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**Development of new methodology toward C-C bond formation  
with halogenated Weinreb amide for synthesis of  
halogenated natural product**

A Thesis Presented to Hokkaido University

For

Doctor's Degree



by

*Nurcahyo Iman Prakoso*

Division of Environmental Materials Science

Graduate School of Environmental Science

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## **CHAPTER 1**

### **General Introduction**

## 1-1 Halogenated Natural Products

Secondary metabolite compounds are unique compounds produced in limited quantities. The function of secondary metabolites is to defend themselves from unfavorable environmental conditions, i.e., to overcome pests and diseases,<sup>1</sup> attract pollinators,<sup>2</sup> and as signaling molecules.<sup>3</sup> In short, secondary metabolites are used by organisms to interact with their environment.

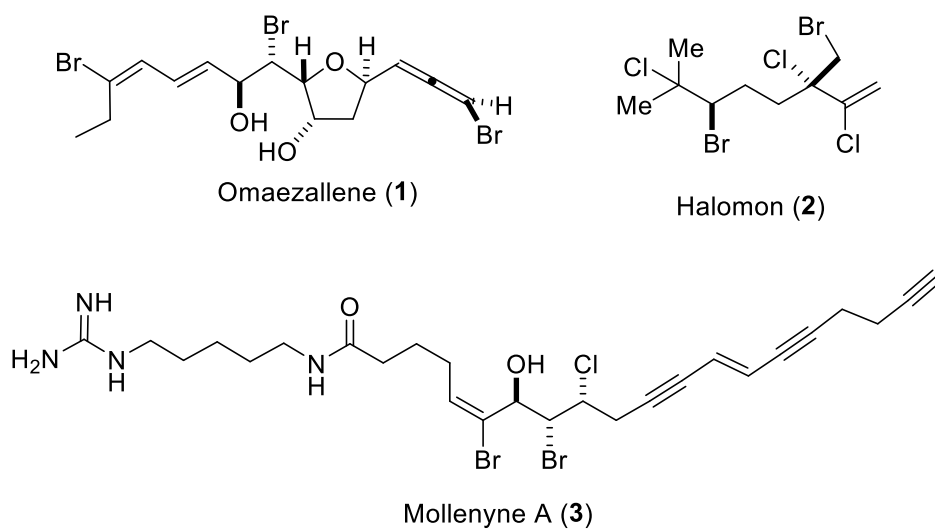
Nowadays, halogenated natural products are currently an object of interest for researchers. As a result, many of them have done impressive recent work in the isolation and synthesis field. Halogenated natural compounds are secondary metabolites that contain fluorine (rarely), chlorine, bromine, iodine in their carbons chain and can be isolated from living organisms such as algae, marine bacteria, sponges, phytoplankton, tunicates, worms, corals, bacteria, fungi, terrestrial plants, lichens, and other microorganisms.<sup>4</sup>

In general, the production of secondary metabolites is triggered by conditions in which organisms are stressed due to environmental conditions, nutrient depletion, and limited growth conditions. Individual or multienzyme complexes will produce secondary metabolites through oxidative mechanisms during these conditions (enzymatic halogenation), though direct halogenation via halide anion incorporation is also known to proceed through both enzymatic and nonenzymatic pathways.<sup>5</sup> Since ancient times, this biosynthetic mechanism has been the most common route.<sup>6</sup>

The number of discoveries and developments of halogenated natural product has reached a high significance until more than 5000 compounds and continues a steady increase.<sup>7</sup> Most of them can be found in great abundance in marine environment since this ecosystem possess a very wide variety of organisms which could be the origin for these substances.<sup>4d</sup> There are many variety of compounds ranging from peptides, lipids, polyketides, indoles, terpenes, acetogenins and phenols to volatile halogenated hydrocarbons.<sup>8</sup>

The halogen substituents often provide marine natural products with interesting key features. Biological properties from halogenated marine natural products have been researched for decades to show antibacterial, antifungal, antiviral, anti-inflammatory, antiproliferative, antifouling, antifeedant, cytotoxic, ichthyotoxic, and insecticidal activities. All of that properties have a massive benefit for human beings.<sup>2</sup> Some examples of halogenated natural products that have great potential are shown in Figure 1-1; omaezallene (**1**) with potent antifouling activity toward the cypris larvae of the barnacle *Amphibalanus amphitrite*, halomon (**2**) with a inhibit of DNA methyltransferase for combatting cancer, and mollenyne A (**3**) with cytotoxicity against human colon tumor cells.<sup>9</sup>

Figure 1-1. Structure of Omaezallene (**1**), Halomon (**2**) and Mollenyne A (**3**)



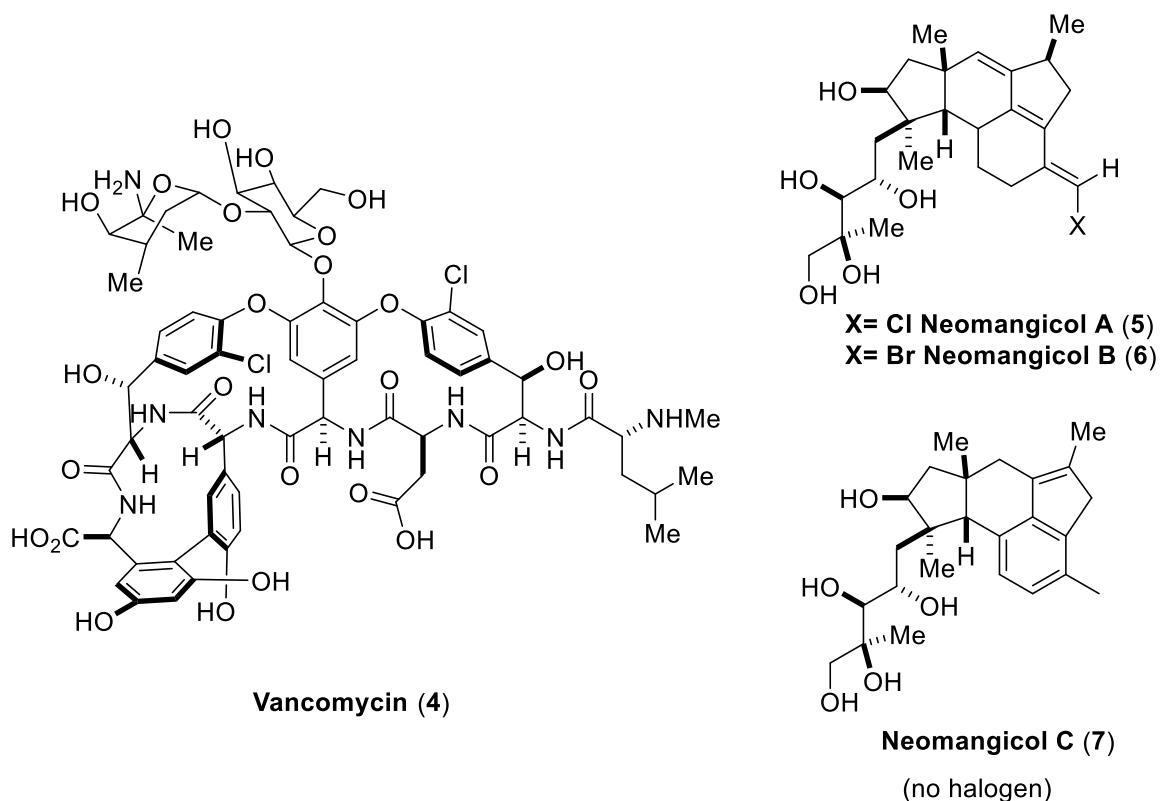
The supply of these natural products is required for further biological studies. However, today's challenges and problems are the minimal supply of these natural products, making it difficult to study their activities. In addition, the development of synthetic methods for these compounds, e.g., total synthesis, is urgently needed for continuing the study process.



## 1-2 Potential of biological activities from halogenated natural products

Halogenated natural products are often found in land and marine organisms, and have unique biological activities. Surprisingly, the presence of these halogen substituents is significant for determining these natural products biological activity (Figure 1-2). These phenomena can be observed in some following examples. Two chlorine substituents are necessary to achieve the clinically active conformation in vancomycin (**4**) as antibiotics for the medication of *S. aureus* infections through the control of atropisomer distribution.<sup>10</sup>

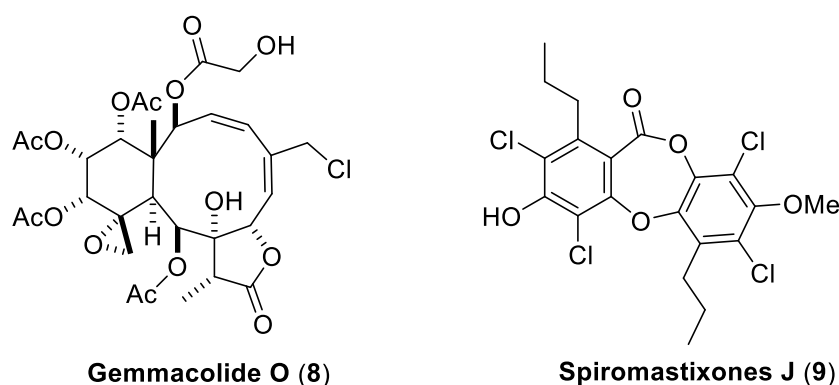
Figure 1-2. Structure of Vancomycin (**4**), Neomangicol A (**5**), B (**6**) and C (**7**)



The presence of a halogen substituent is also relevant for the biological activity of neomangicol A (**5**) and B (**6**) as halogenated sesterterpenes. These compounds exhibit significant cytotoxicity against human colon tumor cells, HCT-116.<sup>11</sup> However, its analog compound, neomangicol C (**7**), has no activity due to the absence of halogen substituents. Because of the

importance of halogen substituents in influencing the biological activity of halogenated natural products, many screenings or assays were carried out to seek information and classify these compounds according to their potential, i.e., antibacterial, antifungal, antiviral, antiparasitic, antiproliferative, antifouling, and cytotoxic. In the field of antibacterial (Figure 1-3), Gemmacolide O (**8**) was isolated from South China Sea gorgonian, *Dichotella gemmacea*, and showed great potential antibacterial activity against the Gram-negative bacterium *Escherichia coli*, with 13.0 mm radii of the inhibition zones in agar diffusion assays (Penicillin= 15.0 mm). Spiromastixones J (**9**) isolated from the deep-sea fungus *Spiromastix sp.*, display impressive antibacterial activity (MIC values) against Gram-positive bacteria like *S. aureus* (0.125  $\mu\text{g/mL}$ ), *B. thuringensis* (0.25  $\mu\text{g/mL}$ ), and *B. subtilis* (0.125  $\mu\text{g/mL}$ ).<sup>12</sup>

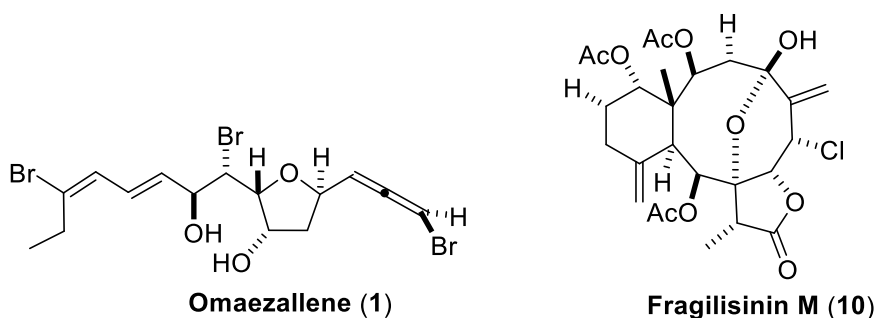
Figure 1-3. Structure of Gemmacolide O (**8**) and Spiromastixones J (**9**)



Some halogenated natural products also have an antifouling activity that is very important to prevent the undesirable accumulation of marine benthic in a ship's hull (Figure 1-4). Omaezallenes (**1**) was isolated, synthesized, and showed great potential as antifouling agent against cypris larvae of the barnacle *Amphibalanus Amphitrite* with  $EC_{50} = 0.22 \mu\text{g/mL}$  for isolated compound and  $EC_{50} = 0.46 \mu\text{g/mL}$  for synthesized compound.<sup>9a</sup> Moreover, for the

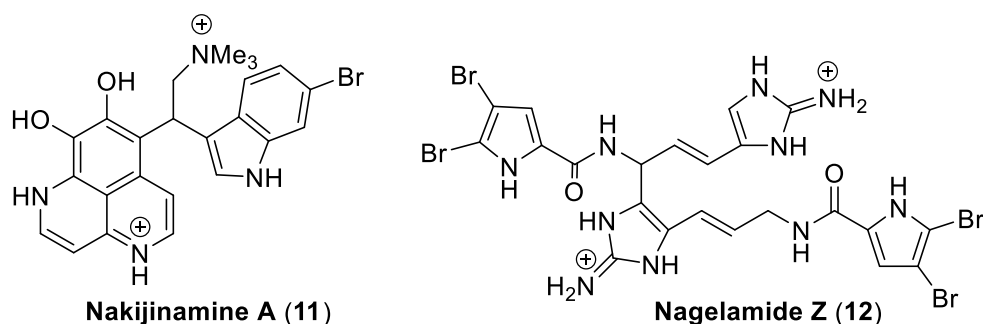
same larvae, another antifouling agent was observed. Fragilisinin M (**10**) displays potent antifouling activity ( $EC_{50} = 5.6 \mu\text{M}$ ).<sup>13</sup>

Figure 1-4. Structure of Omaezallene (**1**) and Fragilisinin M (**10**)



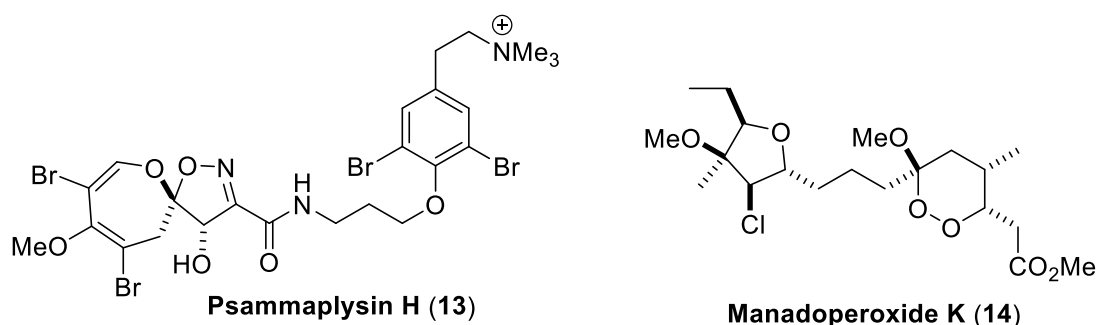
In addition to their often antibacterial and antifouling activity, there are still many marine halogenated products with potent antifungal properties are known (Figure 1-5).<sup>14</sup> Nakijinamine A (**11**) was isolated from the Okinawa sponge, *Suberites sp.* and showed antifungal activity towards *Candida albicans* ( $IC_{50} = 0.25 \mu\text{g/mL}$ ), *Cryptococcus neoformans* ( $IC_{50} = 0.5 \mu\text{g/mL}$ ), and *Trichophyton mentagrophytes* ( $IC_{50} = 0.25 \mu\text{g/mL}$ ). Nagelamide Z (**12**) was isolated from *Agelas sp.*, also has antifungal activity against several fungi like *Candida albicans* ( $IC_{50} = 0.25 \mu\text{g/mL}$ ), *Trichophyton mentagrophytes* ( $IC_{50} = 4.0 \mu\text{g/mL}$ ), *Cryptococcus neoformans* ( $IC_{50} = 2.0 \mu\text{g/mL}$ ), and *Aspergillus niger* ( $IC_{50} = 4.0 \mu\text{g/mL}$ ).

Figure 1-5. Structure of Nakijinamine A (**11**) and Nagelamide Z (**12**)



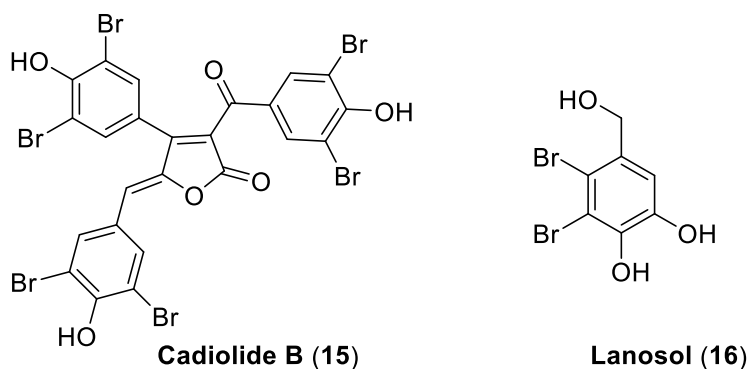
Halogenated natural products also have antiparasitic functions against parasitic diseases, i.e., malaria, trypanosomiasis (sleeping sickness), and lymphatic filariasis (elephantiasis). These diseases usually happen in sub-tropical and tropical countries, put many people at risk, and account for millions of deaths annually. A screening of the Australian sponge *Pseudoceratina sp.* has obtained the psammaplysin H (**13**) (Figure 1-6) and displays potent antimalarial activity against the chloroquine-sensitive (3D7) line of *Plasmodium falciparum* ( $IC_{50} = 0.41 \pm 0.1 \mu M$ ). On the other hand, manadoperoxides K (**14**) was isolated from the Indonesian sponge *Plakortis cfr. lita* display the greatest activity against *Trypanosoma brucei rhodesiense* with  $IC_{50} = 0.087 \mu g/mL$ .<sup>15</sup>

Figure 1-6. Structure of Psammaplysin H (**13**) and Manadoperoxides K (**14**)



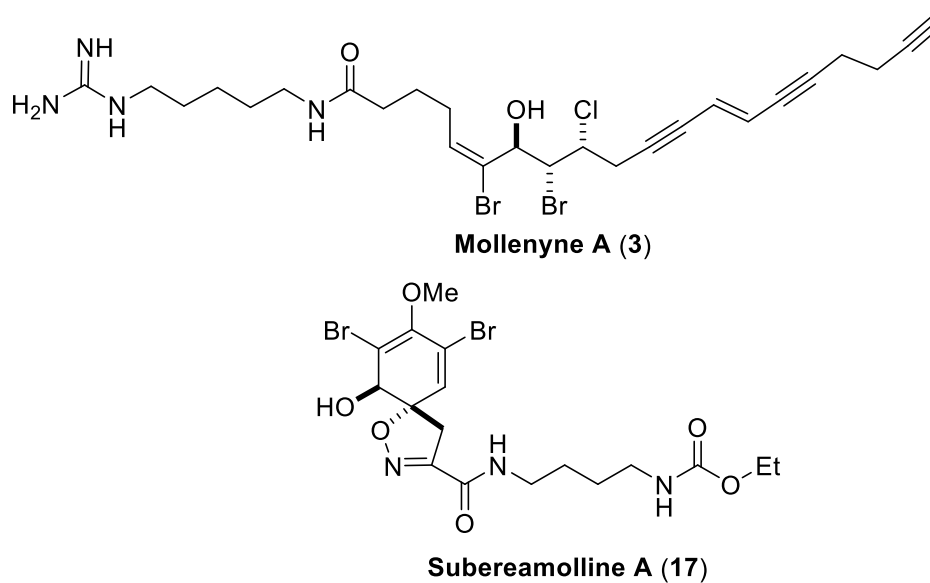
Humans also have to compete with deadly viruses, harmful bacteria, fungi, and parasites. In this situation, some halogenated natural products are well-known as an active antiviral to solve this problem (Figure 1-7).<sup>16</sup> Cadiolide B (**15**), successfully isolated from the Indian Ocean ascidian, *Synoicum sp.* and active against the Japanese encephalitis virus at a concentration of  $1 \mu g/mL$ . The known one of polybromocatechols, lanosol (**16**), isolated from the Korean red alga *Neorhodomela aculeata*, and has promising activity as an antiviral compound against the human rhinovirus HRV2, ( $IC_{50} = 2.50 \mu g/mL$ ).

Figure 1-7. Structure of Cadiolide B (15) and Lanosol (16)



Moreover, cancer and tumor have become an enormous concern to humankind in the world. However, on another side, the marine environment provides many active compounds that are potentially against cancer or tumor cells. Mollenyne A (3) (Figure 1-8) was isolated from sponge *Spirastrella mollis* and exhibits significant cytotoxicity against human colon tumor cells HCT-116 ( $IC_{50} = 1.3 \mu\text{g/mL}$ ).<sup>9c</sup> Subereamolline A (17) was isolated from the Red Sea sponge *Pseudoceratina arabica* from Hurghada at the Egyptian coast. It has promising activity against the highly metastatic MDA-MB-251 human breast cancer cell ( $IC_{50} = 1.7 \mu\text{M}$ ).<sup>17</sup>

Figure 1-8. Structure of Mollenyne A (3) and Subereamolline A (17)



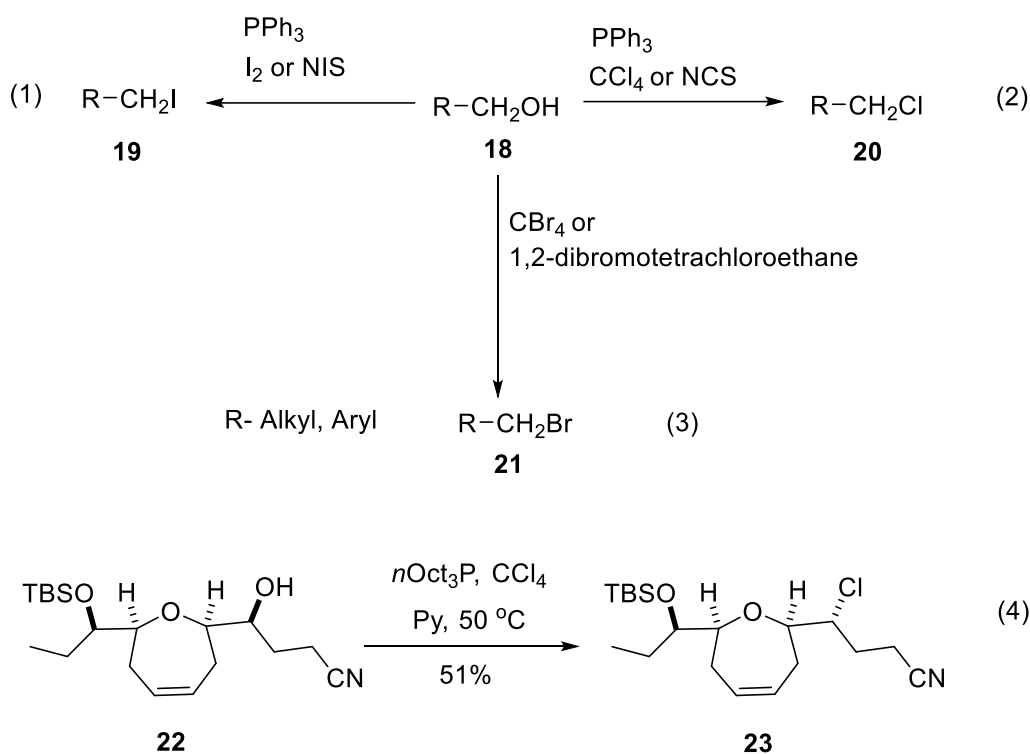
### 1-3 Strategies toward the halogenation to acyclic and cyclic carbon chain in natural products synthesis

In simple terms, halogenation is a reaction to introduce halogen atom(s) into an organic molecule. The introduction of halogen atom(s) occurs through an addition reaction or a substitution reaction. These reactions involve the addition of a molecular halogen such as chlorine, bromine, iodine, or fluorine ( $\text{Cl}_2$ ,  $\text{Br}_2$ ,  $\text{I}_2$ , or  $\text{F}_2$ ) or hydrohalogenation using: hydrogen chloride, hydrogen bromide, hydrogen iodide, or hydrogen fluoride ( $\text{HCl}$ ,  $\text{HBr}$ ,  $\text{HI}$ , or  $\text{HF}$ ).

Natural products containing carbon-halogen bonds are one of important group of natural products with various biological activities that are unique and beneficial to humans. With many natural products having stereogenic centers containing halogens, the development of synthetic methods has also been carried out because it is a challenge for researchers in organic synthesis. Many researchers have focused on and developed the halogenation reactions under various conditions. Therefore, several halogenation reactions that are related to this study are presented as the follows.

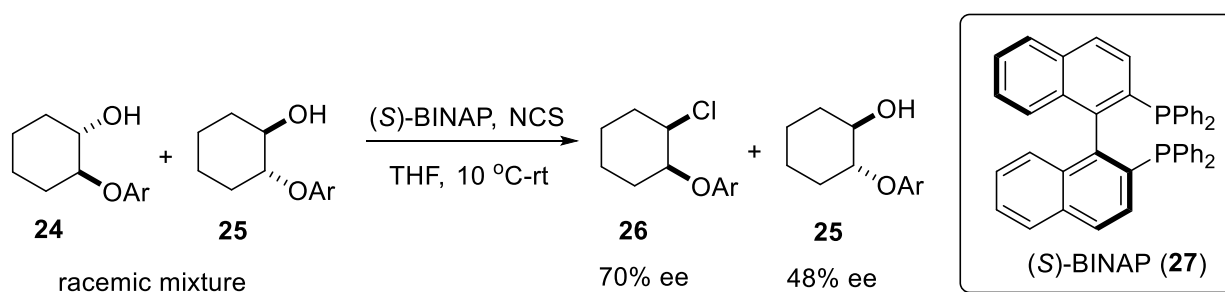
The  $\text{S}_{\text{N}}2$  substitution of the hydroxy groups with halide has been used for direct installment of halogen-containing stereocenters. Appel reaction is a conversion of hydroxy group to alkyl halides using  $\text{Ph}_3\text{P}$  and a halonium species such as  $\text{Cl}^{\oplus}$  or  $\text{Br}^{\oplus}$  under mild reactions. This halonium source such as  $\text{CCl}_4$  or  $\text{NCS}$  to produce alkyl chloride **20**,  $\text{CBr}_4$  or 1,2-dibromotetrachloroethane to produce alkyl bromide **21**, and use iodine or  $\text{NIS}$  to make alkyl iodide **19** (Scheme 1-1, eqn (1-3)). Halogenation of primary alcohol produces  $\text{S}_{\text{N}}2$  products. However, the  $\text{S}_{\text{N}}1$  reaction also competes in secondary alcohols **22** to obtain an inversion product or mixture of diastereomers of chloride **23** (Scheme 1-1, eqn (4)).<sup>18</sup>

Scheme 1-1. Appel reaction



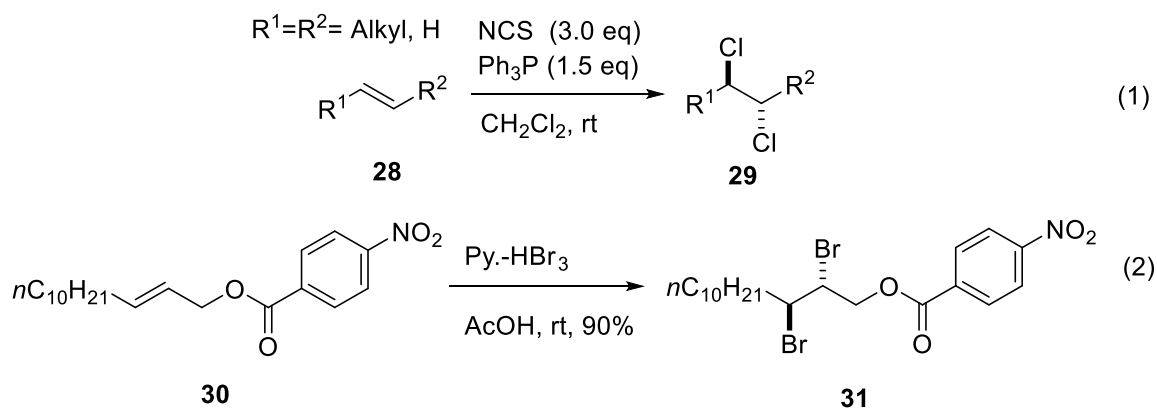
Sekar and co-workers reported the  $\text{S}_{\text{N}}2$  halogenation of a hydroxy group in cyclic alcohol system (Scheme 1-2). They used *N*-chlorosuccinimide (NCS) as the chlorinating agent and chiral BINAP to the racemic-2-aryloxy cyclic alcohol **24** and **25** to produce the optically active chloride **26** (70% ee) in inversion condition and unreacted alcohol **25** (48% ee).<sup>19</sup>

Scheme 1-2.  $\text{S}_{\text{N}}2$  halogenation of a hydroxyl group in cyclic alcohol



1,2-Dihalogenations of double bond are very important and classic reactions. However, further developments of this reaction are progressing to proceed under mild conditions. Yoshimitsu and co-workers successfully reported that a 2:1 mixture of NCS and Ph<sub>3</sub>P promote 1,2-*anti*-chlorination of olefins **28** in excellent yields of *anti*-dichloride **29** (Scheme 1-3, eqn (1)). These methods can apply to *E*- or *Z*-olefin to make *anti*- or *syn*-dichlorides.<sup>20</sup> Not only organochlorine, but also some organobromine with sp<sup>3</sup>C–Br (sp<sup>3</sup>carbon–bromine) bonds attract attention because they are often found in a natural product. Djerassi and Scholz in 1948 introduced pyridinium tribromide as a brominating agent because its reactivity is similar to molecular bromine (Br<sub>2</sub>). Moreover, this reagent is more easily handled and weighed precisely, becoming an essential factor in reaction. Nishiyama and co-workers have successfully applied the use of this reagent with excellent results in their synthesis work (Scheme 1-3, eqn (2)).<sup>21</sup>

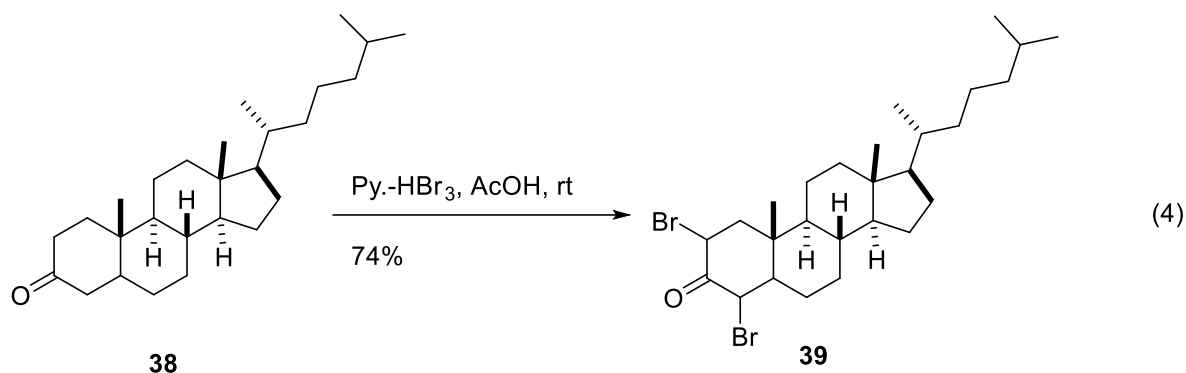
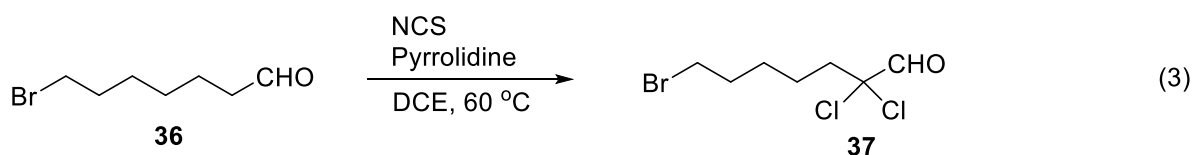
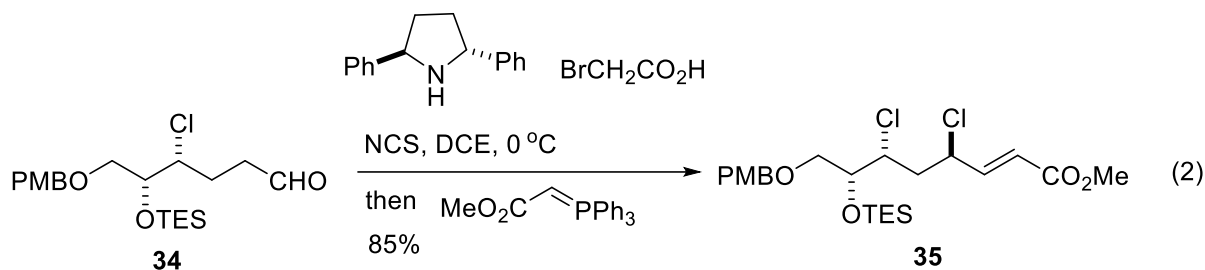
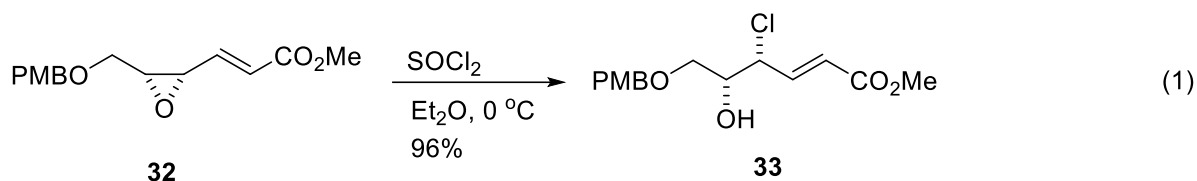
Scheme 1-3. Olefin dichlorination and dibromination



Halogenation is also often used for regioselective ring-opening of the chiral epoxide and diastereoselective chlorination of aldehyde at  $\alpha$ -position, as a strategy in the total synthesis of natural product. In recent works, my research group has achieved some excellent results related with halogenation reaction as a part of a synthetic study.<sup>22</sup>



Scheme 1-4. Selective chlorination reaction

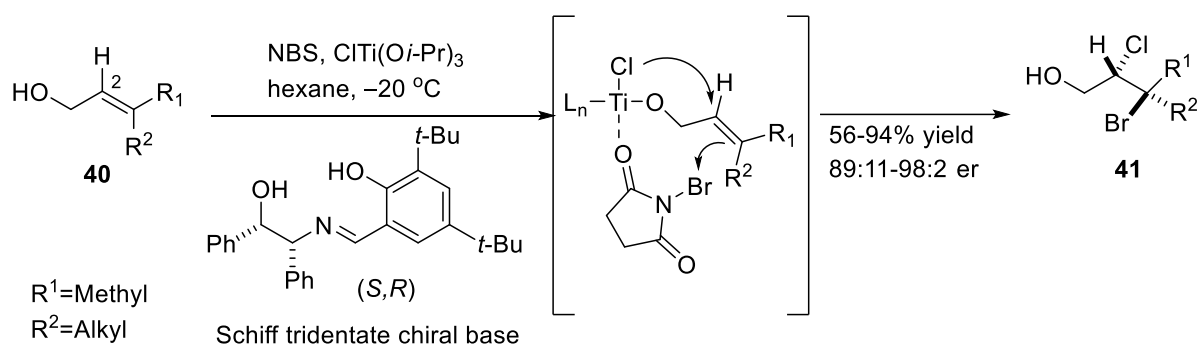


First, the regioselective ring opening of the epoxide **32** by chloride using  $\text{SOCl}_2$  to produce chlorohydrin **33** in excellent yield (Scheme 1-4, eqn (1)). In another side, from a deep investigation of catalysts, additives and temperatures, optimal reaction conditions was found for diastereoselective chlorination in  $\alpha$ -position to **34** with a great diastereoselectivity ratio  $>20:1$  using a combination of organocatalyst  $(R,R)$ -2,5-diphenylpyrrolidine,  $\text{NCS}$ , and bromoacetic acid in 1,2-dichloroethane at  $0\text{ }^\circ\text{C}$  to obtain **35** (Scheme 1-4, eqn (2)).  $\alpha,\alpha$ -Dihalogenation (chlorination) of aldehyde **36** was successfully carried out without producing by-products such as  $\alpha$ -monochloroaldehyde or aldol products by reacting  $\text{NCS}$  and pyrrolidine

at 60 °C to gave **37** (Scheme 1-4, eqn (3)). In the ketone system,  $\alpha,\alpha$ -dihalogenation (bromination) can be applied with pyridinium tribromide as a brominating agent as in the bromination reaction of the 3-ketosteroid **38** to 2,4-dibromocholestanone **39** (Scheme 1-4, eqn (4)).<sup>21a</sup>

Enantioselective bromochlorination of allylic alcohols has become a recent topic to be developed where the problem of reaction selectivity is potentially complicated because regioisomeric products can be formed. Burns and co-workers recently developed catalytic enantioselective bromination (Scheme 1-5). This group reported a novel catalytic system involving *N*-bromosuccinimide, chlorotitanium triisopropoxide, and a Schiff tridentate chiral base catalyst for the enantioselective bromochlorination of allylic alcohols **40** to generate bromochlorinated alcohols **41**.<sup>23</sup>

Scheme 1-5. Enantioselective bromochlorination of allylic alcohols



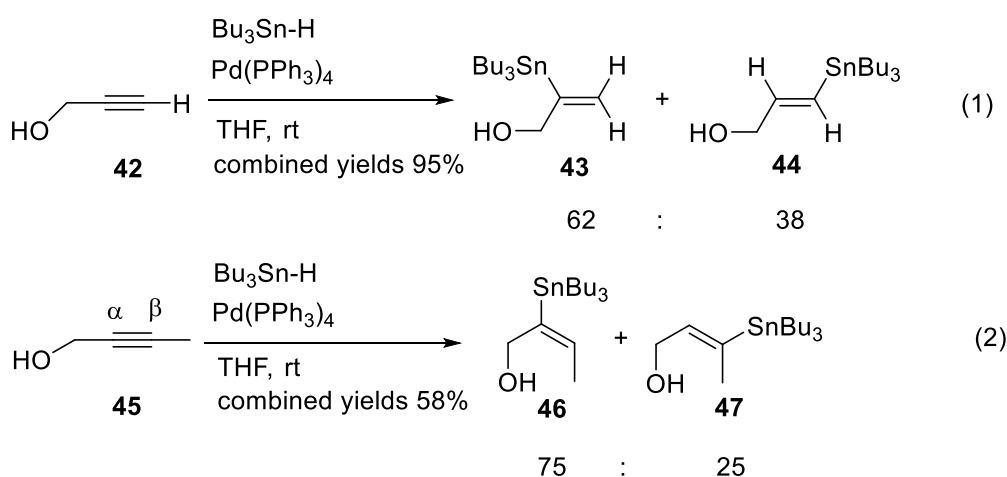
This interhalogenation reaction is rationalized by the complexed intermediate which enables the regioselectivity of bromide and chloride. The hydroxy moiety interacts with chlorotitanium triisopropoxide, rigidifying the system and potentially improving stereocontrol. The reaction was followed by electrophilic bromination using NBS to form of a complexed intermediate consisting of hydroxy moiety, chlorotitanium triisopropoxide and NBS. Even if this process is

rendered facial selective, there remains a regioselectivity challenge in the subsequent nucleophilic chlorination that attacks the two chiral positions in bromonium species. However, the rigidity of complexed intermediate can catalyze bromochlorination that favors *anti*-Markovnikov halide addition to C2 and regioselectivity was maintained.

#### 1-4 Synthetic study on construction of *E*- and *Z*-bromoolefin

*E*- or *Z*-Bromoolefin are also found in natural products which makes the synthesis of this unit very important. On the other hand, this unit is used as materials for vinylolithiums, vinyl Grignard reagents, alkynes,  $\alpha$ -halo ketones, and heterocycles preparation.<sup>24</sup> Several research groups have reported approaches toward *E*- or *Z*-bromoolefin construction. Halogenation of *E*- or *Z*-alkenylstannanes affords *E*- or *Z*-haloolefin.<sup>25</sup> Therefore, the reactivity and selectivity of this hydrostannation reaction become a very important step because halogenation at the end of the reaction is quite easy.

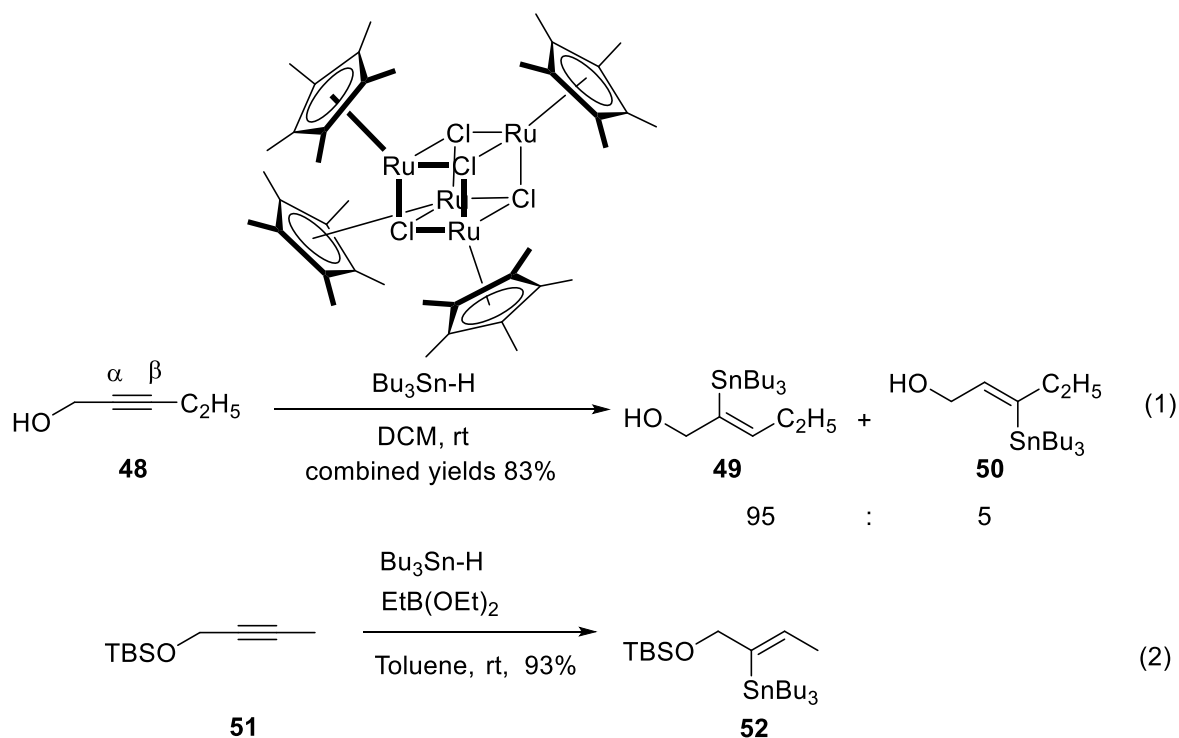
Scheme 1-6. Palladium-catalyzed hydrostannation of alkynes



Generally, palladium-catalyzed hydrostannation of alkynes gives *E*-alkenylstannanes through *syn*-addition. For terminal alkynes **42** (Scheme 1-6, eqn (1)), the reaction produces high

combined yields of products with moderate regioselectivity (62:38) between **43** and **44** respectively. Exclusive *syn*-addition, producing the  $\beta$ -*E*-adduct and the  $\alpha$ -isomer, occurs during the reaction. The reactivity and selectivity controlled by many factors, of which the structure of the alkyne substrate plays an important role. Evidently, hydrostannation to propargyl alcohol **45** give same reactivity and regioselectivity as well as terminal alkynes (Scheme 1-6, eqn (2)). The presence of propargyl heteroatom does not enhance the reactivity, although it gives fair selectivity (75:25) between **46** and **47**.<sup>26</sup>

Scheme 1-7. Z-Alkenylstannanes formation using ruthenium and boron as catalysts

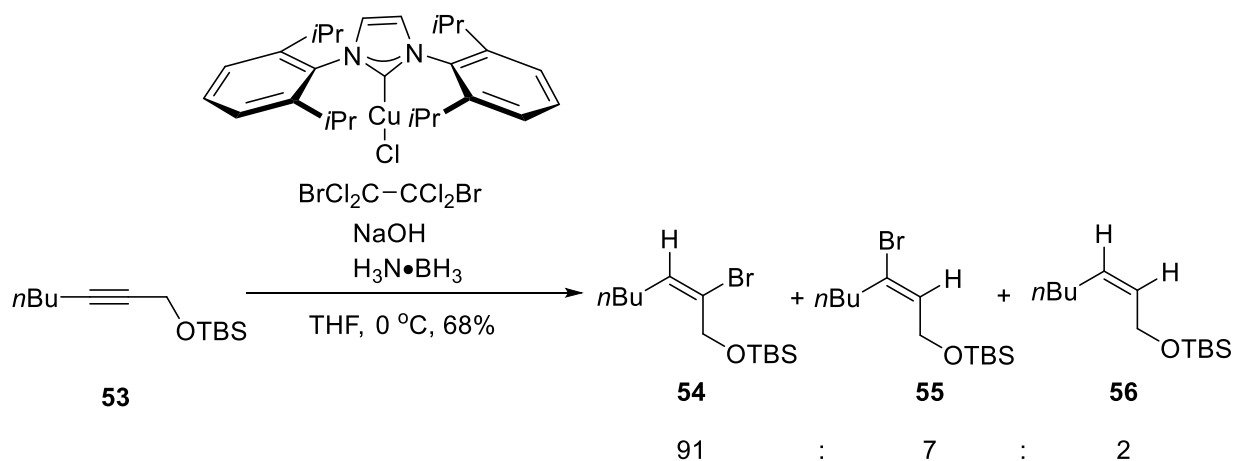


Other catalysts with ruthenium (Scheme 1-7, eqn (1)) and boron (Scheme 1-7, eqn (2)), promote *Z*-alkenylstannanilation of alkyne through *anti*-addition. Fürstner and co-workers reported that hydrostannation of unsymmetrical internal alkynes **48** provides the *anti*-addition products **49** and **50** in almost exclusive formation of a single  $\alpha$ -isomer in the presence of ruthenium-complex catalyst. Moreover, Froese and co-workers also presented that the presence

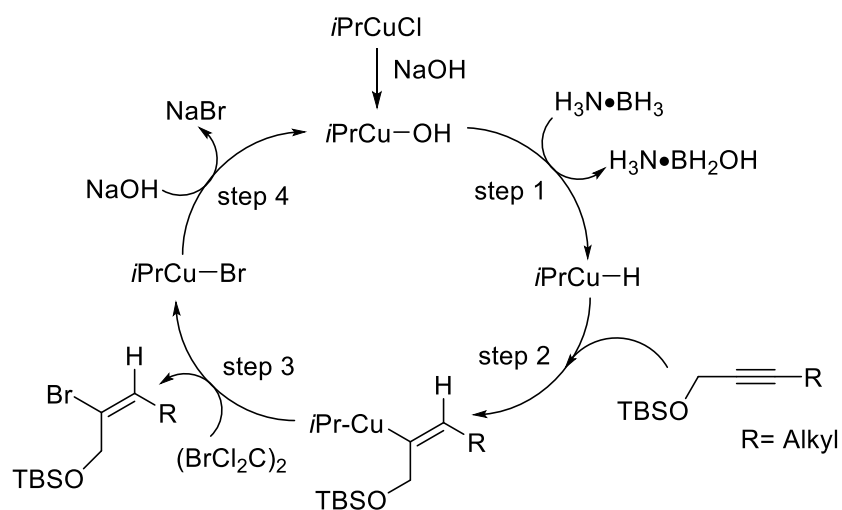
of EtB(OEt)<sub>2</sub> influences selectivity toward the formation of *Z*-alkenylstannanes from an *anti*-addition process and produce excellent desired products **52**.<sup>27</sup>

Teichert and co-workers propose a shorter pathway in *E*-bromoolefin preparation (Scheme 1-8). Based on their development, internal alkynes **53** was stereoselectively hydrohalogenated to the corresponding vinyl bromides **54** and **55** with halogen electrophiles (BrCl<sub>2</sub>C-CCl<sub>2</sub>Br) and copper catalysts. The catalytic cycle involves the transmetalation of copper hydroxide with the ammonia borane to form copper hydride (step 1), which, after hydrocupration of the alkyne (step 2), provides an alkenyl copper intermediate. Subsequent electrophilic bromination of the alkenyl copper intermediate (step 3) provides the desired product and copper bromide. Catalyst turnover (step 4) is accomplished by ligand substitution in the presence of NaOH (Scheme 1-9). Brominated allyl silyl ether products have been isolated with good stereoselectivity (*E/Z* > 95:5), and with acceptable to good regioselectivity ratio 91:7:2.<sup>28</sup>

Scheme 1-8. Hydrobromination of internal alkynes

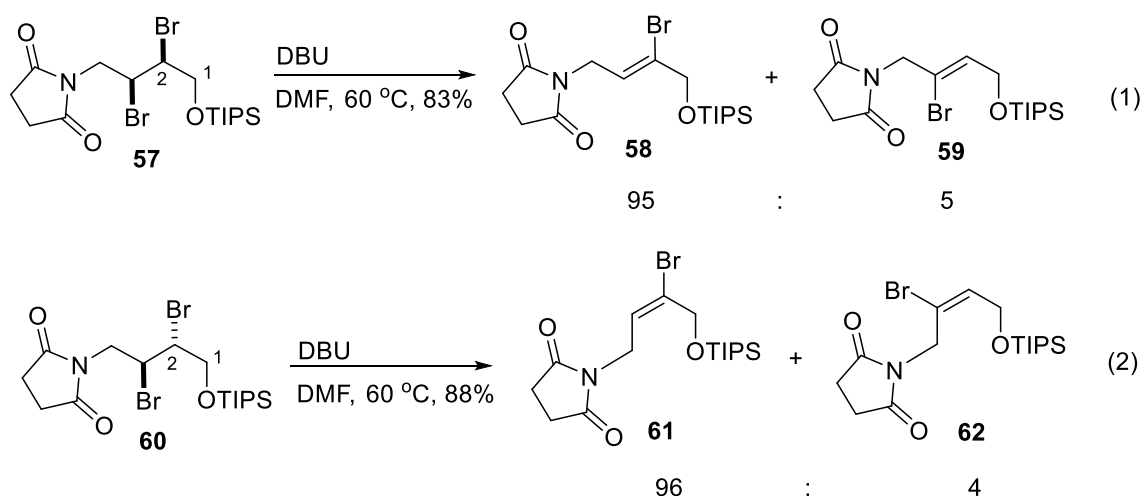


Scheme 1-9. Mechanism of hydrobromination of internal alkynes



Other unique approaches without catalyst are also reported to create another bromoolefin in excellent reactivity and selectivity. Nishiyama and Saito's groups reported that the regioselective HBr elimination reaction of vicinal dibromides having an imide group under basic condition by 1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU) can produce *E*-bromoolefin (**61** and **62**) (Scheme 1-10, eqn (2)) or *Z*-bromoolefin (**58** and **59**) (Scheme 1-10, eqn (1)) in good yield and high regioselectivity. Based on their explanation, DBU-promoted HBr-elimination is affected by the electronic interaction of the neighbouring heteroatoms. The elimination selectivity is more directly affected by the electronegativity of the oxygen atoms themselves than the electron-withdrawing effects. However, the presence of electron-withdrawing groups also increases the electronegativity of the oxygen atom thereby enhancing the acidity of the hydrogen at the target position. Steric interaction also does not affect selectivity. The configuration of desired products (*E*- or *Z*-olefin) are determined by the starting materials. HBr-elimination to *anti*-dibromide provides *E*-bromoolefin and *syn*-dibromide provides *Z*-bromoolefin.<sup>21b,24</sup>

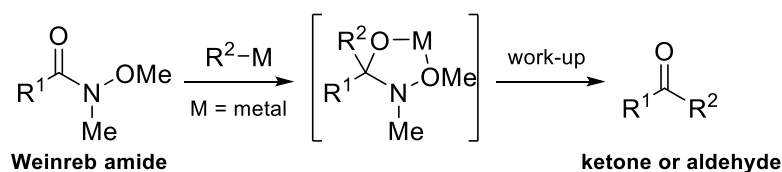
Scheme 1-10. Regioselective HBr elimination reaction of vicinal dibromides



### 1-5 Synthetic study utilizing Weinreb amide

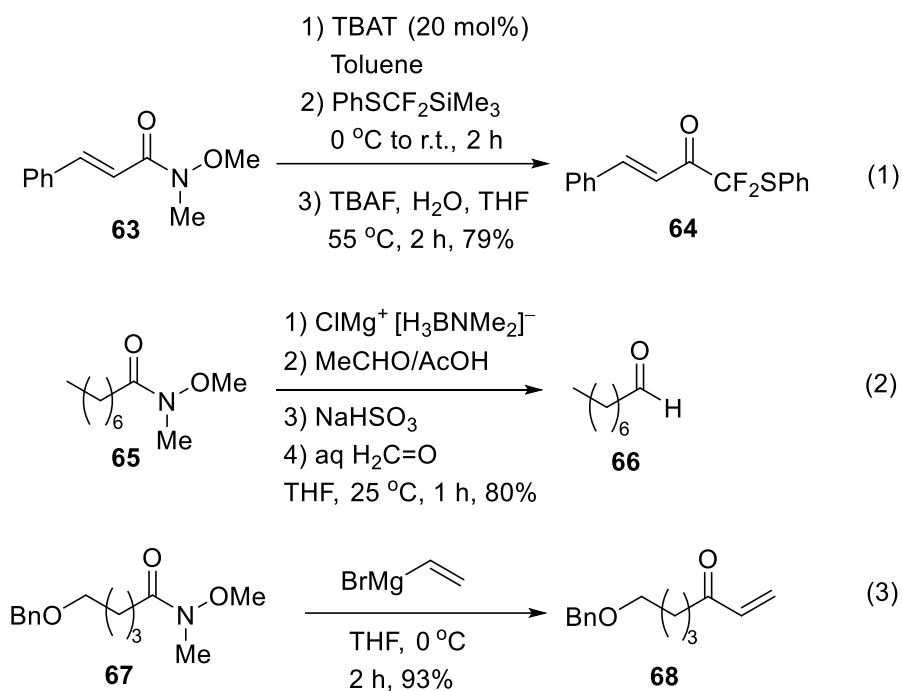
*N*-methoxy-*N*-methyl amide often called Weinreb amide is a very useful precursor in organic synthesis, especially for preparing ketones and aldehydes by treatment with nucleophiles (Grignard reagent, alkyl lithium, lithium enolate, phosphonium ylides, LiAlH<sub>4</sub>, DIBAL-H, etc.). Nahm and Weinreb first developed this reaction in 1981 and rapidly became popular. This amide has a unique property that can receive only one equivalent of a nucleophile to form a stable intermediate with high chemoselectivity, making an addition of a second equivalent difficult (Scheme 1-11). It can be useful for the synthesis of ketone, aldehyde, and  $\beta$ -ketoester.<sup>29</sup>

Scheme 1-11. Reactivity of Weinreb amide



The utilization of Weinreb amide is very wide in the field of organic synthesis.<sup>30</sup> Some examples from other research groups showed the effectivity of Weinreb amide for nucleophilic addition and reduction. Kuhakarn and co-workers have accomplished nucleophilic addition reaction with Weinreb amide **63** to give difluoromethyl ketones **64** in good yield (Scheme 1-12, eqn (1)). The advantages of Weinreb amide are evident when an amide with  $\alpha$ -hydrogen is used. In the reaction reported by Singaram and He (Scheme 1-12, eqn (2) and (3)), the reduction and addition reactions in an basic condition well and gave high yields without any interaction with acidic  $\alpha$ -hydrogen (**65** to **66** and **67** to **68**).

Scheme 1-12. Utilization of Weinreb amide in organic synthesis

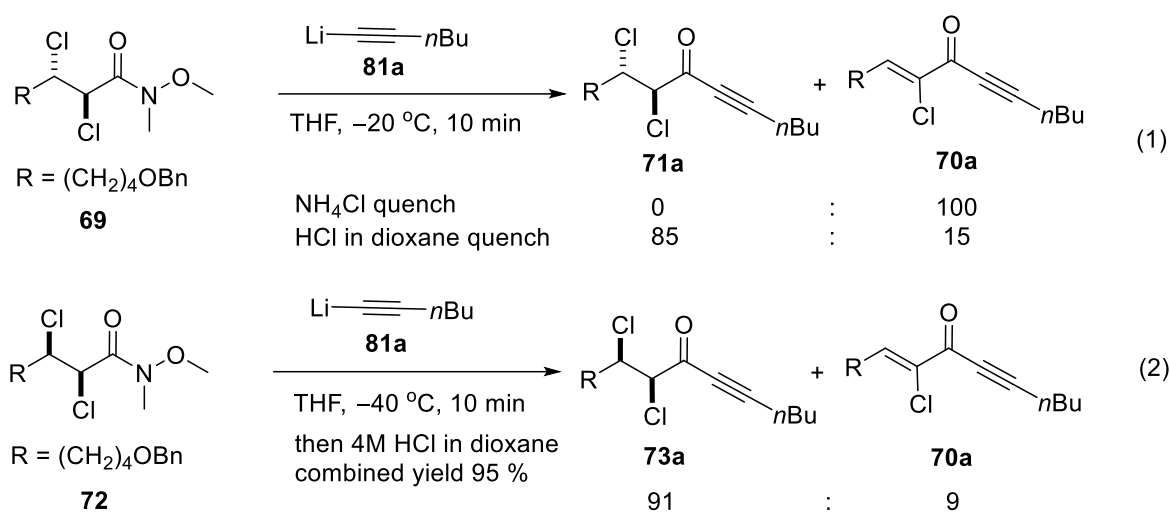




## 1-6 Overview of this thesis: Synthetic study on halogenated natural products

In order to synthesize halogen-containing compounds, further synthetic methodologies would be developed prior to the synthesis of the natural product. However, many reactions are focusing on the installation of halogen atoms. On the other hand, new methodologies with halogenated compounds are rare to overcome a novel property of the halogen atom, such as high activity toward  $\beta$ -elimination reaction of carbonyl compound. In this thesis, new effective synthetic methodologies via Weinreb amide will be described as the main study. The latest is its use in the synthesis of  $\alpha,\beta$ -dichlorinated ketones, which has been completed with excellent results by our research group.<sup>31</sup> The synthesis of  $\alpha,\beta$ -dichlorinated ketones is very challenging because the substrate used is  $\alpha,\beta$ -dichlorinated Weinreb amide. In nucleophilic addition to the substrate **69**, it is possible that the basicity of the nucleophile induces an undesired  $\beta$ -elimination reaction between the  $\alpha$ -proton and  $\beta$ -halogen (Scheme 1-13, eqn (1)) and produces **70a**. Through tremendous effort in exploring optimization conditions to obtain ketone products, our research group finally found a solution by adding 4 M HCl in dioxane as a quenching agent. It can change the direction of the reaction towards the desired product,  $\alpha,\beta$ -dichlorinated ketones in high product ratios of up to 85:15 for *anti*-dichloro ketone **71a** (Scheme 1-13, eqn (1)) and 91:9 for *syn*-dichloro ketone **73a** (Scheme 1-13, eqn (2)) whereas normal quenching using saturated  $\text{NH}_4\text{Cl}$  solution resulted the formation of elimination products **70a**. Author next examined other quenching conditions and nucleophiles for the addition reactions will explain in more detail in Chapter 2.

