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# Diastereospecific epoxidation and highly regioselective ring-opening of (+)-valienamine: practical synthesis of (+)-valiolamine

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ABSTRACT

An efficient and practical synthesis of (+)-valiolamine starting from readily available aminocyclitol (+)-valienamine in five steps and up to 80% total yield in gram-scale quantities is reported. Diastereospecific epoxidation by means of substrate directable reaction and regioselective ring-opening of corresponding epoxide are the key reactions in the synthesis, which circumvent laborious purification of products using chromatographical separation. The detailed mechanisms of epoxidation and ring-opening attacked by halide, including the directing and steric hindrance effect, are also discussed.



## 1. Introduction

Aminocyclitols,[1] such as valienamine (**3**), validamine (**4**), and their analogues,[2] were first isolated as the fragments of the pseudooligosaccharides validamycin A (**1**) and fully characterized to possess more or less enzyme inhibitory activity toward certain glycosidases (Fig. 1).[3] Valiolamine (**6**) was also detected and isolated from the fermentation broth of *Streptomyces hygroscopicus subsp. limoneus* IFO12703 first[4] and later found to be one of the components of validamycin G (**2**).[5] **6** has been found to be more potent inhibitor against α-glucosidase, maltase, isomaltase, and sucrase compared to **3**, **4**, and hydroxyvalidamine (**5**).[6] This subsequently resulted in extensively chemical modification of **6** and led to the preparation of voglibose (coded as AO-128) (**7**), a clinically useful drug in the treatment of diabetes.[7]

Unfortunately, the concentration of either **6** or **2** in the fermentation broth of microorganism is relatively low.[4,5] Therefore, the product isolated directly from fermentation broth cannot meet the demands for the production of pharmaceuticals. Thus, chemical synthesis starting from readily available compounds is regarded as the best solution to this problem. The syntheses of **6** in racemic forms have been reported almost exclusively by Ogawa et al.[8] Optically active pure **6** has been synthesized in four reported different ways: 1) from **3** or **4** via stereospecific transient halo cyclic carbamate intermediates[9]; 2) from D-glucose via valiolone involving a stereospecific intramolecular aldol[10] or Wittig[11] cyclization, 3) from (−)-*vibo*-quercitol[12] by biotransformation of *myo*-inositol[13]; 4) from 2,3,5-tri-*O*-benzyl-*D*-arabinose via ring closing metathesis (RCM)[14]; 5) from $C_2$-symmetric L-tartaric acid via RCM and cyclization of an unsaturated carbonimidothioate.[15]

Except the first one, all the methods abovementioned have elaborate synthetic routes involving novel methodologies, but some disadvantages, such as rare starting raw materials, expensive and toxic reagents, and long linear synthetic route, which resulted in low yields. The conversion from **3** or **4**, therefore, has a better foreground of practical application in industry, due to the abundant raw materials (the major components of validamycins are validamycin A and B, which can be efficiently converted into valienamine by biodegradation) and a relatively shorter route. So far, both the semi-synthesis of valiolamine and the corresponding reparation of voglibose are from **3**. Despite this, the stereoselective conversion of **3** into **6** first reported by Fukase et al.[9] was not wholly satisfactory, as corrosive and lachrymatory reagents, such as benzyl chloroformate and bromine were used inevitably. These are inconsistent with the concept of green chemistry that use of safe, environment-benign substances.

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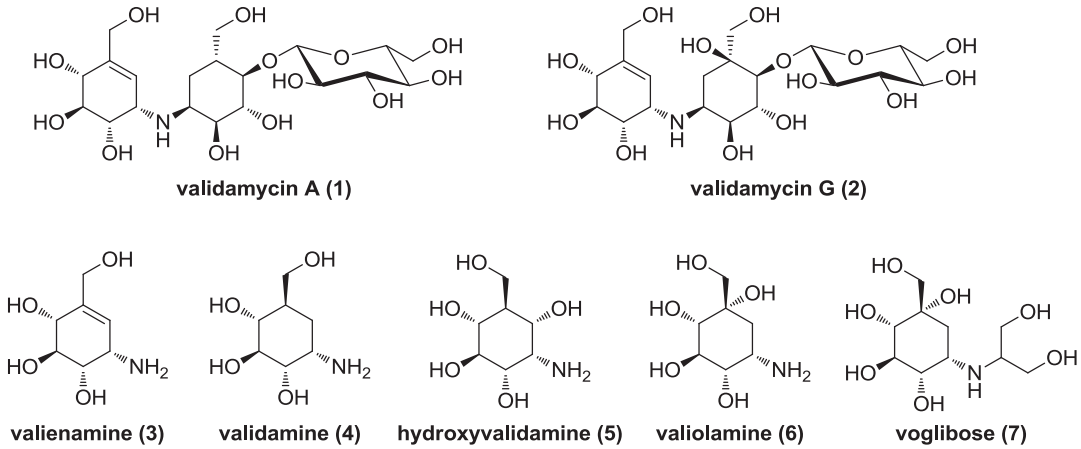


