# An Efficient Synthesis of Allosamidin

Gangliang Huang,* Shuangquan Shu

College of Chemistry, Chongqing Normal University, Chongqing 400047, P. R. of China
Fax +(86)013068336573; E-mail: huangdoctor226@163.com

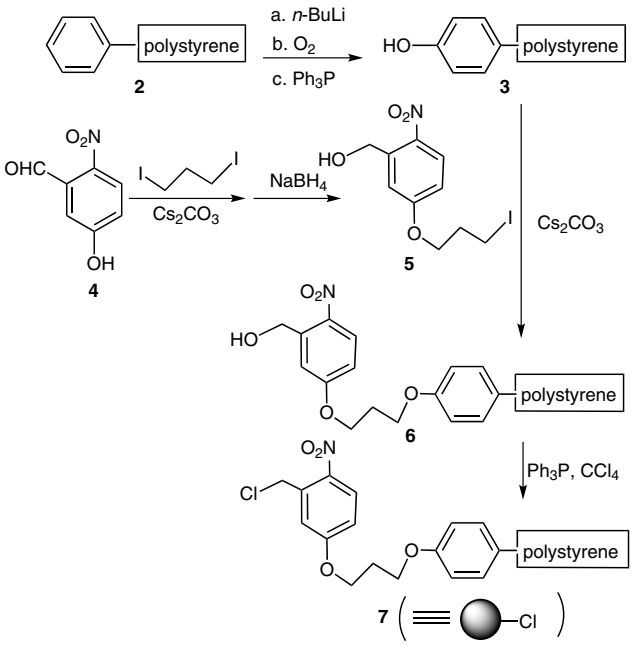
*Received: 19.04.2012; Accepted after revision: 16.05.2012*

**Abstract:** The solid-phase synthesis of allosamidin was investigated. After two *N*-benzyloxycarbonyl (Cbz)-protected trichloroacetimidate donors were synthesized, the solid-phase synthesis was performed using polystyrene as support and an *o*-nitrobenzyl ether tether as linker. The target allosamidin was efficiently obtained by iterative glycosylation reactions, catalytic hydrogenation, acetylation, deacetylation, and photolysis.

**Key words:** carbohydrates, solid-phase synthesis, chitinase, inhibitors, glycosylation

The pseudotrisaccharide allosamidin (**1**) is a potent chitinase inhibitor that demonstrates biological activities against insects and fungi.[1] The synthetic methods used for compound **1** were reviewed,[1–4] but it has mainly been synthesized by traditional organic synthetic methods. With each synthetic step, the process becomes more complex, and the cost of mass production increases, which has constrained the general use of compound **1** in agriculture. We have also synthesized allosamidin **1** by a combination of solid-phase and liquid-phase methods,[5] but the target compound **1** must still be purified by size-exclusion chromatography at the last step. Thus, the synthetic methods applied to allosamidin (**1**) do not fully take advantage of the merits of solid-phase synthesis. Thus, if compound **1** could be synthesized by solid-phase methods in every step, the purification process would be simplified to filtration and washing to remove excess reactants or byproducts. Towards this end, a solid-phase synthesis of allosamidin (**1**) was investigated.

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

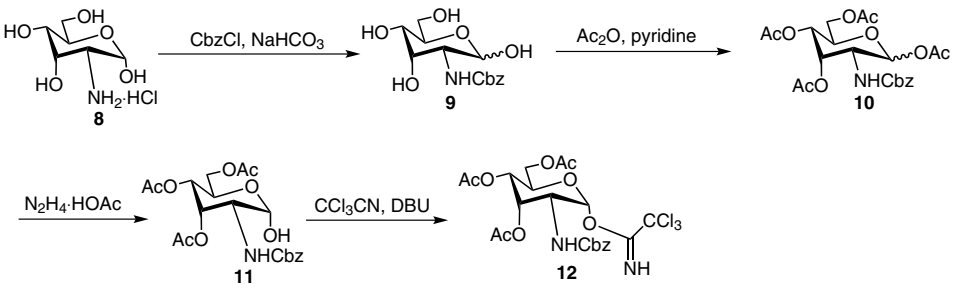



**Scheme 1** Synthesis of chlorinated and polystyrene-bound *o*-nitrobenzyl ether **7**

α-D-Allosamine hydrochloride salt (**8**) was prepared according to the method described by Jeanloz.[6] Treatment of compound **8** with benzyloxycarbonyl (Cbz) chloride in the presence of $NaHCO_3/H_2O$ yielded *N*-Cbz-protected allosamine **9** in 85% yield. Acetylation of compound **9** by treatment with $Ac_2O$ in pyridine generated tetraacetate **10** as a mixture of α/β isomers in a ration of 4:1. The anomeric acetyl group was selectively removed by using hydrazine acetate in DMF to afford hemiacetal **11**. Reaction of **11** with $CCl_3CN$ in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) exclusively afforded α-trichloroacetimidate donor **12** in 82% yield (Scheme 2).

