



Title	Development of new methodology toward C-C bond formation with halogenated Weinreb amide for synthesis of halogenated natural product [an abstract of entire text]
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## 学位論文の要約

博士（環境科学）

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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 study, the author has described new effective synthetic methodologies via Weinreb amide to synthesize  $\alpha,\beta$ -dichlorinated ketones as a powerful method in halogenated construction. Furthermore, synthetic efforts for the central part construction from mollenyne A, which is divided into the *E*-bromoolefin and the halohydrin construction also presented.

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  $\alpha$ -chlorination with aldehyde are highlighted.

In Chapter 2, the author discusses the development of new effective synthetic methodologies via Weinreb amide. Towards the development of new effective methods for synthesizing  $\alpha,\beta$ -dichlorinated ketone via Weinreb amide, the diastereomers, *anti*- and *syn*-dichloroamide were employed for the optimization of the reaction conditions with

alkyl lithium and Grignard reagent. Work-up with commercially available 4 M HCl in dioxane is very important because it encourages selectivity and avoids  $\beta$ -elimination reaction to give a high desired product ratio up to 95:5 compared with  $\alpha,\beta$ -unsaturated ketone as undesired product although aqueous work-up resulted in undesired compound formation (Figure 1).

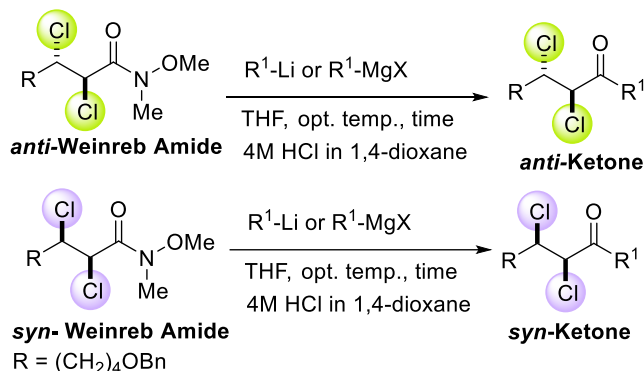


Figure 1. Nucleophilic addition to *anti*- and *syn*-dichloroamide

Two diastereomers, *anti*- and *syn*-dichloroamide showed different reactivity against some nucleophiles, assuming the difference in stability of five-membered ring intermediates (Figure 2). Alkyl lithium reagent is more effective nucleophile than Grignard reagent during these reactions. This invention would be a powerful method for the elongation of hydrocarbon frameworks densely functionalized with chlorine atoms and opens up opportunities for reactions related to the preparation of halogenated natural compounds.

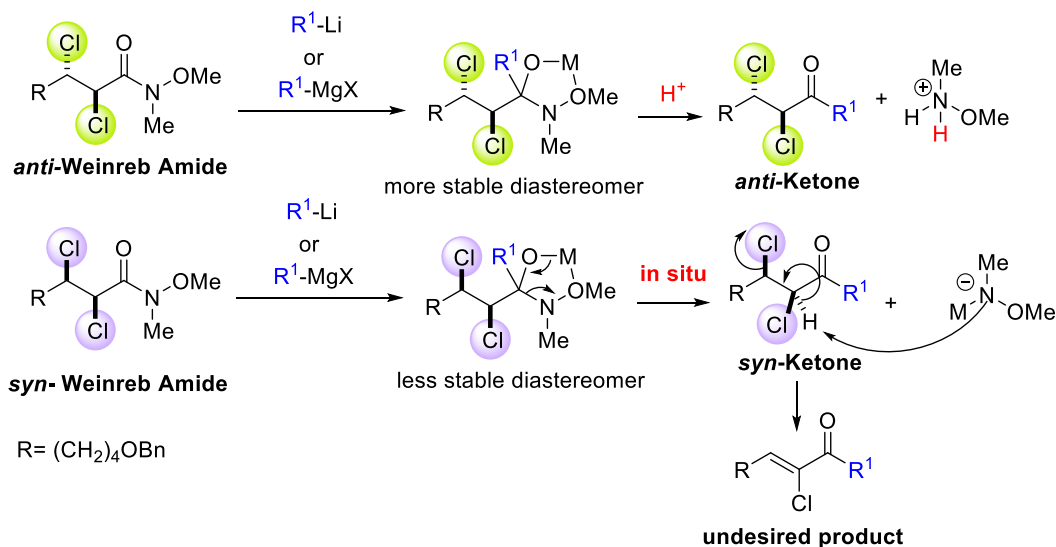


Figure 2. Proposed mechanism concerning different reactivity between *anti*- and *syn*-dichloroamide

