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Synthesis of Demethylallosamidin, a Yeast Chitinase Inhibitor; Use of Disaccharide Glycosyl Donor Carrying Novel Neighboring Group

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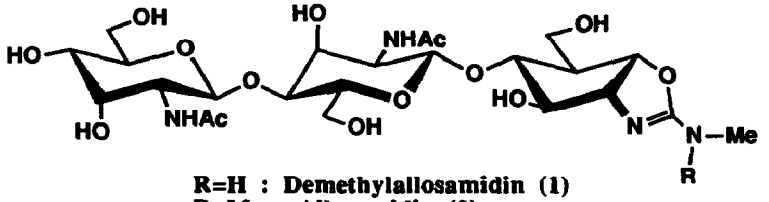
Abstract: *In the synthesis of novel pseudotrisaccharide called demethylallosamidin, a thioglycoside carrying the 2-acetamido group served as an efficient glycosyl donor through undergoing specific N,O-isopropylidenation at the 2- and 3-positions which prohibits oxazoline ring formation during the glycosidation reaction.*

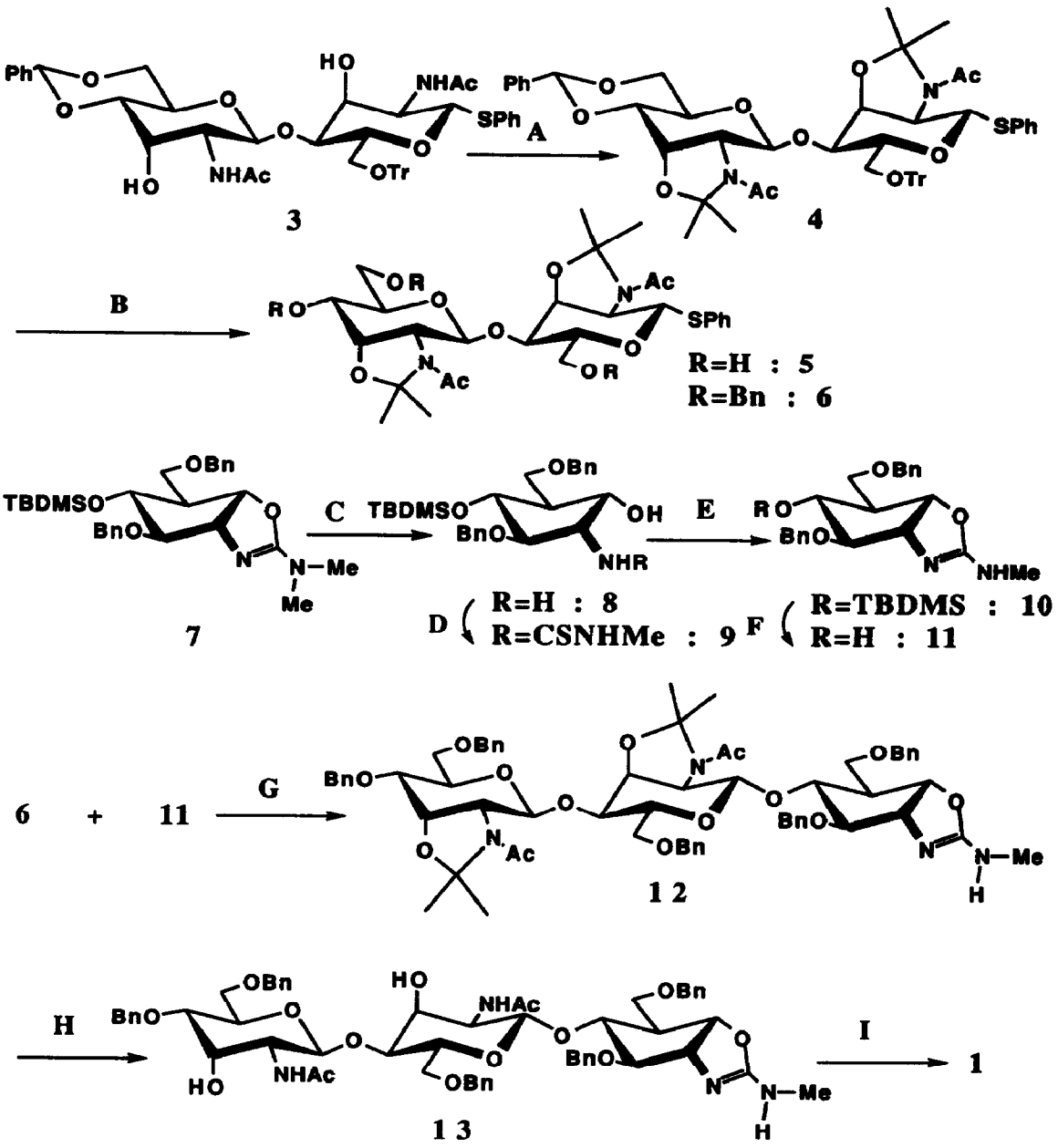
Demethylallosamidin (**1**) is a member of the allosamidin family produced by *Streptomyces* sp. but its producibility is much lower than that of allosamidin (**2**).[1] The only structural difference between **2** and **1** is whether extra methyl group is present or not, on the terminal methylamino group in the pseudotrisaccharide molecule. Although both **1** and **2** are powerful inhibitors of insect chitinase,[1] their inhibitory activities against yeast chitinase are quite different. Thus, **1** inhibited *Saccharomyces* chitinase 100 times as potent as **2** and was also effective for inhibition of chitinase of pathogenic yeast such as *Candida albicans*.[2]