Scheme 1-13. Nucleophilic addition to  $\alpha,\beta$ -dichlorinated Weinreb amides

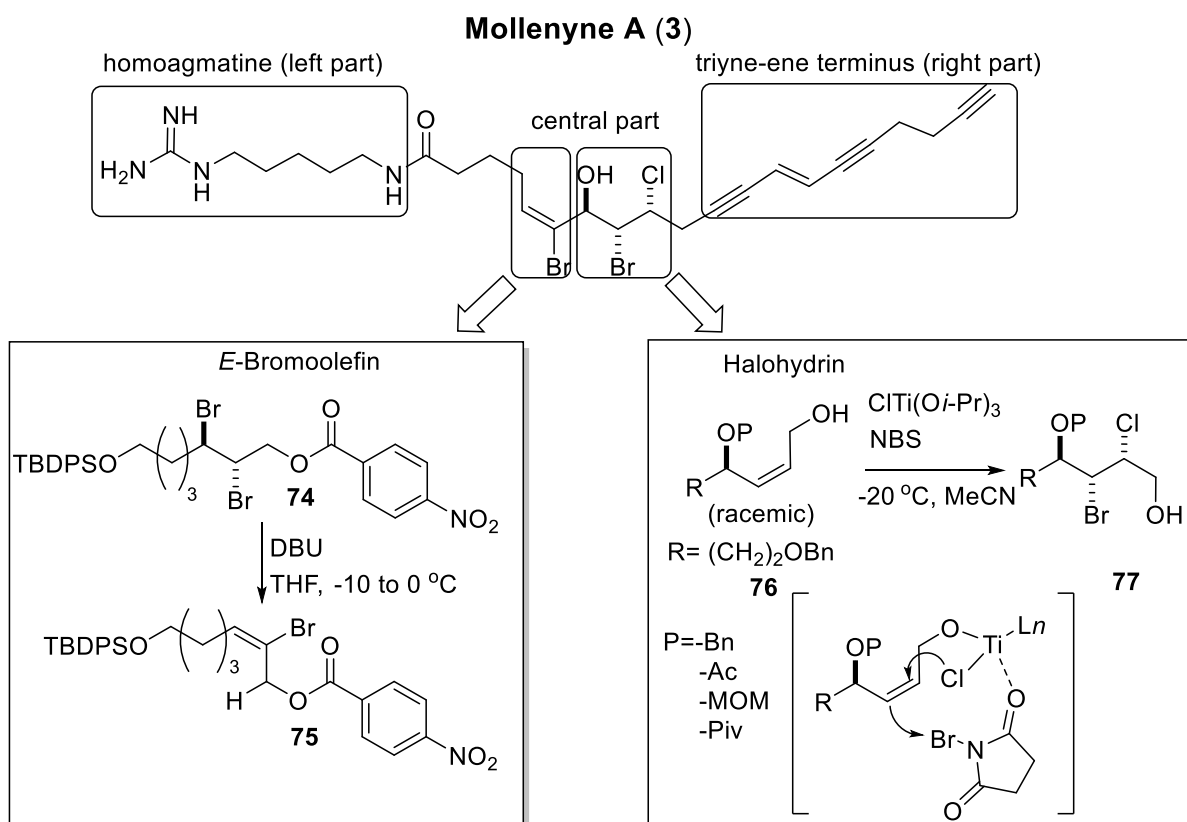


This invention would be a powerful method for the elongation of hydrocarbon frameworks densely functionalized with chlorine atoms and opens up opportunities for reactions related to the preparation of halogenated natural compounds such as halohydrin construction. For example, it can be applied in some synthetic studies of halogenated natural compounds that have halohydrin part, such as mollenyne A (**3**) or chlorosulfolipids (CSLs) because the normal synthetic pathways from  $\alpha,\beta$ -dichlorinated aldehyde never gave the target product.<sup>22,32</sup>

In addition, a synthesis study of a halogenated compound, Mollenyne A was also carried out as part of this thesis. Mollenyne A (**3**) was isolated from the sponge *Spirastrella mollis* from Plana Cays, Bahamas by Molinski's group and has a biological activity as an anti-tumor potential in human colon tumor cells (HCT-116, with  $\text{IC}_{50} = 1.3\text{ }\mu\text{g/mL}$ ).<sup>9c</sup> Mollenyne A includes three important fragments (Scheme 1-14), homoagmatine (left part), allylic alcohol flanked by halogenated carbons (central part) and tryne-ene terminus (right part). Due to the promising the biological activity as well as the intriguing chemical structure, the synthetic study of Mollenyne A has been started by author for abundant supply. The central part can be divided into two parts, the *E*-bromoolefin and halohydrin. The *E*-bromoolefin moiety was prepared with *anti*-dibromo benzoate **74** via regio- and stereoselective *E*-elimination. *p*-Nitrobenzoyl group induced the desired elimination reaction through increase of the acidity of

the hydrogen at the target position.<sup>21b,24</sup> On the other hand, the halohydrin was also investigated with racemic model alcohol **76**. Based on crucial findings by Burns,  $\text{TiCl}(\text{O}i\text{-Pr})_3$  as a  $\text{Cl}^\ominus$  source and NBS as a  $\text{Br}^\oplus$  source were used in the regioselective bromochlorination reaction to produce **77**.<sup>23</sup> Effects of a substituent on hydroxy group toward diastereoselectivity are examined by author in Chapter 3.

Scheme 1-14. Synthetic study plan



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## **CHAPTER 2**

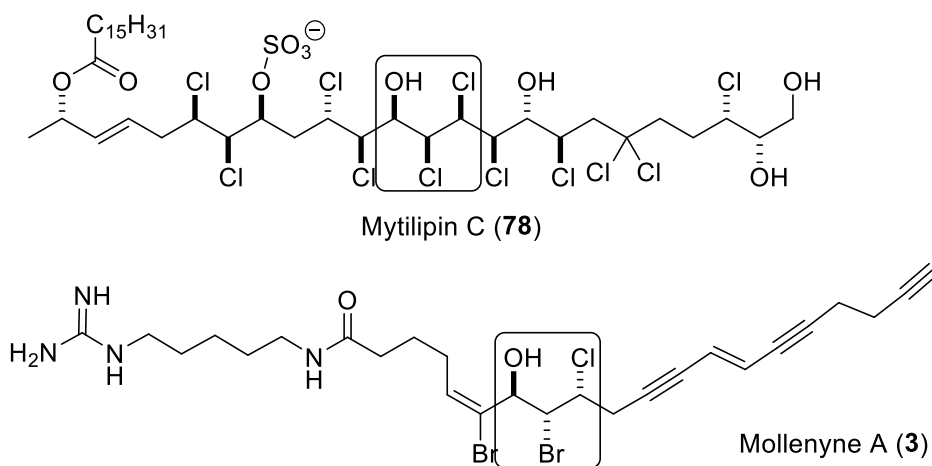
### **Synthesis of $\alpha,\beta$ -dichlorinated ketones with Weinreb amide**



## 2-1 Introduction

Natural products including halogen atoms are often found in land and marine organisms, and have unique biological activities. As examples, two halogenated natural products (Figure 2-1); mytilipin C (**78**) with antiproliferation activity against WEHI164 and J774 cells<sup>1</sup> and mollenyne A (**3**) with cytotoxicity against human colon tumor cells.<sup>2</sup> The two compounds have a similar part, the halohydrin part. In order to synthesize halogenated compounds with halohydrin part (highlighted by squares), effective synthetic methodologies are limited. Access to that part can be approached via some methods and Weinreb amide is one of the alternatives. Before the synthesis of natural halogenated products, development of new effective synthetic methodologies via Weinreb amide would be planned.

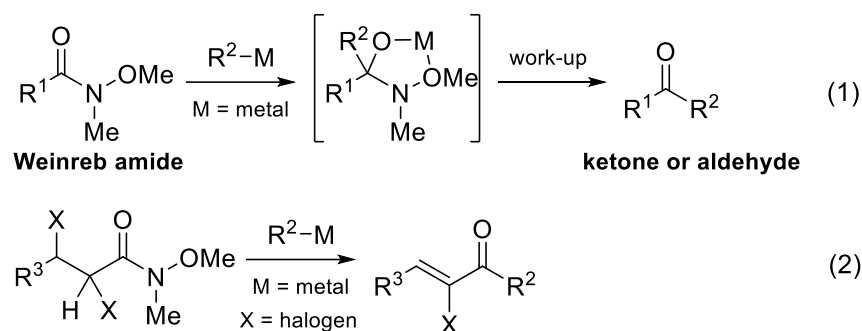
Figure 2-1. Structure of Mytilipin C (**78**) and Mollenyne A (**3**)



Weinreb amide has rapidly become popular in organic synthesis because it can be useful for the synthesis of ketone, aldehyde,  $\beta$ -ketoester by addition of nucleophile such as Grignard or alkyl lithium reagents (Scheme 2-1 eqn 1).<sup>4</sup> This amide is used in some construction of natural products and frequently becomes one of the crucial steps.<sup>3</sup> Although the use of Weinreb amides is extensive in various synthetic endeavors, to the best of my knowledge, the nucleophilic addition to  $\alpha,\beta$ -dihalogenated Weinreb amide has not been reported, excepting for  $\beta$ -fluoride<sup>5</sup>

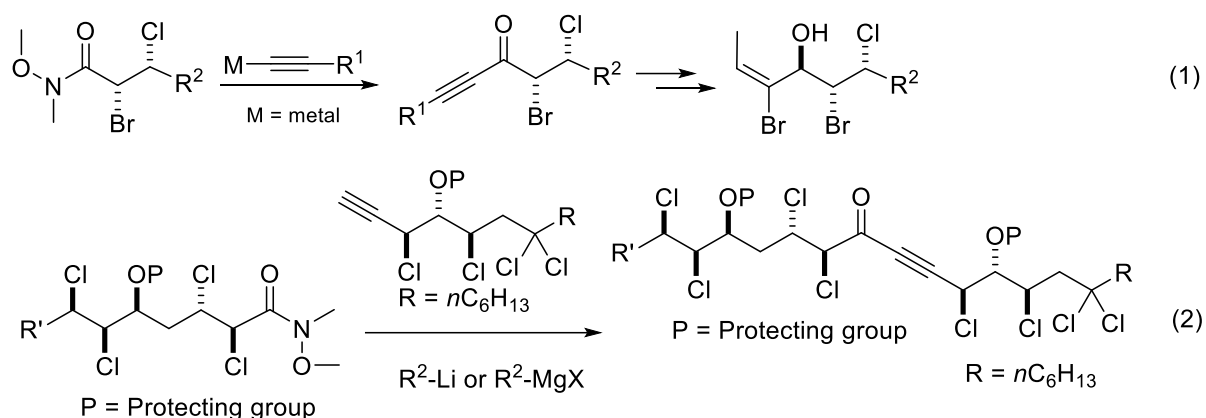
or no  $\alpha$ -proton<sup>6</sup> in the amide. This is because the basicity of the nucleophile potentially encourages side reactions to induce an undesired  $\beta$ -elimination reaction between  $\alpha$ -proton and  $\beta$ -halogen. The abstraction of the acidic proton of the desired compound by the additional R<sup>2</sup> group is thought to be the reason (Scheme 2-1 eqn 2).

Scheme 2-1. Reactivity of Weinreb amide



As extensive halogenated natural products have been isolated,<sup>7</sup> new methodology for the addition of nucleophiles to Weinreb amide with halides enables rapid access to the synthesis of halogenated natural products, such as chlorosulfolipids (CSLs), a member of natural products having many chlorides on a simple alkyl chain.<sup>8,9</sup> Nowadays, our group is currently focused on developing the use of Weinreb amide as an important step in synthesizing mytilipin C and Mollenyne A. One of our concerns is the construction of the halohydrin part. We envisioned that the reaction between the halogenated Weinreb amide with an acetylide could be a key step (Scheme 2-2). Furthermore, it needs to be studied more intensively using model compounds. If this plan is successful, the reaction can be continued to the following reaction, such as selective reduction, hydrogenation and halogenation. In this chapter, the author shows development of new effective methods for synthesizing  $\alpha,\beta$ -dichlorinated ketone as the target products by nucleophilic addition to the corresponding  $\alpha,\beta$ -dichlorinated Weinreb amide.

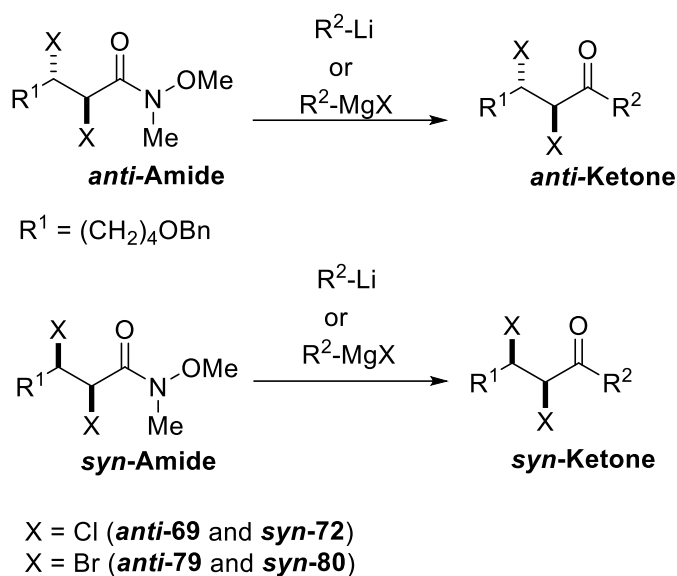
Scheme 2-2 Construction process of halohydrins groups from Mytilipin C and Mollenyne A



## 2-2 Study Plan

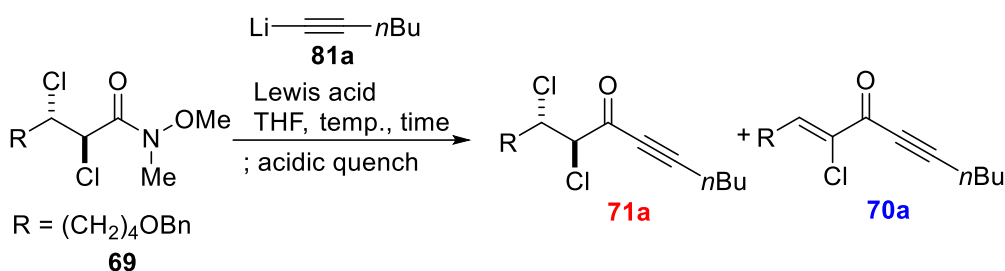
In this study, author planned to overcome the lability of  $\alpha,\beta$ -dichlorinated Weinreb amide using model substrates. Amide *anti-69* and *syn-72* were employed to optimize the reaction conditions about temperature and quench conditions with the acetylide prepared from 1-hexyne and  $nBuLi$  or Grignard reagent as a nucleophile (Scheme 2-3). According to the synthesis pathway presented in the Scheme 2-2, this acetylide is important in constructing process of halohydrins groups from Mytilipin C and Mollenyne A. After the investigation using chlorinated Weinreb amide was completed and successful, the study will continue using brominated Weinreb amide *anti-79* and *syn-80*.

Scheme 2-3. Nucleophilic addition to  $\alpha,\beta$ -dihalogenated Weinreb amide



### 2-3 Optimization with *anti*-dichlorinated Weinreb amide

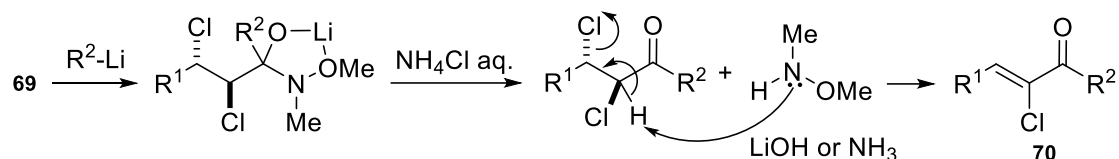
First, *anti*-dichloroamide **69** as a model substrate was used in the optimization of nucleophilic addition reaction with  $n\text{BuC}\equiv\text{CLi}$  (**81a**) generated from 1-hexyne and  $n\text{BuLi}$ . Results of the optimizations are shown in Table 2-1. Treatment of **69** with 3.0 equivalents of **81a** at 0 °C, -40 °C or -78 °C followed by acidic quench with  $\text{NH}_4\text{Cl}$  gave only the undesired  $\alpha,\beta$ -unsaturated ketone **70a** as a main product without formation of the desired *anti*-dichloroketone **71a** (entry 1-3). Lowering the reaction temperature from 0 °C to -40 °C or -78 °C cannot inhibit  $\beta$ -elimination reaction between  $\alpha$ -proton and  $\beta$ -halogen. In fact, the nucleophilic addition cleanly took place in these reactions.  $\alpha,\beta$ -Unsaturated ketone **70a** was obtained in high yield at 0 °C or -40 °C (entries 1 and 2) and when the reaction at -78 °C resulted in partial recovery of **69** (entry 3). As shown in Scheme 2-4, author envisioned that abstraction of  $\alpha$ -proton from **71a** occurred by basic substances generated during the treatment of aqueous  $\text{NH}_4\text{Cl}$ , such as lithium *N*-methoxy-*N*-methylamide,  $\text{LiOH}$ , and/or  $\text{NH}_3$ , due to weak acidity of  $\text{NH}_4\text{Cl}$ . Because the presence of water in the quenching process potentially generates basic substances, the use of an appropriate acid such as anhydrous acetic acid or hydrochloric acid would afford the target.

Table 2-1. Optimization of reaction conditions<sup>a</sup>

entry	<b>81a</b> (equiv.)	Lewis Acid <sup>b</sup>	Temp. (°C)	Time (min)	Acidic quench <sup>c</sup>	Ratio ( <b>69</b> : <b>71a</b> : <b>70a</b> ) <sup>d</sup> and Combined yield ( <b>71a</b> + <b>70a</b> )
1	3.0	–	0	30	<i>sat.</i> NH <sub>4</sub> Cl	0:0:100, 96%
2	3.0	–	–40	30	<i>sat.</i> NH <sub>4</sub> Cl	0:0:100, 94%
3	3.0	–	–78	30	<i>sat.</i> NH <sub>4</sub> Cl	35:0:65, 59%
4	3.0	–	0	30	CH <sub>3</sub> COOH	0:58:42, 95%
5	3.0	–	0	30	1 M HCl in H <sub>2</sub> O	0:61:39, 92%
6	3.0	–	0	10	4 M HCl in H <sub>2</sub> O	0:74:26, 91%
7	3.0	–	0	10	(CH <sub>3</sub> CO) <sub>2</sub> O	0:71:29, 96%
8	3.0	–	0	30	4 M HCl in dioxane	0:76:24, 93%
9	3.0	–	0	10	4 M HCl in dioxane	0:85:15, 98%
10 <sup>e</sup>	3.0	–	0	10	4 M HCl in dioxane	0:86:14, 96%
11	3.0	–	–20	10	4 M HCl in dioxane	0:81:19, 95%
12	1.5	–	0	10	4 M HCl in dioxane	0:79:21, 94%
13	1.5	BF <sub>3</sub> ·OEt <sub>2</sub>	0	30	4 M HCl in dioxane	64:26:10, 30%
14	1.5	MgBr <sub>2</sub> ·OEt <sub>2</sub>	0	30	4 M HCl in dioxane	58:32:10, 39%
15	1.5	CeCl <sub>3</sub>	0	30	4 M HCl in dioxane	10:60:30, 81%

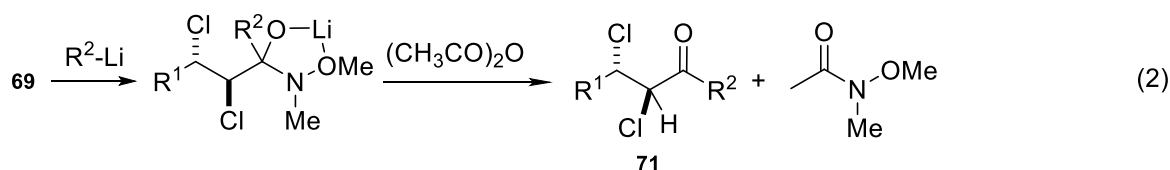
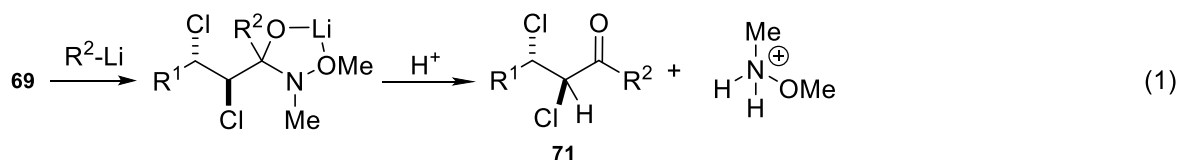
<sup>a</sup>Reaction conditions: 0.3 mmol of **69** was used. <sup>b</sup>1.5 equiv. of Lewis acid was used. <sup>c</sup>5.0 equiv. of acid was used except for NH<sub>4</sub>Cl. <sup>d</sup>ratio of **69**, **71a**, and **70a** was estimated by crude <sup>1</sup>H NMR. <sup>e</sup>Cold HCl in dioxane was used with slowly addition.

Scheme 2-4. Proposed reaction pathway to provide unsaturated ketone **70**



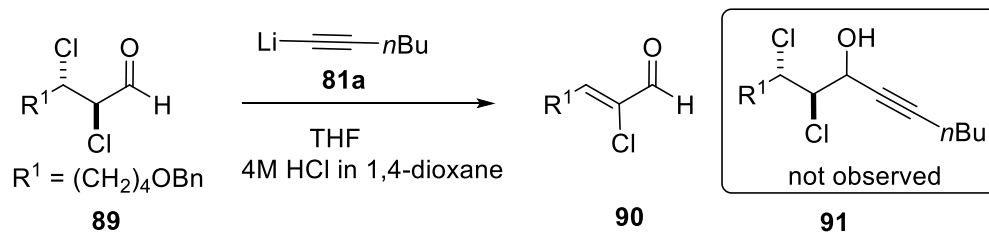
In order to inhibit the abstraction of  $\alpha$ -proton during work-up process to generate the target **71a**,  $\text{CH}_3\text{COOH}$  was used. As expected, **71a** was obtained along with **70a** in 58:42 ratio, when the reaction was quenched with 5.0 equivalent of  $\text{CH}_3\text{COOH}$  (entry 4). Quench using aqueous 1 M HCl and 4 M HCl increased the amount of **71a** (61:39, entry 5) and (74:26, entry 6) respectively. These results clearly shows the product ratio was affected by the acidity of acid employed (Scheme 2-5 eqn 1). Unfortunately, the addition of acetic anhydride (Scheme 2-5 eqn 2), which is expected to be able to capture the amine species as acetamide that are released during the reaction, is not enough to increase the desired product ratio (entry 7). Finally, the encouraging results were obtained where the ratio of **71a** to **70a** was considerably improved up to 86:14 through work-up with commercially available 4 M HCl in dioxane (entries 8-12).

Scheme 2-5. Proposed reaction pathway to improve the ratio of **71** using acid and acetic anhydride



The absence of water in the reaction seems crucial in increasing the desired product ratio. The presence of water can trigger hydrolysis to release amine, which can abstract  $\alpha$ -hydrogen to give the undesired compound **70** during the quench operation (Scheme 2-4). Remarkably, the reaction of **69** with 1.5 equivalent of **81a** (entry 12) gave almost the same result with 3.0 equivalent of **81a** (entry 8). In this case, quench with 4 M HCl in dioxane is very important to improve the ratio of desired products. On the other hand, the addition of Lewis acid, which is expected to improve the ratio, was not effective in the selective synthesis of **71a** (entries 13-15). Additionally, nucleophilic addition with  $\alpha,\beta$ -dichlorinated aldehyde **89** instead of the corresponding amide toward homologation reaction just provided  $\beta$ -eliminated aldehyde **90** (Scheme 2-6), suggesting the Weinreb amide is a promising precursor toward homologation reaction through the addition reaction. As described above, preparation of  $\alpha,\beta$ -dichlorinated ketone from the corresponding  $\alpha,\beta$ -dichlorinated Weinreb amide could first be achieved.

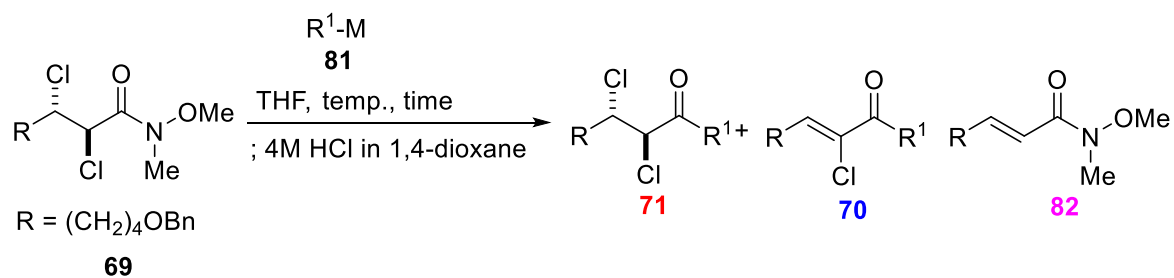
Scheme 2-6. Nucleophilic addition with  $\alpha,\beta$ -dichlorinated aldehyde **89**



Furthermore, the addition reactions of **69** were next examined by using other nucleophiles. The nucleophilic addition reactions were carried out with 1.5 equivalent of nucleophiles. After further optimizations, the results along with the reaction conditions are presented in Table 2-2. As shown in entries 1 and 2, treatment of **69** with *n*BuLi (**81b**) in the manner of different reaction temperature influenced the ratios of residual substrate **69** and products (**71b** and **70b**). *anti*-Dichloroketone **71b** was selectively formed in high yield at higher temperature ( $-20$  °C) (entry 2). A high yield of *anti*-dichloroketone **71c** was obtained selectively by using PhLi (**81c**)

(entry 3). In this case, using a low temperature ( $-20\text{ }^{\circ}\text{C}$ ) is thought to reduce the intermolecular collisions in the nucleophilic addition reaction, making it run more selectively than at higher temperatures.

Table 2-2. Examination of the addition reactions using other nucleophiles to **69**<sup>a</sup>



entry	$\text{R}^1\text{M}$ (1.5 equiv.)	Temp. ( $^{\circ}\text{C}$ )	Time (min)	Ratio ( <b>69</b> : <b>71</b> : <b>70</b> ) <sup>b</sup> and combined yield ( <b>71</b> + <b>70</b> )
1	<i>n</i> BuLi ( <b>81b</b> )	$-40$	30	19: <b>58</b> : <b>23</b> , 79%
2	<i>n</i> BuLi ( <b>81b</b> )	$-20$	30	0: <b>89</b> : <b>11</b> , 98%
3	PhLi ( <b>81c</b> )	$-20$	30	0: <b>85</b> : <b>15</b> , 94%
4	$\text{CH}_3\text{MgBr}$ ( <b>81d</b> )	0	120	0: <b>91</b> : <b>9</b> , 98%
5	$\text{CH}_2=\text{CHMgCl}$ ( <b>81e</b> )	0	120	0: <b>95</b> : <b>5</b> , 97%
6	<i>n</i> C <sub>5</sub> H <sub>11</sub> MgBr ( <b>81f</b> )	0	120	0: <b>87</b> : <b>13</b> , 96%
7	PhMgBr ( <b>81g</b> )	0	120	13: <b>51</b> : <b>36</b> , 83%
8	PhMgBr ( <b>81g</b> )	0	240	0: <b>64</b> : <b>36</b> , 96%
9	$\text{HC}\equiv\text{CMgCl}$ ( <b>81h</b> )	0	120	0: <b>35</b> : <b>65</b> , 90%
10	<i>n</i> BuC $\equiv$ CMgCl ( <b>81i</b> )	0	10	100: <b>0</b> : <b>0</b>
11	<i>n</i> BuC $\equiv$ CMgCl ( <b>81i</b> )	0	240	0: <b>55</b> : <b>45</b> , 81%
12	<i>i</i> PrMgBr ( <b>81j</b> )	0	240	<b>82</b> (93%)

<sup>a</sup>Reaction conditions: 0.3 mmol of **69** was used. <sup>b</sup>ratio of **69**, **71**, and **70** was estimated by crude <sup>1</sup>H NMR.

It was turned out that Grignard reagents are also good nucleophiles for the addition reactions to  $\alpha,\beta$ -dichlorinated Weinreb amide. Treatment of **69** with  $\text{CH}_3\text{MgBr}$  (**81d**),  $\text{CH}_2=\text{CHMgCl}$  (**81e**), or *n*C<sub>5</sub>H<sub>11</sub>MgBr (**81f**) gave *anti*-dichloroketone **71d**, **72e** or **73f**, respectively, in high



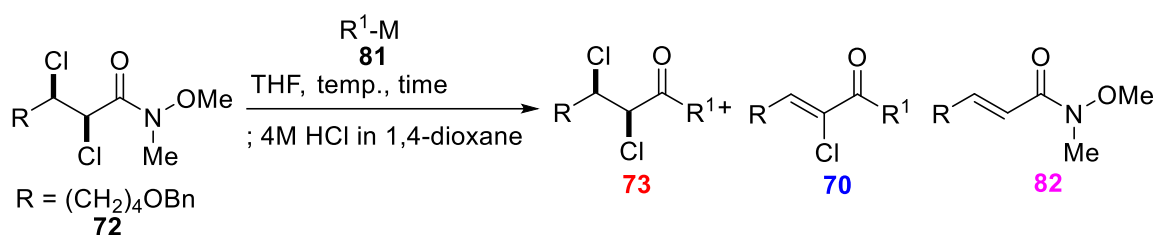
yields with great selectivity (entries 4-6). The higher reaction temperature and longer reaction time due to the lower reactivity of Grignard reagent than organolithium as a nucleophile.<sup>10</sup> However, the reactions with PhMgBr (**81g**), HC≡CMgCl (**81h**) and *n*BuC≡CMgCl (**81i**) afforded product with a low selectivity ratios (entries 7-11) in contrast to that observed in the reactions with the corresponding Li-reagents, PhLi (**81c**) (entry 3) and *n*BuC≡CLi (**81a**) (Table 2-1, entry 9), respectively. The lack of nucleophilicity followed by the long reaction time required to complete the reaction makes the selectivity of the desired product became low. Surprisingly, when **69** was reacted with *i*PrMgBr (**81j**),  $\alpha,\beta$ -unsaturated amide **82** was only produced without nucleophilic addition products (entry 12). The author believes that *i*PrMgBr (**81j**) has a high reducing ability that can initiate the reduction of a chlorine atom at the  $\alpha$ -position of the carbonyl group.<sup>11</sup>

#### 2-4 Optimization with *syn*-dichlorinated Weinreb amide

*syn*-Dichloroamide **72** was also employed as a model substrate in the nucleophilic addition reaction. Some treatments related with reaction conditions were examined to **72** for discovering the efficient formation of desired *syn*-dichloroketone **73**. After further optimizations, the results along with the reaction conditions are presented in Table 2-3. As shown in entries 1 and 2, during the reactions of **72** with *n*BuC≡CLi (**81a**), higher ratio of *syn*-dichloroketone **73a** was obtained at lower temperature (−40 °C) where the higher reaction temperature (−20 °C) decreases the selectivity of the reaction. In general, all treatments to **72** using lower temperature if compared with **69**. These treatments can reduce the intermolecular collisions in the reaction to produce high selectivity products because the reactivity between **72** and **69** seems different. The addition reaction to **72** with *n*BuLi (**81b**) at low temperature (−40 °C) also provided *syn*-dichloroketone **73b** in high yield (entry 3). In general, the reactions of *syn*-dichloroamide **72** with *n*BuC≡CLi (**81a**) and *n*BuLi (**81b**) smoothly proceeded with high selectivities to give **73a**

and **73b** in high yields similarly to those of *anti*-dichloroamide **69** with **81a** (Table 2-1, entry 9) and **81b** (Table 2-2, entry 2) although the addition of **72** requires lower reaction temperature than that of **69**. However, in contrast to the reaction of **69** with **81c** (Table 2-2, entry 3), treatment of **72** with PhLi (**81c**) just produced elimination product **70c** as a sole product (entry 4).

Table 2-3. Examination of the addition reactions using other nucleophiles to **72**<sup>a</sup>

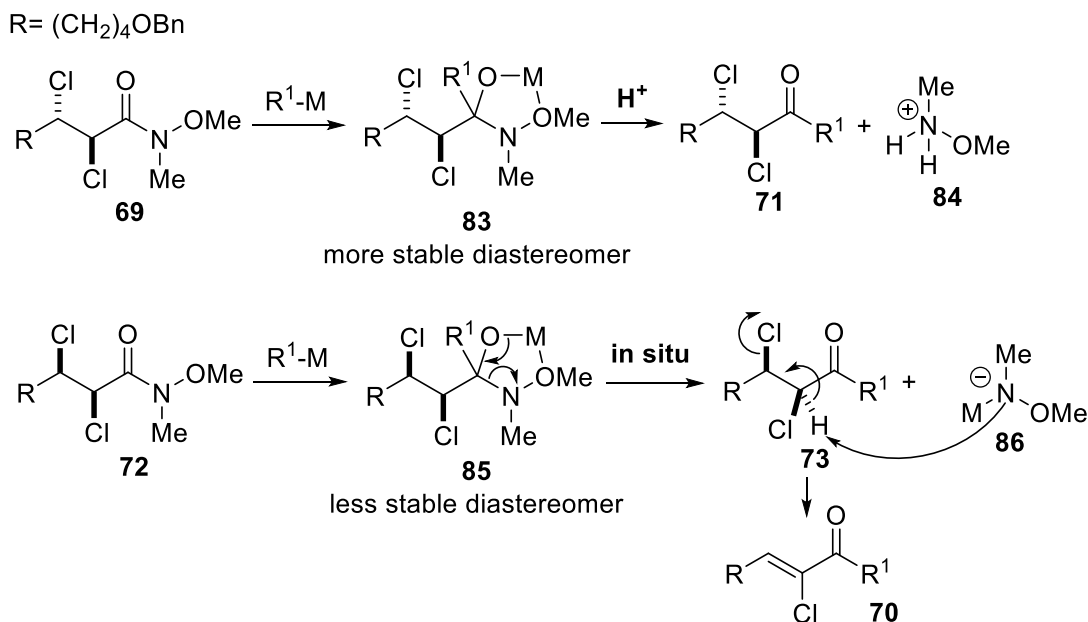


entry	R <sup>1</sup> M (1.5 equiv.)	Temp. (°C)	Time (min)	Ratio ( <b>72</b> : <b>73</b> : <b>70</b> ) <sup>b</sup> and combined yield ( <b>73</b> + <b>70</b> )
1	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>	-20	10	0: <b>81</b> : <b>19</b> , 94%
2	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>	-40	10	0: <b>91</b> : <b>9</b> , 95%
3	<i>n</i> BuLi ( <b>81b</b> )	-40	30	0: <b>83</b> : <b>17</b> , 95%
4	PhLi ( <b>81c</b> )	-20	30	0: <b>0</b> : <b>100</b> , 78%
5	CH <sub>3</sub> MgBr ( <b>81d</b> )	0	120	0: <b>0</b> : <b>100</b> , 94%
6	CH <sub>3</sub> MgBr ( <b>81d</b> )	-20	120	0: <b>88</b> : <b>12</b> , 95%
7	CH <sub>2</sub> =CHMgCl ( <b>81e</b> )	0	120	0: <b>0</b> : <b>100</b> , 90%
8	CH <sub>2</sub> =CHMgCl ( <b>81e</b> )	-40	30	45: <b>0</b> : <b>55</b> , 51%
9	<i>n</i> C <sub>5</sub> H <sub>11</sub> MgBr ( <b>81f</b> )	-20	120	0: <b>54</b> : <b>46</b> , 90%
10	PhMgBr ( <b>81g</b> )	-20	120	26: <b>0</b> : <b>74</b> , 74%
11	HC≡CMgCl ( <b>81h</b> )	0	120	100: <b>0</b> : <b>0</b>
12	<i>i</i> PMgBr ( <b>81j</b> )	0	240	<b>82</b> (90%)

<sup>a</sup>Reaction conditions: 0.3 mmol of **72** was used. <sup>b</sup>Ratio of **72**, **73**, and **70** was estimated by crude <sup>1</sup>H NMR. <sup>c</sup>3.0 equiv. of **81a** was used.

Among Grignard reagents screened,  $\text{CH}_3\text{MgBr}$  (**81d**) was found to be a good nucleophile in the reaction of **72** at a lower temperature ( $-20\text{ }^\circ\text{C}$ ) (entries 6), wherein higher temperature ( $0\text{ }^\circ\text{C}$ ) just produced elimination product **70d** (entries 5). The addition reaction with  $n\text{C}_5\text{H}_{11}\text{MgBr}$  (**81f**) could produce *syn*-dichloroketone **73f** as a major product in moderate yield and low selectivity (entry 9). However, other Grignard reagents **81e**, **81g**, and **81h** were not effective for the formation of **73** (entries 7, 8, 10, and 11), showing different reactivity of **69** with **81e**, **81g**, and **81h** (Table 2-2, entry 5-9). Treatment of **72** with  $\text{CH}_2=\text{CHMgCl}$  (**81e**) at  $0\text{ }^\circ\text{C}$  afforded elimination product **70e** as a single product, and the reaction at a lower temperature ( $-40\text{ }^\circ\text{C}$ ) resulted in the recovery of residual substrate **72** along with elimination product **70e** (entries 7 and 8). Similar to the reductive elimination reaction of **69** with *i*PrMgBr (**81j**) (Table 2-2, entry 10), treatment of **72** with *i*PrMgBr (**81j**) only generated  $\alpha,\beta$ -unsaturated amide **82** without nucleophilic addition products (entry 12).

Scheme 2-7. Proposed mechanism concerning different reactivity between **69** and **72**



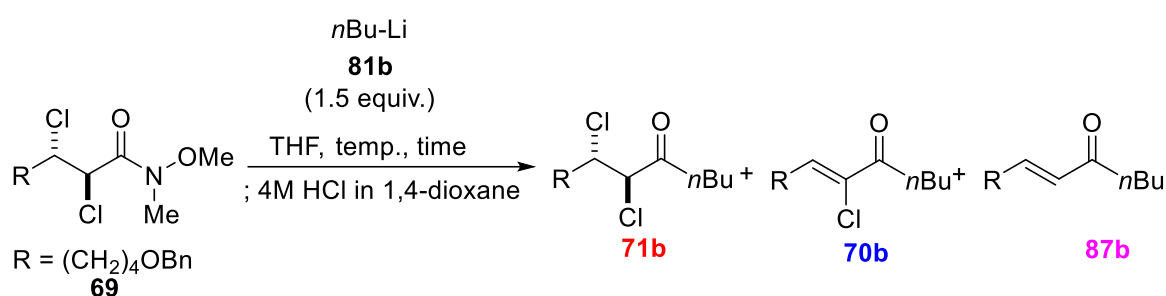
Based on the obtained results, diastereomers *anti*-dichloroamide **69** and *syn*-dichloroamide **72**, showed different reactivity toward the nucleophilic addition reaction. *syn*-Dichloroamide

**72** looks easier to interact with nucleophiles to form elimination product **70** than *anti*-dichloroamide **69**. Because of this occurrence, author proposed the reason for the different reactivity in Scheme 2-7 by envisioning the stability of five-membered ring intermediates **83** and **85** formed by the addition of nucleophiles to **69** and **72**, respectively.

In order to confirm the hypothesis, *anti*-dichloride **69** would be treated in the addition reaction at higher temperature because it was expected that higher temperature may accelerate the dissociation of **83**. As shown in Table 2-4, the nucleophilic addition of *anti*-dichloroamide **69** using 1.5 equivalents *n*BuLi (**81b**) at 0 °C (entry 1) increased the ratio of the eliminated products **70b**, showing enhancement of reaction temperature affects the formation of eliminated products compared to the nucleophilic addition reaction of **69** using **81b** at -20 °C (Table 2-2, entry 2). Clearly, it is worth conveying that formation of **70b** take place via *anti*-dichloroketone **71b** and the subsequent elimination reaction before acidic quenching with anhydrous HCl in dioxane. In addition, lithium or magnesium *N,O*-dimethylhydroxyamide **86**, released during this reaction, can act as a base to abstract the  $\alpha$ -proton of **73** to generate an elimination product **70**. Furthermore, the nucleophilic addition reactions of **69** using **81b** at room temperature were investigated (entries 2-4). Surprisingly, an unexpected product  $\alpha,\beta$ -unsaturated ketone **87b** without chlorine atom was observed along with **70b** in the crude <sup>1</sup>H NMR spectrum analysis (entry 2), but **71b** was not detected. Longer reaction time also increased the ratio of **87b** along with the longer reaction time, although combined yield decrease (entries 3 and 4). For the formation of **87b**, two reaction pathways were possible; (1) *n*BuLi is a reductant of chloride, or (2) **86**, shown in Scheme 2-7, acts as a reducing agent, generated from *N,O*-dimethylhydroxyammonium chloride and *n*BuLi. Verification of these two possibilities was carried out through a control experiment using a mixture of **71b** and **70b** (94:6) prepared according to the conditions in Table 2-2 entry 2. First, the **71b** and **70b** (94:6) mixture was reacted with *n*BuLi at room temperature to yield **70b** as a single product, meaning

that *n*BuLi acts as a base to abstract the  $\alpha$ -proton in this reaction (Scheme 2-8). On the other hand, reaction of **71b** and **70b** (94:6) with **86** prepared from *N,O*-dimethylhydroxyammonium chloride and *n*BuLi afforded **70b** and **87b** (89:11). This result shows that **86** has a potential to reduce chlorine atoms attached to the  $\alpha$ -position of the carbonyl group. To the best of my knowledge, this is a first example of reducing ability of lithium *N,O*-dimethylhydroxyamide.

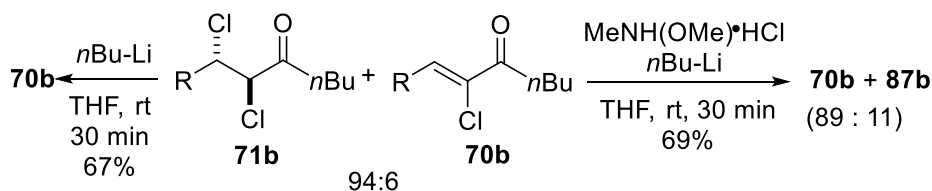
Table 2-4. Nucleophilic addition of **69** using *n*BuLi<sup>a</sup>



entry	Temp.	Time	Ratio ( <b>71b</b> : <b>70b</b> : <b>87b</b> ) <sup>a</sup> and combined yield ( <b>71b</b> + <b>70b</b> + <b>87b</b> )
1	0 °C	10 min	<b>62</b> : <b>38</b> : <b>0</b> , 97%
2	rt	30 min	<b>0</b> : <b>55</b> : <b>45</b> , 72%
3	rt	12 h	<b>0</b> : <b>49</b> : <b>51</b> , 61%
4	rt	24 h	<b>0</b> : <b>40</b> : <b>60</b> , 39%

<sup>a</sup>Reaction conditions: ratio of **71b**, **70b**, and **87b** was estimated by crude <sup>1</sup>H NMR.

Scheme 2-8. Reactivity of lithium *N*-methyl-*O*-methylamide **86**



## 2-5 Attempts of nucleophilic addition reaction with *anti*-dibrominated Weinreb amide

With the effective methods for the preparation of  $\alpha,\beta$ -dichlorinated ketone from the corresponding  $\alpha,\beta$ -dichlorinated Weinreb amide,  $\alpha,\beta$ -dibrominated Weinreb amide was also employed in the nucleophilic addition reaction. Some screenings of reaction conditions with *anti*-dibromoamide **79** were attempted for efficient formation of desired *anti*-dibromoketone **88**. Results are depicted in Table 2-5. As shown in entries 1, 2 and 3, during the reactions of **79** with  $n\text{BuC}\equiv\text{CLi}$  (**81a**), *anti*-dibromoketone **88a** resulted in elimination products **87a** and **82**. On the other hand, the addition of Lewis acid was not effective to increase the selectivity of **88a** (entries 4-8). The nucleophilic addition reaction with  $n\text{BuLi}$  (**81b**) also provided elimination product **87b** and **82** (entry 9). Although both of the reactions of *anti*-dibromoamide **79** with  $n\text{BuC}\equiv\text{CLi}$  (**81a**) and  $n\text{BuLi}$  (**81b**) proceeded to give elimination product **87** and **82**, treatment of **79** with  $\text{PhLi}$  (**81c**) and  $\text{CH}_3\text{MgBr}$  (**81d**) just produced elimination product **87** as a sole product in stark contrast to the other reaction (entries 10 and 11). Among Grignard reagents such as  $\text{CH}_2=\text{CHMgCl}$  (**81e**),  $n\text{C}_5\text{H}_{11}\text{MgBr}$  (**81f**),  $\text{PhMgBr}$  (**81g**) and  $\text{HC}\equiv\text{CMgCl}$  (**81h**) examined, formation of **88** was not observed (entries 12, 13, 14, and 15). Similarly as previous reaction, treatment of **79** with  $i\text{PrMgBr}$  (**81i**) only generated **82** (entry 16).

Scheme 2-9. Proposed mechanism concerning different reactivity of *anti*-dibromoamide

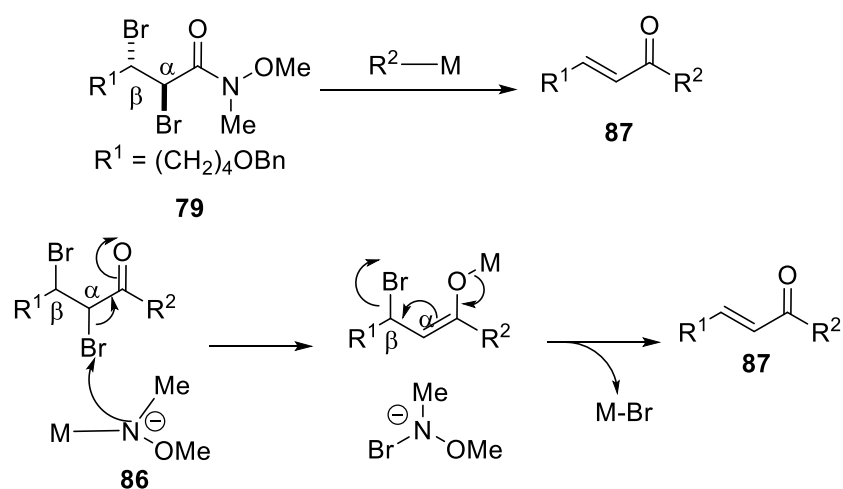
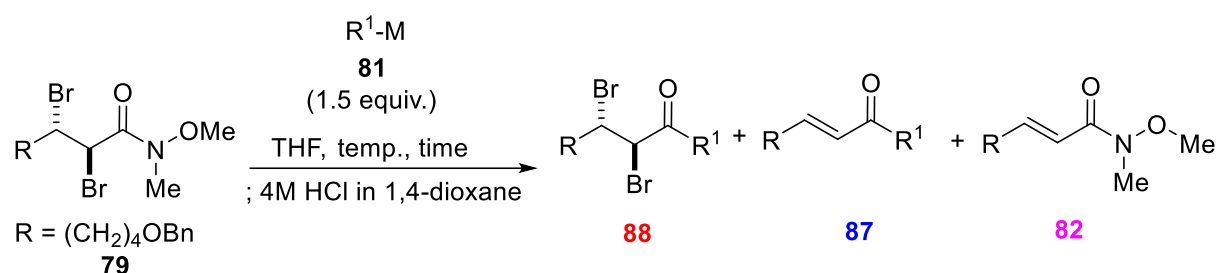


Table 2-5. Nucleophilic addition reaction with **79**<sup>a</sup>

entry	$R^1M$ (1.5 equiv.)	Lewis Acid <sup>b</sup>	Temp. (°C)	Time (min)	Ratio ( <b>79</b> : <b>88</b> : <b>87</b> : <b>82</b> ) <sup>b</sup> and combined yield ( <b>88</b> + <b>87</b> + <b>82</b> )
1	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>		-20	10	19:0:46:35, 74%
2	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>		0	10	0:0:55:45, 90%
3	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>		0	30	0:0:82:18, 95%
4	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>	BF <sub>3</sub> ·OEt <sub>2</sub>	0	30	31:0:35:34, 61%
5	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>	MgBr <sub>2</sub> ·OEt <sub>2</sub>	0	30	23:0:33:44, 65%
6	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>	CeCl <sub>3</sub>	0	30	33:0:21:46, 62%
7	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>	InCl <sub>3</sub>	0	30	No Reaction
8	<i>n</i> BuC≡CLi ( <b>81a</b> ) <sup>c</sup>	ZnCl <sub>2</sub>	0	30	No Reaction
9	<i>n</i> BuLi ( <b>81b</b> )		0	30	0:0:87:13, 95%
10	PhLi ( <b>81c</b> )		0	30	0:0:100:0, 78%
11	CH <sub>3</sub> MgBr ( <b>81d</b> )		0	120	0:0:100:0, 94%
12	CH <sub>2</sub> =CHMgCl ( <b>81e</b> )		0	120	0:0:52:48, 90%
13	<i>n</i> C <sub>5</sub> H <sub>11</sub> MgBr ( <b>81f</b> )		0	120	0:0:54:46, 90%
14	PhMgBr ( <b>81g</b> )		0	120	0:0:83:17, 74%
15	HC≡CMgCl ( <b>81h</b> )		0	120	0:0:0:100 (88%)
16	<i>i</i> PMgBr ( <b>81i</b> )		0	240	0:0:0:100 (86%)

<sup>a</sup>Reaction conditions: 0.3 mmol of **79** was used. <sup>b</sup>1.5 equiv. of Lewis acid was used. <sup>c</sup>3.0 equiv. of **81a** was used. <sup>d</sup>ratio of **79**, **88**, **87**, and **82** was estimated by crude <sup>1</sup>H NMR.

It has been revealed that *anti*-dibromoamide **79** showed extremely different reactivity toward the addition reaction, compared with *anti*-dichloroamide **69** and *syn*-dichloroamide **72**. Same as previous reason explained in Scheme 2-6, it is thought that the generation of **87** is due to in-

situ formation of **86**. Moreover, this factor is also enhanced by the character of Br amide at  $\alpha$ -position, which is easier to be reduced by the nucleophile or **86** than chloride. After the reductive removal of Br atom to form enolate,  $\beta$ -elimination is induced to form **87** (Scheme 2-9). Although lower temperature may avoid the formation of **86**, lower conversion of **79** is also concerned as shown in entry 1. For these reasons, further studies with **79** or *syn*-dibromide **80** were not carried out.



In conclusion of this chapter, effective syntheses of  $\alpha,\beta$ -dichlorinated ketones from  $\alpha,\beta$ -dichlorinated Weinreb amides were accomplished in high selectivity. Work-up with commercially available 4 M HCl in dioxane is very important because it encourages the selectivity and avoids  $\beta$ -elimination reaction in the synthesis of  $\alpha,\beta$ -dichlorinated ketone to give a high desired product ratio up to 95:5 compared with  $\alpha,\beta$ -unsaturated ketone **70** as an undesired product. More clearly, the 4 M HCl in dioxane avoids the abstraction of  $\alpha$ -hydrogen by amine released during the addition reaction. Diastereomers, *anti*-dichloroamide **69** and *syn*-dichloroamide **72**, showed different reactivity to some nucleophiles, and alkyllithium reagent is more effective nucleophile than Grignard reagent during these reactions. Furthermore, nucleophilic addition reaction to  $\alpha,\beta$ -dichlorinated aldehyde 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 abstracts 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 **69** and **72** show different stability under thermal conditions. Also, amide **86** is revealed to have a potential to reduce chloride at  $\alpha$ -position of carbonyl group. This is a first example. On the other hand, these methods 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.

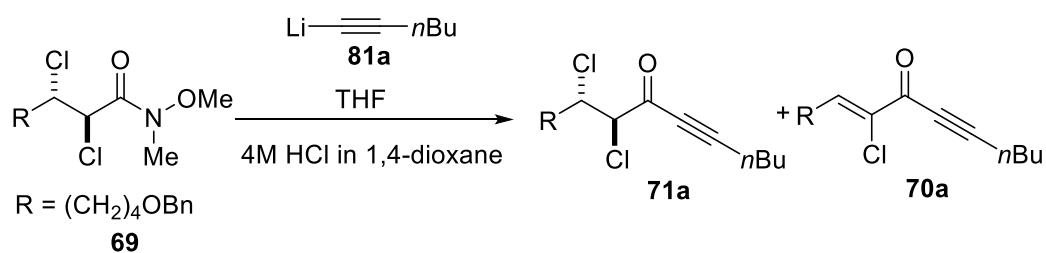
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## Experimental Section of Chapter 2

Tetrahydrofuran (THF) was purchased from Kanto Chemical Co. Inc. Dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) was distilled from  $\text{CaH}_2$ . All commercially obtained reagents were used as received. The IR spectra were recorded on a JASCO FTIR-4100 Type A spectrometer using a NaCl cell. The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded using a JNM-EX 400 (400 MHz and 100 MHz) spectrometer. Chemical shifts were reported in ppm relative to  $\text{CHCl}_3$  in  $\text{CDCl}_3$  for  $^1\text{H}$  NMR ( $\delta = 7.26$ ) and  $^{13}\text{C}$  NMR ( $\delta = 77.0$ ) and  $\text{CHD}_2\text{OH}$  in  $\text{CD}_3\text{OD}$  for  $^1\text{H}$  NMR ( $\delta = 3.35$ ) and  $^{13}\text{C}$  NMR ( $\delta = 49.3$ ). Splitting patterns for  $^1\text{H}$  NMR were designated as “s, d, t, q, m, dt, dd, and td”. These symbols indicate “singlet, doublet, triplet, quartet, multiplet, doublet/triplet, doublet/doublet, and triplet/doublet” respectively. All commercially obtained reagents were employed as received. Analytical TLC was carried out using pre-coated silica gel plates (Wako TLC Silicagel 70F<sub>254</sub>). Wakogel 60N 63-212  $\mu\text{m}$  was used for column chromatography. Reversed-phase high performance liquid chromatography (HPLC) was carried out using HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5  $\mu\text{m}$ ,  $\phi 8.0 \times 250$  mm).

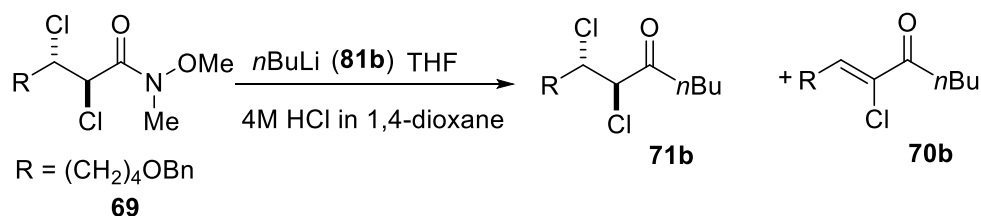


**Ketone 71a and 70a.** To a solution of 1-hexyne (0.109 mL, 0.957 mmol) in THF (5.0 mL) was added  $n\text{BuLi}$  (0.601 mL, 0.957 mmol, 1.59 M) at  $0^\circ\text{C}$  to give **81a**. After 30 minutes, a solution of **69** (111 mg, 0.319 mmol) in THF (3.0 mL) was added. The mixture was stirred for 10 minutes at  $0^\circ\text{C}$ , quenched with 0.390 mL of 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in*

*vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (116 mg, 98%) of dichloro ketone **71a** and unsaturated ketone **70a** with ratio 85:15. For further purification, the partial (ca. 10.0 mg) of mixture products were separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5  $\mu\text{m}$ ,  $\phi 8.0 \times 250$  mm, elution with  $\text{H}_2\text{O}$ :Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **71a** as a colorless oil and **70a** as a colorless oil.

