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TOTAL SYNTHESIS OF (-)-ALLOSAMIDIN, AN INSECT CHITINASE INHIBITOR, EMPLOYING CHITIN AS A KEY STARTING MATERIAL

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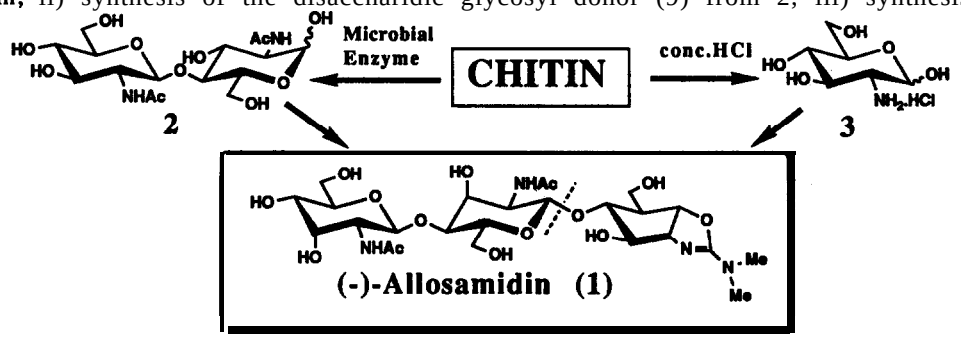
Abstmct: (-)-Allosamidin (1), a novel insect chitinase inhibitor. was stereoselectively synthesisedfrom di- and monosaccharidic constituents of chitin, N, N'-diacetylchitobiose (2) and D-glucosamine (3).

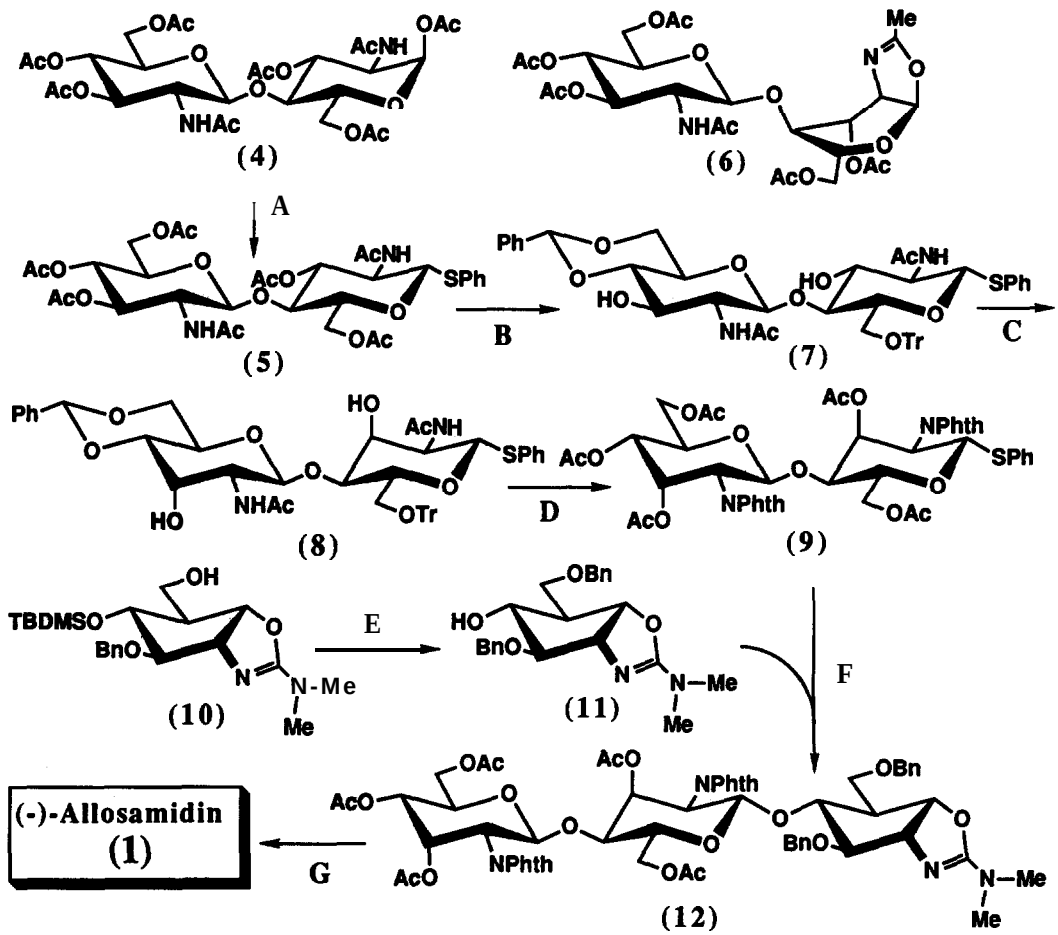
Our recent studies have mainly focused on the preparation of simple oiigosaccharides by limited degradation of parent polysaccharides and their use as key starting compounds for the synthesis of various bioactive and/or biologically important substances with saccharidic structure. [1] These procedures transfer the internal glycosidic linkages in the starting oligosaccharides into the target molecules, saving many laborious glycosidation reactions. Along this line, we now report a total synthesis of (-)-Allosamidin **(1),** an insect chitinase inhibitor, employing disaccharidic and monosaccharidic constituents of **chitin** as key starting materials for preparation of two synthons needed. The monosaccharidic starting compound was used as a **chiral** pool for one synthon. These synthetic processes are quite novel, resembling the biosynthetic pathway2 of **1** and show definite difference from the ones appearing in the recent papers3 by two other groups on the synthesis of **1.**

