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A Concise and Efficient Synthesis of (–)-Allosamizoline

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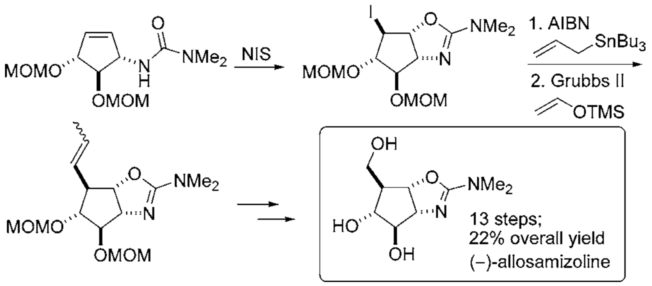
ABSTRACT

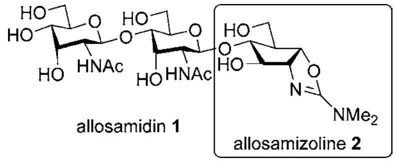


A regio- and stereocontrolled total synthesis of (–)-allosamizoline is described. The key steps for this synthesis are ring-closing metathesis to form the cyclopentene core, halocyclization to afford the oxazoline ring, and finally stereoselective alkene radical addition followed by an alkene isomerization reaction to install the hydroxymethyl group. (–)-Allosamizoline was prepared in a total of 13 steps and 22% overall yield.

The polysaccharide chitin,[1] a distinctive element of insects and fungi, is the main structural component of insect exoskeletons[2] and fungal primary cell walls.[3] As chitinase is involved in the biological manipulation of chitin, compounds that inhibit chitinases have been shown to act against both insects and fungi and could be of great agrochemical significance.

Isolated by Sakuda et al.[4,5] in 1987 from mycelial extracts of *Streptomyces* sp. No. 1713, allosamidin **1** (Figure 1) inhibits all characterized family 18 chitinases.[6]

The hydrolysis of allosamidin **1** has revealed that the β-(1,4)-linked pseudotrisaccharide structure consists of two units of *N*-acetyl-D-allosamine and an aglycon unit, named allosamizoline **2** (Figure 1). A published crystal structure of allosamidin **1** bound to hevamine, a plant chitinase/lysozyme, indicated that the aglycon portion was held by hydrogen bonding to amino acids at the center of the active site.[7]



allosamidin **1**

allosamizoline **2**

Figure 1. Allosamidin and allosamizoline.

Initial tests showed that allosamidin **1** inhibited the chitinases of the silkworm, *Bombyx mori*, in vitro and prevented its larval ecdysis in vivo; these data suggest that the compound acts as a chitinase inhibitor in vivo.[5] The inhibition activity of **1** toward chitinase [$ID_{50} = 0.386$ μmol][8] coupled with the chemically interesting structure

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[6] Rao, F. V.; Houston, D. R.; Boot, R. G.; Aerts, J. M. F. G.; Sakuda, S.; Van Aalten, D. M. F. *J. Biol. Chem.* **2003**, *278* (22), 20110.

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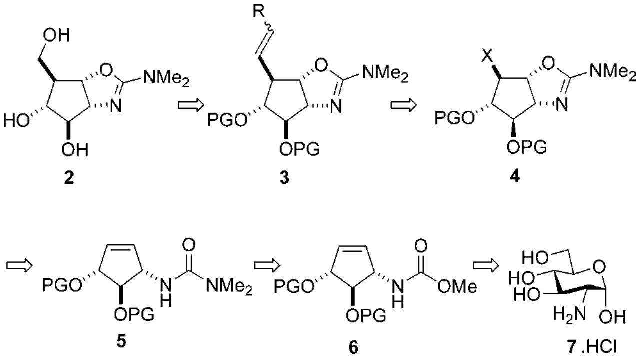
of its carbocycle fragment (allosamizoline **2**) have resulted in a considerable interest among the synthetic community.[9]

A total of 10 syntheses of allosamizoline **2**[10] and 4 syntheses of allosamidin **1**[10h,i,11] have been reported so far. Two noteworthy syntheses of (−)-allosamizoline, both 11 steps long, are by Simpkins (<5% overall yield)[10b] and Imperiali (27% overall yield, but which uses stoichiometric thallium and mercury).[10g] Mention should also be made of a short route to (±)-allosamizoline by Trost that was accomplished in seven chemical operations and that has the ability to provide (−)-allosamizoline by incorporation of an enantioselective desymmetrization step.[10a]

We report, herein, our synthesis of (−)-allosamizoline **2**, which utilizes the following key steps: ring-closing metathesis (RCM) to form the cyclopentene core, halocyclization to afford the oxazoline ring, and finally stereoselective alkene radical addition followed by an isomerization reaction to install the hydroxymethyl group.

