이학석사학위논문

Synthetic Studies toward Madeirolide A

마데이롤라이드 에이의 합성 연구

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서울대학교 대학원

화학부 유기화학전공

백 인 환

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ABSTRACT

Madeirolide A is isolated from the marine sponge *Leiodermatium* sp., and has been shown to be a potent growth inhibitor of *Candida albicans*, a pathogenic fungus. Madeirolide A has a complicated structure with a 24-membered macrolactone and 16 stereocenters. The bioactivity and structural complexity make madeirolide A an attractive target for total synthesis. Our approach for the synthesis of madeirolide A is based on the assembly of four fragments – C1-C10 fragment (A ring), C11-C19 fragment (B ring), C20-C27 fragment (C ring), and cinerulose fragments. Using a free radical-mediated reductive cyclization method developed from our group, three oxacycles in the compound have been envisioned to be efficiently created under novel photoredox catalysis of an iridium complex. Described in this thesis are the synthetic studies of the three fragments of madeirolide A.

Keyword : Madeirolide A, Total synthesis, Photoredox catalysis, Aldol reaction, Ireland-Claisen rearrangement, Tsuji-Trost reaction

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INTRODUCTION

1. Background

Madeirolide A is a macrolide extracted from *Leiodermatium* species, a deep-water sponge. This compound was isolated by Wright and Winder[1] in Florida Atlantic University. Both madeirolides A (**1**) and B (**2**) were shown to possess inhibitory activity against the fungal pathogen *Candida albicans* with fungicidal MIC values of 12.5 and 25 μg/mL, respectively.[2] Some limited anticancer activity was also reported. Structurally, madeirolide A and B possess a 24-membered macrolactone ring with three oxacycle rings and glycone, and 16 stereocenters. Its partial synthesis was reported by Paterson, Carter and Lee.[3]

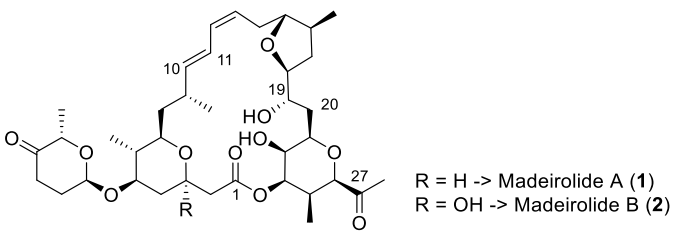

Figure 1. Madeirolides

Madeirolides bear considerable structural resemblance to the tunicate metabolite, mandelalide family (mandelalide A-E) of macrolides. Mandelalide A, a reported bioactive macrolide extracted from an ascidian species of the genus *Lissoclinum*, has a very similar structure with madeirolide A. Its potency to remove a variety of cancer cells prompted many chemists to synthesize this molecule, resulting in the reported 6 total syntheses since 2012.[4][5] The structure of mandelalide A was revised by Xu and Ye. They reported that the stereochemistry of carbon 17, 18, 20, 21 and 23 should be reversed compared to the first report, confirming that its stereochemistry resembles that of the madeirolide family.

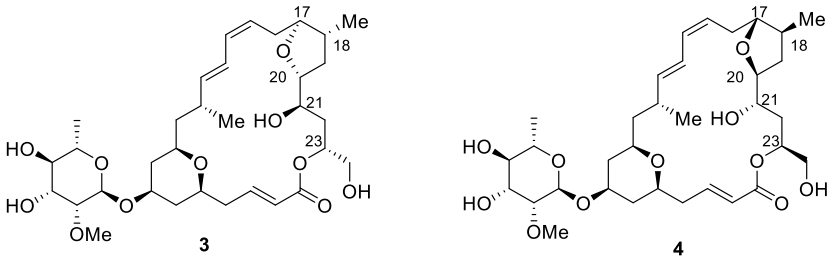

Figure 2. First Reported Structure of Mandelalide A (**3**) and Structural Revision by Xu and Ye (**4**)

Leiodelides (also known as leiodolide) were extracted from

Leiodermatium species, the same species from which madeirolide A was isolated. Many partial syntheses were reported for leiodelide A.[6] Leiodelide B is not fully structurally assigned due to many stereogenic centers. Fürstner named its unknown stereochemistry "leiodolide puzzle", because the spectra of C4, C5 and C13-differentiated diastereomers did not match with the reported spectra.[7]

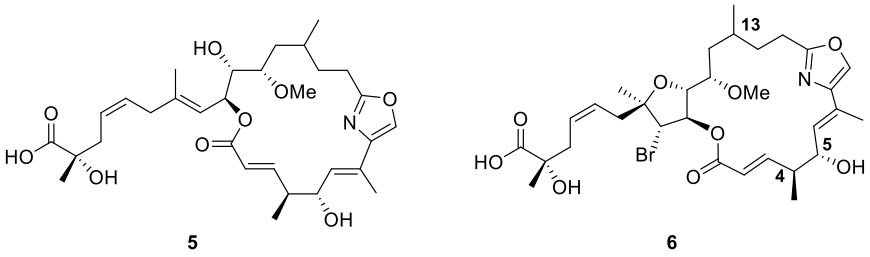

Figure 3. Structure of Leiodelide A (**5**) and B (**6**)

The highly potent anti-cancer molecule leiodermatolide A was also obtained from *Leiodermatium*. The structure of (-)-leiodermatolide A was fully assigned, and its total synthesis has been completed. It has been shown that leiodermatolide A has excellent bioactivity, stopping tubulin creation and inhibiting growth of seven lines of human cancer cells with a GI_{50} of 3 nM. The proposed mechanism of bioactivity is that leiodermatolide A does not interact with tubulin directly, but

targeting centrosome.[8]

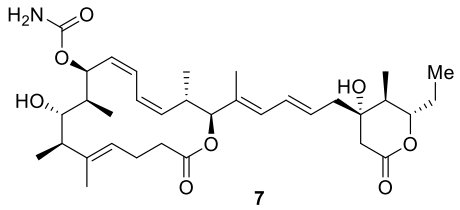

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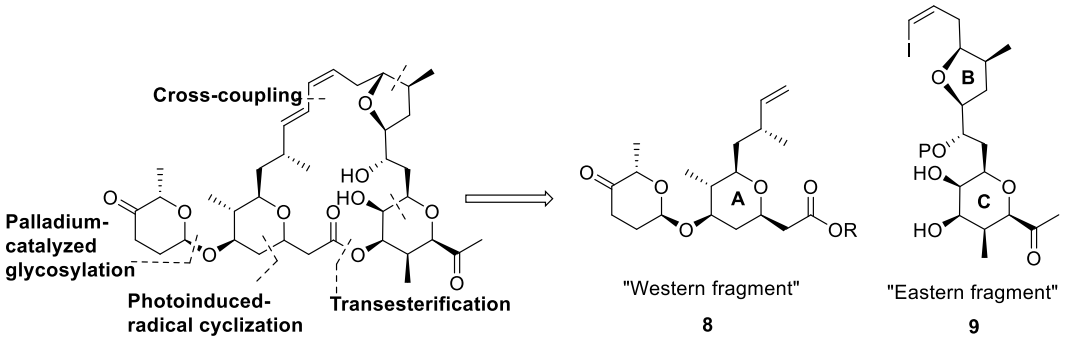
Figure 4. Structure of (-)-Leiodermatolide (**7**)

2. Retrosynthetic Analysis of Madeirolide A

Madeirolide A has four oxacycles, a cinerulose ring, two tetrahydropyran rings and one 2,5-cis-tetrahydrofuran ring, which has a 2,6-*cis*-substituted system. It was envisioned that these cyclic fragments could be synthesized via the photoredox catalyst-mediated reductive cyclization developed by H. Kim and C. Lee.[9] Using this reaction, the synthesis of these 3 rings was expected to be feasible, with high 2,6- or 2,5-cis-selectivity. The large macrolactone could be synthesized through esterification and cross-coupling reactions. Also, the cinerulose sugar ring could be added by the palladium-catalyzed glycosylation developed by the Feringa, O'Doherty and Lee groups.[10] Based on this approach, madeirolide A can be divided into

two parts, the western and eastern fragments. The eastern fragment could be further divided to the upper tetrahydrofuran (10) and lower tetrahydropyran (11) rings. These three fragments are named “A ring”, “B ring”, and “C ring” respectively.



Scheme 1. Two Fragments and Key Steps toward Synthesis of Madeirolide A

The strategy used to combine B ring and C ring would be the Michael reaction between the alcohol and the terminal ynone. Two oxacycles in the eastern fragment, B and C rings, would be yielded from the similar radical cyclization conditions which were applied to synthesize A ring.

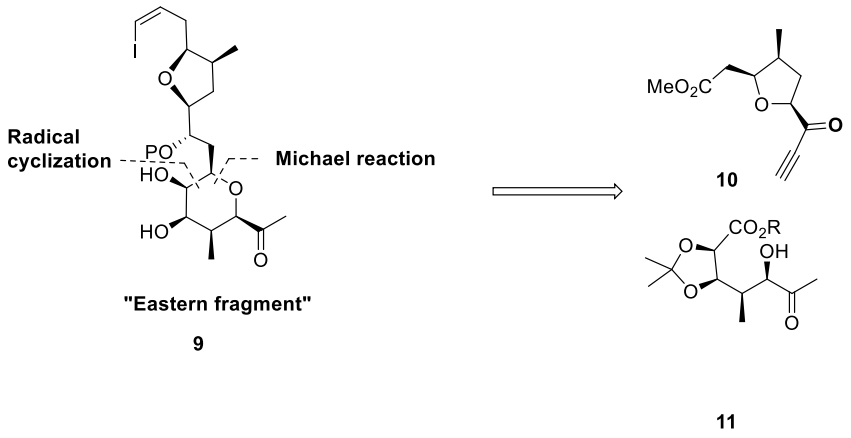
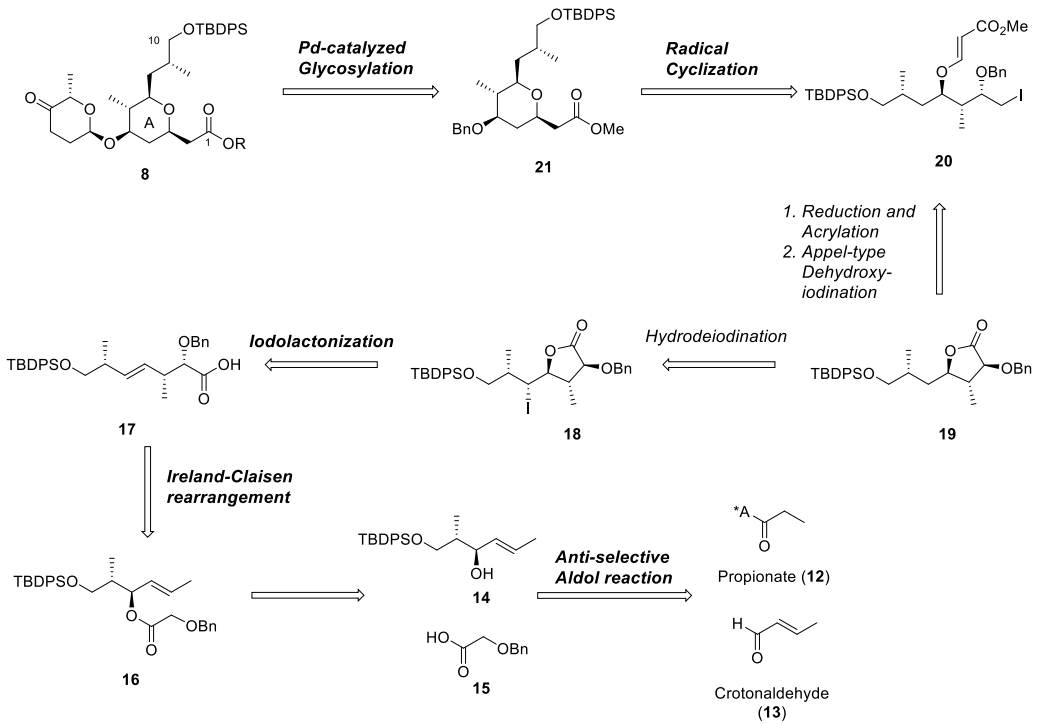


Figure 5. Eastern Fragment of Madeirolide A

RESULT AND DISCUSSION

1. Synthetic Studies toward C1-C10 Fragment of Madeirolide A

1.1. Synthetic Plan for C1-C10 Fragment of Madeirolide A

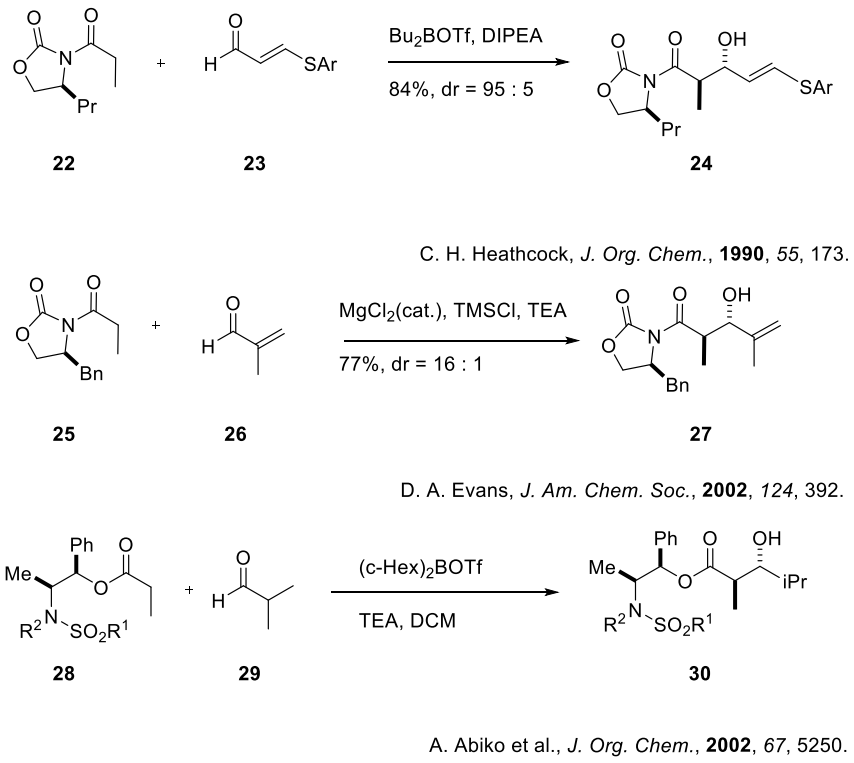


Scheme 2. Synthetic Plan for C1-C10 Fragment of Madeirolide A

A more specific synthetic plan is retrosynthetically drawn in Scheme 2. Our synthetic plan was based on the radical cyclization concept which would enable the formation of 2,6-cis-substituted tetrahydropyran ring from alkyl iodide **20** by using an iridium

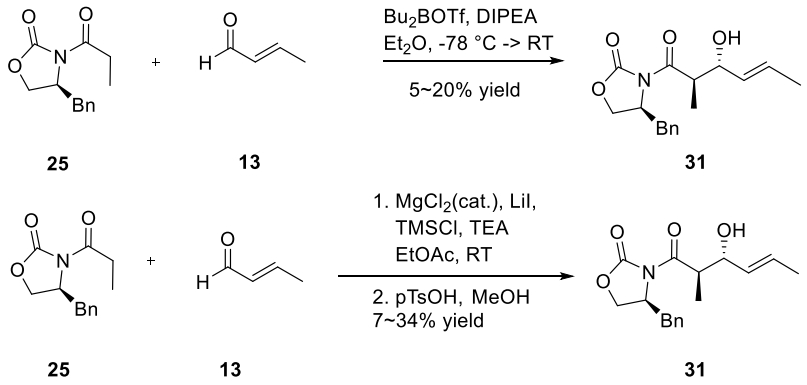
photocatalyst in the presence of a reductant. After synthesizing oxacycle **21**, the final palladium-catalyzed glycosylation would afford the western fragment, **8**. The aglycon of the western fragment of the madeirolide A (**21**) would arise from alkyl iodide **20**. From lactone **19**, its reduction, secondary alcohol acrylation and an Appel-type reaction for the primary alcohol will afford photocatalysis substrate **20.** Hydrodeiodination reaction will remove the iodide from **18** to yield lactone **19**. Ireland-Claisen rearrangement of **16** will afford acid **17**, and its iodolactonization product would be **18**. EDC coupling between alcohol **14** and carboxylic acid **15** will yield ester **16**. Diastereo- and enantioselective aldol reaction between **12** and **13**, reduction for chiral auxiliary removal and primary alcohol protection give **14**. The very first reaction for the synthesis of the western fragment involves propionate **12** and crotonaldehyde (**13**).

1.2. Anti-selective Aldol Reactions



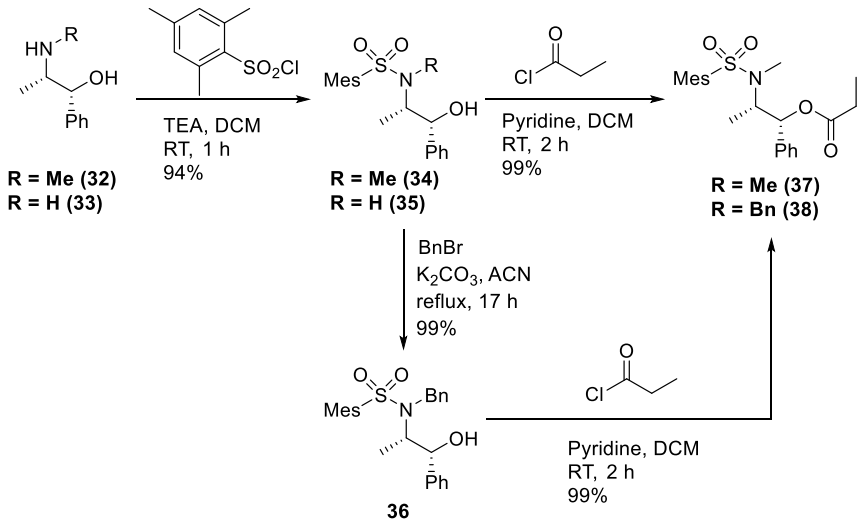
Scheme 3. Selected Examples of Anti-selective Aldol Reactions

Anti-selective diastereoselective and enantioselective aldol reactions have been well studied in organic synthesis (**Scheme 3**).[11][12]



Scheme 4. Synthesis of Aldol product via Heathcock's or Evans' conditions

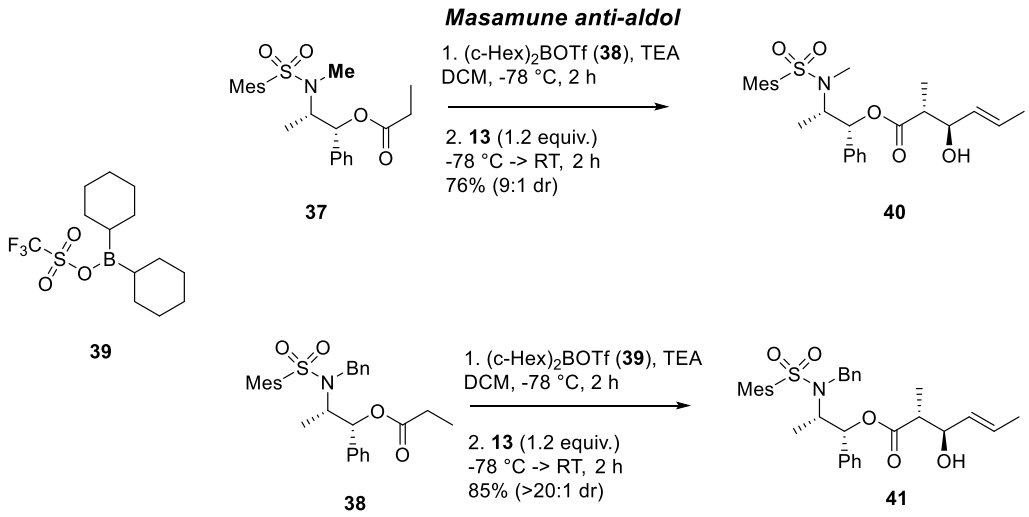
When Heathcock's and Evans' conditions were applied with propionate and crotonaldehyde, only low yield (<30%) of aldol product **31** could be obtained (Scheme 4).



Scheme 5. Preparation of Chiral auxiliary-added Propionate

Abiko's conditions[11d] using ephedrine- or norephedrine-derived chiral auxiliary gave high yield (Scheme 5). Thus, commercially available (-)-ephedrine (32) was selected for the very first material to synthesize madeirolide A. Only one step was required for the preparation of the chiral auxiliary. A mesitylenesulfonyl group was introduced to (-)-(1R,2S)-ephedrine to afford ephedrine-derived chiral auxiliary 34. Also, (-)-norephedrine (33) was selected to prepare its derivative, Masamune-type auxiliary 36.

From the ephedrine-derived propionate 37, a Masamune anti-selective aldol reaction with aldehyde 13 gave 40 with 76% yield as an inseparable mixture of 9:1 diastereomers (Scheme 6). A diastereomeric excess of 80% with the production of an inseparable minor diastereomer did not seem very adequate in modern organic chemistry. Thus, we sought a strategy using a more selective chiral auxiliary.