Treatment of compound **10** with hydrazine acetate in the presence of DMF gave hemiacetal **11**, which was used without further purification. The mixture was then reacted with *tert*-butyldimethylsilyl TBDMSCl and imidazole to yield exclusively the β-anomer of the corresponding TBDMS derivative **13**. Deacetylation of compound **13** with NaOMe/MeOH afforded TBDMS 2-deoxy-*N*-benzyloxycarbonylamino-β-D-allopyranoside **14** in 95% yield. Treatment of **14** with benzaldehyde dimethylacetal afforded the 4,6-*O*-benzylidene derivative **15**, which was treated with $Ac_2O$ and pyridine to obtain acetate **16** in 94% yield. Regioselective reductive cleavage of benzylidene acetal **16** with $CF_3COOH/Et_3SiH$ at 0 °C afforded 6-*O*-benzyl acceptor **17** in 86% yield. Compound **17** was re-

*SYNLETT* 2012, 23, 1829–1831
Advanced online publication: 22.06.2012
DOI: 10.1055/s-0032-1316547; Art ID: ST-2012-R0424-L




**Scheme 2** Synthesis of *N*-Cbz-protected donor **12**

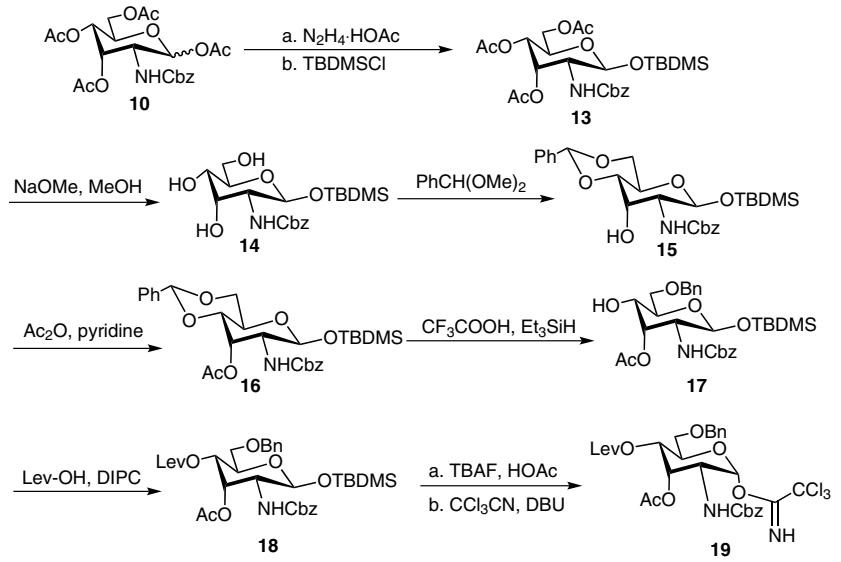
acted with levulinic acid in the presence of *N*,*N*'-diisopropylcarbodiimide (DIPC) to yield the orthogonally protected allosamine **18** in 95% yield. The anomeric TBDMS group was removed by treatment with tetrabutylammonium fluoride (TBAF) in the presence of acetic acid, then the crude product was reacted with $CCl_3CN$ in the presence of DBU to afford the α-trichloroacetimidate donor **19** (Scheme 3).

Diol **20** (Scheme 4) was prepared according to the method described by Griffith and Danishefsky.[7] The C-3 hydroxy group of **20** was selectively benzylated by using stannylene methodology[8] to provide the dibenzylated building block **21** in 60% yield. Glycosylation reactions were performed using 3.0 equivalents of donor and 1.2 equivalents of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as promoter to activate the trichloroacetimidate donor. At low temperature, TMSOTf-promoted glycosylation of the trichloroacetimidate donor **19** with the 6-*O*-benzylallosamizoline alcohol acceptor **21** gave the corresponding O-perprotected β-pseudodisaccharide in 75% yield. The product was analyzed by high-pressure liquid chromatography (HPLC) after cleavage of polystyrene and linker by irradiation from the O-perprotected β-pseudodisaccharide. Cleavage of the levulinoyl ester was performed by using hydrazine acetate dissolved in MeOH to obtain acceptor **22**. After glycosylation of **22** with donor **12**, the saccharide-bound resin was catalytically hydrogenated to cleave Cbz and Bn and obtain building block **23** in 96% yield. The resulting mixture was then acetylated with $Ac_2O$/pyridine and deacetylated with $NH_3$/MeOH, respectively. After each of the reactions mentioned above was finished, the resin was filtered and washed. Efficient cleavage of the allosamidin fragment from the resin was demonstrated by irradiation of building block **24** to afford target allosamidin **1**[9] in 94% yield, which did not require further purification by flash column chromatography.

In summary, the solid-phase synthesis of allosamidin **1** was studied. With polystyrene resin as support and an *o*-nitrobenzyl ether tether as linker, a good yield was obtained by iterative glycosylation reactions, catalytic hydrogenation, acetylation, deacetylation, and photolysis, respectively.

