Recent Progress on Synthesis and Activities of Allosamidin and Its Analogues

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Abstract: The pseudotrisaccharide allosamidin **1** is a potent family-18 chitinase inhibitor, and it demonstrates biological activities against insects and fungi. Recent development for the synthesis and activities of compound **1** and its analogues was reviewed. Huang *et al.* described the solid-phase synthesis of allosamidin **1** and its analogues, which were obtained by iterative glycosylation reactions, catalytic hydrogenation, acetylation, and deacetylation, respectively. It indicated that di-*N*-acetyl-β-chitobiosyl allosamizoline was strongly against insect chitinase from *Bombyx mori*. Withers and his co-workers have synthesized chitobiose and chitotriose thiazolines, which exhibit chitinase inhibition activity.

Keywords: Allosamidin, analogues, synthesis, activities, recent development.

1. INTRODUCTION

The fungi produce chitinases to modify chitins as the major cell wall components, and the insects require chitinases for the partial degradation of their old exoskeletons. So, it indicates the potential utility of chitinases as targets for the development of antifungal agents and biological insecticides (namely chitinase inhibitors*)*. In 1986, Suzuki and collaborators [1,2], while screening metabolites of actinomycetes, reported the discovery of a potent chitinase inhibitor which they isolated from the mycelial extract of *Streptomyces* sp. No. 1713. Chemical and spectroscopic data as well as degradation studies were used in the elucidation of its novel structure, which was shown to be that of a pseudotrisaccharide containing two β-linked *N*-acetyl-2-amino-2-deoxy-D-allopyranoside units. This novel disaccharide is linked to an aminocyclopentitol moiety (i.e. allosamizoline **2**, Fig. **1**) at its reducing end. The new family-18 chitinase inhibitor was named allosamidin **1**. Its unique chemical structure made allosamidin an attractive synthetic target, resulting in many publications about the total syntheses of allosamidin **1** and its analogues [3-29]. The choice of glycosidation method to assemble the component units of the allosamidin and its analogues constitutes the essential difference between each of the reported total syntheses. Ensuring exclusive β-selectivity is the primary goal of these glycosylation methods. Herein, the recent development for the synthesis and activities of compounds **1** and its analogues was reviewed as follows.

2. SYNTHESIS OF ALLOSAMIDIN 1 AND ITS ANALOGUES

The first total synthesis of allosamidin **1** was reported by Griffith and Danishefsky [3]. This method is particularly interesting for constructing glycosides comprising β-linked 2-deoxy-D-allosamine units, as the amino function is introduced on the hindered α -face in concert with β-glycoside formation.

The total synthesis of allosamidin **1** also was reported by Vasella's and Trost's groups [4-6]. They employed the trichloroacetimidate glycosidation method to couple the *N*-acetyl-D-allosamine units together, which subsequently was coupled to the racemic carbocyclic diol. The disaccharide donor was obtained in a convergent fashion from D-glucosamine and coupled regioselectively with the aminocyclopentitol diol. But, as the latter component was racemic, the coupling inevitably led late in the synthesis to 50 % of an unwanted diastereomer. The latter compound did nevertheless show interesting biological activity.

Kuzuhara's total synthesis of allosamidin **1** [7] involves an *N*-iodosuccinimide (NIS)-promoted coupling of the appropriately protected (-)-allosamizoline derivative with a chitin-derived disaccharide thioglycoside donor.

Takahashi and collaborators [8], using alcohol and a strategy paralleling their approach to allosamidin **1**, reported the first total synthesis of the natural product demethyl-allosamidin.

Ferrier and co-workers [9] about the synthesis of allosamidin **1** chose to use the trichloroacetimidate glycosidation method for coupling of their aminocyclopentanol acceptor. The latter was obtained by selective protection of carbocycle, an intermediate in their total synthesis of allosamizoline **2**. The coupling strategy reported by Vasella and Trost parallels closely the approach reported by these authors.