Scheme 6. Masamune anti-aldol reaction

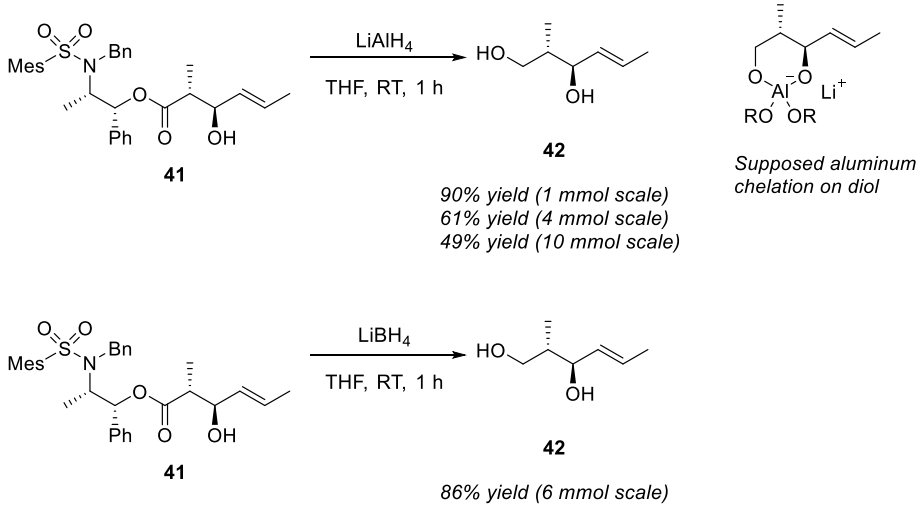
With the norephedrine-derived chiral auxiliary, the anti-selective aldol reaction of 38 gave higher yield with excellent diastereomeric ratio (>20:1). Fortunately, aldol product 41 could be obtained from large scale reaction (>10 g) without much decrease in yield.

1.3. Ireland-Claisen Rearrangement

1.3.1. Preparation of Substrate: Reduction of Aldol Product

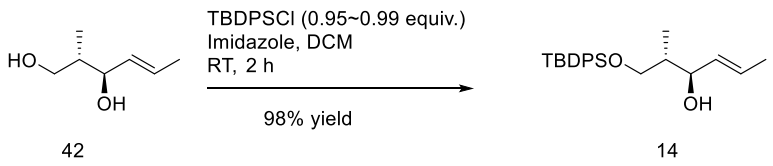
After the aldol reaction, the chiral auxiliary should be removed through reduction with hydrides (Scheme 7). With $LiAlH_4$, only a moderate yield (49~75% yield) could be obtained when the scale of the reaction mixture was larger than 500 mg (c.a. 1 mmol). Over 95% of the chiral auxiliary could be recovered. Instability of allylic diol **42** and aluminum chelation with two hydroxy groups could be the factors for lowering the yield, since the side product could not be separated or even observed in NMR.

Fortunately, when the reduction was carried out with 2 equivalents of $LiBH_4$, decrease of yield in larger scale experiment was not observed. In a 6-mmol scale (3.4 g) experiment, a yield of 87% was observed with nearly quantitative recovery of the chiral auxiliary.



Scheme 7. Auxiliary Removal via Reduction Using $LiAlH_4$ and $LiBH_4$

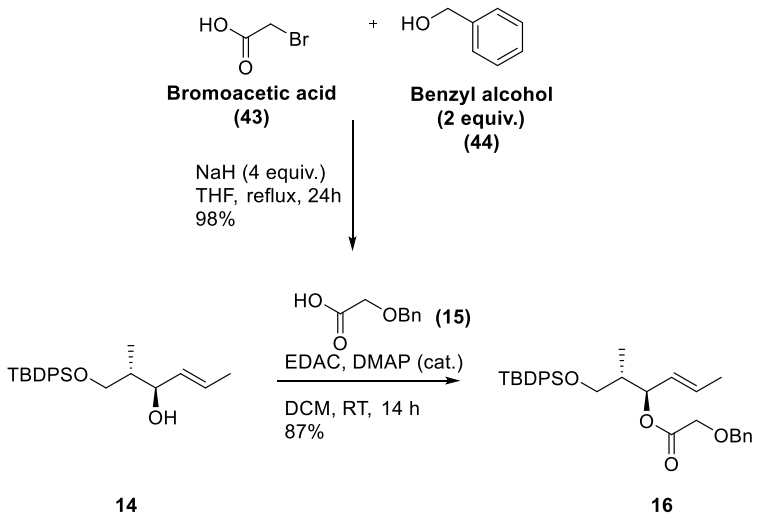
In order to protect the primary alcohol prior to esterification of the secondary alcohol which was required for the subsequent Ireland-Claisen rearrangement, a substoichiometric amount of TBDPSCl (0.95~0.99 equivalent to diol) was reacted with diol **42** to provide mono-alcohol **14** in 98% yield (Scheme 8).



Scheme 8. Primary Alcohol Protection

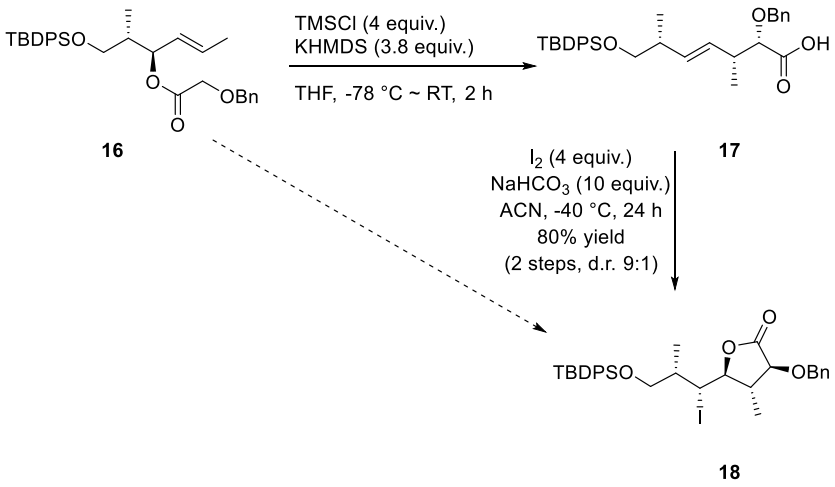
For the preparation of a substrate for Ireland-Claisen rearrangement, the TBDPS-protected alcohol **14** was esterified with acid **15**, which was synthesized from bromoacetic acid (**43**) and benzyl alcohol (**44**) using a known standard method (Scheme 9).[13]

The EDC coupling of **14** and **15** in the presence of DMAP catalyst proceeded smoothly to give ester **16** in 87% yield.



Scheme 9. Preparation of Substrate to Ireland-Claisen Rearrangement

1.3.2. Ireland-Claisen Rearrangement

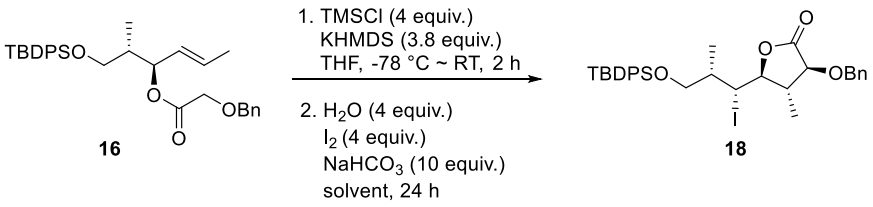


Scheme 10. Tandem Reaction of Ireland-Claisen Rearrangement and Iodolactonization

For the Ireland-Claisen rearrangement that would make a new C-C bond, while breaking a C-O bond of the allylic ester functional group, ester **16** was treated with excess amounts of potassium hexamethyldisilazide and TMSCl (**Scheme 10**). Upon warming the silyl ketene acetal to a room temperature, the desired Claisen rearrangement took place to give rise to the two-carbon elongated product, which was isolated in the form of a carboxylic acid as a

single isomer.

The carboxylic acid was then subjected to iodolactonization at 0 ℃ or room temperature (Table 1). Although the reaction did provide the iodolactone, only a selectivity lower than a 3:1 ratio was obtained. Changing the solvent to toluene, THF, or DCM increased the rate of the reaction, but the diastereomeric excess in these cases were found to be lower (~2:1). In contrast, when acetonitrile was used as solvent at -40 ℃, the diastereoselectivity of the iodolactonization was dramatically increased to 9:1.



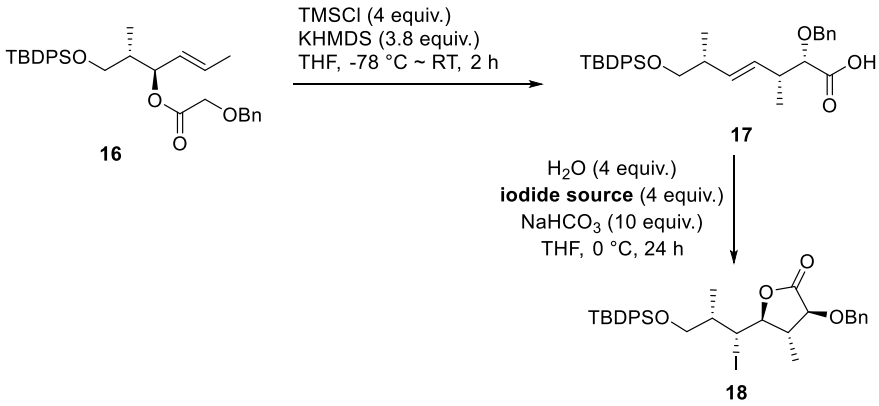
Solvent	Temperature	Yield	d.r.
THF	0 °C	80 %	2:1
Acetonitrile	0 °C	70 %	3:1
Toluene	-40 °C	69 %	2:1
Acetonitrile	-40 °C	69 %	9:1

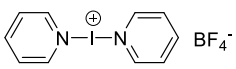
Table 1. Solvent Screening of Iodolactonization

1.3.3. One-pot Modification

It would be efficient and advantageous if one-pot tandem Ireland-Claisen rearrangement and iodolactonization could be performed without solvent change or work-up. But when the reaction was carried out with one-pot process, the maximum diastereoselectivity was only 3.3:1, lower than the 9:1 ratio obtained from the two-step process.

Screening of iodine source was conducted (Table 2). Iodine crystal, iodine monochloride (ICl), N-iodosuccinimide (NIS) and Barluenga's reagent (bis(pyridine)iodonium(I) tetrafluoroborate) were among the reagents tested. With iodine monochloride, the conversion was low even after 24 hours at room temperature. In the case of Barluenga's reagent, diastereoselectivity was almost 1:1 with poor conversion. In a similar vein, N-iodosuccinimide produced only a trace amount of iodolactone 18 with 3.2:1 diastereoselectivity.





Barluenga's reagent

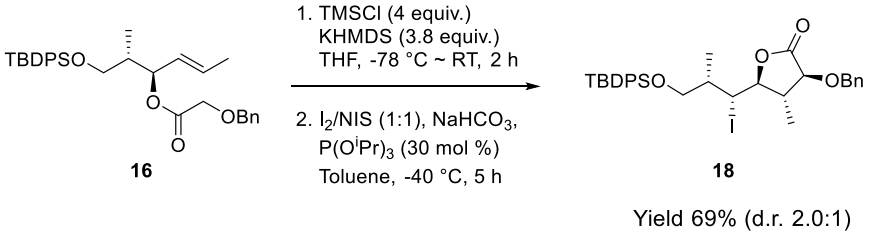
I source	16	17	18	d.r.
I_2	trace	0%	71%	3.3:1
ICl	36%	39%	21%	2.7:1
Barluenga's reagent	42%	25%	32%	1:1.1
N-iodosuccinimide [a]	n.d.	n.d.	<5%	3.2:1

[a] Complex mixture.

Table 2. Iodine Source Screening of Iodolactonization

Prof. Kazuaki Ishihara has reported many phosphite-catalyzed or phosphate-catalyzed, highly efficient iodolactonization reactions,[14] which have been developed into enantioselective iodolactonization methods adopting chiral phosphate catalysts. Based on these results,

it was anticipated that a faster reaction rate might increase diastereoselectivity. Thus, some phosphite and phosphate additives were tested for the iodolactonization reaction conditions, such as triphenylphosphite and triisopropylphosphite, while iodine source was changed to molecular iodine/N-iodosuccinimide 1:1 mixture following Ishihara's reaction conditions (Scheme 11). However, yield was not improved, and the diastereoselectivity was decreased compared with the reaction without additives. Therefore, it was concluded that the most critical factors affecting the diastereoselectivity of iodolactonization were solvent and temperature.



Scheme 11. Phosphite effect test.

The stereochemistry of the major product was determined by NOE experiments. The stereochemical issues were two-fold, i) the facial selectivity with respect to the pre-existing three stereocenters in acid 17 and ii) the relative stereochemistry between the C-I and C-O

bonds arising from iodolactonization. The hydrogen located at C3 position, and the hydrogen located at C5 position exhibited NOE interactions. Also, the hydrogen of the methyl group showed an NOE with the C2 axial hydrogen (Figure 6).

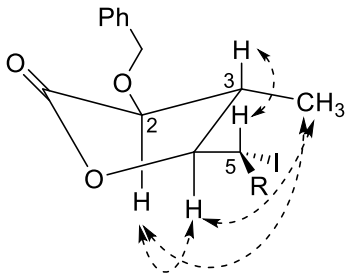
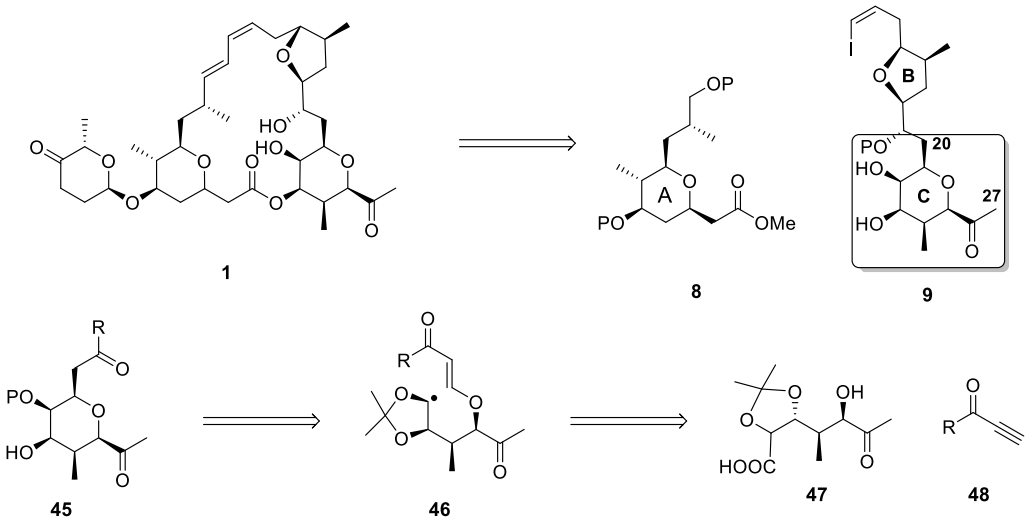


Figure 6. Exhibition of NOE interactions

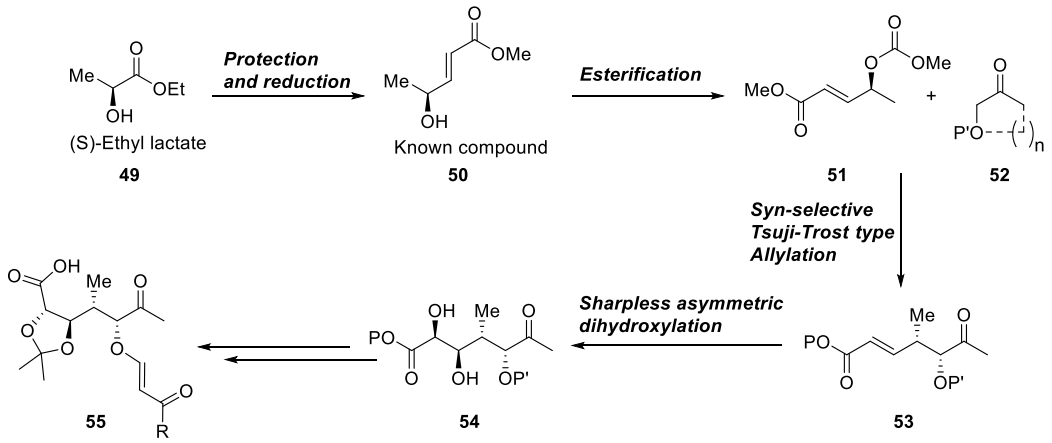
2. Studies toward C20-C27 Fragment of Madeirolide A

2.1. Retrosynthetic Analysis toward C20-C27 Fragment of Madeirolide A



Scheme 12. Retrosynthetic Analysis of C20-C27 Fragment of Madeirolide A

Due to the pentasubstituted pyran ring which have substituents in all-cis configuration, the C ring system, or C20-C27 fragment, is the most challenging part to synthesize. Also, the α-position of the methyl ketone can be easily epimerized, which requires adequate protection.

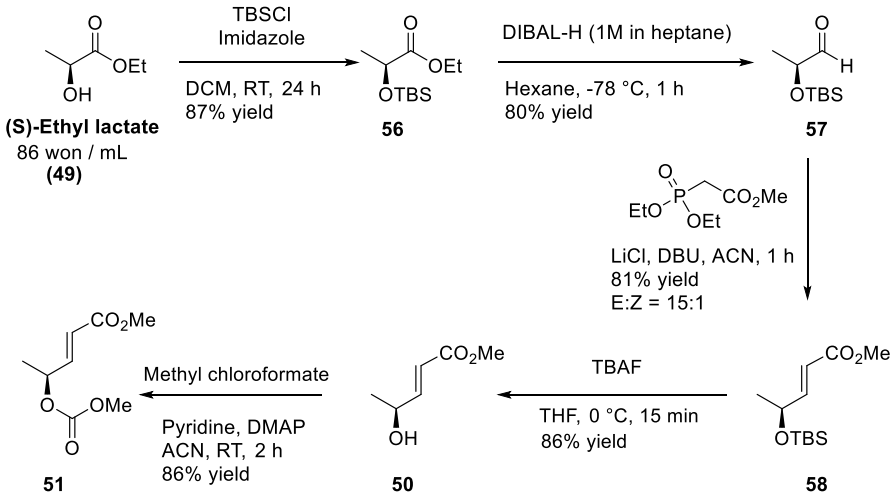


Scheme 13. Synthetic Plan for C20-C27 Fragment of Madeirolide A

Synthesis of 55 is challenging due to the presence of many oxygen atoms in an only 8-carbon unit. Furthermore, this fragment has four stereocenters and three of them have hydroxyl groups. To prepare this goal structure, two of the hydroxyl groups would be introduced via Sharpless asymmetric dihydroxylation, and the rest of them could be created from a syn-selective Tsuji-Trost-type reaction. Although many syn-aldol products can be synthesized using chiral auxiliary, it would be valuable to develop a palladium-catalyzed route that gives an aldol-like product without using chiral auxiliary. The chiral auxiliary-free approach has many advantages, including decrease of overall reaction steps and cost.

2.2. Attempted Tsuji-Trost reaction

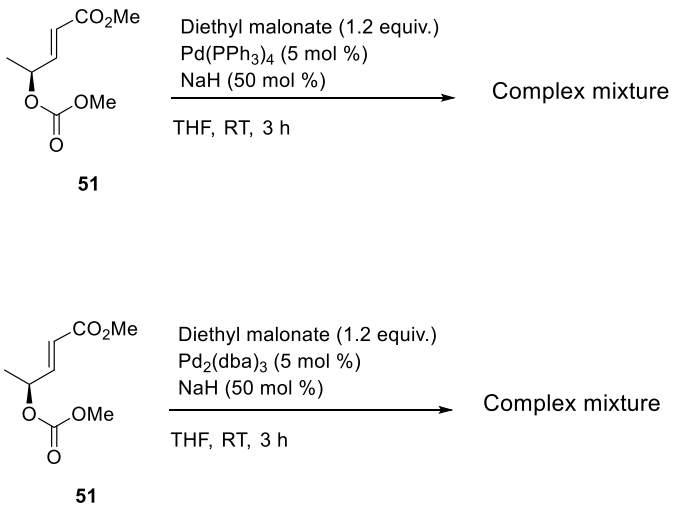
2.2.1. Intermolecular Allylic Alkylation



Scheme 14. Synthesis of Enantiopure Allylic Alcohol

Inspired by the result of Dr. Matunas,[15] a model study for allylic alkylation via palladium catalysis was conducted. From (S)-ethyl lactate, the sequence of TBS protection, reduction, and HWE reactions gave TBS-protected allylic alcohol 58. Using TBAF, the TBS protection group was cleanly removed to furnish the desired allylic alcohol 50. The reaction of 50 with methyl chloroformate in the presence of pyridine and catalytic DMAP base produced methyl carbonate 51 in high yield.

The palladium-catalyzed allylic alkylation of **51** was first tested with diethyl malonate nucleophile. However, under two different conditions using different palladium source, only complex mixtures were formed.



