Solid-Phase Synthesis of Di-*N*-Acetyl-β-Chitobiosyl Allosamizoline

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Abstract: The solid-phase synthesis of di-*N*-acetyl-β-chitobiosyl allosamizoline **2** was reported. After the 6-*O*-benzyl allosamizoline **16**, *N*HCbz trichloroacetimidate donors **7**, and **14** were synthesized; solid-phase synthesis was performed using the Wang resin as support. The target di-*N*-acetyl-β-chitobiosyl allosamizoline **2** was obtained by iterative glycosylation reactions, catalytic hydrogenation, acetylation, and deacetylation, respectively.

Keywords: Allosamidin analogue, di-*N*-acetyl-β-chitobiosyl allosamizoline, glycosylation reactions, solid-phase synthesis, trichloroacetimidate donors, wang resin.

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*)*. The allosamidins are just a potent class of pseudodisaccharide and pseudotrisaccharide chitinase inhibitors. The parent compound, allosamidin **1** (Fig. **1**), was isolated from *Streptomyces* fermentations twenty-four years ago [1]. In 1993, Terayama *et al.* reported in detail that the allosamidin analogue, i.e. *N,N'*-diacetyl-β-chitobiosyl allosamizoline **2**, exhibited inhibitory activity against some chitinases, and it was synthesized by the conventional organic synthesis method [2].

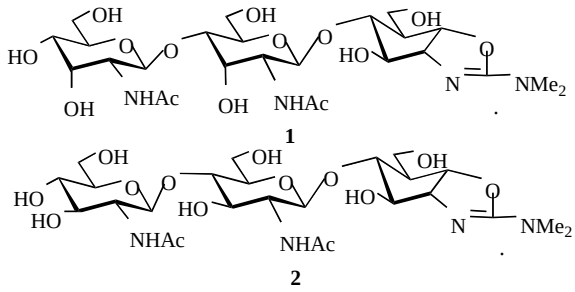

Fig. (1). The structures of allosamidin **1**, and di-*N*-acetyl-β-chitobiosyl allosamizoline **2**.

The solid-phase synthesis is a rapid and efficient method to synthesize oligosaccharides [3, 4]. Therefore, it also is intended to prepare di-*N*-acetyl-β-chitobiosyl allosamizoline **2** by solid-phase synthesis. So, it is easier to remove excess reactants or byproducts in the course of multi-step synthesis. The solid-phase synthesis of di-*N*-acetyl-β-chitobiosyl allosamizoline **2** was described as follows.

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RESULTS AND DISCUSSION

Treatment of α-D-glucosamine hydrochloride salt **3** with benzyloxycarbonyl (Cbz)-Cl in the presence of $NaHCO_3$/H_2O yielded *N*-benzyloxycarbonyl protected glucosamine **4** in 88 % yield. Acetylation of compound **4** by means of Ac_2O in pyridine obtained tetraacetate **5** as a mixture of α/β isomers in 4:1. The anomeric acetyl group was selectively removed using hydrazine acetate in DMF to afford hemiacetal **6**. Reaction of compound **6** with CCl_3CN in the presence of 1,8-diaza[5.4.0]bicycloundec-7-ene (DBU) exclusively afforded α-trichloroacetimidate donor **7** in 85 % yield (Scheme **1**).

Treatment of compound **5** with hydrazine acetate in the presence of DMF obtained hemiacetal **6**, which was used without further purification. Then, the mixture was reacted with *tert*-butyldimethylsilyl (TBDMS)-Cl and imidazole to yield exclusively the β-anomer of the corresponding TBDMS derivative **8**. Deacetylation of compound **8** with NaOMe/MeOH afforded TBDMS 2-deoxy-*N*-benzyloxycarbonylamino-β-D-glucopyranoside **9** in 96 % yield. Treatment of compound **9** with benzaldehyde dimethylacetal afforded the 4,6-*O*-benzylidene derivative **10**. Compound **10** was treated with Ac_2O and pyridine to obtain acetate **11** in 94 % yield. Regioselective reductive cleavage of benzylidene acetal **11** with CF_3COOH/Et_3SiH at 0 °C afforded 6-*O*-Bn acceptor **12** in 85 % yield. Compound **12** was treated with levulinic acid in the presence of *N,N'*-diisopropylcarbodiimide (DIPC) to yield the orthogonally protected glucosamine **13** in 94 % yield. The anomeric TBDMS group was removed using tetrabutylammonium fluoride (TBAF) in the presence of acetic acid. Then, the crude product was reacted with CCl_3CN in the presence of DBU to afford the α-trichloroacetimidate donor **14** (Scheme **2**).