Recently, we succeeded in a total synthesis of **2** by coupling a fully protected 2-deoxy-2-phthalimido-β-D-allopyranosyl-(1→4)-2-deoxy-2-phthalimido-D-allopyranosyl moiety with partially protected five-membered aminocyclitol named allosamizoline.[3] The glycosyl donor of disaccharide structure and the cyclitol acceptor were prepared from *N,N'*-diacetylchitobiose and D-glucosamine hydrochloride, respectively.



R=H : Demethylallosamidin (1)
R=Me : Allosamidin (2)

In this communication, we wish to describe the first total synthesis of **1**,[4] which involves employment of a novel type of glycosyl donor carrying an unusually protected amino group at the C-2 position and efficient conversion of allosamizoline derivative previously synthesized by us into a demethyl type of glycosyl acceptor. Phenyl thioglycoside derivative (**3**)[3] was also used as the precursor of glycosyl donor as well as the



Reagents: (A) Isopropenylmethylether, d-camphorsulfonic acid (cat.), acetone-CH_2Cl_2, rt, 3hr, quant. (B) i) 80% AcOH, rt, 3 days, ii) BnBr, NaH, n-Bu_4NI, DMF, 0℃, 81% (2 steps) (C) $NH_2NH_2 \cdot H_2O$, EtOH, 80℃, 8hr, 60% (D) CH_3NCS, DMF-EtOH, rt, 3hr, quant. (E) HgO (excess), THF, rt, 2days, 91% (F) 1M HCl-THF, 65℃, 6hr, 89% (G) N-iodosuccinimide (2.5 eq.), TfOH (cat.), MS 4Å, CH_2Cl_2, -18℃, 1.5hr, 60% (H) conc.HCl-MeOH (1:9), rt-40℃, 65% (I) H_2, 10% Pd/C, MeOH-AcOH-H_2O (5:1:1), 91%.

synthesis of **2**. In the case of **2**, acetamido groups were replaced with phthalimido groups before glycosidation reaction since acetamido group might interfere the glycosidation through thioglycoside activation by forming an oxazoline ring. If such undesired participation of the acetamide group could have been suppressed, its temporary replacement with the phthalimido group and later regeneration would have been unnecessary. This expectation was actually realized in the synthesis of **1**.