## Acknowledgment

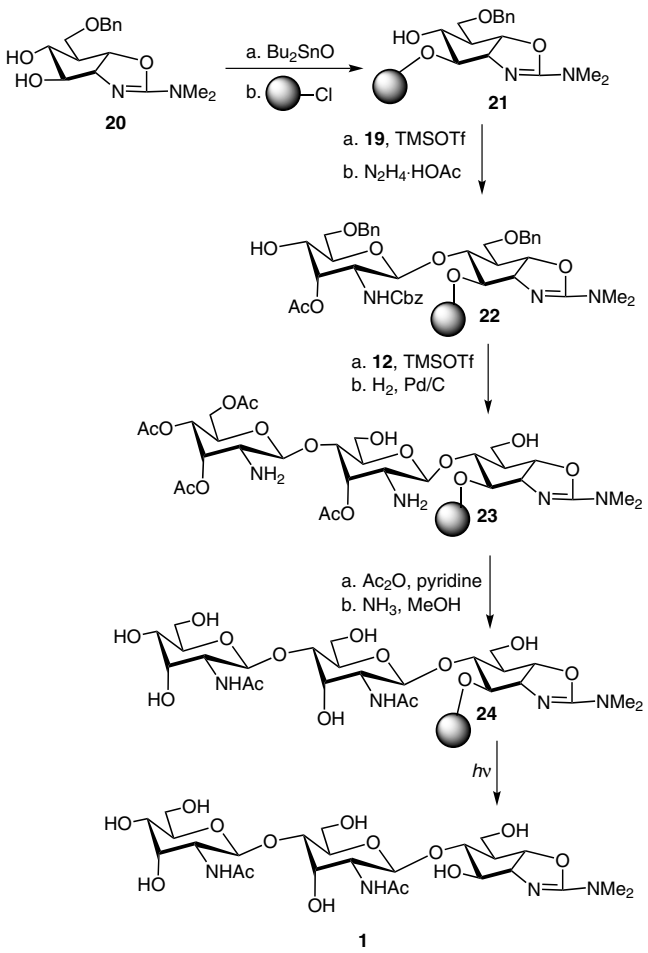
The work was supported by Open Foundation from Tertiary College of Chongqing Engineering Research Center of Bioactive Substance and Ministry of Education Engineering Research Center of Active Substance & Biotechnology (No. GCZX2012-2), Key Foundation of Chongqing Normal University (No. 10XLZ004), and Chongqing Education Commission Foundation (No. KJ080810), China.




**Scheme 3** Synthesis of *N*-Cbz donor **19**






**Scheme 4** The solid-phase synthesis of allosamidin **1**

## References and Notes


(1) Huang, G. L. *Curr. Org. Chem.* **2012**, *16*, 115.
(2) Huang, G. L. *Mini-Rev. Med. Chem.* **2012**, *12*, 665.
(3) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779.
(4) Andersen, O. A.; Dixon, M. J.; Eggleston, I. M.; vanAalten, D. M. *Nat. Prod. Rep.* **2005**, *22*, 563.
(5) Huang, G. L.; Dai, Y. P. *Synlett* **2010**, 1554.
(6) Jeanloz, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 2591.
(7) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863.
(8) Huang, G. L.; Yang, Q. *Lett. Org. Chem.* **2010**, *7*, 396.
(9) **Allosamidin 1**: IR (KBr): 3500, 3365, 1652, 1550, 1060 $cm^{-1}$; $^1H$ NMR (300 MHz, $D_2O$): δ = 5.37 (dd, *J* = 8.7, 4.9 Hz, 1 H, H-1), 4.80 (d, *J* = 8.5 Hz, 1 H, H-1″), 4.78 (d, *J* = 8.3 Hz, 1 H, H-1′), 4.37 (dd, *J* = 8.7, 4.1 Hz, 1 H, H-2), 4.36 (t, *J* = 2.9 Hz, 1 H, H-3′), 4.30 (t, *J* = 5.0 Hz, 1 H, H-3), 4.07 (t, *J* = 2.8 Hz, 1 H, H-3″), 3.92–2.66 (m, 12 H), 3.61 (dd, *J* = 12.0, 6.5 Hz, 1 H, H-6′), 3.09 (s, 3 H, $NCH_3Me$), 3.08 (s, 3 H, $NCH_3Me$), 3.67–3.63 (m, 1 H, H-5), 2.09 (s, 3 H, $NHCOCH_3$), 2.07 (s, 3 H, $NHCOCH_3$); $^{13}C$ NMR (75 MHz, $D_2O$): *δ* = 174.03, 173.79, 160.61, 100.58, 99.92, 86.79, 85.01, 80.48, 76.90, 73.63, 72.59, 70.11, 68.95, 66.40, 64.18, 60.97, 60.84, 59.20, 53.01, 52.63, 51.42, 37.60, 37.41, 22.05; ESI-MS: *m*/*z* = 645.2 $[M + Na]^+$.