

Synthetic Studies on Altemicidin: Stereocontrolled Construction of the Core Framework

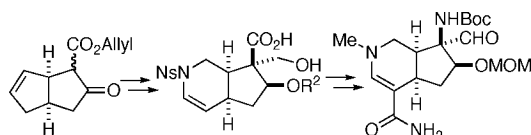
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Received August 9, 2007

ABSTRACT



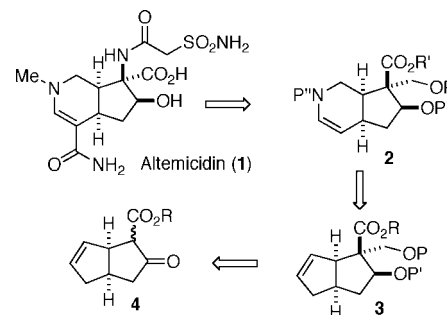
The stereoselective synthesis of the key intermediate for altemicidin has been accomplished. The synthesis commenced with a bicyclo[3.3.0] framework, which was readily obtained via an intramolecular C–H insertion reaction. A Curtius rearrangement was employed as a key step to stereoselectively construct the β -hydroxyl α -disubstituted- α -amino acid structure. Synthesis of vinylogous urea was achieved using hydrolysis of nitrile intermediate.

Altemicidin (**1**), a six-azainden monoterpene alkaloid isolated from the *Actinomycete* strain by Takeuchi et al. in 1989,¹ has exhibited potent acaricidal activity, as well as the inhibition of tumor cell growth. Furthermore, acylated analogues of **1** have recently been shown to be strong inhibitors of isoleucyl, leucyl, and valyl tRNA synthetase.² Although this remarkable biological activity, coupled with its highly complex structure, has made **1** an attractive target for total synthesis, only Kende has reported the total synthesis of **1** in 1995.³ The unique β -hydroxyl α -disubstituted- α -amino acid structure⁴ and its potent bioactivities have prompted us to investigate its total synthesis. Herein, we

report a stereocontrolled synthesis of key intermediate **19** for the total synthesis of **1**.

The heart of our synthetic plan is illustrated in Scheme 1.

Scheme 1. Structure and Synthetic Strategy of **1**



The highly polar sulfonamide and vinylogous urea would be introduced in a later stage of the synthesis. Because a

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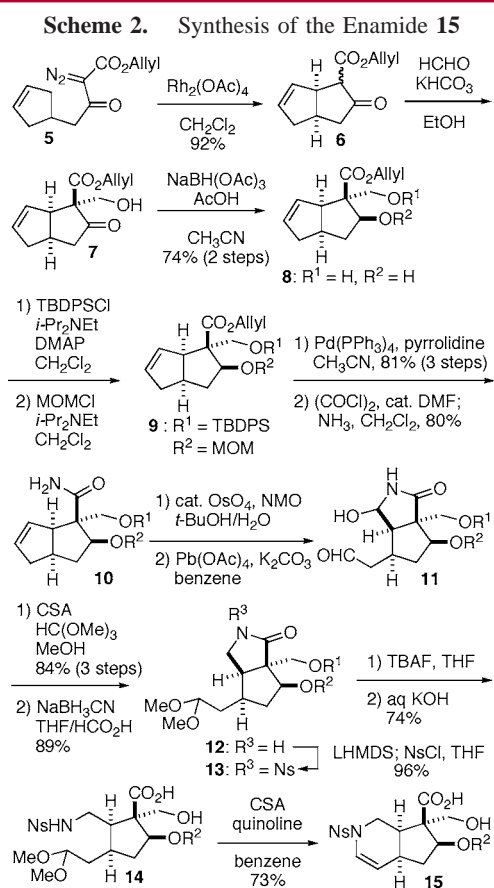
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Curtius rearrangement⁵ could incorporate nitrogen onto the quaternary carbon of **2**, azabicyclo[4.3.0]skeleton **2** would serve as a key intermediate. The cyclic enamide would be constructed from cyclopentene **3** by cleaving the double bond and subsequently introducing nitrogen and recyclization. The quaternary carbon and the secondary alcohol would be stereoselectively installed by employing β -ketoester **4**. Recently, we developed an efficient synthesis of optically active bicyclo[3.3.0] framework **4** using an intramolecular C–H insertion reaction.⁶ Thus, the present synthetic study has an advantage that is readily applicable to enantioselective synthesis.

