이학석사학위논문

Synthetic studies toward akuammiline alkaloids via a biomimetic pathway

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지도교수 이 홍 근

이 논문을 이학석사학위논문으로 제출함

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Synthetic studies toward akuammiline alkaloids via a biomimetic pathway

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By

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In Organic Chemistry

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Department of Chemistry

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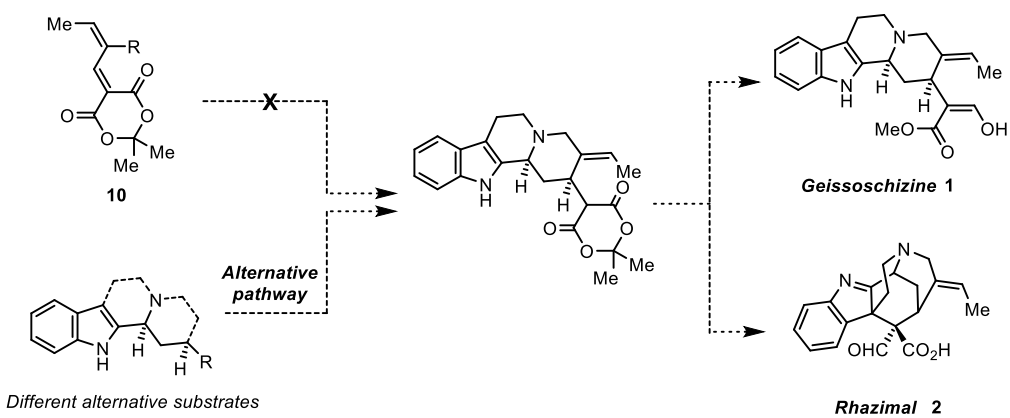
Seoul National University

ABSTRACT

In this chapter, initial synthetic strategy towards natural product rhazimal **2** via intermediate geissoschizine **1** is proposed, which involved Knoevenagel condensation, asymmetric 1,4 addition, and gold-catalyzed formal Pictet-Spengler cyclization. Synthetic efforts toward preparation of one of the key intermediate, α,β,γ-conjugated system **10** are demonstrated and major drawbacks of the sequence are highlighted. Alternatively, revised synthetic strategy is commenced. Its key features are represented as rigidity-dependent [3,3]-Ireland-Claisen type sigmatropic rearrangement to build direct C7-C16 bond, and later-stage functionalization to obtain unique (*E*)-ethylidene moiety.



Keywords: Total synthesis, natural product, biomimetic synthesis, rhazimal, geissoschizine, akuammiline, [3,3]-Ireland-Claisen type sigmatropic rearrangement

