(+)-Batzellaside B, a piperidine alkaloid isolated from a sponge Batzella sp. : Determination of absolute configurations and the first total synthesis

（課程博士・様式７）（Doctoral qualification by coursework,Form 7）

学 位 論 文 要 旨

Abstract of Doctoral Thesis

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論文題目：Batzella 属の海綿より単離されたピペリジンアルカロイド (+)-batzellaside B
－構造決定と初の全合成－
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論文要旨：

Abstract : Biologically active natural products are secondary metabolites synthesized by many living organisms. They have made an enormous contribution to human health due to the fact that many of them were applied as pharmaceutics such as antibiotic, penicillin G or an anticancer agent, paclitaxel. An important family of natural products is represented by nitrogen-containing molecules called alkaloids, which have provided many powerful medicines including analgesic drug, morphine, and antimalarial agent, quinine. Among them, six-membered *N*-heterocycles known as piperidine alkaloids are the largest class being widely widespread in nature. Remarkably, polyhydroxylated piperidine alkaloids (iminosugars) have been found to display beneficial therapeutic activities as sugar-mimicking glycosidases and galactosidases inhibitors. Pharmaceutical potential of iminosugars, imparted by clinical approval of miglitol and miglustat for treatment of type II diabetes and Gaucher disease, respectively, has generated a huge interest in their synthesis resulting in development of a wide range of synthetic methods. The commonly used strategies for the construction of polyhydroxylated piperidine system involve nucleophilic displacement of a leaving group, intramolecular Mitsunobu and aza-Michael reactions, electrophile-induced cyclization of aminoalkene, intramolecular cyclization of an aminoaldehyde, intramolecular reductive amination and ring closing metathesis (RCM).

(+)-Batzellasides A-C are a novel class of azasugars isolated in 2004 from *Batzella* sp., collected off the west coast of Madagascar, which represent a first example of iminosugars from marine organism. These naturally occurring products showed antibacterial potency against *Staphylococcus epidermidis* with MICs of ≤6.3 μg/mL, thus serving as new potent antibacterial agents. The unique structural properties of

batzellasides related to the presence of long alkyl side chains bearing uncommon, configurationally undefined C8 stereocenters provide an intriguing extension of the iminosugar frameworks for the inhibition of glucosidases and galactosidases, thereby attracting attention to the research field of contemporary drug discovery.

Unfortunately, the low natural abundance of batzellasides has limited their availability, further impeding complete understanding of absolute configurations and extensive studies on development of biologically potent analogues. Although it is believed that synthetic approach to these alkaloids would address this supply problem, no reports have appeared previously describing successful studies on the synthesis of these compounds. From these reasons, batzellasides became target of my study, while my synthetic efforts have focused on (+)-batzellaside B as a represent member of this new class of natural products.

The first synthetic strategy involved known 2,3,5-tri-*O*-benzyl-L-arabinose derivative as a chiral source. Starting from this compound, the synthesis of (+)-batzellaside B and its C8-epimer was achieved in 22 steps with overall yields of 3.9% and 5.4%, respectively. In the course of the synthetic studies the absolute configurations of (+)-batzellaside B also have been unambiguously determined to be 1*S*,3*S*,4*S*,5*R*,8*S* by the modified Mosher's analysis of the synthetic intermediate prepared through the separate route.

Efforts to develop more concise and efficient synthetic pathways toward (+)-batzellaside B using the same starting material failed due to occurrence of side reactions. Alternatively, a new synthetic approach to (+)-batzellaside B from commercially available L-pyroglutamic acid has been explored. Starting from this chiral material, the formal total synthesis accessible to the heterocyclic hemiaminal, a key intermediate elaborated commonly in the first total synthesis, has been achieved in an efficient 21-step protocol in 7.1% overall yield. The key synthetic step involved Sharpless asymmetric dihydroxylation of an olefinic substrate functionalized with acetoxy group to introduce two chiral centers diastereoselectively into the structure.

Furthermore, study on the the allylation at C1 position allowed to exemplify the stereospecificity of this reaction by performing the procedures with AllylTMS and two types of Lewis acids. An effective modification of the synthetic sequences for construction of C8 stereocenter have been also explored using stereoselective reduction of a relevant ketone. It was found that reaction performed under the conditions using $LiEt_3BH$ in TBME at -78 °C allows an asymmetric access to an intermediate alcohol required in the advance stage of the synthesis in 99% yield with a 74% de.

The above studies represent the precursor works on determination of absolute configurations and total synthesis of (+)-batzellaside B, which provided two alternative approaches to this natural product.