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# Stereoselective allylation of acyclic and chiral α-amino-β-Hydroxy aldehydes part 2: Application to the formal synthesis of the polyhydroxylated γ-amino acid (+)-Detoxinine

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ABSTRACT

Stereoselective allylations of acyclic, chiral α-amino-β-hydroxy aldehydes mediated by $BF_3{\cdot}OEt_2$ and its application to the formal synthesis of the polyhydroxylated γ-amino acid (+)-detoxinine are described. The reactions of *syn*-α-NHCbz-β-OTBS substrates mediated by $BF_3{\cdot}OEt_2$ afforded *syn*-selective products. The same reaction conditions gave *anti*-selective products from *syn*-α-NCbzBn-β-OTBS substrates. A hydrogen-bonded transition state and Felkin-Anh model have been suggested to account for the stereochemical outcomes of the two reactions, respectively. One of the allylation products was used for the formal synthesis of the polyhydroxylated γ-amino acid (+)-detoxinine.



## 1. Introduction

α-Amino alcohols or vicinal amino alcohols are crucial structural motifs for natural products and medicinal agents.[1] β-Amino-α,γ-diols, a class of amino polyols, are ubiquitous in bioactive natural products.[2] We have previously reported the synthesis of β-amino-α,γ-diols via stereoselective allylation of α-amino-β-hydroxy aldehydes.[3]

In our previous study, the reactions of *syn*-α-NHCbz-β-OTBS substrates mediated by $SnCl_4$ and allyltrimethylsilane were reported. Herein we describe the reactions of *syn*-α-NHCbz-β-OTBS substrates mediated by $BF_3{\cdot}OEt_2$ and allyltributyltin (Fig. 1). Furthermore, this methodology was used in a formal synthesis of the polyhydroxylated γ-amino acid (+)-detoxinine **3**.

(−)-Detoxinine **2** is a polyhydroxylated γ-amino acid with three contiguous chiral centers (Fig. 2). The detoxin complex, which is applied as selective antagonists against the nucleoside antibiotic blasticidin S, was isolated from *Streptomyces caespitosus* var. *detoxicus* 7072 $Gc_1$.[4] Detoxin $D_1$ **1** is the most active component of the complex.[5] Coadministration of blasticidin S and detoxin $D_1$ **1** reduces the cytotoxicity of the antibiotic without reducing its curative effect in the treatment of rice blast disease.[6] (−)-Detoxinine **2** is the core scaffold of the detoxin complex. (+)-Detoxinine **3** is the unnatural enantiomer of (−)-detoxinine **2**.

The interesting highly functionalized amino acid structural feature of the detoxin complex has attracted considerable attention, which has led to many syntheses of the enantiomers of detoxinine (−)-**2** and (+)-**3** being achieved.[7] Denmark et al. reported the synthesis of (−)-detoxinine **2** by tandem cycloaddition of nitroalkenes.[7f] Reißig et al. reported the synthesis of (−)-detoxinine **2** via the addition of lithiated methoxyallene to α-hydroxy aldimine.[7h] Huang et al. reported the formal synthesis of (−)-detoxinine **2** using a hydroboration-based method.[7j] Mulzer et al. reported the total synthesis of (+)-detoxinine **3** via addition of an ester enolate to an *O*-silylated hydroxyproline aldehyde.[7e]

Herein we report the stereoselective allylation of α-amino-β-hydroxy aldehydes and its application to the formal synthesis of the polyhydroxylated γ-amino acid (+)-detoxinine **3**.

## 2. Results and discussion

The retrosynthetic analysis shown in Scheme 1 suggests that (+)-detoxinine **3** can be synthesized by a reported method from **4**.[7h] In turn, **4** can be derived from the deprotection of pyrrolidine derivative **5**, which can be obtained from cyclization of compound

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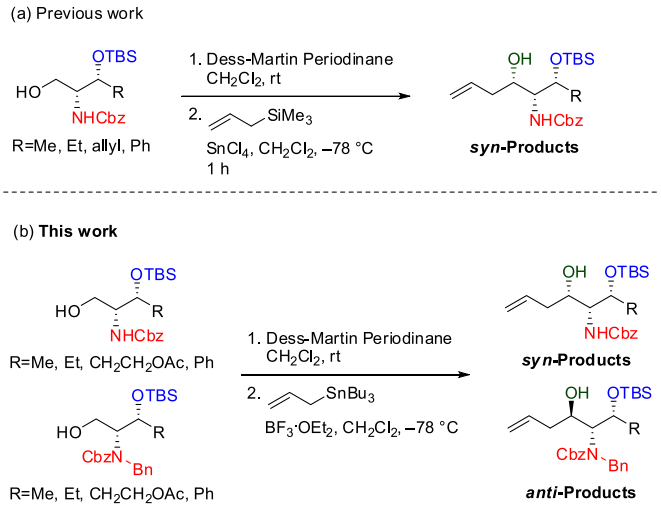