On the other hand, nucleophilic addition reaction to  $\alpha,\beta$ -dichlorinated aldehyde (Figure 3) instead of the corresponding amide just provided  $\beta$ -eliminated aldehyde, suggesting the Weinreb amide is a promising precursor toward homologation reaction through the addition reaction. This is because the nucleophile acts as a base to abstract the  $\alpha$ -proton rather than addition to carbonyl group of  $\alpha,\beta$ -dichlorinated aldehyde to generate an elimination product. It is suggested that the five-membered ring intermediates, formed by addition of nucleophile from *anti*- and *syn*-dichloroamide show different stability under thermal conditions.

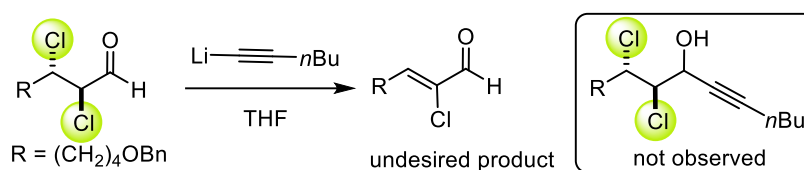


Figure 3. Nucleophilic addition to *anti*-dichloroaldehyde

Also, the lithium amide, produced during the reaction, is revealed to have a potential to reduce chloride at  $\alpha$ -position of the carbonyl group. Due to this property, the current method is difficult to apply to  $\alpha,\beta$ -dibrominated Weinreb amide because the character of Br amide at  $\alpha$ -position is easy to be reduced by the nucleophile or an amine that is released during addition reaction encourages an undesired  $\beta$ -elimination reaction (Figure 4).

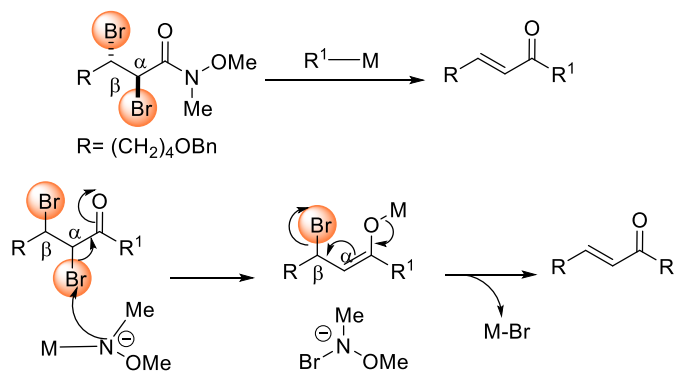


Figure 4. Proposed mechanism concerning different reactivity of *anti*-dibromoamide

In chapter 3 of this thesis, author have engaged total synthesis 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. Author focused on the central part *E*-bromoolefin and halohydrin constructions because these become very important step in this study. *E*-bromoolefin part was well prepared with high yield (83%) via regio- and stereoselective *E*-elimination of *anti*-dibromide compound using DBU as a base in the presence of *p*-

nitrobenzoyl group (Figure 5). *p*-Nitrobenzoyl as an electron-withdrawing group enhances the acidity of the desired hydrogen. This strategy was found more useful than hydrostannation reaction to propargyl alcohol, which produces low yield with lower regioselectivity.