Scheme 15. Attempted Tsuji-Trost Reaction with Malonate Nucleophile

2.2.2. Allylic Alkylation Using Mixed Allylic Carbonate

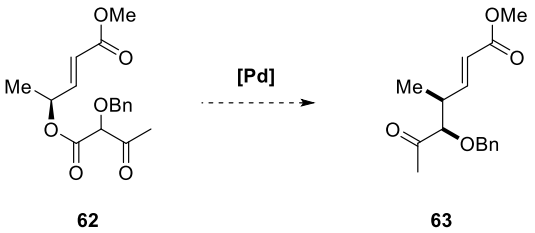
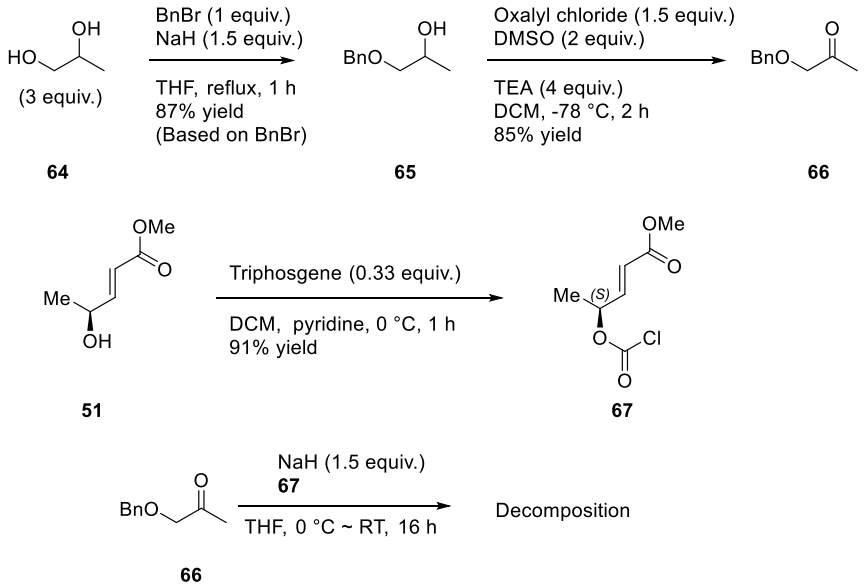


Figure 7. Desired Palladium Catalysis from Mixed Allylic Carbonate

It is known that an intramolecular, decarboxylative Tsuji-Trost type reaction can give an allylic alkylation product equivalent to that from a ketone enolate (Figure 7). [16] If this type of a reaction can be carried out with diastereo- and enantioselectivity, the palladium-catalyzed asymmetric allylic alkylation will provide the same product resulting from an Evans chiral auxiliary approach. To synthesize ester 62, the reaction with benzyl-protected hydroxyacetone and acyl chloride was attempted.

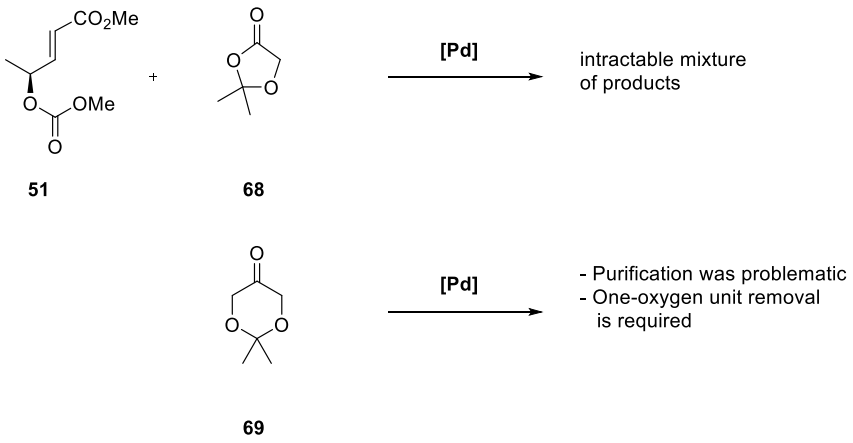


Scheme 16. Allylic Alkylation Using Mixed Allylic Carbonate

From 1,2-propanediol (64), benzyl-protected hydroxyacetone 66 could be synthesized with relatively high yield in 2 steps. On the

other hand, alcohol 51 was reacted with triphosgene to form chloroformate 67, which was used without purification. The reaction of 67 with an enolate of 66, however, led to decomposition

2.2.3. Allylic Alkylation Using Cyclic Pronucleophiles



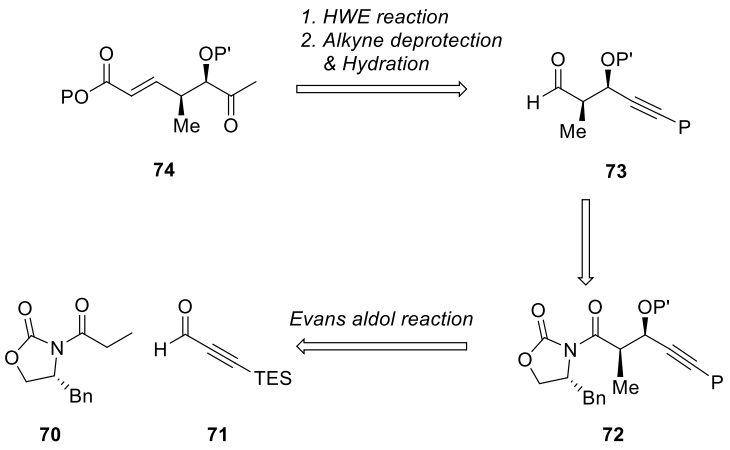
Scheme 17. Reactions with Cyclic Nucleophiles

The diastereoselectivity of the Tsuji-Trost reaction with two stereogenic centers is known to be inclined to anti when the substrate is a linear alkyl system. On the other hand, cyclic enolates tend to give syn allylation. Thus, it was hoped that the allylic alkylation of a cyclic enolate such as 68 and 69 with 51 would form the C-C bond with desired methyl and hydroxyl stereocenters.

Unfortunately, the Tsuji-Trost reaction of **51** with **68** or **69** did not generate the desired allylic alkylation product. In the case of the reaction with **68**, only an intractable mixture of products was formed. While a small amount of the product (< 20%) was produced from the reaction with **69**, purification was problematic. Furthermore, the necessary removal of one-oxygen unit from the product appeared non-promising, negating potential advantages of this approach over the aldol route.

2.3. Aldol reaction

2.3.1. Revised Retrosynthesis for C20-C27 Fragment

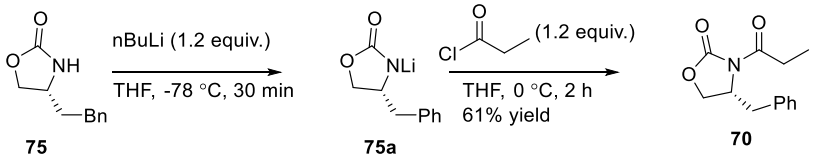


Scheme 18. Retrosynthetic Analysis of the Substrate for Radical Cyclization

An alternative strategy based on an aldol reaction with an alkynal would seem to have advantages. First, an alkyne has lower reactivity compared to a methyl ketone or its ketal-protected form, preventing potential side reactions. Second, in an unpublished result in our laboratory, it was found that the alcohol adjacent to the ketone, protected as a ketal, was not reactive in the Michael reaction with an alkynone, a key step combining two oxacycles in the final stage of the synthesis of the eastern fragment of madeirolide A. In addition, a terminal alkyne can be easily transformed to a methyl ketone through

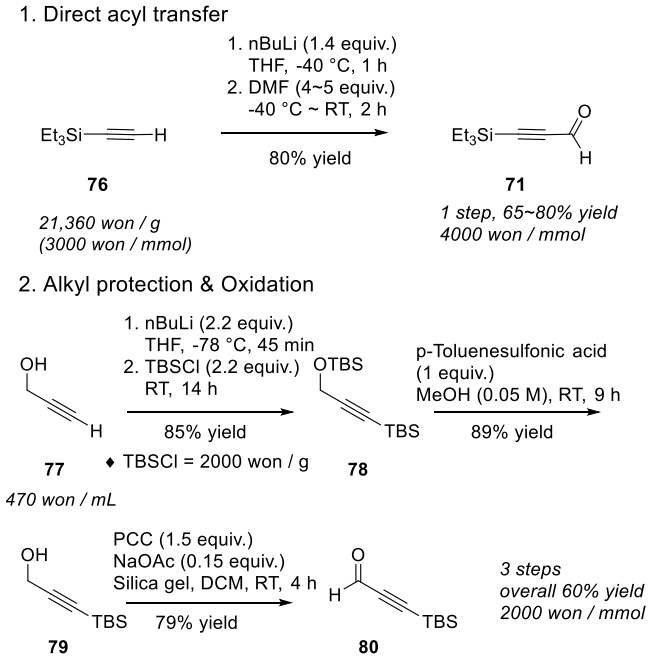
Markovnikov hydration using classical oxymercuration or modern gold or platinum catalyzed reactions. For these reasons, a terminal alkyne seemed to be a good selection as a masked form of a methyl ketone. [17]

2.3.2. Preparation of Aldol Substrates



Scheme 19. Propionylation of Evans chiral auxiliary

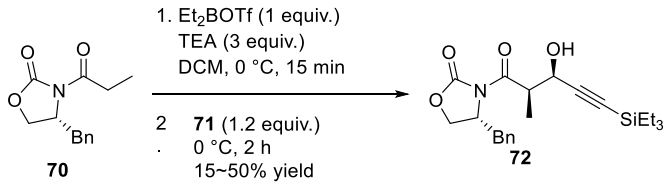
Propionylation of (R)-4-benzyloxazolidin-2-one (75) afforded chiral auxiliary-attached propionate 70. Terminal protected alkynal 71 could be synthesized from trialkylsilylacetylene (76) via acyl transfer, or trialkylsilane-protected propargyl alcohol via oxidation. Although the formylation was more expeditious, the route from propargyl alcohol was more cost-efficient and easier to scale up.



Scheme 20. Two Methods to Synthesize Silyl-protected Ynal

In practice, direct acyl transfer reaction of dimethylformamide with lithiated triethylsilylacetylene gave the desired aldehyde. However, purification was problematic because of an unidentified side product having a R_f value similar to the desired product. Typically, two or three rounds of successive column chromatography were necessary to obtain over 80% of the product cleanly. The sequence involving alkynyl protection of propargyl alcohol (77) and oxidation could be carried out in 60% overall yield. In this route TBS-protected alkynal 80 could be afforded.

2.3.3. Syn-selective Aldol Reaction



Scheme 21. Syn-selective Aldol Reaction

Surprisingly, the aldol reaction between propionamide **70** and silyl-protected aldehyde **71** was somewhat sluggish and not very effective. The yield was not consistent; generally the yield was 15~50%, rather low compared to well-known aldol reaction. The same result was obtained when TBS-protected aldehyde **80** instead of TES-protected aldehyde **71** was used. It was presumed that purity of triethylborane and trifluoromethanesulfonic acid was not sufficiently good for the generation of the Et_2BOTf reagent. In order to pursue the route shown in **Scheme 18**, this aldol reaction must be improved.

CONCLUSION

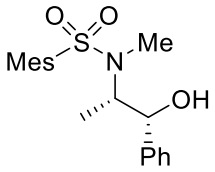
In conclusion, synthetic studies described in this dissertation demonstrate the utility of diastereoselective aldol reactions for the preparation of subunits which are required for the total synthesis of the marine natural product, madeirolide A.

The C1-C10 fragment could be synthesized using radical cyclization as the key step. Further studies starting from lactone **18** would be needed in order to utilize the already prepared fragment. The C20-C27 fragment could be synthesized from an Evans aldol product, but the yield of the reaction should be improved. If the optimization studies proved successful, the subsequent Sharpless asymmetric oxidation would give a *syn*-diol product required for further elaborations. Despite structural similarities to mandelalide A, which have been synthesized several times, madeirolide A has not succumbed to the total synthesis effort. It is hoped that our studies on the syntheses of three fragments will ultimately lead to the first total synthesis of madeirolide A.

EXPERIMENTALS

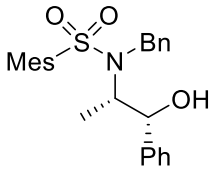
General information. NMR spectra were obtained on an Agilent 400-MR DD2 Magnetic Resonance System (400 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million (δ) relative to tetramethylsilane ($Si(CH_3)_4$) as an internal standard unless otherwise indicated, and coupling constants in Hertz (Hz). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, b = broad. IR spectra were measured on a Thermo Scientific Nicolet 6700 spectrometer. High resolution mass spectra were recorded from the Organic Chemistry Research Center (Seoul) on a Bruker Compact using electrospray ionization (ESI) method. The progress of the reaction was checked on thin layer chromatography (TLC) plates (Merck 5554 Kiesel gel 60 F_{254}), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into a vanillin solution (15.0 g of vanillin and 2.5 mL of concentrated sulfuric acid in 250 mL of ethanol), a potassium permanganate solution (3.0 g of potassium permanganate, 20.0 g of

potassium carbonate, and 5.0 mL of 5% aqueous sodium hydroxide solution in 300 mL of water), a ceric ammonium molybdate solution (0.5 g of ceric ammonium sulfate, 12 g of ammonium molybdate and 15 mL of concentrated sulfuric acid in 235 mL of water). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60). All solvents were obtained by passing through activated alumina columns of solvent purification systems from Glass Contour. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI, Acros, Alfa Aesar, or Samchun Fine Chemicals.



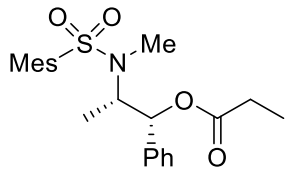
Synthesis of **33**. Ephedrine (4.13 g, 25 mmol) was placed in the dry round-bottom flask and DCM (25 mL) was added. The reaction mixture was cooled to 0 ℃, and TEA (4.88 mL, 35 mmol, 1.4 equiv.) was added dropwise. After 5 minutes, 2-mesitylenesulfonyl chloride (6.02 g, 27.5 mmol, 1.1 equiv.) solution in 25 mL of DCM was added dropwise and stirred 3 hours at the room temperature. After the reaction was completed, the reaction mixture was quenched with 10 mL of water. The mixture was washed successively with 2 M HCl,

water, saturated aqeuous sodium bicarbonate solution, and brine, and dried over anhydrous magnesium sulfate. The filtered organic solution was concentrated to give an oily residue, which was dissolved in small amount of chloroform. To this solution was added n-hexane in portions with swirling to cause crystallization. An additional hexane (300 mL) was added and the crystalline sulfonamide (8.09 g, 93% yield) was isolated by filtration. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (m, 5H), 7.18-7.14 (m, 2H), 6.89 (s, 1H), 4.93 (t, 1H), 3.88 (dq, 1H), 2.86 (s, 3H), 2.51 (s, 6H), 2.28 (s, 3H), 2.00 (d, 1H), 1.15 (d, 3H).

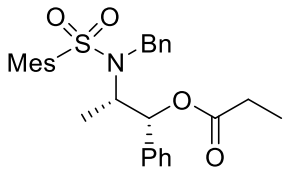


Synthesis of **35**. 2-Mesitylenesulfonyl chloride (2.18 g, 10 mmol) was added to a stirred solution of norephedrine (1.51 g, 10 mmol) and triethylamine (1.67 mL, 12 mmol) in DCM (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was washed successively with 2 M HCl, water, saturated aqueous sodium bicarbonate solution, and brine, and dried over anhydrous sodium sulfate. The filtered organic solution was concentrated to give an oily residue, which was dissolved in small

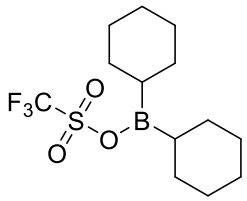
amount of DCM. To this solution was added n-hexane in portions with swirling to cause crystallization. An additional hexane (300 mL) was added and the crystalline sulfonamide (3.14 g) was isolated by filtration. Concentration of the mother liquor and recrystallization gave the small amount of sulfonamide (60 mg, total yield 96%). After transferred to a round-bottom flask, the sulfonamide product **34** was mixed with K_2CO_3 (1.73 g, 12.5 mmol) and benzyl bromide (1.31 mL, 11 mmol) in acetonitrile (40 mL), and the resulting mixture was heated under reflux for 17 h. The cooled mixture was filtered and the salt was washed with diethyl ether 3 times. The organic layers were combined, concentrated, and purified by flash chromatography (Hexane:EtOAc 8:1) to afford alcohol S1 (4.04 g, 9.5 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.16 (m, 8H), 7.12 – 7.05 (m, 2H), 6.92 (s, 2H), 5.01 (br s, 1H), 4.77 (d, J = 16.1 Hz, 1H), 4.54 (d, J = 16.1 Hz, 1H), 3.83 (dq, J = 7.1, 1.9 Hz, 1H), 2.65 (s, 6H), 2.29 (s, 3H), 2.13 (d, -OH, 1H), 1.03 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.6, 142.1, 140.2, 138.6, 133.5, 132.1, 128.6, 128.2, 127.7, 127.4, 127.2, 125.5, 76.7, 59.7, 49.1, 23.0, 20.9, 9.9.



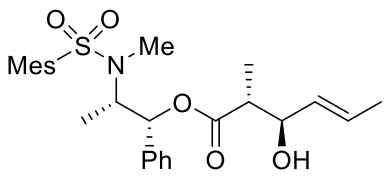
Synthesis of **36**. Into the dry flask, **33** (9.31 g, 26.8 mmol), pyridine (2.8 mL, 35 mmol, 1.3 equiv.), and DCM (100 mL) was added and stirred 10 minutes at 0 ℃. Propionyl chloride (2.58 mL, 29.5 mmol, 1.1 equiv.) was added dropwise in the reaction mixture. After the color turns pale yellow, the reaction mixture was stirred 2 hours more at the room temperature. the mixture was washed successively with 100 mL each of water, 1 M HCl, water, saturated sodium bicarbonate solution, and brine, and dried over anhydrous sodium sulfate. The filtered organic solution was concentrated to give a crystalline residue, which was triturated with hexanes to give ester **36** (10.9 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.21-7.13 (m, 3H), 7.00-6.98 (d, 2H), 6.85 (s, 2H), 5.70 (d, J = 7Hz, 1H), 3.98 (quin, 1H), 2.75 (s, 3H), 2.40 (s, 6H), 2.34 (dq, J = 7Hz, 2H), 2.28 (s, 3H), 1.28 (d, J = 7Hz, 3H), 1.11 (t, J = 7Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 142.3, 140.4, 138.1, 132.2, 131.9, 128.3, 127.9, 126.2, 77.5, 55.5, 28.2, 27.8, 22.6, 20.9, 12.3, 9.0.



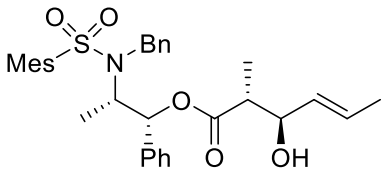
Synthesis of **37**. Propionyl chloride (1.05 mL, 12 mmol) was added dropwise to a solution of the chiral auxiliary **35** (4.60 g, 10.8 mmol) and pyridine (1.13 mL, 14 mmol) in DCM (60 mL) at 0 ℃. After stirred at room temperature for 1 h, the mixture was washed successively with 100 mL each of water, 1 M HCl, water, saturated sodium bicarbonate solution, and brine, and dried over anhydrous sodium sulfate. The filtered organic solution was concentrated to give a crystalline residue, which was triturated with hexanes to give ester **37** (4.97 g, 10.4 mmol, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.12 (m, 8H), 6.93 – 6.89 (m, 2H), 6.86 (s, 2H), 5.83 (d, *J* = 3.9 Hz, 1H), 4.70 (d, *J* = 16.6 Hz, 1H), 4.60 (d, *J* = 16.7 Hz, 1H), 4.03 (dq, *J* = 6.9, 4.0 Hz, 1H), 2.50 (s, 6H), 2.26 (s, 3H), 2.22 – 2.04 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 142.5, 140.2, 138.7, 138.5, 133.3, 132.1, 128.4 (2C), 127.7, 127.3, 127.1, 125.9, 76.7, 56.7, 48.1, 27.4, 23.0, 20.9, 12.7, 8.8.



Synthesis of Boron reagent **38**. An dry round-bottom flask capped with a rubber septum was charged with distilled cyclohexene (11.2 mL, 126 mmol) and anhydrous hexane (30 mL) and kept at 0 ℃ under nitrogen. Borane-dimethyl sulfide complex (5 mL, 60 mmol) was added slowly during 45 minutes with stirring, and then the whole reaction mixture was stirred for 3 h at 0 ℃. After the hydroboration reaction, trifluoromethanesulfonic acid (4.8 mL, 60 mmol) was added via syringe with one portion and stirred 30 minutes at 60 ℃, and the reaction mixture was left for 30 minutes with stirring. Two layers appeared, and the top layer was transferred into a dry round-bottom storage flask via cannula and cooled to -20 ℃. After the solid appeared, supernatant liquid was displaced and the solid was weighed. The solid was dissolved with dry hexane solution for aldol reaction.

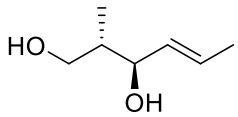


Synthesis of aldol product **39**. To the 500mL round-bottom flask, **36** (3.63 g, 9 mmol) and DCM (40 mL), TEA (3.1 mL, 2.4 equiv.) was added and cooled to -78 ℃. After 5 minutes, **38** (0.5 M solution in hexane, 36 mL. 18 mmol, 2 equiv.) was added in three portion and stirred 2 hours at -78 ℃. After that crotonaldehyde (1 mL, 1.3 equiv.) was added dropwise and stirred 1 hour at -78 ℃, another an hour at the room temperature. the reaction mixture was quenched by addition of pH 7 buffer solution (0.1 M phosphate buffer, 40 mL) and hydrogen peroxide (34.5% aqueous solution, 15 mL), and was diluted with methanol (100 mL). The residue was partitioned between water and DCM, and the aqueous layer was extracted with DCM 3 times. The combined organic layers were washed with water and brine, and dried over with sodium sulfate. The filtered organic solution was concentrated and purified. Flash chromatography (Hexane:EtOAc 4:1) afforded a mixture of product **39** (3.23 g) and cyclohexanol (0.48 g). 0.54 g of starting material was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.21-7.13 (m, 3H), 7.00-6.98 (d, J = 7.5Hz, 2H), 6.85 (s, 2H), 5.75 (d, J = 5Hz, 1H), 5.67 (q, J = 10Hz, 1H), 5.40 (dq, 1H), 4.10 (q, 1H), 3.99 (quin, 1H), 2.76 (s, 3H), 2.55 (quin, 1H), 2.41 (m, 6H), 2.27 (s, 3H), 1.68 (d, J = 7Hz, 3H), 1.55 (s, 2H), 1.28 (d, J = 7Hz, 3H), 1.06 (d, J = 8.5Hz, 3H).