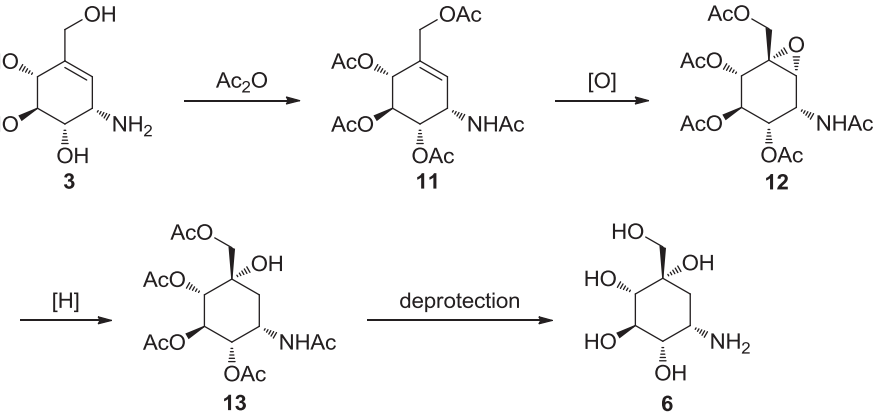

**Fig. 1.** Structure of validamycin A, G and selected aminocyclitols.

We explored the more practical procedure and have developed an alternative one without employing benzyl chloroformate for amino protection and bromine for halolactonization, allowing truly industrial production of **6** via diastereospecific epoxidation and highly regioselective ring-opening in a large scale with no chromatographical purification.

## 2. Results and discussion

Epoxides (or oxiranes) are frequently used in synthesis, because the oxirane functionality cannot only be stereoselectively introduced into a molecule under specified conditions, but also react with a large number of nucleophiles to yield valuable bifunctional compounds in a fairly simple procedure, which is regioselective in most cases.[16] Therefore, in the present synthesis, we planned to take full advantage of abovementioned epoxide's characteristics. Initially, we designed the route via epoxidation and ring-opening by hydride as shown in Scheme 1. Two issues of great concern to us were whether the valienamine epoxide (**12**) would be stable and the epoxidation would be diastereoselectively or not, which is the core step in this synthesis. Based on consulting literature, it was found that, as early as in 1988, Ogawa et al.[17] had synthesized two stereoisomers of valienamine epoxide via epoxidation of *N*-acetylvalienamine with *m*CPBA, or via the bromohydrin by treatment with potassium carbonate, in order to confirm the configuration of the epoxide group in the natural product NS-504. However, the valienamine epoxide they obtained was racemic and the yields were both very low in two methods (37% and 28%) and column chromatography was unavoidable.[17] Although this result was discouraging and should be improved, it was proved that the racemic valienamine epoxide could be synthesized. Moreover, the configuration of epoxide ring could be controlled to *cis* to amide at C-6 by the directing effect of the latter, according to the rules summarized by Hoveyda and Evans in their excellent review.[18] The details in the epoxidation would be discussed below, including the directing and steric hindrance effect afforded by different allylic groups.

Initially, in order to prevent oxidation at the amino group and simplify the isolation of intermediates and product from the reaction mixture, **3** was peracetylated. Subsequently, in the transformation of **11** into corresponding epoxide (Scheme 2), we had run into obstacles. 1.50 equiv *m*CPBA, a conventional peracid in laboratory, was used in dichloromethane at reflux for 48 h. Unfortunately, it did not give the desirable result, and only 38% epoxide (with 30% isolated yield) was detected in the crude product by quantitative $^1$H NMR with remaining starting material (entry 6, Table 1). Other peracids were also attempted, including acetic peracid (entry 1 and 2, Table 1) and Payne oxidation system (entry 3, Table 1) and modified Payne oxidation system (entry 4, Table 1) developed by us.[19] However, none of them could give better results than *m*CPBA. To obtain better yield, more oxidative reagent (3.0 equiv) was added and meanwhile the reaction time was prolonged to 72 h, and the reaction gave an appropriate yield (88%) (entry 7, Table 1). Subsequently, the reaction was improved (entry 10, Table 1) by employing Kishi's epoxidation[20] at elevated temperatures in the presence of radical inhibitor (4,4′-thiobis(6-*tert*-butyl-*m*-cresol)), which prevented thermal decomposition of




**Scheme 1.**