Chlorination of Wang resin with $SOCl_2$ seemed to be ill-advised, as the resulting hydrogen chloride solution would likely cleave the acid-labile benzylic ether linkage from the solid support. Herein, the Wang resin was chlorinated using triphenylphosphine and triphosgene (BTC) [5] to obtain the Wang-chlorinated resin **15** in 82 % yield (Scheme **3**).

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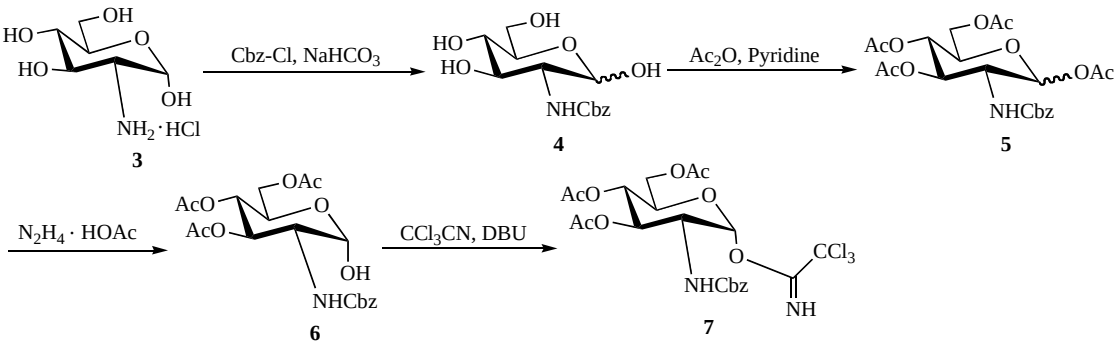
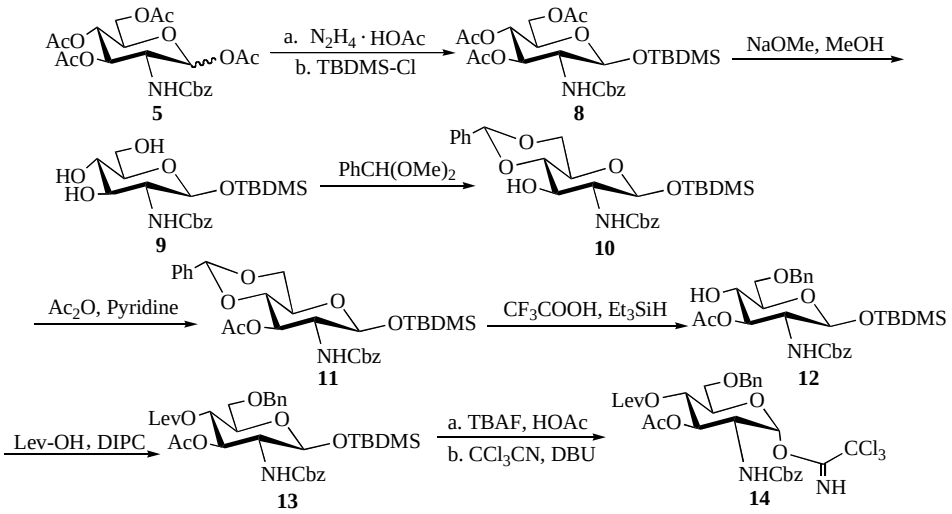
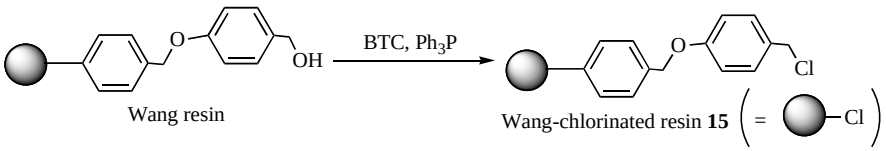


Scheme 1. Synthesis of *N*-Cbz protected donor **7**.



