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Synthesis of di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline

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The synthesis of di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline **2** was investigated. The synthesis was processed using the *N*-benzyloxycarbonyl (Cbz) protected trichloroacetimidates **11** and **13** as donors, polystyrene as support, and *o*-nitrobenzyl ether tether as linker. The target compound **2** was efficiently yielded by three glycosylations, catalytic hydrogenolysis, acetylation, deacetylation, and photolysis, respectively.

Keywords: di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline, synthesis, glycosylation, analogue

INTRODUCTION

The allosamidin **1** (Fig. 1) is a well-known pseudotrisaccharide, and it is a typical chitinase inhibitor. Compound **1** has the important biological activities, for example, acting as insecticide and fungicide [1]. It has been reported about the synthetic methods of allosamidin **1** and its analogues [2-3], and these compounds mostly were synthesized by the liquid-phase synthesis. The methods have multiple steps and the manufacturing costs are high, which prevents allosamidin **1** and its analogues from being widely utilized in agriculture. The compound **1** was synthesized by the solid/liquid phase methods [1]. However, but the allosamidin **1** must be purified to use column chromatography in the final step. Therefore, it doesn't fully utilize the strongpoint of solid-phase synthesis to synthesize compound **1**. Namely, one can distinctly avoid the purification process if the allosamidin **1** is synthesized by total solid-phase method. So, the redundant reactants or outgrowths can be removed by filtrating and washing. For such point of view, the solid-phase synthesis of di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline **2** was re-studied herein.

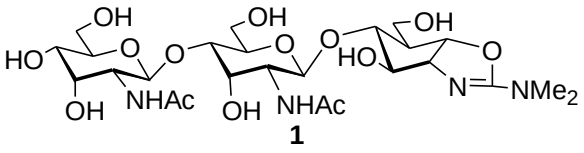

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Fig. 1 Structures of allosamidin **1**.

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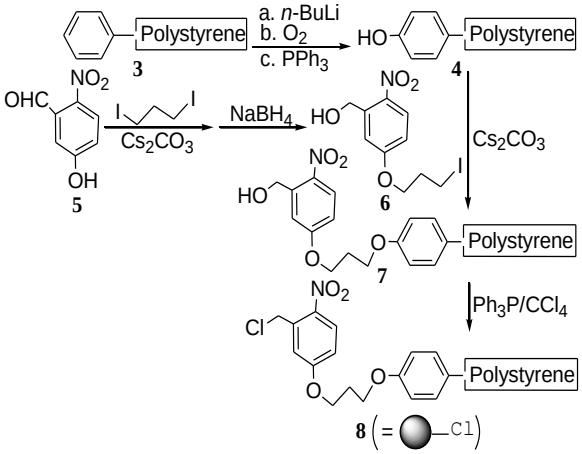


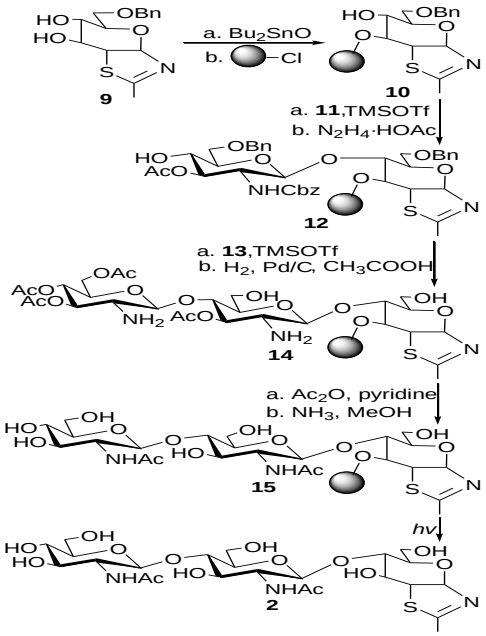
Scheme 1 Preparation of the chlorinated *o*-nitrobenzyl ether polystyrene **8**.

