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Total synthesis of (+)-valienamine and (−)-1-*epi*-valienamine via a highly diastereoselective allylic amination of cyclic polybenzyl ether using chlorosulfonyl isocyanate

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ABSTRACT

The total synthesis of (+)-valienamine and (−)-1-*epi*-valienamine was concisely accomplished from readily available D-glucose via a highly diastereoselective amination of chiral benzylic ether using chlorosulfonyl isocyanate, intramolecular olefin metathesis, and diastereoselective reduction of cyclic enone using L-Selectride as the key steps.

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1. Introduction

Glycosidases are involved in a wide range of important biological processes, such as intestinal digestion, post-translational processing of glycoproteins, and lysosomal catabolism of glycoconjugates.[1] Thus, glycosidase inhibitors have received much attention for the treatment of diabetes,[2] viral infections,[3] malaria,[4] and cancer.[5] The majority of these inhibitors are azasugars, in which an oxygen atom in a monosaccharide is replaced by a nitrogen atom. Azasugars are often found in natural plants and microorganisms. While these azasugars have been extensively studied, the development of carbasugars as glycosidase inhibitors has received little attention.

(+)-Valienamine (**1**) is a polyhydroxylated unsaturated carbasugar that was first isolated from microbial degradation of validoxylamine A (**3**) with *Pseudomonas denitrificans* in 1972.[6] Later, it was derived from degradation of validoxylamine A with *Flavobacterium saccharophilum*[7] or from NBS-mediated selective cleavage of C–N bond in validoxylamine A or its derivatives.[8] (+)-Valienamine is also an essential core unit in many kinds of pseudo-oligosaccharides, e.g., acarbose, validamycins, amylostatins, adiposins, salbostatin, and acarviosin.[9] In particular, acarbose (**4**) is known as a highly potent inhibitor of α-glucosidases in the human digestive tract.[10] Consequently, acarbose can delay the breakdown of ingested carbohydrates and control the resorption of glucose from the intestines. Acarbose (Glucobay™) is currently used as an anti-diabetic drug for the treatment of type II diabetes mellitus (Fig. 1).

Due to the unique structural feature and interesting biological property, a number of efforts have been devoted to the development of various approaches for the efficient synthesis of (+)-valienamine (**1**). Paulsen et al. reported the first synthesis of **1** starting from L-quebrachitol via Mitsunobu-type inversion of an allylic hydroxyl group to an azido group.[11] Since the pioneering work of Paulsen, several approaches have been attempted regarding the preparation of (+)-valienamine (**1**).[12–15] Given the structural relationship of (+)-valienamine with carbohydrates,[12] α-amino acids,[13] and (−)-quinic acid,[14] it is not surprising that most syntheses use these compounds as starting materials. The chiral pool approach can be extremely attractive if nature happens to provide an abundant supply of an inexpensive starting material appropriate for the synthetic target. One of other syntheses relies on a series of Diels–Alder reactions to generate a cyclohexene framework.[15]

In a recent example using a carbohydrate as a chiral pool, Yan and co-workers reported the total synthesis of **1** from D-tartaric acid

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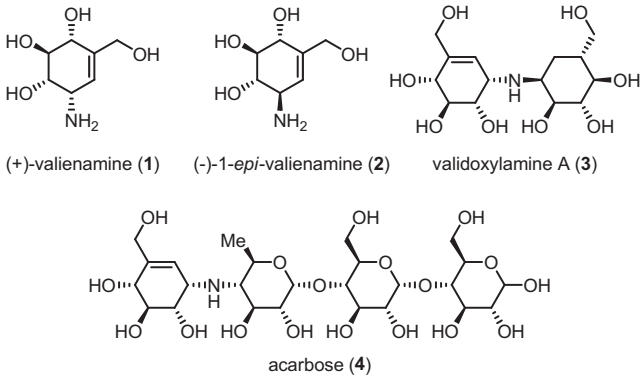