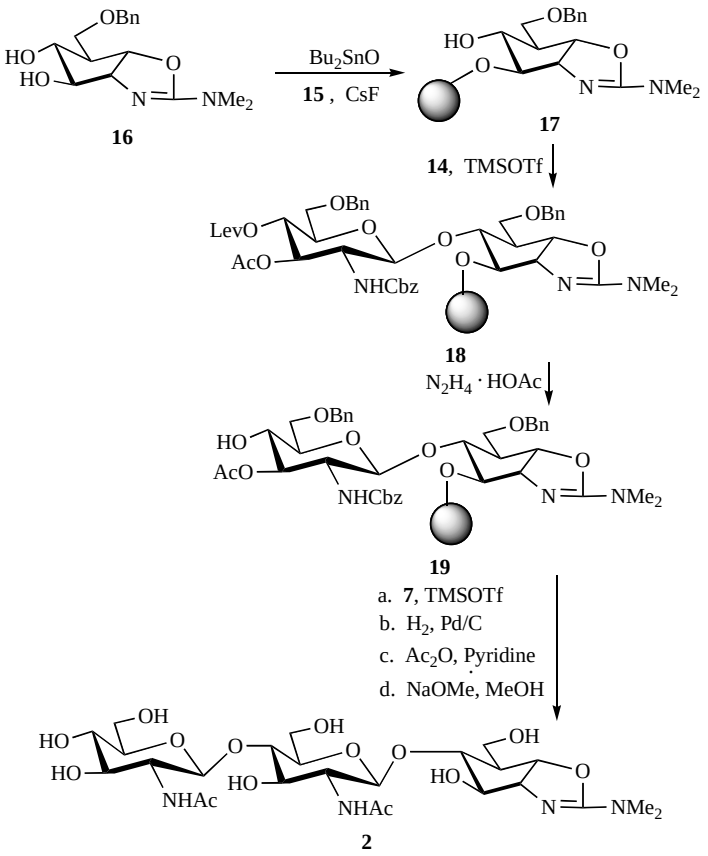
Scheme 2. Synthesis of *N*-Cbz-Donor **14**.



Scheme 3. Preparation of Wang-chlorinated resin **15**.

The Wang resin is a polymer support, and contains a linker. The C-3 hydroxyl group of compound **16** was selectively benzylated with the Wang-chlorinated resin **15** by the way of stannylene methodology [3] to provide the dibenzylated building block **17** in 45 % yield (Scheme **4**). Glycosylation reactions were performed using 3.0 equiv. of donor and 1.2 equiv. of trimethylsilyl trifluromethane-sulfonate (TMSOTf) as promoter for the activation of trichloroacetimidate donor. At low temperature, TMSOTf-promoted glycosylation of the trichloroacetimidate donor **14** with the 6-*O*-benzylallosamizoline alcohol acceptor **17** gave the corresponding β-pseudodisaccharide **18** in 72 % yield. The yield was analyzed by high pressure liquid chromatography (HPLC) after cleavage of Wang resin with trifluoroacetic acid from building block **18**. Levulinoyl ester is used as an orthogonal protecting group, which can be efficiently cleaved to liberate the free hydroxyl site for further glycosylation. Cleavage of the levulinoyl ester was performed using hydrazine acetate dissolved in MeOH to obtain the acceptor **19**. After the acceptor **19** was glycosylated with the donor **7**, 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 (91 % yield). Then, the resulting mixture was acetylated with Ac_2O/pyridine and deacetylated with NaOMe/MeOH, respectively, to obtain a crude product. The crude product was purified by size-exclusion chromatography on Biogel P4 to afford the corresponding target pseudotrisaccharide **2** in 75 % yield for the last three steps. The amino group is protected with Cbz. Due to the neighboring group participation of Cbz during the glycosylation reactions, the β-linkage is easy to form.

In summary, the solid-phase synthesis of di-*N*-acetyl-β-chitobiosyl allosamizoline **2** with *N*HCbz protected glycosamine donors has been studied. With Wang resin,



Scheme 4. Solid-phase synthesis of di-*N*-acetyl-β-chitobiosyl allosamizoline **2**.

good yields were obtained throughout the iterative assemblies.

ACKNOWLEDGEMENTS

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