Student Number: 2015-20396

CHAPTER ONE

Synthetic Efforts toward Rhazimal

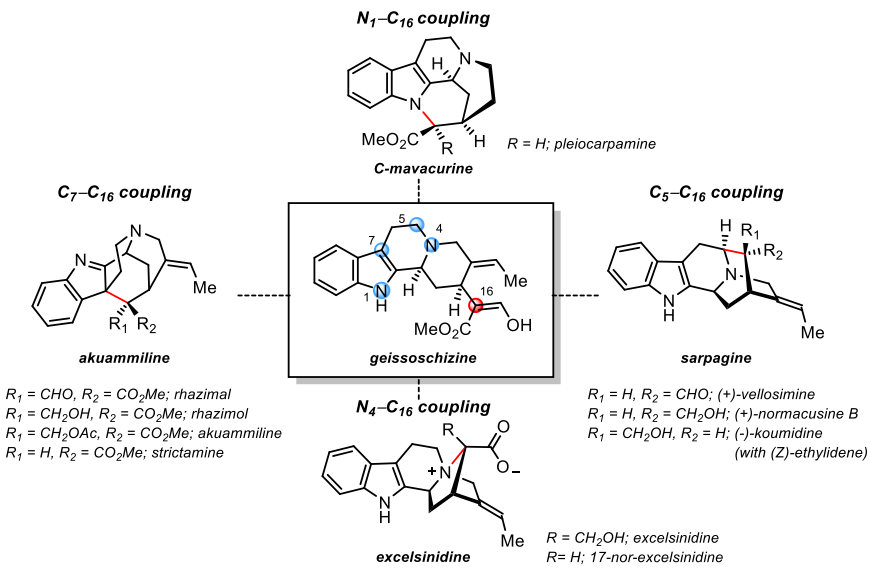
CONTENTS

1. INTRODUCTION

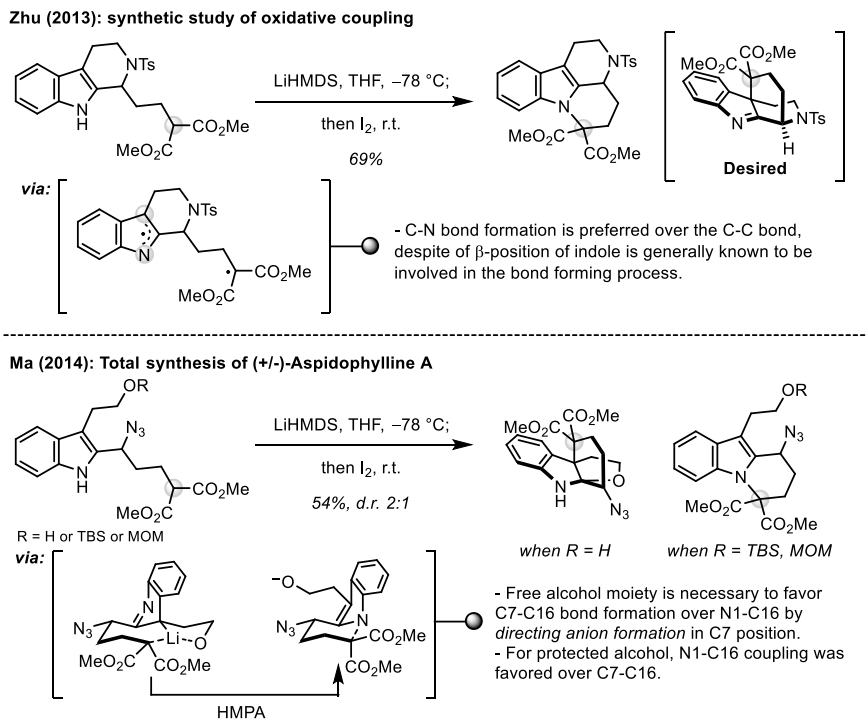
The akuammiline alkaloid is a family of monoterpene indole alkaloids, which was first isolated in 1932.[1] Since then, akuammiline scaffolds have been fascinating targets of many synthetic groups due to their characteristic chemical structures and various biological activities. Intensive preliminary studies have shown the possible bioactivities of akuammiline, along with its biosynthetic route.

Biosynthetic route suggested that wide range of alkaloids including akuammiline family are derived from natural product geissoschizine.[2] Geissoschizine, in fact, is a very powerful intermediate which can visit various core structures of wide range of related natural product via single bond formation, such as N1-C16 bond for mavacurine, C5-C16 bond for sarpagine, N4-C16 bond for excelsinidine, and C7-C16 bond for akuammiline (Figure 1).[3] This direct connection between C7 and C16 provides unique methanoquinolizidine core and forms natural product rhazimal which is also widely known as intermediate towards different akuammiline alkaloids through reactions such as ring migration.[4]

Figure 1. Direct Access towards the Mavacurans, Akuammilans, and Excelsinidines via Geissoschizine.



Due to its potential as versatile intermediate for collective syntheses of diverse natural products, geissoschizine has aroused intensive efforts for biomimetic synthesis via geissoschizine over the past few decades. Bioinspired syntheses of marvacuran, sarpagine, and excelsinidine through direct coupling have been reported recently. [5] However, to the best of our knowledge, biomimetic synthesis of rhazimal via oxidative coupling of C7-C16 bond has not reported up to date.