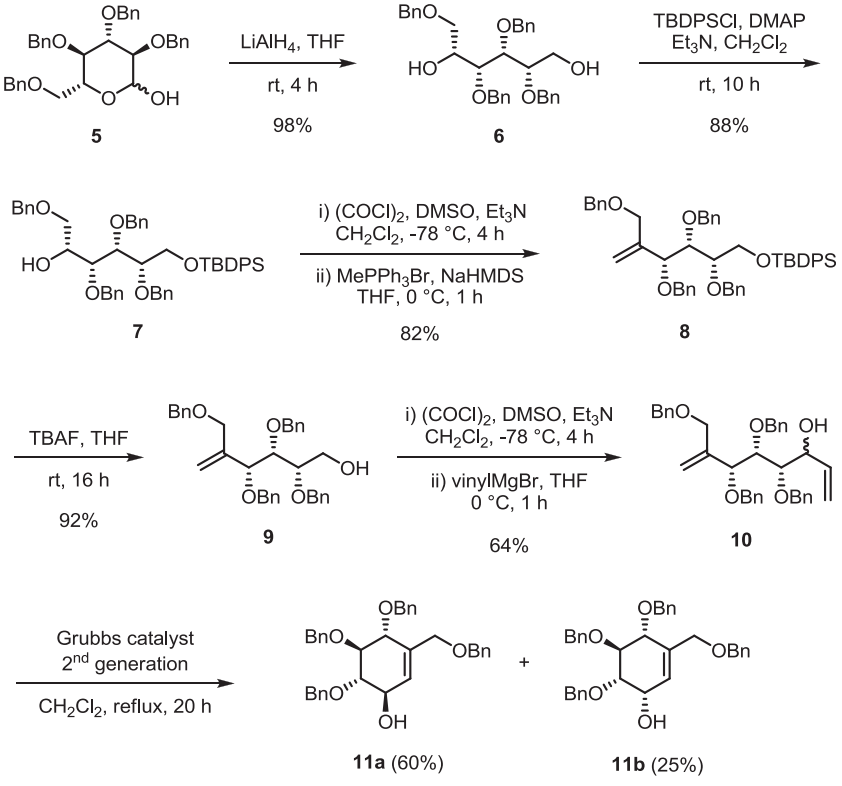
Fig. 1. Structures of (+)-valienamine (**1**), (−)-1-*epi*-valienamine (**2**), validoxylamine A, (**3**) and acarbose (**4**).

through iodine-promoted cyclization of an unsaturated carbon-imidothioate for the diastereoselective installation of amine and hydroxyl units.[12e] In another example using a chiral pool, Kim et al. described the asymmetric total synthesis of **1** using readily available D-glucose as a starting material via ring-closing metathesis followed by diastereoselective addition of an azido group under Mitsunobu conditions.[12c] In a representative example of asymmetric synthesis, Trost and co-workers demonstrated the asymmetric total synthesis of **1** via palladium-catalyzed regioselective and diastereoselective *cis*-hydroxyamination of vinyl epoxide and isocyanate as the key steps.[15c] Li et al. reported the asymmetric total synthesis of **1** using *anti*-amino alcohol generated from diastereoselective reductive coupling between alkyne and Garner's aldehyde.[13b]

herein describe an asymmetric total synthesis of (+)-valienamine (**1**) and its 1-epimer **2** starting from commercially available D-glucose via highly regioselective and diastereoselective allylic amination of cyclic polybenzyl ethers using chlorosulfonyl isocyanate, intramolecular olefin metathesis followed by diastereoselective reduction of cyclic enone using L-Selectride as the key steps.

2. Results and discussion

The total synthesis of (+)-valienamine (**1**) began with benzyl-protected lactol **5** prepared from commercially available D-glucose according to the reported literature (Scheme 1).[17]



Scheme 1.

As part of an ongoing research program aimed at the total synthesis of biologically active polyhydroxylated alkaloids,[16] we

Reduction of **5** and subsequent protection of primary alcohol using TBDPSCl afforded compound **7** in high yields. Swern

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