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Liquid-phase synthesis of N,N'-diacetyl-β-chitobiosyl allosamizoline

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Liquid-phase synthesis of N,N'-diacetyl-β-chitobiosyl allosamizoline 2 was studied. The N-benzyloxycarbonyl (Cbz) protected trichloroacetimidate donors 3 and 5 were prepared according to the routine method. The target allosamidin analogue 2 was high-efficiently synthesized by iterative glycosylation reactions, catalytic hydrogenation, acetylation, and deacetylation, respectively.

Keywords: N,N'-diacetyl-β-chitobiosyl allosamizoline, liquid-phase synthesis, trichloroacetimidate donors

INTRODUCTION

This pseudo-trisaccharide allosamidin **1** (Fig. 1) is a representative chitinase inhibitor, and it possesses high activities against insects and fungi [1-2]. The synthetic methodologies of compound **1** and its analogues were reported [3-5]. But the approach is more complicated, and the cost of mass production is high in every synthetic method, which restrict allosamidin **1** and its analogues to be widely utilized in agriculture. *N*,*N'*-Diacetyl-β-chitobiosyl allosamizoline **2** has been synthesized by solid-phase method [1,6], but the approach is still a bit longer, and this yield of introducing the solid-phase support is too low. Therefore, the allosamidin analogue **2** has been tried to synthesize by liquid-phase method in this paper, which is based on its reported solid-phase method, but the solid-phase support does not be introduced.

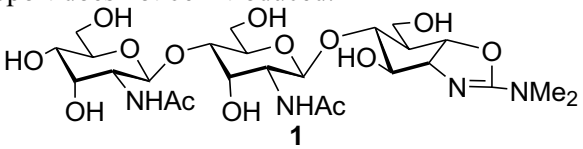

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Fig. 1 Structure of allosamidin **1**.

RESULTS AND DISCUSSION

The most important concept behind carbohydrate synthesis is glycosylation reaction to involve glycosyl donor and glycosyl acceptor. The retrosynthetic analysis of *N*,*N'*-diacetyl-β-chitobiosyl allosamizoline **2** was shown in Scheme 1. It indicated that the synthetic strategy for target compound **2** was in reverse order for the installation of subunits **3**, **5**, and **6**. It also has shown the effectiveness of glycosyl trichloroacetimidates as donors in the glycosidic bond formation. Levulinoyl ester is used as an orthogonal protecting group, which can be efficiently cleaved to liberate the free hydroxyl site for further glycosylation. The amino group is protected with benzyloxycarbonyl (Cbz). Due to the neighboring group participation of Cbz during glycosylation reaction, the β-linkage is easy to form. Cbz and Bn can be removed by catalytic hydrogenation.

The 3,6-di-*O*-benzylallosamizoline **6** (Scheme 2) was prepared according to the approach that described by Griffith and Danishefsky [7]. Glycosylation reactions were gone along using 3.0 equiv. of donor and 0.1 equiv. of trimethylsilyl trifluromethanesulfonate (TMSOTf) as promoter to activate trichloroacetimidate donor. At low temperature, TMSOTf-promoted glycosylation of the *N*-Cbz protected trichloroacetimidate donor **5** [8-9] with intermediate **6** yielded the O-perprotected β-pseudodisaccharide in 83% yield. Cleavage of the levulinoyl ester was carried out with hydrazine acetate dissolved in MeOH to form the acceptor **4**. After acceptor **4** was glycosylated with the *N*-Cbz protected trichloroacetimidate donor **3** [8-9], the obtained pseudo-trisaccharide was catalytically hydrogenated for cleavage of Cbz and Bn to yield building block **7** in 96% yield. Then, the intermediate **7** was acetylated with Ac_2O/pyridine and deacetylated with NH_3/MeOH, respectively. After purification by column chromatography, the target compound **2** was obtained in 97% yield.