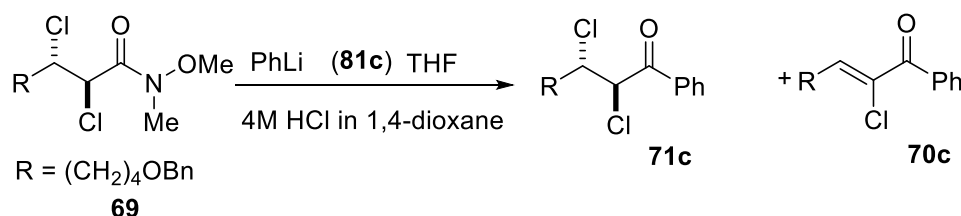
**71a**: IR (neat) 3019, 2960, 2936, 2214, 1726, 1683, 1647, 1215, 756, 699, 669  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  0.94 (3H, t,  $J = 7.3$  Hz), 1.46-1.81 (9H, m), 2.06-2.18 (1H, m), 2.48 (2H, t,  $J = 6.8$  Hz), 3.51 (2H, t,  $J = 5.8$  Hz), 4.35 (1H, td,  $J = 9.2, 2.4$  Hz), 4.46 (1H, d,  $J = 8.8$  Hz), 4.49 (2H, s), 7.24-7.33 (5H, m);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  13.7, 19.2, 22.9, 23.4, 29.9, 30.7, 34.4, 61.6, 66.9, 70.8, 73.9, 78.8, 100.2, 128.6, 128.8, 129.3, 139.8, 179.8; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{20}\text{H}_{26}\text{O}_2\text{Cl}_2\text{Na}$  391.1202; Found 391.1201.

**70a**: IR (neat) 3065, 3019, 2959, 2936, 2865, 2214, 1716, 1649, 1617, 1216, 759, 698, 667  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  0.94 (3H, t,  $J = 7.3$  Hz), 1.43-1.50 (2H, m), 1.46-1.66 (6H, m), 2.45-2.52 (4H, m), 3.51 (2H, t,  $J = 6.3$  Hz), 4.49 (2H, s), 7.25-7.32 (5H, m), 7.46 (1H, t,  $J = 7.3$  Hz);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  13.8, 19.2, 23.0, 25.5, 30.3, 30.6, 30.8, 70.7, 73.9, 78.5, 98.6, 128.6, 128.8, 129.3, 136.1, 139.7, 149.3, 173.0; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{20}\text{H}_{25}\text{O}_2\text{ClNa}$  355.1435; Found 355.1438.



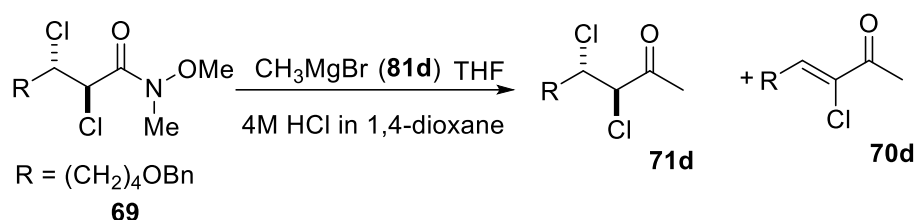
**Ketone 71b.** To a solution of **69** (157 mg, 0.451 mmol) in THF (5.0 mL) was added *n*BuLi (**81b**) (0.427 mL, 0.680 mmol, 1.59 M) at  $-20$   $^\circ\text{C}$ . The mixture was stirred for 30 minutes,

quenched with 0.560 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (155 mg, 98%) of dichloro ketone **71b** and unsaturated ketone **70b**. For further purification to obtain pure **71b**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5 μm, φ8.0×250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **71b** as a colorless oil: IR (neat) 3063, 3029, 2957, 2933, 2868, 1729, 1495, 1454, 1103, 735, 698, 664 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 0.91 (3H, t, *J* = 7.3 Hz), 1.31-1.38 (2H, m), 1.53-1.79 (7H, m), 2.08-2.10 (1H, m), 2.64-2.75 (2H, m), 3.50 (2H, t, *J* = 5.8 Hz), 4.32 (1H, td, *J* = 9.2, 2.4 Hz), 4.49 (2H, s), 4.51 (1H, d, *J* = 8.7 Hz), 7.24-7.33 (5H, m); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) δ 14.1, 23.1, 23.3, 26.4, 29.9, 34.6, 40.7, 61.5, 64.3, 70.9, 73.9, 128.6, 128.8, 129.3, 139.7, 203.7; HRMS (ESI) *m/z*: [M + Na]<sup>+</sup>; Calcd for C<sub>18</sub>H<sub>26</sub>O<sub>2</sub>Cl<sub>2</sub>Na 367.1202; Found 367.1202.



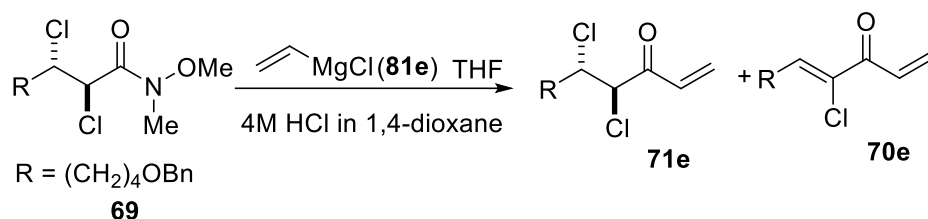
**Ketone 71c.** To a solution of **69** (50.0 mg, 0.144 mmol) in THF (2.0 mL) was added PhLi (**81c**) (0.120 mL, 0.216 mmol, 1.80 M) at -20 °C. The mixture was stirred for 30 minutes, quenched with 0.200 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (49.0 mg, 94%) of dichloro ketone **71c** and unsaturated ketone **70c**. For further purification to obtain pure **71c**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL,

DEVELOASIL C30-UG 5  $\mu\text{m}$ ,  $\phi 8.0 \times 250$  mm, elution with  $\text{H}_2\text{O}:\text{Acetonitrile} = 80:20$  to  $0:100$  gradiently for 90 min, 2 mL/min) to afford **71c** as a colorless oil: IR (neat) 3062, 3030, 2941, 2864, 1695, 1596, 1580, 1449, 1100, 738, 688,  $663\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  1.27-1.93 (5H, m), 2.24-2.30 (1H, m), 3.53 (2H, t,  $J = 5.8$  Hz), 4.50 (2H, s), 4.51 (1H, td,  $J = 9.2$ , 2.4 Hz), 5.53 (1H, d,  $J = 9.7$  Hz), 7.24-7.33 (5H, m), 7.54 (2H, dd,  $J = 8.7$ , 7.8 Hz), 7.64-7.68 (1H, m), 8.05 (2H, dd,  $J = 7.3$ , 1.4 Hz);  $^{13}\text{C NMR}$  ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  23.3, 30.0, 34.5, 58.5, 61.4, 70.9, 73.9, 127.7, 128.6, 128.8, 129.3, 130.0, 135.3, 136.0, 139.7, 193.2; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{20}\text{H}_{22}\text{O}_2\text{Cl}_2\text{Na}$  387.0889; Found 387.0888.



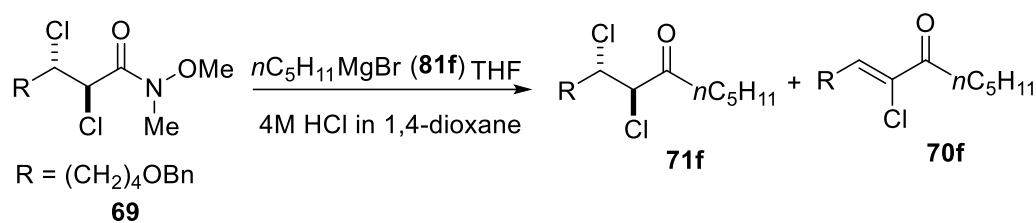
**Ketone 71d.** To a solution of **69** (114 mg, 0.327 mmol) in THF (4.0 mL) was added  $\text{CH}_3\text{MgBr}$  (**81d**) (0.163 mL, 0.491 mmol, 3.00 M) at  $0^\circ\text{C}$ . The mixture was stirred for 2 hours, quenched with 0.460 mL 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (97.0 mg, 98%) of dichloro ketone **71d** and unsaturated ketone **70d**. For further purification to obtain pure **71d**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOASIL C30-UG 5  $\mu\text{m}$ ,  $\phi 8.0 \times 250$  mm, elution with  $\text{H}_2\text{O}:\text{Acetonitrile} = 80:20$  to  $0:100$  gradiently for 90 min, 2 mL/min) to afford **71d** as a colorless oil: IR (neat) 3031, 2940, 2866, 1721, 1495, 1454, 1100, 739, 714,  $698\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  1.53-1.80 (5H, m), 2.07-2.17 (1H, m), 2.31 (3H, s), 3.50 (2H, t,  $J = 5.8$  Hz), 4.33 (1H, td,  $J = 9.2$ , 2.4 Hz), 4.49 (2H, s), 4.50 (1H, d,  $J = 7.3$  Hz), 7.26-7.34 (5H, m);  $^{13}\text{C NMR}$  ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  23.4,

26.9, 29.9, 34.6, 61.6, 65.4, 70.9, 73.9, 128.6, 128.8, 129.3, 139.7, 201.4; HRMS (ESI) m/z: [M + Na]<sup>+</sup>; Calcd for C<sub>15</sub>H<sub>20</sub>O<sub>2</sub>Cl<sub>2</sub>Na 325.0732; Found 325.0728.

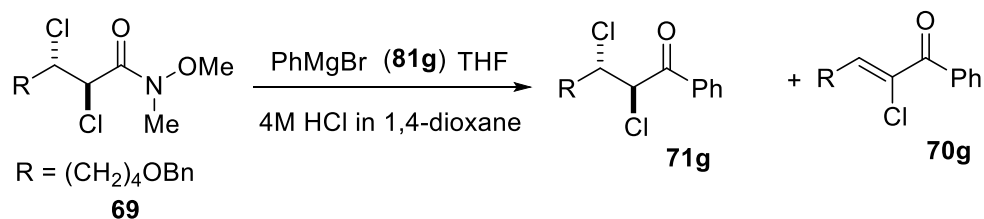


**Ketone 71e.** To a solution of **69** (131 mg, 0.376 mmol) in THF (4.0 mL) was added VinylMgCl (**81e**) (0.427 mL, 0.680 mmol, 1.35 M) at 0 °C. The mixture was stirred for 2 hours, quenched with 0.460 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (115 mg, 97%) of dichloro ketone **71e** and unsaturated ketone **70e**. For further purification to obtain pure **71e**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5 μm, φ8.0×250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **71e** as a colorless oil: IR (neat) 3063, 3029, 2930, 2866, 1725, 1558, 1455, 1275, 1101, 714, 700, 667 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.61-1.81 (5H, m), 2.13-2.17 (1H, m), 3.50 (2H, t, *J* = 5.8 Hz), 4.31 (1H, td, *J* = 9.2, 2.4 Hz), 4.49 (2H, s), 4.51 (1H, d, *J* = 8.8 Hz), 5.96 (1H, dd, *J* = 10.4, 0.9 Hz), 6.45 (1H, dd, *J* = 17.5, 0.9 Hz), 6.62 (1H, dd, *J* = 17.5, 10.2 Hz), 7.26-7.35 (5H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 22.2, 29.1, 33.6, 59.7, 61.5, 69.8, 72.9, 127.5, 127.6, 128.3, 131.5, 132.1, 138.4, 190.7; HRMS (ESI) m/z: [M + Na]<sup>+</sup>; Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>2</sub>Cl<sub>2</sub>Na 337.0732; Found 337.0728.

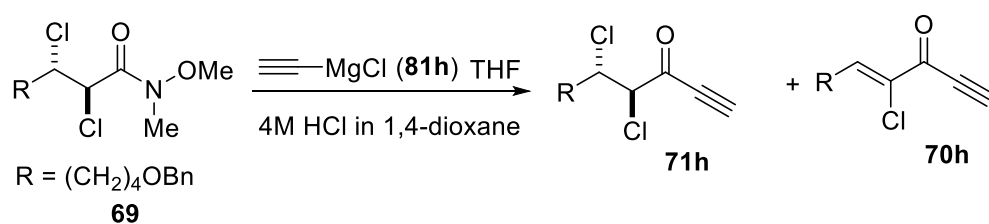




**Ketone 71f.** To a solution of **69** (110 mg, 0.315 mmol) in THF (5.0 mL) was added *n*C<sub>5</sub>H<sub>11</sub>MgBr (**81f**) (0.236 mL, 0.473 mmol, 2.00 M) at 0 °C. The mixture was stirred for 2 hours, quenched with 0.390 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (109 mg, 96%) of dichloro ketone **71f** and unsaturated ketone **70f**. For further purification to obtain pure **71f**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5 μm, φ8.0×250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **71f** as a colorless oil: IR (neat) 3064, 3031, 2931, 2862, 1730, 1558, 1455, 1274, 1101, 739, 698, 663 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 0.90 (3H, t, *J* = 6.8 Hz), 1.27-1.36 (4H, m), 1.53-1.79 (7H, m), 2.07-2.16 (1H, m), 2.63-2.74 (2H, m), 3.51 (2H, t, *J* = 5.8 Hz), 4.32 (1H, td, *J* = 9.2, 2.4 Hz), 4.49 (2H, s), 4.51 (1H, d, *J* = 9.3 Hz), 7.23-7.33 (5H, m); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) δ 14.3, 23.3, 23.5, 24.1, 29.9, 32.2, 34.6, 40.9, 61.5, 64.3, 70.9, 73.9, 128.6, 128.8, 129.3, 139.7, 203.7; HRMS (ESI) *m/z*: [M + Na]<sup>+</sup>; Calcd for C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>Cl<sub>2</sub>Na 381.1358; Found 381.1353.



**Ketone 71g.** To a solution of **69** (111 mg, 0.319 mmol) in THF (4.0 mL) was added PhMgBr (**81g**) (0.159 mL, 0.478 mmol, 3.00 M) at 0 °C. The mixture was stirred for 4 hours, quenched with 0.390 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (111 mg, 96%) of dichloro ketone **71g** and unsaturated ketone **70g**. For further purification to obtain pure **71g**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5 μm, φ8.0×250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **71g** as a colorless oil: IR (neat) 3063, 3030, 2939, 2865, 1695, 1596, 1580, 1449, 1273, 1100, 746, 688, 663 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 1.27-1.93 (5H, m), 2.24-2.30 (1H, m), 3.53 (2H, t, *J* = 5.8 Hz), 4.50 (2H, s), 4.51 (1H, td, *J* = 9.2, 2.4 Hz), 5.53 (1H, d, *J* = 9.7 Hz), 7.24-7.33 (5H, m), 7.54 (2H, dd, *J* = 8.7, 7.8 Hz), 7.64-7.68 (1H, m), 8.05 (2H, dd, *J* = 7.3, 1.4 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) δ 23.3, 30.0, 34.5, 58.5, 61.4, 70.9, 73.9, 127.7, 128.6, 128.8, 129.3, 130.0, 135.3, 136.0, 139.7, 193.2; HRMS (ESI) *m/z*: [M + Na]<sup>+</sup>; Calcd for C<sub>20</sub>H<sub>22</sub>O<sub>2</sub>Cl<sub>2</sub>Na 387.0889; Found 387.0888.

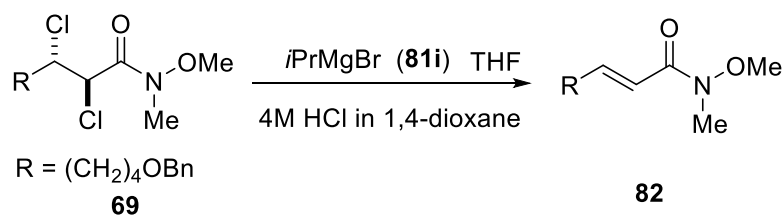


**Ketone 71h and 70h.** To a solution of **69** (64.2 mg, 0.184 mmol) in THF (2.0 mL) was added HC≡CMgCl (**81h**) (0.553 mL, 0.277 mmol, 0.500 M) at 0 °C. The mixture was stirred for 4 hours, quenched with 0.230 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture

(52.0 mg, 90%) of dichloro ketone **71h** and unsaturated ketone **70h** with ratio 35:65. For further purification, the partial (ca. 10.0 mg) of mixture products were separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5  $\mu\text{m}$ ,  $\phi 8.0 \times 250$  mm, elution with  $\text{H}_2\text{O}:\text{Acetonitrile} = 80:20$  to  $0:100$  gradiently for 90 min, 2 mL/min) to afford **71h** as a colorless oil and **70h** as a colorless oil.

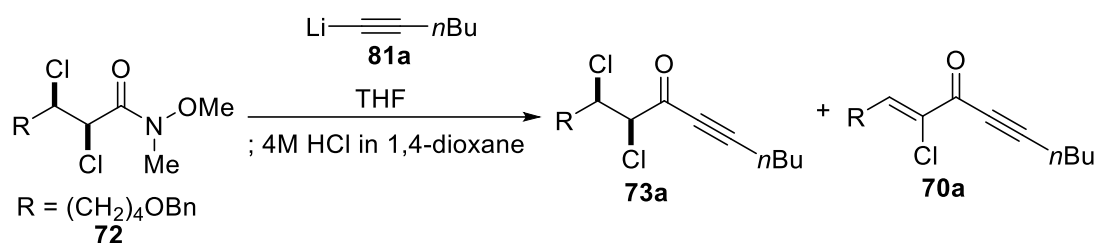
**71h**: IR (neat) 3273, 3066, 2921, 2851, 2098, 1697, 1660, 1587, 1455, 1259, 1101, 909, 735,  $698\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.55-1.80 (5H, m), 2.10-2.16 (1H, m), 3.41 (1H, s), 3.50 (2H, t,  $J = 5.8$  Hz), 4.31-4.32 (2H, m), 4.51 (2H, s), 7.25-7.35 (5H, m);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  22.1, 28.9, 33.3, 59.5, 64.8, 69.8, 72.9, 78.1, 82.5, 127.5, 127.6, 128.3, 138.4, 177.7; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{16}\text{H}_{18}\text{O}_2\text{Cl}_2\text{Na}$  335.0576; Found 335.0581.

**70h**: IR (neat) 3251, 3064, 2925, 2855, 2096, 1717, 1659, 1614, 1455, 1233, 1101, 883, 733,  $698\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.67-1.70 (4H, m), 2.53 (2H, q,  $J = 7.3$  Hz), 3.34 (1H, s), 3.51 (2H, t,  $J = 5.8$  Hz), 4.51 (2H, s), 7.26-7.35 (5H, m), 7.46 (1H, t,  $J = 7.3$  Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  24.3, 29.3, 29.8, 69.6, 72.9, 78.5, 81.3, 127.5, 127.5, 128.3, 134.9, 138.3, 149.3, 171.1; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{16}\text{H}_{17}\text{O}_2\text{ClNa}$  299.0809; Found 299.0801.



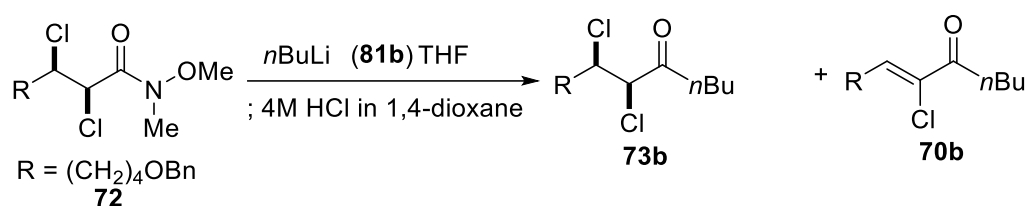
**Amide 82.** To a solution of **69** (182 mg, 0.524 mmol) in THF (6.0 mL) was added  $i\text{PrMgBr}$  (**81i**) (1.07 mL, 0.786 mmol, 0.730 M) at  $0\text{ }^\circ\text{C}$ . The mixture was stirred for 4 hours, quenched with 0.650 mL 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by

silica gel column chromatography (EtOAc:Hexane = 2:98) to give unsaturated amide **82** (135 mg, 0.487 mmol, 93%) as a colorless oil: IR (neat) 3063, 3029, 2936, 2857, 1664, 1633, 1495, 1455, 1412, 1379, 1273, 1104, 997, 746, 737, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.54-1.60 (2H, m), 1.61-1.67 (2H, m), 2.25 (2H, q,  $J = 7.3$  Hz), 3.23 (3H, s), 3.48 (2H, t,  $J = 6.3$  Hz), 3.68 (3H, s), 4.49 (2H, s), 6.39 (1H, d,  $J = 15.6$  Hz), 6.97 (1H, dt,  $J = 15.7, 6.8$  Hz), 7.26-7.34 (5H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  24.8, 29.1, 32.1, 32.7, 61.5, 69.8, 72.7, 118.7, 127.4, 127.5, 128.2, 138.3, 147.4, 166.8; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{Na}$  300.1567; Found 300.1567.

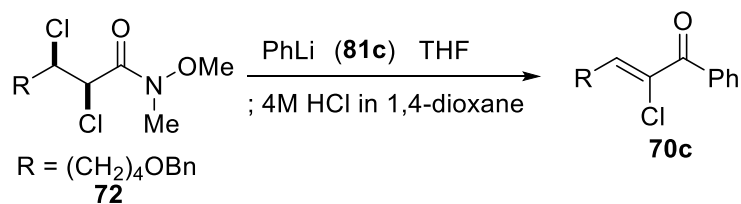


**Ketone 73a.** To a solution of 1-hexyne (0.083 mL, 0.722 mmol) in THF (4.0 mL) was added  $n\text{BuLi}$  (0.453 mL, 0.722 mmol, 1.59 M) at  $0^\circ\text{C}$  to give **81a**. The mixture was cooled at  $-40^\circ\text{C}$  and added cold solution of **7** (84.0 mg, 0.241 mmol) in THF (3.0 mL), stirred for 10 minutes at  $-40^\circ\text{C}$ , quenched with 0.310 mL 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (84.0 mg, 95%) of dichloro ketone **73a** and unsaturated ketone **70a**. For further purification to obtain pure **73a**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5  $\mu\text{m}$ ,  $\phi 8.0 \times 250$  mm, elution with  $\text{H}_2\text{O}$ :Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **73a** as a colorless oil: IR (neat) 3030, 2956, 2933, 2863, 2211, 1697, 1671, 1653, 1102, 771, 736, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$

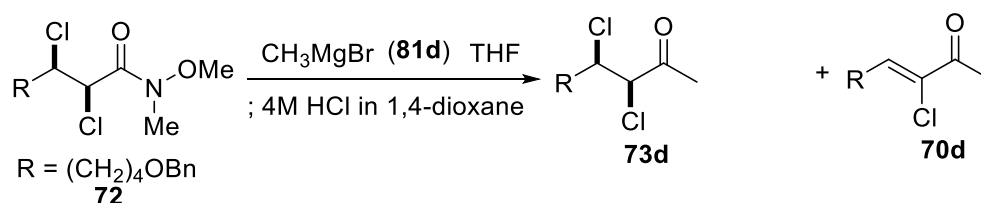
NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  0.75 (3H, t,  $J = 7.3$  Hz), 1.25-1.46 (8H, m), 1.71 (2H, q,  $J = 7.3$  Hz), 2.29 (2H, t,  $J = 6.8$  Hz), 3.32 (2H, t,  $J = 5.8$  Hz), 4.30 (2H, s), 4.49 (1H, td,  $J = 7.1, 3.4$  Hz), 4.70 (1H, d,  $J = 3.4$  Hz), 7.26-7.33 (5H, m); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz)  $\delta$  13.7, 19.3, 22.9, 24.2, 29.9, 30.6, 36.6, 62.6, 70.8, 70.9, 73.9, 79.3, 101.1, 128.6, 128.8, 129.3, 139.7, 180.4; HRMS (ESI)  $m/z$ : [M + Na]<sup>+</sup>; Calcd for C<sub>20</sub>H<sub>26</sub>O<sub>2</sub>Cl<sub>2</sub>Na 391.1202; Found 391.1203.



**Ketone 73b.** To a solution of **72** (54.0 mg, 0.155 mmol) in THF (2.0 mL) was added *n*BuLi (**81b**) (0.145 mL, 0.232 mmol, 1.59 M) at  $-40$  °C. The mixture was stirred for 30 minutes, quenched with 0.200 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (51.0 mg, 95%) of dichloro ketone **73b** and unsaturated ketone **70b**. For further purification to obtain pure **73b**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5  $\mu\text{m}$ ,  $\phi$ 8.0 $\times$ 250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **73b** as a colorless oil: IR (neat) 3063, 3030, 2956, 2933, 2865, 1717, 1540, 1455, 1397, 1100, 772, 737, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz)  $\delta$  0.91 (3H, t,  $J = 7.3$  Hz), 1.28-1.37 (2H, m), 1.49-1.66 (6H, m), 1.86 (2H, q,  $J = 6.8$  Hz), 2.71 (2H, t,  $J = 7.3$  Hz), 3.50 (2H, t,  $J = 5.8$  Hz), 4.48 (2H, s), 4.54 (1H, td,  $J = 7.1, 3.4$  Hz), 4.77 (1H, d,  $J = 3.4$  Hz), 7.24-7.33 (5H, m); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz)  $\delta$  14.2, 23.1, 24.2, 26.5, 29.9, 36.6, 40.7, 63.1, 69.6, 70.9, 73.9, 128.6, 128.8, 129.3, 139.7, 205.1; HRMS (ESI)  $m/z$ : [M + Na]<sup>+</sup>; Calcd for C<sub>18</sub>H<sub>26</sub>O<sub>2</sub>Cl<sub>2</sub>Na 367.1202; Found 367.1200.

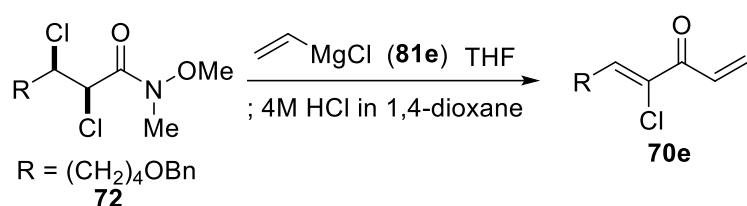


**Ketone 70c.** To a solution of **72** (87.0 mg, 0.249 mmol) in THF (3.0 mL) was added PhLi (**81c**) (0.207 mL, 0.373 mmol, 1.80 M) at  $-20\text{ }^\circ\text{C}$ . The mixture was stirred for 30 minutes, quenched with 0.310 mL 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give unsaturated ketone **70c** (65.0 mg, 0.197 mmol, 78%) as a colorless oil: IR (neat) 3063, 3031, 2941, 2861, 1718, 1688, 1670, 1449, 1273, 1177, 713, 696, 666  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  1.34-1.66 (4H, m), 2.49 (2H, td,  $J = 7.3, 6.8$  Hz), 3.50 (2H, t,  $J = 5.8$  Hz), 4.47 (2H, s), 6.70 (1H, t,  $J = 7.3$  Hz), 7.24-7.30 (5H, m), 7.47 (2H, dd,  $J = 8.7, 7.8$  Hz), 7.57-7.61 (1H, m), 7.65 (2H, dd,  $J = 7.3, 1.4$  Hz);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  25.5, 30.3, 30.5, 70.8, 73.9, 128.6, 128.8, 129.3, 129.6, 130.3, 133.7, 134.1, 138.2, 139.7, 147.1, 191.9; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{20}\text{H}_{21}\text{O}_2\text{ClNa}$  351.1122; Found 351.1123.



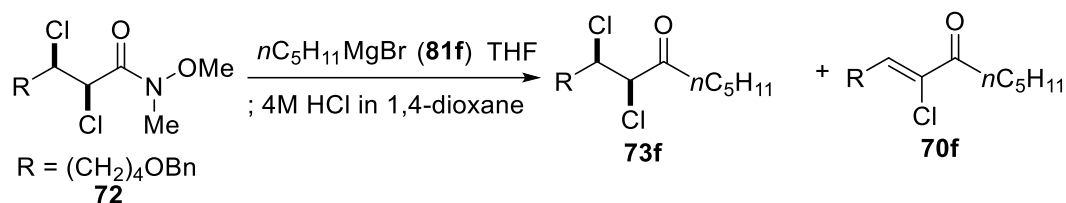
**Ketone 73d.** To a solution of **72** (88.0 mg, 0.253 mmol) in THF (3.0 mL) was added  $\text{CH}_3\text{MgBr}$  (**81d**) (0.126 mL, 0.378 mmol, 3.00 M) at  $-20\text{ }^\circ\text{C}$ . The mixture was stirred for 2 hours, quenched with 0.310 mL 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc,

washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (73.0 mg, 95%) of dichloro ketone **73d** and unsaturated ketone **70d**. For further purification to obtain pure **73d**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5 μm, φ8.0×250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **73d** as a colorless oil: IR (neat) 3032, 2937, 2864, 1717, 1496, 1455, 1099, 1026, 737, 714, 699 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 1.40-1.55 (4H, m), 1.77-1.88 (2H, m), 2.24 (3H, s), 3.41 (2H, t, *J* = 5.8 Hz), 4.39 (2H, s), 4.46 (1H, td, *J* = 9.2, 2.4 Hz), 4.69 (1H, d, *J* = 2.9 Hz), 7.16-7.23 (5H, m); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100 MHz) δ 24.2, 27.9, 29.9, 36.7, 62.8, 69.9, 70.9, 73.9, 128.6, 128.8, 129.3, 139.7, 202.9; HRMS (ESI) *m/z*: [M + Na]<sup>+</sup>; Calcd for C<sub>15</sub>H<sub>20</sub>O<sub>2</sub>Cl<sub>2</sub>Na 325.0732; Found 325.0733.



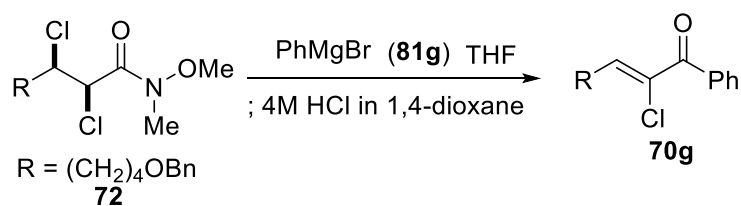
**Ketone 70e.** To a solution of **72** (71.4 mg, 0.205 mmol) in THF (3.0 mL) was added VinylMgCl (**81e**) (0.146 mL, 0.308 mmol, 2.10 M) at 0 °C. The mixture was stirred for 2 hours, quenched with 0.250 mL 4.00 M HCl in 1,4-dioxane then excess of H<sub>2</sub>O, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give unsaturated ketone **70e** (52.0 mg, 0.187 mmol, 90%) as a colorless oil: IR (neat) 3029, 2932, 2862, 1717, 1652, 1616, 1455, 1274, 1101, 714, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 1.60-1.70 (4H, m), 2.42-2.52 (2H, m), 3.51 (2H, t, *J* = 5.8 Hz), 4.48 (2H, s), 5.84 (1H, dd, *J* = 10.4, 1.9 Hz), 6.31 (1H, dd, *J* = 16.8, 1.9 Hz), 7.11 (1H, dd, *J* = 17.5, 10.2 Hz), 7.18 (1H, t, *J* = 6.8 Hz), 7.25-

7.32 (5H, m);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  25.4, 30.3, 30.6, 70.8, 73.9, 128.6, 128.8, 129.3, 130.7, 131.9, 135.2, 139.7, 145.1, 185.7; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{16}\text{H}_{19}\text{O}_2\text{ClNa}$  301.0965; Found 301.0959.



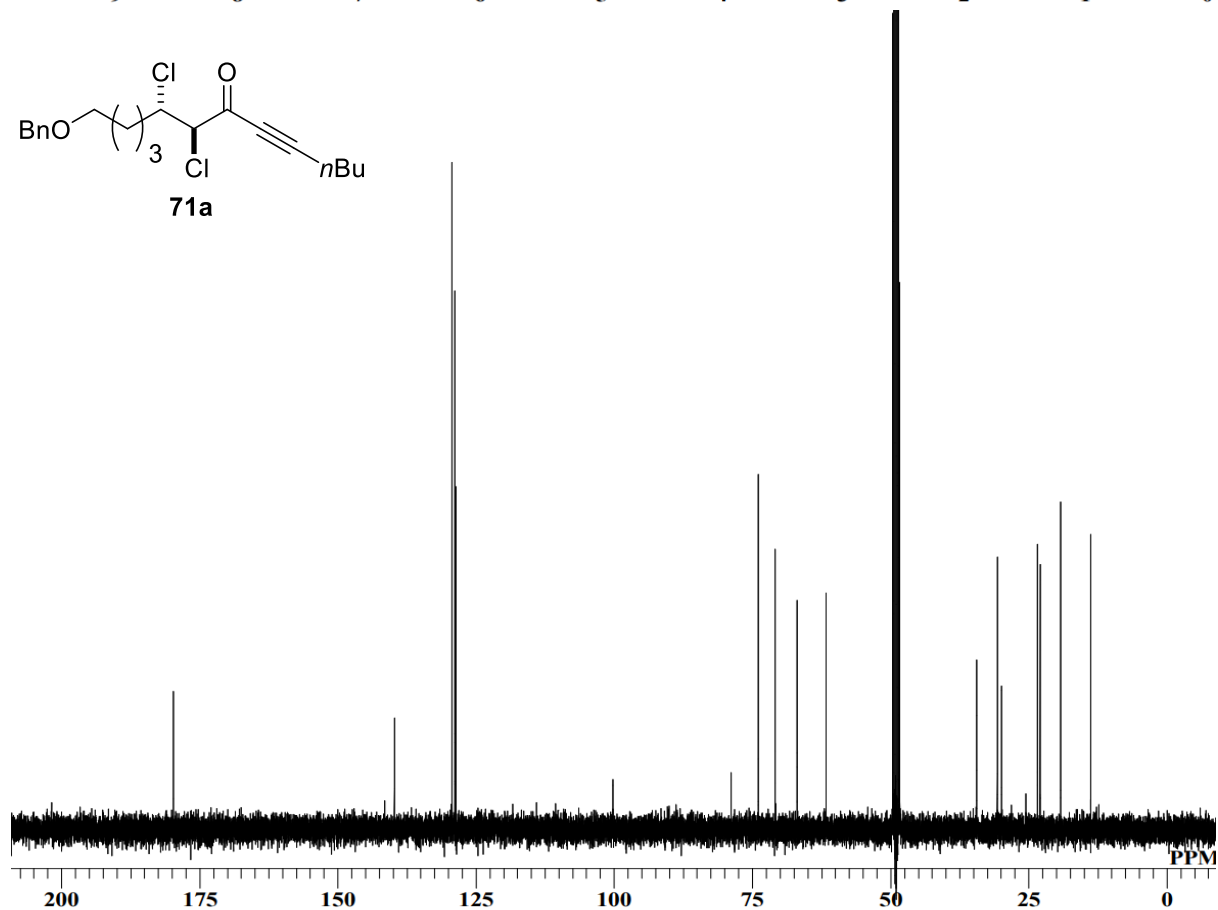
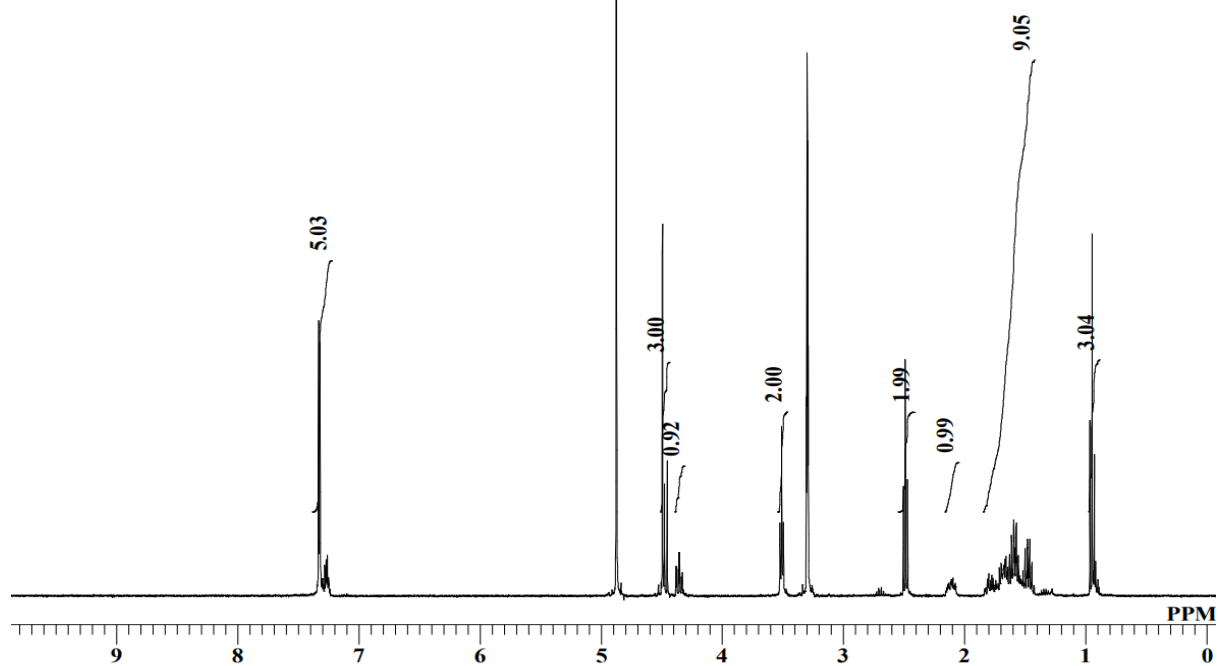
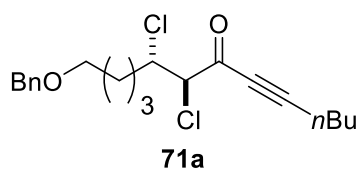
**Ketone 73f.** To a solution of **72** (83.0 mg, 0.238 mmol) in THF (3.0 mL) was added  $n\text{C}_5\text{H}_{11}\text{MgBr}$  (**81f**) (0.178 mL, 0.358 mmol, 2.00 M) at  $-20$  °C. The mixture was stirred for 2 hours, quenched with 0.290 mL 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give a mixture (77.0 mg, 90%) of dichloro ketone **73f** and unsaturated ketone **70f**. For further purification to obtain pure **73f**, a partial (ca. 10.0 mg) of the mixture was separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5  $\mu\text{m}$ ,  $\phi 8.0 \times 250$  mm, elution with  $\text{H}_2\text{O}$ :Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **73f** as a colorless oil: IR (neat) 3068, 3030, 2931, 2859, 1717, 1558, 1455, 1362, 1100, 772, 735, 697  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  0.90 (3H, t,  $J = 6.8$  Hz), 1.27-1.34 (4H, m), 1.48-1.66 (6H, m), 1.87 (2H, q,  $J = 6.8$  Hz), 2.70 (2H, t,  $J = 6.8$  Hz), 3.50 (2H, t,  $J = 5.8$  Hz), 4.48 (2H, s), 4.53 (1H, td,  $J = 6.8, 3.4$  Hz), 4.76 (1H, d,  $J = 2.9$  Hz), 7.24-7.33 (5H, m);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  14.2, 23.5, 24.1, 24.2, 29.9, 32.2, 36.6, 40.9, 63.0, 69.6, 70.9, 73.9, 128.6, 128.8, 129.3, 139.8, 205.0; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{19}\text{H}_{28}\text{O}_2\text{Cl}_2\text{Na}$  381.1358; Found 381.1358.

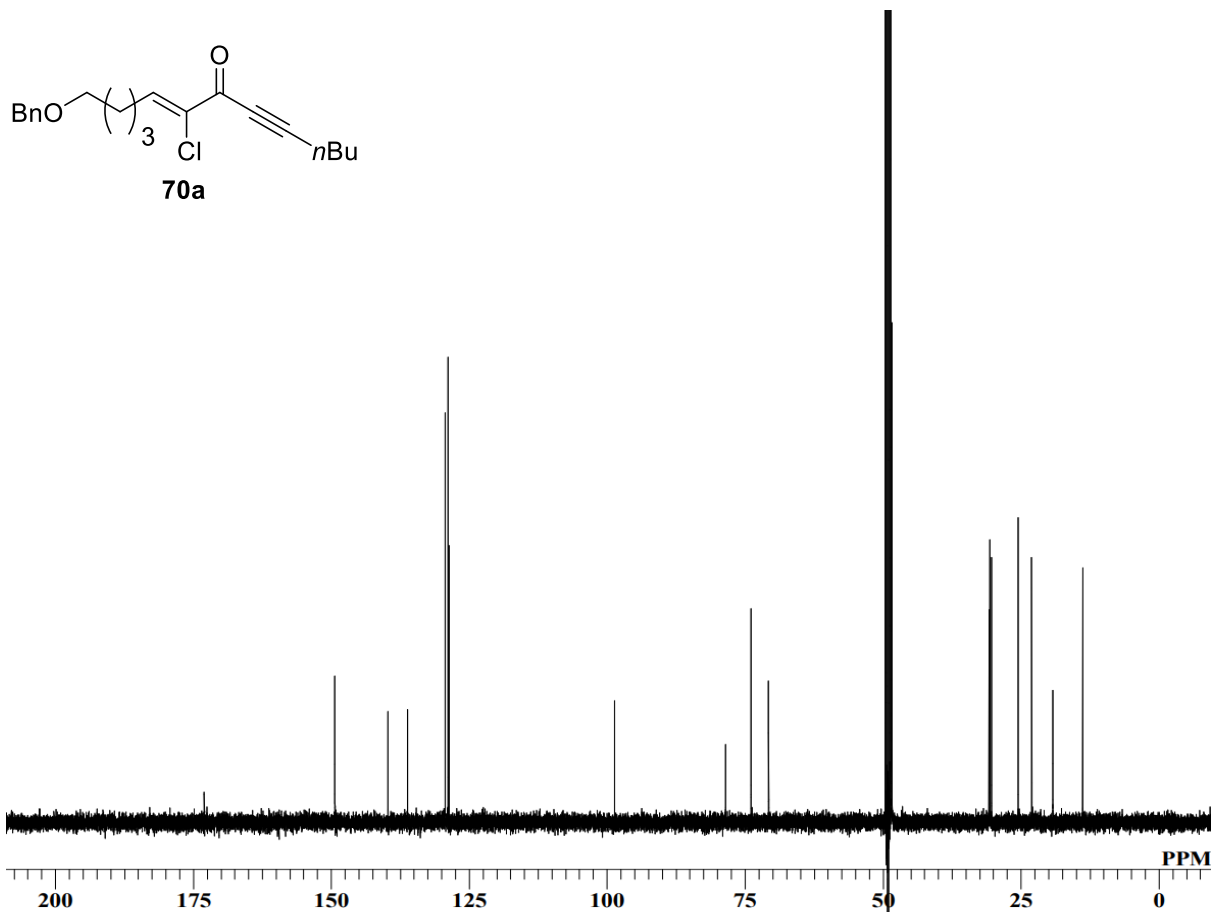
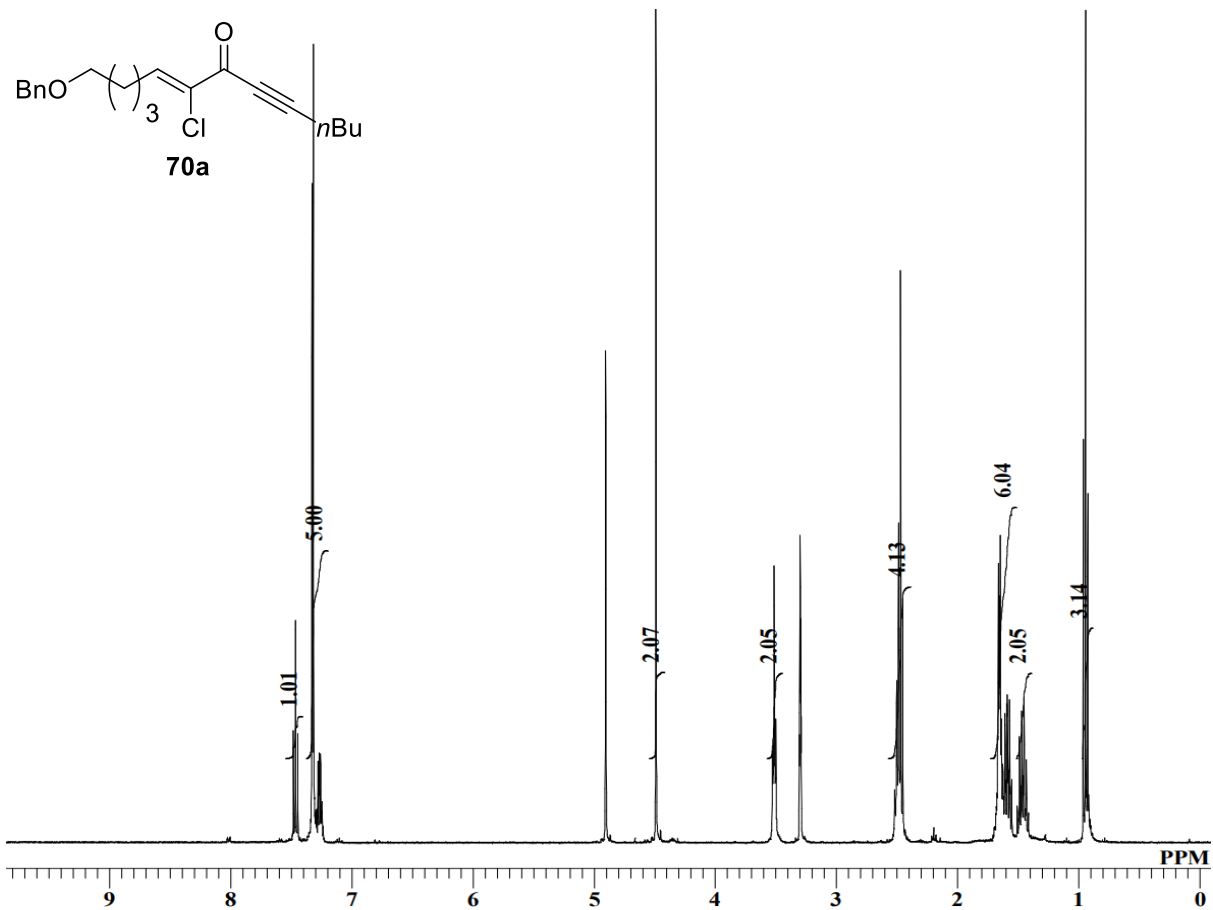


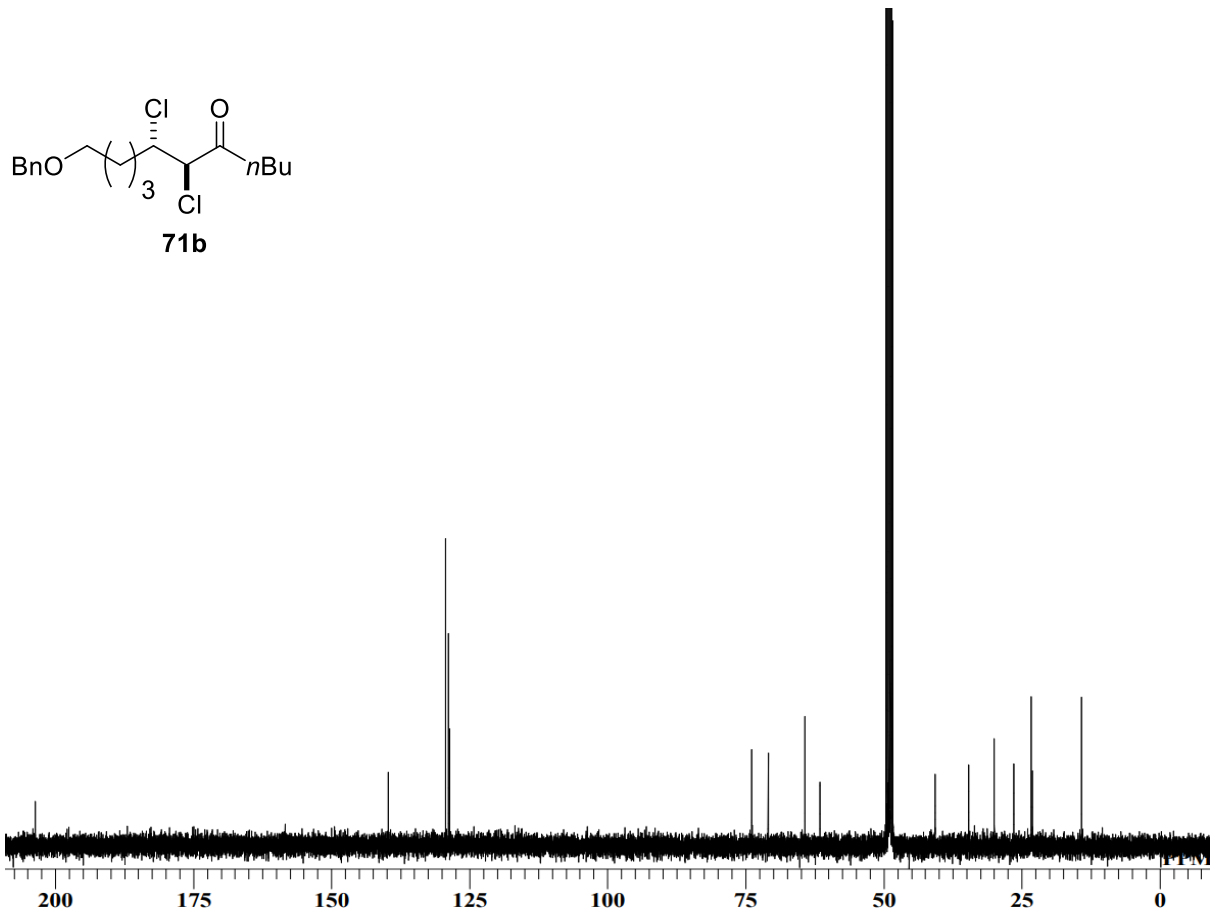
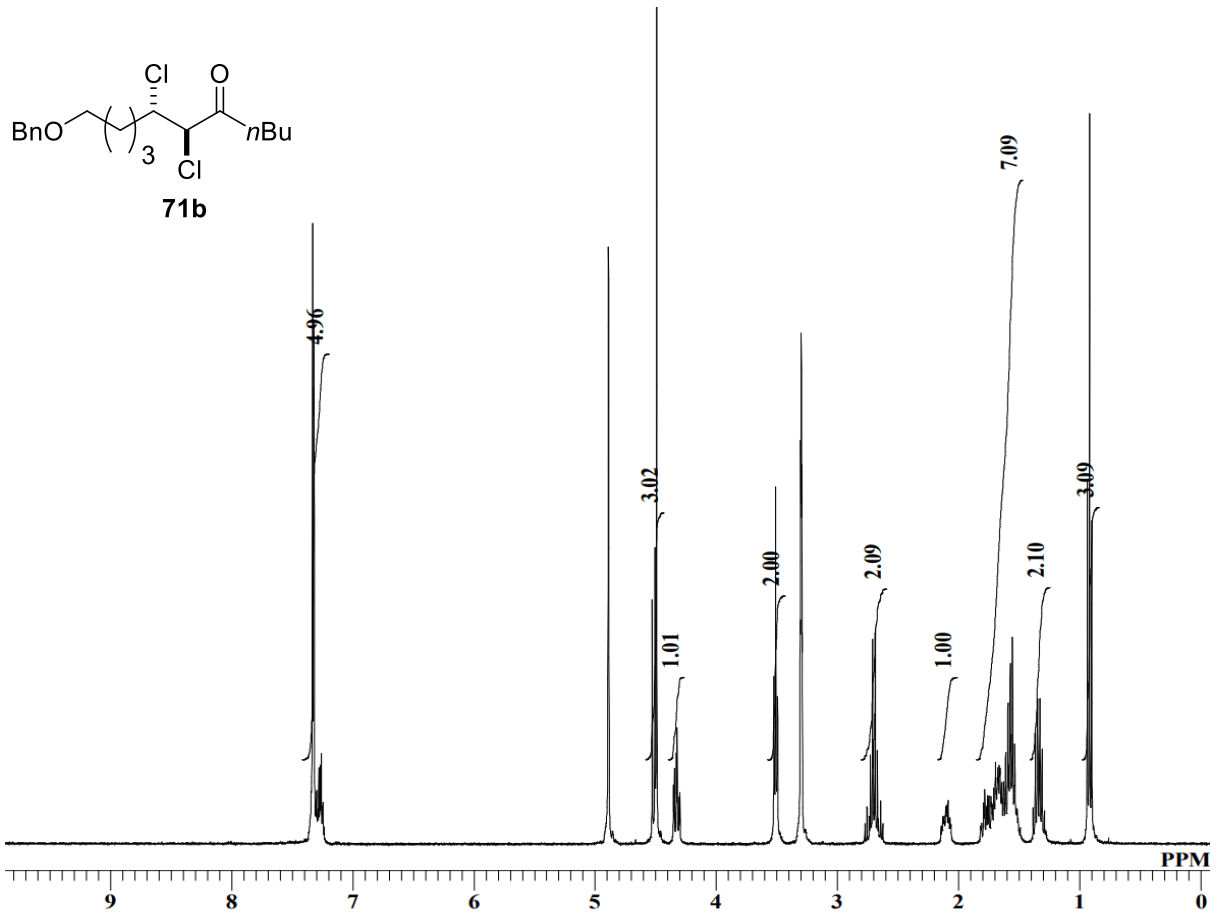


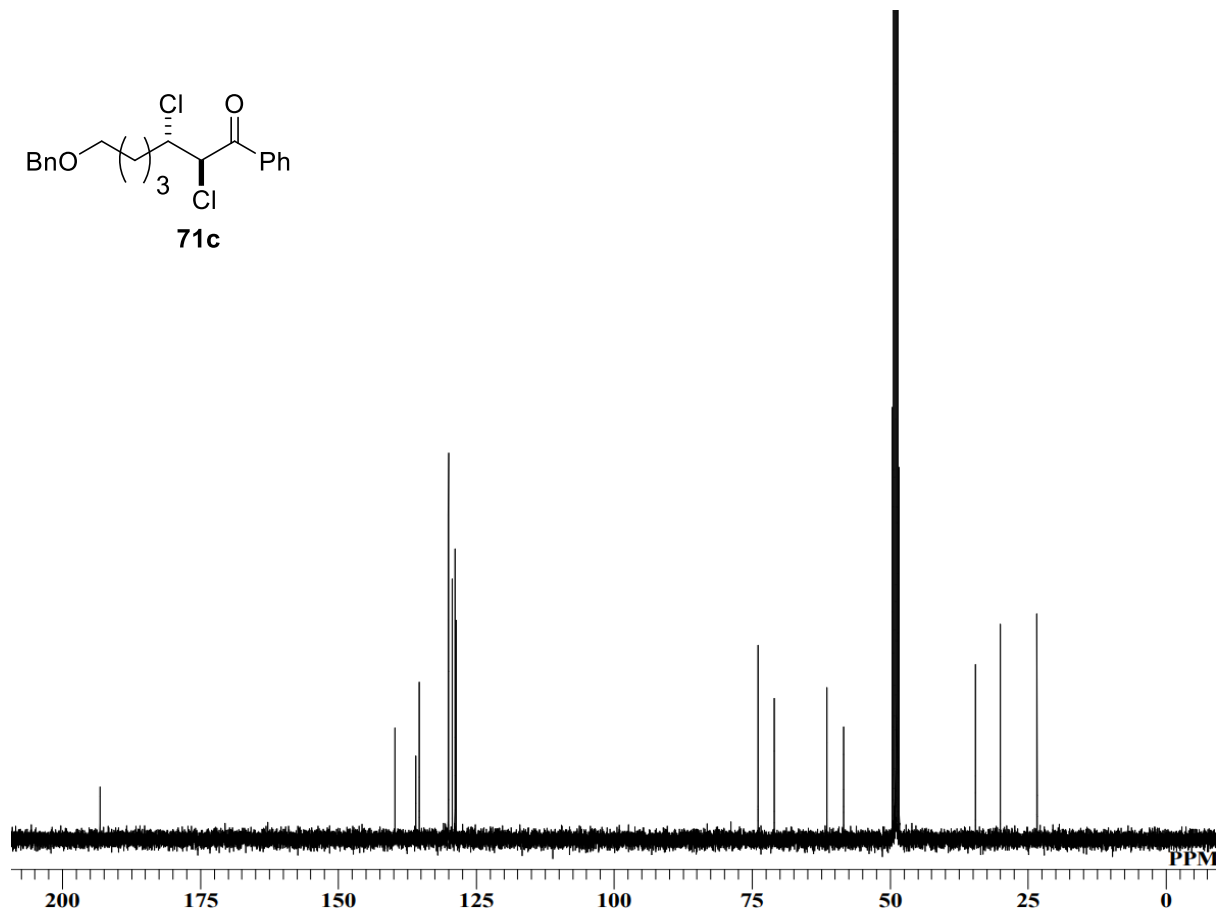
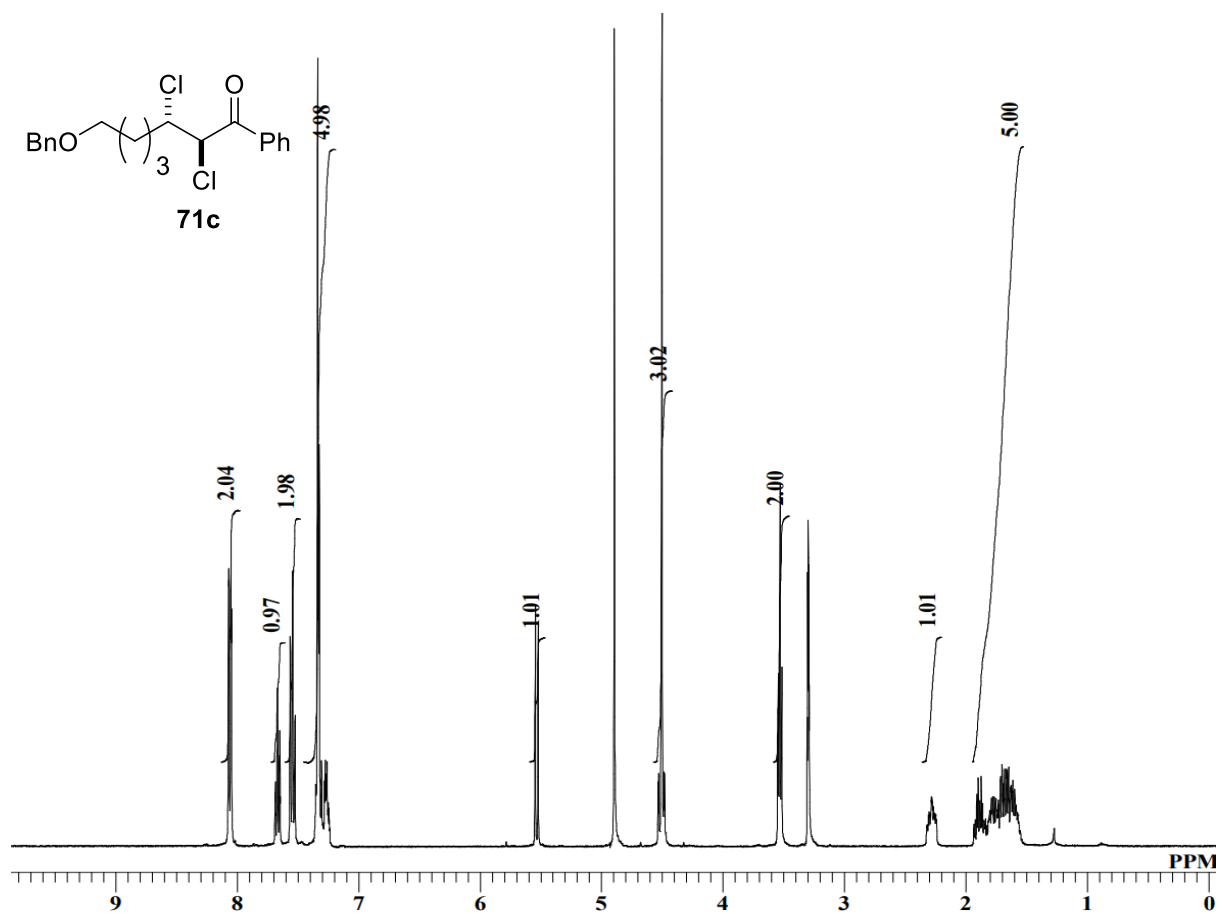
**Ketone 70g.** To a solution of **72** (103 mg, 0.295 mmol) in THF (3.0 mL) was added PhMgBr (**81g**) (0.147 mL, 0.442 mmol, 3.00 M) at  $-20\text{ }^\circ\text{C}$ . The mixture was stirred for 2 hours, quenched with 0.360 mL 4.00 M HCl in 1,4-dioxane then excess of  $\text{H}_2\text{O}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 2:98) to give unsaturated ketone **70g** (62.0 mg, 0.189 mmol, 74%) as a colorless oil: IR (neat) 3063, 3031, 2941, 2861, 1718, 1688, 1670, 1449, 1273, 1177, 713, 696, 666  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  1.34-1.66 (4H, m), 2.49 (2H, q,  $J = 6.8$  Hz), 3.50 (2H, t,  $J = 5.8$  Hz), 4.47 (2H, s), 6.70 (1H, t,  $J = 7.3$  Hz), 7.24-7.30 (5H, m), 7.47 (2H, dd,  $J = 8.7, 7.8$  Hz), 7.57-7.61 (1H, m), 7.65 (2H, dd,  $J = 7.3, 1.4$  Hz);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz)  $\delta$  25.5, 30.3, 30.5, 70.8, 73.9, 128.6, 128.8, 129.3, 129.6, 130.3, 133.7, 134.1, 138.2, 139.7, 147.1, 191.9; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{20}\text{H}_{21}\text{O}_2\text{ClNa}$  351.1122; Found 351.1123.

