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STEREOCONTROLLED SYNTHESIS OF (-)-ALLOSAMIZOLINE USING D-GLUCOSAMINE AS A CHIRAL TEMPLATE

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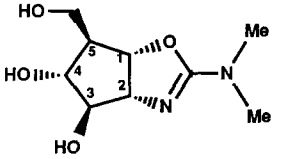
Key Words: (-)-Allosamizoline; insect chitinase inhibitor; allosamidin; D-glucosamine; ring contraction reaction

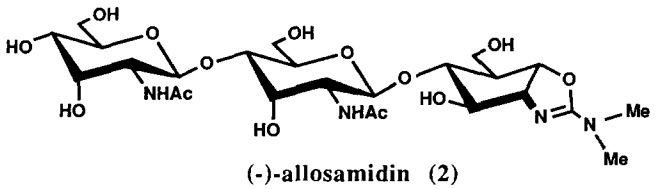
Abstract: *(-)-Allosamizoline (1), a core component of novel insect chitinase inhibitor, allosamidin (2), was stereoselectively synthesized from D-glucosamine (3), using an efficient ring contraction reaction as a key step.*

In 1986, Sakuda et al.[1] isolated a novel insect chitinase inhibitor named (-)-allosamidin from the mycellium of *Streptomyces* sp. no. 1713 and elucidated its structure by extensive spectroscopic analyses and degradation studies. The proposed pseudotrisaccharidic structure consists of a unique aminocyclitol moiety termed (-)-allosamizoline and (1→4)-linked disaccharide made up of a couple of *N*-acetyl-β-D-allosamine residues. The intriguing structure and biological activity of allosamidin have attracted many attentions of chemical and biological researchers.[2]

Allosamizoline is a highly oxygenated cyclopentanoid possessing a peculiar 2-dimethyl amino oxazoline ring. Initially, the relative stereochemistry at C-3 and C-4 of allosamizoline was assigned as cis relationship but that assignment was later revised [3] as depicted in the molecular structure **1**; i.e., trans relationship. Recently, Trost et al.[4] reported the synthesis of (±)-allosamizoline, which established the relative stereochemistry concerning its cyclopentane ring moiety. The absolute configuration of (-)-allosamizoline was elucidated as **1** by the exciton chirality method using its benzoate derivatives.[5] In connection with our studies directed towards total synthesis of (-)-allosamidin (**2**), we report herein a stereocontrolled synthesis of (-)-allosamizoline (**1**) from D-glucosamine hydrochloride (**3**) as a chiral template, which finally determines the absolute configuration of **1**.