Compound **1** was isolated from the mycellium of ***Streptomyces*** sp. no. 1713 and elucidated to have an unique pseudotrisaccharide structure consisting of a **2-acetamido-2-deoxy-β-D-allopyranosyl-(1→4)-2-acetamido-2-deoxy-β-D-allopyranosyl** moiety and a novel five membered aminocyclitol derivative termed **(-)-allosamizoline.**[4] Our synthetic strategy involved: **i)** establishment of large scale preparation of ***N,N'*-diacetylchitobiose** (2) from **chitin;** ii) synthesis of the disaccharidic glycosyl donor (9) from 2; iii) synthesis of



aminocyclitol glycosyl acceptor (11) from D-glucosamine ·HCl (3); iv) coupling of 9 and 11 and subsequent deprotections.

Although we had already reported the restricted degradation of chitin into 2 through a fermentation process[5], it was still unsatisfactory for large scale preparation of 2. Such situation prompted us to examine enzymatic degradation of chitin. Incubation of colloidal chitin with chitinase (EC 3.2.1.14, St. grissus, SIGMA) at 40°C around pH 6 for 7-10days under vigorous stirring and acetylation of the products after removal of the unreacted colloidal chitin by filtration gave hundreds gram of crystalline a-peracetate (4) of 2.6



Reagents : (A) PhSTMS (4eq.), ZnI_2 (6~8eq.), dichloroethane, 50°C, 87%, (B) i) NaOMe, MeOH-CH_2Cl_2, ii) $PhCH(OMe)_2$, p-TsOH, DMF. iii) TrCl, pyridine-DMF, 71% (3steps) (C) i) MsCl, pyridine, 92%. ii) NaOAc, H_2O, 2-methoxyethanol, 825, (D) i) 80% AcOH, ii) 1M NaOH, iii) Phthalic anhydride, Et_3N, MeOH, iv) Ac_2O, pyridine, 41% (4steps) (E) i) benzyl 2,2,2-trichloroacetimidate, TfOH, CH_2Cl_2-hexane, ii) 1M HCl, THF, 61% (2steps). (F) N-iodosuccinimide, TfOH, MS 4A, CH_2Cl_2, 0°C, 40%. (G) i) aq. CH_3NH_2, ethanol, ii) Ac_2O, MeOH, ii) H_2, 10% Pd-C, AcOH-MeOH-H_2O, 66% (3steps).

Synthesis of 9 from 4 proceeded through such three stages as phenylthioglycoside formation → the configurational inversion at C-3 and C-3' utilizing participation of the neighboring acetamido groups → replacement of N-protection with phthaloyl groups.