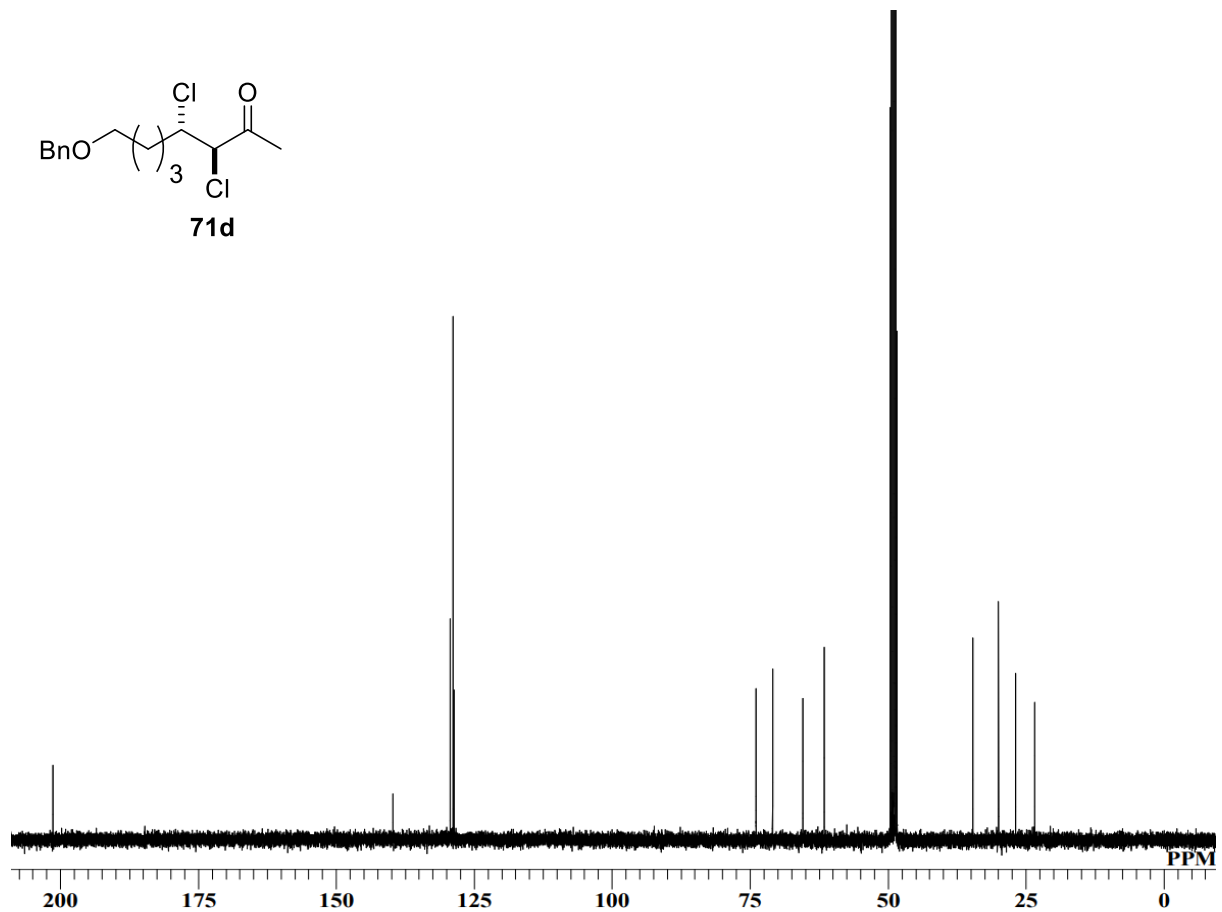
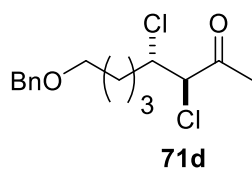
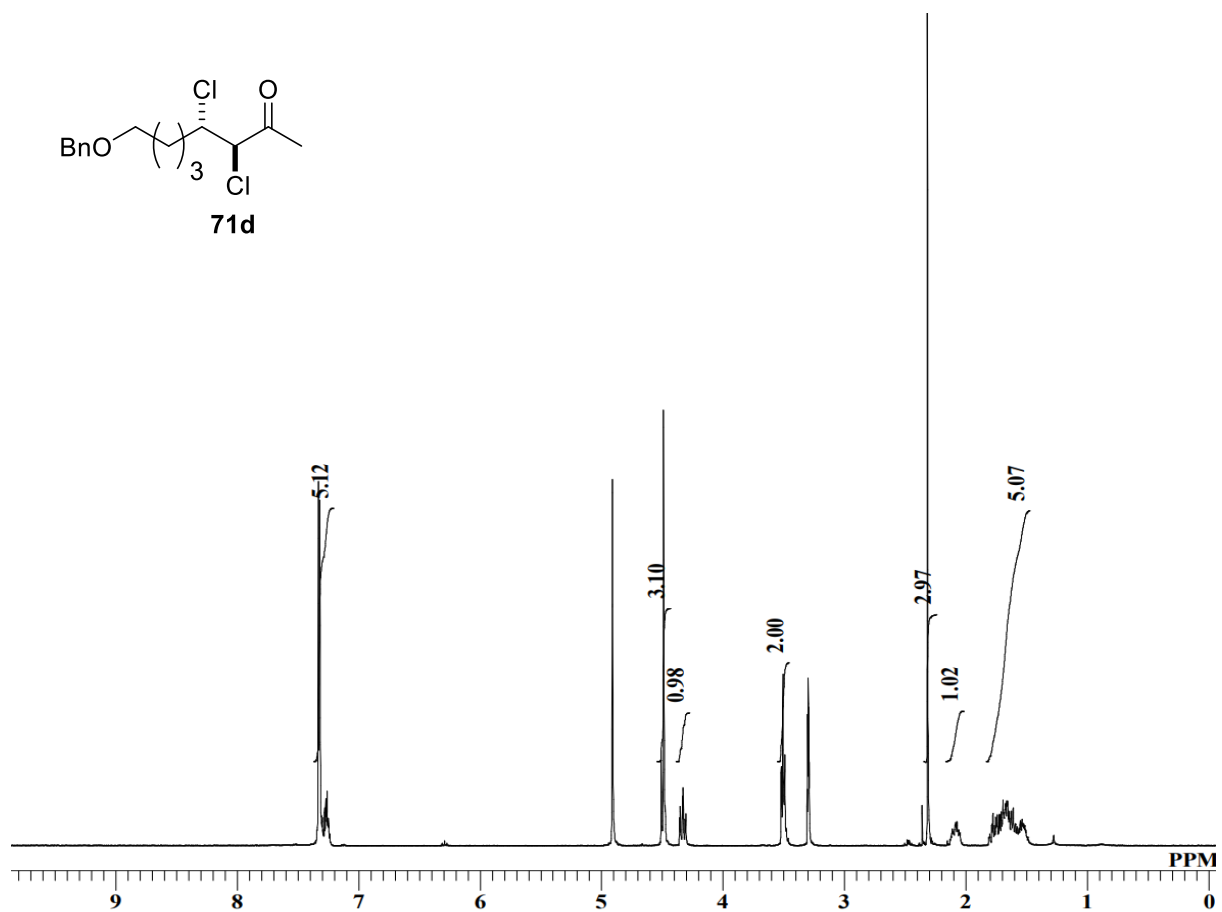
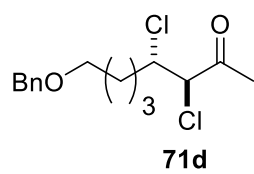
## NMR Spectra for Chapter 2

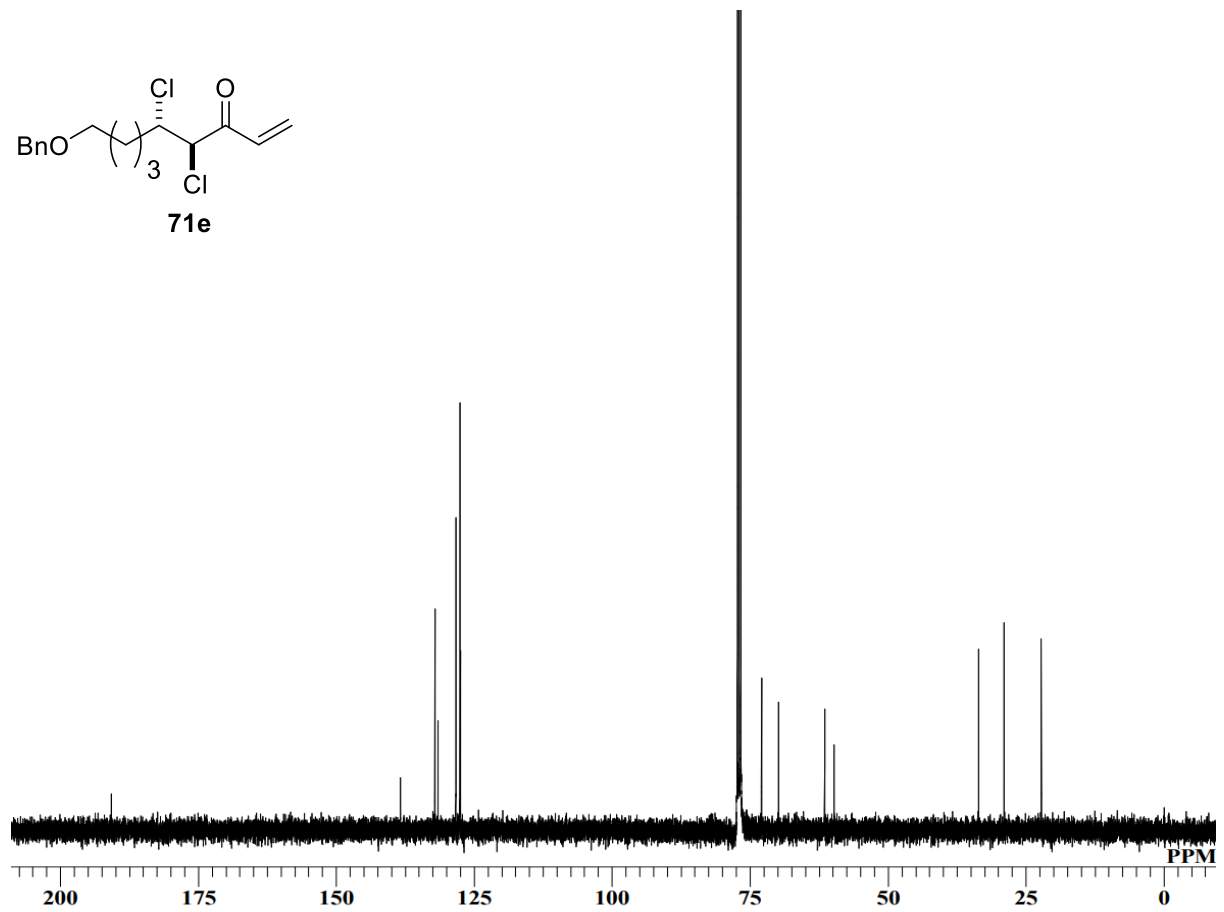
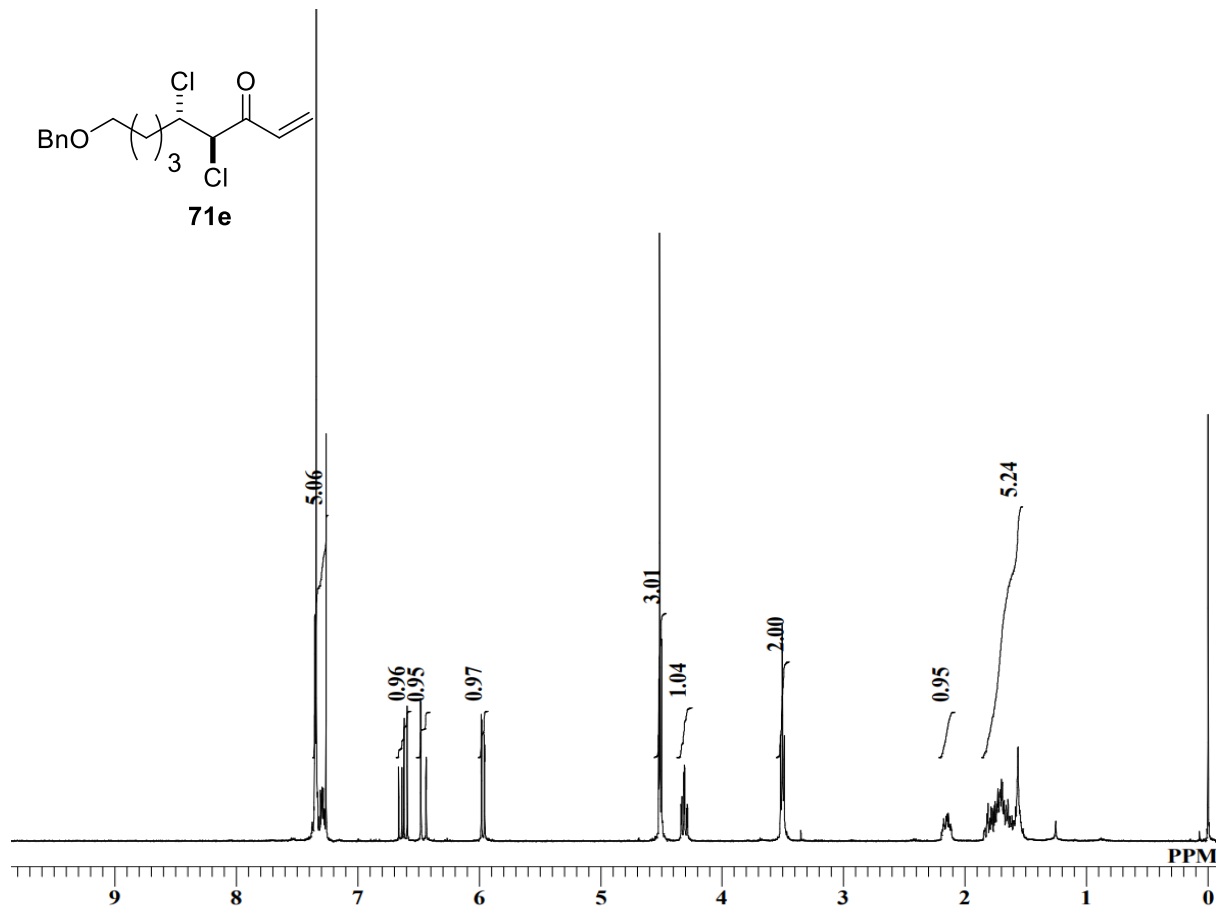


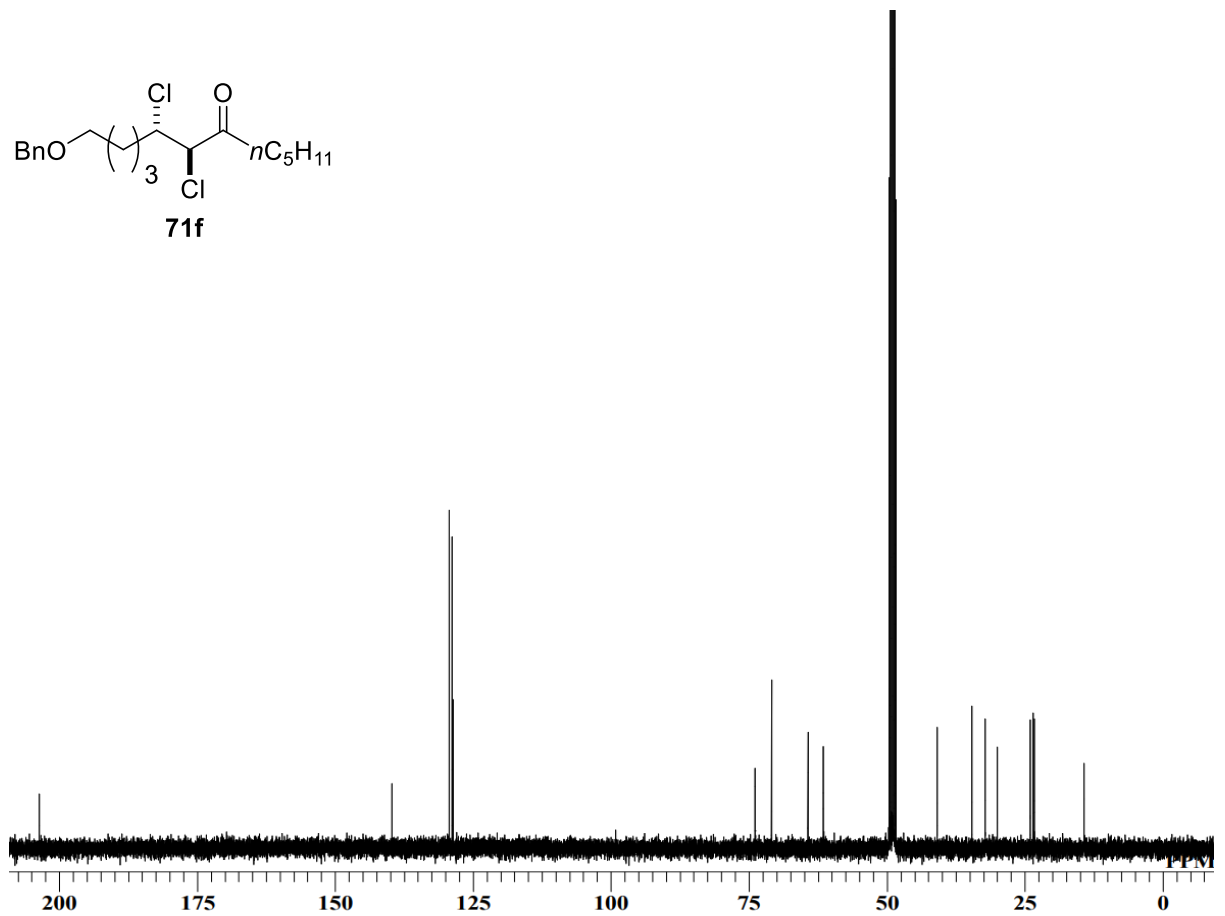
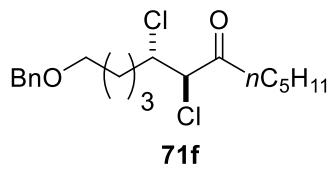
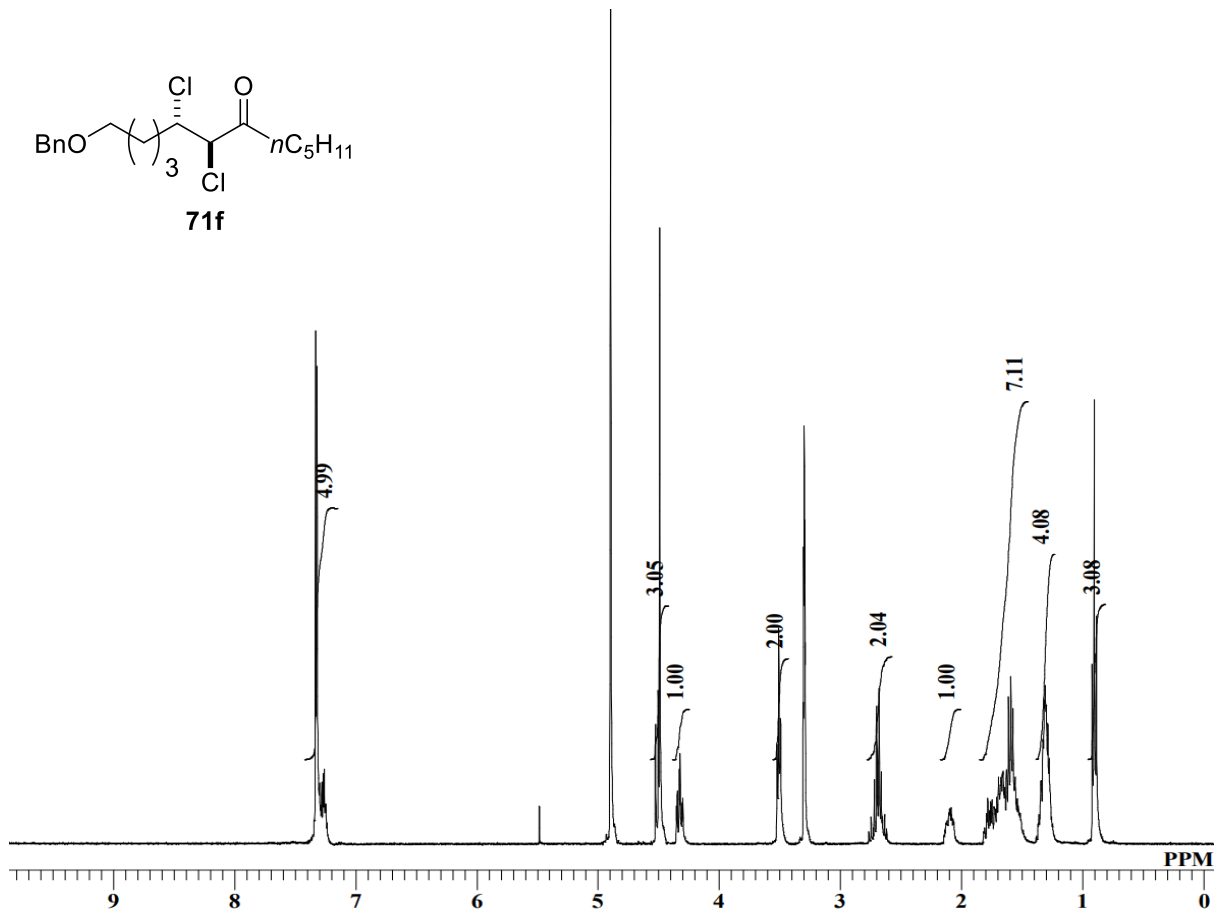
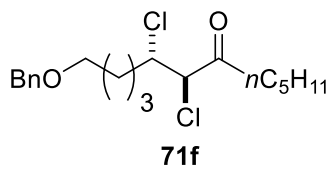




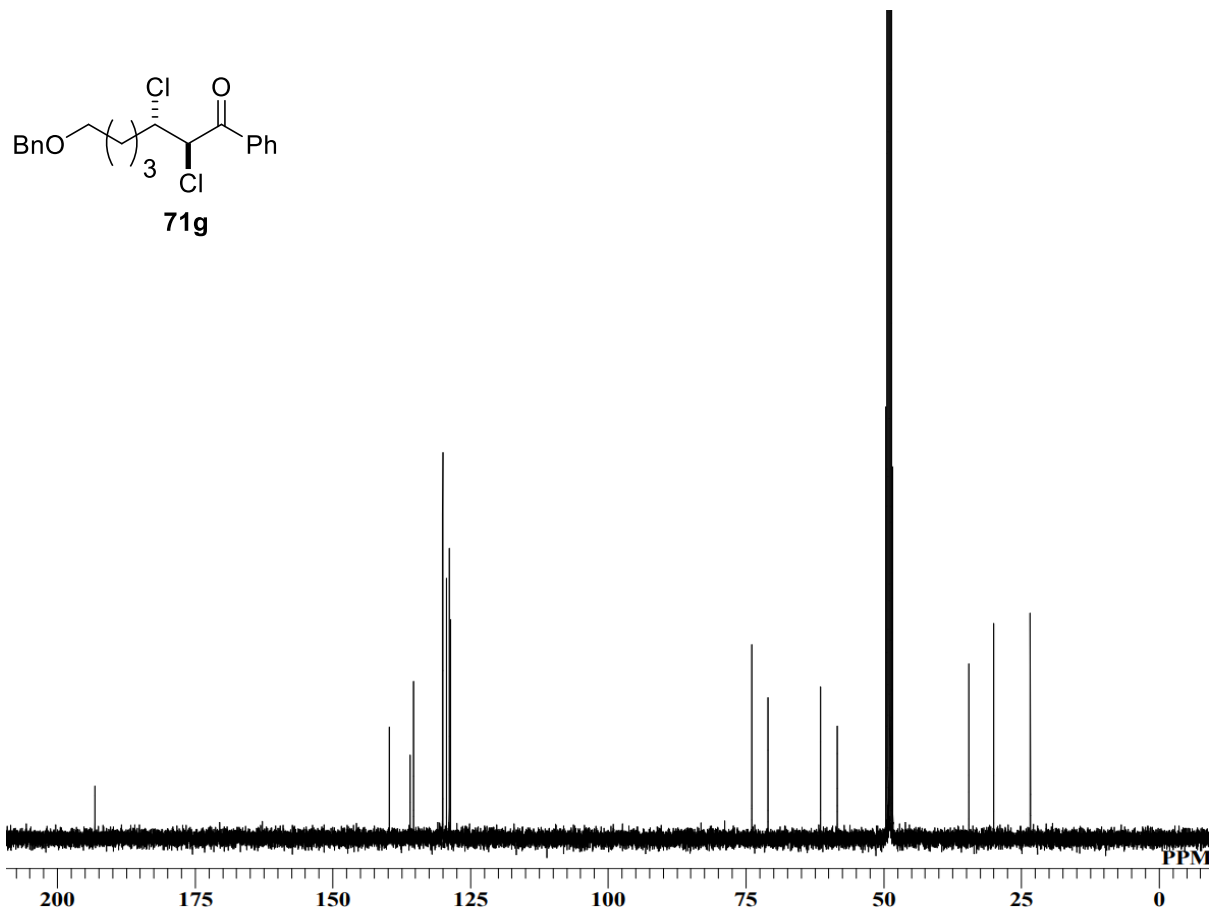
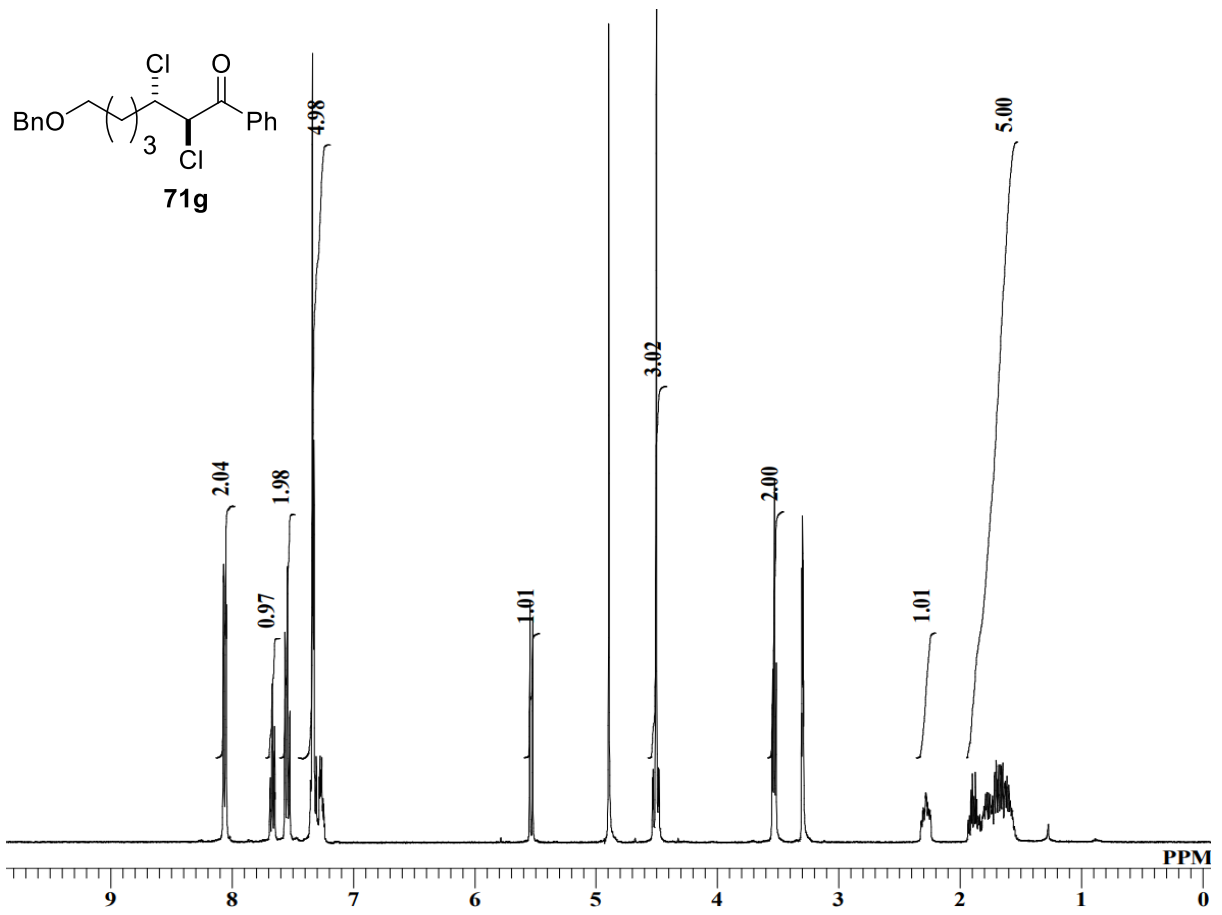


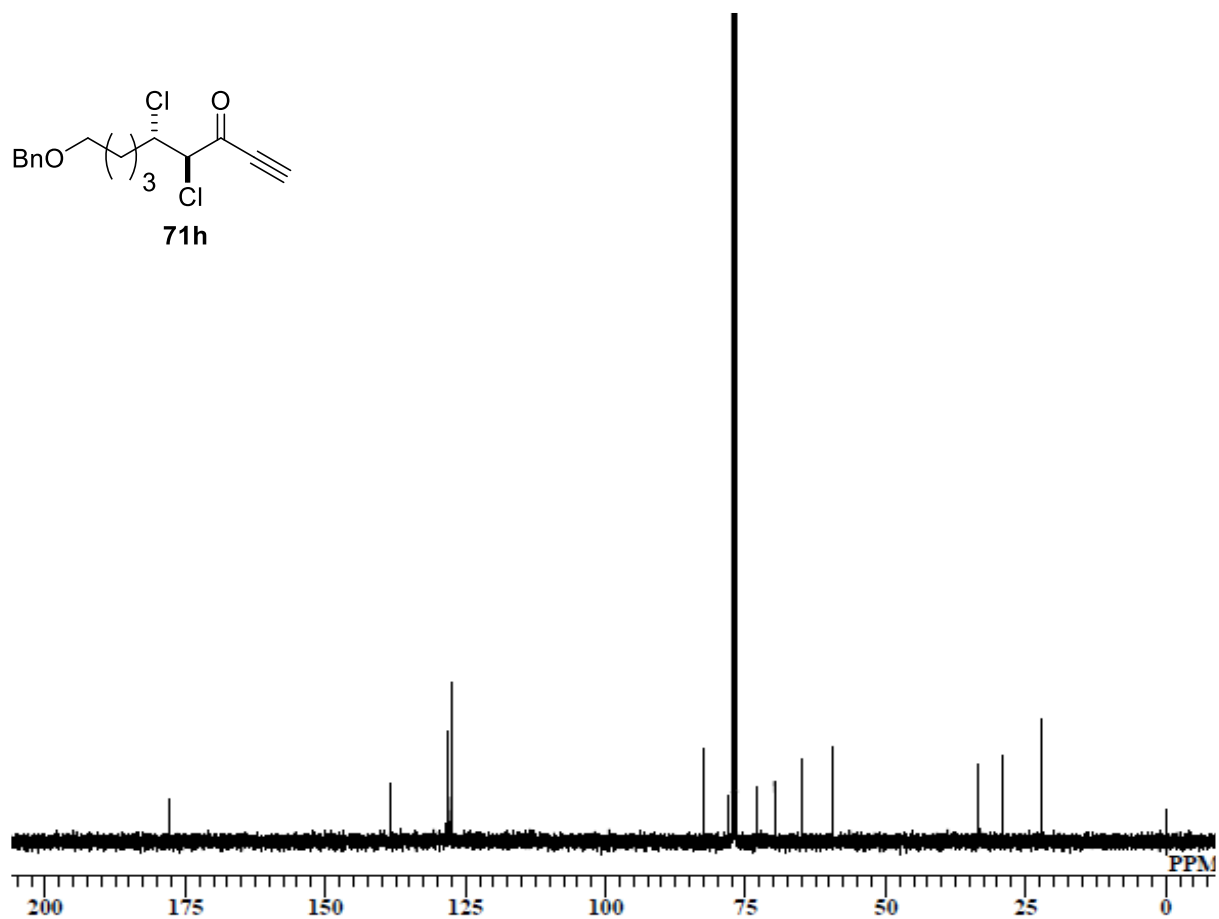
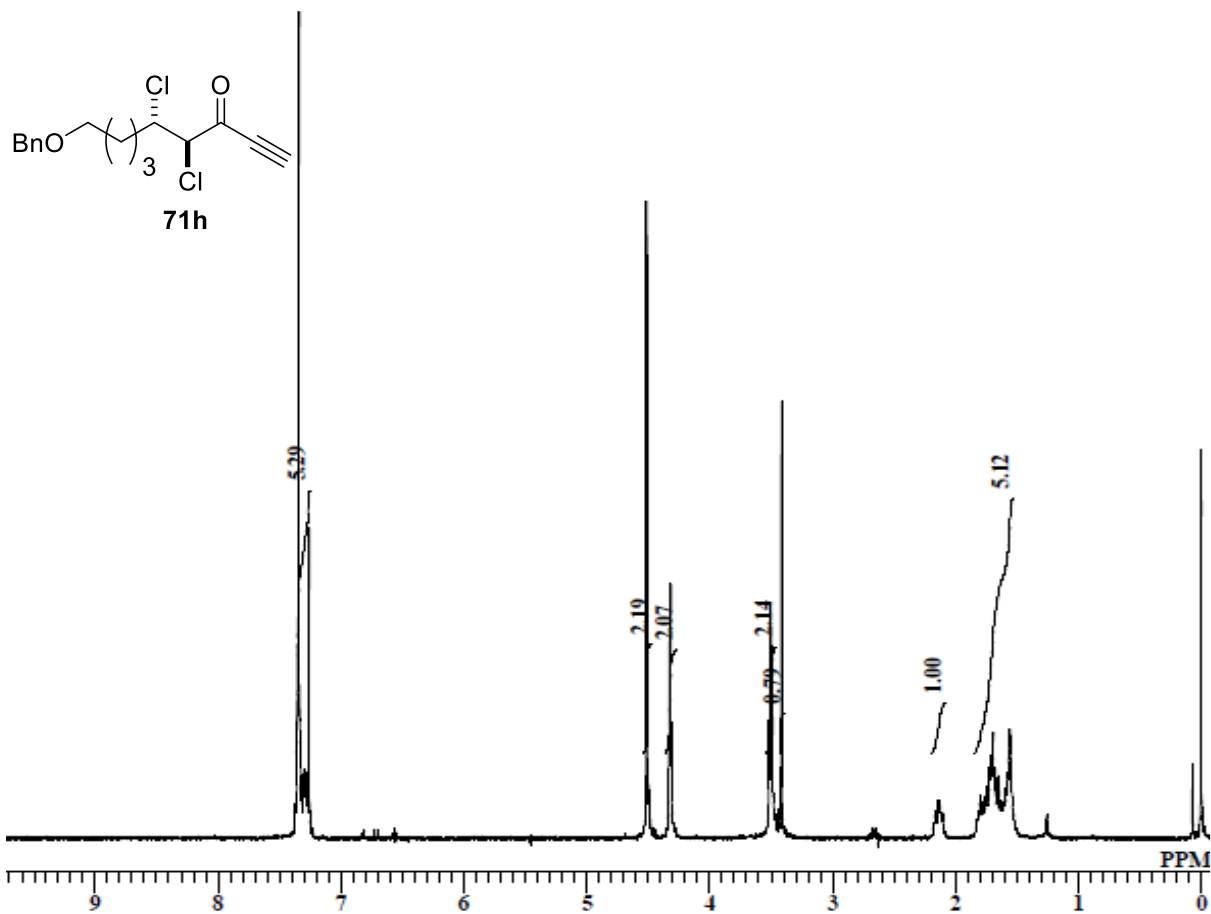


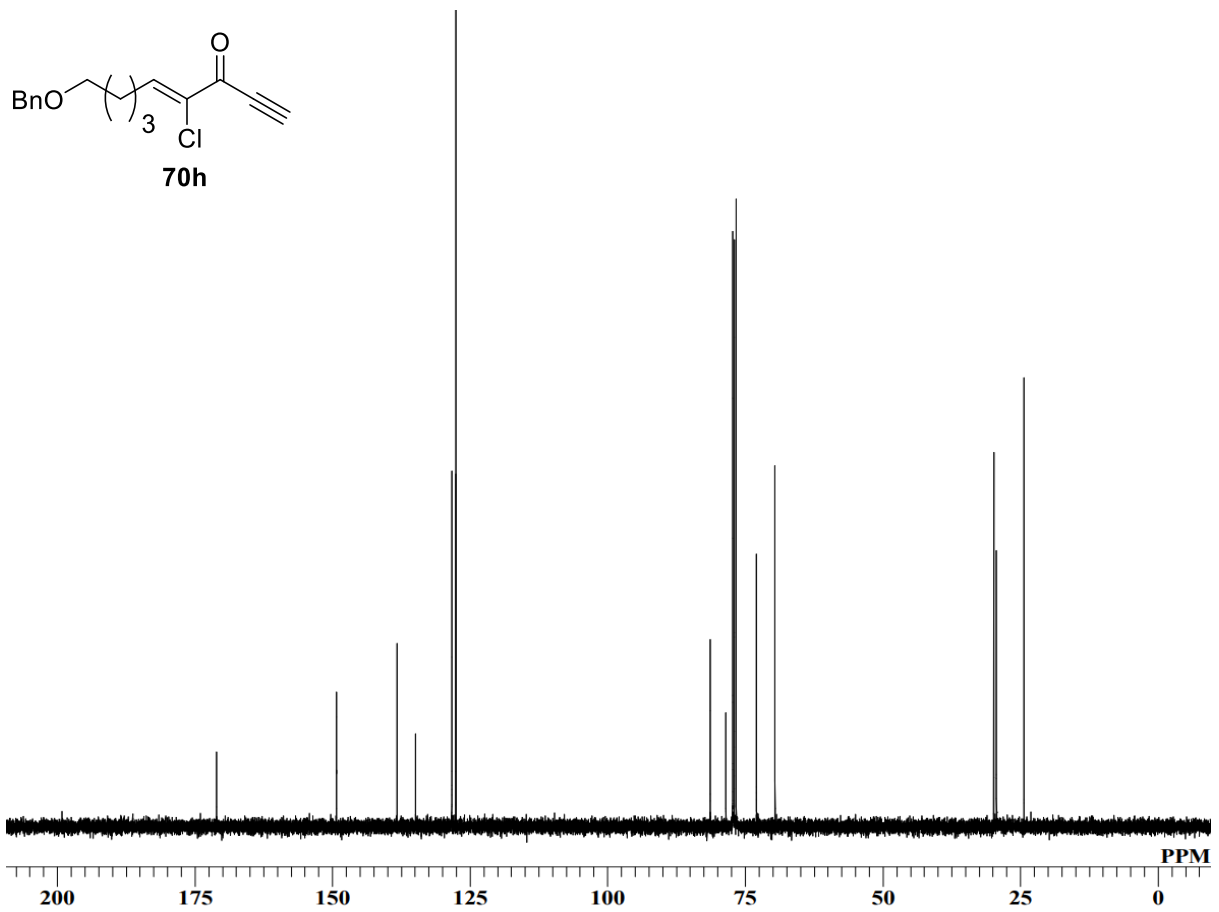
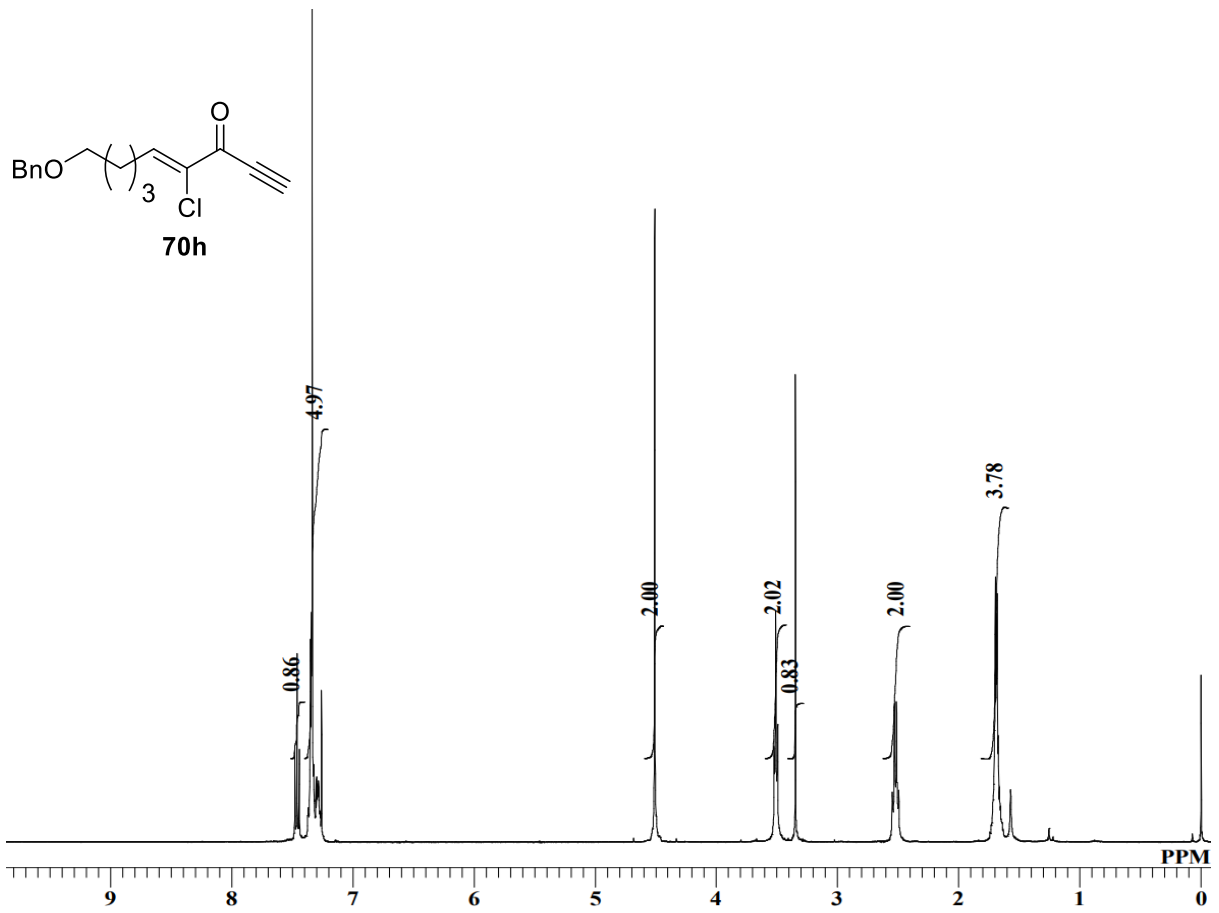


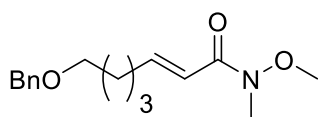




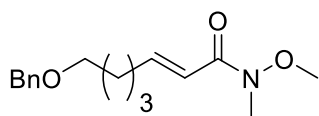
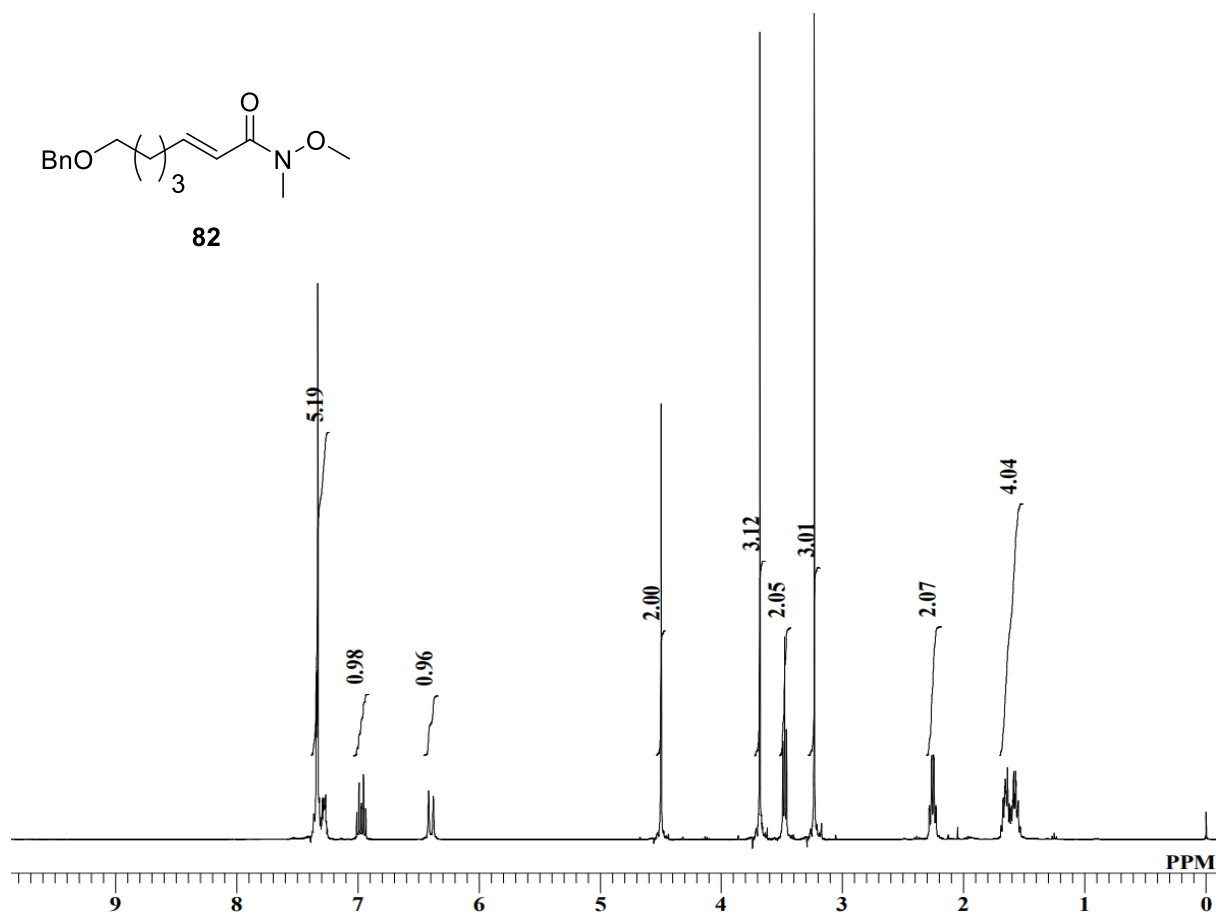




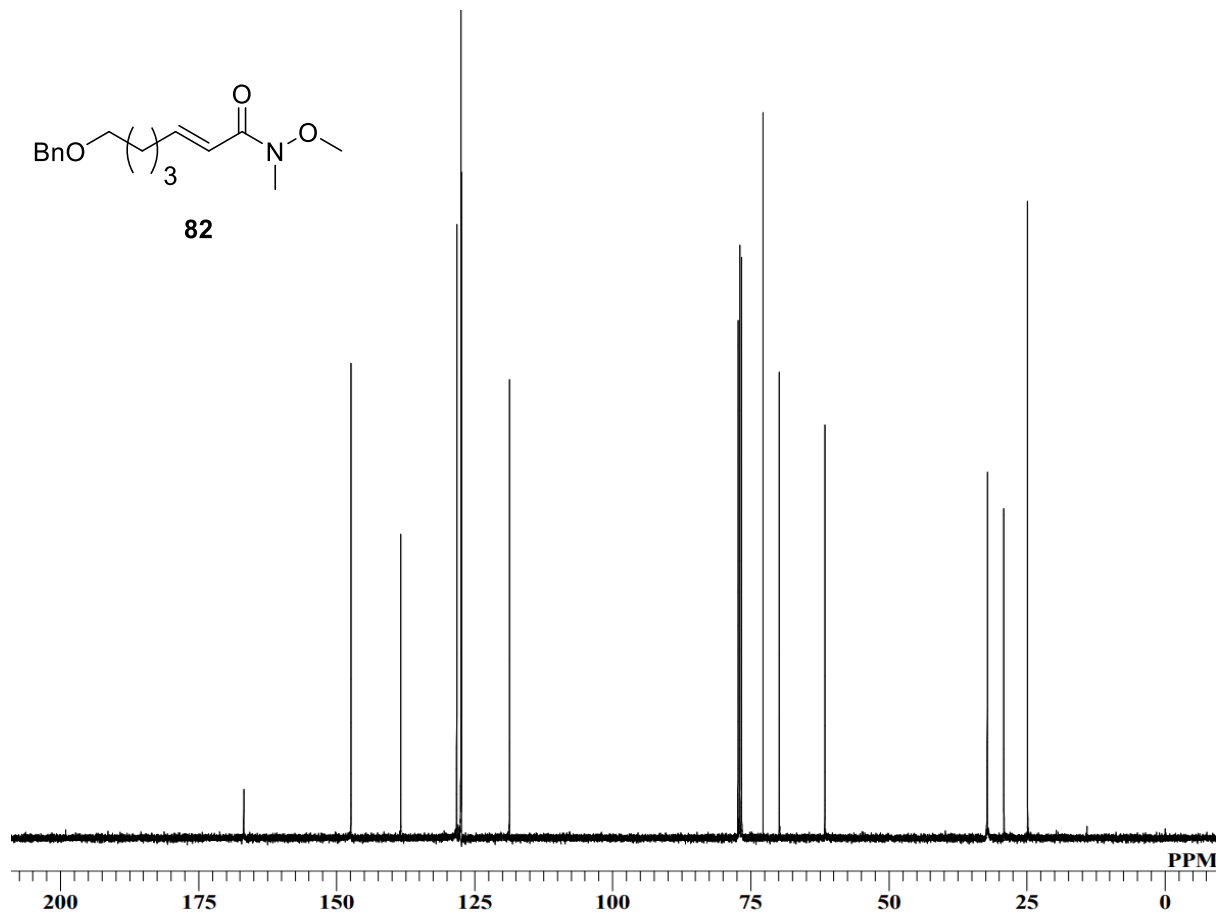


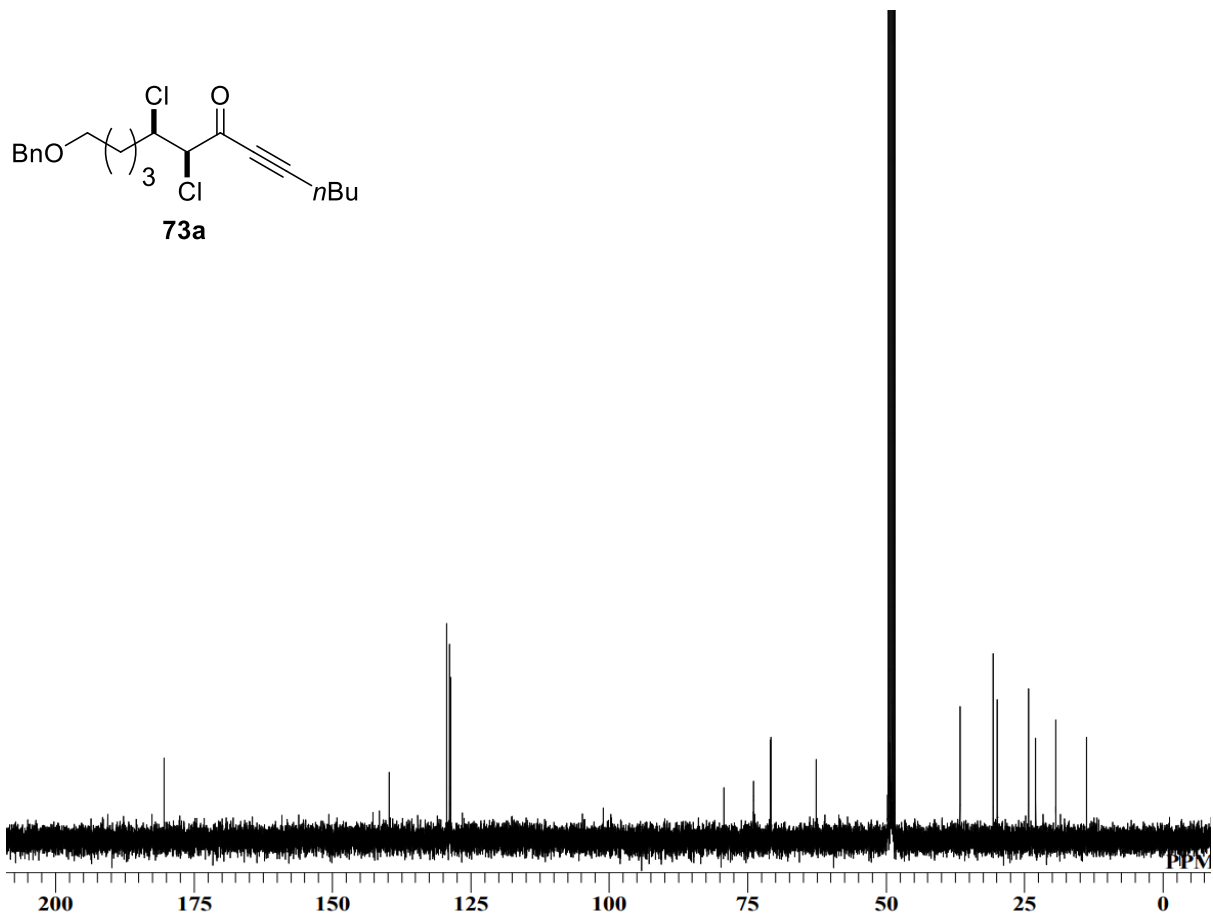
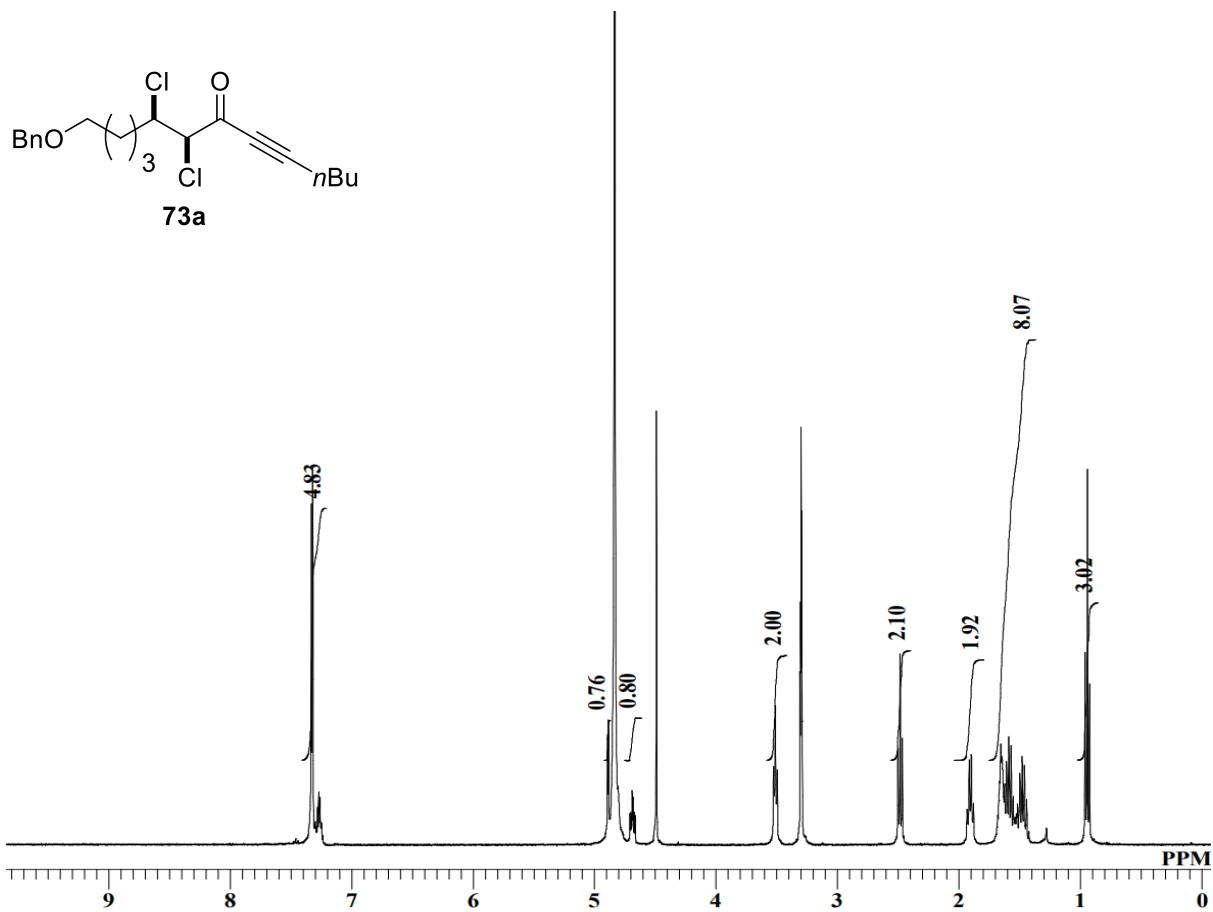