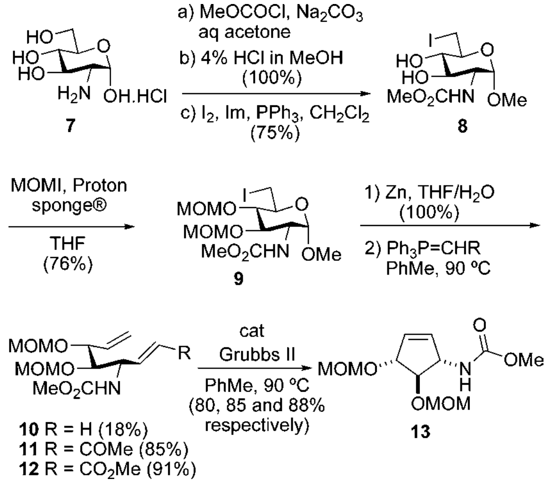
Our retrosynthetic analysis of allosamizoline **2** is shown in Scheme 1. It involved the preparation of the primary hydroxymethyl functionality through reductive ozonolysis of alkene **3**. A stereoselective alkene radical addition reaction to halide **4** could provide the required vinyl-oxazolidinone **3**. Moreover, the halide **4** could easily be the result of a halocyclisation reaction of urea **5**. As a result of the nature of the cyclization, the halogen atom at the C-5 position should have complete *anti*-selectivity with respect to the oxazoline ring. Urea **5** could be derived directly from methylcarbamate **6**. Finally, selective iodination of D-glucosamine **7**, followed by Vasella reductive fragmentation, Wittig reaction, and RCM could provide the key cyclopentenyl compound **6**.

Scheme 1. Retrosynthetic Analysis



Thus, commercially available D-glucosamine **7** was protected to give primary iodide **8** in 75% yield (Scheme 2).

Scheme 2. Synthesis of Cyclopentane **13**



Curiously, all efforts to make the *N*,*N*-dimethyl urea analogue of **8** with dimethylcarbamyl chloride failed; interestingly, we could find no literature examples of glucosamine reacting with this type of carbonyl electrophile.

A protecting group was required for diol **8**, and the methoxymethyl (MOM) group was chosen because of its ability to tolerate strongly basic reagents[12] and exposure to the second generation Grubbs catalyst.[13] Treatment of diol **8** with chloromethyl methyl ether (MOMCl) in CH_2Cl_2 in the presence of Hunig's base gave a bis-protected primary alkylchloride. This byproduct could arise by chloride ion (generated in situ when MOMCl reacted with the substrate) displacing the primary iodide. The problem was solved by using commercially available iodomethyl methyl ether (MOMI) to give the bis-protected product **9** in 76% yield and with 22% of the equivalent mono-protected product recovered for recycling.

Vasella reductive ring cleavage[14] of substrate **9** with zinc in a mixture of THF/H_2O at reflux gave an unstable aldehyde. However, this aldehyde was clean and was used for the subsequent Wittig step without further purification. The Wittig olefination was first tested by forming the ylide in situ with methyl triphenylphosphonium bromide and *n*-BuLi. After much investigation, varying the reaction temperature and time,[15] the respective bis-alkene **10** could be obtained