Synthesis of **40**. Into a flame-dried round-bottom flask were placed ester **37** (1.30 g, 2.7 mmol), triethylamine (0.75 mL, 6.5 mmol) and DCM (13.5 mL) under nitrogen. The solution was cooled to -78 °C and a solution of dicyclohexylboron trifluoromethanesulfonate (0.9 M in hexane, 6 mL, 5.4 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 2 h, after which crotonaldehyde (0.28 mL, 3.3 mmol) was slowly added over 1 h. After stirred at -78 °C for 1 h, warmed to room temperature over 1 h, the reaction mixture was quenched by addition of pH 7 buffer solution (10 mL) and hydrogen peroxide (34.5% aqueous solution, 4 mL), and was diluted with methanol (25 mL). The whole mixture was stirred overnight and concentrated. The residue was partitioned between water and DCM, and the aqueous layer was extracted with DCM 3 times. The combined organic layers were washed with water and brine, and dried over with sodium sulfate. The filtered organic solution was concentrated. Flash chromatography (Hexane-EtOAc 20:1) gave aldol **40** (1.22 g, 2.2 mmol, 83%) as sticky, colorless oil. 160 mg (0.33

mmol) of starting material was recovered. $[\alpha]_d^{20}$ = 28.0 (c 1.25, $CHCl_3$); IR (neat) 3519, 3028, 2981, 2938, 1738, 1604, 1454, 1496, 1379, 1321, 1206, 1152, 1055, 1013, 967, 929, 858, 758, 730, 699, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 8H), 6.89 (s, 2H), 6.83 (d, *J* = 7.9 Hz, 2H), 5.81 (d, *J* = 4.0 Hz, 1H), 5.78 – 5.65 (m, 1H), 5.42 (ddd, *J* = 15.2, 7.5, 1.2 Hz, 1H), 4.80 (d, *J* = 16.6 Hz, 1H), 4.57 (d, *J* = 16.6 Hz, 1H), 4.16 – 4.02 (m, 2H), 2.51 (s, 6H), 2.49 – 2.44 (m, 1H), 2.29 (s, 3H), 1.69 (d, *J* = 6.5 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 142.7, 140.4, 138.8, 138.4, 133.6, 132.3, 131.1, 129.6, 128.5, 128.5, 128.0, 127.7, 127.3, 126.0, 78.4, 75.0, 56.9, 48.4, 45.8, 23.1, 21.0, 17.9, 14.2, 13.5; HRMS (ESI) m/z calc. for $[C_{32}H_{39}NO_5S+Na]$: 572.2447, found: 572.2441



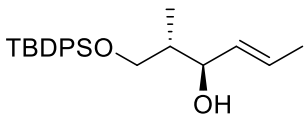
Synthesis of **41**.

A) Reduction with $LiAlH_4$. $LiAlH_4$ (70 mg, 1.8 mmol) and THF (10 mL) were added to a dry round-bottom flask equipped with a magnetic stirring bar. The mixture was cooled to 0 °C and stirred for 10 min.

To this suspension was added dropwise a THF solution (5 mL) of aldol **40** (830 mg, 1.5 mmol). After stirring was continued at room temperature for 1 h, the reaction mixture was quenched with aqueous solution of Rochelle salt (saturated, 60 mL) and stirred overnight. The resulting slurry was partitioned between water and Et_2O, and the aqueous layer was extracted 5 times with Et_2O. The combined organics were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (Hexane:EtOAc 5:1 -> 1:1) provided diol **13** (176 mg, 90% yield) as a colorless liquid.

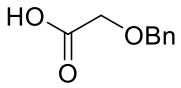
B) Reduction with $LiBH_4$. Into the dry round-bottom flask, aldol product **40** (3.3 g, 6 mmol) and THF (60 mL) was added and stirred 15 minutes at 0 ℃. To this solution was added dropwise a $LiBH_4$ (2M in tetrahydrofuran, 6.6 mL, 13.2 mmol, 2.2 equiv.). After an hour stirring, the mixture was quenched with 5 mL of water, and separated with water/diethyl ether. The aqueous phase was extracted 5 times with diethyl ether. The combined organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated, and the crude product was mixed with methanol (10 mL) and concentrated to remove borane from the diol. After that it was purified via column chromatography (Hexane:EtOAc 5:1 -> 1:1) to afford the pure diol product **41** (672 mg, 86% yield) as colorless liquid.

R_f 0.06 (hexane–EtOAc, 2:1); $[\alpha]_d^{20}$ = + 9.27 (c 1.0, $CHCl_3$); IR (neat, ν_{max}) 3355, 2961, 2881, 1672, 1450, 1378, 1333, 1261, 1082, 1007, 967, 927, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (dt, *J* = 15.6, 6.3 Hz, 1H), 5.47 (dd, *J* = 15.2, 7.7 Hz, 1H), 3.91 (td, *J* = 7.9, 2.3 Hz, 1H), 3.70 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.58 (dd, *J* = 11.0, 7.6 Hz, 1H), 3.31 (br s, 1H), 3.08 (br s, 1H), 1.83 – 1.72 (m, 1H), 1.69 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 132.8, 128.3, 79.0, 67.6, 40.1, 17.7, 13.5; HRMS (ESI) m/z calc. for $[C_7H_{14}O_2+Na]$: 153.0891, found: 153.0886.



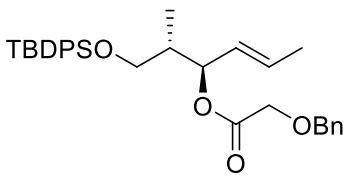
Synthesis of **14**. TBDPSCl (1.7 mL, 6.6 mmol) was added to a solution of diol **41** (783 mg, 6.0 mmol) and imidazole (531mg, 7.8 mmol) in DCM (60 mL) at 0 °C. After stirring for 1 h, the reaction mixture was partitioned with water and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (Hexane:EtOAc 20:1) provided alcohol 14 (2.25 g, 98%) as a colorless liquid. R_f 0.44 (hexane:EtOAc 5:1) $[\alpha]_d^{20}$ = + 15.96 (c 1.0, $CHCl_3$); IR (neat, ν_{max}) 3443, 3071, 2959,

2931, 2858, 1471, 1428, 1390, 1362, 1188, 1111, 1007, 967, 928, 863, 823, 741, 702, 613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.61 (m, 4H), 7.56 – 7.31 (m, 6H), 5.73 (dq, *J* = 15.1, 6.4 Hz, 1H), 5.50 (dd, *J* = 15.3, 7.3 Hz, 1H), 4.06 (t, *J* = 7.2 Hz, 1H), 3.79 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.63 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.6 (s, 1H), 1.84 (ddd, *J* = 14.3, 7.2, 4.2 Hz, 1H), 1.73 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H), 0.81 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 135.7, 134.9, 133.0, 132.7, 129.9, 127.9, 127.8, 77.8, 68.7, 40.3, 26.9, 19.2, 17.9, 13.5; HRMS (ESI) m/z calc. for $[C_{23}H_{32}O_2Si+Na]$: 391.2069, found: 391.2064.



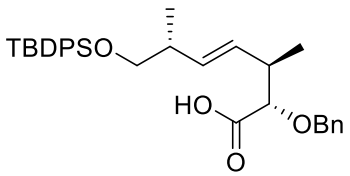
Synthesis of **15**. Benzyl alcohol (4.31 mL, 41.6 mmol, 2 equiv.) was added to a suspension of NaH (60% dispersion in mineral oil, 3.2 g, 80 mmol, 4 equiv.) in THF (80 mL) at 0 °C. After the gas evolution ceased (ca. 5 min), a solution of bromoacetic acid (2.89 g, 20.8 mmol) in THF (10 mL) was added dropwise and the resulting mixture was heated under reflux for overnight. The reaction mixture was cooled to room temperature, quenched with water, and partitioned with saturated NaHCO3 solution and EtOAc. The aqueous layer was

washed away with EtOAc (2 times), and 12 N HCl was added to acidify the aqueous phase (pH < 4). The aqueous layer was extracted with EtOAc (3 times) and the combined organics were dried over Na_2SO_4 and filtered. Concentration gave acid **15** (3.37g, 98% yield) as a yellow liquid. R_f 0.12 (hexane:EtOAc:AcOH, 80:20:1); ^1H NMR (400 MHz, $CDCl_3$): δ 9.74 (br s, 1H), 7.41-7.32 (m, 5H), 4.67 (s, 2H), 4.17 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.9, 136.6, 128.6, 128.2, 128.1, 73.4, 66.5.



Synthesis of **16**. A suspension of EDAC·HCl (1.07 g, 5.6 mmol) in DCM (5 mL) was added to a mixture of alcohol **14** (1.48 g, 4.0 mmol), acid **15** (800 mg, 4.8 mmol), DMAP (48 mg, 0.4 mmol) and DCM (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 13 h, poured into water and extracted with EtOAc. The organic layers were washed with saturated $NaHCO_3$ solution 3 times, saturated NH_4Cl solution 2 times, and brine once, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (Hexane:EtOAc 15:1)

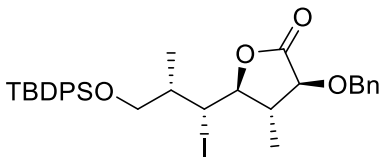
provided ester 9 (1.98 g, 93%) as a colorless liquid. R_f 0.60 (Hexane:EtOAc 5:1); $[\alpha]_d^{20}$ = +3.52 (c 1.0, $CHCl_3$); IR (neat, ν_{max}) 3069, 2960, 2932, 2858, 1752, 1471, 1428, 1390, 1262, 1198, 1112, 1028, 967, 823, 741, 702, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 4H), 7.43 – 7.29 (m, 11H), 5.83 – 5.72 (m, 1H), 5.46 – 5.32 (m, 2H), 4.58 (s, 2H), 3.99 (s, 2H), 3.53 (d, *J* = 5.6 Hz, 2H), 2.04 – 1.95 (m, 1H), 1.68 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.06 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.4, 135.6, 131.2, 129.6, 128.4, 128.0, 127.6, 126.8, 77.3, 73.2, 67.3, 65.0, 39.5, 26.8, 19.2, 17.8, 12.6; HRMS (ESI) m/z calc. for [$C_{32}H_{40}O_4Si$+ Na]: 539.2594, found: 539.2588.



Synthesis of carboxylic acid **17**. Freshly distilled TMSCl (0.29 mL, 2.3 mmol) was added to a solution of ester **16** (300 mg, 0.58 mmol) in THF (15 mL) at −78 °C. After stirring at −78 °C for 20 min, KHMDS (0.5 M in toluene, 1.2 mL, 2.3 mmol) was added dropwise. After stirring at −78 °C for 30 min, the reaction mixture was allowed to warm up to room temperature and stirred for additional 2 h, after

which it was poured into a 1:1 mixture of saturated aqueous NH_4Cl and 1 M HCl solutions. After extraction with EtOAc (3 times), the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide crude acid **16** (305 mg) as yellowish sticky oil.

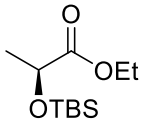
$[\alpha]_d^{20}$ = −10.34 (c 1.0, $CHCl_3$); IR (neat, ν_{max}) 3030, 2958, 2930, 2857, 1717, 1589, 1567, 1458, 1427, 1387, 1214, 1111, 1027, 1027, 972, 939, 823, 739, 702, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.65 (m, 4H), 7.43 – 7.29 (m, 11H), 5.53 – 5.42 (m, 2H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 3.88 (d, *J* = 4 Hz, 1H), 3.54 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.46 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.41 – 2.31 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 137.0, 137.0, 135.8, 134.5, 134.4, 134.1, 130.5, 130.5, 129.7, 128.6, 128.3, 128.3, 128.2, 127.7, 82.1, 73.4, 68.8, 40.0, 39.3, 27.0, 19.5, 16.8, 15.1.; HRMS (ESI) m/z calc. for $[C_{32}H_{40}O_4Si+Na]$: 539.2594, found: 539.2589.



Synthesis of iodolactone **18**. The crude acid **17** was dissolved in acetonitrile (10 mL) and mixed with sodium bicarbonate (487 mg, 5.8 mmol). To this solution cooled to −40 °C was added dropwise a MeCN solution (10 mL) of iodine (589 mg, 2.3 mmol). After stirring at −40 °C for 24 h, the reaction mixture was diluted with Et_2O and quenched by addition of saturated $Na_2S_2O_3$ solution. The mixture was extracted with ether (3 times) and the combined organic extracts were washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (Hexane:EtOAc 10:1) provided an inseparable diastereomeric mixture (dr = 9:1) of iodide 17 (321 mg, 85%) as a colorless liquid.

R_f 0.55 (hexane–EtOAc, 5:1); $[\alpha]_d^{20}$ = −35.57 (c 1.0, $CHCl_3$); IR (neat, ν_{max}) 3069, 2959, 2931, 2858, 1786, 1589, 1459, 1427, 1388, 1324, 1183, 1107, 979, 824, 807, 741, 700, 639, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.58 (m, 4H), 7.58 – 7.27 (m, 11H), 4.94 (d, *J* = 12.1 Hz, 1H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.36 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.73 (d, *J* = 4.8 Hz, 1H), 3.51 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.38 (t, *J* = 9.7 Hz, 1H), 2.71 – 2.36 (m, 1H), 1.84 – 1.50 (m, 1H), 1.25 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 9H), 0.79 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 136.9, 135.8, 135.6, 133.4(2C), 129.9, 129.8, 128.7,

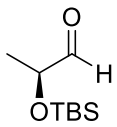
128.4, 128.3, 127.9, 127.8, 85.6, 79.3, 72.3, 68.1, 43.7, 42.5, 36.3, 26.9, 19.3, 17.9, 13.6; HRMS (ESI) m/z calc. for [$C_{32}H_{39}IO_4Si$+ Na]: 665.1560, found: 665.1555.



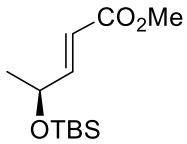
(Ester form)

Synthesis of **55**. (S)-ethyl lactate (2.85 mL, 25 mmol), tert-butyldimethylchlorosilane (TBSCl, 3.77 g, 25 mmol, 1.0 equiv.) and imidazole (2.04 g, 30 mmol, 1.2 equiv.) was added. The reaction mixture was dissolved in dichloromethane, and stirred 24 hours at the room temperature. After the reaction was completed, the reaction mixture was partitioned with sat. NH_4Cl (aq) / DCM. The aqueous layer was extracted 3 times with DCM, and the combined organic layer was washed with brine 2 times. The organic solvents were evaporated after the solution was dried with sodium sulfate and filtered. The column chromatography (Hexane:EtOAc = 50:1) gave the pure, colorless liquid **55** (5.06 g, 21.7 mmol, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 6.5 Hz, 1H), 4.09 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 8.0 Hz, 3H), 0.82 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 68.3, 60.6, 31.5, 25.6 (2C), 22.6, 21.1, 18.2, 14.1, -

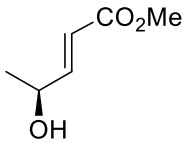
5.2.



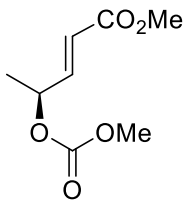
Synthesis of **56**. Ester **55** (2.1 g, 9 mmol) was added into the flame-dried round-bottomed flask, and dissolved in hexane (50 mL). The solution was put into the dry ice-acetone bath (-78 ℃) and stirred 30 minutes. After that diisobutylaluminum hydride (10 mL, 1M solution in heptane, 10 mL, 1.1 equiv.) was added slowly over 10 minutes, and stirred 50 minutes. After the reaction was completed, the reaction mixture was warmed to 0 ℃, and 0.7 mL of sodium hydroxide (2N in water) was added to precipitate the aluminum slurry, and dried with magnesium sulfate and stirred 30 minutes at room temperature. After that the reaction mixture was filtered through sintered filter glass. The organic phase was concentrated to give transparent liquid product **56** (1.382 g, 7.33 mmol, 82% yield). Without further purification the product was used to the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 4.08 (dd, J = 7.0, 1.3 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H), 0.90 (s, 9H), 0.08 (d, J = 4.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 74.0, 25.9, 18.3, -4.6.



Synthesis of **57**. Aldehyde **56** (1.07 g, 5.7 mmol) was dissolved in acetonitrile. In the dry round-bottomed flask, lithium chloride (288.3 mg, 6.8 mmol, 1.2 equiv.) was added, and dissolved in acetonitrile (57 mL). After that methyl diethyl phosphonoacetate (1.3 mL, 6.8 mmol, 1.2 equiv.) and TEA (0.81 mL, 5.8 mmol, 1.02 equiv.) was added and stirred 15 minutes at the room temperature before the aldehyde solution was added, and stirred 12 hours at the room temperature. After the reaction was completed, the reaction mixture was quenched with sat. NH_4Cl (aq.), and partitioned with diethyl ether/water. The combined organic solution was dried with sodium sulfate, and filtered. Concentration of the filtrate gave the crude mixture. Column chromatography (Hexane:EtOAc = 50:1) gave the pure product **57**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, J = 15.6, 4.0 Hz, 1H), 5.98 (dd, J = 15.4, 1.5 Hz, 1H), 4.44 (m, 1H), 3.72 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 152.2, 118.5, 67.6, 51.4, 25.8, 23.5, 18.2, -5.0.



Synthesis of **49**. Enoate **57** (236.5 mg, 0.97 mmol) was added in the dry round-bottomed flask, and THF (2.5 mL) was added and stirred at the room temperature. TBAF (2.5 mL, 1M in THF, 2.5 mmol, 2.5 equiv.) was added, and stirred 10 minutes. After the reaction was completed the reaction mixture was partitioned with EtOAc/ H_2O. The aqueous layer was extracted with EtOAc 3 times. The combined organic phase was dried with sodium sulfate and concentrated *in vacuo* to give crude product. Column chromatography (Hexane:EtOAc = 4:1) gave the purified product of alcohol **49**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, J = 15.6, 4.8 Hz, 1H), 6.02 (dd, J = 15.6, 1.5 Hz, 1H), 4.50 (m, 1H), 3.73 (s, 3H), 1.32(d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 151.4, 119.2, 66.8, 51.7, 22.4.

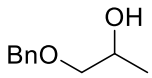


Synthesis of **50**. Chiral alcohol **49** (90 mg, 0.7 mmol) was added in the dry round-bottomed flask, and 7mL of DCM was added. Pyridine

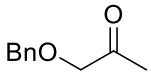
(0.11 mL, 1.4 mmol, 2 equiv.) was added, and finally methyl chloroformate (1.05 mmol, 0.08 mL, 1.5 equiv.) was injected. After 3 hours, when the solution turns transparent with white precipitate, the reaction mixture was partitioned with EtOAc/H_2O, The aqueous layer was extracted with EtOAc 3 times. The combined organic phase was dried with sodium sulfate and concentrated in vacuo to give crude product. Column chromatography (Hexane:EtOAc = 10:1) gave the carbonate **50** (22 mg, 21% yield) and starting material **32** (63 mg, 70% recovered). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (ddd, *J* = 15.6, 4.9, 2.0 Hz, 1H), 6.02 (dd, *J* = 15.2, 3.7 Hz, 1H), 5.35 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 1.43 (dd, *J* = 6.8, 2.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 154.8, 145.7, 121.0, 72.8, 54.9, 51.8, 19.7.

Palladium metal catalysis of **50**. In the dry flask, $Pd_2(dba)_3$ (15 mg, 0.005 mmol, 10 mol %) and **50** was added and diluted with THF(1 mL). And, in separate round-bottom flask, sodium hydride (48 mg, 60% in mineral oil, 50 mol %) and diethyl malonate (0.13 mL, 1.2 mmol) was added. After 5 minutes, a quarter portion of the diethyl malonate part was added to palladium flask. The reaction mixture was stirred 48 hours at the room temperature. The reaction mixture was diluted with DCM and separated with DCM/water. The aqueous phase was

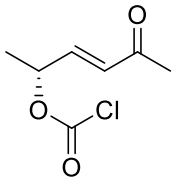
extracted with DCM 3 times, and the combined organic mixture was washed with brine. Separated organic layer was dried with magnesium sulfate. Filtering and concentration of the solution gave the crude product.



Synthesis of **64**. To a suspension of sodium hydride (60 wt% in mineral oil, 1.05 g, 26 mmol) in THF (125 mL) was added 1,2-propanediol (5.5 mL, 75 mmol, 3 equiv.) dropwise at 0 ℃. The solution was stirred for 5 minutes at room temperature. To the solution was added benzyl bromide (3.0 mL, 25 mmol) and the reaction mixture was refluxed for an hour. The reaction mixture was quenched with sat. NH4Cl (aq.) at 0 ℃, and the organic layer was separated and aqueous layer was extracted with diethyl ether twice. The combined organic layer was washed with brine and dried over magnesium sulfate before filtered. The solvent was evaporated in vacuo to give the crude product. This crude product was used without purification.

