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ENANTIOSPECIFIC TOTAL SYNTHESIS OF (-)-ALLOSAMIZOLINE, AN AMINOCYCLITOL MOIETY OF THE INSECT CHITINASE INHIBITOR ALLOSAMIDIN

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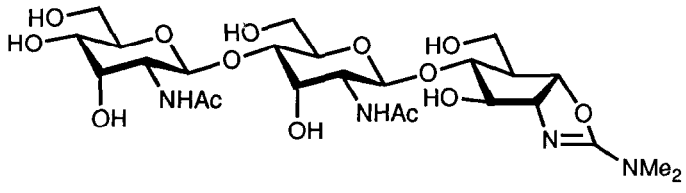
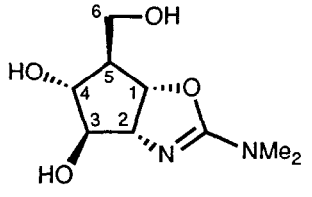
Summary: Total synthesis of (-)-allosamizoline (**2**), an aminocyclitol moiety of the insect chitinase inhibitor allosamidin (**1**) has been enantiospecifically synthesized from D-glucosamine by using an intramolecular cycloaddition of the nitrile oxide to an olefin as a key step.

Allosamidin (**1**), isolated[1] from the mycelial extract of *Streptomyces* sp. no. 1713, exhibits the inhibitory activity against the chitinases of the silkworm, *Bombyx mori, in vitro,* and prevents its larval ecdysis *in vivo.* It has been thought that the chitinase inhibitor would be the good models for insect growth regulators.[2] Allosamidin (**1**) consists of 2 equiv. of N-acetyl-D-allosamine, the first example in nature, and 1 equiv. of a new aminocyclitol **2**, named allosamizoline.[3] The relative configuration of allosamizoline (**2**) was initially suggested to be the 3,4-cis diol[3a] and later revised to the 3,4-trans,[3b] and finally the absolute configuration was elucidated by the exciton chirality method using its 3,4-bis[*p*-(dimethylamino)benzoyl]-6-trityl derivative.[3c] We wish to describe here the enantiospecific total synthesis[4] of (-)-allosamizoline (**2**) by using an intramolecular cycloaddition of the nitrile oxide to an olefin as a key step. By the similar methodology, we have already succeeded in the total syntheses of glycosidase inhibitors, cyclophellitols,[5] which are the highly oxygenated cyclohexane compounds.[6]

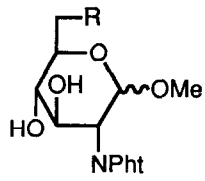


1: Allosamidin

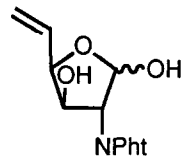


2: Allosamizoline

Our synthesis began with D-glucosamine, which might be the biosynthetic precursor of **2**.[3c] 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranose, readily prepared from D-glucosamine hydrochloride by the Lemieux procedure,[7] was treated with 1%



3: R = OH
4: R = I



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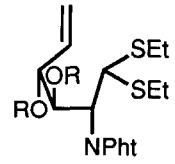
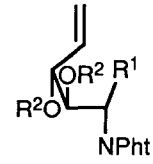
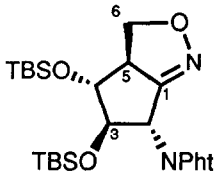


6: R = H
7: R = TBS



8: R^1 = CHO, R^2 = TBS
9: R^1 = CH=NOH, R^2 = TBS



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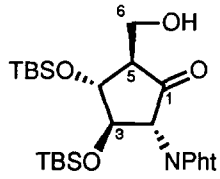

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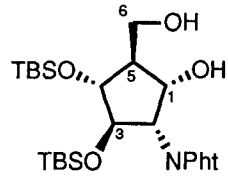

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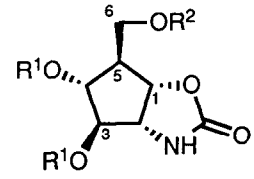