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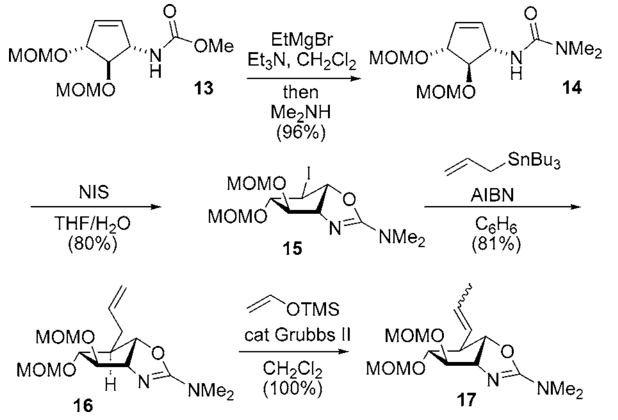
in only 18% yield. Several hypotheses were invoked to explain this low yield; one of these was that the reaction conditions were basic enough to decompose the aldehyde or deprotonate the acidic carbamate N*H* proton. Since the terminal substituents on the alkenes are not incorporated into the RCM product, the use of a less basic ylide (i.e., a stabilized one) could address this issue. Gratifyingly, this proved to be the case. Reacting the respective aldehyde with stabilized ylides such as 1-triphenylphosphoranylidene-2-propanone and (methoxycarbonylmethylen)triphenylphosphorane gave bis-alkenes **11** and **12**, respectively. In addition, subsequent RCM of the three bis-alkenes **10**, **11**, and **12** afforded cyclopentane **13** in very good yields.[14b]

Scheme 3. Synthesis of Oxazolines **16** and **17**

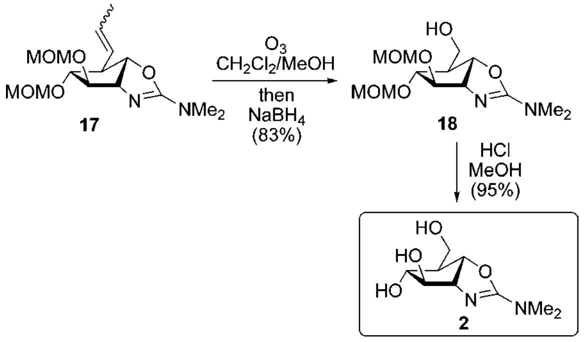


Basha's[16] procedure successfully provided urea **14** from methylcarbamate **13** in excellent yields. This reaction is based upon the formation of a magnesium salt between Me_2NH and a Grignard reagent and its subsequent displacement of an alkoxy group from the methyl carbamate **13**. Following work of Tsoi,[17] who reported the convertion of a urea into a *N*,*N*-dimethylamine substituted oxazoline ring in the presence of bromine, halocyclization with NIS successfully yielded iodo-oxazoline **15** in very good yield.

The preparation of a C-5 vinyl intermediate from iodo-oxazoline **15** through a one-step reaction was first envisioned. The stereoselective radical addition of styrene using a cobalt-catalyzed Heck-type reaction only gave 61% yield of impure product.[18] It was then decided to prepare the desired C-5 vinyl intermediate from the iodo-oxazoline **15** through a two-step procedure, Keck allyl addition, followed by the alkene isomerization. In practice, the Keck allylation addition reaction was stereoselective and afforded allyl-oxazoline **16** as a single diastereoisomer whereby the carbon group had been introduced onto the least hindered face of the molecule.[19] Furthermore, it was found that the terminal alkene **16** could be isomerized in the presence of vinyloxytrimethylsilane and second generation Grubbs catalyst.[20] This ruthenium hydride (generated in situ) catalyzed isomerization gave a *trans:cis* (2.3:1) mixture of propenyl-oxazoline **17** in quantitative yield. The two-step sequence provides an interesting alternative way to vinylate a radical.[21]

Propenyl-oxazoline **17** was subjected to reductive ozonolysis to afford hydroxymethyl-oxazoline **18** in 83% yield (Scheme 4). This intermediate was finally converted into (−)-allosamizoline **2** after MOM deprotection with acid. The spectroscopic data of this compound (and its HCL salt) were in accord with those reported in the literature.

Scheme 4. Total Synthesis of (−)-Allosamizoline **2**



In summary, we have reported the synthesis of (−)-allosamizoline **2** in a total of 13 steps and 22% overall yield from D-glucosamine. The key steps in this sequence include a Vasella reductive ring cleavage of a 6-iodopyranoside to afford an aldehyde that was then converted into a bis-alkene through a Wittig reaction, ring-closing metathesis of the bis-alkene intermediate to form the cyclopentene core of the molecule, Basha's procedure to convert the methylcarbamate-cyclopentene into a urea-cyclopentene, halocyclization of the urea to afford the dimethylamine-oxazoline ring, and finally a stereoselective alkene radical addition reaction followed by alkene isomerization and ozonolysis to install the hydroxymethyl group in position C-5. Studies toward the total synthesis of allosamidin are currently underway.

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Supporting Information Available: Experimental and NMR spectral data and characterizations for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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