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Original article

Concise synthesis of 1-*epi*-castanospermine

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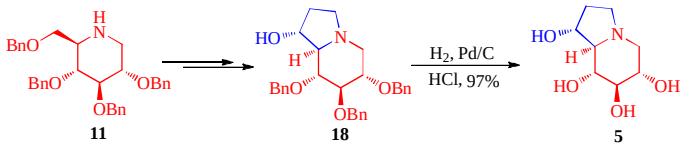
ABSTRACT

1-*epi*-Castanospermine (**5**) was synthesized from readily available 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**11**) in 9 steps and 21% overall yield, with selective debenzylation, Barbier reaction and reductive amination as the main reaction steps.

Graphical abstract



1-*epi*-Castanospermine (**5**) was synthesized from readily available 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**11**) in 9 steps and 21% overall yield, with selective debenzylation, Barbier reaction and reductive amination as the main reaction steps.

1. Introduction

Polyhydroxylated indolizidines are an important class of naturally occurring alkaloids with castanospermine (**1**), swainsonine (**2**), 6-*epi*-castanospermine (**4**) *etc*. as representatives. Most of these alkaloids are known as potent glycosidase inhibitors [1], and exhibit diverse biological activity especially as potential therapeutic agents in the treatment of cancer [2], diabetes [3], obesity [4], and HIV [5].

As one of the most-studied polyhydroxylated indolizidines, castanospermine (**1**) (Fig. 1) was first isolated in 1981 from Australian legume *Castanospermum australe* [6] and then from the dried pod of *Alexa leiopetala* [7] as a powerful inhibitor of α- and β-glucosidases [8]. In order to clarify the structure activity relationship (SAR) and to search for pharmaceutical lead compounds, a number of natural or unnatural analogues of **1** have been synthesized and studied for their biological activities. Amongst these analogues, the naturally occurring 6-*epi*-castanospermine (**4**) was proved to be a potent inhibitor of amyloglucosidase [9], the unnaturally occurring 1-*epi*-castanospermine (**5**) was found to be a potential anti-AIDS lead compound [10] and 1-deoxy-6-*epi*-castanospermine (**6**) exhibited competitive inhibition of lysosomal α-mannosidase [11]. Of course, the most successful castanospermine analogue developed till now must be 6-*O*-butanoyl-castanospermine (**7**, celgosivir), which is currently undergoing phase II clinical trials for treatment of hepatitis C [12]. All of the above analogues, including compound **5**, the synthetic C-1 diastereomer of castanospermine, have been extensively studied for more efficient synthetic methodologies in order to establish detailed structure-activity relationship (SAR) [10, 13]. Herein we reported the stereoselective synthesis of 1-*epi*-castanospermine (**5**) from readily available starting material 2,3,4,6-tetra-*O*-benzyl-1-deoxynojirimycin (**11**).

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