Synthesis of bicyclo[3.3.0] framework **6** was accomplished via a rhodium carbenoid-mediated C–H insertion reaction of diazoester **5**.⁷ Although optically active **6** was readily available, the racemic form was employed in this preliminary study (Scheme 2). Upon treatment of β -ketoester **6** with



formalin in the presence of a catalytic amount of KHCO₃, hydroxymethylation proceeded smoothly to afford **7**.⁸ Sub-

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sequent stereoselective reduction of **7** with NaBH(OAc)₃⁹ gave **8**. Because alkylation occurred from the convex face of **6** and reduction proceeded via chelating with the primary hydroxyl group of **7**, the stereoselective construction of **8** was efficiently accomplished. After protecting the primary alcohol as TBDPS and the secondary alcohol with MOM ether, the conversion to cyclic enamide from **9** was examined.

Because directly installing the nitrogen group is difficult after oxidative cleavage of the double bond of **9**, an intermolecular delivery of nitrogen was employed. Deprotection of the allyl group of **9**, conversion to the acid chloride, and treatment with ammonia gave amide **10**. After dihydroxylation of **10**, treating with Pb(OAc)₄ generated dialdehydes where the amide nitrogen selectively attacked the closer aldehyde to provide hemiaminal **11**. After conversion to the dimethyl acetal and methyl hemiaminal, selective reduction of hemiaminal was achieved by treatment with NaBH₃CN to give lactam **12**. The opening the γ lactam of **12** was achieved by combining the activation by Ns imide^{10,11} and using the neighboring effect of the primary alcohol for the lactam intermediate. Treatment of **12** with LHMDS and NsCl proceeded smoothly to provide **13**. After removal of the TBDPS group with TBAF and subjection to aqueous KOH, lactam cleavage occurred smoothly to give **14**. Presumably this reaction proceeds through the β -lactone intermediate. Conversion of **14** into cyclic enamide **15** was performed by treatment with CSA and quinoline.

With requisite enamide **15** in hand, we then focused our attention on introducing a nitrogen atom onto the quaternary carbon and a Cl unit onto the enamide, as shown in Scheme 3. Upon treatment of **15** with DPPA¹² and Et₃N, the rearrangement proceeded easily to give **16**. The oxazolidinone ring of **16** was formed by trapping in situ generated isocyanate by the primary alcohol. After formylation of enamide by modified Vilsmeier reaction,¹³ the amide group was protected as a Boc imide. Subsequent N-methylation was carried out by the deprotection of the Ns group and treatment with LHMDS and MeI. Conversion from the aldehyde to the nitrile group was performed by treatment with hydroxylamine and subsequent addition of acetic anhydride to the oxime intermediate to provide **18**.¹⁴ After hydrolysis of the oxazolidinone ring under basic conditions, oxidation to the corresponding aldehyde was achieved by Dess–Martin oxidation.¹⁵ Conversion from the nitrile group to the desired amide was performed by treatment with a

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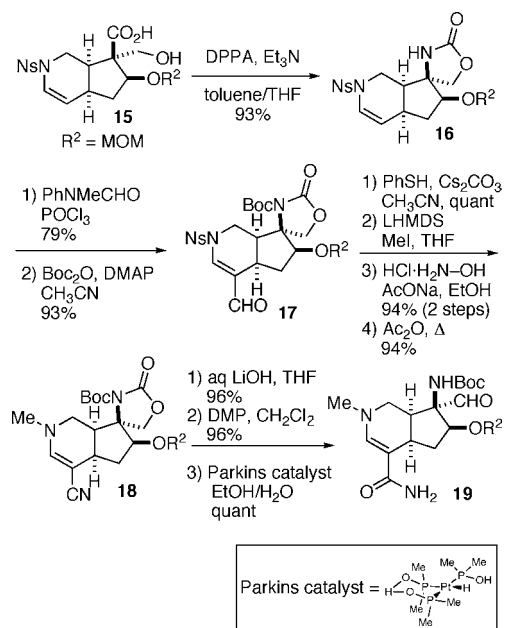
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Scheme 3. Synthesis of the Key Intermediate **19**



catalytic amount of Perkins reagent¹⁶ in the presence of water to give the desired **19**. Because deprotection of the Boc group and MOM ether and subsequent incorporation of sulfonamide

have already been reported by Kende in a similar compound, we have now focused our attention on the synthesis of optically active **1** beginning with chiral **6**, which has already been reported by our group.

Thus, we accomplished the stereoselective synthesis of key intermediate **19**, which contains four sequential stereocenters and vinylogous urea, for the total synthesis of **1**. The synthesis employed a bicyclo[3.3.0] framework, which was readily obtained by a desymmetric C–H insertion reaction. We are currently investigating the synthesis of (–)-altemicidin (**1**).

Acknowledgment. This work was financially supported by the SUNBOR Foundation, Uehara Memorial Foundation, and a Grant-in-Aid for Scientific Research on Priority Areas 17025011 from The Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL701940F

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