The solid-phase synthesis is a rapid and efficient method to synthesize oligosaccharides [30,31]. It is easier to remove excess reactants or byproducts in the course of multi-step synthesis of oligosaccharides. The most important concept behind the oligosaccharide synthesis is the glycosylation reaction, which involves glycosyl donor and glycosyl

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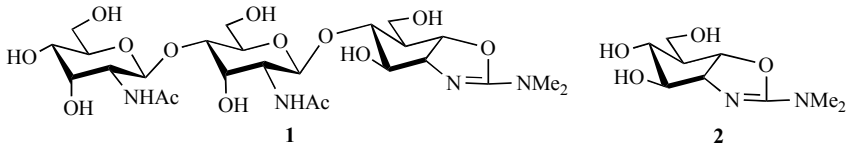
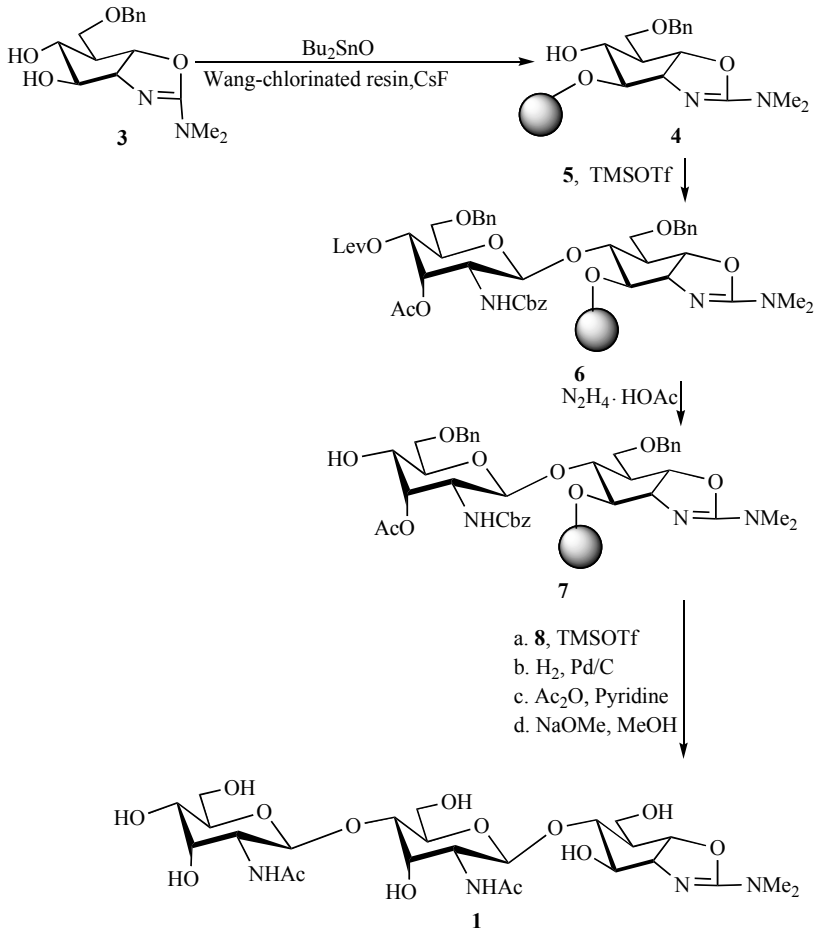


Fig. (1). The structures of allosamidin **1** and allosamizoline **2**.