RESULTS AND DISCUSSION

Polystyrene **3** (Scheme 1) was functionalized to phenolic polystyrene **4** by reaction with *n*-BuLi, oxygen, and PPh_3, respectively. The linker, *o*-nitrobenzyl ether tether, was used because it was easy to attach and cleave. So, the available 5-hydroxy-2-nitrobenzaldehyde **5** was reacted with 1,3-diiodopropane in DMF under the alkaline condition, and then directly was reduced with $NaBH_4$ to offer iodobenzyl alcohol **6** in 93% yield for the above two steps. Compound **6** was attached to phenolic polystyrene **4** via its linker with Cs_2CO_3 to provide the conjugate **7** in 91% yield based on mass gain of the polymer. Chlorination of compound **7** with Ph_3P/CCl_4 obtained the chloride **8** in 86% yield.

The *N*-glycothiazoline **9** was obtained according to the reported method [4]. The C-3 hydroxyl group

of diol **9** was selectively benzylated with chloride **8** and Bu_2SnO [1] to afford the intermediate **10** in 60 % yield (Scheme 2).



Scheme 2 The synthesis of di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline **2**.

Glycosylation reactions were gone along using donor (3.0 equiv.) and trimethylsilyl trifluromethanesulfonate (TMSOTf, 0.1 equiv.) as catalyzer to activate the trichloroacetimidate donor. Under zero temperature, TMSOTf-catalyzed glycosylation of trichloroacetimidate donor **11** under the protection of *N*-benzyloxycarbonyl (Cbz) [5] with the 6-*O*-benzylallosamizoline acceptor **10** yielded the O-perprotected β-pseudodisaccharide in 70 % yield. The yield was proved by the analysis of high pressure liquid chromatography (HPLC) after removal of the polystyrene and *o*-nitrobenzyl ether tether by photolysis from the O-perprotected β-pseudodisaccharide. This method for yield calculation was analogous to the following process. The levulinoyl ester was removed with hydrazine acetate and MeOH to obtain acceptor **12**. After the acceptor **12** was reacted with trichloroacetimidate donor **13** under the protection of *N*-Cbz [5], the resin-bound saccharide was hydrogenated with Pd/C and acetic acid for removal of Cbz and Bn to provide intermediate **14** in 88 % yield. Whereafter, the resulting mixture was acetylated with Ac_2O-pyridine and deacetylated with NH_3-MeOH, respectively. After above-mentioned reactions were finished, the resin was filtrated and washed, respectively. Efficient removal of the di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline **2** moiety from linker was achieved by photolysis of intermediate **15** to offer the target compound **2** [6] in 91 % yield. It wasn't necessary to re-purify di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline **2** because it had the high purity.

CONCLUSION

The solid-phase synthesis of di-*N*-acetyl-β-chitobiosyl *N*-glycothiazoline **2** was reported herein. With the support polystyrene and the linker *o*-nitrobenzyl ether tether, the satisfying yield for compound **2** was obtained by three glycosylations, hydrogenation with Pd/C-acetic acid, acetylation, deacetylation, and photolysis, respectively.

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Compound 2: ^{1}H NMR (CD_3OD, 300 MHz): 1.94, 2.01 (2s, 6H, $COC\underline{H}_3$), 2.24 (br s, 3H, oxazoline $C\underline{H}_3$), 3.17-3.28 (m, 5H), 3.28-3.50 (m, 3H), 3.52-3.71 (m, 6H), 3.82 (d, 1H), 3.88 (d, 1H), 4.27-4.39 (m, 1H, H-2), 4.45, 51 (2d, 2H, H-1", 1'"), 4.65 (br s, 1H, H-3), 6.31 (d, 1H, H-1).

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СИНТЕЗА НА ДИ- *N*-АЦЕТИЛ-В-ХИТОБИОЗИЛ *N*-ГЛИКОТИАЗОЛИН

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(Резюме)

Изследвана е синтезата на ди- *N*-ацетил-β-хитобиозил *N*-гликотиазолин **2**. Синтезата е извършена използвайки *N*-benzyloxycarbonyl (Cbz), защитени трихлор-ацетимидати **11** и **13** като донори, полистирен като носител и *o*-нитробензил-етер като свързващ агент. Целевото съединение **2** беше получено с високи ефективност и добив съответно чрез три гликолизирания, каталитична хидрогенолиза, ацетилиране, деацетилиранеи фотолиза.