The above reaction sequence seemed to contain some problem because most of usual aminosugar thioglycosidations had been conducted using N-phthaloyl derivatives,7 but not N-acetyl ones.8 We succeeded in developing an efficient way to change 4 into the β-thioglycoside derivative 5. Thus, 4 was treated with PhSTMS (4eq.) in the presence of ZnI_2 (6~8eq.)[9] at 50°C, giving 5[10], mp 300°C; ^{1}H-NMR (500MHz, CDC13) δ: 4.58 (d, J=8.5Hz, H-l'), 4.67 (d, J=10Hz, H-l), in 87% yield. Apparently, this reaction must have proceeded via an oxazoline intermediate 65 because it was detectable on t. 1. c. in the course of the reaction and a similar treatment with PhSTMS-ZnI_2 (4eq.) of 6 separately derived from 4 resulted in 5 in good yield. Use of TMSOTf[7] instead of ZnI_2 resulted in a lower yield of 5. After Zemplen de-0-acetylation of 5, the resulting pentaol was subjected to successive benzylidenation ($PhCH(OMe)_2$, p-TsOH) and tritylation (TrCl, pyridine-DMP) to give 7, mp 223°C; $[\alpha]_D^{23}$ -75° (c=0.4, CHCl3); ^{1}H-NMR δ: 3.65 (t, J=10Hz, H-3'). 3.73 (t, J=9.5Hz, H-3). The two hydroxyl groups of 7 were sulfonylated by treatment with MsCl in pyridine and the resulted dimesylate was solvolyzed in the presence of NaOAc in aq. 2-methoxyethanol, giving 8 with &o-configuration, mp 169°C; $[\alpha]_D^{23}$ -60°; ^{1}H-NMR δ: 4.03 (t, J=3.0Hz, H-3'), 4.20 (t, J=3.0Hz, H-3). in good yield. The &o-configuration of 8 was determined by these ^{1}H-NMR spectral data. The lower chemical shift and smaller coupling constants of two protons at C-3 and C-3' positions of 8 than those of 7 indicate the presence of axially oriented hydroxyl groups. In order to prepare for the stereoselective glycosidation reaction expected, N-acetyl groups were replaced with phthaloyl groups. After removal of the O-protecting group of 8 under acidic conditions, N-acetyl groups were hydrolyzed under basic conditions and the resulted compound was successively treated with phthalic anhydride in methanol and Ac_2O in pyridine, giving the synthon 9, $[\alpha]_D^{23}$ +11°, in 41% overall yield.

Glycosyl acceptor 11 was derived from the cyclitol derivative 10. which used to be the final intermediate in the course of our previous synthesis of allosamizoline.[11] After unsuccessful attempts for benzylations under conventional basic conditions, 10 underwent smooth 0-benzylation by treatment with benzyl 2, 2, 2-trichloroacetimidate in acidic condition (TfOH, CH_2Cl_2-hexane),[12] giving a fully protected compound, from which ı-butyldimethylsilyl group was removed with dil. HCl to afford 11, mp 119°C (lit[3a]; 120°C) in 61% yield.

Coupling between the glycosyl donor 9 and the acceptor 11 was conducted by the Fraser-Reid's procedure.[13] Thus, 9 and 11 (3.0 mole eq.) were treated with *N*-iodo-succinimide (2.5 eq.) and TfOH in the presence of MS 4A in CH_2Cl_2 at 0°C, giving fully protected allosamidin derivative 12, ^{1}H-NMR δ: 2.28 (m, H-5), 2.66 (s, $-NMe_2$), 4.93 (dd, J=10, 3.0Hz, H-4"), 5.53 (t, J=3.0Hz, H-3"), 5.76 (t, J=3.0Hz, H-3'), 5.98 (d, J=8.5Hz, H-l'), 6.04 (d, J=8.6Hz, H-l"), in 40% yield.14 Finally, removal of all protecting groups from 12 was performed in a continuous manner. After simultaneous hydrolysis of *N*-phthaloyl and 0-acetyl groups had been conducted under mild conditions by the action of

CH_3NH_2,[15] the resulted compound successively underwent N-acetylation (Ac_2O, MeOH) and hydrogenolysis of *O*-benzyl groups (H_2, 10% Pd-C, AcOH-MeOH-H_2O), giving **1**, mp. >220°C (dec); $[\alpha]_D^{21}$ -23° (0.1M AcOH), lit.4 mp.>228°C (dec); $[\alpha]_D^{22}$ -24.8° (0.1M AcOH). ^1H- and ^{13}C-NMR spectra were identical with those of natural (-)-allosamidin (1) in all respects.

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