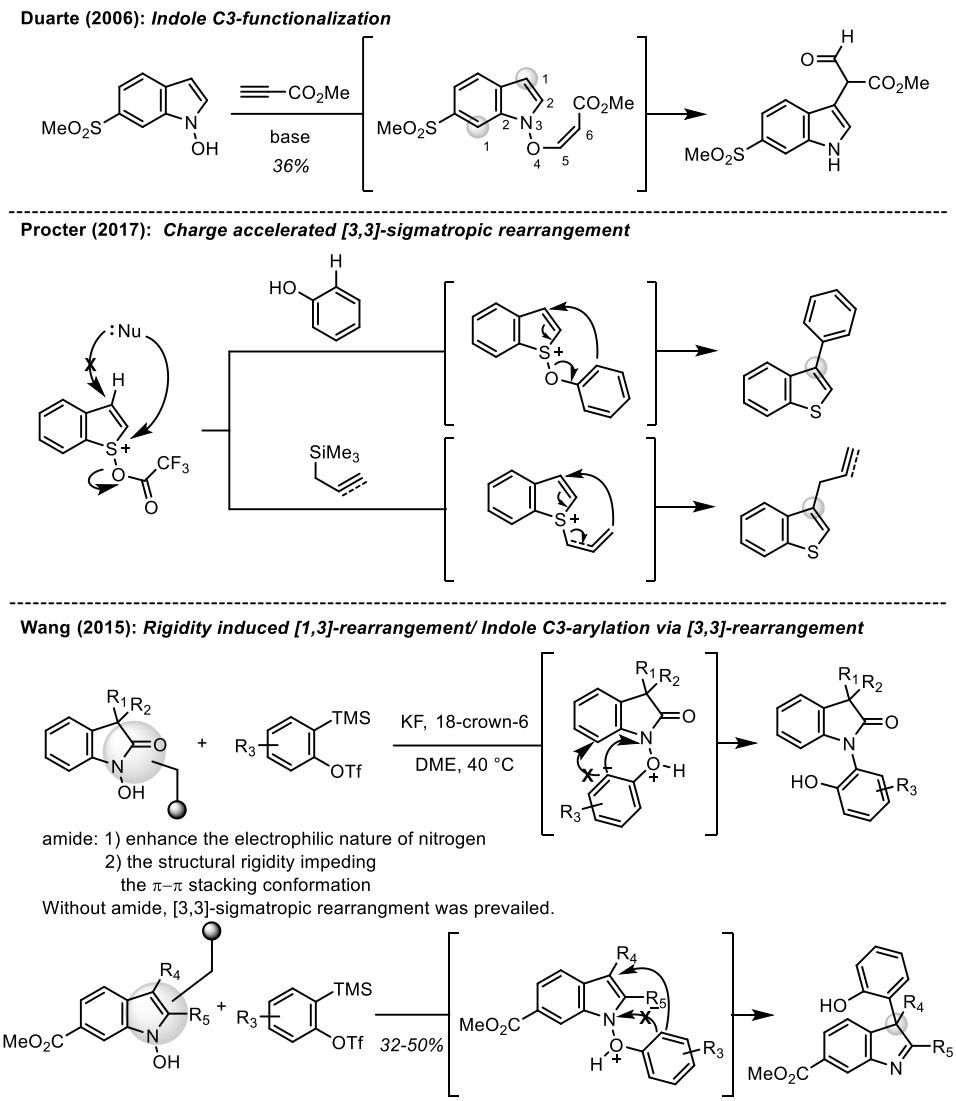


Scheme 1. Synthetic Approach towards Bioinspired C7-C16 Oxidative Coupling and Application in Complex Molecule Synthesis.

The initial enlightening studies towards biomimetic oxidative coupling have been demonstrated (Scheme 1). Zhu and coworkers[6] examined intramolecular oxidative coupling of dianion to form C7-C16 bond in simplified tricyclic system. Interestingly, N1-C16 bond was formed, implying that the N1-C16 cyclization was prevailed over C7-C16 cyclization which can possibly provide strained bridged ring system. Ma and coworkers[5b] adopted Zhu's

method, establishing C7-C16 bond via radical cyclization using indole substrate. Ma highlighted that free alcohol moiety is necessary to favor C7-C16 bond formation over N1-C16 by directing anion formation in C7 position. For protected alcohol, N1-C16 coupling was favored over C7-C16.