13: R^1 = TBS, R^2 = H
14: R^1 = R^2 = Ac

HCl-MeOH at 60°C for 5 d to afford the α and β mixture (α : β = 1 : 3.5) of methyl glycoside **3**[8] in 60 % yield from D-glucosamine. Iodination[9] of **3** with iodine, triphenylphosphine, and imidazole in CH_2Cl_2 at 35°C for 4 d gave the iodide **4**[10] in 90% yield (mp 204 ~ 205°C). Reductive β-elimination of **4** by active zinc[11] in THF at 25°C for 1.5 h afforded the 5-enofuranose **5** concomitant with the reductively dehalogenated C-6 product. Treatment of this mixture with ethanthiol and conc. HCl (0°C, 18 h) gave the dithioacetal **6**[10] [61 % from **4**; $[\alpha]_D$ -11° (c 0.77, $CHCl_3$)] which was silylated with TBSOTf and 2,6-lutidine in CH_2Cl_2 (0°C, 2 h) to give the disilylether **7**[10] [90 %; $[\alpha]_D$ -56° (c 1.04, $CHCl_3$)]. After dethioacetalization ($HgCl_2$-$CaCO_3$, 80 % aq. acetone, 25°C, 12 h) of **7**, the resulting aldehyde **8** was treated with NH_2OH•HCl in pyridine at 25°C for 18 h to afford the oxime **9** (81 % from **7**). Intramolecular cycloaddition[5] of **9** was best realized by using 0.7 M aq. NaOCl in CH_2Cl_2 at 0°C for 18 h to produce the isoxazoline **10**[10] as a single product [91 %; mp 125.5 ~ 126.5°C; $[\alpha]_D$ -6° (c 0.99, $CHCl_3$)]. The stereochemistry was assumed considering the results of an intramolecular cycloaddition of glucose-derived nitron to an olefin[6] and ultimately secured by conversion into **2**.

Isoxazoline opening was a troublesome step. Of a variety of conditions including H_2/Raney Ni-W4/AcOH/aq. dioxane[5] and H_2/Raney Ni-W4/$B(OH)_3$/aq. dioxane,[12] ozonolytic cleavage (O_3/O_2, 10 : 1 CH_2Cl_2-MeOH, -78 ~ -30°C, 24 h)[13] of **10** furnished the β-hydroxy ketone **11**[10] [60 % yield based on the reacted **10**; mp 121.0 ~ 122.5°C; $[\alpha]_D$ -51° (c 0.53, $CHCl_3$)]. Hydroxyl-directed reduction of **11** with $Zn(BH_4)_2$ in 1 : 1 THF-ether (0°C, 3 h) afforded a single diol **12**[10] in quantitative yield [mp 102 ~ 103°C; $[\alpha]_D$ +4° (c 0 64, $CHCl_3$)]. The stereochemistry of this diol **12** was confirmed by its transformation to the cyclic carbamate **13**[10] [60 % overall yield; mp 192 ~ 193°C; $[\alpha]_D$ -7° (c 0.39, $CHCl_3$)] by de-N-phthaloylation (NH_2NH_2•H_2O, 95 % aq. EtOH, 70°C, 4 h)

and benzyloxycarbonylation (BnOCOCl, Na_2CO_3, 1 : 2 H_2O-CH_2Cl_2, 0°C, 1.5 h) followed by base treatment (NaH, THF, 25°C, 4 h). Desilylation (1% HCl-MeOH, 25°C, 2.5 h) of **13** followed by acetylation (Ac_2O, pyridine, 25°C, 18 h) gave the triacetate **14**[10] in quantitative yield [$[\alpha]_D$ -25° (c 0.41, $CHCl_3$)]. This triacetate **14** was treated with 4 equiv of MeOTf in CH_2Cl_2[4a] at 25°C for 5.5 h and the intermediary iminomethylether was treated with Me_2N•HCl (TEA, CH_2Cl_2, 25°C, 2 h) in one pot to produce the allosamizoline triacetate. Finally, this was deacetylated with 1M aq. HCl at 50°C for 4.5 h to give (-)-allosamizoline hydrochloride (**2**) in 80 % yield from **14**. The ^1H and ^{13}C NMR spectra and the optical rotation of the synthetic **2** were identical with the authentic data.[3b] Synthetic studies toward the total synthesis of allosamidin (**1**) are now in progress.