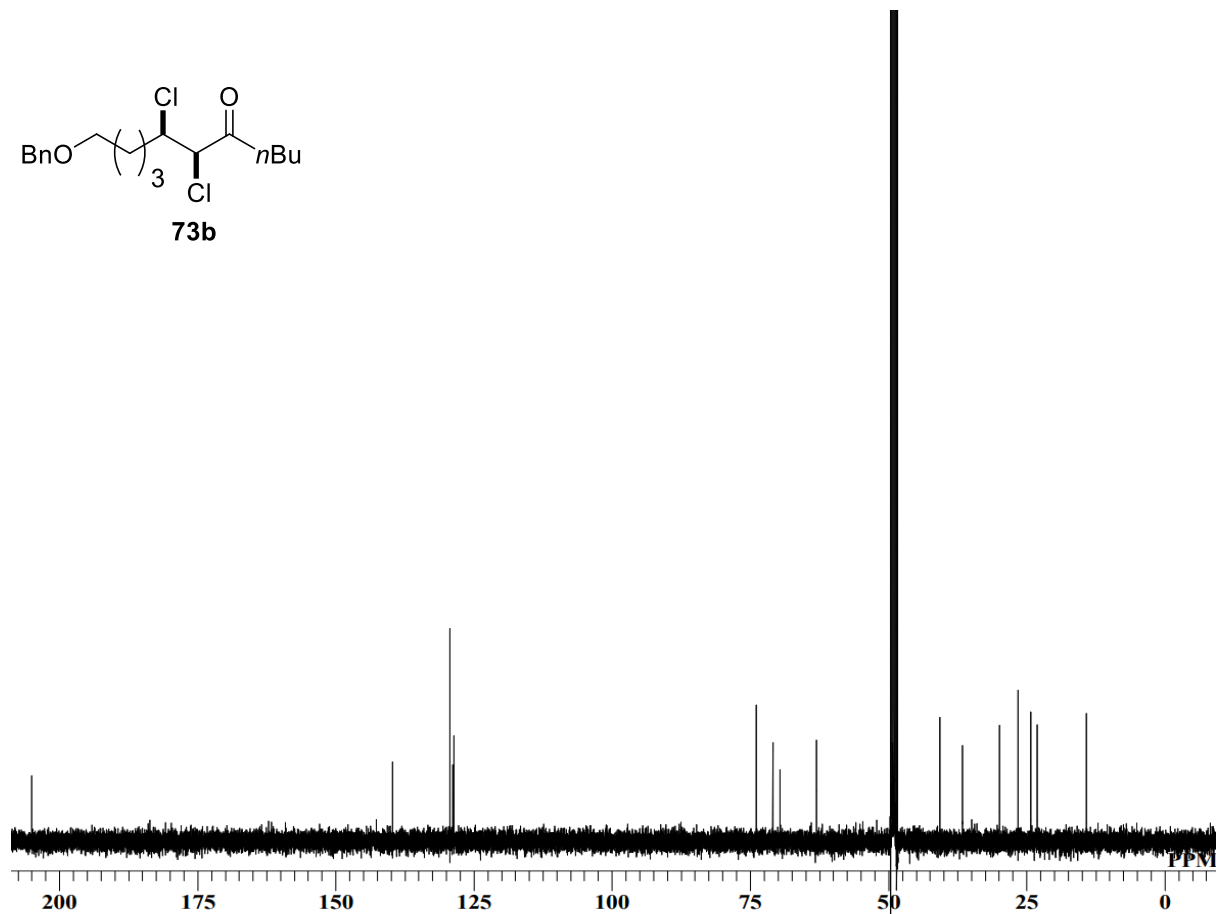
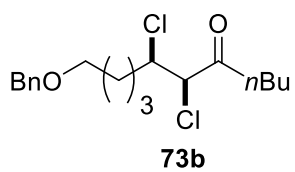
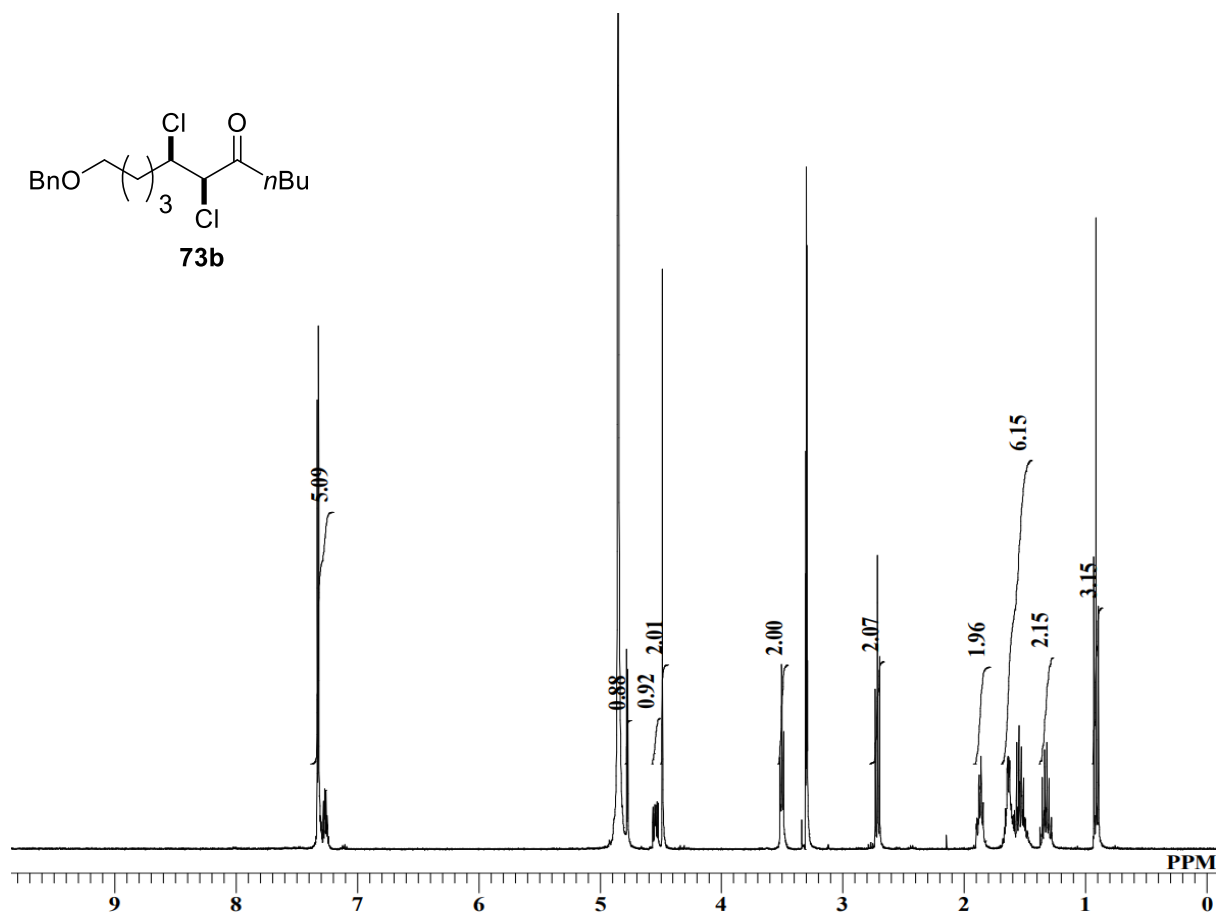
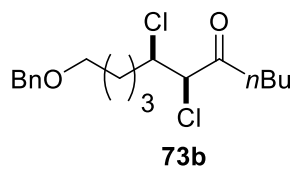
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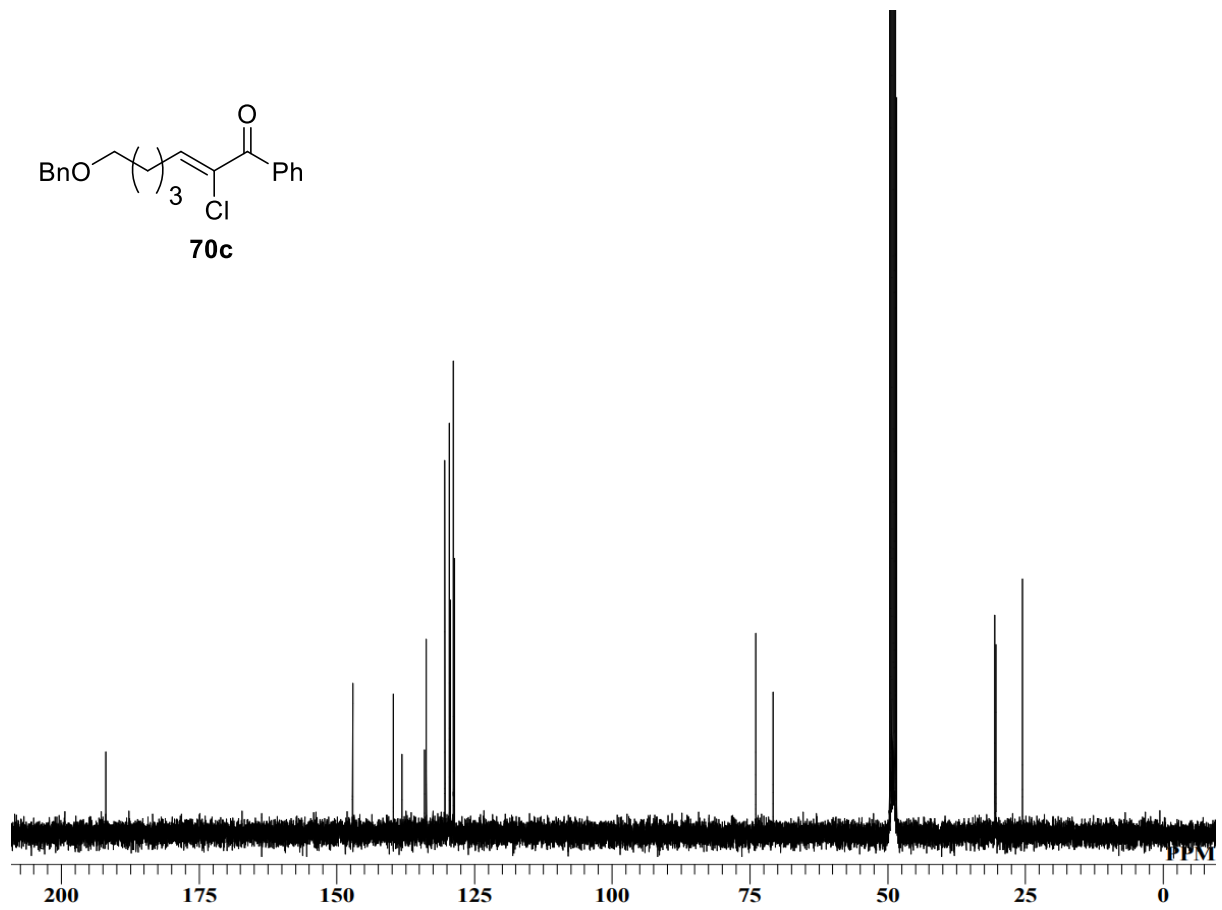
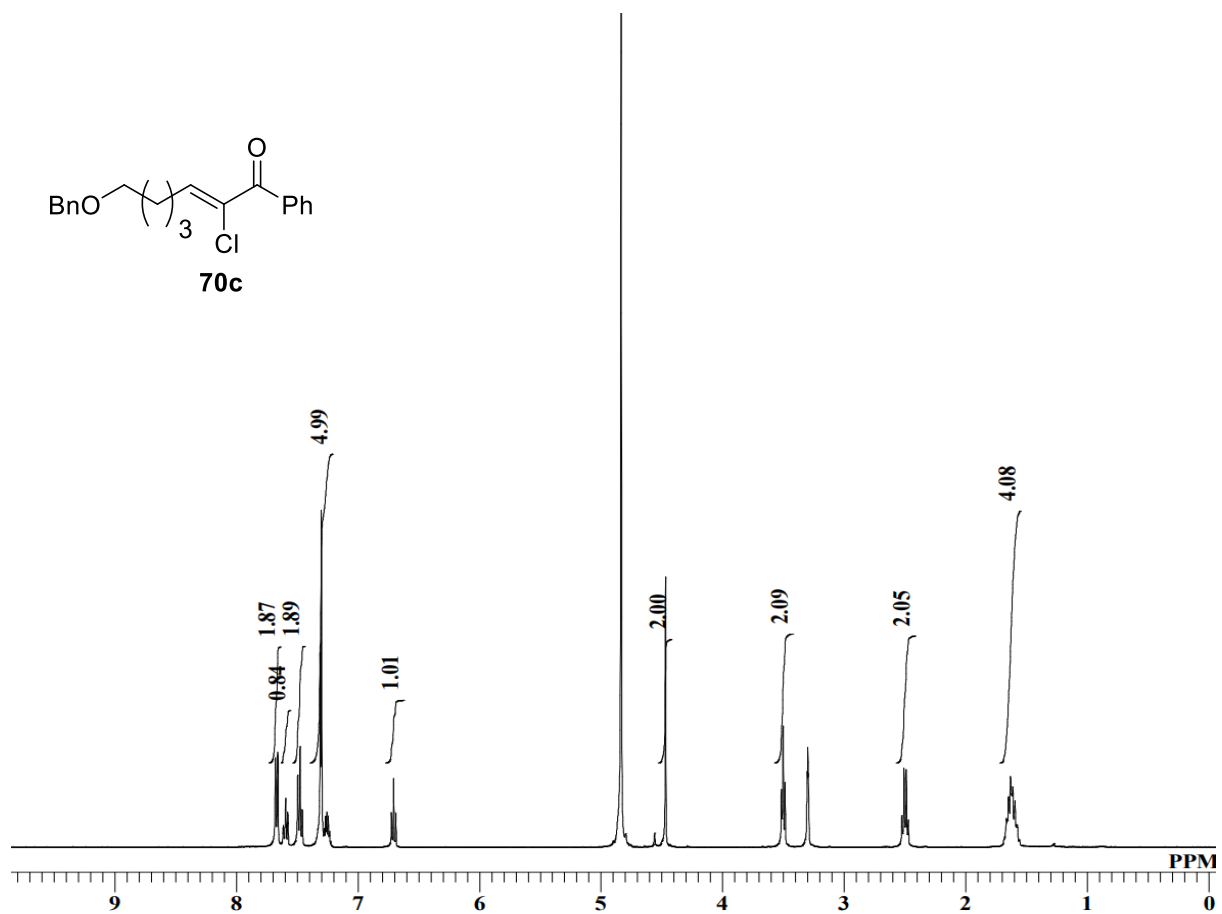


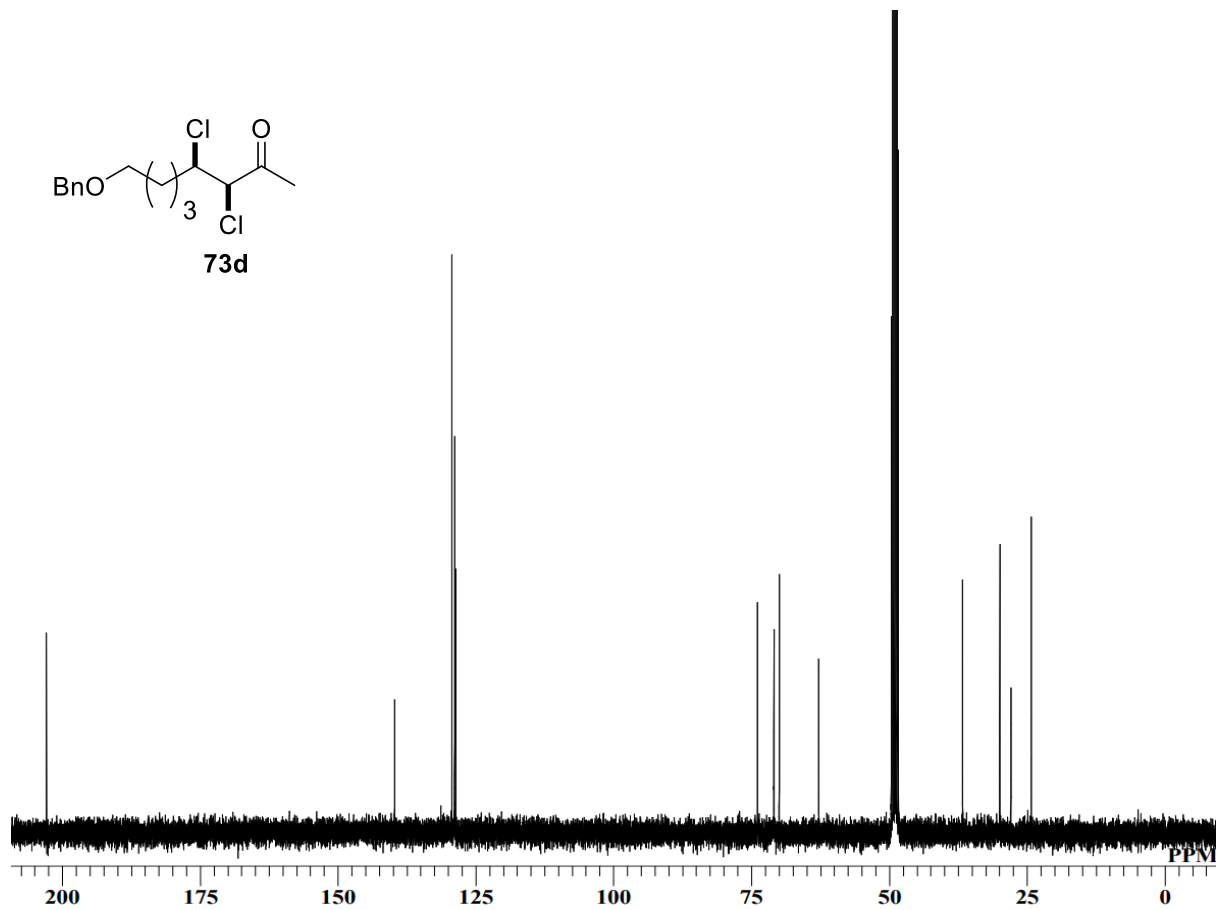
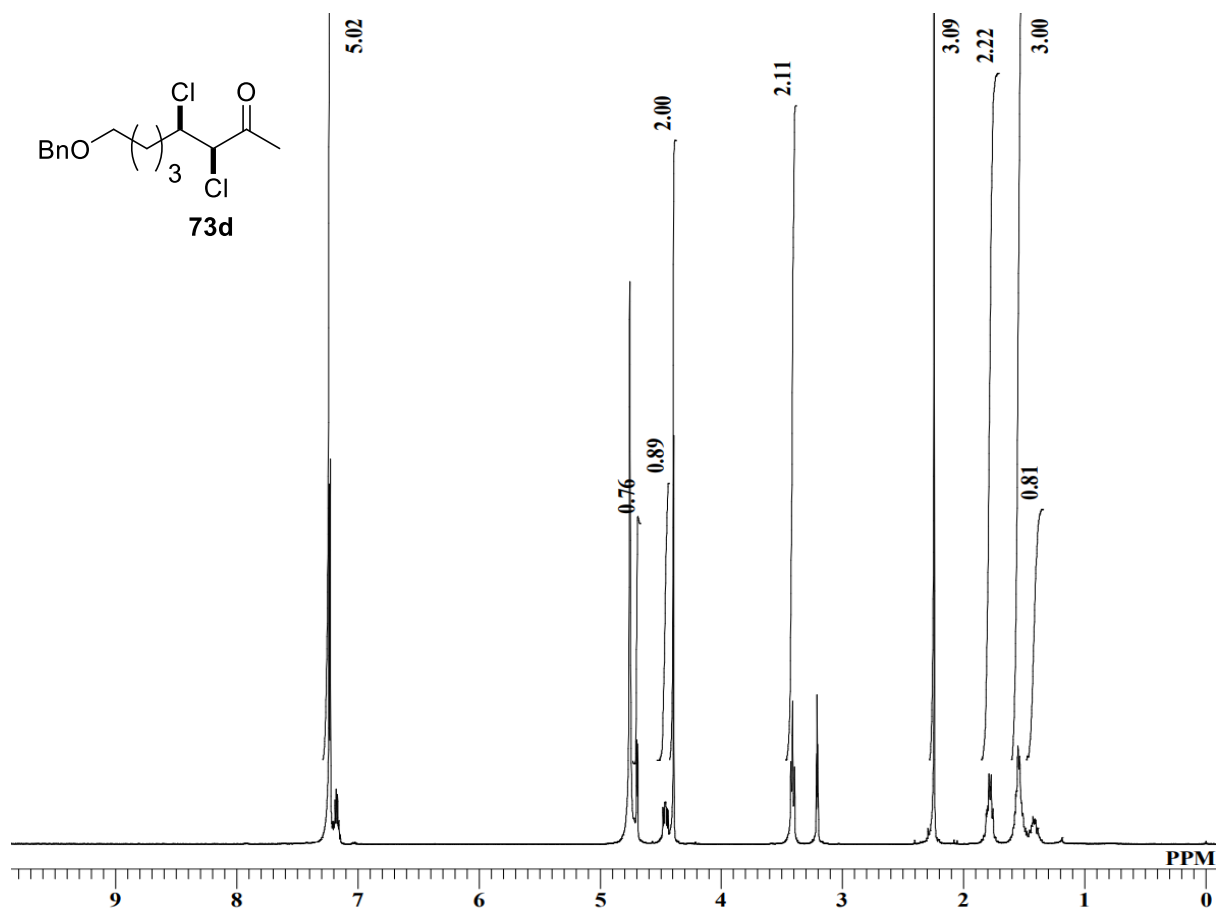
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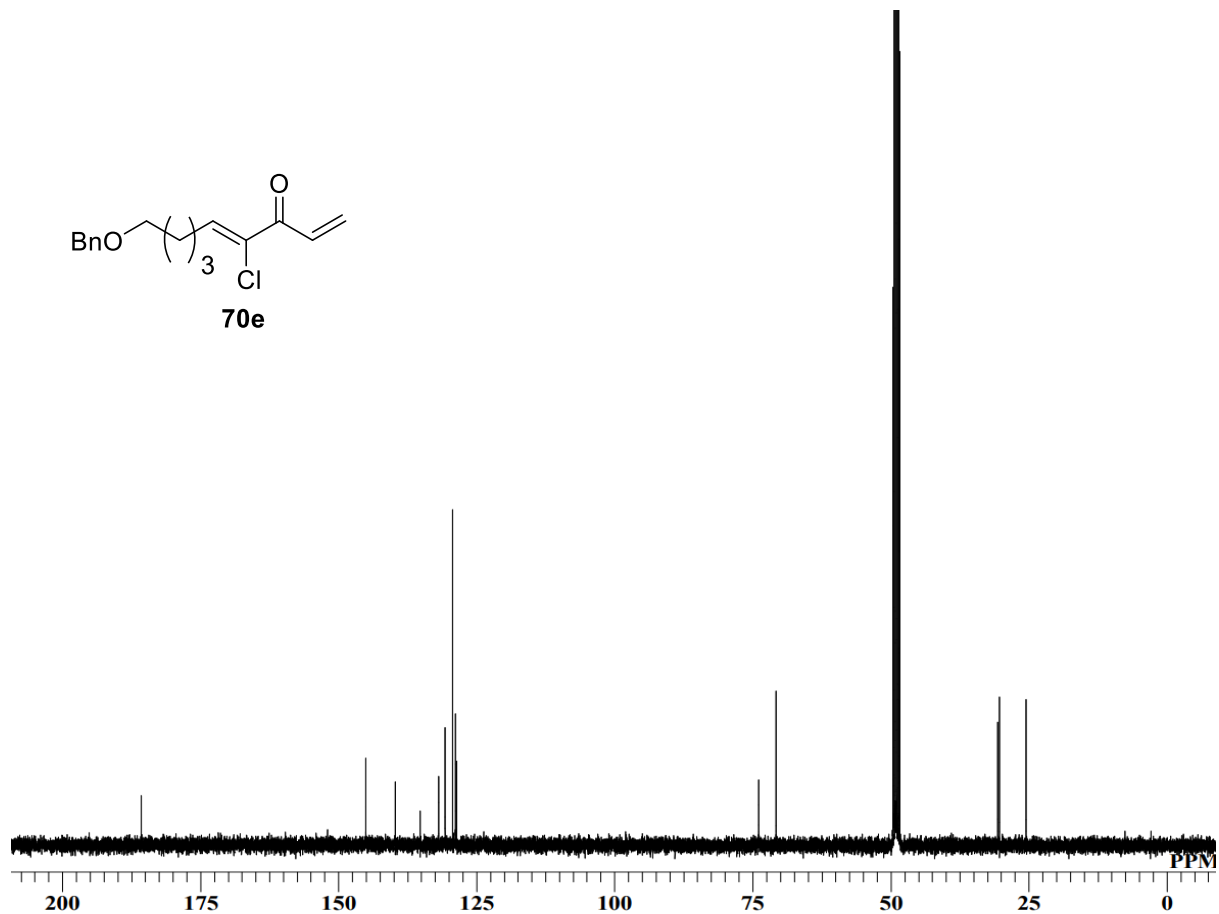
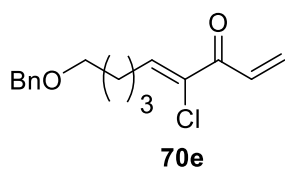
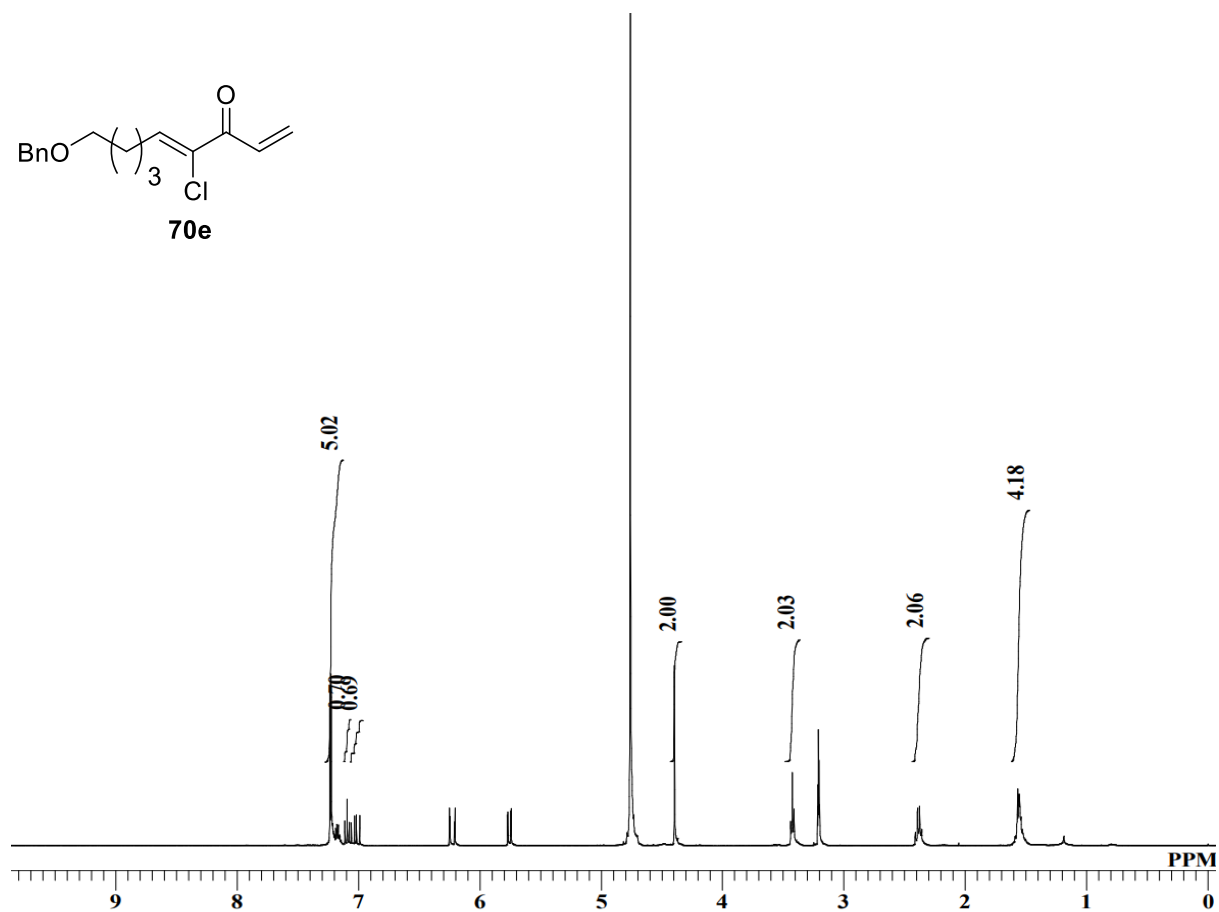
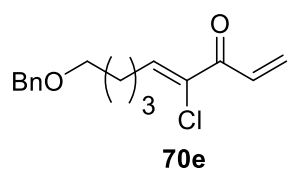


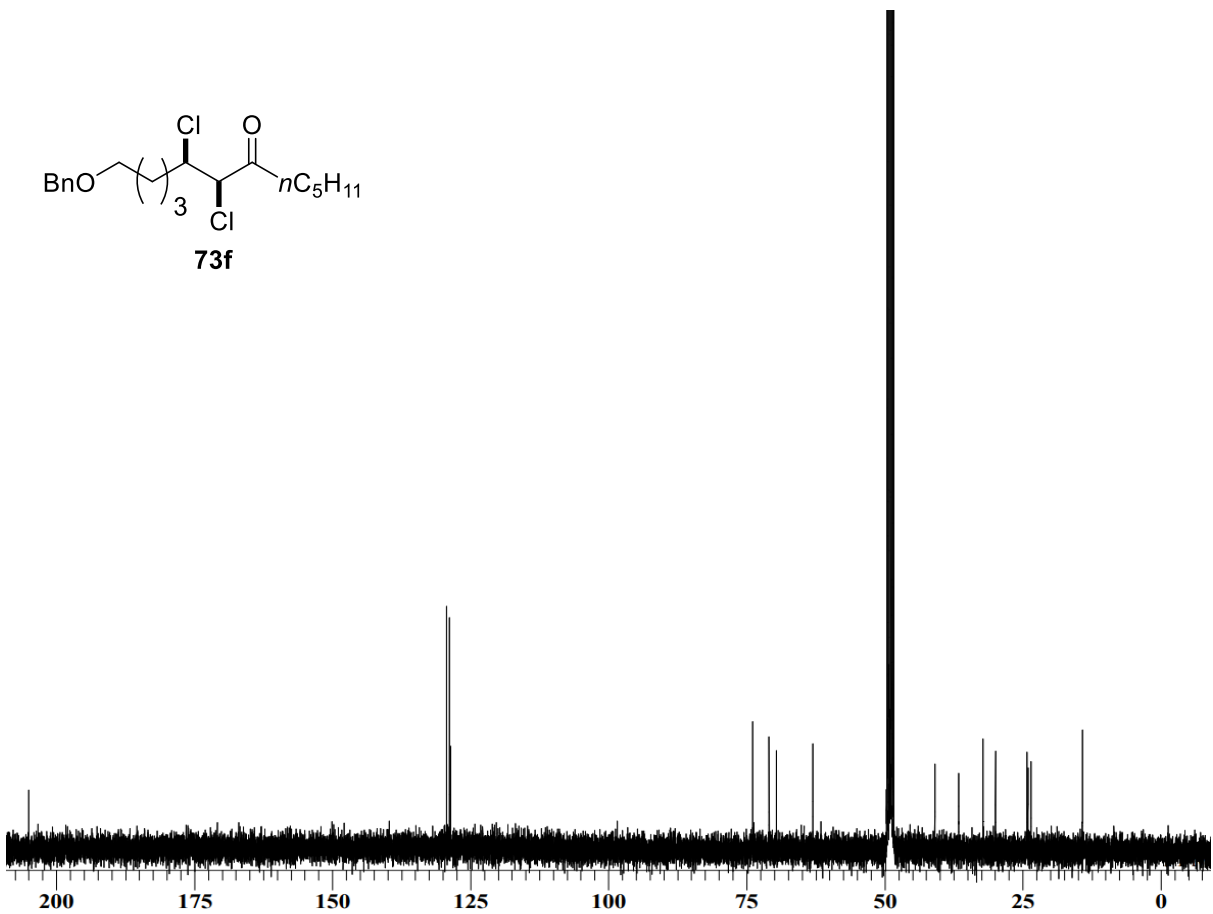
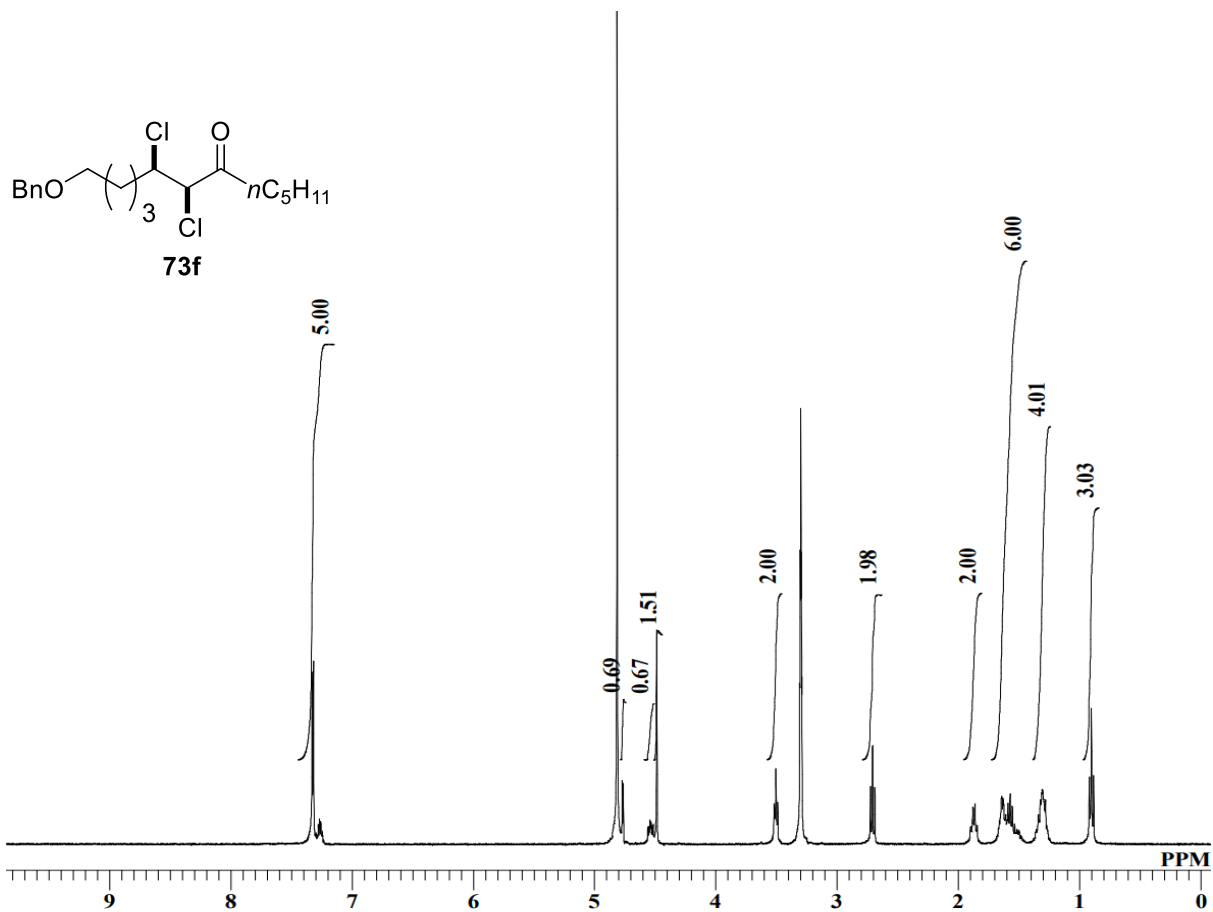


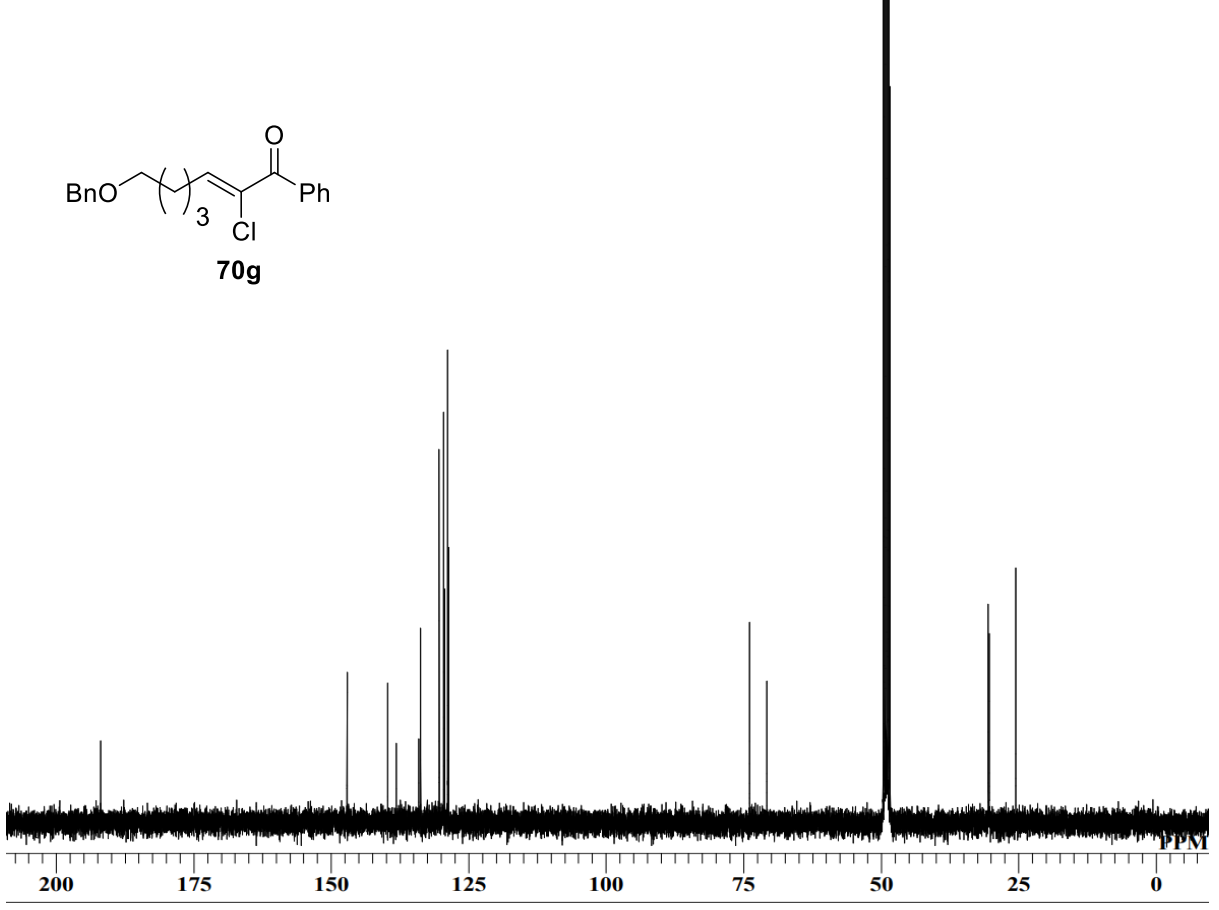
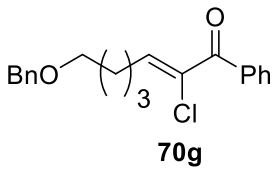
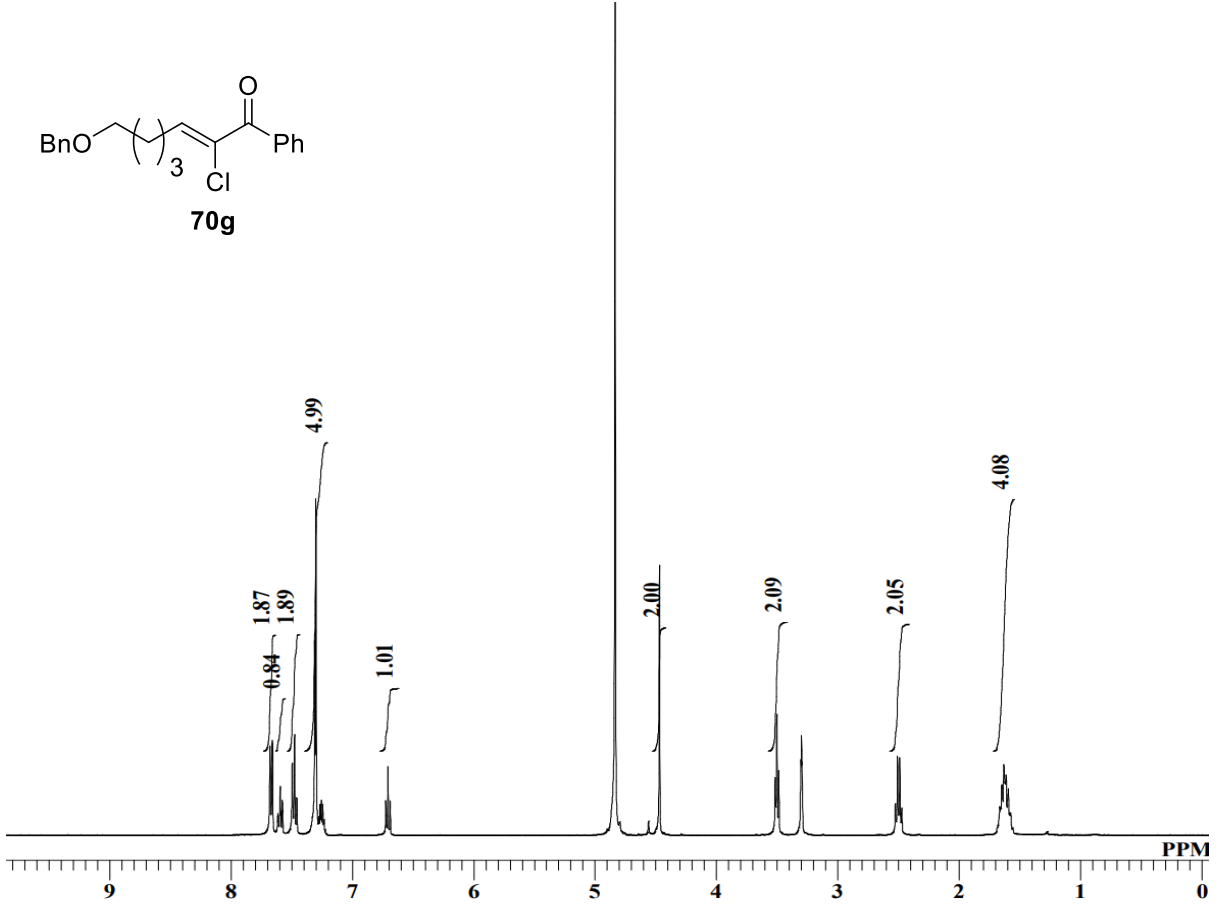
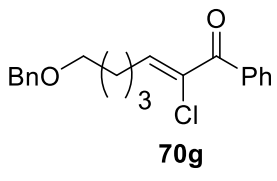












## **CHAPTER 3**

### **Synthetic Study on Mollenyne A**

### 3-1 Introduction

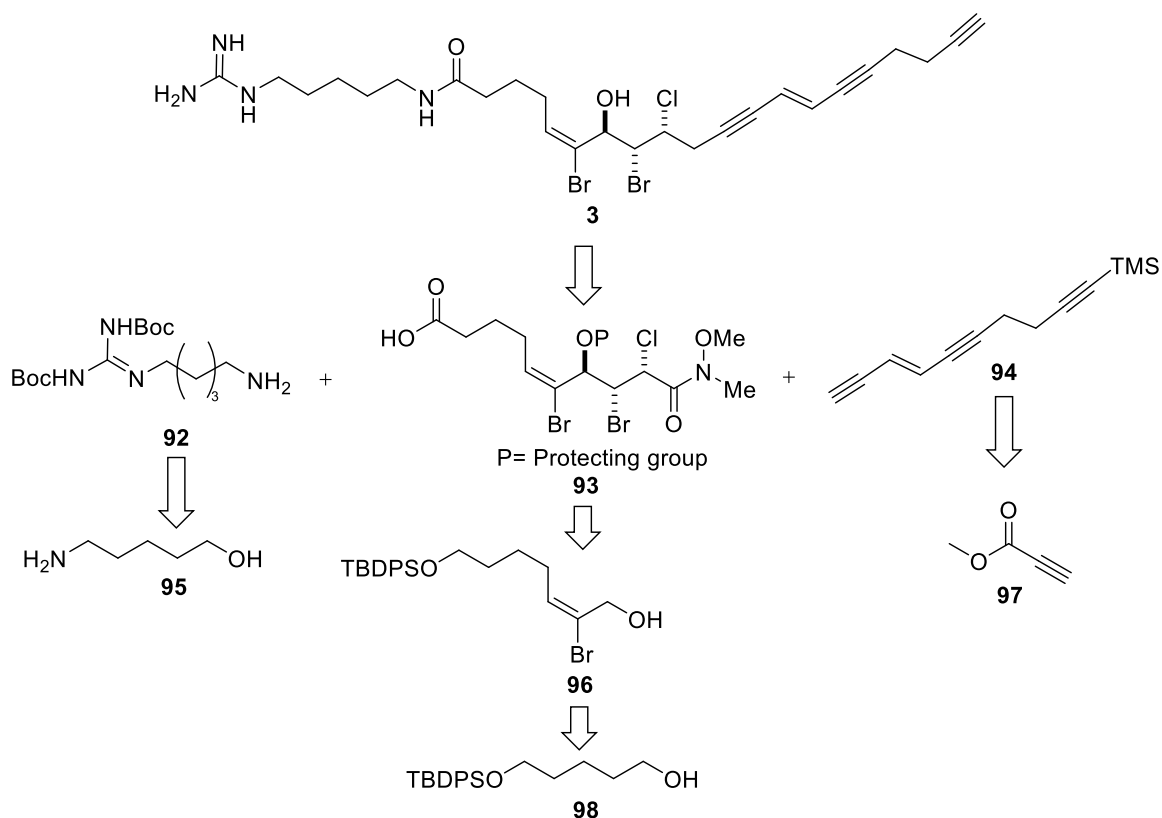
Mollenyne A was isolated from the sponge *Spirastrella mollis* by Molinski's group in 2011 and only 0.5 mg of this compound was isolated from this sponge. It was revealed that mollenyne A exhibits significant cytotoxicity against human colon tumor cells, HCT-116, with  $IC_{50} = 1.3 \mu\text{g/mL}$ . The limited amount makes it difficult to study using this compound for other biological activities. Mollenyne A consists of three important fragments, homoagmatine (left part), allylic alcohol flanked by halogenated carbons (central part) and triyne-ene terminus (right part). All of these three parts are interesting because these can rarely be found in other natural products. The central part can be divided into two parts, the *E*-bromoolefin and halohydrin. In an effort for synthetic study on halogenated natural products, mollenyne A, the development of concise and scalable synthetic methods of its *E*-bromoolefin and halohydrin units are necessary because of limited effective synthetic methodologies. Previously, many methodologies for constructing the halohydrin were reported by other groups, including my groups.<sup>1</sup> In the previously developed methods, alkene, epoxide, or 2-chlorocarboxylic acid were used as a precursor. In order to construct three contiguous stereocenters in mollenyne A, use of these precursors are difficult in the view of stereo- and regioselectivities.<sup>2</sup> For further investigation, this chapter will focus on formation of *E*-bromoolefin and halohydrin construction.

### 3-2 Retrosynthetic Analysis

Retrosynthetic analysis of mollenyne A using a convergent approach is presented in Scheme 3-1. The author envisioned the synthesis of **3** planned via amidation reaction between **92** and **93** and subsequent C-C bond formation reaction between **93** and **94** through nucleophilic addition to Weinreb amide. Synthesis of homoagmatine **92** was planned to start from commercially available 5-Amino-1-pentanol **95**. On the other hand, the triyne-ene terminus **94**

would be prepared from the commercially available methyl propiolate **97**. Eventually, the main focus of this study, allylic alcohol flanked by halogenated carbon **93** is traced from known alcohol **98** with *tert*-butyldiphenylsilyl group.

Scheme 3-1. Retrosynthetic analysis towards the synthesis of Mollenyne A

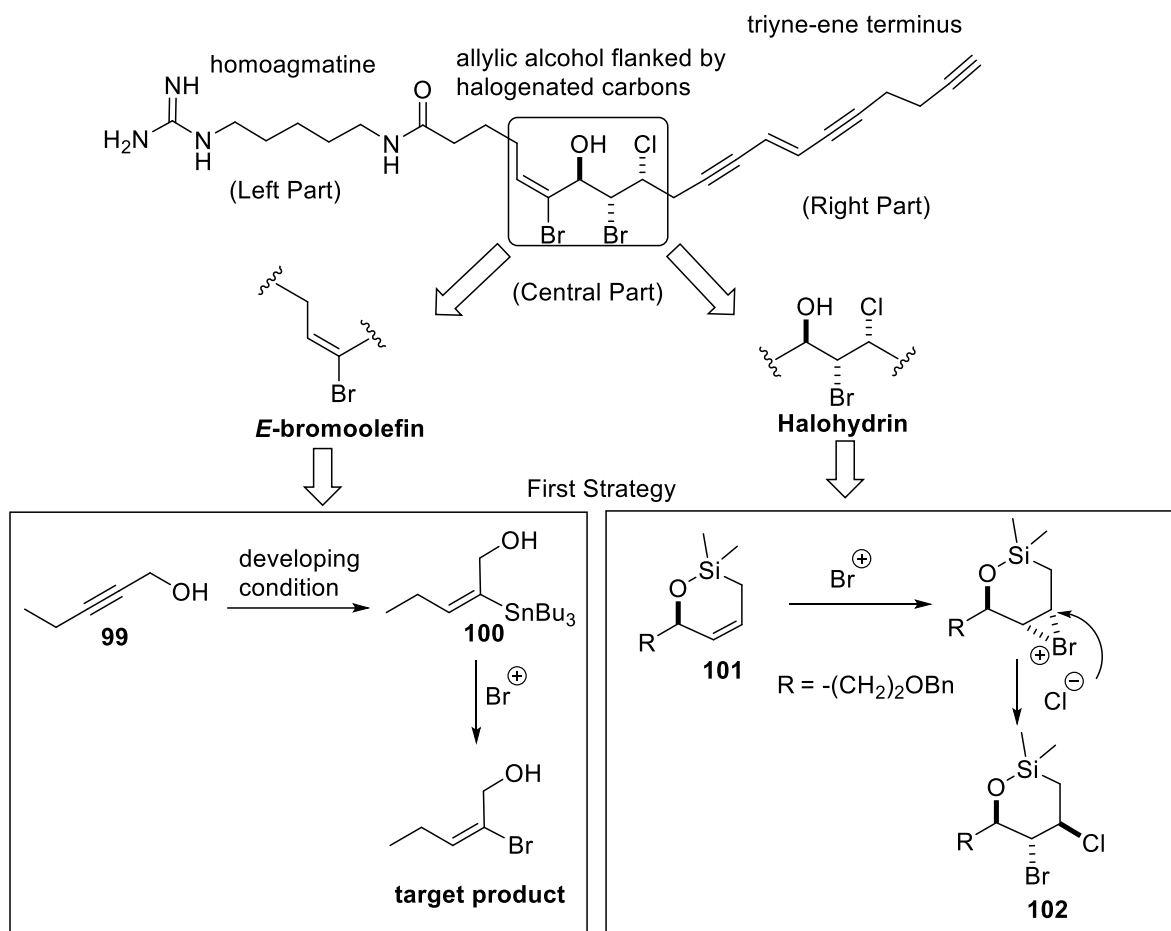


### 3-3 Study Plan toward **93**

In this study, the allylic alcohol flanked by halogenated carbons fragment can be divided into two parts, the *E*-bromoolefin and halohydrin. For effective construction of the two parts, authors have envisioned the use of model compound **99** and **101** in the first strategy of the optimization process. Regio- and stereoselective conversion of model compound **99** to **100** through hydrostannylation reaction enables selective synthesis of the *E*-bromoolefin by the treatment of  $\text{Br}^+$ . Subsequently, model compound **101** includes an allylsilane moiety. Treatment of  $\text{Br}^+$

species would stereoselectively produce bromonium ion, which would be captured by chloride in a regioselective manner due to  $\beta$ -silyl cation effect.

Scheme 3-2. Synthetic study plan for *E*-bromoolefin and halohydrin from central part

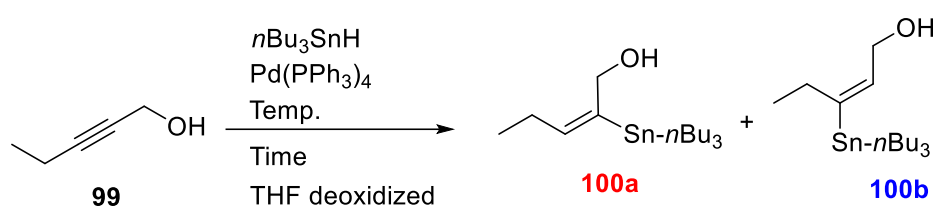


### 3-4 Optimization of *E*-Bromoolefin Formation

First, 2-pentyn-1-ol **99** was used as a model substrate for the optimization of the hydrostannation reaction to generate desired product **100a** using tributyltin hydride ( $n\text{Bu}_3\text{SnH}$ ) and tetrakis triphenylphosphine palladium ( $\text{Pd}(\text{PPh}_3)_4$ ). Results of the optimizations are shown in Table 3-1. Treatment of **99** with 1.5 equivalents of  $n\text{Bu}_3\text{SnH}$  and 0.01 equivalents of  $\text{Pd}(\text{PPh}_3)_4$  at  $0\text{ }^\circ\text{C}$  gave low conversion to **100a** and **100b** with low regioselectivity (entry 1). This treatment was similar to the reference.<sup>3</sup> In an attempt to improve the yield, the reaction temperature from  $0\text{ }^\circ\text{C}$  to room temperature was applied (entries 2, 3 and 5) to slightly improve

the conversion. When the temperature raised to the reflux condition (entry 6) or the equivalent of the reagent is increased (entry 7), significant change of the reactivity was not observed. The regioselectivity in almost entries are include in the range of 5 to 6 : 1 selectivity, except entries 1 and 7 and very low yields from desired product **100a** always obtained.