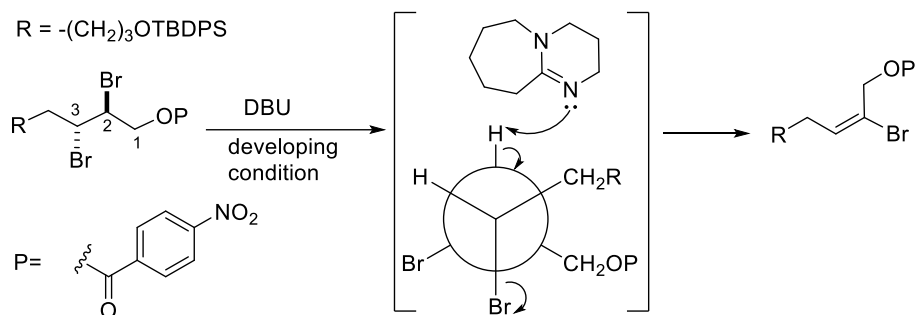


Figure 5. Regioselective elimination reaction to *anti*-dibromide using DBU

The halohydrin as a key part was successfully constructed in the regioselective bromochlorination reaction to the allylic alcohol. The regioselectivity contributed by the rigidity of complexed intermediate and stereogenic center in the model substrate (Figure 6). Current investigations open the possibilities for accomplishing the synthetic study on Mollenyne A, although the improvement is underway.

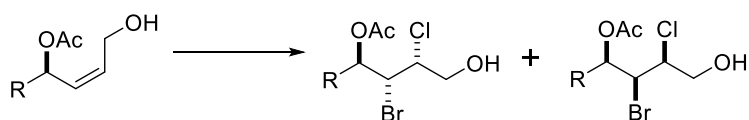


Figure 6. Bromochlorination reaction to the allylic alcohol as a key reaction

On the other hand, with the crucial information related to construction of *E*-bromoolefin and halohydrin from the central part of Mollenyne A, optimization related to amidation reaction for merging the left part with a central part and subsequent C-C bond formation reaction through  $\text{S}_{\text{N}}2$  reaction or cross-coupling reaction, or via Weinreb amide for coupling the right part with central part must be done by using model compounds. After all, the triyne-ene terminus, allylic alcohol flanked by halogenated carbon and homoagmatine will be combined to furnish synthetic Mollenyne A (Figure 7). Comparison of the biological activity between natural Mollenyne A and synthetic Mollenyne A also needed.

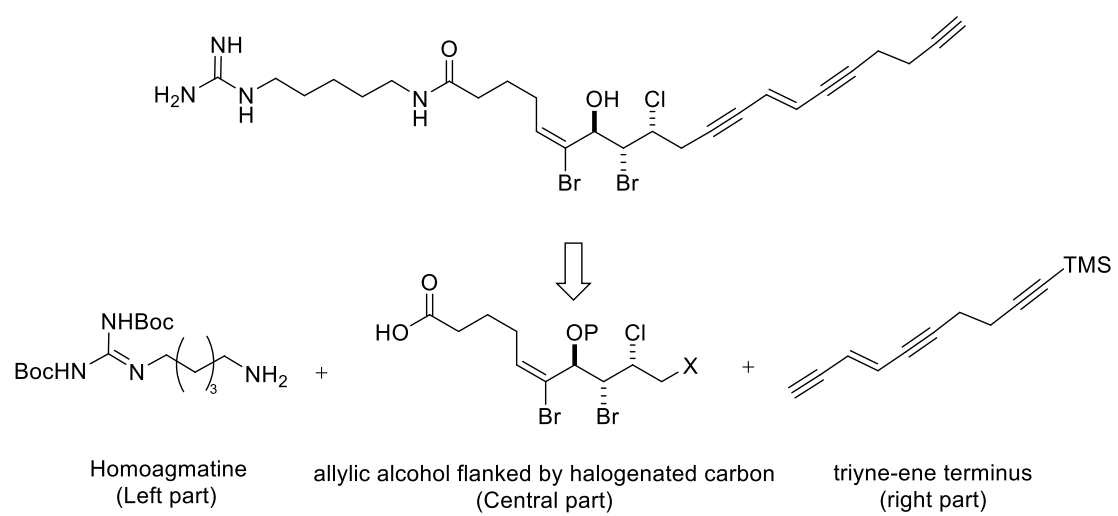


Figure 7. Retrosynthetic analysis towards the synthesis of Mollenyne A