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Grant Title: Decagram-scale synthesis of appetite-suppressant glycosides P57 & gordonoside F

Abstract

Overweight and obesity are increasing health risk worldwide, causing serious diseases such as diabetes, cardiovascular diseases and dyslipidemia. Apart from the changes of dietary and physical activity, the use of appetite suppressant is also a practical way for body weight control. *Hoodia gordonii* (Asclepiadaceae) has been used as an appetite suppressant in Africa for thousands of years. Although its extract has been proposed to be an agent for body weight control, the mechanism of its activities and in vivo targets remain unclear.

Our recent study showed that gordonoside F, a pregnane glycoside isolated from *H. gordonii*, was able to specifically active GPR119 and consequently induce glucose-stimulated insulin secretion both in vitro and in vivo, reducing the food intake in mice. Surprisingly we found P57, the previously known active component, was inactive to GPR119, which implied the existence of different mechanisms of P57.

Complicated composition and limited content make it difficult to isolate enough P57 and gordonoside F from *H. gordonii*. In this case, further biological and pharmacological studies have been suspended. Chemical synthesis become a better choice to provide these compounds in large scale. Herein, we developed an efficient approach to the synthesis of Hoodigogenin A (13 steps, 14% overall yield) in gram-scale from cheap commercial available dehydroepiandrosterone. A glycal method under the promotion of TPHB was applied successfully to the glycosylation of Hoodigogenin A to synthesize P57 precursor in 70% yield with an excellent β-selectivity (β/α = 6: 1). Gordonoside F was also synthesized expeditiously in gram-scale, featuring assembly of the deoxytetrasaccharide with glycosyl *o*-alkynylbenzoates as donors (92% yield, β/α = 9:1, for the glycosylation of the aglycone). These synthetic Hoodia saponins are used in biological and pharmacological studies, and the results will be reported in due course.