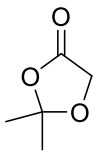


Synthesis of **65**. To a solution of oxalyl chloride (1.3 mL, 15 mmol, 1.5 equiv.) in DCM (50 mL) was added DMSO (1.42 mL, 20 mmol, 2 equiv.) at -78 ℃. The solution was stirred for 15 minutes at that temperature. To the solution was added the obtained crude **64** (1.66 g, 10 mmol) dropwise and the solution was stirred for 45 minutes at -78 ℃. Then TEA (5.6 mL, 40 mmol, 4 equiv.) was added and the reaction mixture was stirred for 20 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes. The reaction mixture was quenched with sat. $NaHCO_3$ (aq.) and organic layer was separated. The aqueous layer was extracted with DCM twice. The combined organic layer was washed with sat. NH_4Cl (aq.) and brine, and dried over magnesium sulfate before filtered. The solvent was evaporated in vacuo to give the crude product. Purification via flash chromatography (Hexane:EtOAc 5:1) gave the purified ketone **65** (1.41 g, 86% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 4H), 7.35-7.30 (m, 1H), 4.61 (s, 2H), 4.07 (s, 2H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 137.2, 128.4 (2C), 128.0, 127.8 (2C), 75.2, 73.2, 26.3.

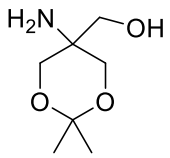


Synthesis of **66**. The solution of pyridine (0.06 mL, 0.74 mmol, 1.1 equiv.) in DCM (1.9 mL) was added dropwise to a stirred solution of triphosgene (67 mg, 0.225 mmol, 0.33 equiv.) and **51** (88 mg, 0.67 mmol) at 0 ℃ under nitrogen atmosphere and stirred 30 minutes at room temperature. The reaction mixture was used to reaction between **65** and **66** directly without any purification process.

Reaction between **65** and **66**. To a solution of 61 (64.4 mg, 0.37 mmol, 1.1 equiv.) in THF (3.3 mL), sodium hydride (60 wt% in mineral oil, 18 mg, 0.43 mmol, 1.3 equiv.) was added and the mixture was stirred at 0 ℃ for 5 minutes, followed by addition of **62** (58.5 mg, 0.33 mmol). The reaction was warmed to room temperature and stirred an hour.

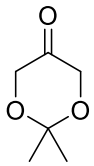


Synthesis of **67**. A suspension of P_2O_5 (1.42 g, 10 mmol) in Et_2O (4 mL) was cooled to -18 ℃, and 0℃ solution of glycolic acid (379 mg, 5 mmol) in acetone (2.85 mL, 39 mmol, 7.8 equiv.) was added dropwise with vigorous stirring. When the P_2O_5 formed a lump, it was kneaded with a spatula. The resulting solution was filtered via short celite pad. Orange, sticky sediment was washed with diethyl ether exhaustively. Concentration of the combined organic phase gave crude product of 61.

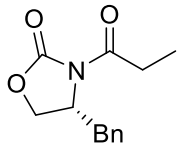


Synthesis of **S1**. Trizma™ hydrochloride (Tris(hydroxymethyl)aminomethane hydrochloride, 1.89 g, 12 mmol) and p-Toluenesulfonic acid monohydrate (0.18 g, 0.6 mmol, 5 mol %) was added to round-bottom flask equipped with magnetic stirring bar. After 10 minutes of stirring, 2,2-dimethoxypropane (1.62 mL, 13.2 mmol, 1.1 equiv.) was added dropwise and stirred 24 hours at the room temperature. After that 0.5 mL of TEA was added and stirred 10 minutes, and allowed to be concentrated in vacuo. The crude product was dissolved in 50 mL of ethyl acetate, and 1.5 mL of triethylamine

was added dropwise to crystallization of the aminoalcohol product **S1**.

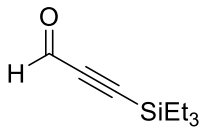


Synthesis of **68**. To a 0 ℃ solution containing **S1** (2.00 g, 12 mmol) and KH_2PO_4 (1.633 g, 12 mmol, 1.0 equiv.) in water (20 mL) was added slowly sodium periodate (2.567 g, 12 mmol, 1.0 equiv.) in water (17.5 mL) over 2 hours and stirred 2 hours at 0 ℃, and overnight at the room temperature. After the reaction was completed, sodium thiosulfate (1.89 g, 12 mmol) was added to the reaction mixture and stirred 15 minutes. The reaction mixture was extracted with dichloromethane 5 times and dried over magnesium sulfate before filtered. The filtrate was concentrated to yield a relatively pure ketone **58**. This molecule was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (s, 4H), 1.45 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 100.0, 66.7(2C), 23.4 (2C).



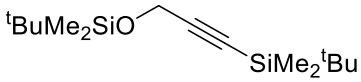
Synthesis of **69**. Into a dried, round-bottom flask equipped with magnetic stirrer was placed 3.8 g (22 mmol) of (R)-4-benzyloxazolidin-2-one. The flask was charged with dry tetrahydrofuran (35 mL). The stirred solution was cooled to -78 ℃, and n-BuLi (1.6 M in hexane, 15.8 mL, 25.3 mmol, 1.15 equiv.) was added dropwise. After the solution was stirred for an hour at -78 ℃, propionyl chloride (2.9 mL, 33 mmol, 1.5 equiv.) was added to the flask and the reaction mixture was warmed to 0 ℃ and stirred for an additional hour. After the addition of 10 mL of water, the mixture was separated with water, and the aqueous phase was extracted with dichloromethane 3 times. The organics extracts were combined, washed with saturated sodium bicarbonate aqueous solution and brine, dried over sodium sulfate and filtered. The filtrate was concentrated and purified via flash chromatography to yield 5.03 g (98% yield) of pure, oily product. Exhaustive solvent removal with high vacuum (~1 mmHg, 24 hours) gave white crystal of the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 4.71-4.64 (dddd, J = 6.8, 4.9, 3.4, 2.8 Hz, 1H), 4.24-4.15 (m, 2H), 3.31 (dd, J = 13.3, 3.5 Hz), 3.00 (dq, J = 17.9, 7.6 Hz, 1H), 2.93 (dq, J = 17.9, 7.3 Hz, 1H), 2.77 (dd, J = 13.9, 10.3 Hz,

1H), 1.21 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 135.3, 129.4, 128.9, 127.3, 66.2, 55.1, 37.9, 29.2, 8.3.

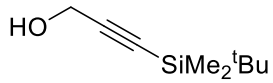


Synthesis of **70**. To the dry round-bottom flask, triethylsilylacetylene (2.5 mL, 13.7 mmol) solution of THF (60 mL) was added and cooled to -40 ℃. After 15 minutes n-BuLi (1.6 M in hexane, 12 mL, 19.2 mmol, 1.4 equiv.) was added dropwise and stirred 1 hours at that temperature. After that dimethylformamide (5.4 mL, 69 mmol, 5 equiv.) was added dropwise. The reaction was completed after 45 minutes of stirring at 0 ℃ and another 90 minutes of stirring at the room temperature. The reaction mixture was separated with saturated ammonium chloride solution. The aqueous phase was extracted with diethyl ether two times, and the combined organic phase was washed with saturated ammonium chloride, saturated sodium bicarbonate, water and brine. The organic solution was dried over sodium sulfate and filtered. Concentration of the filtrate gave the crude product, and three flash chromatography (Hexane:EtOAc 1:0 -> 100:1) gave 1.87 g (80 %) of pure product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H),

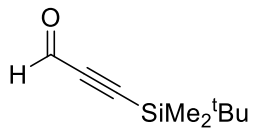
1.02 (t, J = 8.0 Hz, 9H), 0.70 (q, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 103.5, 101.3, 7.2 (3C), 3.7(3C).



Synthesis of **77**. To a round-bottom flask, propargyl alcohol (0.17 mL. 3 mmol) and THF (24 mL) was added, and the reaction mixture was cooled to -78 ℃. After 10 minutes n-BuLi (1.6 M in hexane, 4.5 mL, 7.2 mmol, 2.4 equiv.) was added dropwise and stirred 45 minutes. After that TBSCl (1.085 g, 7.2 mmol, 2.4 equiv.) dissolved in THF (6 mL) was added via syringe, the reaction mixture was warmed to the room temperature, and stirred overnight. The reaction mixture was quenched with 5 mL of water, and it was diluted with diethyl ether and separated with water. The organic phase was washed with saturated ammonium chloride and brine, and it was dried over magnesium sulfate. Concentrated crude product was purified via flash chromatography (Hexane:EtOAc 1:0 -> 100:1) to obtain 712.4 mg (2.50 mmol, 83 %) of pure product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, J = 1.5 Hz, 2H), 0.93 (s, 9H), 0.92 (s, 9H), 0.12 (s, 6H), 0.11 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 26.0, 25.7, 18.3, 16.5, -4.8, -5.1.



Synthesis of **78**. To a round-bottom flask, 72 (712.4 mg, 2.50 mmol) and p-toluenesulfonic acid monohydrate (476 mg, 2.50 mmol) was added and was dissolved in methanol (50 mL). The reaction mixture was stirred 9 hours at the room temperature. After the reaction completed, the solvent was concentrated, and the crude product was purified via flash chromatography (Hexane:EtOAc 10:1) to obtain 378 mg (2.2 mmol, 89 %) of pure product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (d, J = 5.0 Hz, 2H), 1.60 (broad s, 1H), 0.94 (s, 9H), 0.12 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.4, 88.9, 51.7, 25.9, 16.8, -4.7.



Synthesis of **79**. To a round-bottom flask, 73 (378 mg, 2.2 mmol), pyridinium chlorochromate (711.4 mg, 3.3 mmol, 1.5 equiv.), sodium acetate (27 mg, 0.33 mmol, 0.15 equiv.), silica gel (0.66 g) and DCM (4.5 mL) were added. The reaction mixture was stirred 3 hours at the room temperature. After the reaction completed, the reaction mixture

was filtered to a short silica pad, and the filtrate was re-filtered to new silica pad. The reaction mixture was separated with water and the aqueous phase was washed 2 times with DCM. The combined organic phase was washed with saturated sodium bicarbonate, saturated ammonium chloride and brine. The organic solution was dried over sodium sulfate, and filtered. Concentrated product was purified via flash chromatography (Hexane:EtOAc 100:1 -> 20:1) to obtain 292 mg (1.73 mmol, 79 %) of pure product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 4.28 (d, J = 5.0 Hz, 2H), 0.98 (s, 9H), 0.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 103.0, 101.9, 25.9, 16.5, -5.3.

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국문 초록

마데이롤라이드 에이는 레이오더마티움 속의 해면동물로부터 추출된 천연물로 균류에 대해 생장 억제 효과를 보이는 물질이다. 이 물질은 24개의 원자로 구성된 거대 락톤 고리를 포함하는 복잡한 구조를 갖는다. 이러한 생활성과 구조적 복잡성을 가진 마데이롤라이드 에이는 전합성에 도전하기에 가치가 높다고 여겨진다.

복잡한 천연물인 마데이롤라이드 에이를 합성하기 위해 이 분자를 네 개의 부분 구조로 나누어 합성을 수행할 계획이다. 또한, 분자 내에 존재하는 테트라하이드로파이란 및 테트라하이드로퓨란 고리를 이리듐 광촉매를 활용하여 본 연구실에서 개발된 환원적 고리화 반응으로 합성하기 위한 전략을 수립하였다. 이 논문에서는 마데이롤라이드 에이를 합성하기 위해 해당 천연물의 C1-C10 부분구조와 C20-27 부분구조를 합성하는 방법에 대해 기술하였다.

주요어: 마데이롤라이드 에이, 전합성, 광촉매 반응, 알돌 반응, 아일랜드-클라이젠 재배열 반응, 츠지-트로스트 반응

학번: 2014 - 22399

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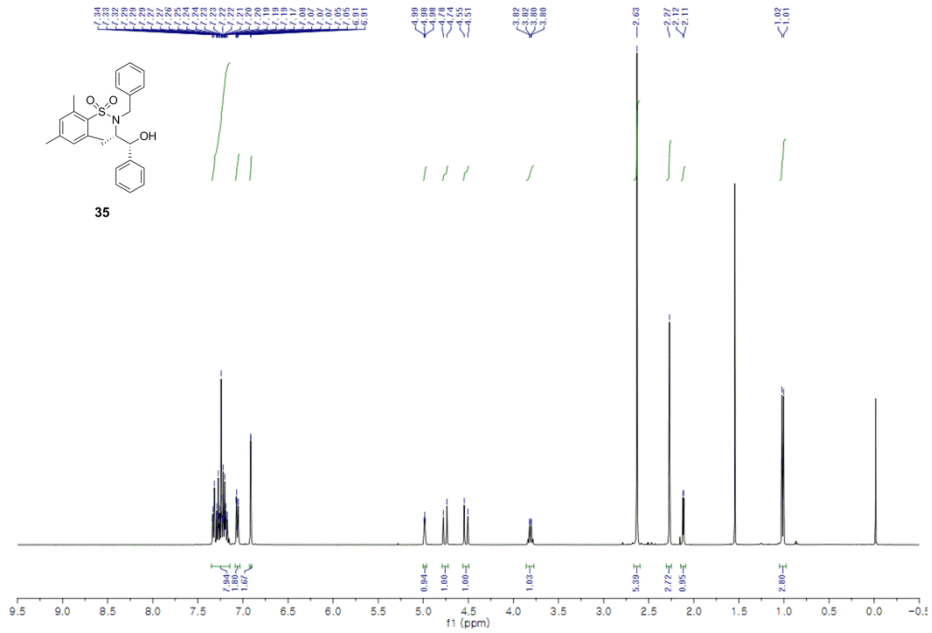
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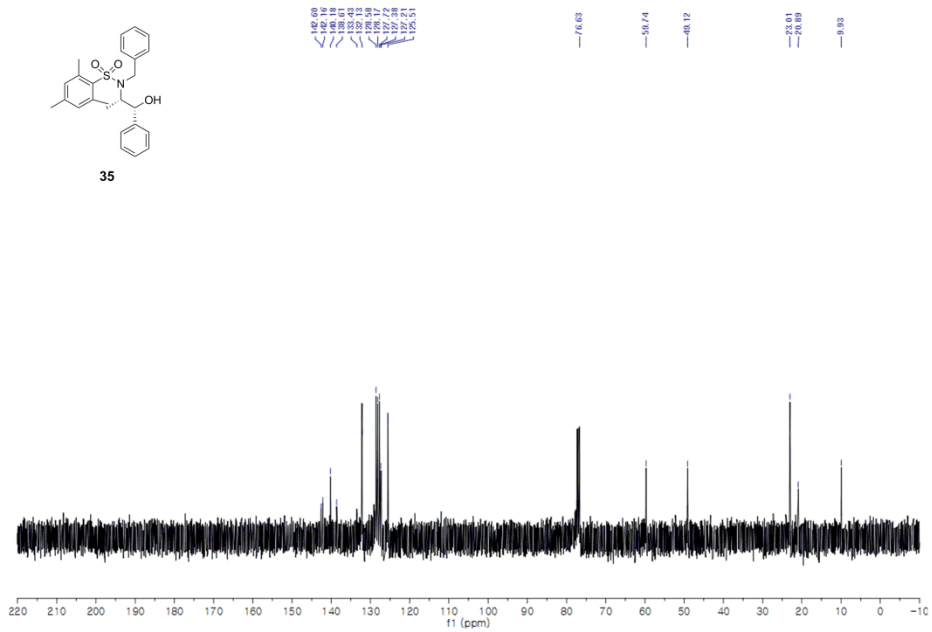
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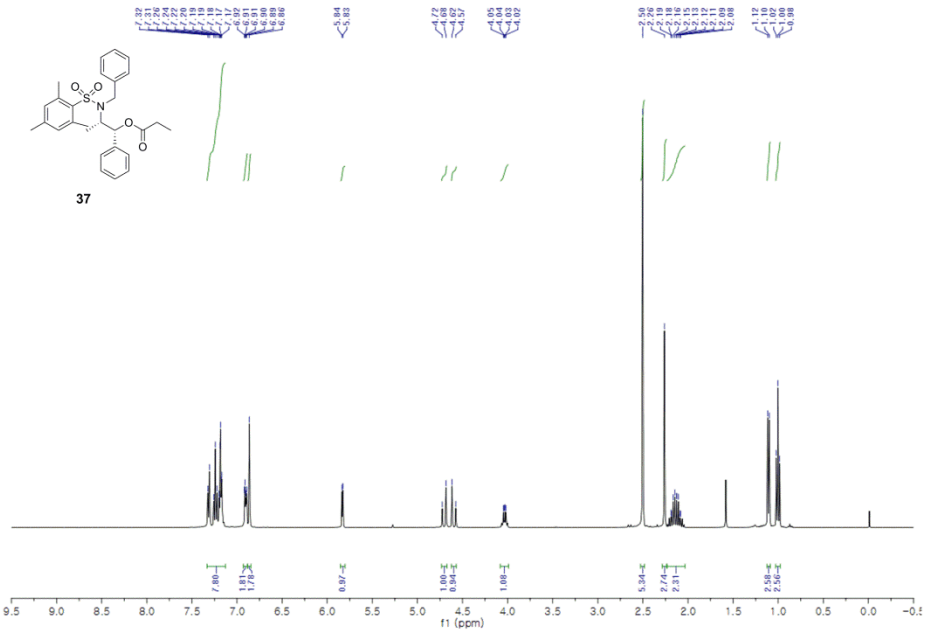

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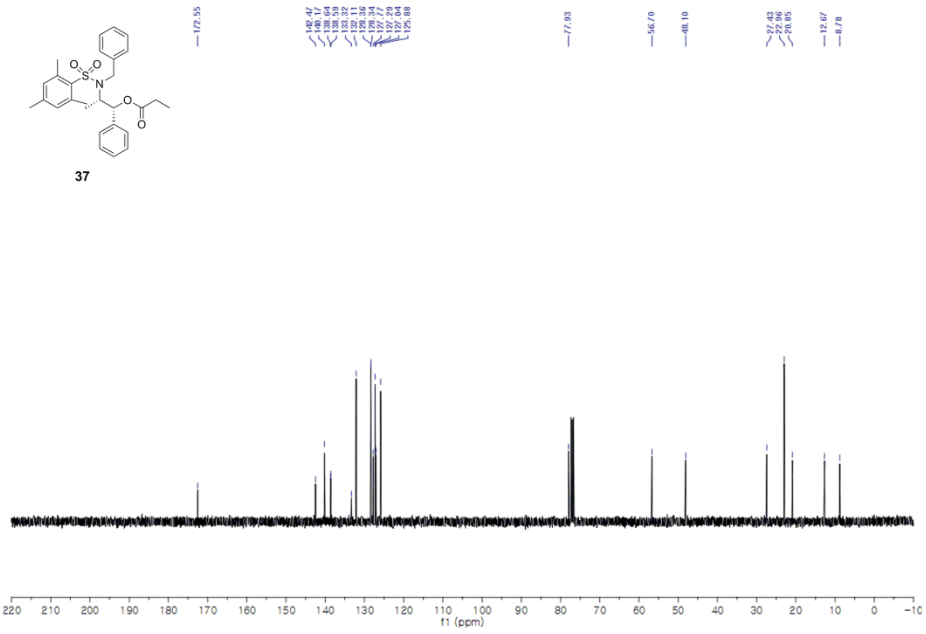