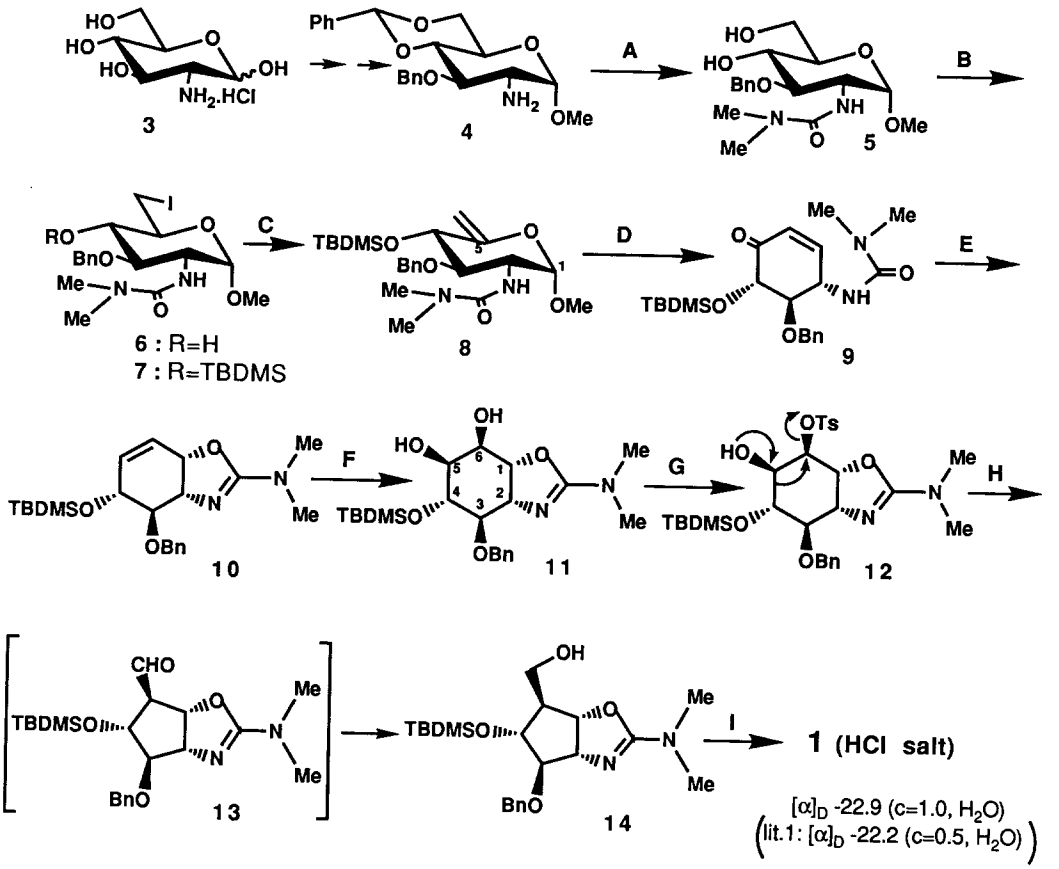


(-)-allosamizoline (1)



(-)-allosamidin (2)

The strategy of our synthesis of **1** involves: 1) use of the chiralities of C-2, C-3, and C-4 of **3**, 2) stereoselective formation of two more chiral centers needed, 3) construction of the necessary ring system through such a sequence as pyranose→cyclohexane→cyclopentane. Methyl 2-amino-4,6-*O*-benzylidene-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**4**) [6], readily accessible from **3**, was converted into *N*,*N*-dimethylurea derivative, which underwent hydrolysis to give diol **5**, mp 99-101°; $[\alpha]_D^{21}$ +137° (c = 1.0, $CHCl_3$).[7] Selective iodination



Reagents: (A) 1) Me_2NCOCl, Et_3N, CH_2Cl_2, 2) aq. AcOH (91% from **4**); (B) 1) *N*-iodosuccinimide, triphenylphosphine, THF, 2) TBDMSOTf, 2,6-lutidine, CH_2Cl_2 (71% from **5**); (C) *t*-BuOK, THF, 96%; (D) 1) $HgSO_4$, 5mM H_2SO_4-acetone, 2) MsCl, pyridine (65% from **8**); (E) 1) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 2) Ms_2O, Et_3N, CH_2Cl_2 (86% from **9**); (F) OsO_4, $Me_3N \rightarrow O$, *t*-BuOH-H_2O, 92%; (G) *p*-TsCl, DMAP, pyridine-CH_2Cl_2, 86% (91% based on **11** consumed); (H) L-Selectride®, THF, 65°, 86%; (I) 1) 1M HCl, aq. THF, 2) H_2, 10% Pd-C, 0.1M HCl-H_2O (90% from **14**)

of **5** was achieved by treatment with *N*-iodosuccinimide-triphenylphosphine [8] in THF, giving iodide **6**, $[\alpha]_D^{21}$ +92° (c=1.0, $CHCl_3$). The secondary hydroxyl group was protected as *t*-butyldimethylsilyl (TBDMS) ether using *t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) [9] to give **7**, mp 117-118°; $[\alpha]_D^{21}$ +121° (c=1.0, $CHCl_3$), in 71% overall yield. Dehydroiodination of compound **7** with *t*-BuOK gave a labile enol ether **8**, mp 90-91°; $[\alpha]_D^{21}$ +129° (c=1.0, $CHCl_3$); IR ν_{max}(KBr)cm^{-1}: 1660, 1625, 1520 ; ^{1}H-NMR ($CDCl_3$, 500MHz) δ: 4.71 (d, J=1.5Hz, H-6), 4.75 (d, J=3.4Hz, H-1), 4.85 (d, J=1.5Hz, H-6'), in 96% yield. For conversion of the ring system from pyranose to cyclohexane, the modified Ferrier reaction[10] was employed. Thus, **8** was treated with $HgSO_4$ (0.1 eq.) in 5mM H_2SO_4-dioxane at 60° to provide a crude ketol, which was, without purification, submitted to β-elimination reaction with MsCl-pyridine to afford enone **9**, mp 112-113°; $[\alpha]_D^{21}$ +191° (c=1.0, $CHCl_3$); IR ν_{max}(KBr)cm^{-1}: 1690, 1623, 1520; ^{1}H-NMR ($CDCl_3$) δ: 5.99 (dd, J=10, 2.2Hz, H-3), 6.80 (dd, J=10, 2.7Hz, H-2). In order to construct the dimethylamino oxazoline ring with simultaneous formation of a new chiral center, the enone **9** was stereoselectively reduced with $NaBH_4$-$CeCl_3 \cdot 7H_2O$ in MeOH and the resulting allylic alcohol was treated with methanesulfonic anhydride-triethylamine in CH_2Cl_2 [11], giving the desired oxazoline derivative **10**, $[\alpha]_D^{21}$ +25° (c=1.0, $CHCl_3$); IR ν_{max}(film) cm^{-1}: 1648, in 86% yield. When **10** was oxidized with OsO_4 in the presence of $Me_3N \rightarrow O$ in aq. *t*-BuOH, the reagent attacked the C-C double bond exclusively from the convex face, giving the *vic*-diol **11**, mp 183-184°; $[\alpha]_D^{21}$ +19° (c=1.0, $CHCl_3$); IR ν_{max} (KBr)cm^{-1}: 3430, 3080, 1638; ^{1}H-NMR($CDCl_3$)δ: 2.90 (s, $(CH_3)_2$-N), 3.47 (dd, J=6.4, 5.9Hz, H-3), 3.73 (dd, J=4.6, 2.9Hz, H-5), 3.89 (dd, J=5.9, 4.6Hz, H-4), 4.06 (dd, J=5.4, 2.9Hz, H-6), 4.22 (dd, J=8.5, 6.4Hz, H-2), 4.62 (dd, J=8.5, 5.4Hz, H-1).