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10) All compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were measured using a 0.5 dm tube at 25°C. Significant ^{1}H NMR spectral data (270 MHz, $CDCl_3$, δ: TMS = 0 or $CHCl_3$ = 7.26) are the following. **4**: δ (TMS = 0) 3.36 (0.67H, s, α-OMe), 3.47 (2.33H, s, β-OMe), 4.90 (0.22H, d, α-H-1, $J_{1,2}$ = 3.6 Hz), 5.17 (0.78H, d, β-H-1, $J_{1,2}$ = 8.4 Hz). **6**: δ (TMS = 0) 1.11 and 1.33 (each 3H, each t, 2xSCH$_2$*Me*, J = 7.6 Hz), 4.65 (1H, d, H-1, $J_{1,2}$ = 11.8 Hz), 5.24 (1H, br d, H-6cis, $J_{5,6}$ = 10.2 Hz), 5.28 (1H, br d, H-6trans, $J_{5,6}$ = 17.0 Hz), 5.85 (1H, ddd, H-5, $J_{4,5}$ = 6.4 Hz). **7**: δ ($CHCl_3$ = 7.26) 0.07, 0.13, 0.14, and 0 21 (each 3H, each s, 4xSiMe), 0.91 and 1.02 (each 9H, each s, 2x*t*-Bu), 4.64 (1H, ddd, H-6cis, $J_{5,6}$ = 11.4 Hz, J_{gem} = 2.0 Hz), 4.93 (1H, d, H-1, $J_{1,2}$ = 11.0 Hz), 5.12 (1H, ddd, H-6trans, $J_{5,6}$ = 17.8 Hz), 5.89 (1H, ddd, H-5, $J_{4,5}$ = 3.0 Hz). **10**: δ ($CHCl_3$ = 7.26) 3.91 (1H, dd, H-4, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 7.2 Hz), 3.99 (1H, dd, H-6, $J_{5,6}$ = 13.2 Hz, J_{gem} = 7.8 Hz), 4.16 (1H, dddd, H-5, $J_{5,6'}$ = 7.8 Hz, $J_{2,5}$ = 2.0 Hz), 4.69 (1H, dd, H-3, $J_{2,3}$ = 8.0 Hz), 4.78 (1H, dd, H-6'), 5.02 (1H, dd, H-2). **11**: δ ($CHCl_3$ = 7.26) 1.79 (1H, dd, OH, $J_{6,OH}$ = 4 Hz, $J_{6',OH}$ = 6.0 Hz), 2.64 (1H, ddd, H-5, $J_{4,5}$ = 10 Hz, $J_{5,6}$ = 4 Hz, $J_{5,6'}$ = 3 Hz), 4.56 (1H, d, H-2, $J_{2,3}$ = 10 Hz). **12**: δ ($CHCl_3$ = 7.26) 1.85 (1H, dd, 6-OH, J = 4 and 6 Hz), 2.39 (1H, m, H-5), 2 89 (1H, d, 1-OH, J = 10 Hz), 4.22 (1H, ddd, H-1, $J_{1,2}$ = 8 Hz, $J_{1,5}$ = 6 Hz), 4.51 (1H, dd, H-2, $J_{2,3}$ = 6 Hz). **13**: δ ($CHCl_3$ = 7.26) 2.49 (1H, br dd, 6-OH), 4.01 (1H, dd, H-2, $J_{1,2}$ = 2 Hz, $J_{2,3}$ = 8 Hz), 5.18 (1H, dd, H-1, $J_{1,5}$ = 8 Hz), 5.35 (1H, br s, NH). **14**: δ (TMS = 0) 2.10, 2.11, and 2.13 (each 3H, each s, 3xOAc), 2.63 (1H, dddd, H-5), 3.95 (1H, dd, H-2, $J_{1,2}$ = 9.2 Hz, $J_{2,3}$ = 4.2 Hz), 4.22 (2H, d, 2xH-6, $J_{5,6}$ = $J_{5,6'}$ = 5.0 Hz), 4.76 (1H, dd, H-3, $J_{3,4}$ = 7.8 Hz), 4.87 (1H, dd, H-1, $J_{1,5}$ = 6.0 Hz), 5.25 (1H, dd, H-4, $J_{4,5}$ = 10.0 Hz), 5.77 (1H, br s, NH). **2**: δ (D_2O, DOH = 4.80) 2.43 (1H, m, H-5), 3.09 and 3.11 (each 3H, each s, NMe$_2$), 3.74 (1H, dd, H-6, $J_{5,6}$ = 7 Hz, J_{gem} = 12 Hz), 3.83 (1H, dd, H-4, $J_{3,4}$ = 7 Hz, $J_{4,5}$ = 8 Hz), 3.90 (1H, dd, H-6', $J_{5,6'}$ = 5 Hz), 4.34 (1H, dd, H-2, $J_{1,2}$ = 9 Hz), 5.37 (1H, dd, H-1, $J_{1,5}$ = 5 Hz). ^{13}C NMR spectrum (67.5 MHz, D_2O, dioxane = 67.4) of **2**: δ 38.1, 38.3, 52.1, 60.1, 64.3, 75.6, 82.4, 87.4, 161.4.

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