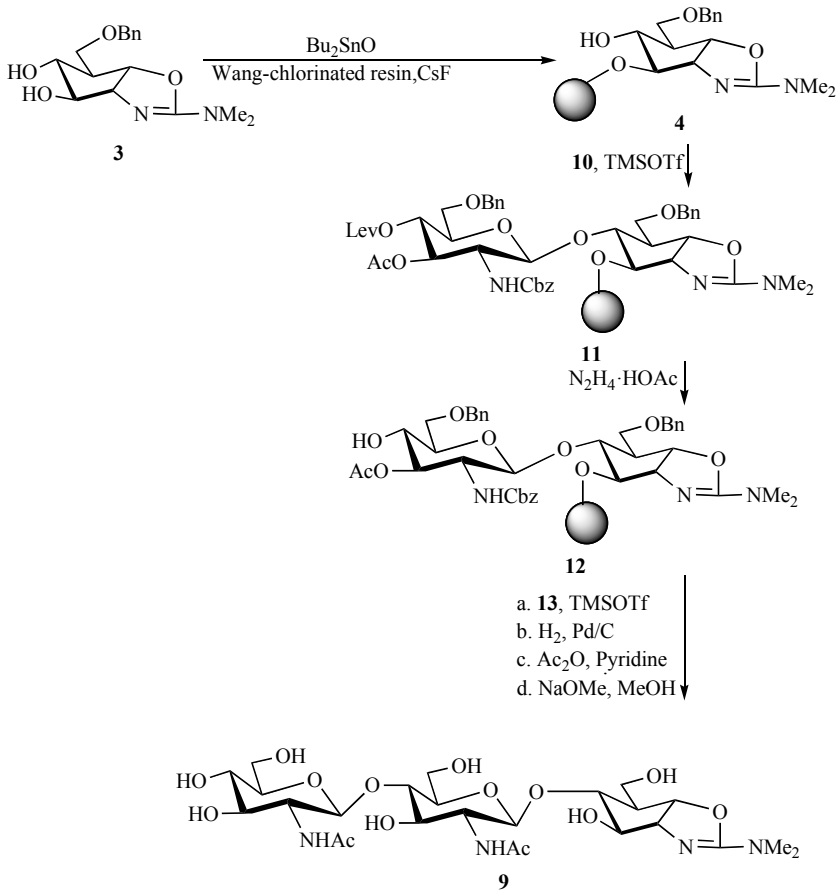
acceptor. In this respect, Huang and Dai have also developed the solid-phase synthesis of allosamidin **1** [32] (Scheme **1**).

The diol **3** (Scheme **1**) was prepared with the approach that described by Griffith and Danishefsky [33]. The C-3 hydroxyl group of compound **3** was selectively benzylated by the way of stannylene methodology [34] to provide the dibenzylated building block **4** in 45 % yield. Glycosylation reactions were performed using 3.0 equiv. of donor and 1.2 equiv. of trimethylsilyl trifluromethanesulfonate (TMSOTf) as promoter for the activation of trichloroacetimidate donor. At low temperature, TMSOTf-promoted glycosylation of the trichloroacetimidate donor **5** with the 6-*O*-benzylallosamizoline alcohol acceptor **4** gave the corresponding β-pseudodisaccharide **6** in 68 % yield. The yield was analyzed by high pressure liquid chromatography (HPLC) after cleavage of Wang resin with trifluoroacetic acid from building block **6**. Cleavage of the levulinoyl ester was performed using hydrazine acetate dissolved in MeOH to obtain the acceptor **7**. After the acceptor **7** was glycosylated with the donor **8**, resin was washed, filtered, and dried under the vacuum overnight. The saccharide bound resin was catalytically hydrogenated to cleave the Cbz, Wang resin, and Bn (90 % yield). Then, the resulting mixture was acetylated with Ac_2O/pyridine and subsequently deacetylated with NaOMe/MeOH to obtain a crude product. The crude product was purified by size-exclusion chromatography on Biogel P4 to afford the corresponding target pseudotrisaccharide **1** in 71 % yield for the last 3 steps.

In 1993, Terayama et al. reported in detail that the allosamidin analogue, i.e. *N*,*N*′-diacetyl-β-chitobiosyl allosamizoline **9**, exhibited inhibitory activity against some chitinases, and it was synthesized by the conventional organic synthesis method [21]. The analogue **9** was stereoselectively synthesized through the coupling reaction between the disaccharide thioglycoside derivative and allosamizoline derivative. The solid-phase synthesis of di-*N*-



Scheme 1. Solid-phase synthesis of allosamidin **1**.



Scheme 2. Solid-phase synthesis of di-*N*-acetyl-β-chitobiosyl allosamizoline **9**.

acetyl-β-chitobiosyl allosamizoline **9** also was investigated as the one of allosamidin **1** (Scheme **2**) [35].

