SUMMARY OF Ph.D. DISSERTATION

School	Student Identification Number	SURNAME, First name
Scienece and Technology		AOKI, Shin-ya

Title

Total Synthesis of Spiro-Heterocyclic γ-Lactam Natural Products

（スピロ環状構造を有するγ–ラクタム型天然有機化合物の全合成）

Abstract

Pseurotins A−E are a class of secondary microbial metabolites, which were isolated from the cultures of *Pseudeurotium ovalis* (Ascomycetes) in 1976. Pseurotin F_2 was also isolated from *Aspergillus fumigatus* DSM 6598. Among them, pseurotin A has a potent neurite formation activity to PC12 pheochromocytoma cells. Pseurotins possess a highly functionalized 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione skeleton with three contiguous stereogenic centers. In 2002, structurally related azaspirene was isolated from a fungus *Neosartorya* sp. This antibiotic inhibits the endothelial migration induced by vascular endothelial growth factor. These formidable molecular architectures as well as intriguing biological profiles make these natural products attracting synthetic targets.

Toward the total syntheses of pseurotins A and F_2, two types of γ-lactones were synthesized from D-glucose as the right part of the natural products. The asymmetric spiro-carbon in the pseurotins was constructed efficiently by the stereoselective vinyl Grignard addition to C3 in the 3-ulose derivative. Introduction of the left part was carried out by the aldol reaction of the γ-lactones with (2*S*,3*S*,4*Z*)-2,3-bis(methoxymethoxy)hept-4-en-1-al derived from D-glucose. The coupling reaction was best achived using potassium-enolate generated from one of the two γ-lactones, i.e., (2*S*,3*S*,4*R*)-4-benzyl-2-(1-propanoyl)-2,3-bis(triethylsilyloxy)-4-butanolide. In further synthetic venture via several steps including the 3(2*H*)-furanone formation, the lactone-lactam conversion and benzylic oxidation, the total syntheses of pseurotins A and F_2 was accomplished. For the total synthesis of azaspirene, the common potassium-enolate was utilized. The left part in the antibiotic was introduced by the aldol reaction with LiBr-coordinated (*E*,*E*)-2,4-heptadienal. By a similar synthetic pathway, the total synthesis of azaspirene was completed.