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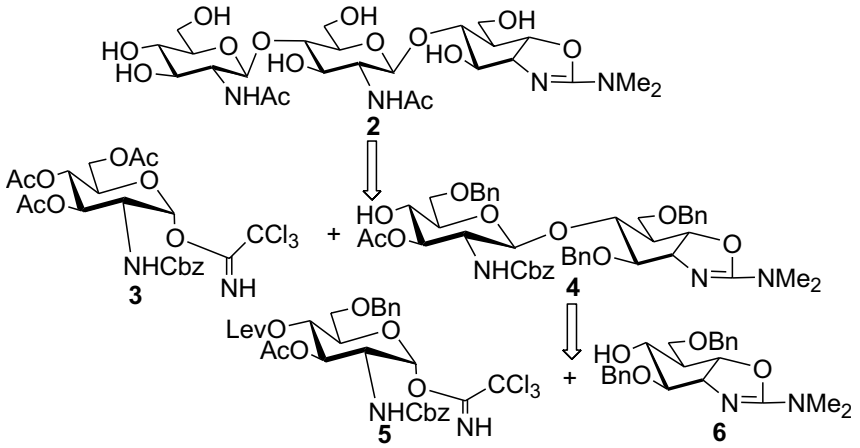
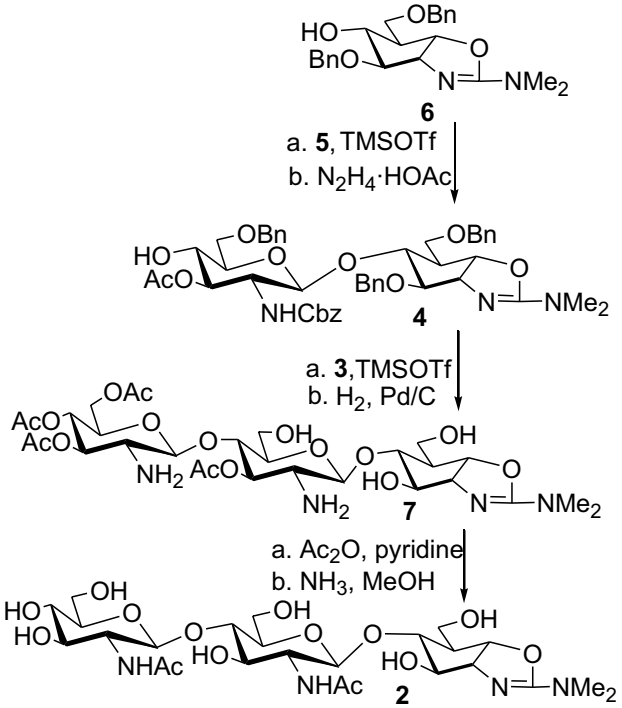


Scheme 1 Retrosynthetic analysis of *N*,*N'*-diacetyl-β-chitobiosyl allosamizoline **2**.



Scheme 2 The liquid-phase synthesis of *N*,*N'*-diacetyl-β-chitobiosyl allosamizoline **2**.

CONCLUSION

The liquid-phase synthesis of *N*,*N'*-diacetyl-β-chitobiosyl allosamizoline **2** was investigated. Compound **2** was obtained by iterative glycosylation reactions, catalytic hydrogenation, acetylation, and deacetylation, respectively.

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***N*,*N'*-Diacetyl-β-chitobiosyl allosamizoline 2:** ^{1}H NMR (300 MHz, D_2O-CD_3COOD) δ 5.04 (dd, 1 H, H-1), 4.58 (d, 1 H, H-1''), 4.54 (d, 1 H, H-1'), 4.14 (dd, 1 H, H-2), 4.06 (dd, 1 H, H-3), 3.94 (dd, 1 H, H-6''b), 3.86 (dd, 1 H, H-6'b), 3.82 (dd, 1 H, H-6b), 3.75 (dd, 1 H, H-6''a), 3.74 (dd, 1 H, H-2''), 3.73 (dd, 1 H, H-2'), 3.72 (dd, 1 H, H-4), 3.70 (dd, 1 H, H-3'), 3.67 (dd, 1 H, H-6'a), 3.66 (dd, 1 H, H-6a), 3.61 (dd, 1 H, H-4'), 3.58 (dd, 1 H, H-3''), 3.56 (m, 1 H, H-5'), 3.51 (m, 1 H, H-5''), 3.47 (dd, 1 H, H-4''), 2.96 (d, 6 H, $N(C\underline{H}_3)_2$), 2.38-2.34 (m, 1 H, H-5), 2.07-2.04 (d, 6 H, 2×$NHCOC\underline{H}_3$).

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ТЕЧНОФАЗНА СИНТЕЗА НА N,N'-ДИАЦЕТИЛ- β - ХИТОБИОЗИЛ АЛОЗАМИЗОЛИН

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(Резюме)

Иследвана беше течнофазната синтеза на N,N'-диацетил- β - хитобиозил алозамизолин **2**. Трихлоацетамидни донори **3** и **5**, защитени с N-бензоилкарбонил(Cbz), бяха приготвени по рутитен метод. Целевият алозамидинов аналог **2** беше синтезиран с висока ефективност чрез итеративни реакции на гликолизация, каталитично хидрогениране, ацетилиране и съответно деацетилизране.