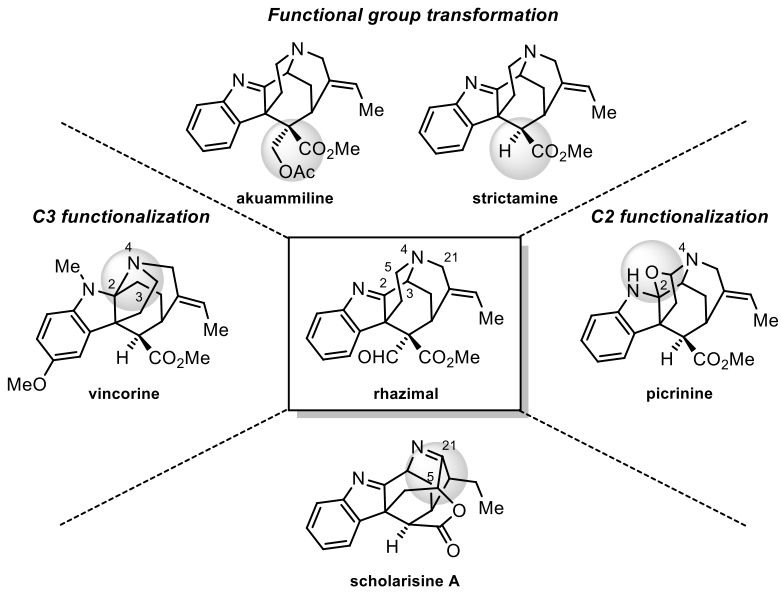
Based on these past pioneering works, we envisioned that intramolecular [3,3]-Ireland-Claisen type sigmatropic rearrangement could be an appealing synthetic approach which avoids previously observed competitivity between two possible N1-C16 C7-C16 and bond formations. Examples of [3,3]-sigmatropic rearrangement for bond formation at the indole 3-position are rare, but not none (Scheme 2).[7] These examples below can support the viability of the strategy, and achievement of [3,3]-Ireland-Claisen type sigmatropic rearrangement in complex molecule will be unprecedented.



Scheme 2. [3,3]-Sigmatropic rearrangement of N-hydroxyindole and related substrate

The ultimate goal of the research is diversification of rhazimal to access other akuammiline alkaloids, which not only includes the members described in Figure 2, but also not limited to. While some molecules are easily accessible from rhazimal via straightforward transformations, syntheses of other alkaloids demand a chemoselective functionalization at N4 and adjacent carbon atoms.

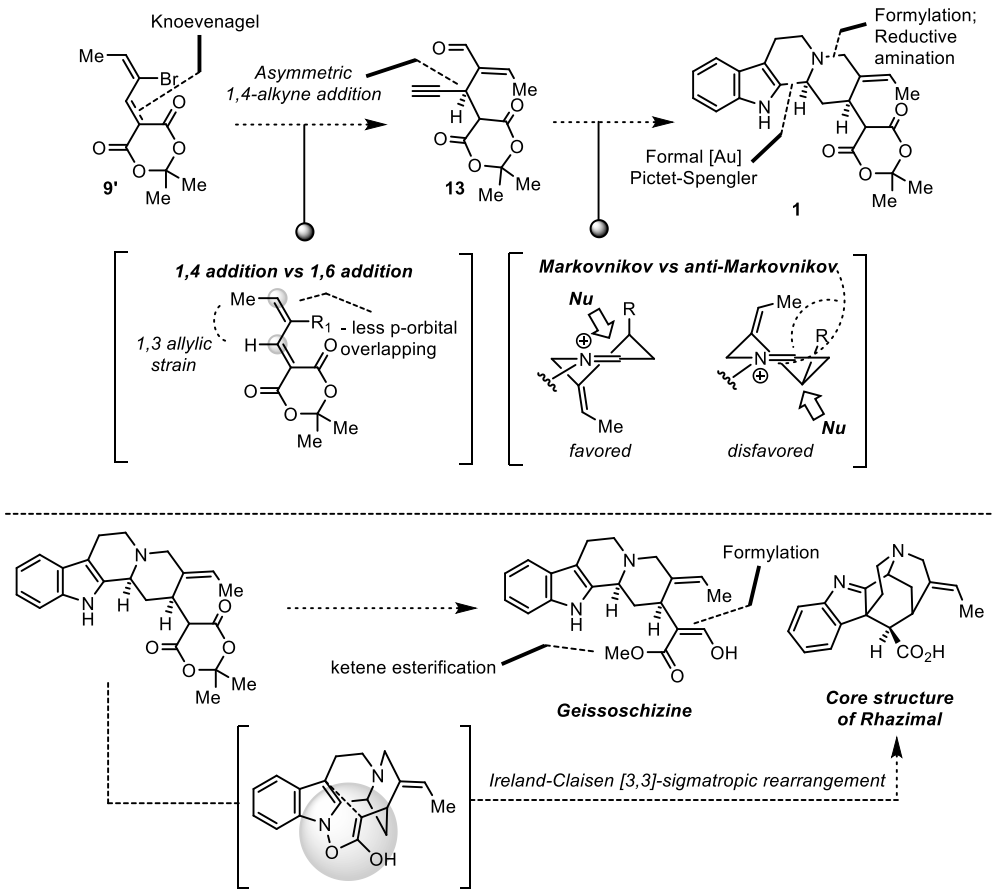
Figure 2. Other Members of Akuammiline Alkaloids