We found that the 2,3:2',3'-di-*N,O*-isopropylidene derivative of **3** could be prepared under acidic conditions without affecting the acid-labile benzylidene and trityl groups and the resulting compound **4** could undergo selective removal of these benzylidene and trityl groups under a little stronger acidic conditions. Thus, compound **3** was treated with isopropenyl methylether in the presence of d-camphorsulfonic acid, giving the diacetonide derivative **4**[5] in high yield. Selective hydrolysis of benzylidene and trityl groups was performed by the action of 80% acetic acid at room temperature for 3 days, giving triol **5**, which was benzylated to give **6**[5] in 81% yield. The acetamido group on C-2 of **6** would be unable to participate in the glycosidation reaction by forming an oxazoline ring because of the absence of a proton on the amido nitrogen and the rigid conformational situation surrounding the acetyl group.

On the other hand, the fully protected allosamizoline **7**[3] was heated in ethanol with hydrazine monohydrate[6] to cleave the oxazoline ring, giving an amino alcohol **8**. Reaction of **8** with methyl isothiocyanate in *N,N*-dimethylformamide-ethanol proceeded smoothly to afford thiourea derivative **9**[5] almost quantitatively. Upon treatment with mercuric oxide (yellow), the formation of an oxazoline ring took place through participation of the vicinal hydroxyl group[7], giving **10**[5] in 91% yield. The silyl group was removed from **10** with dil. HCl, giving the glycosyl acceptor **11**[5].

Glycosidation reaction between **6** and **11** was attempted by the Fraser-Reid's procedure[8] similar to the synthesis of **2** and found to be successful. Thus, **11** and 1.5 equimolar amount of **6** was treated in CH_2Cl_2 at -18℃ with *N*-iodosuccinimide and a catalytic amount of TfOH in the presence of molecular sieves 4Å, giving a fully protected demethylallosamidin derivative **12**[5] in 60% yield.[9] No α-isomer was detectable by TLC and NMR analyses; this was probably ascribable to the steric hindrance arising from the bulky *N,O*-isopropylidene group. It was quite interesting that the yield of the glycosidation between **6** and **11** was much higher than that of a similar glycosidation using the glycosyl donor with phthalimido group as reported[3] previously. Removal of *N,O*-isopropylidene group from **12** was achieved by careful hydrolysis with conc. HCl in methanol[10], giving **13**[5]. Finally, **13** was hydrogenated on Pd-C to remove the benzyl groups, giving the target compound **1**. The compound prepared was completely identical with the authentic natural sample in all physical and spectroscopic respects.

