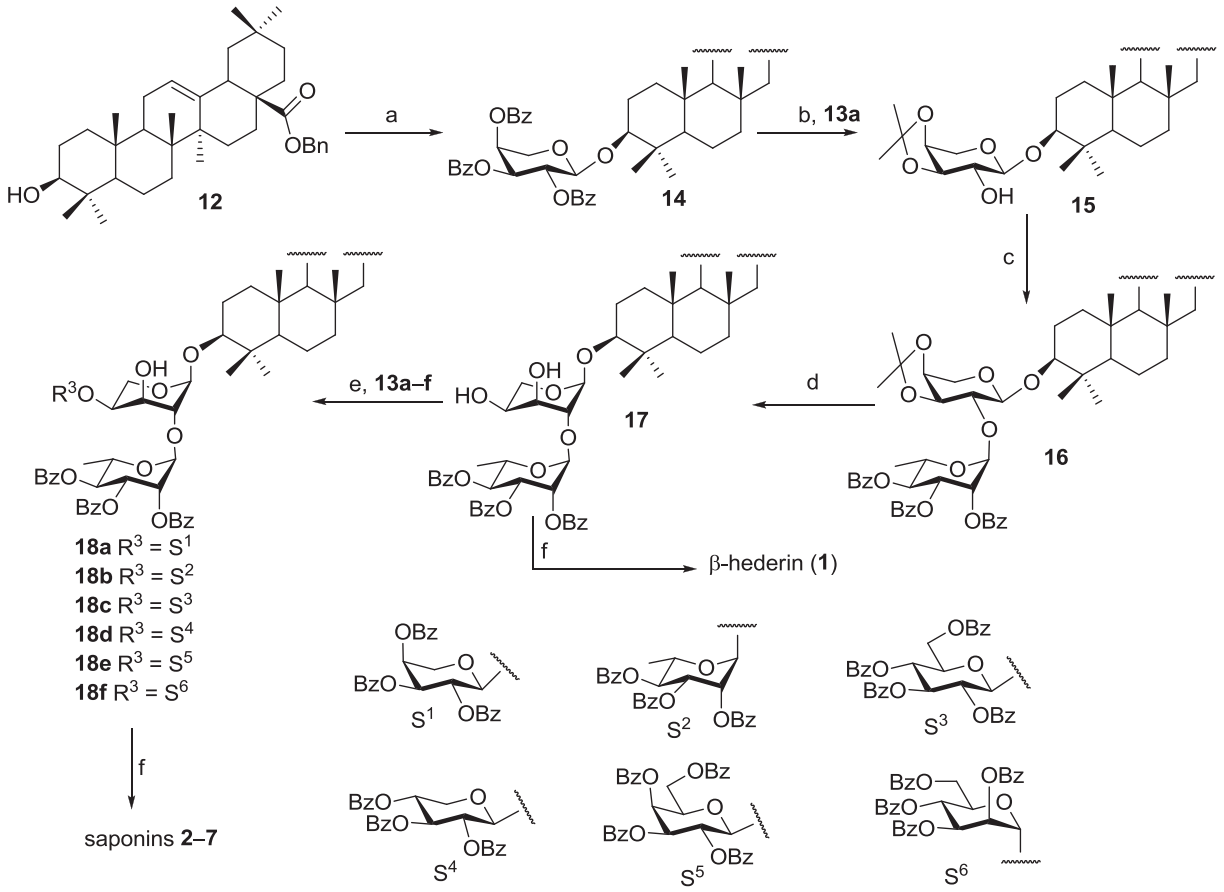


Fig. 1. Structures of saponins **1**–**11**.

[7,8]. Following that protocol, our synthesis commenced with the preparation of *β*-hederin (Scheme 1). Glycosyl trichloroacetimidates (**13a** −**13f**, Fig. 2) were prepared as efficient sugar donors according to the previously reported procedures [22–24]. Briefly, glycosylation of benzyl oleanolate **12** [7] with perbenzoylated arabinosyl trichloroacetimidate **13a** under catalytic trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave monosaccharide **14** in excellent yield [25]. Debenzoylation of **14** using methanolic $NaOCH_3$ in the presence of CH_2Cl_2 followed by isopropylidene formation with 2,2-dimethoxypropane mediated by *p*-toluenesulfonic acid hydrate (*p*-TsOH·H_2O) proceeded smoothly to furnish saponin **15** with 2-OH of arabinosyl moiety free and ready for subsequent glycosylation. Coupling of compound **15** with **13b** was carried out to generate **16** under catalytic amount of



Scheme 1. Synthesis of saponins **1**–**7**. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 4 Å MS, 0 °C; (b) i) $NaOCH_3$, CH_2Cl_2-MeOH, r. t; ii) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, acetone, 0 °C to rt; (c) BF_3. Et_2O, CH_2Cl_2, 4 Å MS, −78 °C; (d) *p*-TsOH·H_2O, CH_2Cl_2-MeOH, rt; (e) TMSOTf, CH_2Cl_2, 4 Å MS, −30 °C, 75%, 72%, 69%, 72%, 70% and 65% for **18a-18f**, respectively; (f) i) 10% Pd-C, H_2, CH_2Cl_2-MeOH; ii) $NaOCH_3$, CH_2Cl_2-MeOH, rt, 86%, 80.4%, 82%, 78%, 80%, 76% and 77.5% for **1**–**7**.