Synthetic Studies on Cyclodepsipeptides Containing Structurally Unusual Amino Acids

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Cyclodepsipeptides containing unusual amino acids are attractive synthetic targets for their structural complexity and biological activities. For a total synthesis of cyclodepsipeptides, the stereoselective synthesis of structurally unusual amino acids as their component, proper selection of a coupling reagent for amide bond formation without epimerization, and the strategy for the coupling of peptide segments and macrocyclization are critical issues in contrast to a synthesis of simple peptides consist of only natural amino acid residues.

Halipeptins are novel cyclodepsipeptides isolated from the marine sponge in 2001. Halipeptin A is known to show strong anti-inflammatory activity *in vivo*. In addition to their potent biological activities, their intriguing structures containing (2*S*,3*S*)-*N*-methyl-5-hydroxyisoleucine (*N*-MeOHIle), methylthiazoline unit and novel highly substituted decanoic acid derivatives called HTMMD/HTMHD prompted us to initiate efforts directed towards the total synthesis. Recently, we have achieved the total synthesis of halipeptin A. Among these fragment, we synthesized *N*-MeOHIle using highly *exo*-selective Michael reaction to the chiral bicyclic lactam as a key step. (3*S*,4*R*,7*S*)-HTMMD was retrosynthetically divided into the C1-C5 and the C6-C10 fragments. The former was synthesized via asymmetric aldol reaction using chiral oxazaborolidinone reagent and the latter was synthesized via proline-catalyzed α-oxidation. The both fragments were coupled by Julia-Kociensky reaction to give the (3*S*,4*R*,7*S*)-HTMMD, to which the introduction of (*S*)-alanine residue was attained by the acid chloride method using AgCN without epimerization. For assembly of the cyclodepsipeptide skeleton, BMTB, acid chloride and HATU strategy were utilized respectively. And we are now working for the total synthesis of papuamides, more complex cyclodepsipeptides.