Monosulfonylation of the hydroxyl group of **11** at the 6-position was needed to prepare the ring contraction reaction substrate examined in the next step. It was found that tosylation of **11** with *p*-TsCl in pyridine-CH_2Cl_2 proceeded rather sluggishly to give monotosyl derivative in 86% yield (91% based on **11** consumed). Very fortunately, the product was identified by ^{1}H-NMR analyses to be the desired 6-tosylate **12**, mp 176-177°; $[\alpha]_D^{21}$ -30° (c=1.0, $CHCl_3$); IR ν_{max}(KBr)cm^{-1}: 3050, 1645, 1340, 1165; ^{1}H-NMR($CDCl_3$)δ: 2.42 (s, CH_3-Ar), 2.79 (s, $(CH_3)_2$-N), 3.71 (dd, J=4.6, 4.3Hz, H-3), 3.87 (m, H-5), 3.97 (dd, J=4.6, 3.7Hz, H-4), 4.34 (dd, J=8.6, 4.3Hz, H-2), 4.78 (dd, J=8.6, 7.3Hz, H-1), 4.90 (dd, J=7.3, 2.8Hz, H-6). Ring contraction of **12** [12] in basic media was regarded as the key step in the synthesis of **1**. As the expected rearrangement product **13** bearing an aldehyde group was assumed to lack stability in basic media, an appropriate basic reducing agent [13] was searched for ring contraction succeeded by immediate reduction of the aldehyde. As the result, L-Selectride® was selected among the several reagents tested. Thus, treatment of **12** with L-Selectride® in THF at 65° resulted in smooth reaction, giving the desired cyclopentanemethanol derivative **14**, mp 113.5-114°; $[\alpha]_D^{21}$ -3° (c=1.0, $CHCl_3$); IR ν_{max}(KBr)cm^{-1}:3350, 1640; ^{1}H-NMR ($CDCl_3$)δ: 2.35 (m, J=5.5, 4.6, 4.3, 3.2Hz, H-5),

2.90 (s, $(CH_3)_2$-N), 3.75 (dd, J=11, 4.3Hz, H-6), 3.79 (dd, J=11, 5.5Hz, H-6'), 3.80 (dd, J=4.0, 2.1Hz, H-3), 3.98 (dd, J=4.6, 4.0Hz, H-4), 4.41 (dd, J=8.2, 2.1Hz, H-2), 4.96 (dd, J=8.2, 3.2Hz, H-1), in 86% yield. Probably, the success of this ring contraction reaction is due to the fact that the fused system of two five membered rings like **14** is more stable than that of the six and five membered rings like **12**.

Finally, the protective groups of **14** were removed by successive treatments with 1M HCl in aq.THF and H_2-10% Pd on carbon in 0.1M HCl-H_2O to give **1** as monohydrochloride in 90% overall yield. Spectral and physical properties including the sign of the specific rotation of the compound prepared were identical in all respects with those reported [1,3] for the natural specimen. In conclusion, the first synthesis of chiral allosamizoline (**1**) was achieved, which gave an unambiguous evidence for its absolute configuration proposed.

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