**Fig. 1.** Allylations of α-amino-β-hydroxy substrates.

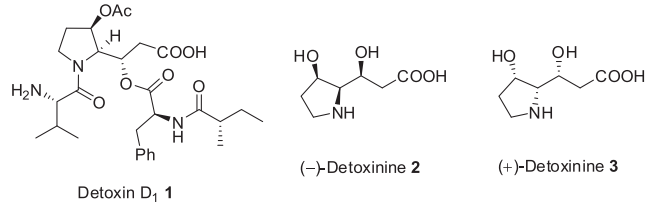



**Fig. 2.** Structures of detoxin $D_1$ **1**, (−)-detoxinine **2**, and (+)-detoxinine **3**.

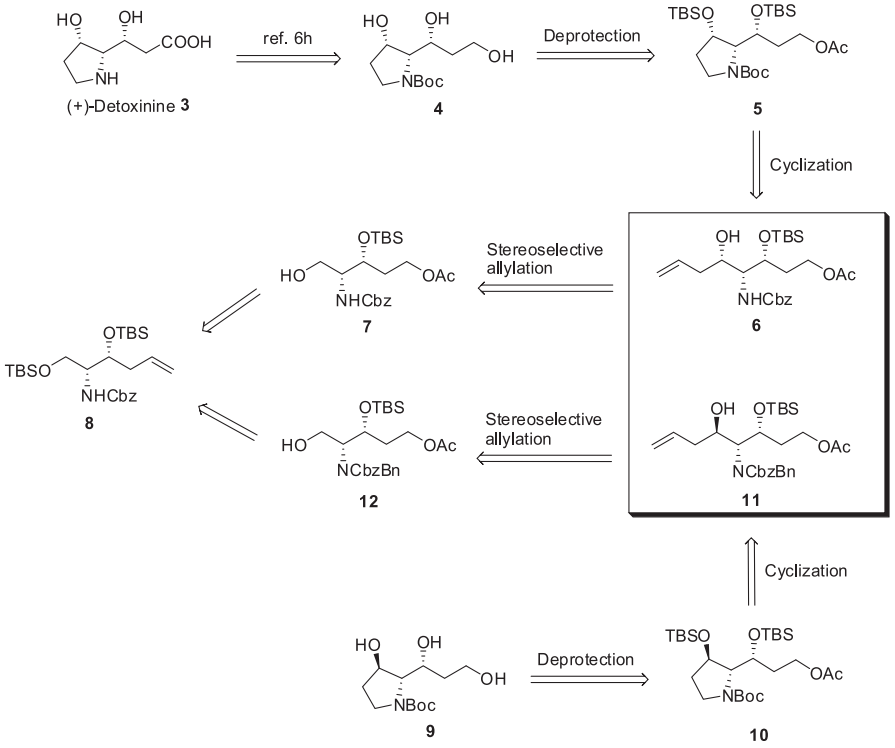
**6**, which contains three contiguous stereogenic centers in its structure. Compound **6** might be derived from α-amino-β-hydroxy alcohol **7** via Dess–Martin oxidation and stereoselective Sakurai type allylation. The α-amino-β-hydroxy alcohol **7** can in turn be obtained from compound **8**. In the same manner, **9** should be accessible via compounds **10**, **11**, and **12**.

Preparation of the α-amino-β-hydroxy alcohols **7** and **12** is shown in Scheme 2. Compound **8** was synthesized from D-serine **13** using a previously reported procedure.[3] Benzylation of **8** furnished CbzBn-protected **14**. Ozonolysis of **8** and **14** followed by a reductive workup furnished the primary alcohols **15** and **16**, respectively. The generated alcohols were protected with acetyl groups to obtain **17** and **18**, which yielded the α-amino-β-hydroxy alcohols **7** and **12**, respectively, via selective desilylation.

In our previous work, we successfully achieved a stereoselective $SnCl_4$-mediated Sakurai-type allylation of non-functionalized α-amino-β-hydroxy substrates.[3] Based on those results, we anticipated that $SnCl_4$-mediated allylation would generate *syn*-alcohols stereoselectively. Unfortunately, this methodology was not applicable to functionalized α-amino-β-hydroxy substrates.

Primary alcohols are easily converted to the corresponding aldehydes without epimerization using Dess–Martin periodinane.[8] As shown in Table 1, in contrast to the previous study that had shown high *syn*-selectivity,[3] the $SnCl_4$-mediated allylation of **7** showed only low diastereoselectivity. To our surprise the *O*-acetyl functionalized substrate caused drastic changes in the diastereoselectivity. This result led us to investigate various Lewis acid-mediated conditions.

The results of the allylation reactions with different allyl reagents using various Lewis acids are shown in Table 2. The $TiCl_4$-mediated reaction of NHCbz substrate **7** with allyltrimethylsilane or allyltributyltin afforded amino alcohols **6** and **6′** in a ratio of 6:1 (entries 3 and 4). The $MgBr_2 \cdot OEt_2$-mediated reaction using allyltrimethylsilane as nucleophile did not occur (entry 5). Instead, the same reaction using allyltributyltin afforded the corresponding product with 4:1 diastereoselectivity in 57% yield (entry 6). The




**Scheme 1.** Retrosynthetic analysis of (+)-detoxinine **3**.