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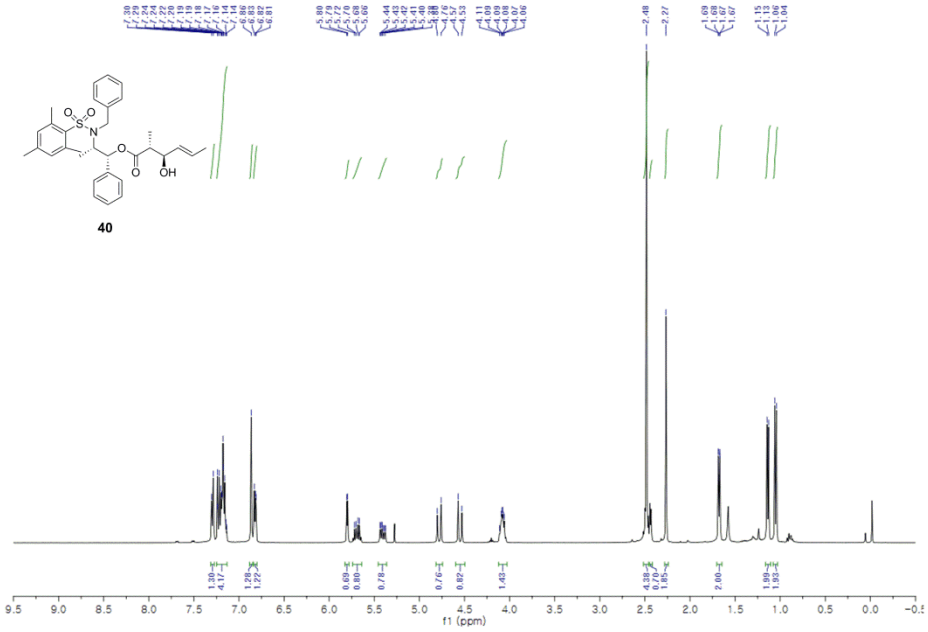
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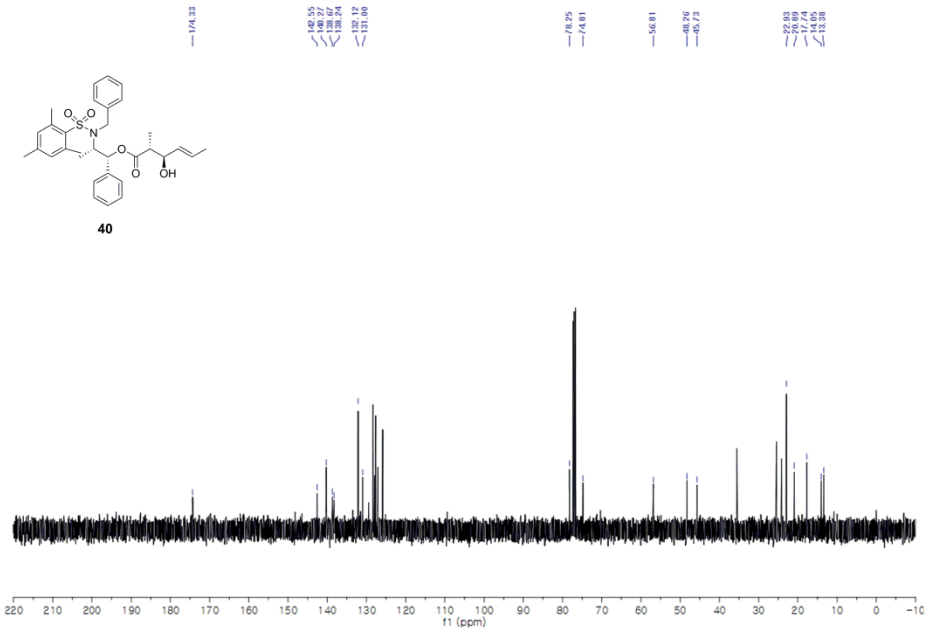
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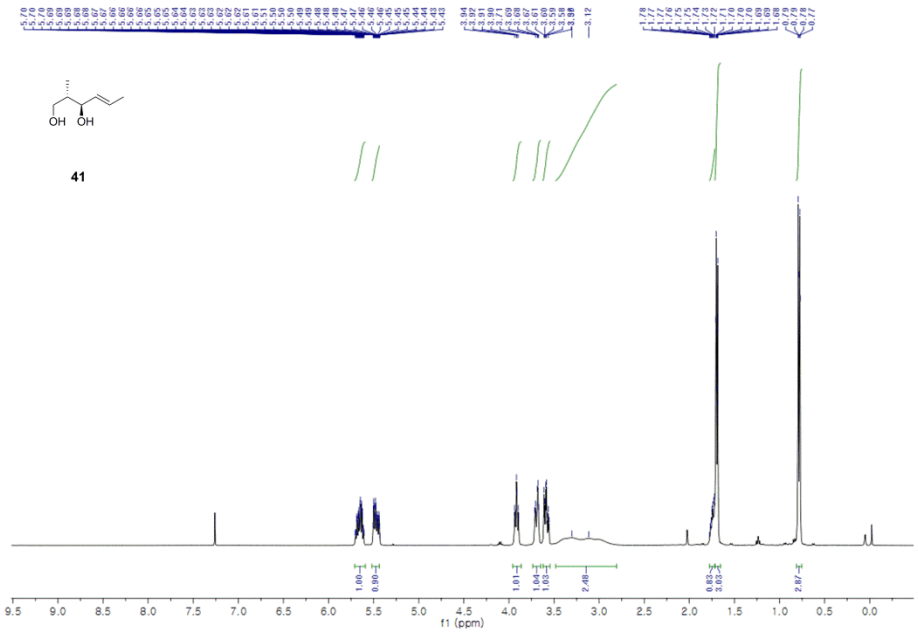
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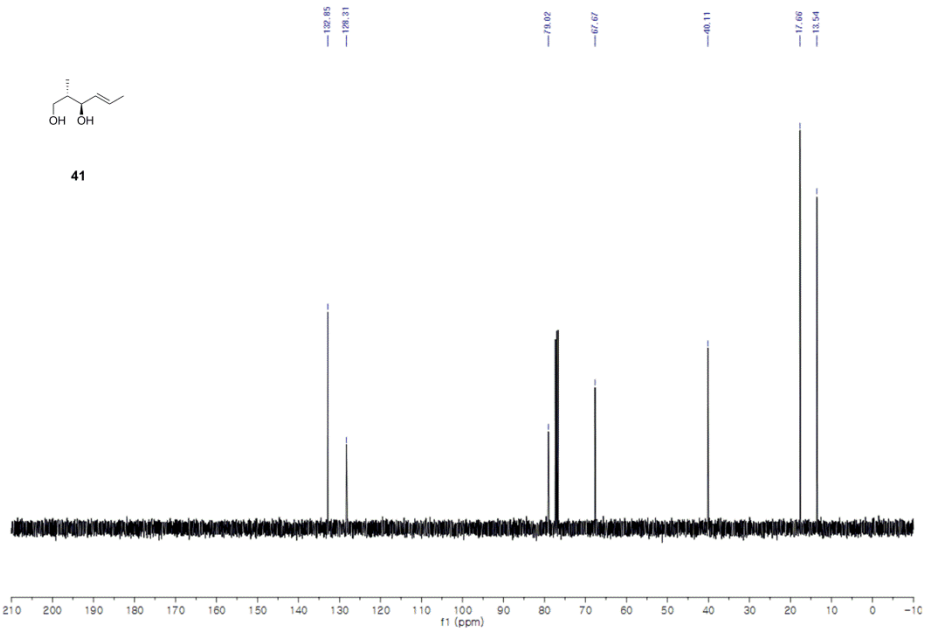
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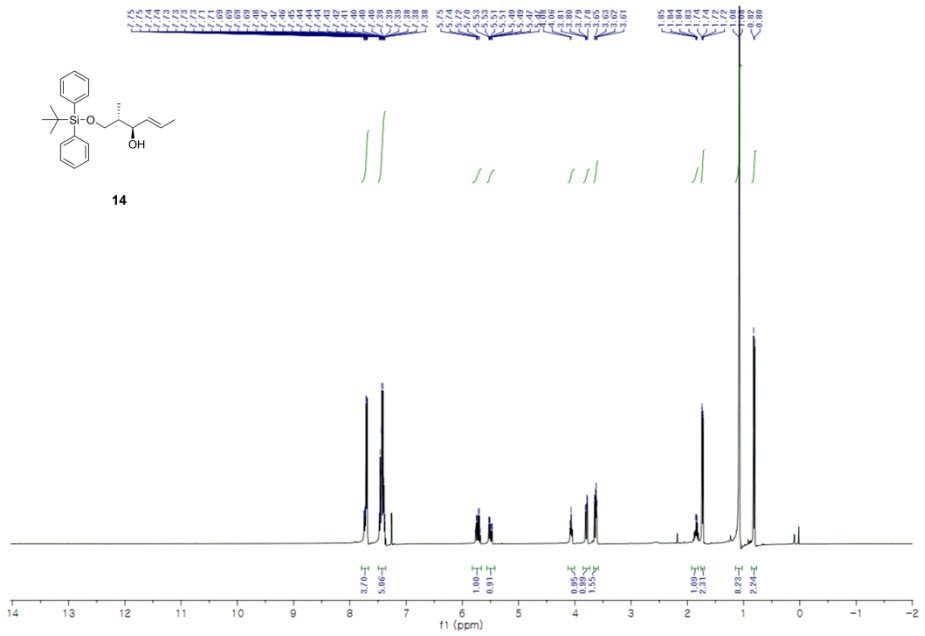
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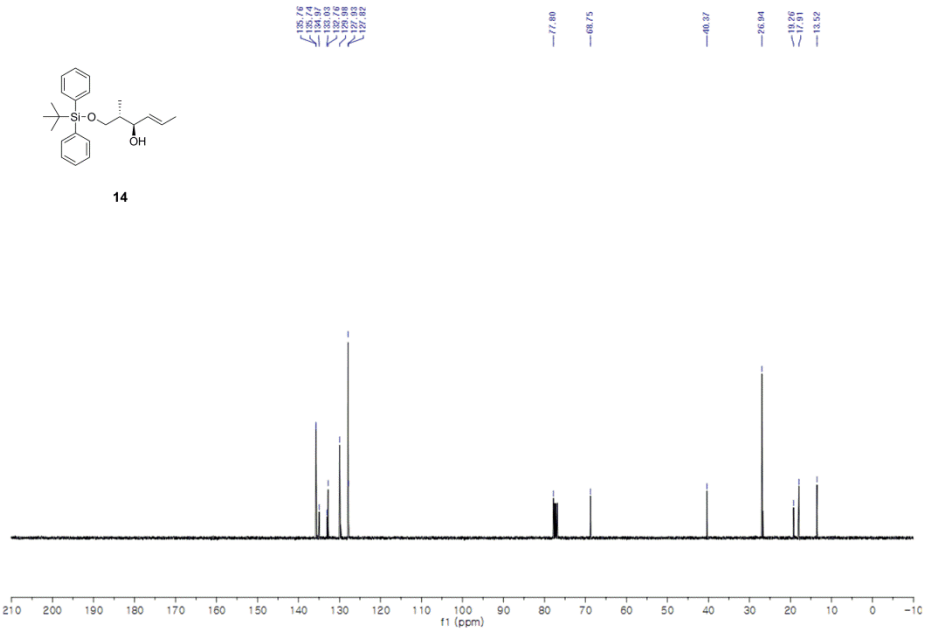
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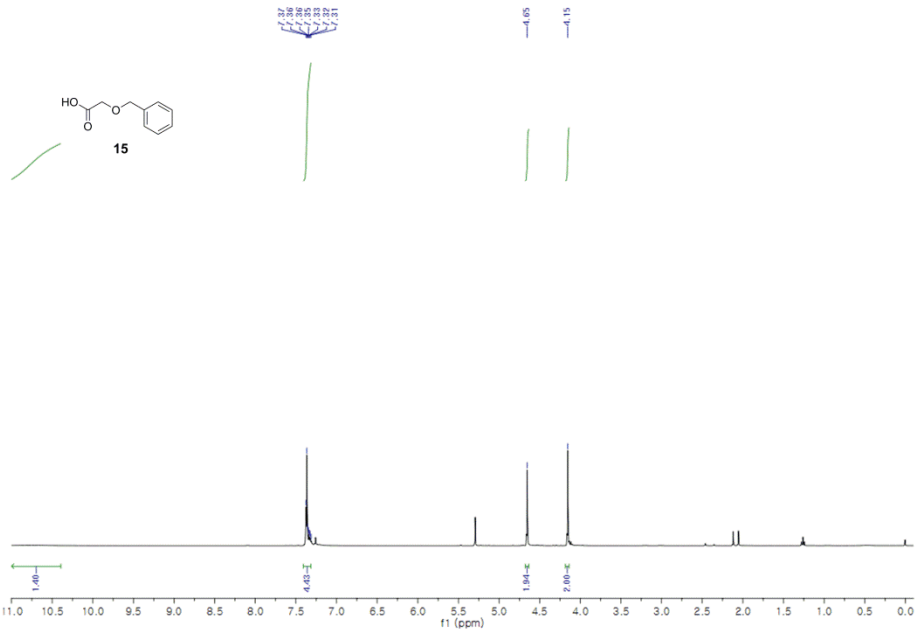
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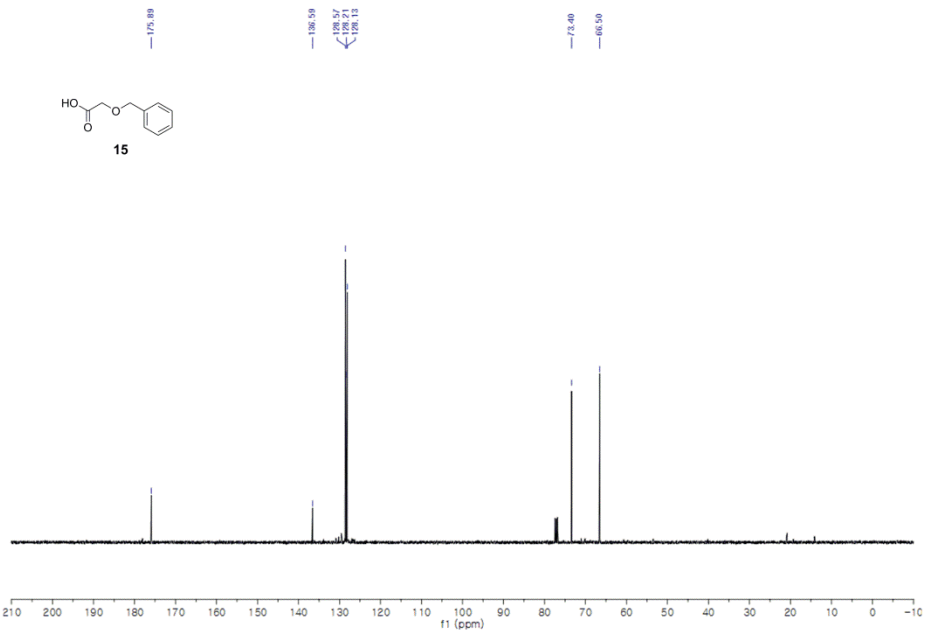
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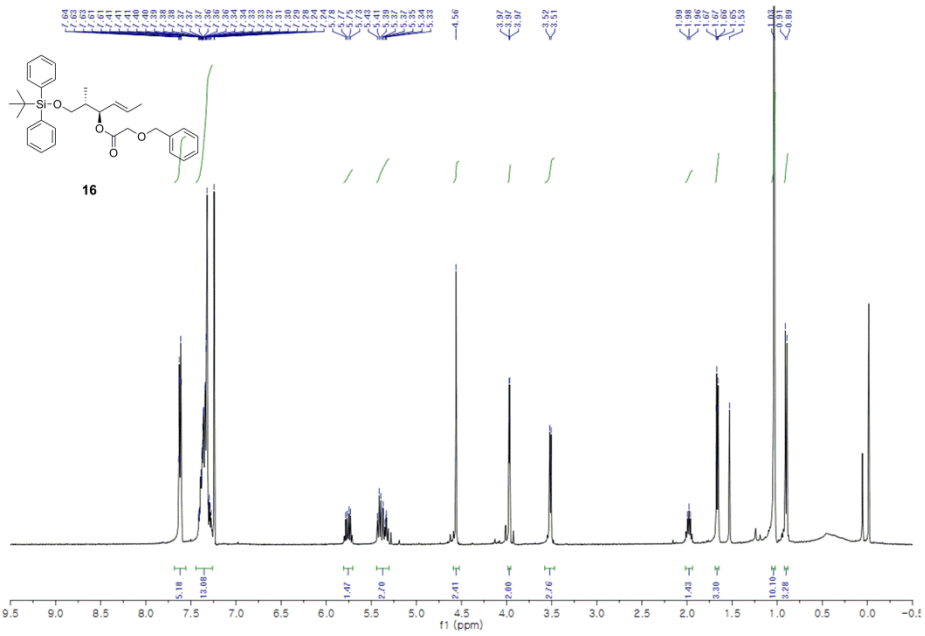
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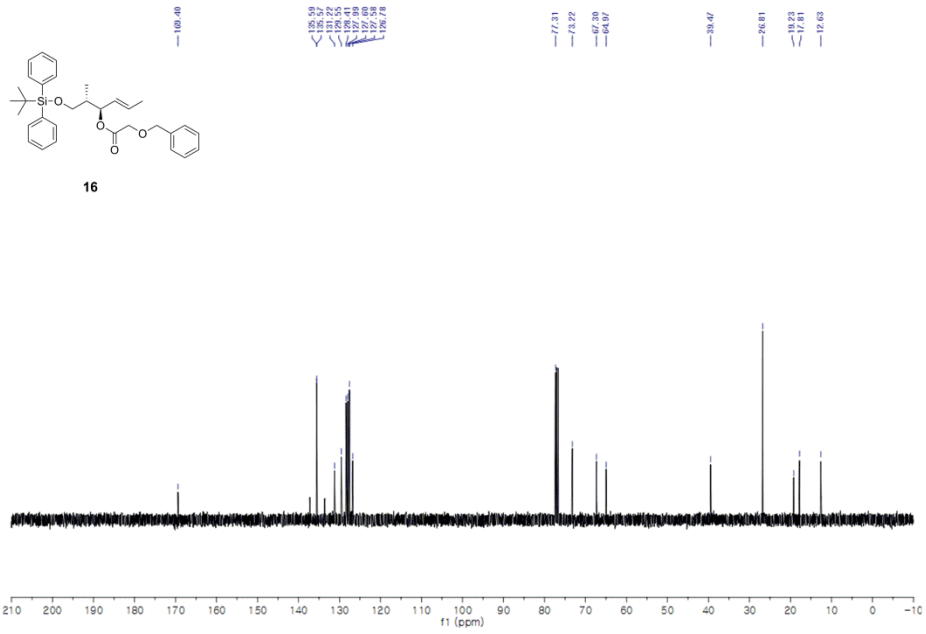
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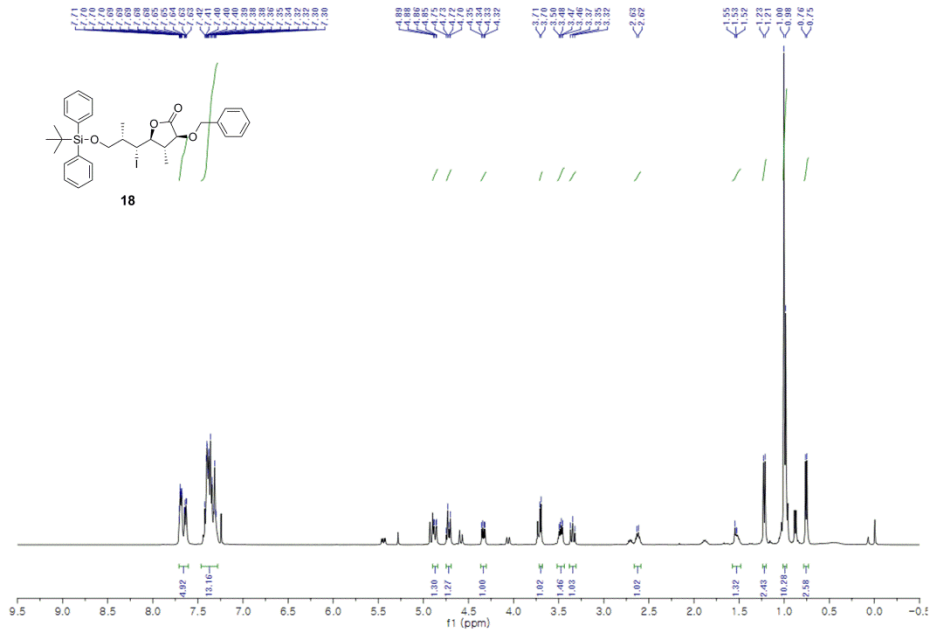
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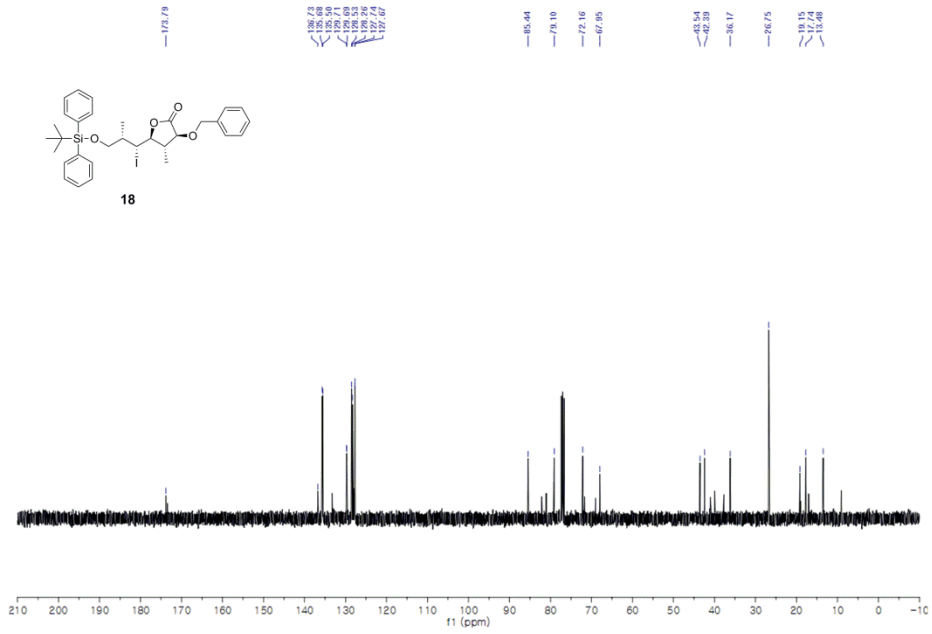
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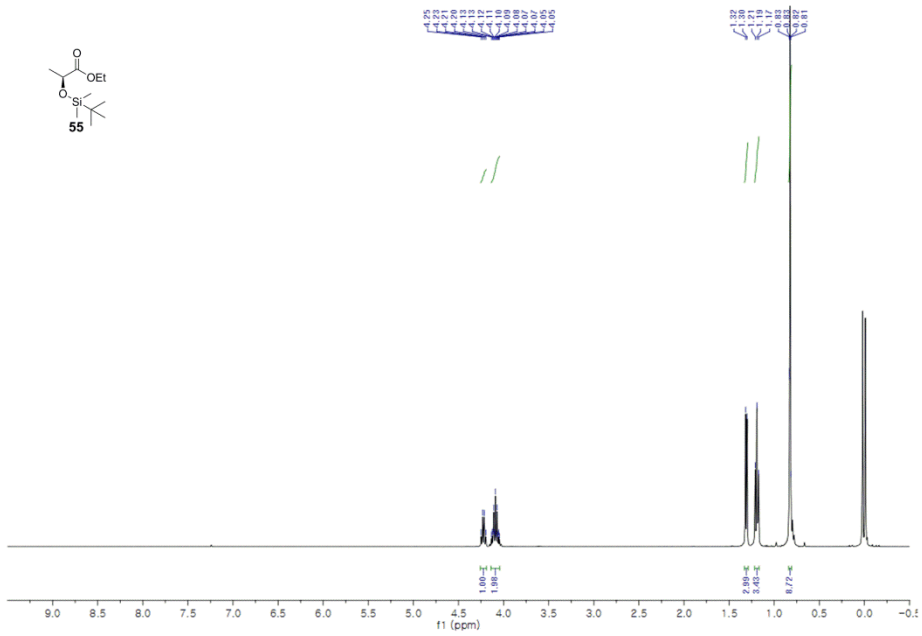
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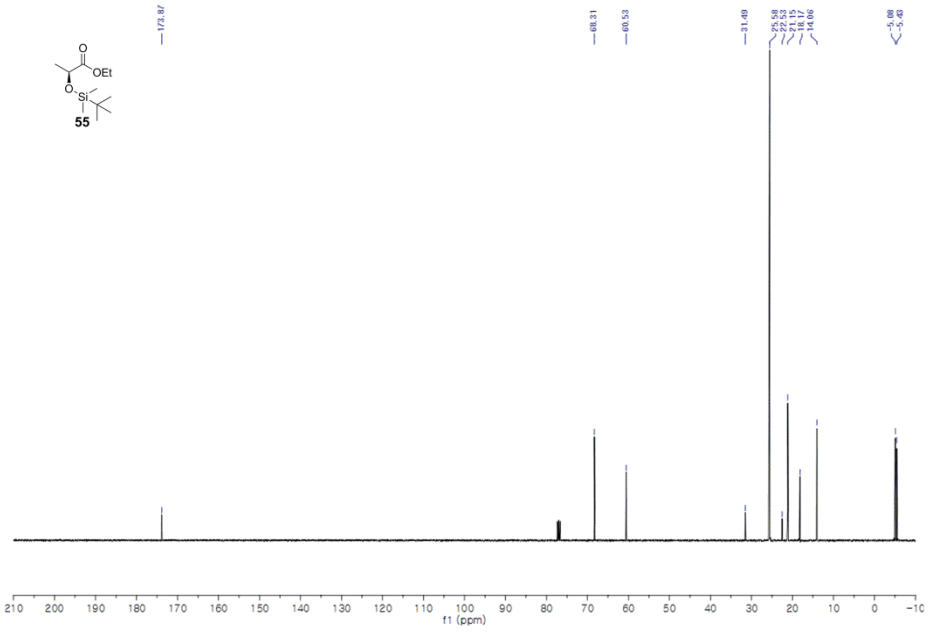
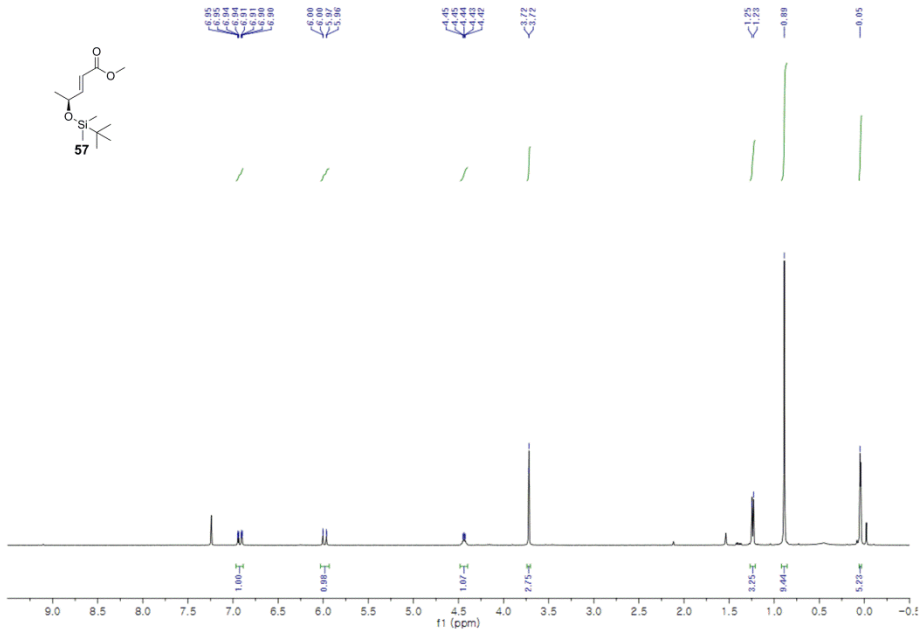
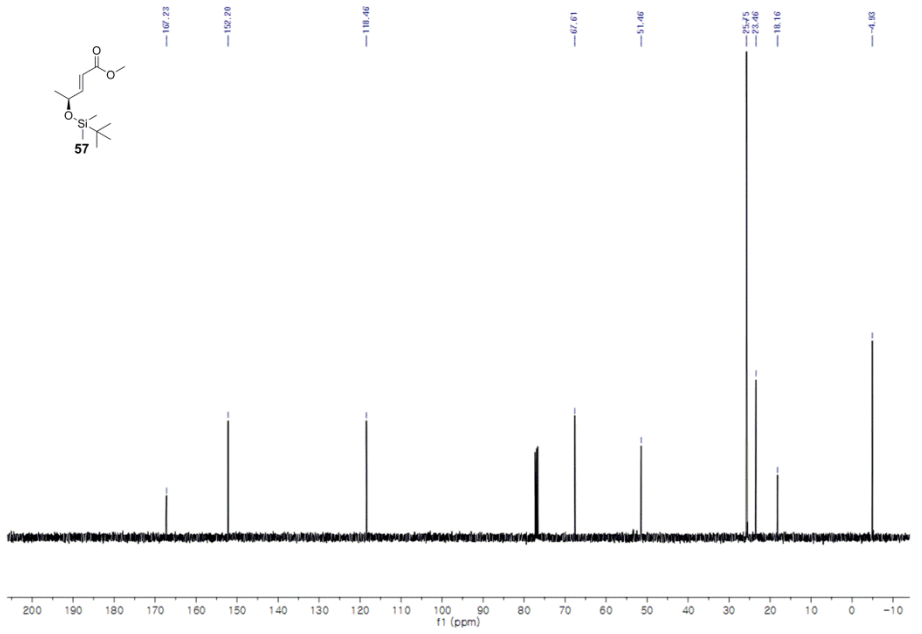
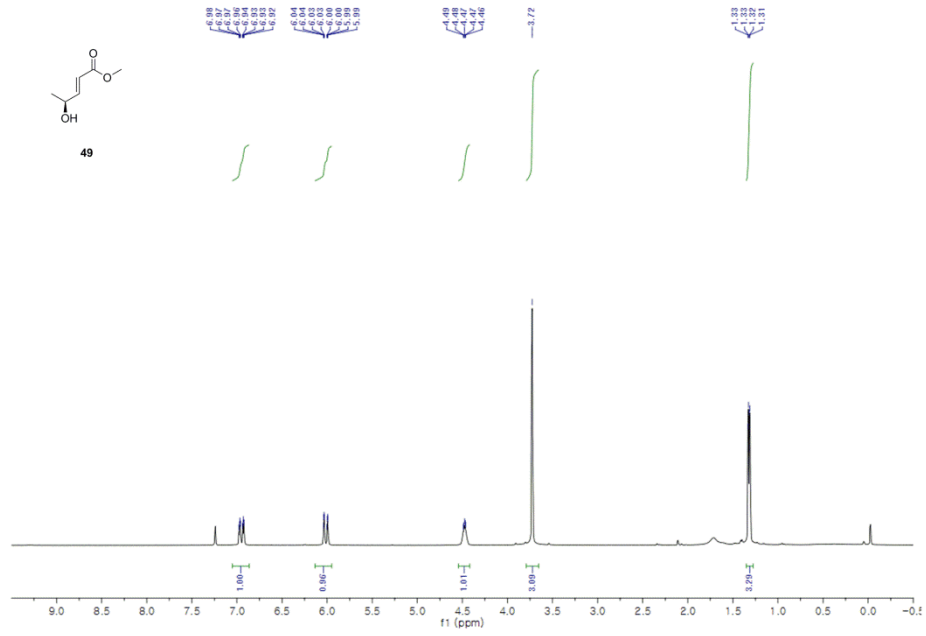
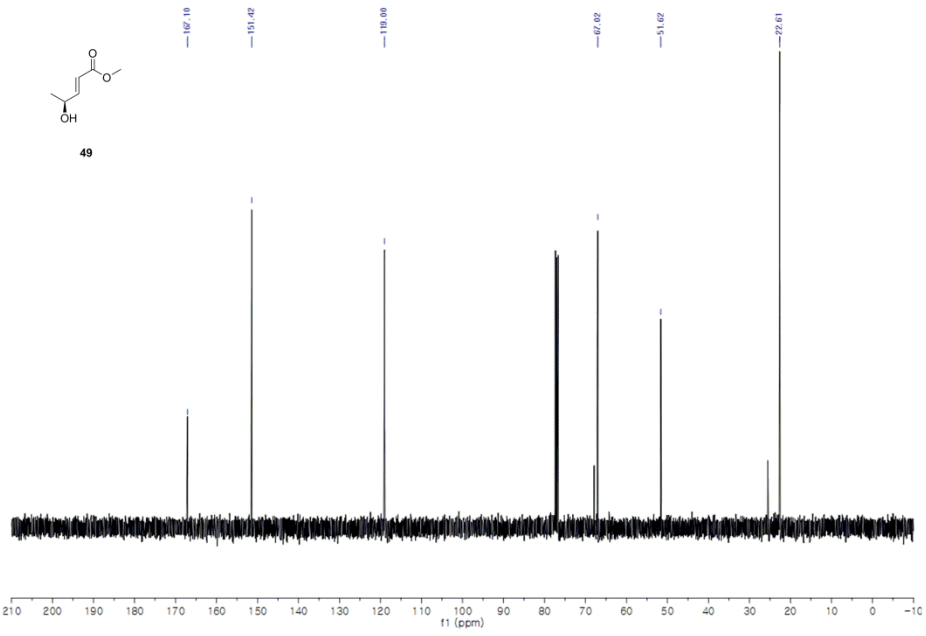
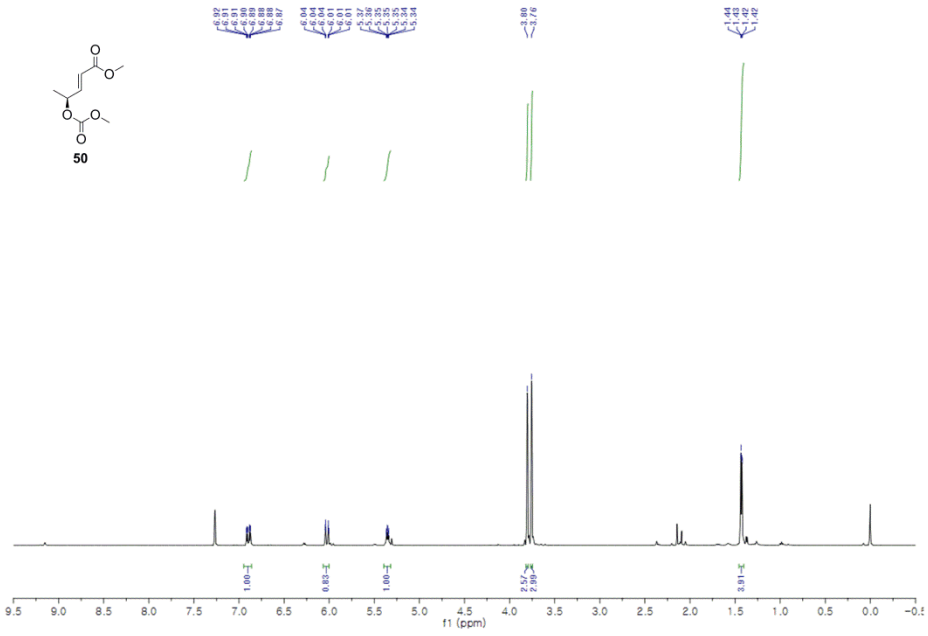