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4. Recently, a chemical conversion of **2** into **1** has been reported. M. Kinoshita, S. Sakuda, and Y. Yamada, *Biosci, Biotech. Biochem.*, **57**, 1699-1703 (1993).
5. All new compounds gave satisfactory results of elemental analyses. Values of $[a]_D$ and δ_H, δ_C were measured for the solution in $CHCl_3$ and $CDCl_3$, respectively, at 23° ±2°. **4**: $[\alpha]_D$ +5.8° (c 0.40); δ_H (400MHz): 4.67 (d, $J_{1',2'}$ 7.0 Hz, H-1'), 4.85 (d, $J_{1,2}$ 9.8 Hz, H-1). **6**: mp 142.5℃; $[\alpha]_D$ -17.3° (c 0.47); δ_H: 1.59, 1.61, 1.63, 1.70, 2.13, 2.20 (18H, each s), 3.73 (dd, $J_{4',5'}$ 11 Hz, $J_{3',4'}$ 3.7 Hz, H-4'), 3.83 (dd, $J_{1',2'}$ 7.9 Hz, $J_{2',3'}$ 4.0 Hz, H-2'), 3.88 (dd, $J_{1,2}$ 9.7 Hz, $J_{2,3}$ 4.0 Hz, H-2), 4.06 (dd, $J_{4,5}$ 10 Hz, $J_{3,4}$ 3.5 Hz, H-4), 4.24 (dd, H-3'), 4.60 (dd, H-3), 4.73 (H-1'), 4.76 (H-1); δ_C (100MHz): 86.9 (C-1), 103.9 (C-1'). **9**: $[\alpha]_D$ +12.5° (c 0.35); IR ν_{max}(film) 3300, 1560, 1252 cm^{-1}. **10**: $[\alpha]_D$ -7.1° (c 1.0); ν 1668 cm^{-1}. **11**: $[\alpha]_D$ -14.6° (c 0.51); ν 3345, 1662 cm^{-1}; δ_H: 2.26 (m, H-5), 2.85 (s, NMe), 3.63 (dd, $J_{6a,6b}$ 9.5 Hz, $J_{6a,5}$ 6.1 Hz, H-6a), 3.67 (dd, $J_{6b,5}$ 5.5Hz, H-6b), 3.76 (dd, $J_{3,4}$ 7.0 Hz, $J_{2,3}$ 4.6 Hz, H-3), 3.93 (dd, $J_{4,5}$ 9.5 Hz, H-4), 4.23 (dd, $J_{1,2}$ 8.6 Hz, H-2), 4.65 (dd, $J_{1,5}$ 6.4 Hz, H-1). **12**: $[\alpha]_D$ +1.0° (c 0.8); δ_H: 2.08, 2.11 (6H, each s, NAc), 2.41 (m, H-5), 2.82 (s, NMe), 3.68 (dd, $J_{1',2'}$ 7.8 Hz, $J_{2',3'}$ 3.9 Hz, H-2'), 3.73 (dd, $J_{4'',5''}$ 9.8 Hz, $J_{3'',4''}$ 3.4 Hz, H-4"), 3.82 (dd, $J_{1'',2''}$ 7.8 Hz, $J_{2'',3''}$ 3.9 Hz, H-2"), 4.03 (dd, $J_{4',5'}$ 9.8 Hz, $J_{3',4'}$ 3.9 Hz, H-4'), 4.04 (dd, $J_{3,4}$ 4.9 Hz, $J_{2,3}$ 2.4 Hz, H-3), 4.12 (dd, $J_{4,5}$ 4.4 Hz, H-4), 4.22 (dd, H-3"), 4.32 (dd, $J_{1,2}$ 8.3 Hz, H-2), 4.53 (dd, H-3'), 4.64 (H-1'), 4.69 (H-1"), 4.77 (dd, $J_{1,5}$ 3.5 Hz, H-1); δ_C: 104.0 (C-1"), 101.0 (C-1'). **13**: $[\alpha]_D$ -35.9° (c 0.15); δ_H: 1.76, 1.83 (6H, each s, NAc), 4.63 (d, $J_{1',2'}$ 8.6 Hz, H-1'), 4.70 (d, $J_{1'',2''}$ 7.6 Hz, H-1"), 4.77 (dd, $J_{1,2}$ 8.2 Hz, $J_{1,5}$ 5.0 Hz, H-1); δ_C: 99.9, 100 (C-1', C-1").
6. J-L. Maloisel, A. Vasella, B. M. Trost, and D. L. van Vranken, *Heiv. Chim. Acta*, **75**, 1515-1526 (1992).
7. S. Ogawa and C. Uchida, *Chem. Lett.*, 173-176 (1993).
8. P. Konradsson, U. E. Udodong, and B. Fraser-Reid, *Tetrahedron Lett.*, **31**, 4313-4316 (1990).
9. Other products were mainly degradation ones derived from glycosyl donor **6**.
10. In addition to **13**, monoisopropylidene derivative was also obtained in 30-35% yield. The latter was again subjected to the same condition to convert to **13**.

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