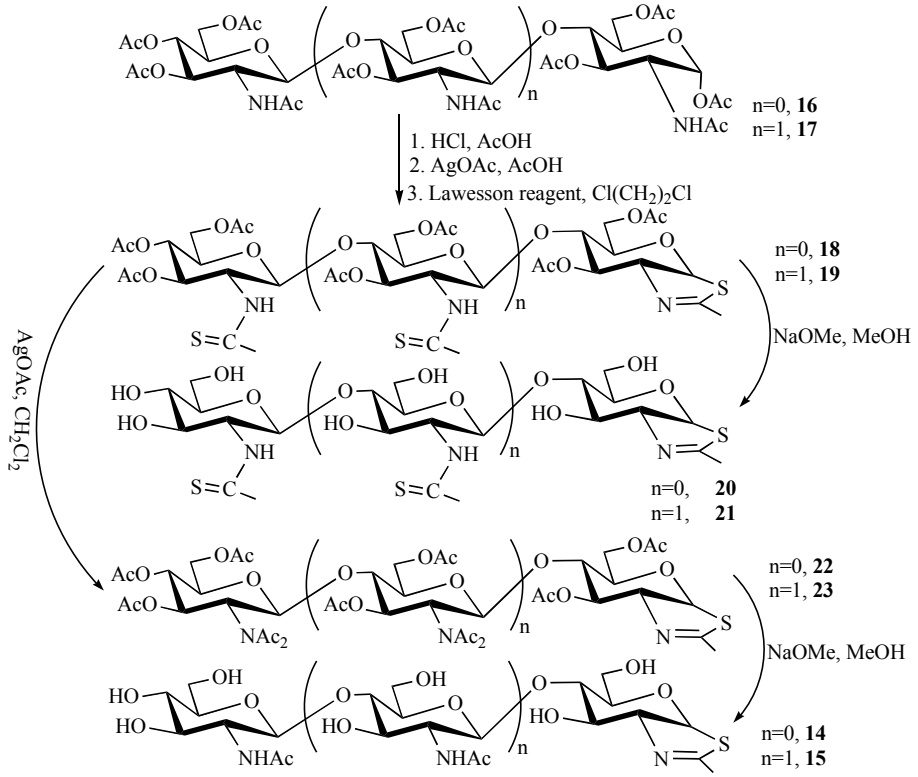
An international team led by Withers S. G. has now developed a novel chitinase inhibitor [36]. The core structural element is a ring-shaped sugar building block fused with a thiazoline, a five-membered ring made from one nitrogen, one sulfur, and three carbon atoms (Scheme **3**). This arrangement imitates a cyclic intermediate formed in the enzymatic degradation of chitin, and docks to the binding sites on chitinase enzymes. To augment the inhibitory effect, the researchers added two or three additional sugar units that resembled those in chitin (chitobiose or chitotriose).

The synthesis of the di- and trisaccharide thiazolines **14** and **15** started with octaacetylchitobiose **16** and undecaacetylchitotriose **17**, respectively (Scheme **3**) [36]. The anomeric configurations of the α-acetoxy groups of compounds **16** and **17** were inverted to give the corresponding β anomers by initial treatment with HCl and AcOH to give the anomeric chlorides, followed by treatment with AgOAc in AcOH. Next, treatment with the Lawesson reagent effected both the conversion of the amides into thioamides as well as intramolecular displacement of the anomeric β-acetoxy group by the sulfur atom of the adjacent thioamide to afford thiazolines **18** and **19**. Portions of each of the per-O-acetylated thiazolines **18** and **19** were deacetylated to give two additional chitinase inhibitors: the chitobiose thiazoline thioamide **20** (89 % yield) and chitotriose thiazoline dithioamide **21** (80 % yield). To reach target compounds **14** and **15**, the thioamides **18** and **19** were converted into the diacetylimides **22** and **23** with silver acetate in dichloromethane (in 81 and 60 % yield, respectively) without damage to the thiazoline moiety. Finally, imides **22** and **23** were O-deacylated and mono-N-deacylated by using sodium methoxide in methanol to give the chitobiose thiazoline **14** (69 % yield) and chitotriose thiazoline **15** (78 % yield).