OEt
Si
55
f1 (ppm)

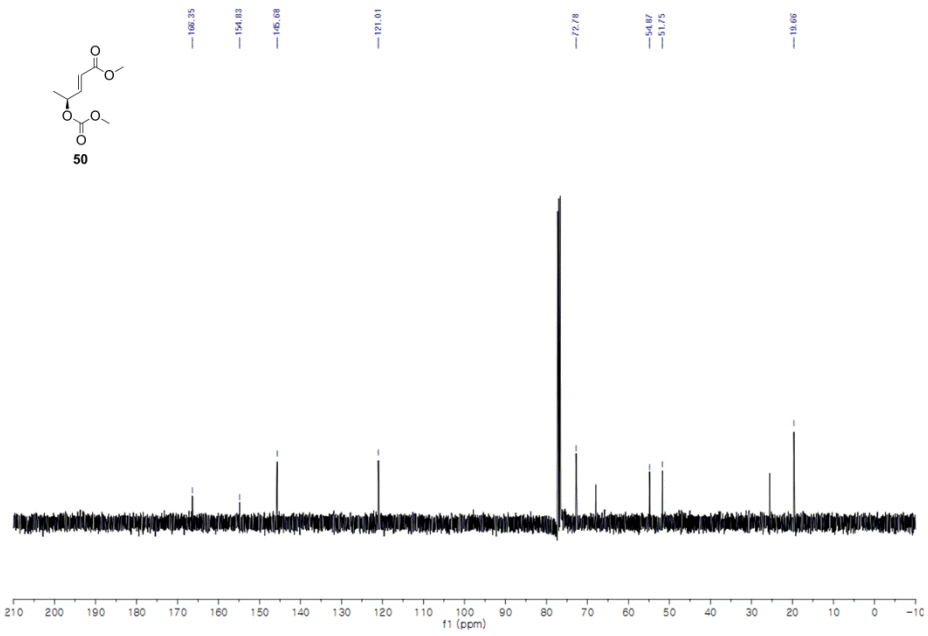

57
6.95
6.95
6.94
6.94
6.91
6.91
6.90
6.90
6.00
6.00
5.97
5.96
4.45
4.45
4.44
4.44
4.43
4.42
3.72
3.72
1.25
1.23
0.89
0.05
1.00
0.98
1.07
2.75
3.25
9.44
5.23
f1 (ppm)

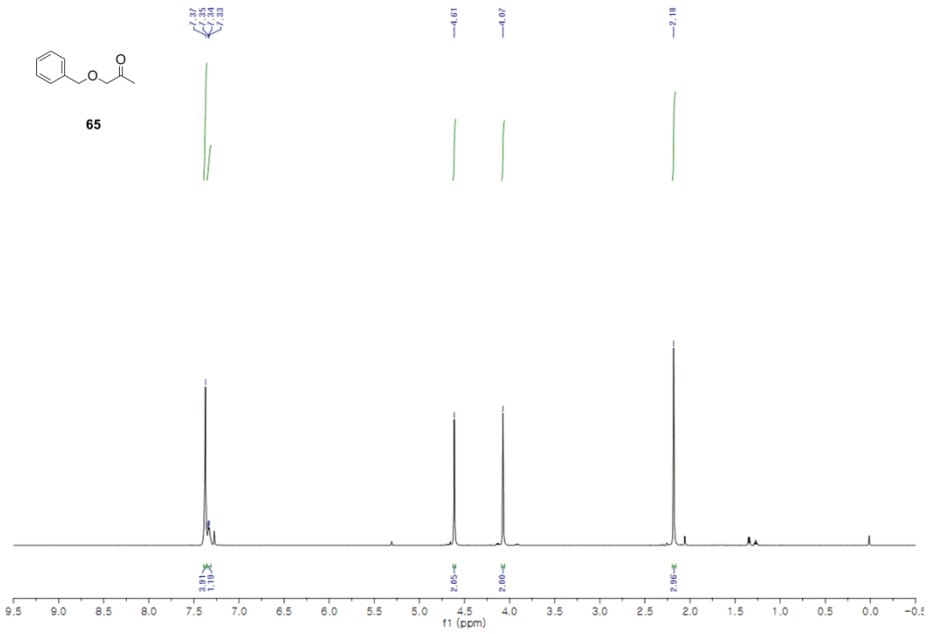

57
167.23
152.20
118.46
67.61
51.46
25.75
25.46
18.16
-4.83
f1 (ppm)

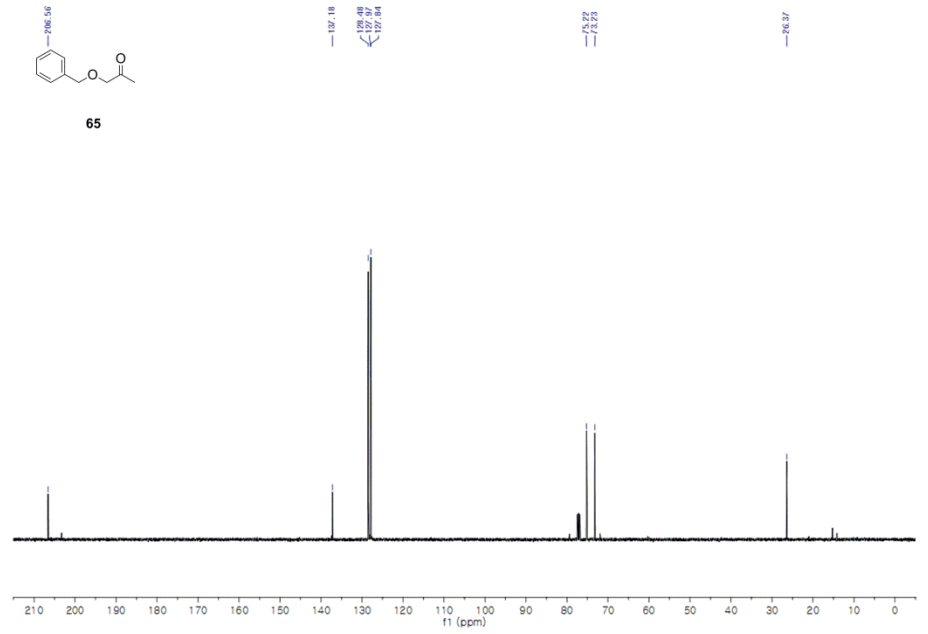

6.98
6.97
6.97
6.96
6.94
6.93
6.93
6.92
6.04
6.03
6.03
6.00
6.00
5.99
4.49
4.48
4.47
4.47
4.46
3.72
1.33
1.33
1.32
1.31
49
1.00
0.96
1.01
3.09
3.29
f1 (ppm)

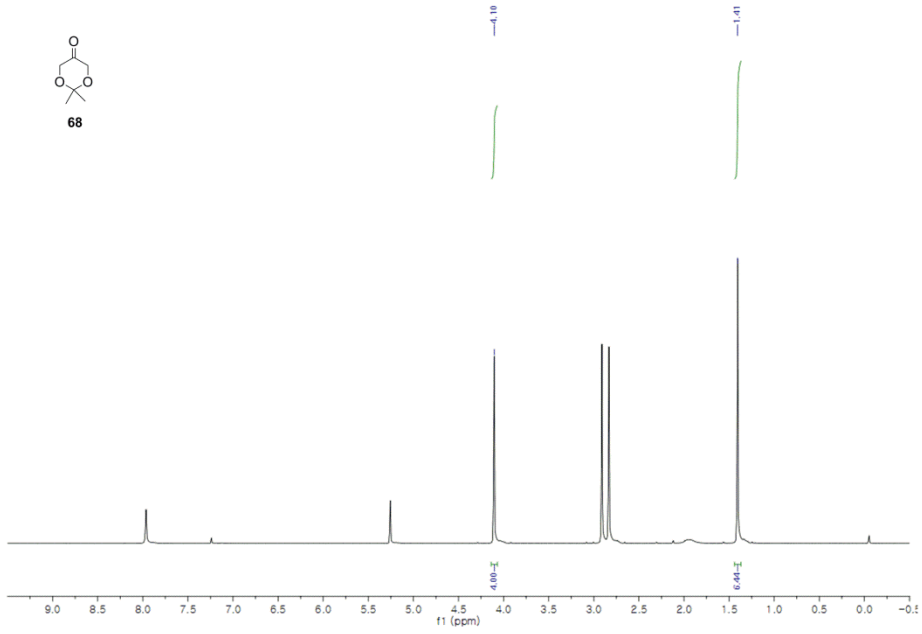

167.10
151.42
119.00
67.02
51.62
22.61
49
f1 (ppm)