Table 3-1. Hydrostannation reaction to **99**<sup>a</sup>



entry	HSn- <i>n</i> Bu <sub>3</sub> (eq)	Pd(PPh <sub>3</sub> ) <sub>4</sub> (eq)	Temp. (°C)	Time (min)	Results <sup>b</sup>
					<b>99:100a:100b</b> (combined yield)
1	1.5	0.01	0	30	89:9:2 (11%)
2	1.5	0.05	0-rt	30	70:25:5 (28%)
3	1.5	0.1	0-rt	30	61:33:6 (29%)
4	1.5	0.1	0-rt	120	59:34:7 (32%)
5	1.5	0.1	rt	30	63:32:5 (30%)
6	1.5	0.1	reflux	30	74:22:4 (25%)
7	2.5	0.1	0-rt	30	54:35:11 (39%)
8	1.5	0.1	rt	overnight	64:33:7 (32%)

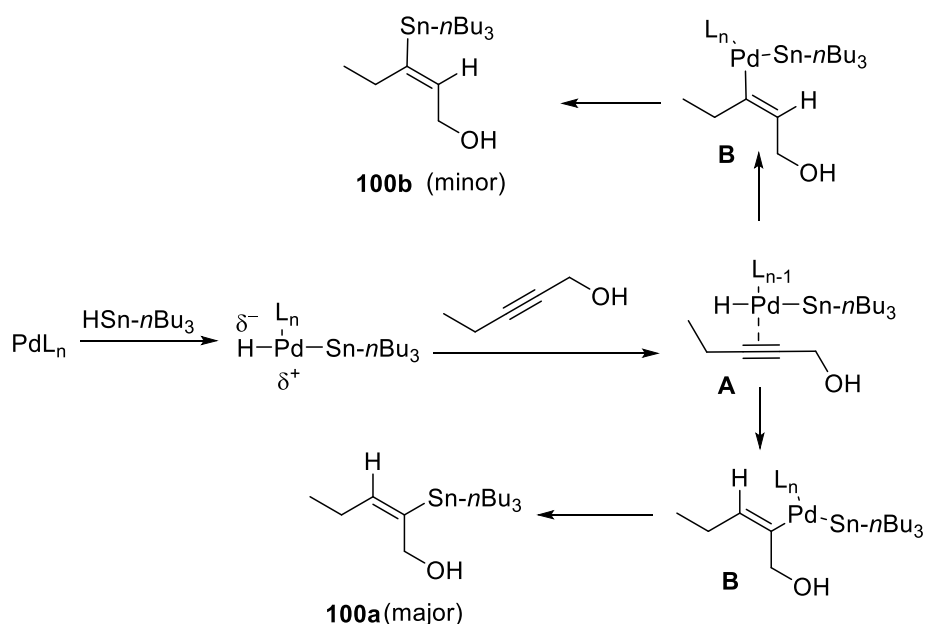
<sup>a</sup>Reaction conditions: 0.2 mmol of **99** was used. <sup>b</sup>ratio of **99**, **100a** and **100b** was estimated by crude <sup>1</sup>H NMR.

The regioselectivity of the addition reaction is controlled by many factors, of which the structure of the alkyne substrate plays a critical role.<sup>3,4</sup> The challenge in this process is the selective synthesis of **100a**. Another group reported that Pd(0)-catalyzed hydrostannylation to



propargyl alcohol gives 75:25 in regioselectivity with moderate yield (58%). This means that the yield obtained in this study is not much different from previous studies, although it is lower than reference.<sup>3</sup> In addition, author believed that there is a high possibility of contamination in the system between sensitive palladium catalysts with oxygen during the process and lowering the yield. Generally, palladium-catalyzed hydrostannation proceeds under milder conditions and resulting in *syn*-stereoselectivity. The selectivity is influenced by the relative size of proximal substituents or steric differentiation, although some results suggest that neighbouring hydroxyl groups might have a directing effect.<sup>5</sup> The mechanism starts from oxidative addition of  $n\text{Bu}_3\text{SnH}$  to the metal center ( $\text{PdL}_n$ ) occurs followed by coordination of the unsaturated bond leading to complex **A**, which may then undergo hydrometalation to give vinylmetal **B** followed by reductive elimination to furnish the organostannane (Scheme 3-3).

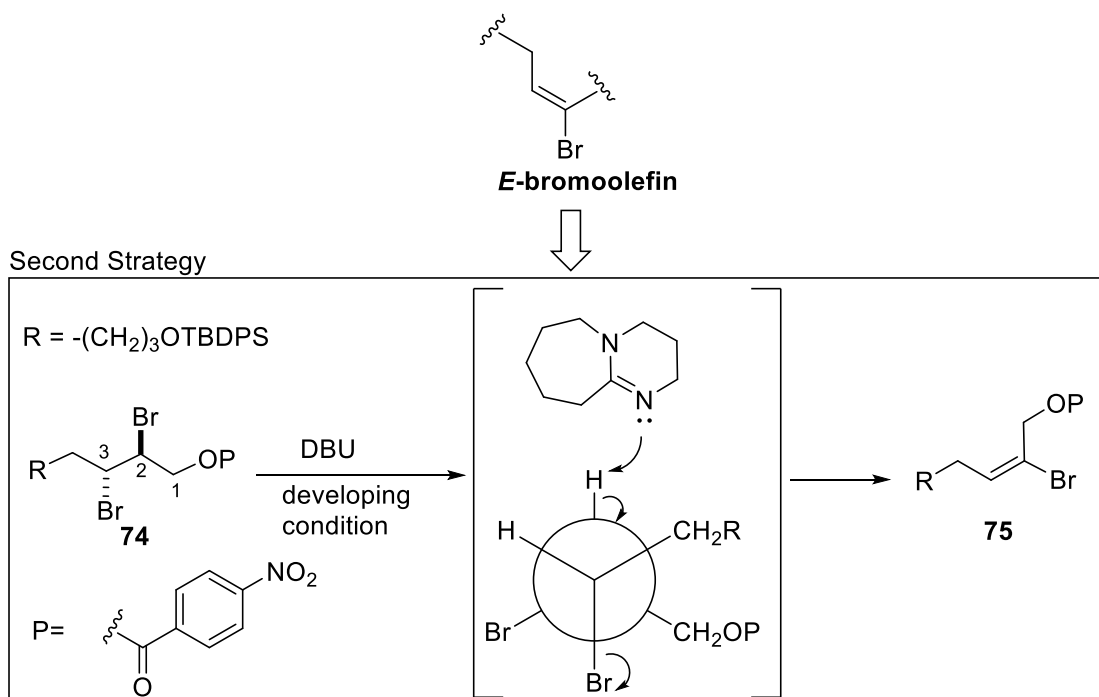
Scheme 3-3. Mechanism of palladium-catalyzed hydrostannation



Because the first strategy did not work well, author continued the optimization to second strategy. The following strategy is the preparation of *E*-bromoolefin by regioselective HBr-elimination reaction from *anti*-1,2-dibromo compounds which inspired by Nishiyama and Saito

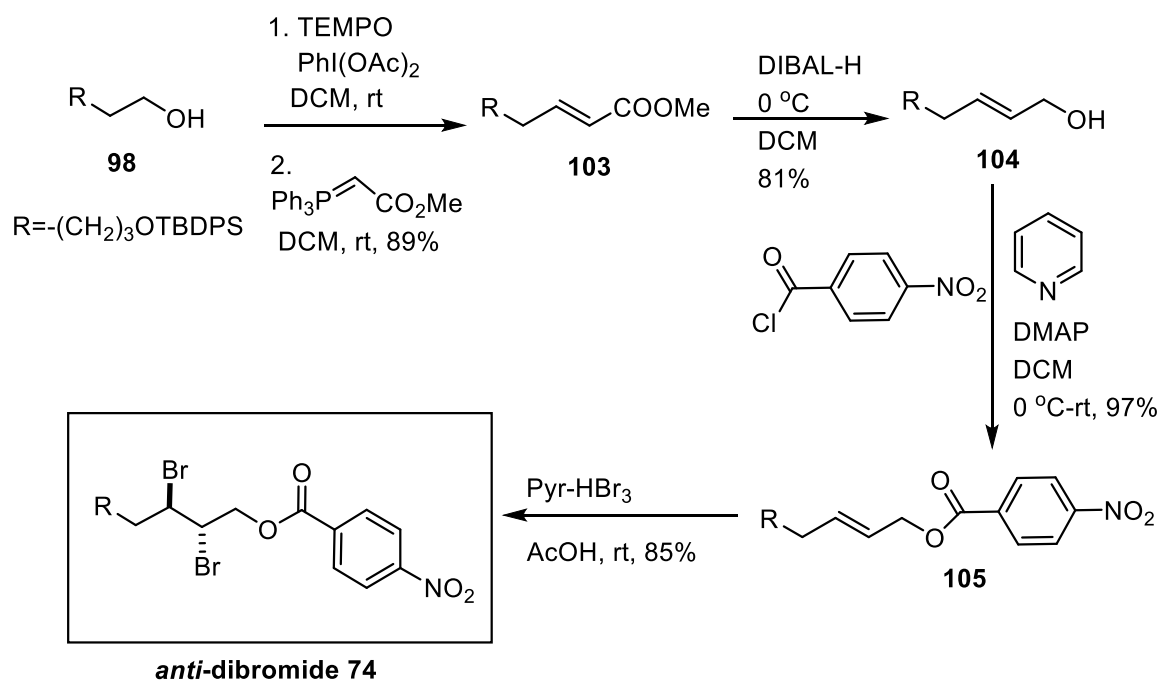
research groups.<sup>6</sup> In this strategy, the DBU would served as a base at C2 to induce regioselective HBr-elimination. Acidity enhancement of proton at C2 caused by electronic interaction between this proton and neighbouring heteroatoms (Scheme 3-4).

Scheme 3-4. Second strategy toward *E*-bromoolefin: regioselective HBr-elimination via DBU



Model compound **74** was prepared from known monoprotected of 1,5-pentanediol with TBDPS as shown in Scheme 3-5.<sup>7</sup> Oxidation of **98** by TEMPO and subsequent treatment of Wittig reagent in one-pot operation to obtain unsaturated ester **103**. The unsaturated ester **103** was reduced to **104** with DIBAL-H. Protection of alcohol **104** with *p*-nitrobenzoyl group gave ester **105** and bromination with Pyr.-HBr<sub>3</sub> yielded the *anti*-1,2-dibromide **74**.

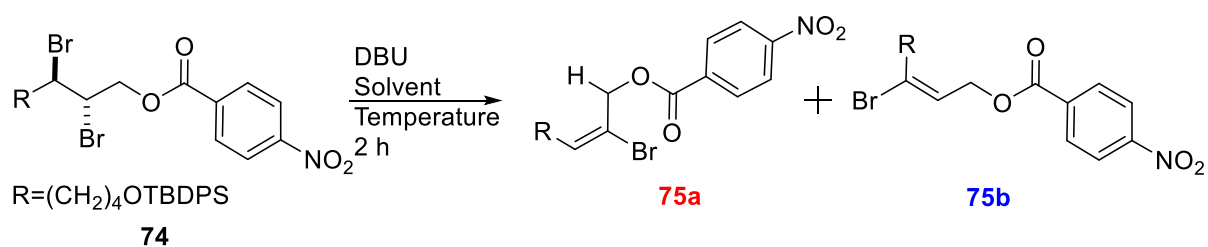
Scheme 3-5. Preparation of *anti*-1,2-dibromide **74**



Optimization for the regioselective elimination reaction with the *anti*-1,2-dibromide **74** and DBU were presented in Table 3-2. The stereoconfiguration of **75a** and **75b** was determined by the  $^1\text{H}$  NMR techniques involving the NOESY analysis. Treatment of **74** with 1.5 equivalents of DBU in DMF as solvent at  $0\text{ }^\circ\text{C}$  to  $50\text{ }^\circ\text{C}$  gave moderate conversion to **75a** and **75b** with good regioselectivity (entry 1). Changing the solvent system (THF) and lowering the reaction temperature improved the regioselectivity (up to 95:5) and yield enhancements (up to 81%) (entry 2-3). The desired compound **75a** could be obtained as a sole product at lower temperature ( $-10\text{ }^\circ\text{C}$  to  $0\text{ }^\circ\text{C}$ ) as presented in entry 4.

The DBU-promoted HBr-elimination is affected by the electronic interaction of the neighbouring heteroatoms. The *p*-nitrobenzoate as electron withdrawing group increased the acidity of the hydrogen at C2 position.<sup>6</sup> Because of this situation, DBU interacted H<sup>1</sup> to produce the bromoolefin **75a** (Scheme 3-6).

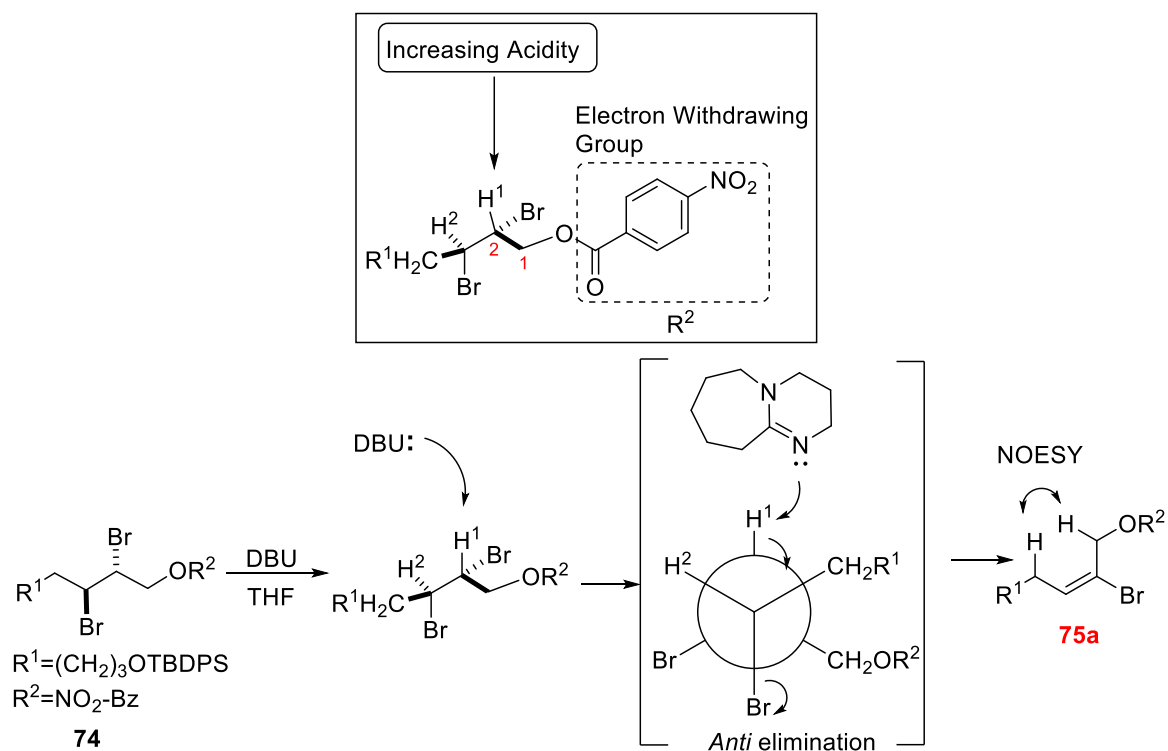
Table 3-2. Regioselective elimination reaction to **74** using DBU<sup>a</sup>



Entry	DBU (eq)	Solvent	Temperature (°C)	Results <sup>b</sup> <b>75a:75b</b> (combined yield)
1	1.5	DMF	0 to 50	<b>84:16</b> (60%)
2	1.5	THF	0 to rt	<b>90:10</b> (78%)
3	1.5	THF	0	<b>95:5</b> (81%)
4	1.5	THF	-10 to 0 then rt	<b>100:0</b> (83%)

<sup>a</sup>Reaction conditions: 0.2 mmol of **74** was used. <sup>b</sup>ratio of **75a** and **75b** was estimated by <sup>1</sup>H NMR analysis.

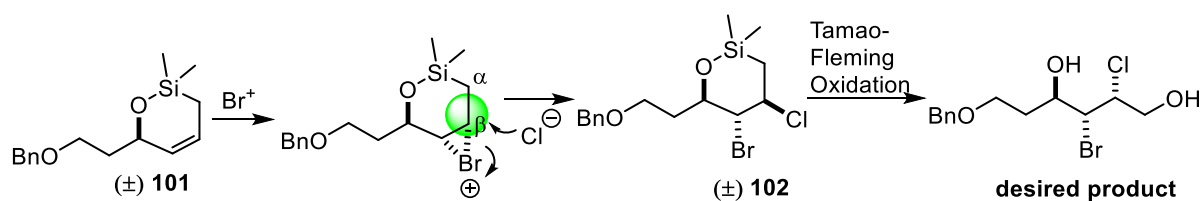
Scheme 3-6. Regioselective *anti*-elimination reaction of the *anti*-1,2-dibromide **74**



### 3-5 Optimization of Halohydrin Formation

On first strategy for constructing the halohydrin part, author designed the bromochlorination model reaction to cyclic allyl silyl ether ( $\pm$ )-**101** as a model compound. As mentioned in the previous page, the application of  $\beta$ -silicon effect would control the regioselectivity between bromide and chloride, i.e., treatment of  $\text{Br}^+$  with ( $\pm$ )-**101** would afford a bromonium cation of which  $\beta$ -position of silicon atom would accept  $\text{Cl}^-$  due to  $\beta$ -silicon effect. Also, the desired stereoconfiguration would be expected to be constructed (Scheme 3-7). After that, the following Tamao Fleming oxidation would provide the desired product.

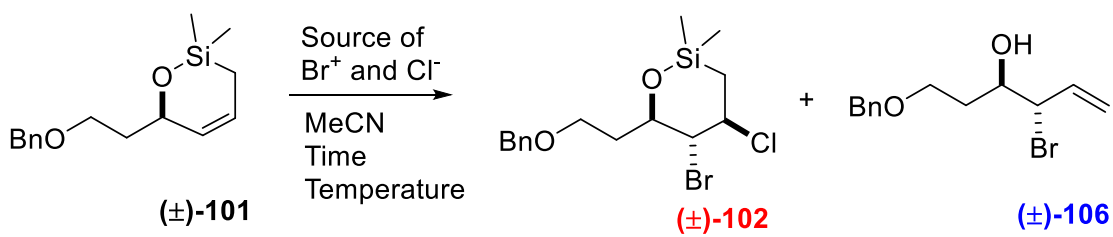
Scheme 3-7. Regioselective bromochlorination cyclic allyl silyl ether ( $\pm$ )-**101**



*N*-Bromosuccinimide (NBS) or 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) were used as bromonium cation sources and some Lewis acids with chloride were screened. Results of the optimizations are shown in Table 3-3. Treatment of ( $\pm$ )-**101** with 1.5 equivalents of the bromonium cation and 1.2 equivalents of the various Lewis acid at some reaction temperature ( $-20\text{ }^\circ\text{C}$ ,  $0\text{ }^\circ\text{C}$  and room temperature) were attempted. In entries 1-6 using NBS, Lewis acid such as  $\text{Et}_4\text{NCl}$ ,  $\text{LiCl}$ ,  $\text{CeCl}_3$ ,  $\text{ClTi}(\text{O}i\text{-Pr})_3$  resulted in undesired ( $\pm$ )-**106** as a main product without any formation of the desired product ( $\pm$ )-**102**. In entries 7-9 using TBCHD, the results were never changed and gave the undesired product ( $\pm$ )-**106**. Lowering the temperature and changing the bromochlorination reagents sources could not improve. Relative configurations

of ( $\pm$ )-**106** were confirmed by epoxide formation to give *anti*-epoxide, suggesting ( $\pm$ )-**106** has *anti*-configuration as shown in the Scheme 3-8.

Table 3-3. Bromochlorination reaction to ( $\pm$ )-**101**<sup>a</sup>



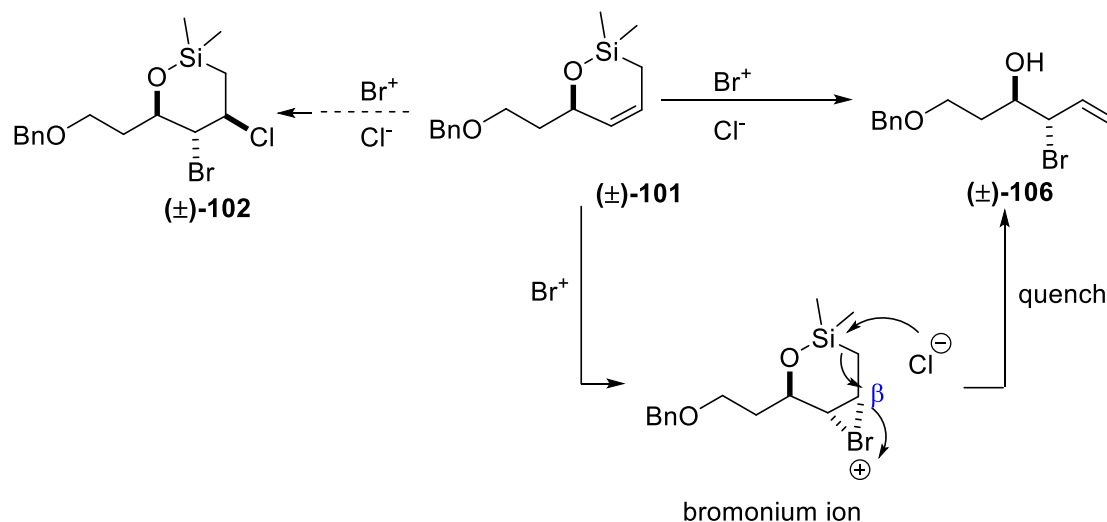
Entry	Br <sup>+</sup> (eq)	Cl <sup>-</sup> (eq)	Temperature (°C)	Time (min)	Results <sup>b</sup> (yield)
1	NBS (1.5)	Et <sub>4</sub> NCl (1.2)	rt	60	<b>106</b> (89%)
2	NBS (1.5)	LiCl (1.2)	rt	60	<b>106</b> (82%)
3	NBS (1.5)	CeCl <sub>3</sub> (1.2)	0-rt	60	<b>106</b> (85%)
4	NBS (1.5)	CeCl <sub>3</sub> (1.2)	0	60	<b>106</b> (82%)
5	NBS (1.5)	ClTi(O <i>i</i> -Pr) <sub>3</sub> (1.2)	0	60	<b>106</b> (84%)
6	NBS (1.5)	ClTi(O <i>i</i> -Pr) <sub>3</sub> (1.2)	-20	110	<b>106</b> (82%)
7	TBCHD (1.5)	LiCl (1.2)	0-rt	60	<b>106</b> (75%)
8	TBCHD (1.5)	CeCl <sub>3</sub> (1.2)	0-rt	60	<b>106</b> (79%)
9	TBCHD (1.5)	Et <sub>4</sub> NCl (1.2)	0-rt	60	<b>106</b> (74%)

<sup>a</sup>Reaction conditions: 0.2 mmol of ( $\pm$ )-**101** was used. <sup>b</sup>ratio of ( $\pm$ )-**102** and ( $\pm$ )-**106** was estimated by <sup>1</sup>H NMR analysis.

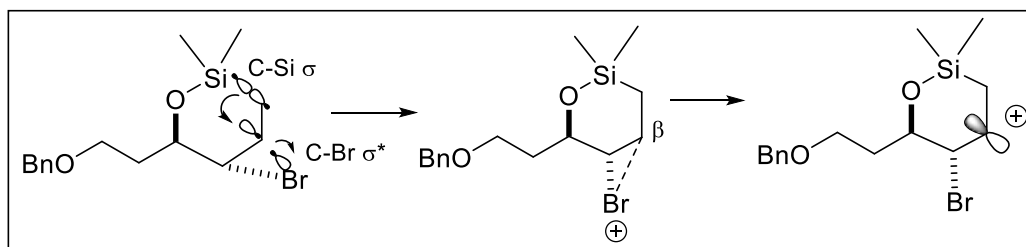
Author has hypothesized the formation of an undesired compound is due to  $\beta$ -silicon effect like in the Hosomi-Sakurai reaction mechanism as shown in Scheme 3-8.<sup>8</sup> In the beginning, NBS or TBCHD affords a bromonium ion from model compound ( $\pm$ )-**101**. Based on the  $\beta$ -silicon effect mechanism, the bromonium ion has any partial overlap of the C-Si  $\sigma$ -orbital with the C-Br  $\sigma^*$ -orbital which accelerates an appearance of positive charge on  $\beta$ -position of the

silicon. Once the positive charge appears, elimination of silicon atom through Si-Cl bond formation is much faster than  $S_N2$  reaction between the bromonium ion and the chloride.

Scheme 3-8. The formation of an undesired compound ( $\pm$ )-106

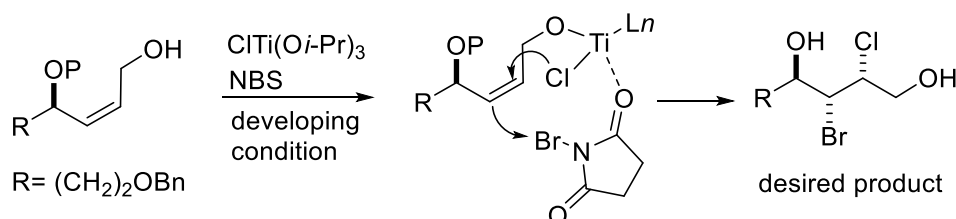


**$\beta$ -silicon effect**



Based on previous result, author step forward to second strategy toward halohydrin preparation. The interhalogenation reaction developed by Burns was chosen (Scheme 3-9). This strategy looks promising for halohydrin construction. With chlorotitanium triisopropoxide and NBS, the sense of regioselectivity was maintained.<sup>9</sup>

Scheme 3-9. Second strategy toward halohydrin: regioselective bromochlorination



The second strategy started from conversion of the 6-membered ring silyl ether (**(±)-101**) to alcohol (**(±)-76**) as model compounds. Tamao-Fleming oxidation and protection of primary alcohol with TBS gave secondary alcohol (**(±)-108**). The secondary hydroxy group was neat protected by benzyl, MOM, acetyl, and pivaloyl protecting groups, respectively of which TBS group was removed to furnish **(±)-76a-d** (Scheme 3-10). With model compound **(±)-76a**, **(±)-76b**, **(±)-76c** and **(±)-76d** in hand, author starts the second strategy optimization for regioselective bromochlorination reaction.

Scheme 3-10. Preparation of model compound **76**

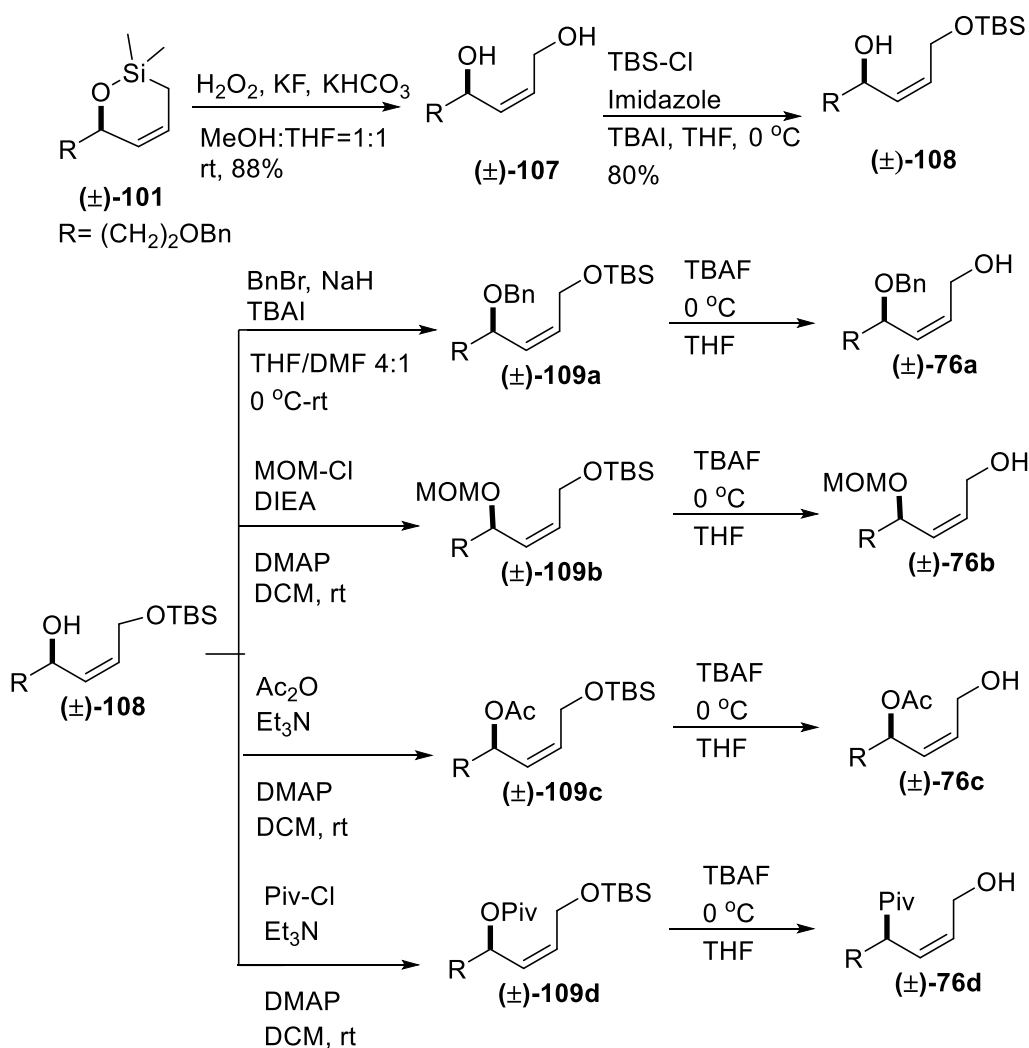
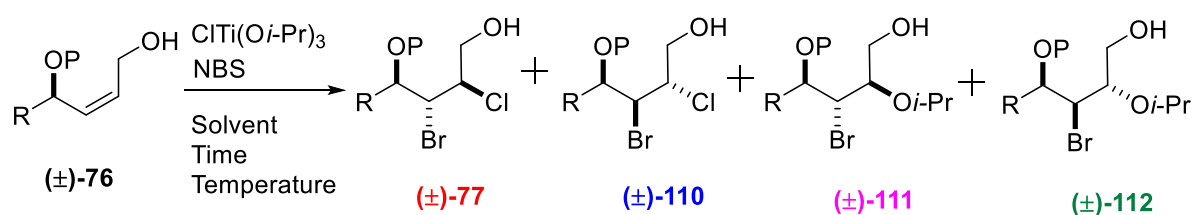
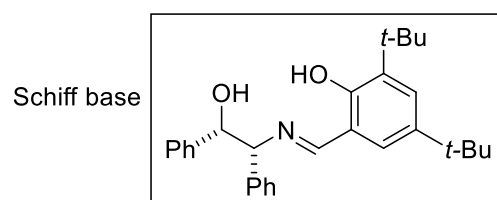




Table 3-4. Regioselective bromochlorination reaction to (±)-**76**<sup>a</sup>



R = (CH<sub>2</sub>)<sub>2</sub>OBn P = Benzyl- (a); MOM- (b); Acetyl- (c); Pivaloyl- (d)



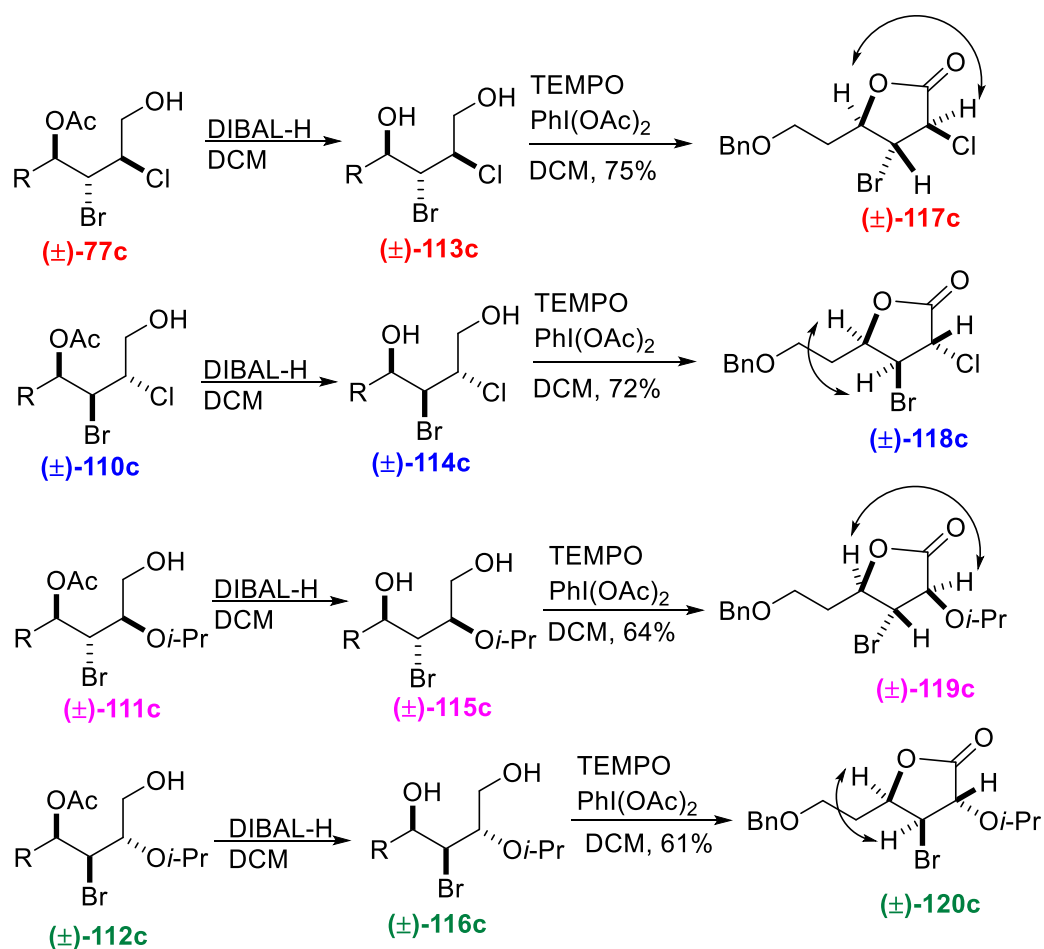
Entry	NBS (eq)	ClTi(Oi-Pr) <sub>3</sub> (eq)	Protecting Group (P)	Solvent	Temp. (°C)	Time (h)	Results <sup>b</sup> <b>76:77:110:111:112</b> (combined yield)
1	1.1	1.2	(a) Bn-	Hexane	-20	12	Unseparable (43%)
2	1.1	1.2	(a) Bn-	MeCN	-20	2	Unseparable (85%)
3	1.1	1.2	(b) MOM-	Hexane	-20	12	Unseparable (40%)
4	1.1	1.2	(b) MOM-	MeCN	-20	2	Unseparable (83%)
5	1.1	1.2	(c) Ac-	Hexane	-20	12	44: <b>30</b> :15: <b>8</b> :3 (46%)
6	1.1	1.2	(c) Ac-	MeCN	-20	2	0: <b>57</b> :28: <b>10</b> :5 (89%)
7 <sup>c</sup>	1.1	1.2	(c) Ac-	MeCN	-20	2	0: <b>54</b> :36: <b>7</b> :3 (85%)
8	1.1	1.2	(d) Piv-	MeCN	-20	2	0: <b>46</b> :43: <b>11</b> :4 (87%)

<sup>a</sup>Reaction conditions: 0.2 mmol of (±)-**76** was used. <sup>b</sup>ratio of (±)-**77**, (±)-**110**, (±)-**111**, and (±)-**112** was calculated after separation by HPLC. <sup>c</sup>Schiff base was used as catalyst according to the report by Burns research group.

The alcohol (±)-**76** with various protecting groups were used for the optimization for the regioselective bromochlorination reaction using ClTi(Oi-Pr)<sub>3</sub> as chloride source and NBS as bromonium ion source according to the report by Burns research group.<sup>9</sup> In entries 1, 3 and 5,

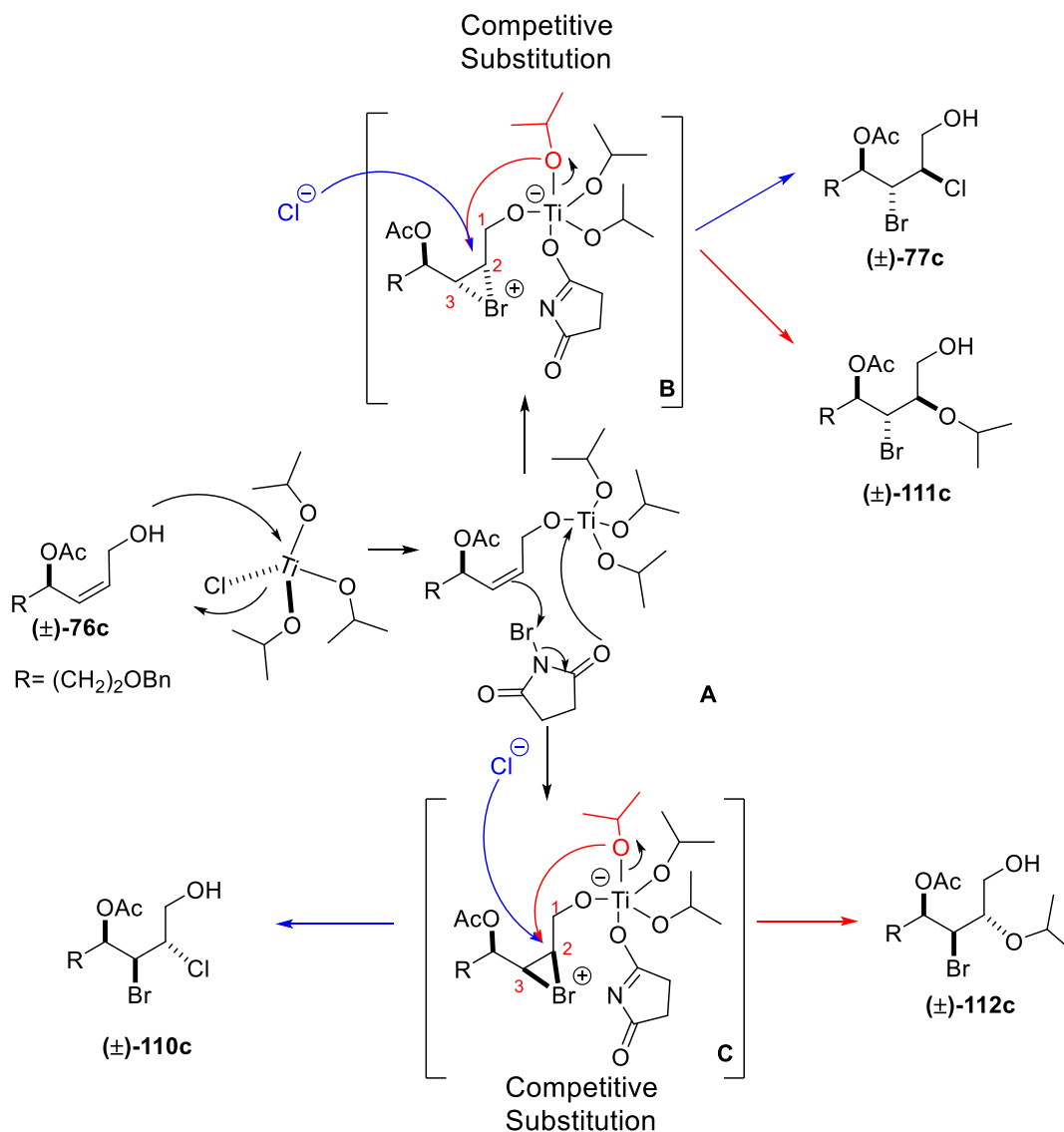
the reference conditions for the reaction temperature ( $-20\text{ }^{\circ}\text{C}$ ) and solvent (hexane) were applied to ( $\pm$ )-**76a-c**, resulting in low conversion. However, author believes that these results are due to solubility problem between reactant and solvent. Thus, when the solvent was changed from hexane to acetonitrile, the starting materials ( $\pm$ )-**76** were consumed completely (entries 2, 4, 6, 7 and 8) to give a mixture of ( $\pm$ )-**77**, ( $\pm$ )-**110**, ( $\pm$ )-**111** and ( $\pm$ )-**112**. Among these products, acetyl protecting group shown in entry 6 was easy to separate all products and determining the ratio by HPLC (57:28:10:5). Compounds ( $\pm$ )-**111** and ( $\pm$ )-**112** were derived from the competition reaction between chloride and isopropoxide from  $\text{ClTi}(\text{O}i\text{-Pr})_3$ . As shown in Scheme 3-11, to determine the structure and ratio for each product, all products obtained from ( $\pm$ )-**76c** were converted to lactone in 2 steps. The chemical structures of the lactones were unambiguously assigned through 1D- and 2D-NMR analysis.

#### Scheme 3-11 Structure determination



The interhalogenation reaction is rationalized by the complexed intermediate (**A**) in Scheme 3-12 which enables the regioselectivity of bromide and chloride. The hydroxy moiety interacts with chlorotitanium triisopropoxide, rigidifying the system and potentially improving regiocontrol. The reaction was followed by electrophilic bromination by NBS to form complexed intermediate (**B** or **C**) consisting of hydroxy moiety, chlorotitanium triisopropoxide and NBS. Concerning to the regioselectivity about nucleophilic chlorination to the bromonium species, the rigidity of complexed intermediate mediated the chloride addition at C2 position. This mechanism follows the report by Burns research group.<sup>9</sup>

Scheme 3-12 Mechanism of bromochlorination reaction

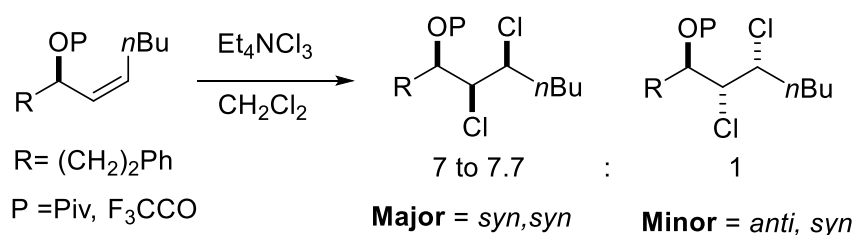


A high diastereoselectivity is expected to be obtained in the bromochlorination reaction. Reflecting on the Vanderwal's studies with *Z*-allylic alcohol derivatives, an allylic strain serves as a valuable stereocontrol element to rationalize chloronium ion formation and gives 1,2-dihalogenation products in a high diastereofacial selective manner (Scheme 3-13). Particularly, pivaloyl and trifluoroacetyl groups showed significant diastereoselectivities.<sup>10</sup> If the current bromonium ion formation proceeds as the chloronium ion, a high diastereofacial selectivity is also expected to be obtained. Stereogenic center in (±)-**76c** is considered to influence the bromochlorination reaction in a diastereoselective manner. However, the current low diastereoselectivity (ca 2:1) and (ca 1:1) when acetyl and pivaloyl are used as protecting groups,

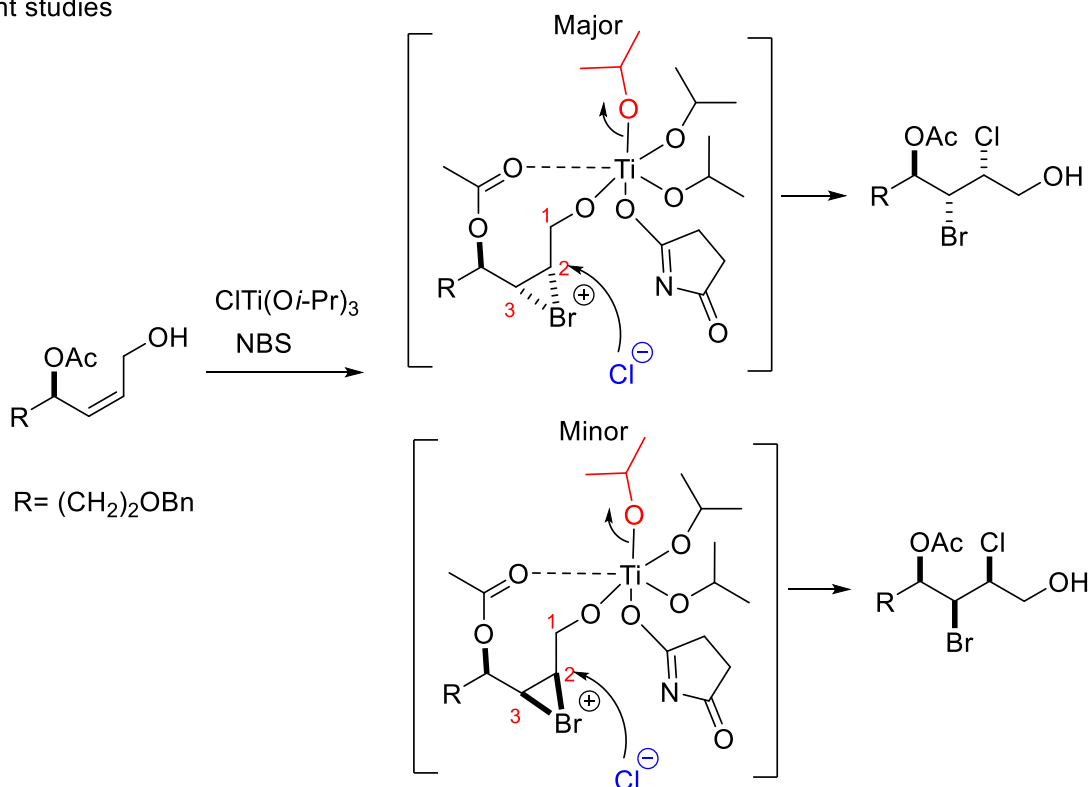
respectively, contradict the previous studies. The use of Schiff base as a catalyst which is proposed by Burns research group to elevate the selectivity, does not provide a significant change. The formation of the isopropoxide during bromochlorination reaction may suggest an unexpected reaction intermediate such as nine-membered ring formation through a coordination between hydroxytitanium and acetate moiety to encourage *anti*, *syn* stereotriad to become a major product. Furthermore, the difference in electron deficiency between acetyl and pivaloyl groups led to different selectivity.

Scheme 3-13 Diastereoselective 1,2-dihalogenation of *Z*-allylic alcohol

Vanderwal's Studies <sup>10</sup>



Current studies



Product selectivity between chloride and isopropoxide during S<sub>N</sub>2 reaction is considered as follow although the original report does not mention the side product by isopropoxide. The ratio of chloride substitution is higher than isopropoxide substitution, meaning that the anion size play an important role in this competition reaction.<sup>11</sup> Therefore, there is still an opportunity to improve this optimization to produce a product with high selectivity in the future.

In conclusion of this chapter, the *E*-bromoolefin part was well prepared as a sole product with high yield (83%) via regio- and stereoselective *E*- elimination of *anti*-dibromo **74** using DBU as a base in the presence of *p*-nitrobenzoyl group. Even though the elimination selectivity using DBU is affected by the electronegativity of the oxygen atoms, *p*-nitrobenzoyl group as electron withdrawing group can make oxygen atoms more electronegative and the acidity enhancement of the desired hydrogen. Comparing with hydrostannation reaction to propargyl alcohol, it just generate desired product in low yield with lower regioselectivity (75:25).

The halohydrin part was constructed using  $\text{TiCl}(\text{O}i\text{-Pr})_3$  as a chloride and NBS as the bromonium ion in the regioselective bromochlorination reaction to the allylic alcohol. The rigidity of complexed intermediate contributed to the regioselectivity. Although use of protective groups such as acetyl and pivaloyl enable detailed structure assignment and evaluation of the product ratio, obtained diastereoselectivity was low (ca 2:1). The intramolecularly competitive substitution occurs in-situ between Cl anion and isopropoxide anion during  $\text{S}_{\text{N}}2$  reaction. In this competition reaction, the anion size play an important role to give higher ratio of product with Cl substituent than isopropoxide substituent.

### References and Notes of Chapter 3

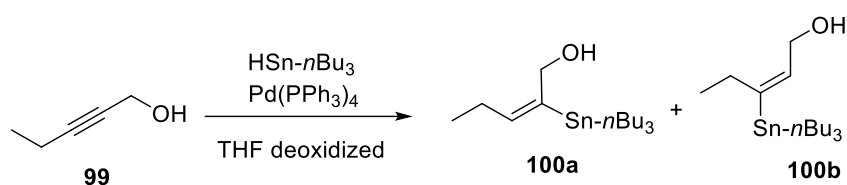
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### Experimental Section of Chapter 3

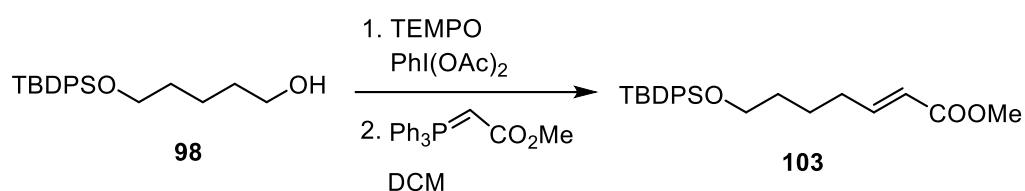
Tetrahydrofuran (THF), methanol (CH<sub>3</sub>OH), and acetonitrile (CH<sub>3</sub>CN) were purchased from Kanto Chemical Co. Inc. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) was distilled from CaH<sub>2</sub>. All commercially obtained reagents were used as received.

The IR spectra were recorded on a JASCO FTIR-4100 Type A spectrometer using a NaCl cell. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded using a JNM-EX 400 (400 MHz and 100 MHz) spectrometer. Chemical shifts were reported in ppm relative to CHCl<sub>3</sub> in CDCl<sub>3</sub> for <sup>1</sup>H NMR (δ = 7.26) and <sup>13</sup>C NMR (δ = 77.0) and CHD<sub>2</sub>OH in CD<sub>3</sub>OD for <sup>1</sup>H NMR (δ = 3.35) and <sup>13</sup>C NMR (δ = 49.3). Splitting patterns for <sup>1</sup>H NMR were designated as “s, d, t, q, m, dt, dd, and td”. These symbols indicate “singlet, doublet, triplet, quartet, multiplet, doublettriplet, doubletdoublet, and tripletdoublet” respectively. All commercially obtained reagents were employed as received. Analytical TLC was carried out using pre-coated silica gel plates (Wako TLC Silicagel 70F<sub>254</sub>). Wakogel 60N 63-212 μm was used for column chromatography. Reversed-phase high performance liquid chromatography (HPLC) was carried out using HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5 μm, φ8.0×250 mm).

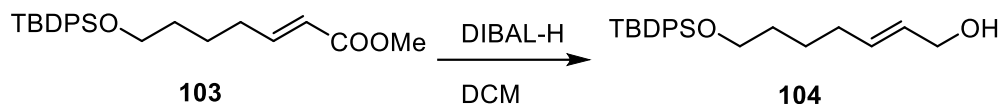


**Alkenylstannane 100a.** To a solution of 2-pentyn-1-ol **99** (0.019 mL, 0.221 mmol) in THF deoxidized (2.0 mL) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (0.025 g, 0.022 mmol) at 0 °C under Ar atmosphere. After 30 minutes, a HSn-*n*Bu<sub>3</sub> (0.148 mL, 0.552 mmol) was added. The mixture was stirred for 30 minutes at room temperature and directly concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 10:90) to give an

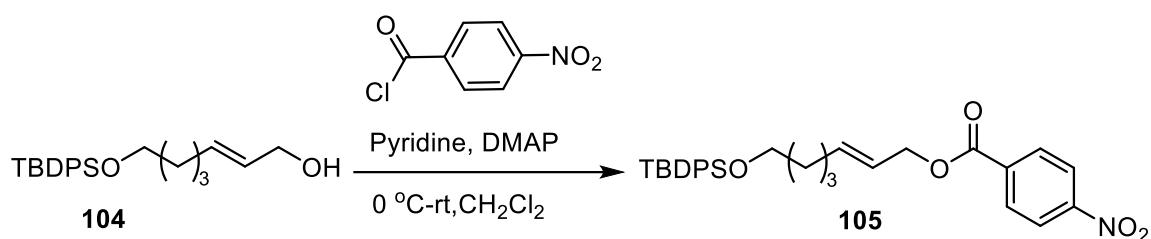
alkenylstannane **100a** (24.6 mg, 30%) as a colorless oil: IR (neat) 3421, 3031, 2945, 2853, 1611, 1461, 1292, 1181, 873, 688, 663  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.81-1.00 (19H, m), 1.22-1.36 (7H, m), 1.43-1.55 (6H, m), 2.04-2.11 (2H, m), 4.35 (2H, s), 5.55 (1H, td,  $J = 6.8, 1.9$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  9.9, 13.7, 14.2, 22.7, 27.4, 29.2, 63.5, 142.1, 144.5; HRMS (ESI)  $m/z$ :  $[\text{M}-\text{H}]^+$ ; Calcd for  $\text{C}_{17}\text{H}_{35}\text{O}^{112}\text{Sn}$  367.1741; Found 367.1747.



**Unsaturated ester 103.** To a solution of monoprotected of 1,5-pentanediol with TBDPS **98** (2.25 g, 6.55 mmol) in  $\text{CH}_2\text{Cl}_2$  (65 mL) was added TEMPO (0.205 g, 1.31 mmol), and  $\text{PhI(OAc)}_2$  (2.32 g, 7.21 mmol) at room temperature under Ar atmosphere. The mixture was stirred at room temperature for 5 hours to give crude aldehyde. The methyl triphenylphosphoranylidenacetate (3.29 g, 9.83 mmol) was added, then the mixture was stirred for 2 hours at room temperature and concentrated *in vacuo* directly. The crude product was purified using silica gel column chromatography (EtOAc:Hexane = 10:90 then 15:85) to afford unsaturated ester **103** as a colorless oil (2.49 g, 6.28 mmol, 95%): IR (neat) 3071, 3049, 3015, 2932, 2857, 1725, 1656, 1460, 1360, 1269, 1110, 823, 740, 687, 613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.05 (9H, s), 1.55-1.57 (4H, m), 2.17-2.18 (2H, m), 3.66 (2H, q,  $J = 7.3$  Hz), 3.72 (3H, s), 5.80 (1H, d,  $J = 15.6$  Hz), 6.96 (1H, dt,  $J = 15.8, 6.2$  Hz), 7.26-7.45 (6H, m), 7.65-7.67 (4H, dd,  $J = 7.3, 1.4$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  19.1, 24.3, 26.8, 31.8, 51.3, 63.3, 120.9, 127.5, 129.5, 133.8, 135.5, 149.4, 167.1; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{24}\text{H}_{32}\text{O}_3\text{SiNa}$  419.2012; Found 419.2011.

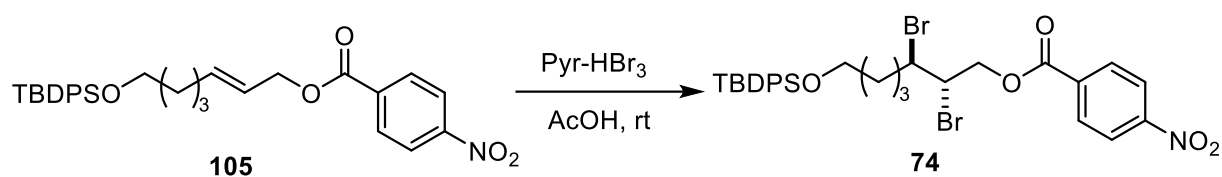


**Unsaturated alcohol 104.** To a solution of unsaturated ester **103** (2.49 g, 6.28 mmol) in  $\text{CH}_2\text{Cl}_2$  (62 mL) was added DIBAL-H (1 M in  $\text{CH}_2\text{Cl}_2$ , 15.7 mL, 15.7 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 30 minutes, quenched with saturated Na-K tartrate, stirred for 2 hours, extracted with  $\text{CH}_2\text{Cl}_2$ , washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 10:90) to give unsaturated alcohol **104** as a colorless oil (1.87 g, 5.08 mmol, 81%): IR (neat) 3336, 3070, 3047, 2931, 2857, 1459, 1427, 1388, 1110, 701, 687, 613  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.04 (9H, s), 1.38 (1H, s), 1.43-1.49 (2H, m), 1.53-1.60 (2H, m), 2.03 (2H, q,  $J = 6.3$  Hz), 3.65 (2H, t,  $J = 12.6$  Hz), 4.09 (2H, d,  $J = 6.2$  Hz), 5.61-5.67 (2H, m), 7.35-7.44 (6H, m), 7.66 (4H, dd,  $J = 7.3, 1.4$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  19.1, 25.3, 26.8, 31.8, 31.9, 63.7, 127.5, 128.9, 129.5, 133.2, 134.0, 135.5; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{23}\text{H}_{32}\text{O}_2\text{SiNa}$  391.2063; Found 391.2060.



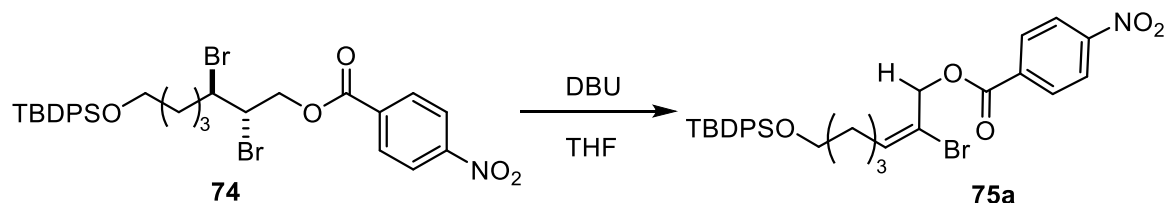
**Unsaturated Ester 105.** To a solution of unsaturated alcohol **104** (1.87 g, 5.08 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added pyridine (0.760 mL, 7.61 mmol) at 0 °C under Ar atmosphere. After 10 minutes, 4-nitrobenzoyl chloride (1.41 g, 7.61 mmol) and DMAP (0.061 g, 0.505 mmol) were added respectively. The mixture was stirred for 2 hours at room temperature,

quenched with saturated  $\text{NH}_4\text{Cl}$ , extracted with  $\text{CH}_2\text{Cl}_2$ , washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 4:96) to give unsaturated ester **105** as a light yellow oil (2.52 g, 4.87 mmol, 96%): IR (neat) 3071, 3050, 2932, 2857, 1725, 1607, 1529, 1488, 1270, 1103, 719, 702, 614  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.04 (9H, s), 1.47-1.60 (4H, m), 2.04-2.11 (2H, m), 3.66 (2H, t,  $J = 6.3$  Hz), 4.79 (2H, d,  $J = 5.8$  Hz), 5.62-5.70 (1H, m), 5.83-5.90 (1H, m), 7.35-7.44 (6H, m), 7.66 (4H, dd,  $J = 7.3, 1.4$  Hz), 8.26 (4H, dd,  $J = 12.1, 1.9$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  19.1, 25.0, 26.8, 31.8, 31.9, 63.6, 66.6, 123.4, 123.5, 127.5, 129.5, 130.7, 134.0, 135.5, 135.7, 137.5, 150.1, 164.5; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{30}\text{H}_{35}\text{NO}_5\text{SiNa}$ ; 540.2176; Found 540.2178.