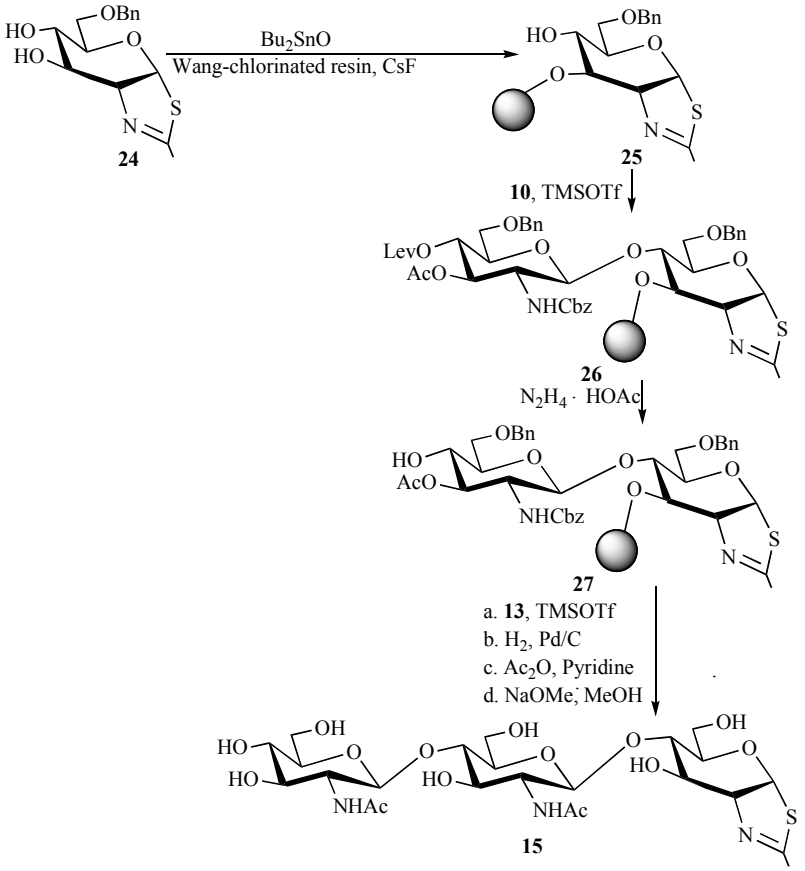
It indicates that Withers and his co-workers have synthesized chitobiose and chitotriose thiazolines (**14** and **15**) by the traditional method. Based on the solid-phase synthesis of allosamidin **1**, Huang and Chen have successfully synthesized compound **15** by the similar method (Scheme **4**) [37]. Compounds **10** and **13** are the corresponding α-trichloroacetimidate donors.

3. ACTIVITIES

The pseudotrisaccharide allosamidin **1** is a potent family-18 chitinase inhibitor with demonstrated biological activity against insects and fungi [38]. The inhibitory activity of di-*N*-acetyl-β-chitobiosyl allosamizoline **9** against chitinases derived from an insect, yeast and mold were tested and compared with that of allosamidin **1**. It indicated that di-*N*-acetyl-β-chitobiosyl allosamizoline could inhibit insect chitinase from *Bombyx mori* [21].



Scheme 3. Synthesis of chitobiose and chitotriose thiazolines (**14** and **15**), and their thioamide analogues (**20** and **21**).



Scheme 4. Solid-phase synthesis of chitotriose thiazoline **15**.

The GlcNAc thiazoline is a very poor inhibitor of ChiA, with K_i>1 mM. However, the addition of one GlcNAc residue in compound **14** improved binding at least 40-fold, and the second GlcNAc residue provided a further 100-fold increase in affinity to bring down the K_i value for the pseudotrisaccharide **15** well below that measured for the inhibition of ChiA by allosamidin (K_i=0.6 μM) [36]. This result stands in contrast to the recent report that a disaccharide thiazoline with an interresidue sulfur linkage was not a significant inhibitor of ChiA; the lack of inhibition observed in that study is presumably due to a different geometry imposed by the thioglycosidic linkage [39].

CONCLUSION

In summary, it indicates that the combinatorial synthesis, including solution-phase synthesis and solid-phase synthesis, can improve synthesis efficiency of allosamidin **1** and its analogues. The final aim for the project is to screen out the high-activity allosamidin analogues.

CONFLICT OF INTEREST

The author reports no conflict of interest.

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