学 位 論 文 内 容 の 要 旨

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学 位 論 文 題 名

Development of new methodology toward C-C bond formation with halogenated Weinreb amide for synthesis of halogenated natural product
（ハロゲン化された天然有機化合物の合成に向けた、ハロゲン化されたワインレブアミドを用いる新規炭素―炭素結合形成反応の開発）

Nowadays, halogenated natural products are currently an object of interest for researchers. As a result, impressive works have been achieved in the isolation and synthetic field. The number of discovered halogenated natural products has reached more than 5000 compounds and continues a steady increase. Most of them were found in marine environment since this ecosystem possesses a wide variety of organisms which can be the origin for these substances. Biological properties of halogenated natural products have been researched for decades to show antibacterial, antifungal, antiviral, anti-inflammatory, antiproliferative, antifouling, antifeedant, cytotoxic, ichthyotoxic, and insecticidal activities. The supply of these natural products is required for further biological studies. Because of the minimal supply of these natural products, making it difficult to study their activities. In addition, the development of synthetic methods for these compounds is urgently needed for continuing the study process. In this thesis, a new effective synthetic methodologies with halogenated Weinreb amide and synthetic efforts for mollenyne A are described.

In chapter 1, the followings reviewed are general introduction of halogenated natural products, their discoveries, developments and their unique biological activities related with beneficial to mankind. Toward the synthesis of the halogenated natural product, halogenation reactions to acyclic and cyclic carbon chain, dehalogenation of olefins and α-chlorination with aldehyde are highlighted. Finally, the motivation and objectives of my research work are mentioned.

Chapter 2 discusses the development of new effective synthetic methodologies via Weinreb amide. The chapter includes detail information related basic concept, reaction development, problem solving, result and spectral data. Actually, new methodologies

with halogenated compounds are rare to overcome a novel property of the halogen atom. A new effective synthesis of α, β-dichlorinated ketone is shown starting from the corresponding *N*,*O*-dimethyl amide which are often called Weinreb amide. The problem to be overcome for the desire product was an abstraction of acidic α-proton. Extensive studies revealed that work-up with commercially available 4 M HCl in dioxane was very important for the selective synthesis of α, β-dichloroketone. Diastereomers, *anti*- and *syn*-dichloroamide showed different reactivity to alkyllithium reagents or Grignard reagents. Synthesis of α, β-dibromoketone was also attempted. During the course of this study, a unique reaction of the eliminating *N*,*O*-dimethylamide has been found.

In Chapter 3 is shown synthetic study of mollenyne A, a halogenated anticancer natural product obtained from a marine sponge. This compound consists of three units, homoagmatine, central part with three halogen atoms including a halohydrin, and ene-yne unit. It was focused on developing effective synthetic methods for constructing the central part, which can be divided to *E*-bromoolefin and halohydrin units. The *E*-bromoolefin moiety was prepared with *anti*-dibromide induced by *p*-Nitrobenzoate via regio- and stereoselective *E*-elimination. On the other hand, the halohydrin moiety was also investigated with racemic model allylic alcohol. Based on a report by Burns, TiCl(O*i*-Pr)$_3$ as a chloride and NBS as the bromonium ion were used in the regioselective bromochlorination reaction to a target compound. This reaction is rationalized by the rigidity of complexed intermediate which enables the regioselectivity of bromide and chloride.

Chapter 4 describes general conclusion for this thesis. Summary of this thesis, overviews of current study, and further applications are mentioned.