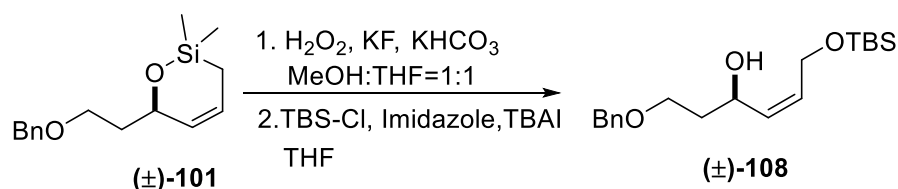


***Anti*-dibromo 74.** To a solution of unsaturated ester **105** (2.52 g, 4.87 mmol) in AcOH (40 mL) was added Pyr.HBr<sub>3</sub> (2.02 g, 6.31 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 2 hours, quenched with saturated  $\text{NaHCO}_3$ , extracted with  $\text{CH}_2\text{Cl}_2$ , washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 5:95) to give *anti*-dibromo **74** as a light yellow oil (2.81 g, 4.14 mmol, 85%): IR (neat) 3071, 3050, 2931, 2892, 2857, 1732, 1608, 1589, 1530, 1428, 1271, 1111, 719, 696  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  1.05 (9H, s), 1.56-1.84 (4H, m), 1.96-2.04 (1H, m), 2.19-2.28 (1H, m), 3.70 (2H, t,  $J = 6.3$  Hz), 4.27 (1H, td,  $J = 8.7, 2.9$  Hz), 4.40-4.45 (1H, m), 4.80-4.95 (2H, m), 7.35-7.44 (6H, m), 7.66-7.72 (4H, m), 8.26 (4H, dd,  $J = 12.2, 2.1$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  19.1, 22.9, 26.8, 31.6 36.5,

52.9, 54.7, 63.3, 68.1, 123.6, 127.6, 129.5, 130.8, 133.8, 134.7, 135.5, 150.7, 163.9; HRMS (ESI) m/z: [M + Na]<sup>+</sup>; Calcd for C<sub>30</sub>H<sub>35</sub>Br<sub>2</sub>NO<sub>5</sub>SiNa 698.0543; Found 698.0540.

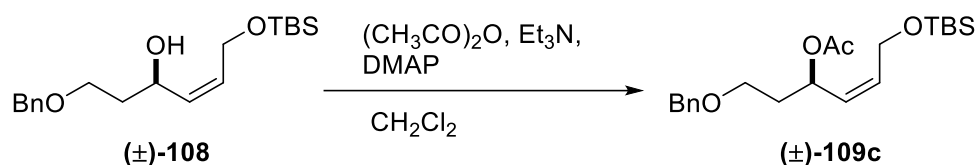


***E*-Bromoolefin 75a.** To a solution of *anti*-dibromo **74** (2.81 g, 4.14 mmol) in THF (40 mL) was added DBU (0.804 mL, 5.38 mmol) at -10 °C under Ar atmosphere. After 30 minutes, the mixture was stirred at 0 °C for 30 minutes and continued to room temperature for 2 hours, quenched with saturated saturated NH<sub>4</sub>Cl, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 10:90) to give *E*-bromoolefin **75a** as a colorless oil (2.05 g, 3.43 mmol, 83%): IR (neat) 3071, 3050, 2997, 2893, 2857, 1732, 1608, 1589, 1529, 1428, 1267, 1102, 719, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.04 (9H, s), 1.55-1.59 (4H, m), 2.19-2.25 (2H, q, *J* = 7.3 Hz), 3.66 (2H, t, *J* = 6.3 Hz), 5.06 (2H, s), 6.20 (1H, t, *J* = 7.8 Hz), 7.35-7.43 (6H, m), 7.63-7.66 (4H, m), 8.25 (4H, dd, *J* = 12.2, 2.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 19.1, 25.3, 26.8, 29.6 31.8, 63.3, 64.6, 116.8, 123.6, 127.6, 129.5, 130.8, 133.8, 135.5, 139.2 150.6, 164.1; HRMS (ESI) m/z: [M + Na]<sup>+</sup>; Calcd for C<sub>30</sub>H<sub>34</sub>NO<sub>5</sub>BrSiNa 618.1284; Found 618.1283.

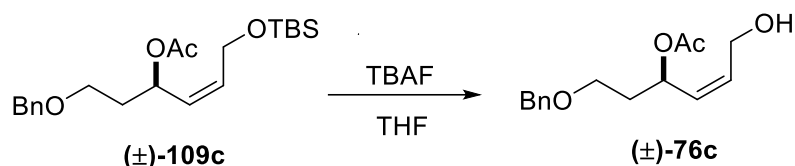


**Partially protected alcohol 108.** To a solution of 6-membered ring silyl ether **101** (1.50 g, 5.71 mmol) in MeOH (15 mL) and THF (15 mL) was added KF (1.66 g, 28.5 mmol), KHCO<sub>3</sub> (1.43 g, 14.3 mmol) and 30% H<sub>2</sub>O<sub>2</sub> (6.17 mL, 199 mmol) respectively at room temperature under Ar atmosphere. The mixture was stirred for 5 hours, quenched with 20% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Then, the unsaturated diol was used directly without any purification.

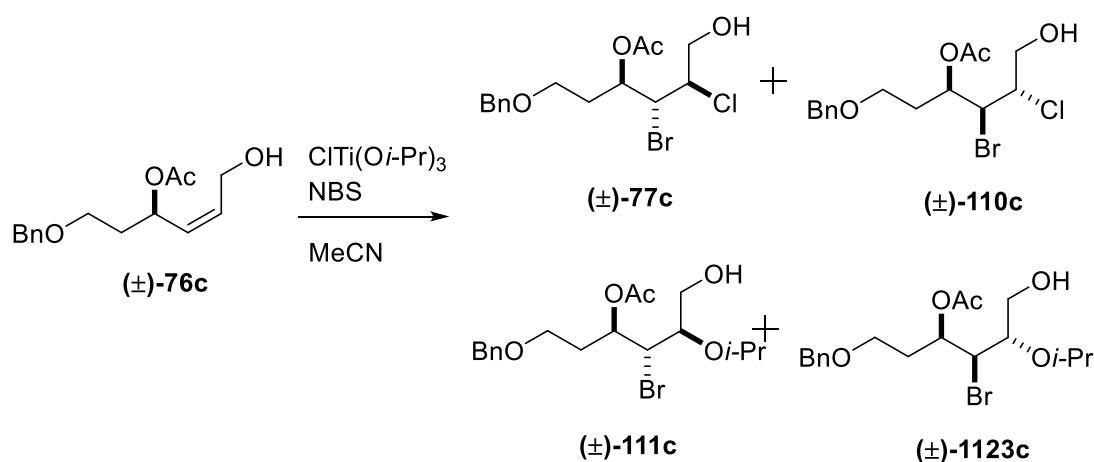
To a solution of crude unsaturated diol (1.10 g, 4.85 mmol) in THF (30 mL) was added *tert*-butyldimethylsilyl chloride (1.10 g, 7.27 mmol), imidazole (0.494 g, 7.27 mmol) and tetrabutylammonium iodide (0.268 g, 0.727 mmol) respectively at 0 °C under Ar atmosphere. The mixture was stirred for 5 hours, quenched with saturated NaHCO<sub>3</sub>, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 10:90) to give partially protected alcohol **108** as a colorless oil (1.31 g, 3.88 mmol, 80%): IR (neat) 3420, 3029, 2953, 2884, 1472, 1455, 1255, 1084, 836, 777, 734, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.01 (6H, s), 0.83 (9H, s), 1.68-1.71 (1H, m), 1.78-1.87 (1H, m), 2.86 (1H, s), 3.52-3.63 (2H, m), 4.13-4.26 (2H, m), 4.44 (2H, s), 4.54-4.59 (1H, m), 5.42-5.55 (2H, m), 7.18-7.29 (5H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ -5.2, 18.3, 25.9, 36.8, 59.5, 66.8, 68.1, 73.6, 127.6, 127.7, 128.4, 130.8, 133.3, 137.9; HRMS (ESI) m/z: [M + Na]<sup>+</sup>; Calcd for C<sub>19</sub>H<sub>32</sub>O<sub>3</sub>SiNa 359.2012; Found 359.2011.



**Olefin with acetyl protection 109c.** To a solution of partially protected alcohol **108** (0.500 g, 1.48 mmol) in  $\text{CH}_2\text{Cl}_2$  (12 mL) was added acetic anhydride (0.420 mL, 4.44 mmol), triethylamine (0.619 mL, 4.44 mmol), and DMAP (0.018 g, 0.148 mmol) respectively at room temperature under Ar atmosphere. Then, the mixture was stirred for 2 hours, quenched with saturated  $\text{NH}_4\text{Cl}$ , extracted with EtOAc, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 10:90) to give partially protected alcohol **108** as a colorless oil (1.31 g, 3.88 mmol, 80%): IR (neat) 3065, 3029, 2954, 2884, 1738, 1472, 1462, 1370, 1239, 1093, 837, 778, 698, 671  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.01 (6H, s), 0.83 (9H, s), 1.72-1.78 (1H, m), 1.89-1.97 (4H, m), 3.38-3.44 (2H, m), 4.21-4.34 (2H, m), 4.37-4.45 (2H, m), 4.54-4.59 (1H, m), 5.26 (1H, td,  $J = 10.2, 1.9$  Hz), 5.55-5.63 (2H, m), 7.19-7.29 (5H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  -5.2, 18.2, 21.1, 25.8, 34.6, 59.6, 66.0, 67.8, 72.9, 127.5, 127.6, 127.7, 128.3, 133.8, 138.2, 170.1; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$ ; Calcd for  $\text{C}_{21}\text{H}_{34}\text{O}_4\text{SiNa}$ ; Found 401.2118; Found 401.2116.

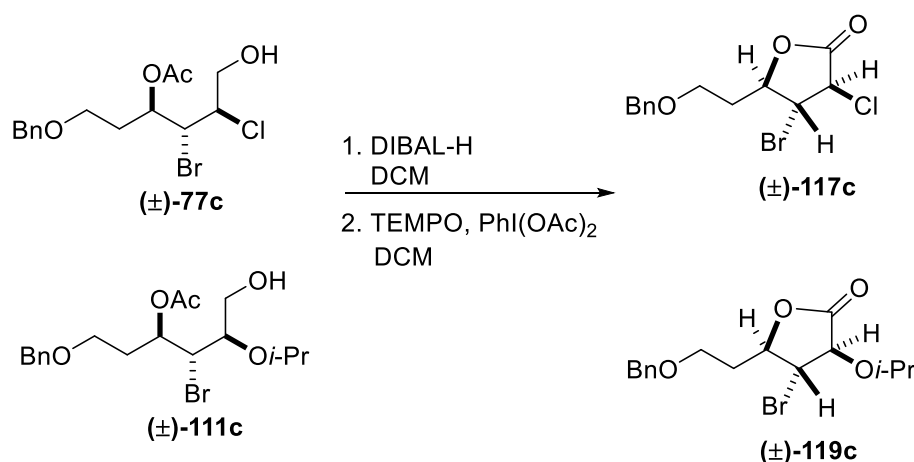


**Allylic alcohol with acetyl protection.** To a solution of crude protected olefin (0.503 g, 1.33 mmol) in THF (13 mL) was added *tert*-butylammonium fluoride (1 M in THF, 1.73 mL, 1.73 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 5 hours, quenched with saturated NH<sub>4</sub>Cl, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 15:85) to give allylic alcohol with acetyl protection **76c** as a colorless oil (0.328 g, 1.05 mmol, 79%): IR (neat) 3445, 3063, 3028, 2940, 2863, 1732, 1660, 1455, 1372, 1236, 1098, 739, 699, 608 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.89-1.97 (2H, m), 2.12 (3H, s), 3.68-3.79 (2H, s), 3.03 (1H, br), 4.51 (2H, s), 4.57-4.85 (3H, m), 5.55-5.63 (2H, m), 7.19-7.29 (5H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 20.9, 36.5, 60.4, 66.8, 68.1, 73.3, 124.7, 127.7, 128.4, 128.5, 136.7, 137.8, 171.1; HRMS (ESI) m/z: [M + Na]<sup>+</sup>; Calcd for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>Na 287.1253; Found 287.1251.





**Bromochlorinated products 77c, 110c, 111c and 112c.** To a solution of allylic alcohol **76c** (208 mg, 0.666 mmol) in MeCN (6 mL) was added ClTi(Oi-Pr)<sub>3</sub> (1 M in hexane, 0.799 mL, 0.799 mmol) at -20 °C under Ar atmosphere. After 30 minutes, a NBS (0.130 mg, 0.732 mmol) was added and the mixture was stirred for 2 hours, quenched with saturated NaHCO<sub>3</sub> and 20% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:Hexane = 5:95 then 15:85) to give a mixture (225 mg, 89%) of bromochlorinated alcohol (**77c** and **110c**) and their side products (**111c** and **112c**) as mixture products. These crude products will be used to lactonization.



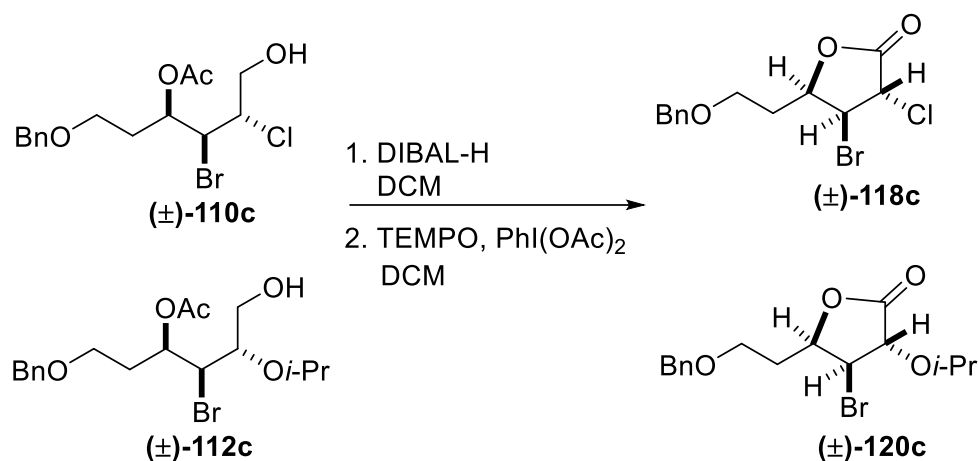
**Lactone 117c and 119c.** To the mixture of bromochlorinated alcohol **77c** and its side product **111c** (128 mg, 0.337 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.5 mL) was added DIBAL-H (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.500 mL, 0.500 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 30 minutes, quenched with saturated Na-K tartrate, stirred for 2 hours, extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Then, crude bromochlorinated diol was used directly without any purification.

To a solution of crude bromochlorinated diol (92.2 mg, 0.273 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was added TEMPO (8.53 mg, 0.055 mmol), and PhI(OAc)<sub>2</sub> (220 mg, 0.683 mmol) at room

temperature under Ar atmosphere. The mixture was stirred at room temperature for 5 hours. The residue was concentrated *in vacuo* directly and purified by silica gel column chromatography (EtOAc:Hexane = 10:90) to give a lactone **117c** and **119c** as a mixture (78 mg, 75%). For further purification, the partial (ca. 10.0 mg) of mixture products were separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5  $\mu$ m,  $\phi$ 8.0 $\times$ 250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **117c** as colorless oils.

**117c**: IR (neat) 3029, 2925, 2858, 1791, 1455, 1174, 1103, 675, 651  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz)  $\delta$  1.18-1.42 (2H, m), 2.60-2.79 (2H, m), 3.21 (1H, s), 3.47 (1H, s), 3.62-3.83 (2H, q, *J* = 7.2 Hz), 4.35-4.41 (1H, m), 6.61-6.87 (5H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  30.8, 42.1, 62.7, 65.4, 73.3, 78.1, 127.7, 127.9, 128.5 137.7, 169,4; HRMS (ESI) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>14</sub>BrClO<sub>3</sub>Na 354.9707; Found 354.9706.

**119c**: IR (neat) 3027, 2924, 2860, 1781, 1488, 1178, 1107, 669, 649  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  1.09 (3H, d, *J* = 5.8 Hz), 1.15 (3H, d, *J* = 5.8 Hz), 1.97-2.01 (1H, m), 2.12-2.18 (1H, m), 3.60-3.66 (3H, m), 4.03 (1H, d, *J* = 3.9 Hz), 4.09 (1H, s), 4.46-4.58 (2H, m), 4.99-5.03 (1H, m), 7.25-7.38 (5H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  22.9, 31.5, 40.1, 65.9, 72.1, 73.3, 79.6, 79.8 127.8, 127.9, 128.5 137.9, 171,5; HRMS (ESI) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>21</sub>BrO<sub>4</sub>Na 379.0515; Found 379.0515.



**Lactone 118c** and **120c**. To the mixture of bromochlorinated alcohol **110c** and its side product **112c** (68 mg, 0.179 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added DIBAL-H (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 0.268 mL, 0.096 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 30 minutes, quenched with saturated Na-K tartrate, stirred for 2 hours, extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Then, crude bromochlorinated diol was used directly without any purification.

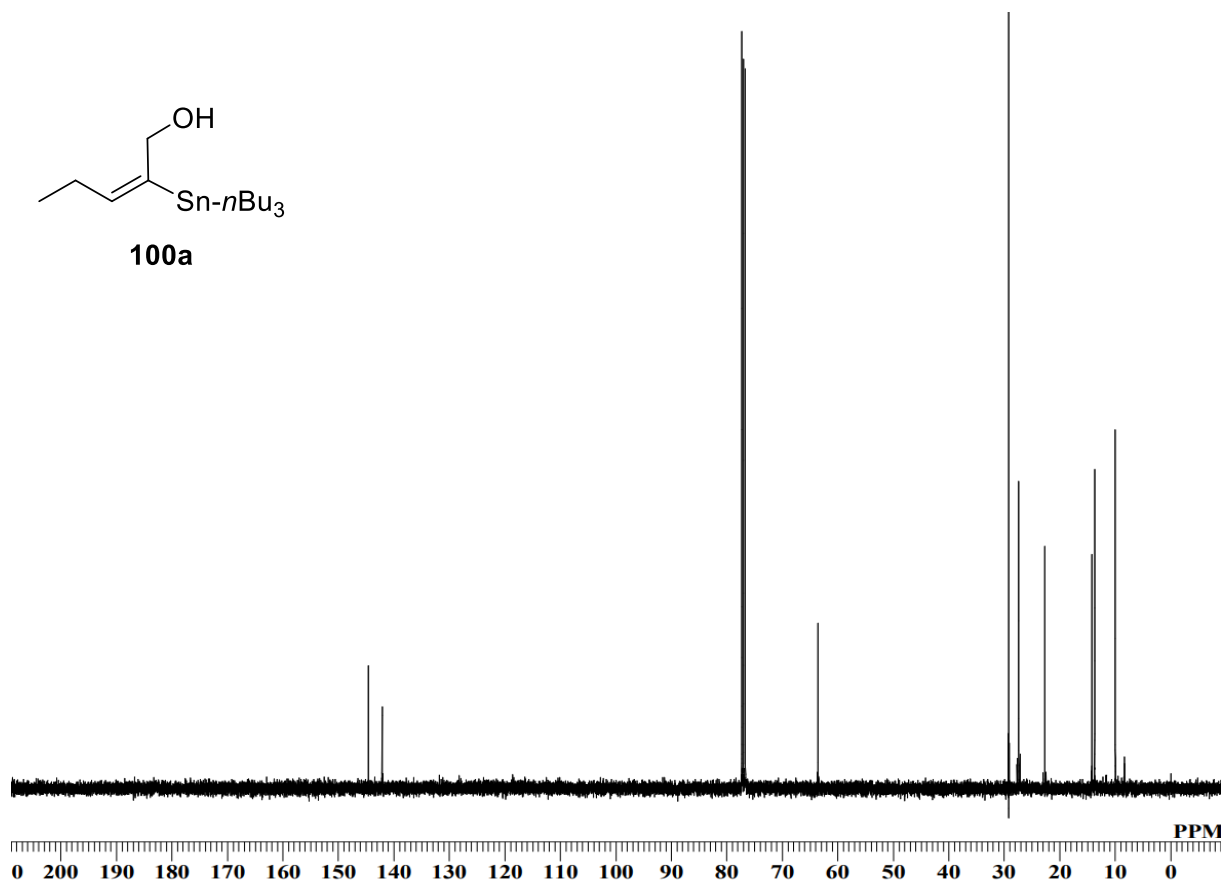
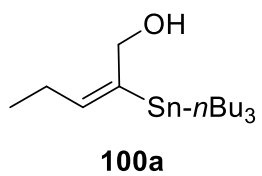
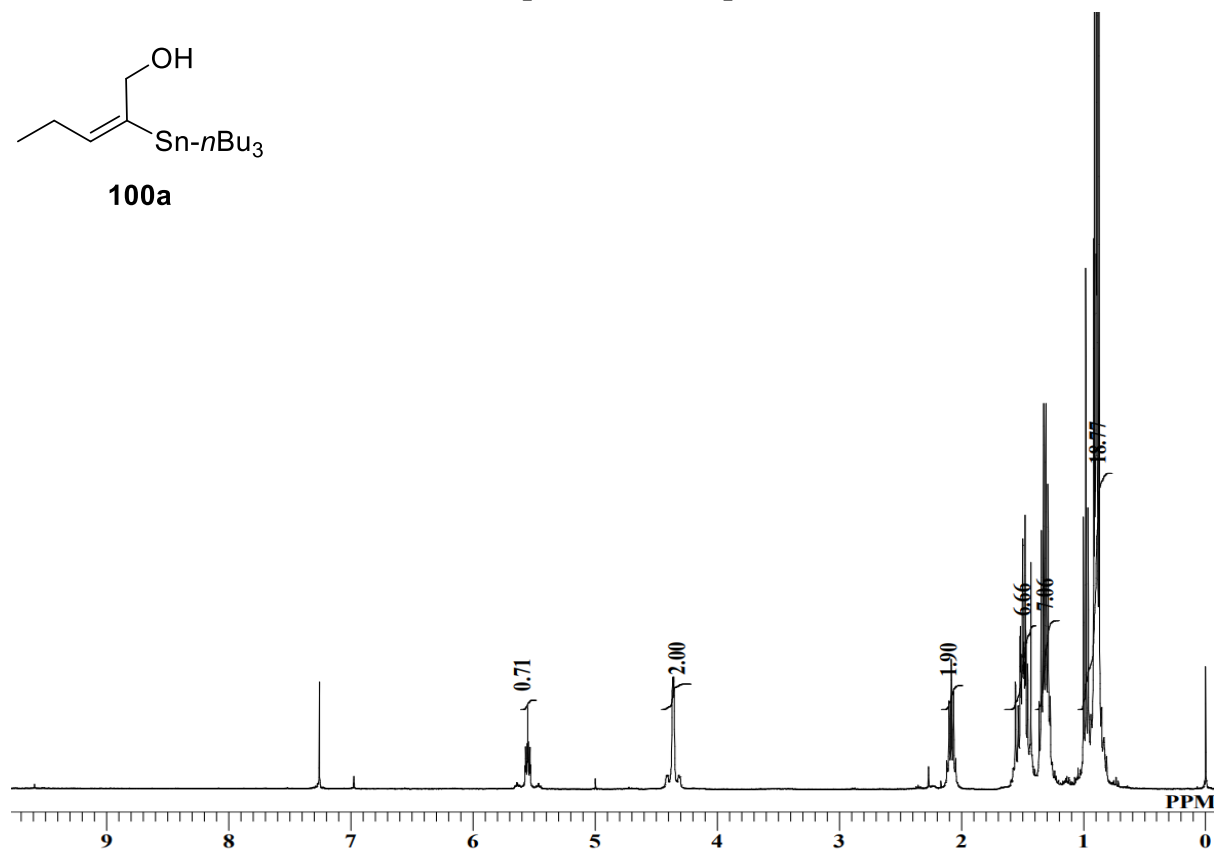
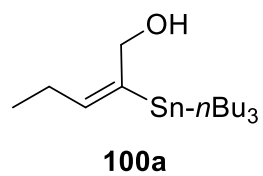
To a solution of crude bromochlorinated diol (45.3 mg, 0.134 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added TEMPO (4.19 mg, 0.027 mmol), and PhI(OAc)<sub>2</sub> (107 mg, 0.335 mmol) at room temperature under Ar atmosphere. The mixture was stirred at room temperature for 5 hours. The residue was concentrated *in vacuo* directly and purified by silica gel column chromatography (EtOAc:Hexane = 10:90) to give a lactone **118c** and **120c** as a mixture (33 mg, 72%). For further purification, the partial (ca. 10.0 mg) of mixture products were separated by HPLC (NOMURA CHEMICAL, DEVELOSIL C30-UG 5 μm, φ8.0×250 mm, elution with H<sub>2</sub>O:Acetonitrile = 80:20 to 0:100 gradiently for 90 min, 2 mL/min) to afford **118c** as colorless oils.

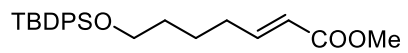
**118c**: IR (neat) 3029, 2925, 2858, 1791, 1455, 1174, 1103, 675, 651 cm<sup>-1</sup>; <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz) δ 1.15-1.39 (2H, m), 2.62-2.79 (2H, m), 3.23 (1H, s), 3.57 (1H, s), 3.70-3.84 (2H, q, *J* =

7.2 Hz), 4.15-4.21 (1H, m), 6.71-6.97 (5H, m)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  33.1, 53.7, 55.8, 65.4, 73.3, 77.8, 127.7, 127.9, 128.5 137.7, 169,1; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{13}\text{H}_{14}\text{BrClO}_3\text{Na}$  354.9707; Found 354.9709.

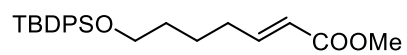
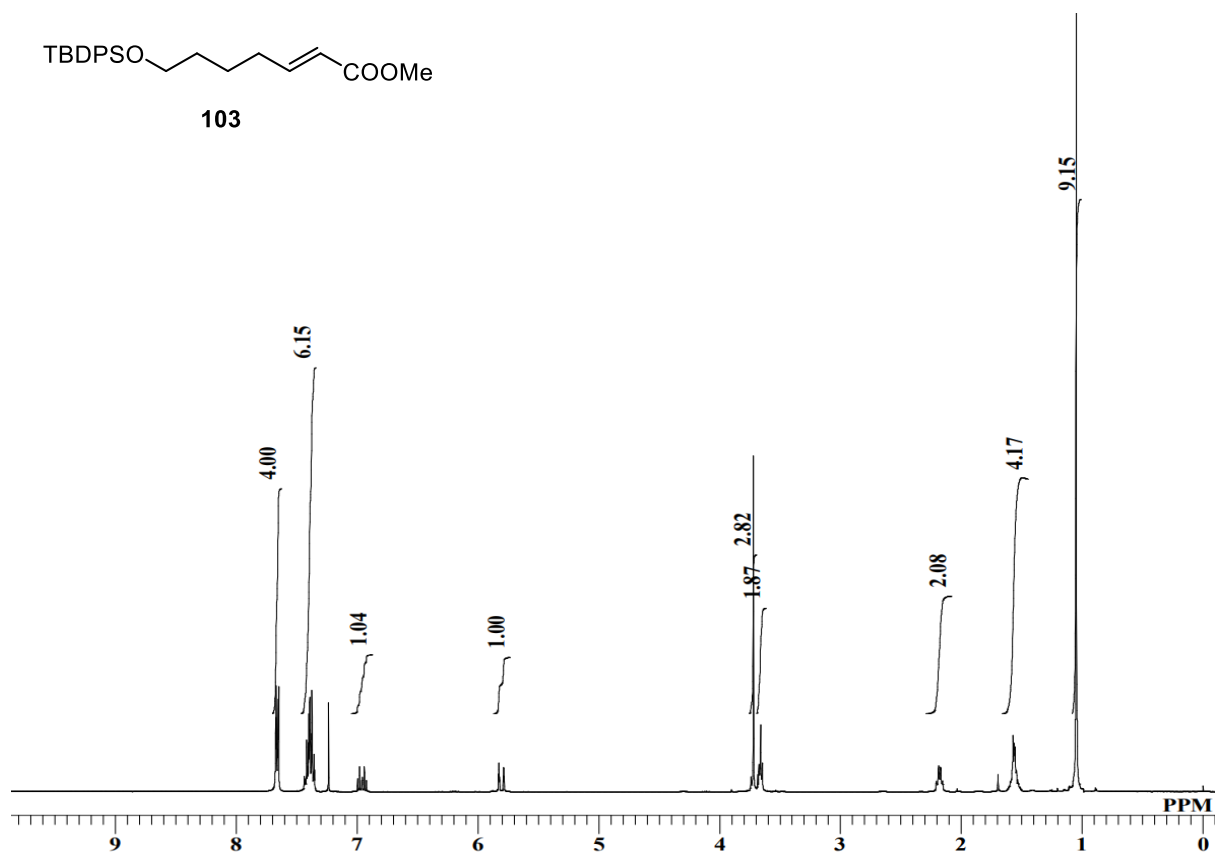
**120c:** IR (neat) 3027, 2924, 2860, 1781, 1488, 1178, 1107, 669, 649  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz)  $\delta$  1.15-1.39 (2H, m), 2.62-2.79 (2H, m), 3.23 (1H, s), 3.57 (1H, s), 3.70-3.84 (2H, q,  $J = 7.2$  Hz), 4.15-4.21 (1H, m), 6.71-6.97 (5H, m)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  22.9, 31.5, 40.1, 65.9, 72.1, 73.3, 79.6, 79.8 127.8, 127.9, 128.5 137.9, 171,5; HRMS (ESI)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{16}\text{H}_{21}\text{BrO}_4\text{Na}$  379.0515; Found 379.0515.

### NMR Spectra for Chapter 3

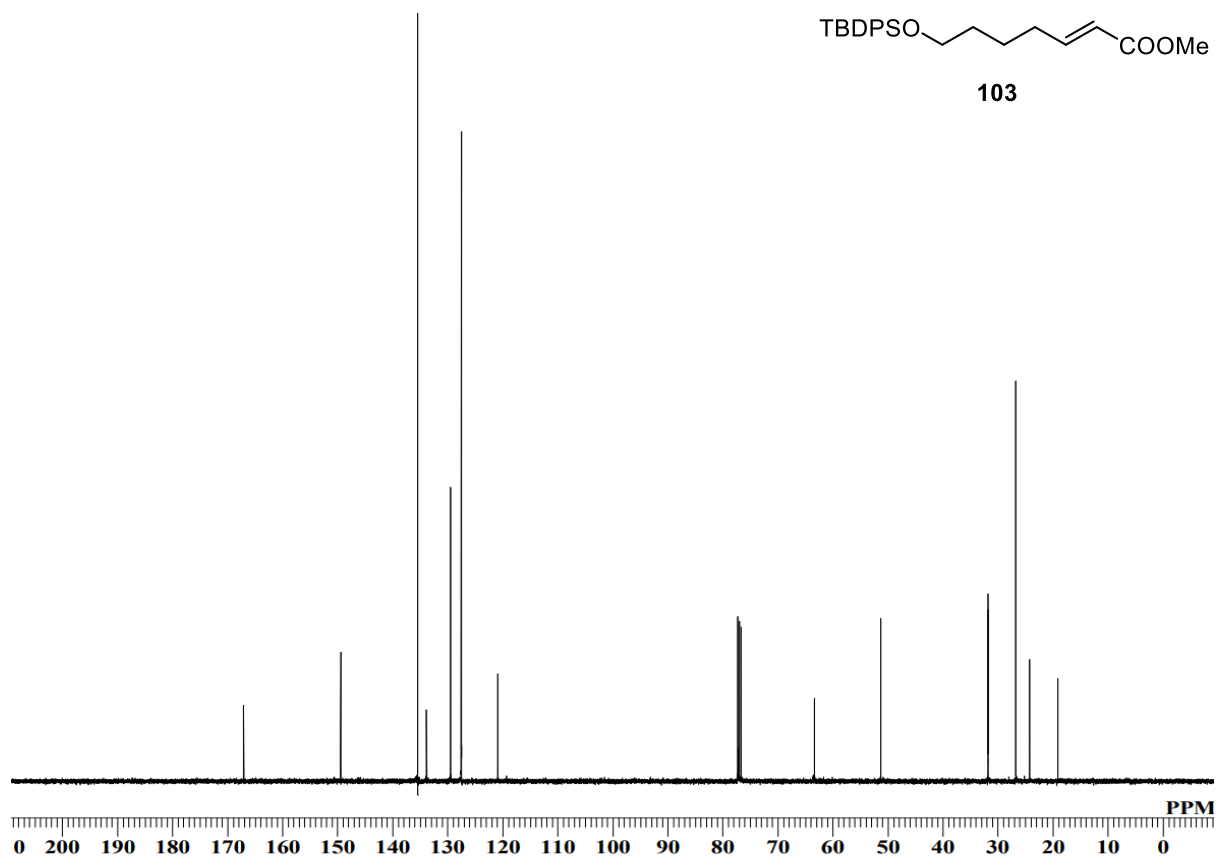


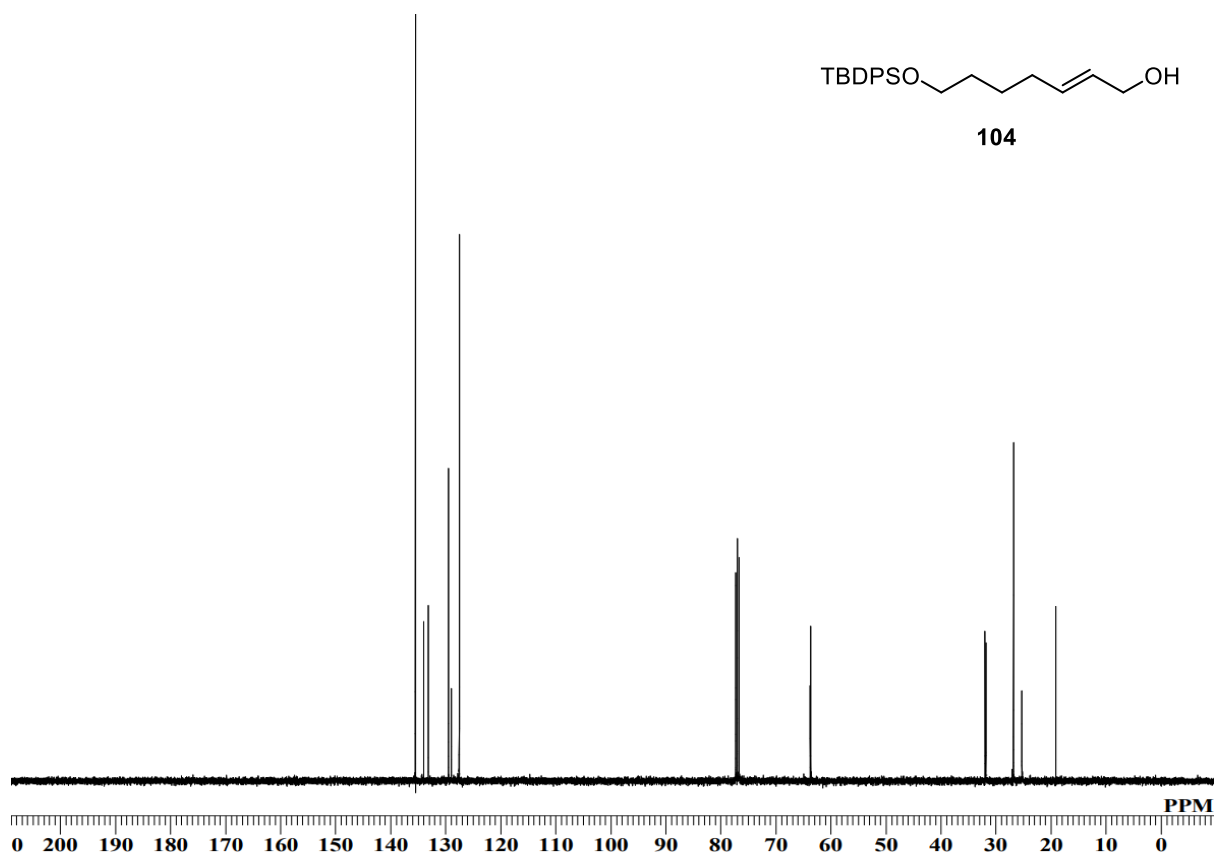
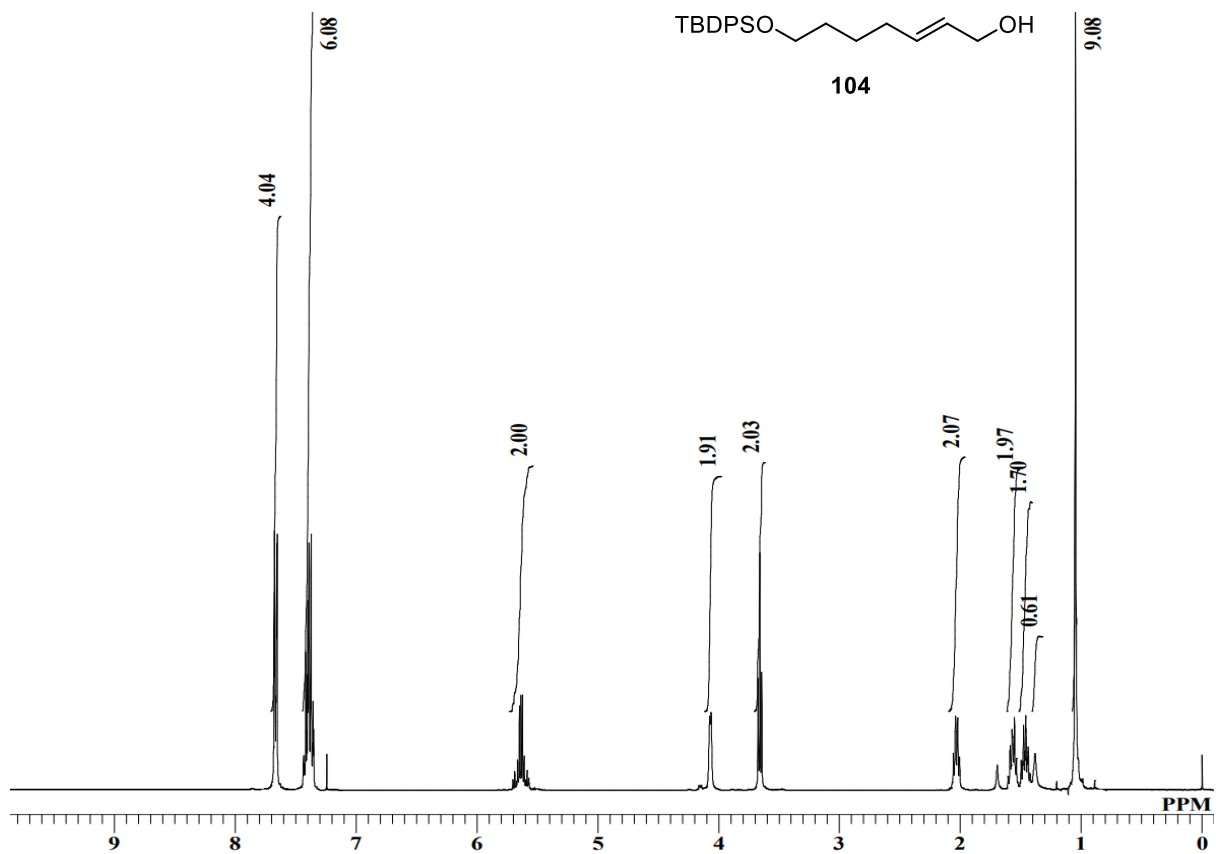


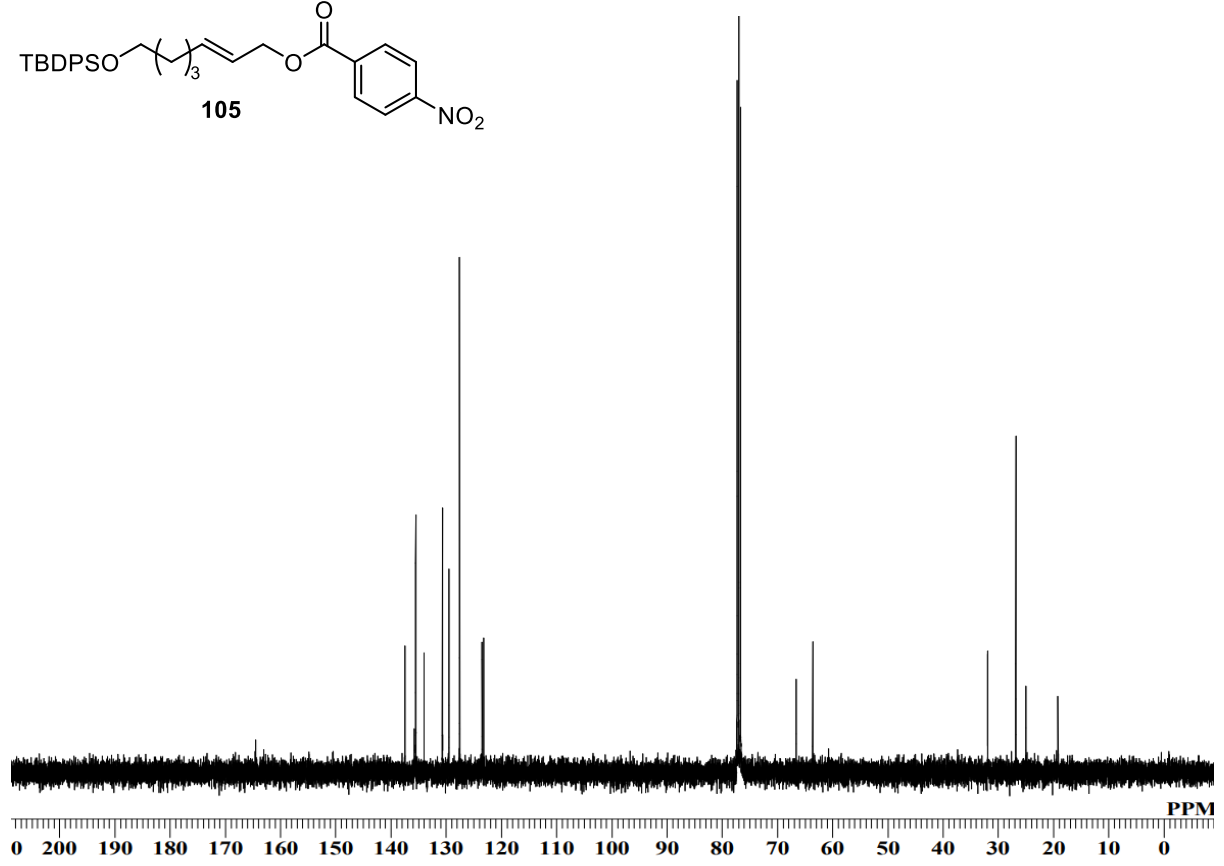
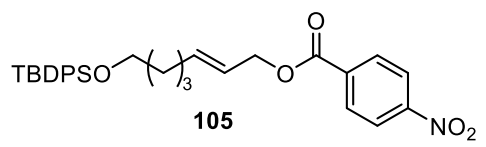
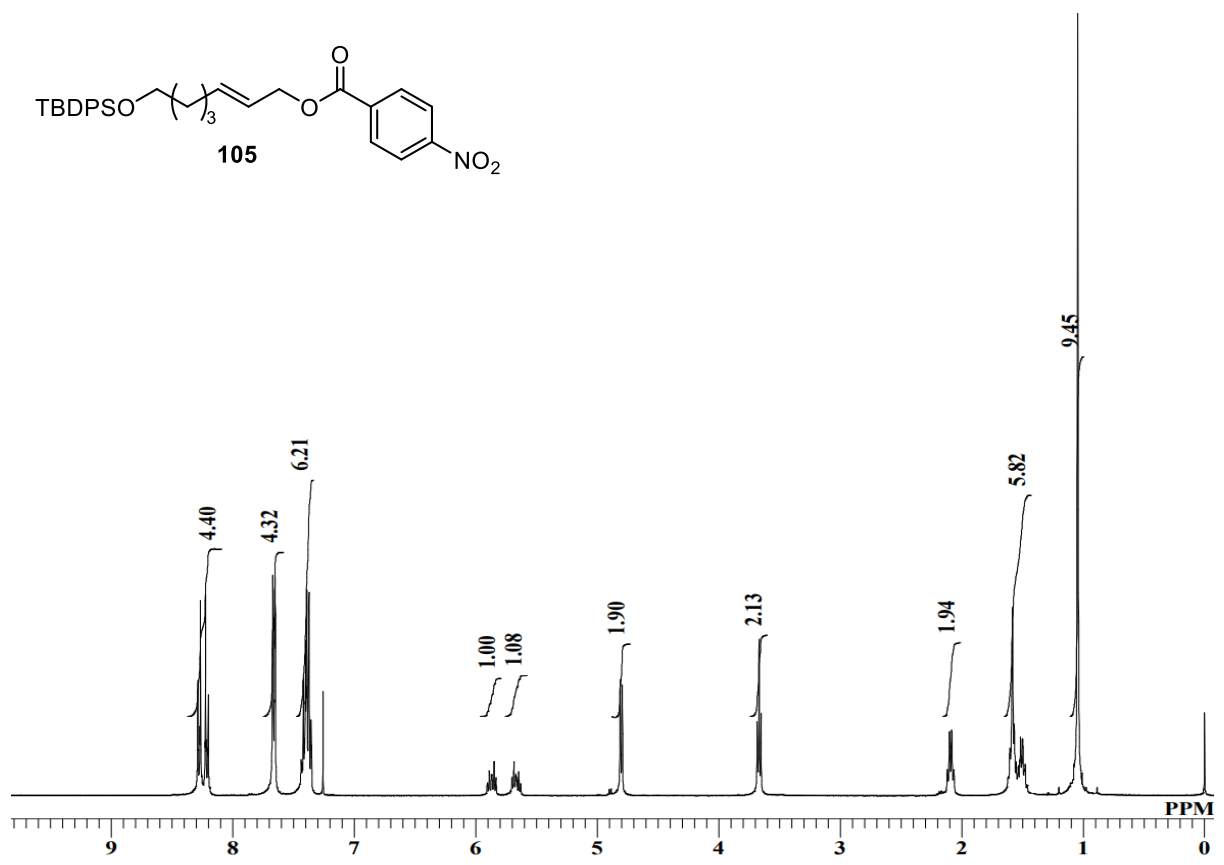
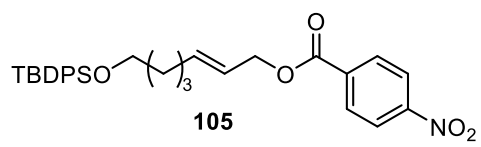
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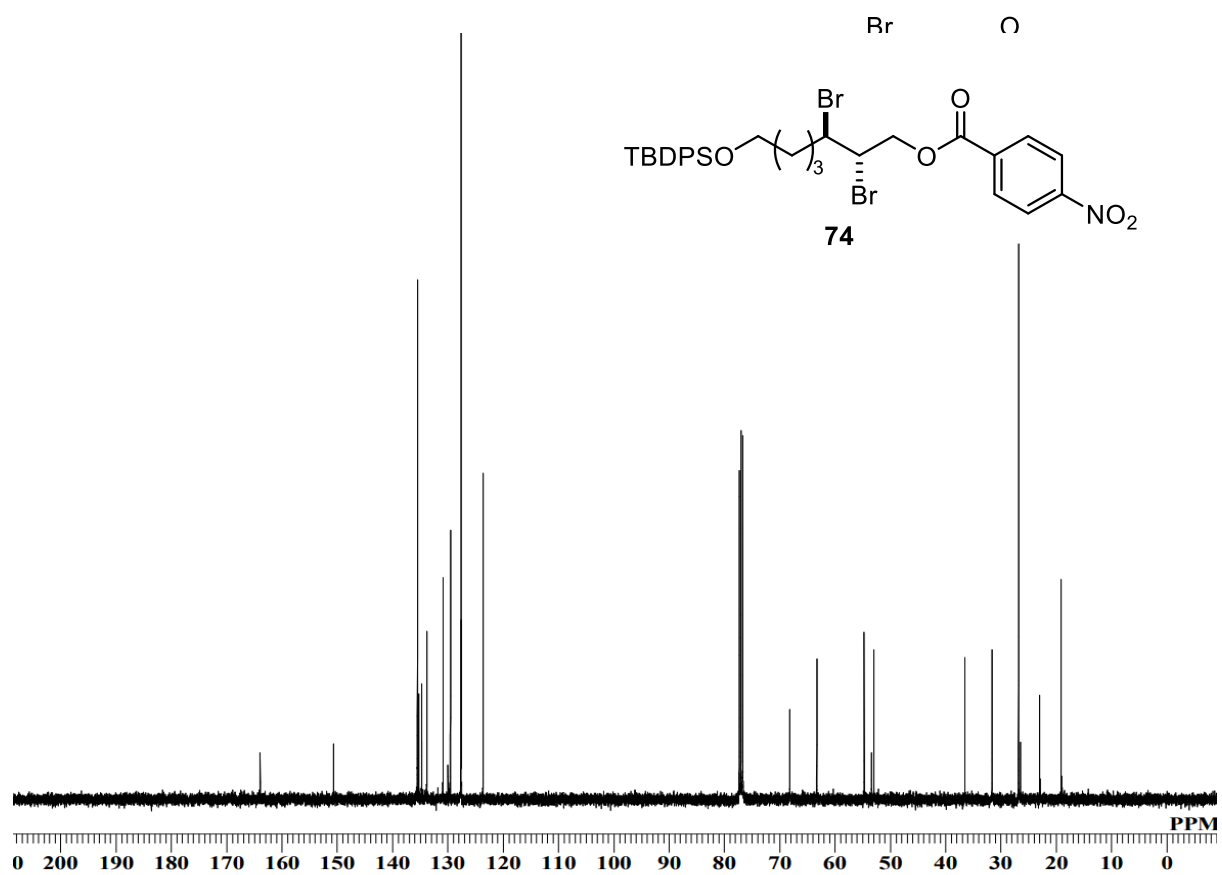
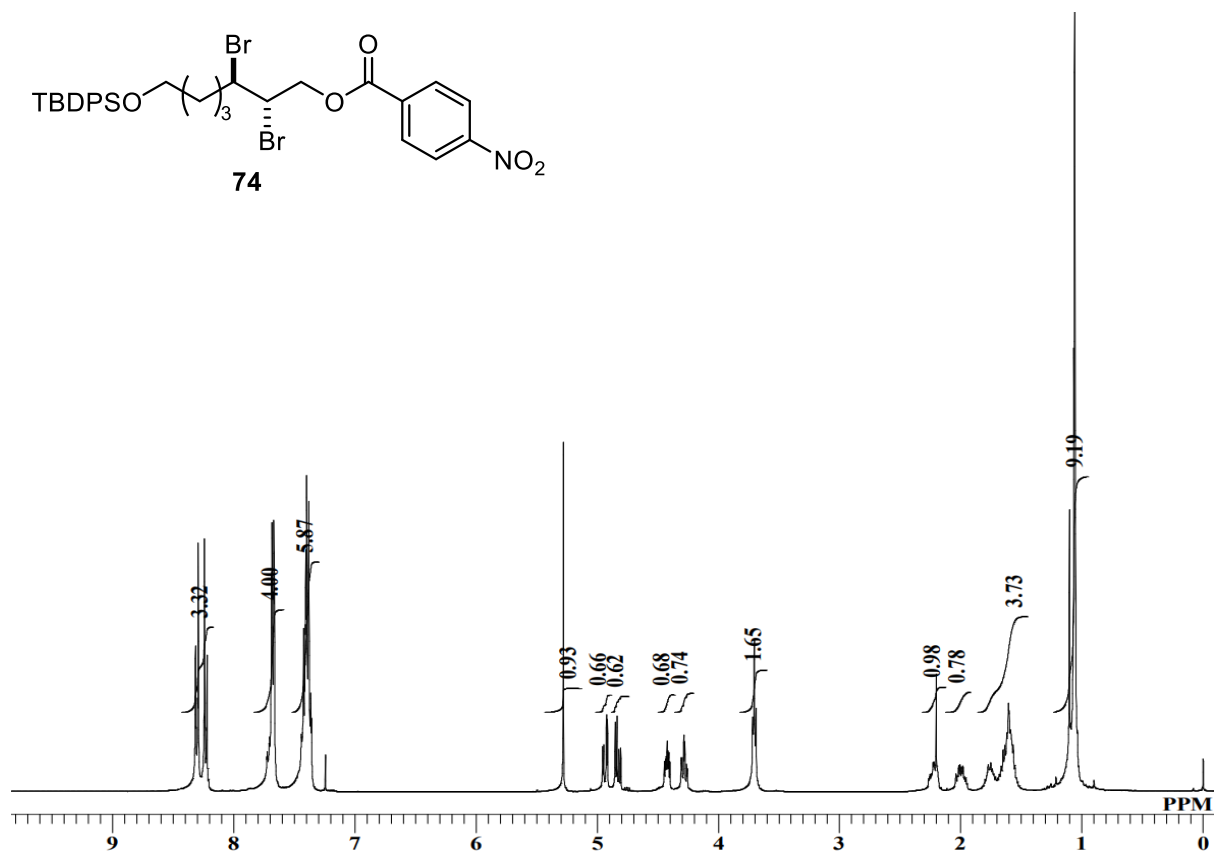
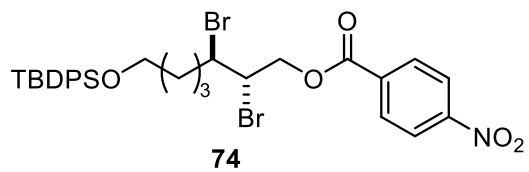
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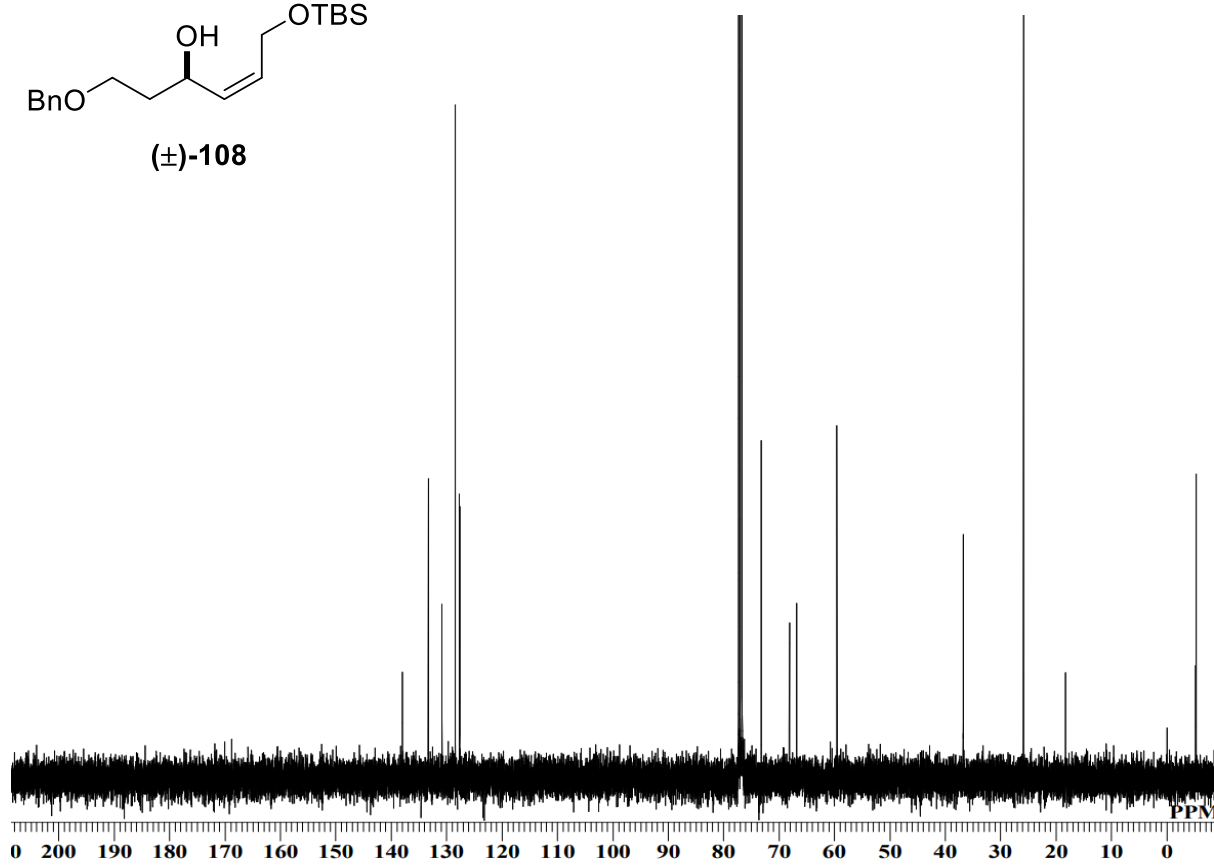
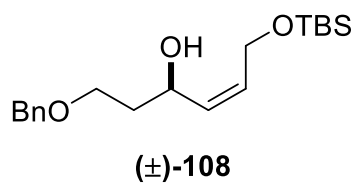
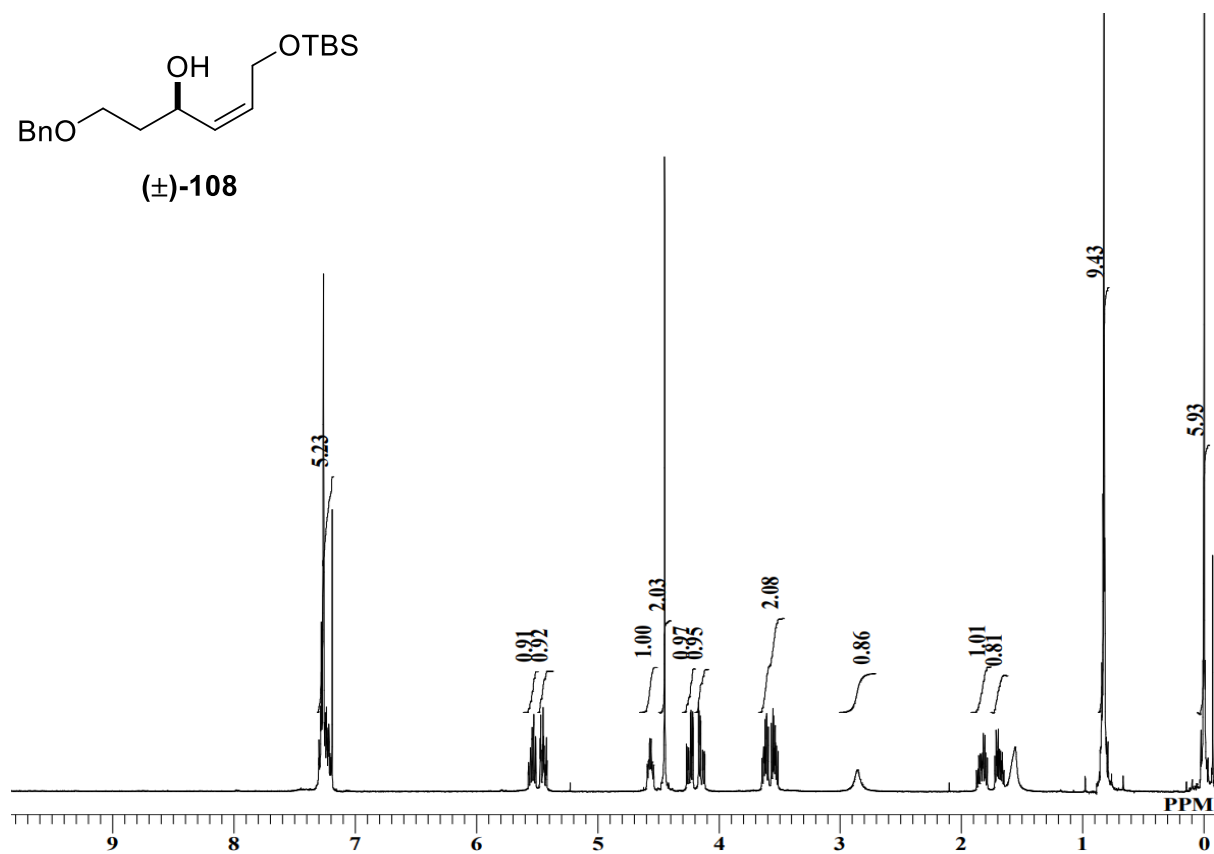
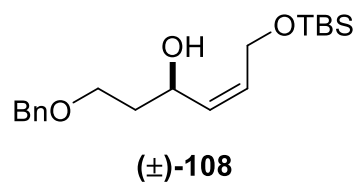