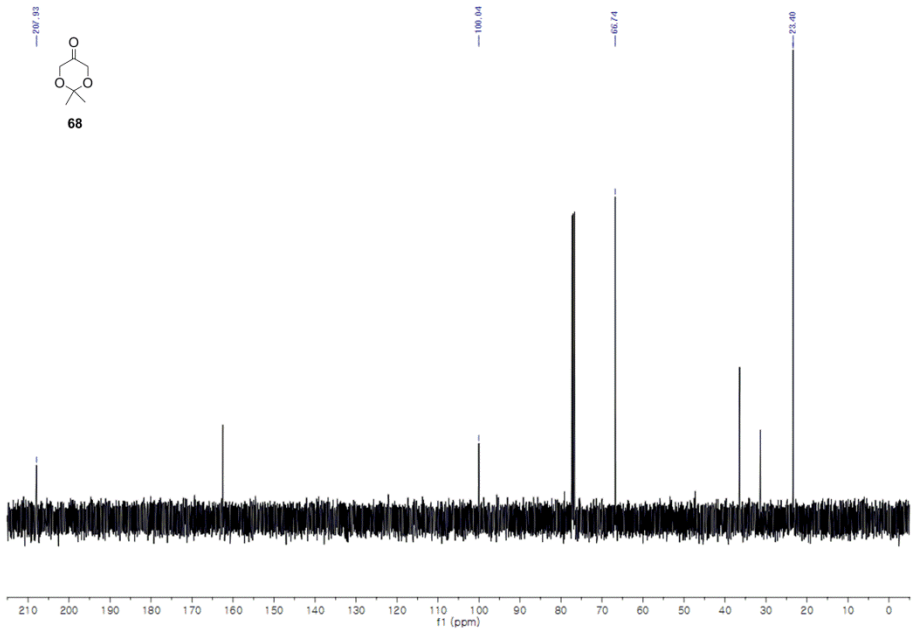

50
6.92
6.91
6.91
6.89
6.89
6.88
6.88
6.87
6.04
6.04
6.04
6.01
6.01
6.01
5.37
5.36
5.35
5.35
5.35
5.34
3.80
3.76
1.44
1.43
1.42
1.42
1.00
0.83
1.00
2.57
2.91
3.91
f1 (ppm)

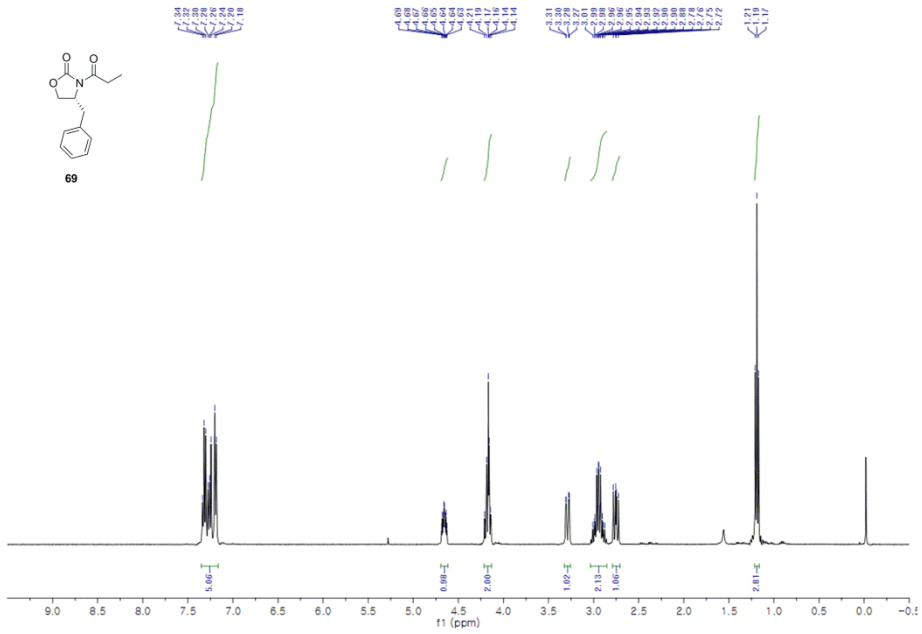

50
166.35
154.83
145.68
121.01
72.78
54.87
51.75
19.66
f1 (ppm)

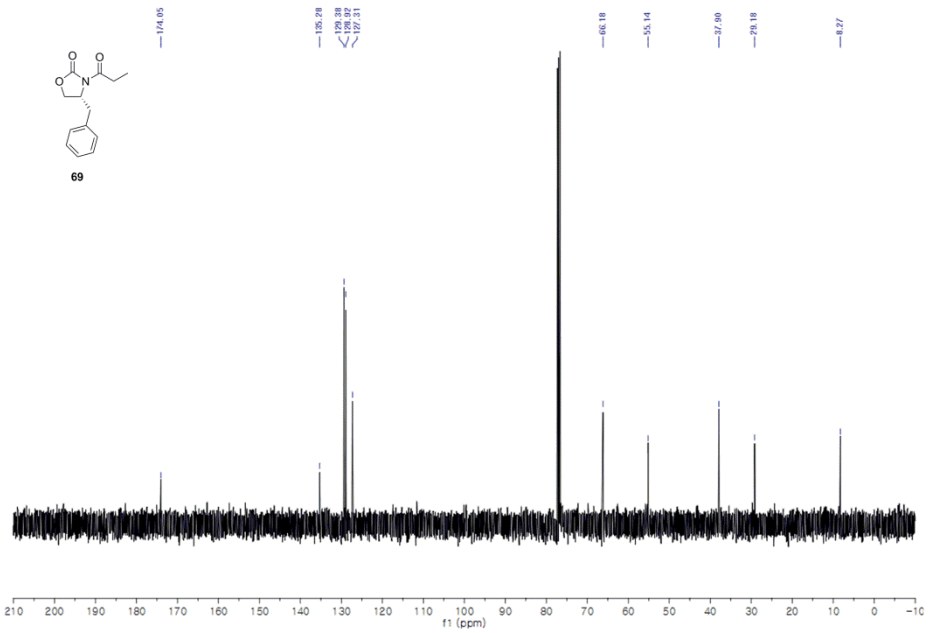

65
7.37
7.35
7.34
7.33
4.61
4.07
2.18
3.91
1.19
2.05
2.00
2.86
f1 (ppm)

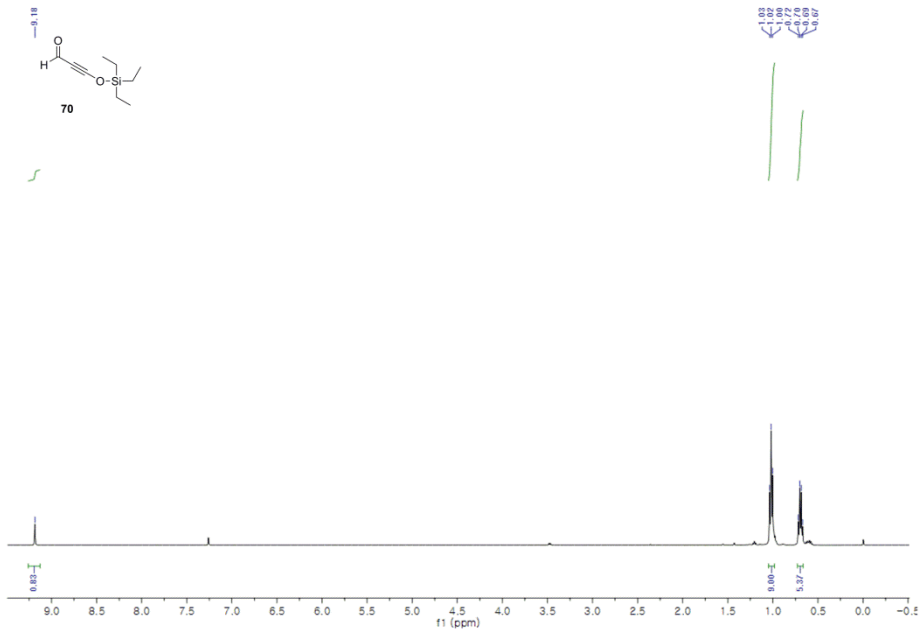

65
206.56
137.18
128.49
128.07
127.84
73.22
73.23
26.37
f1 (ppm)

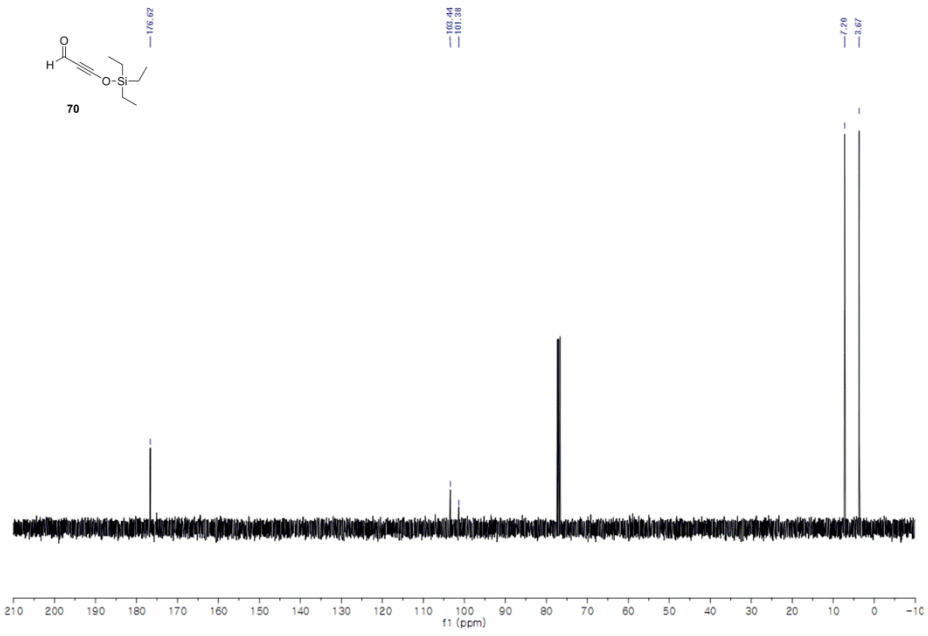

68
4.10
1.41
4.00
6.44
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

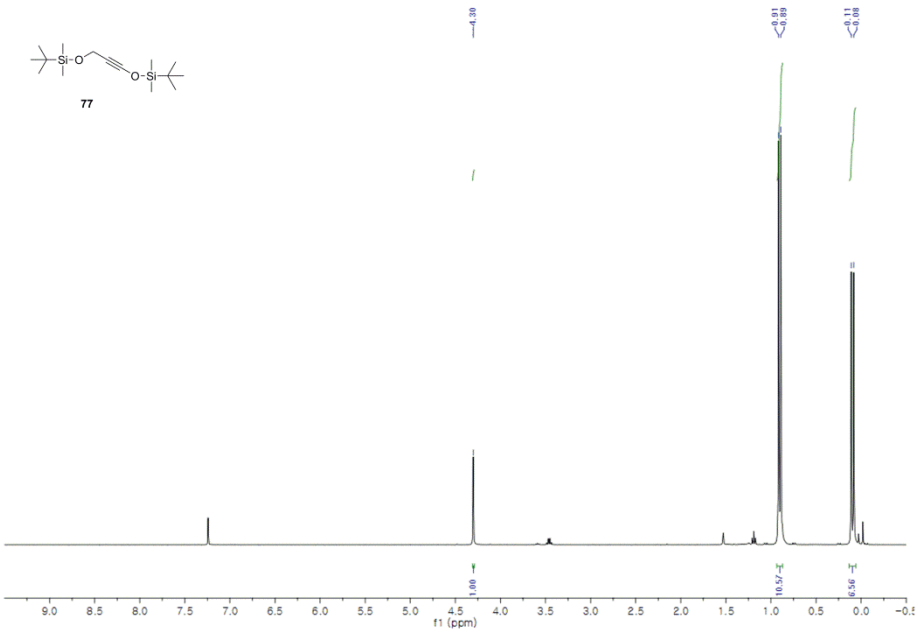

68
209.93
100.04
66.74
23.46
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

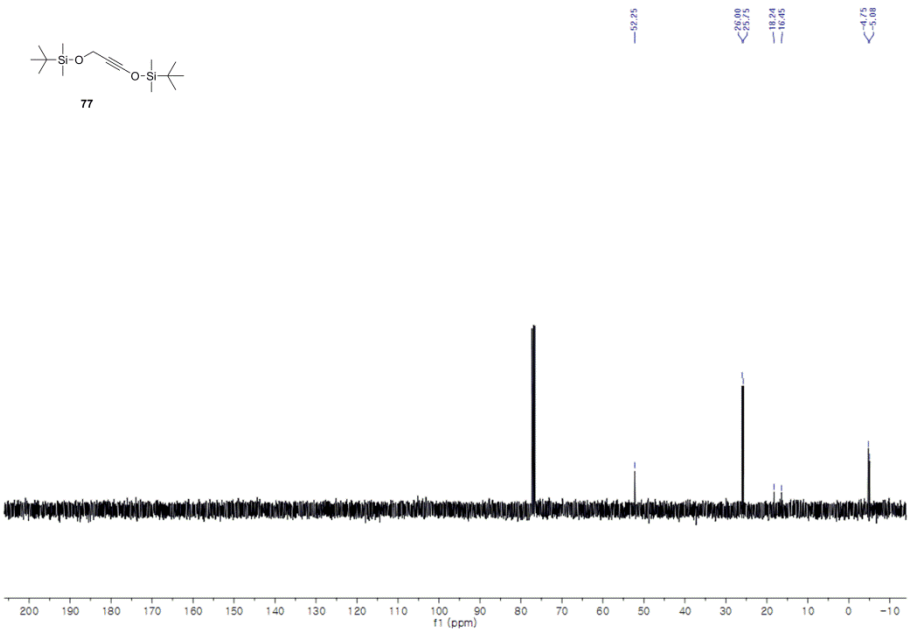

69
f1 (ppm)

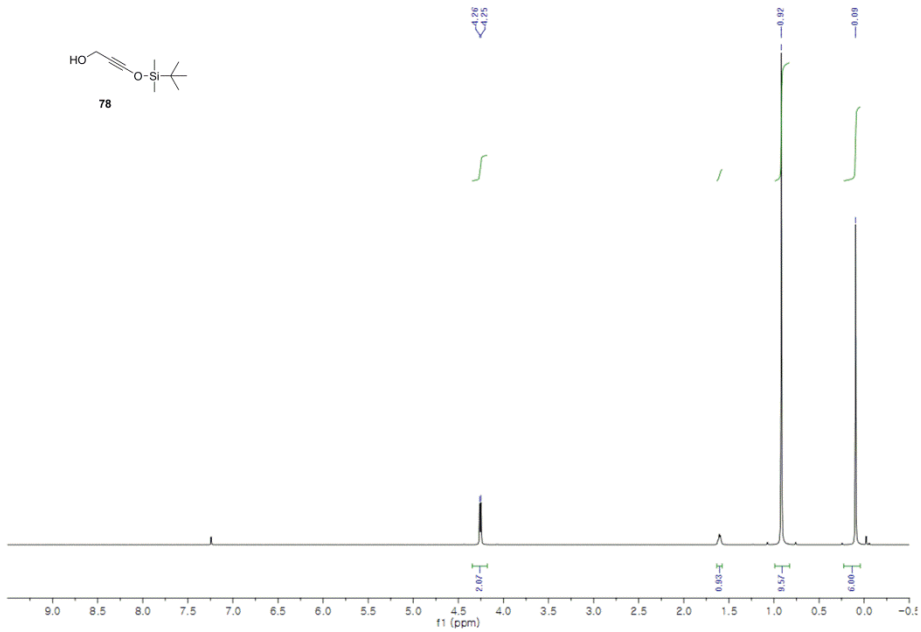

69
f1 (ppm)

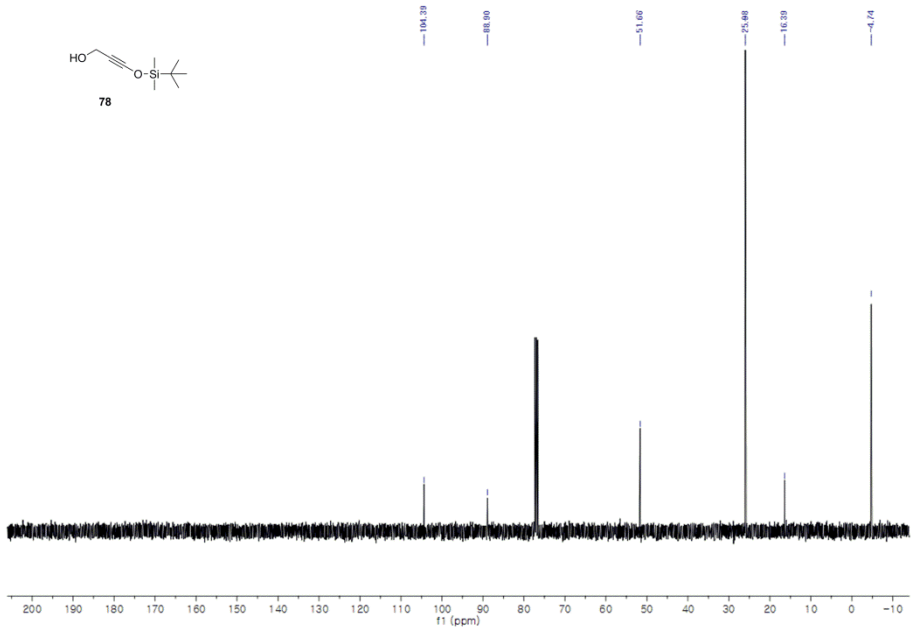

9.18
1.03
1.02
1.00
0.72
0.70
0.69
0.67
70
0.83
9.00
5.37
f1 (ppm)

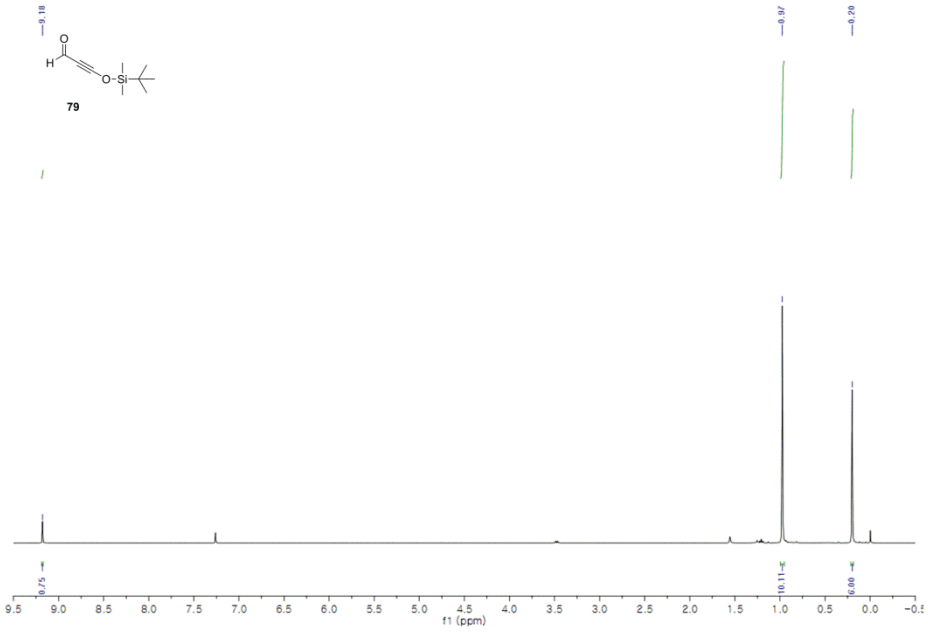

176.62
103.44
101.38
7.29
3.67
70
f1 (ppm)

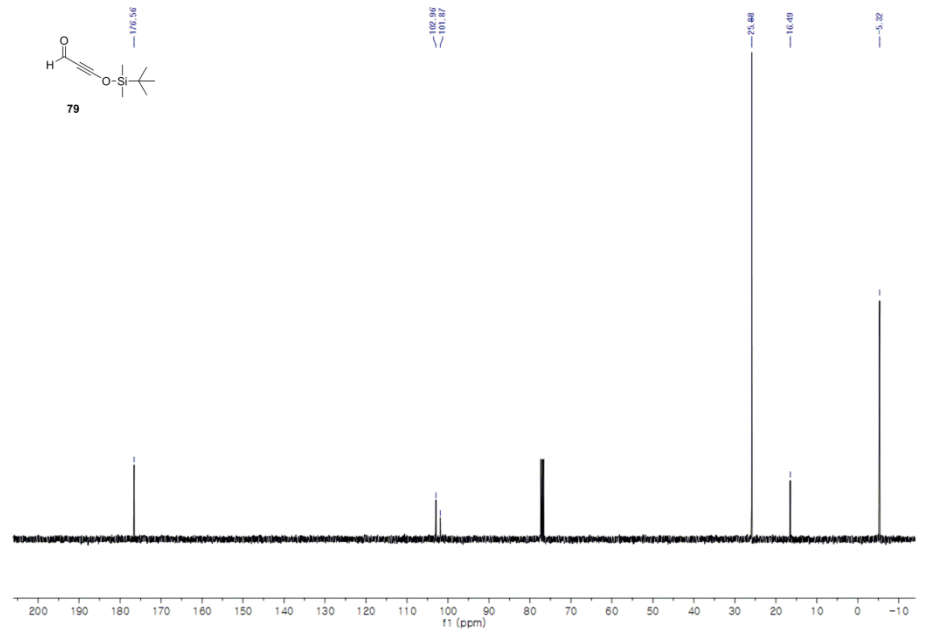

77
4.30
0.91
0.89
0.11
0.08
1.00
10.57
6.56
f1 (ppm)


77
52.25
26.00
25.75
18.24
16.45
-4.75
-5.08
f1 (ppm)


HO
O
Si
78
4.26
4.25
0.92
0.09
2.07
0.93
9.57
6.00
f1 (ppm)


HO
O
Si
78
104.39
88.90
51.66
25.98
16.39
-4.74
f1 (ppm)


9.18
0.97
0.20
79
0.75
10.11
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


176.56
102.99
101.87
25.88
16.49
-5.32
79
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)