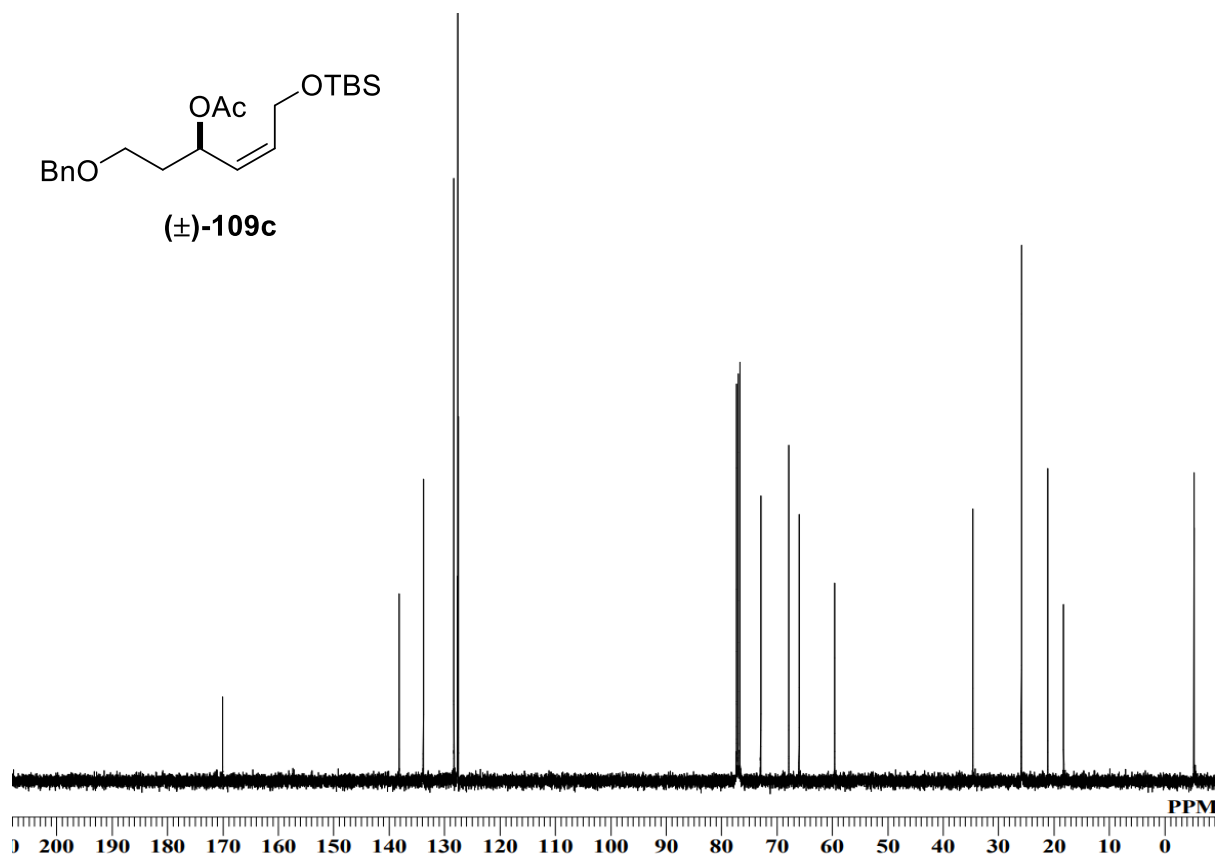
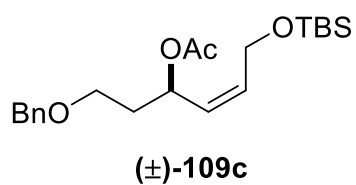
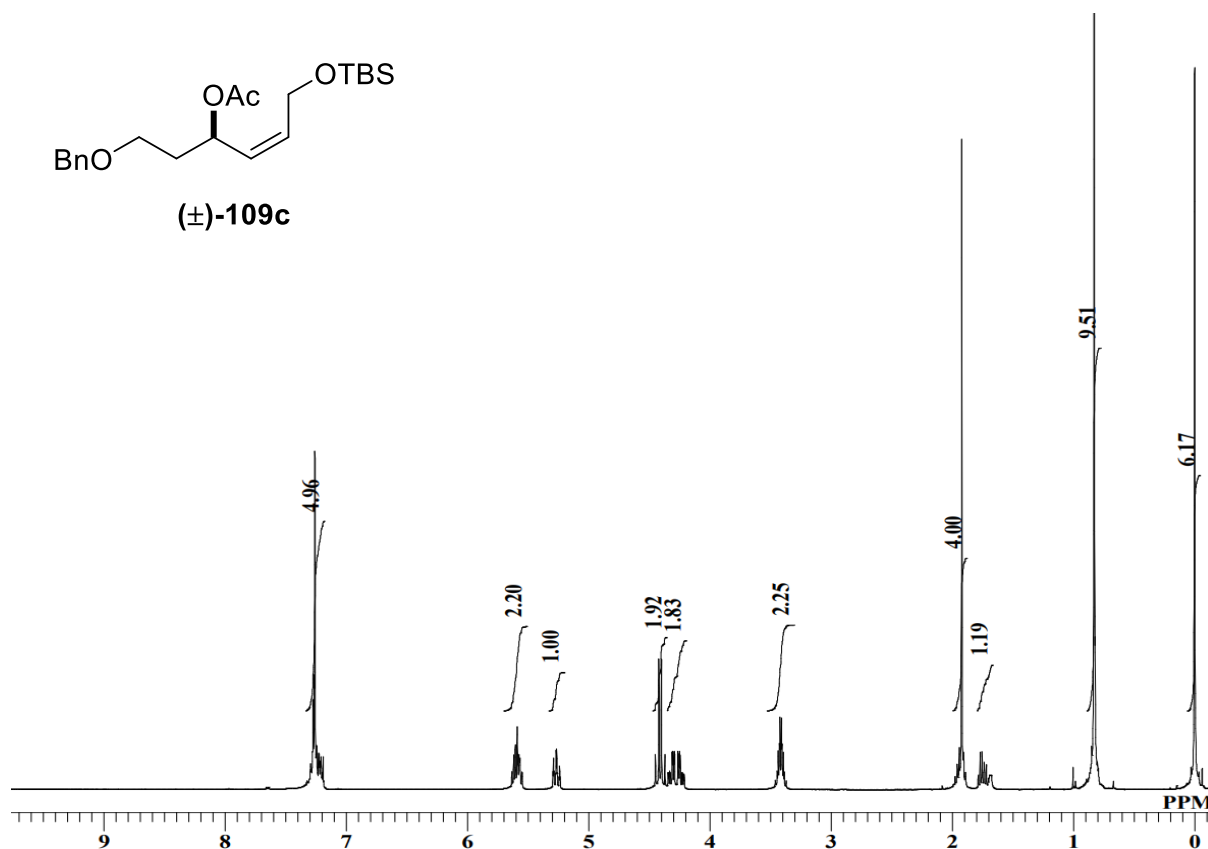
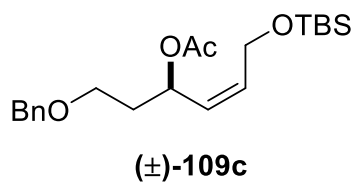


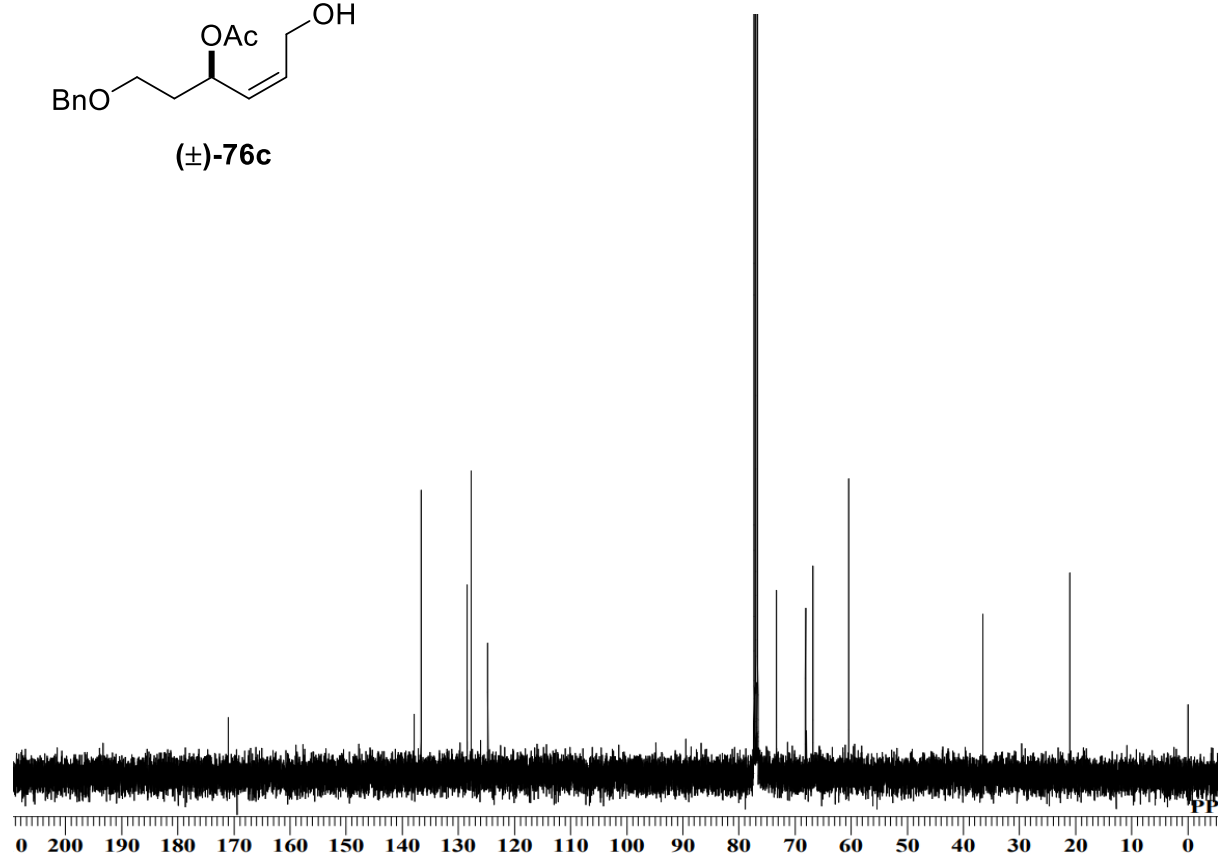
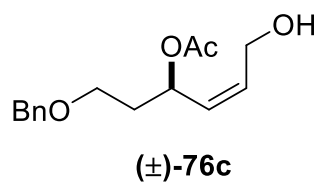
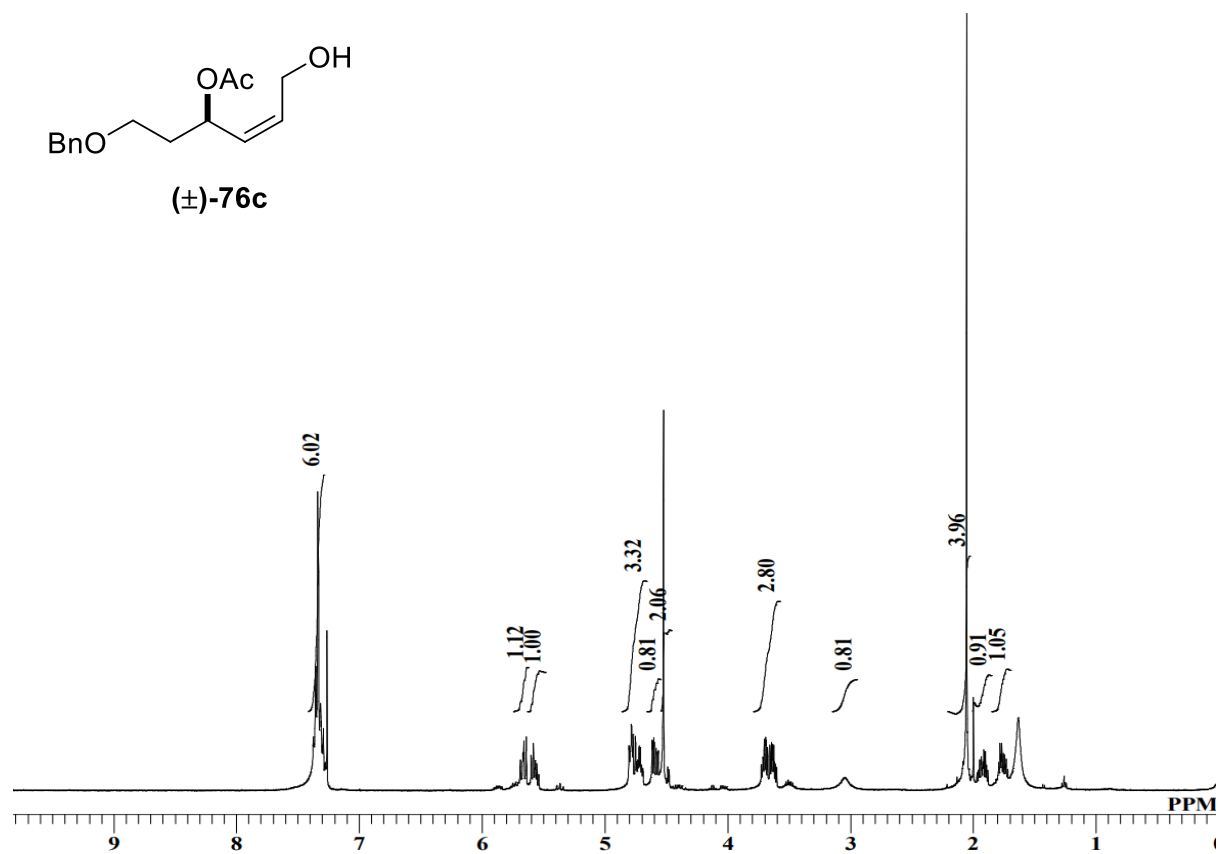
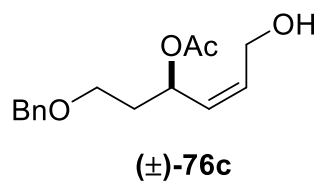


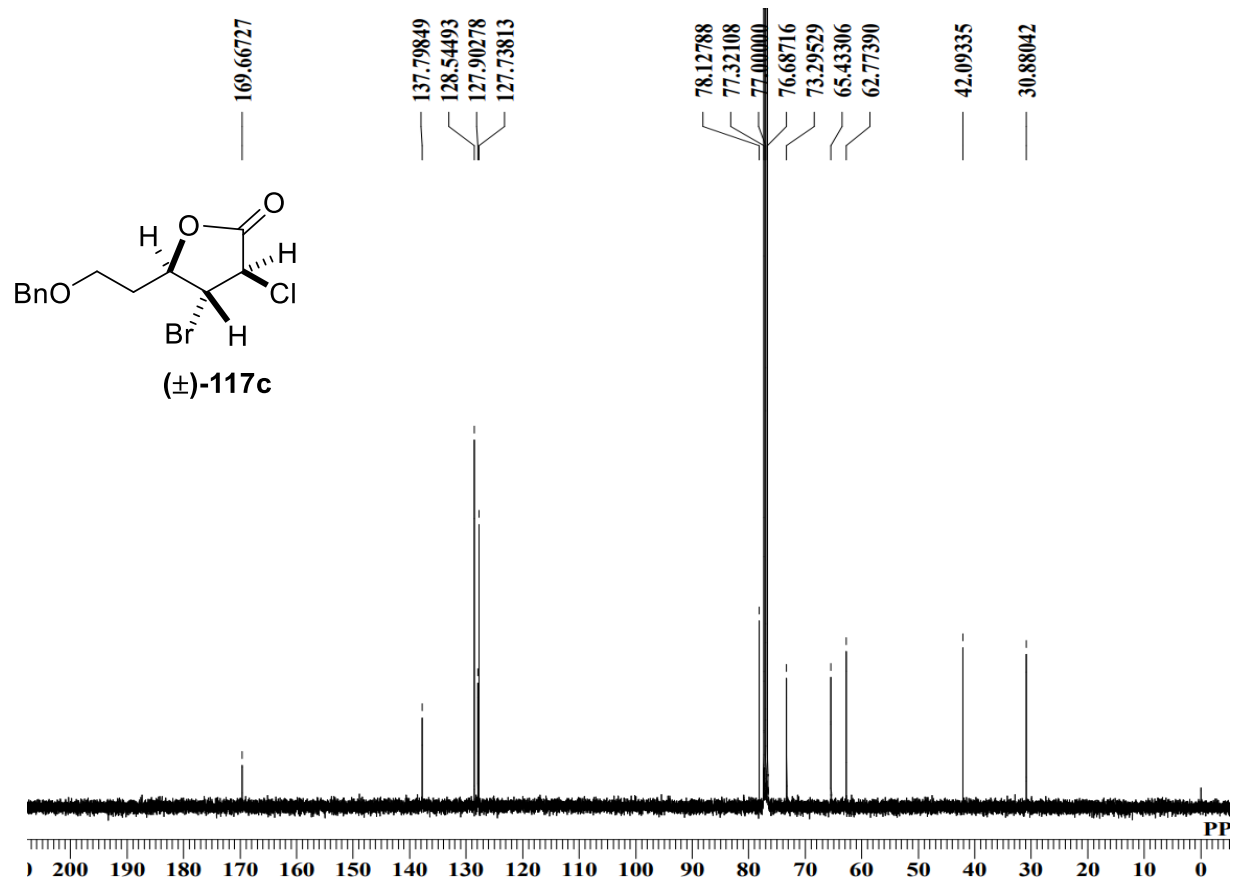
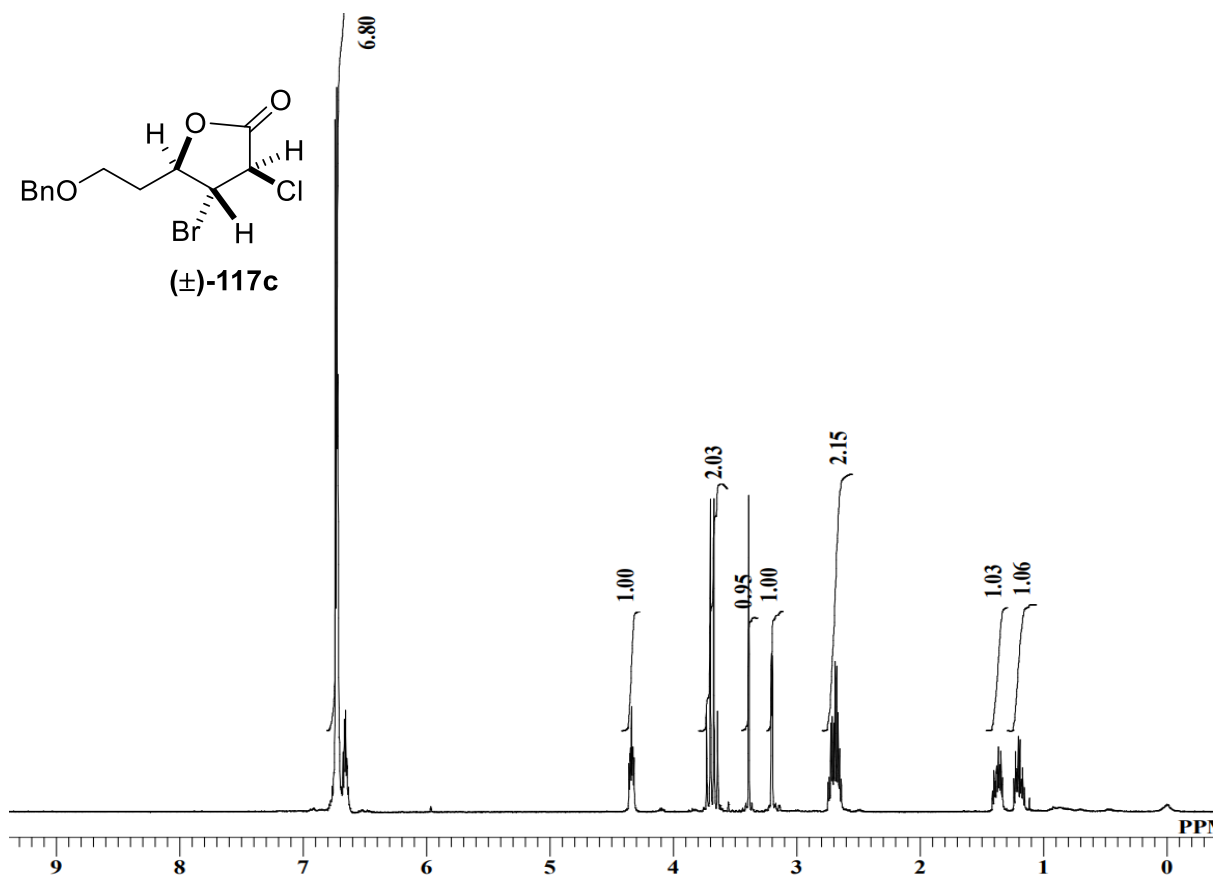


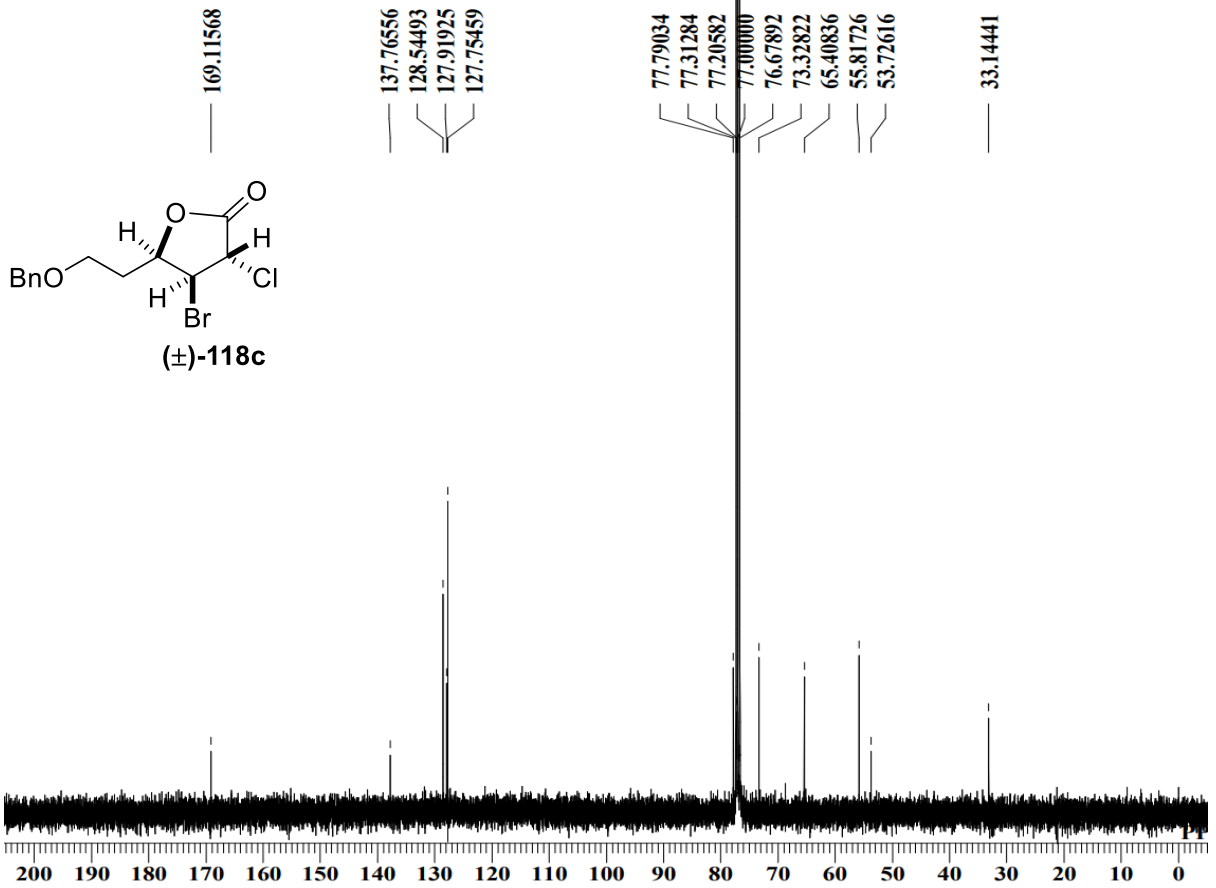
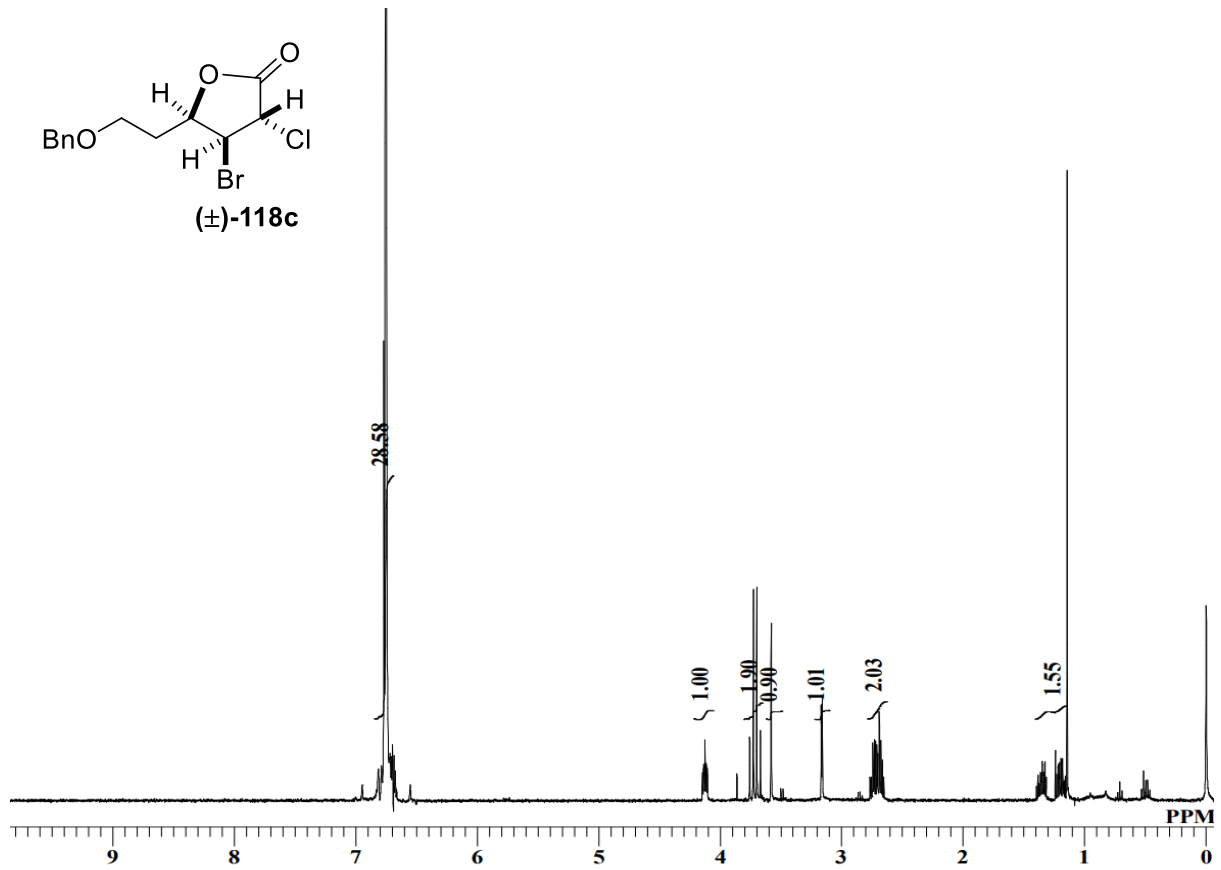
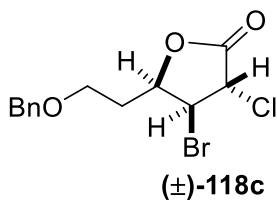


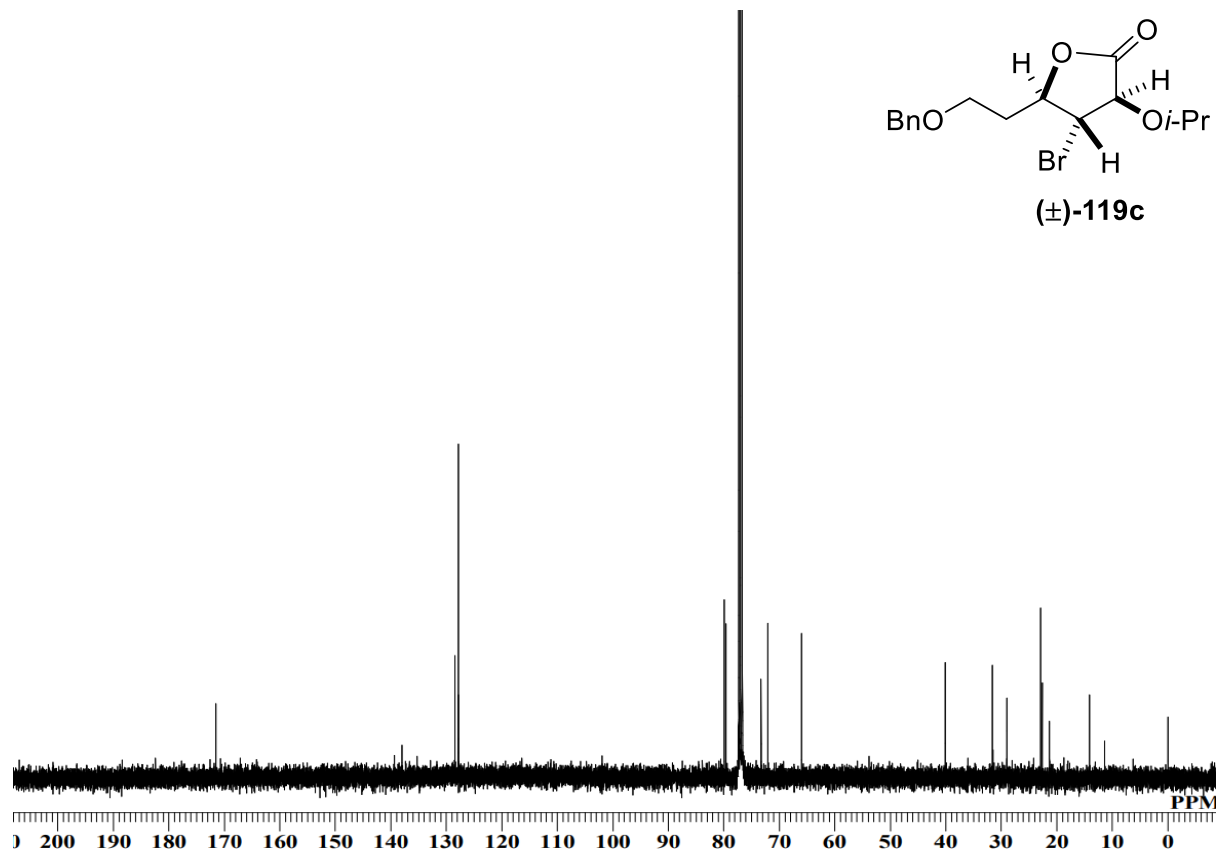
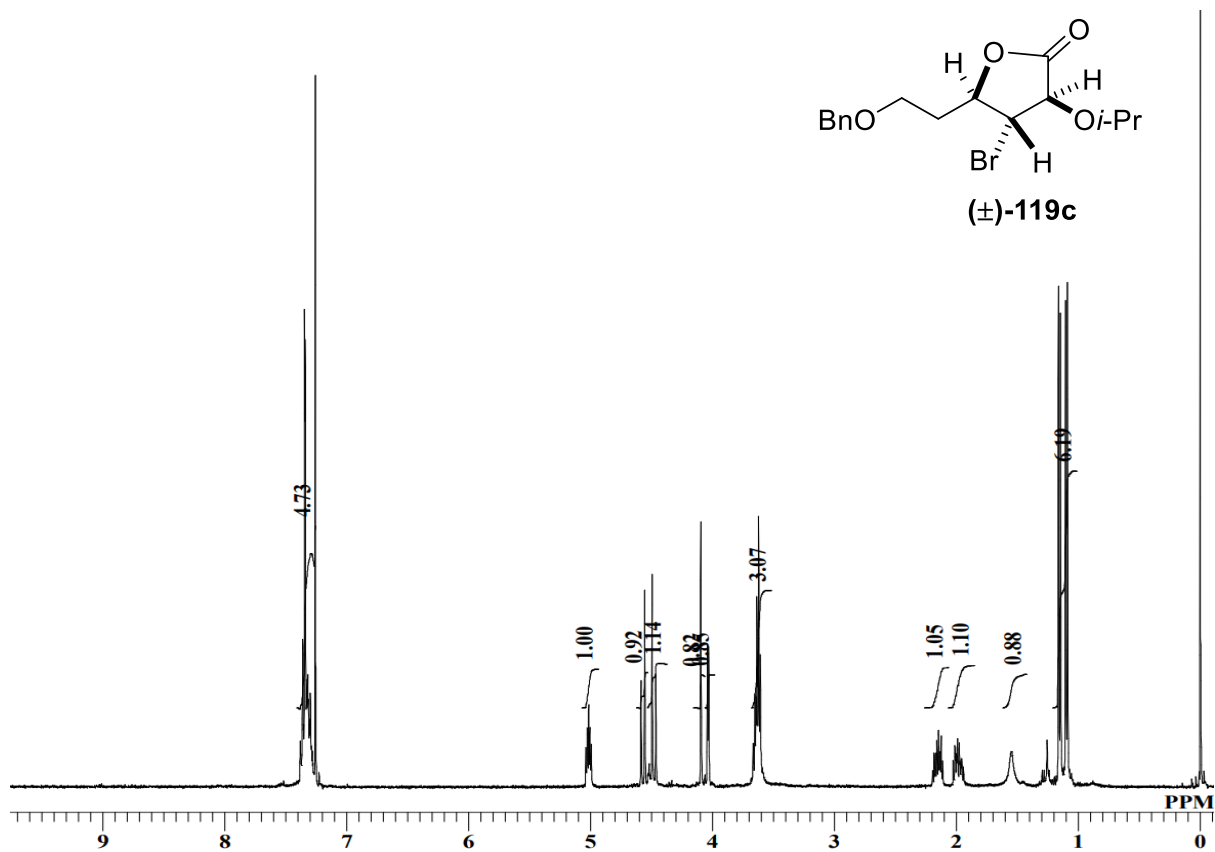




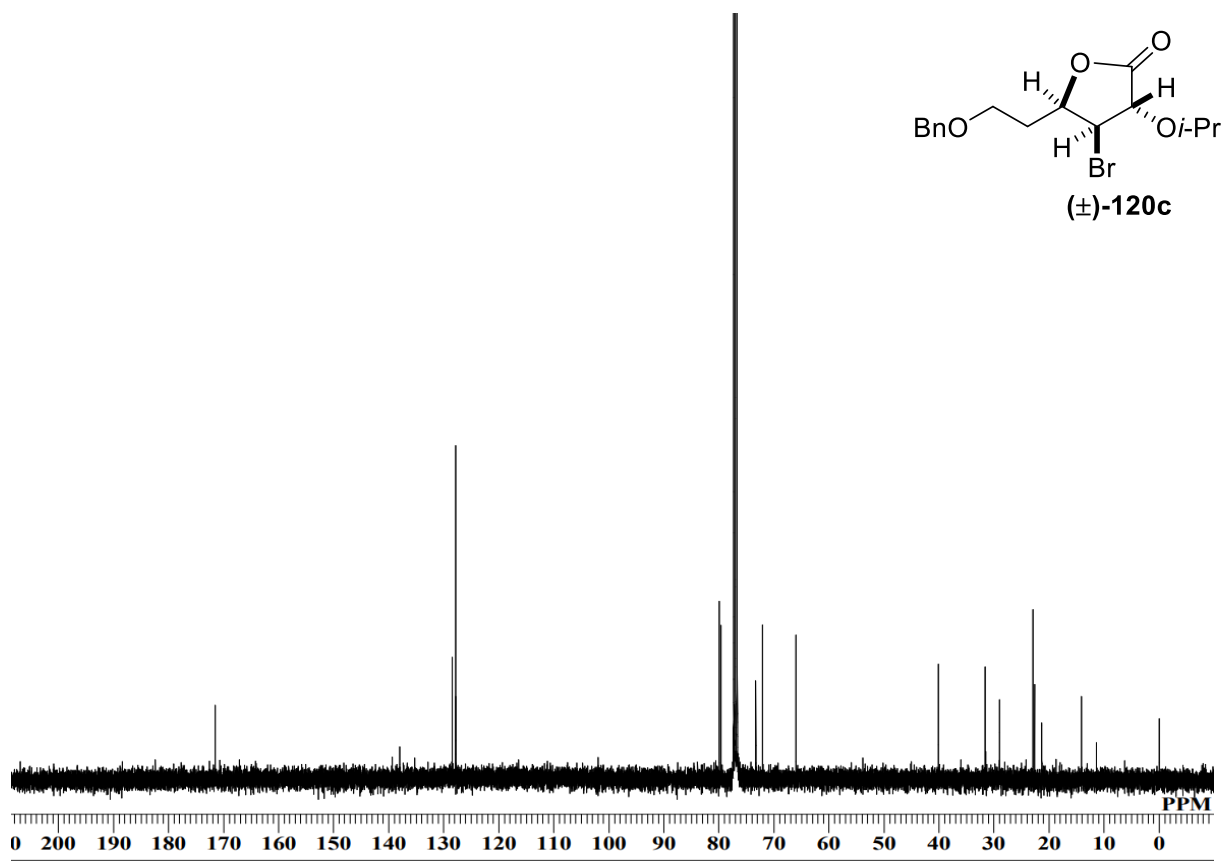
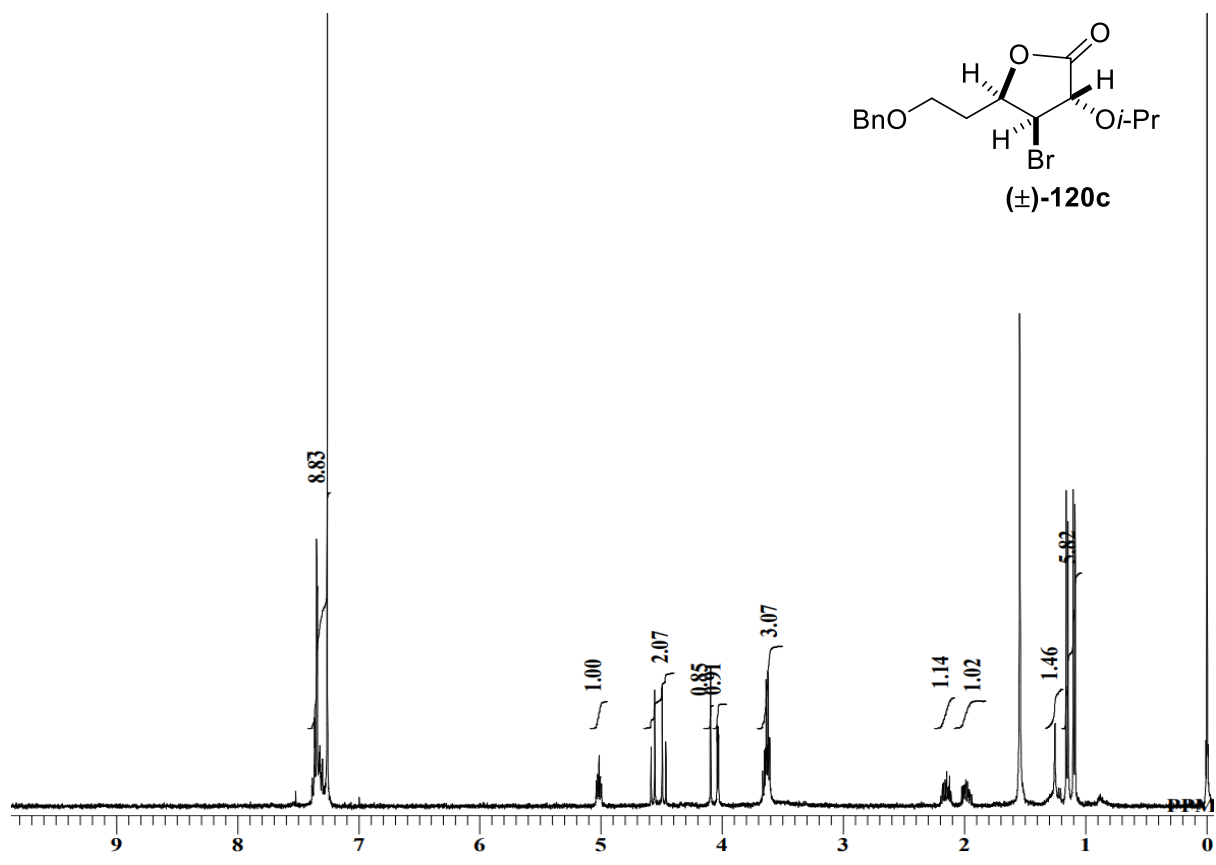








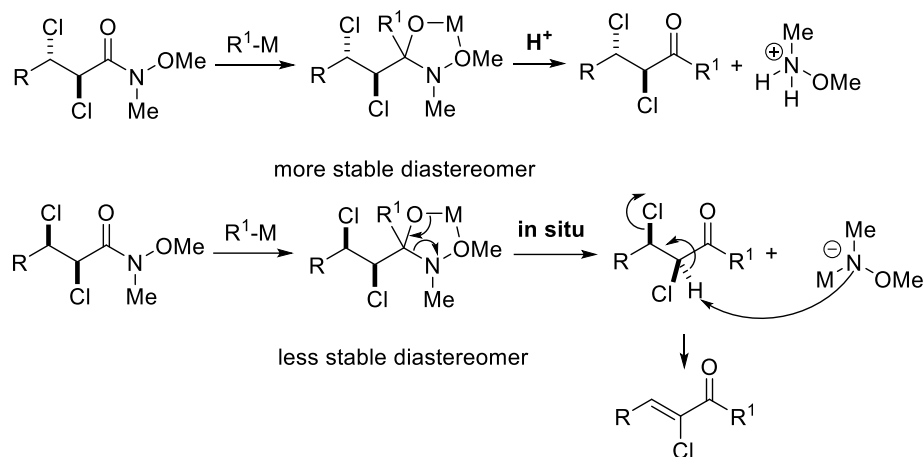




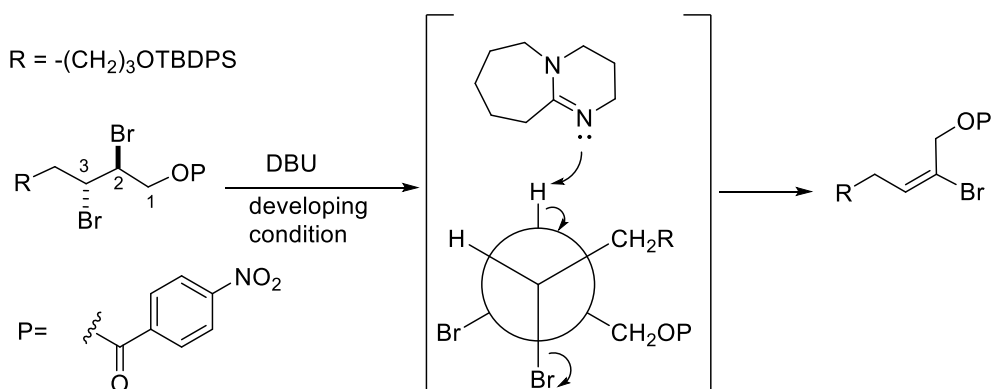
## Summary and Conclusion

The crucial importance of studying and developing a synthetic method for polyhalogenated compounds is inspired by the significant number of discoveries and developments of halogenated natural products with significant activity in recent times. Moreover, the supply of these natural products is limited, which makes it challenging to study their biological activities. On the other hand, many reactions focus on installing halogen atoms when the development of new methodologies with halogenated compounds is rare to overcome a novel property of the halogen atom, such as high activity toward  $\beta$ -elimination reaction of the carbonyl compound. 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.

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. In chapter 2, 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. Two diastereomers, *anti*- and *syn*-dichloroamide showed different reactivity against some nucleophiles, assuming the difference in stability of five-membered ring intermediates. 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.

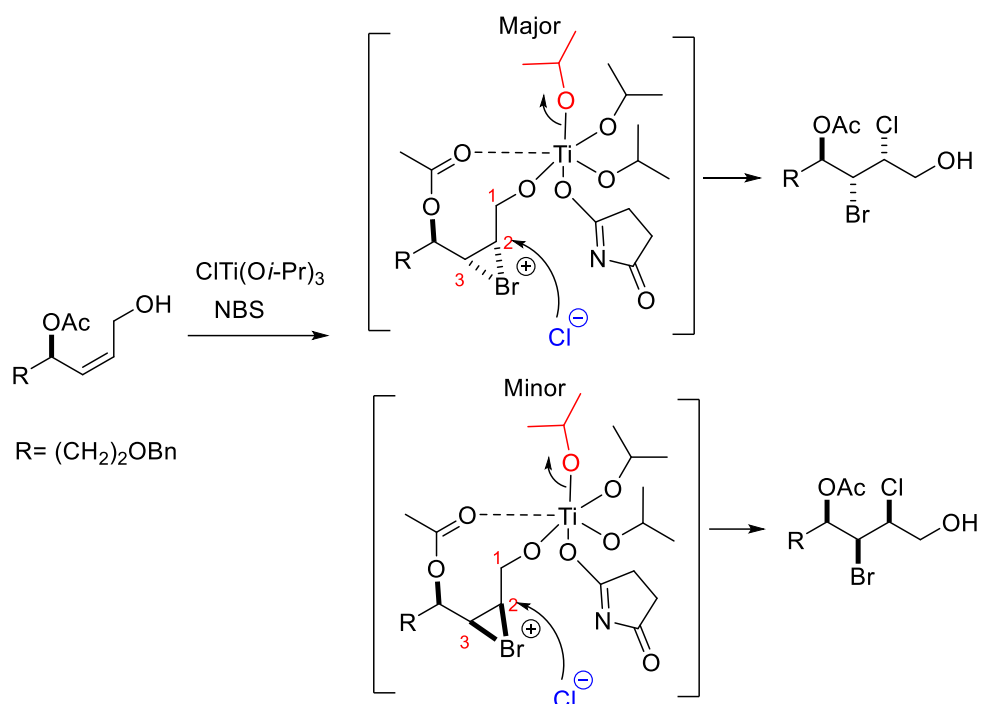


In chapter 3 of this thesis, author have engaged total synthesis of mollenyne A, a halogenated anticancer natural product obtained from a marine sponge. This compound consists of three units, homoagmatine, central part with three halogen atoms including a halohydrin, and ene-yne unit. Author focused on the central part *E*-bromoolefin and halohydrin construction studies. *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. *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.



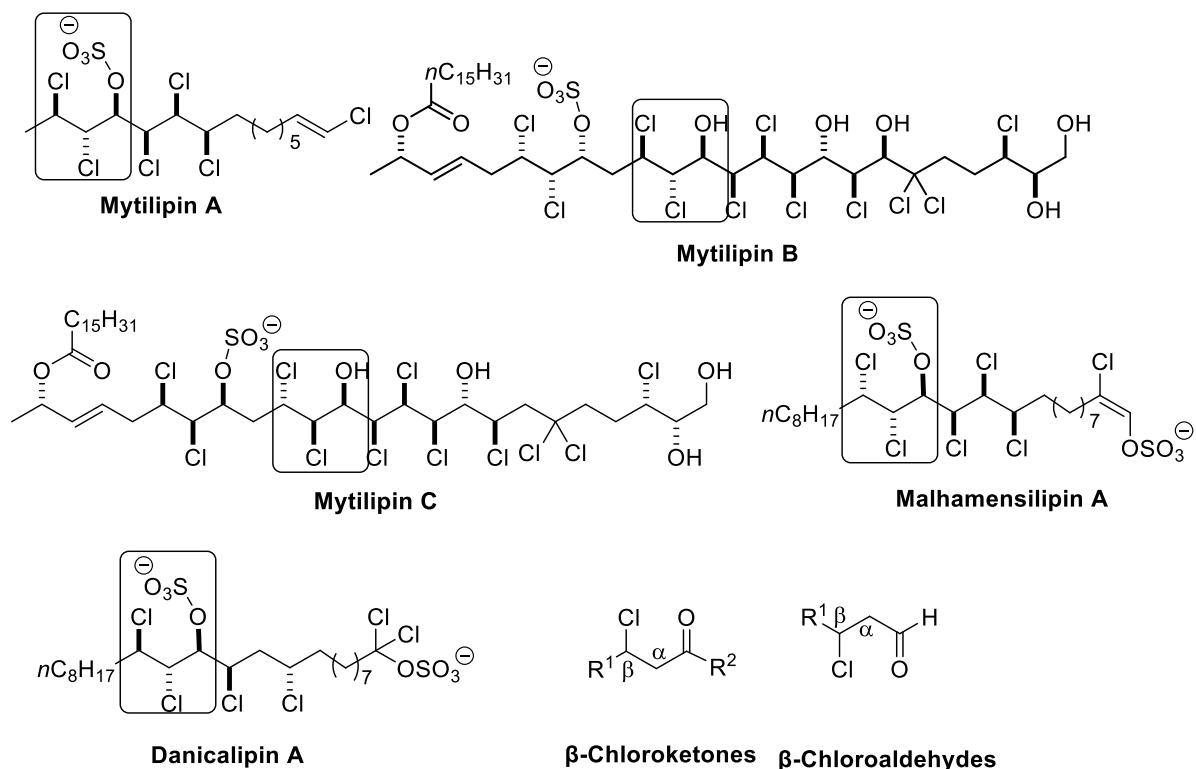
On the other hand, the halohydrin part was successfully constructed using  $\text{TiCl}(\text{O}i\text{-Pr})_3$  as a chloride and NBS as the bromonium ion in the regioselective bromochlorination reaction to the allylic alcohol. The regioselectivity contributed by the rigidity of complexed intermediate and stereogenic center in the model substrate, although low diastereoselectivity (ca 2:1) was

obtained. However, the intramolecularly competitive substitution occurs in-situ between Cl<sup>-</sup> anion and isopropoxide to form undesired side products in low concentration. Current investigations open the possibilities for accomplishing the synthetic study on Mollenyne A, although the improvement is underway.

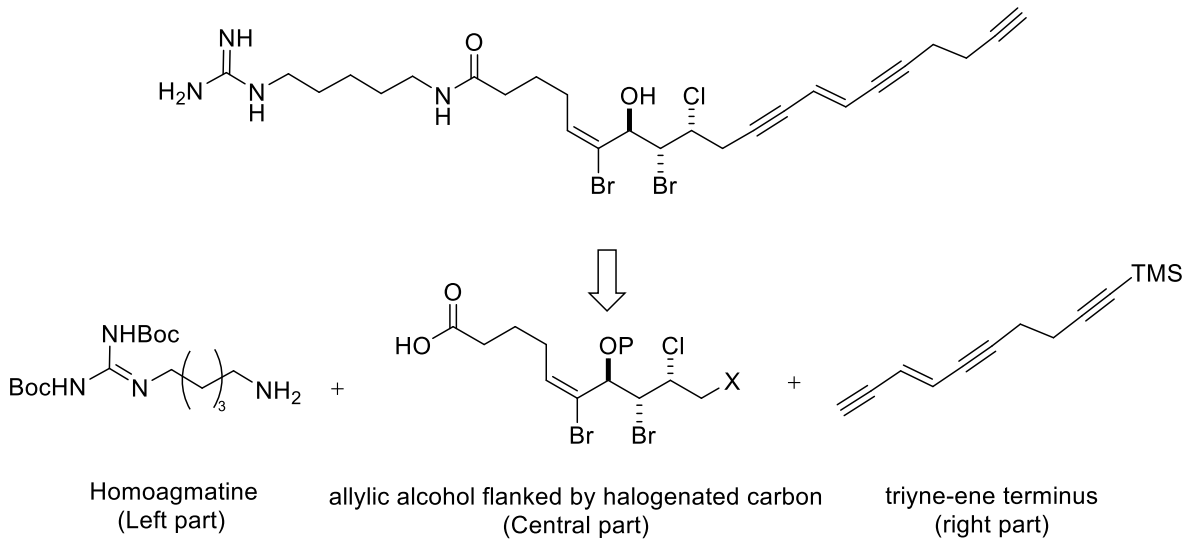


Based on valuable findings in the Weinreb amide study, author envisioned further opportunities to solve some problems in the natural products construction which has halohydrin part, such as chlorosulfolipids (CSLs), a fascinating class of natural products featuring highly chlorinated hydrocarbon scaffolds. In the CSLs construction, the C-C bond formation may become a problem because they have many chlorides, which potentially participate in the elimination reaction during the formation. Some CSLs compound (mytilipin A, mytilipin B, mytilipin C, danicalipin A, and malhamensilipin A) have the halohydrin part (highlighted by a square) in its structure. With inventions related to new effective methods for synthesizing  $\alpha,\beta$ -dichlorinated ketone via Weinreb amide, author believes access to halohydrin part can be realized and gives a new viewpoint on the elongation of chlorinated hydrocarbon frameworks.

With  $\alpha,\beta$ -dichlorinated Weinreb amide, it also opens the opportunity to develop new methods for  $\beta$ -chloroketones or  $\beta$ -chloroaldehydes construction.



On the other hand, with the crucial information related to construction of *E*-bromoolefin and halohydrin from the central part of Mollenyne A, author will continue to accomplish the synthetic study on Mollenyne A. Optimization related to amidation reaction for merging the left part with a central part and subsequent C-C bond formation reaction through  $S_N2$  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 triene-ene terminus, allylic alcohol flanked by halogenated carbon and homoagmatine will be combined to furnish synthetic Mollenyne A. Comparison of the biological activity between natural Mollenyne A and synthetic Mollenyne A also needed.



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