The aim of this chapter is to explore a practical, high-yielding sequence to reach key intermediate 1 and to investigate [3,3]-Ireland-Claisen type sigmatropic rearrangement in the context of new method of biomimetic C7-C16 bond formation.

2. RESULTS and DISCUSSION

2.1 Initial Synthetic Strategy and Synthetic Investigations towards Preparation of Aldehyde 9

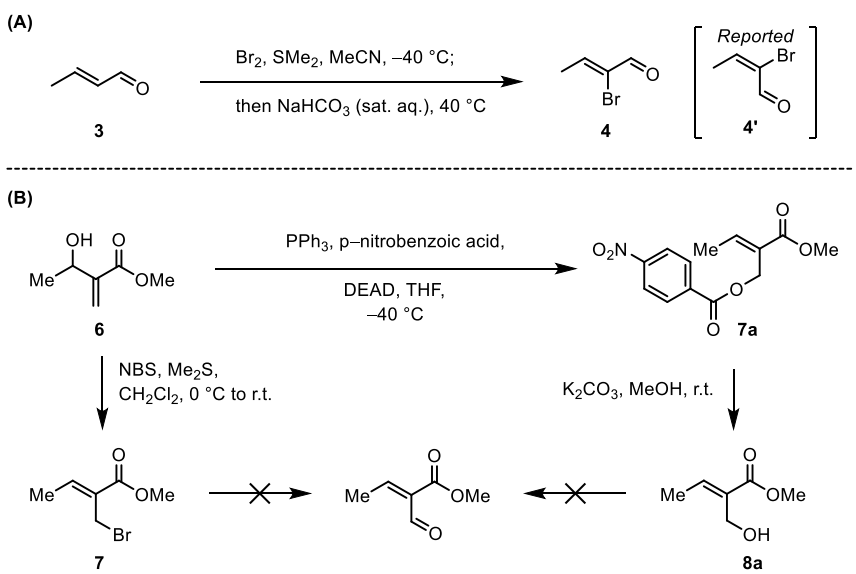


Scheme 3. Synthetic Plan for Rhazimal.

The initial strategy of our synthesis of rhazimal is outlined in Scheme 3. Knoevenagel condensation of aldehyde **4a** and Meldrum's acid could afford α,β,γ-unsaturated adduct **9'** which will undergo conjugate addition of alkynyl nucleophile. We assumed that 1,3-allylic strain in methyl group and C(sp^2)-H will afford slight distortion in overall ethylidene motif, which will lead to less overlapping of p-orbitals. In this context, Nucleophilic addition of alkynyl moiety is expected to occur preferentially toward β position

than γ position. Various well-established asymmetric conjugate addition reactions can be utilized to give desired enantiomer at C15. Formylation, followed by reductive amination with tryptamine and formal Pictet-Spengler cyclization using alkyne moiety as coupling partner, will afford to build key intermediate **1** with tetracyclic core of natural product geissoschizine. Then, key intermediate **1** can undergo thermal decomposition to give ketene, prior to formylation to achieve geissoschizine. In a similar manner, same key intermediate **1** will be able to furnish essential acetyloxyindole after sequential N-oxidation and intramolecular cyclization.

Focused on practical, easy-to-scale-up synthesis of key intermediate **1**, the initial research was initiated from the synthesis of coupling partner of Knoevenagel condensation. Key is to establish (*E*) stereoisomer of ethylidene group in the coupling partner and preserve the configuration. We turned our attention to bromination of crotonaldehyde, which was reported to give desired configuration of (*E*)-ethylidene moiety under certain condition.[8] Unfortunately, however, obtained product was revealed to be a (*E*)-bromobutenal **4**, rather than desired (*Z*)-bromobutenal **4'** (Scheme 4A).

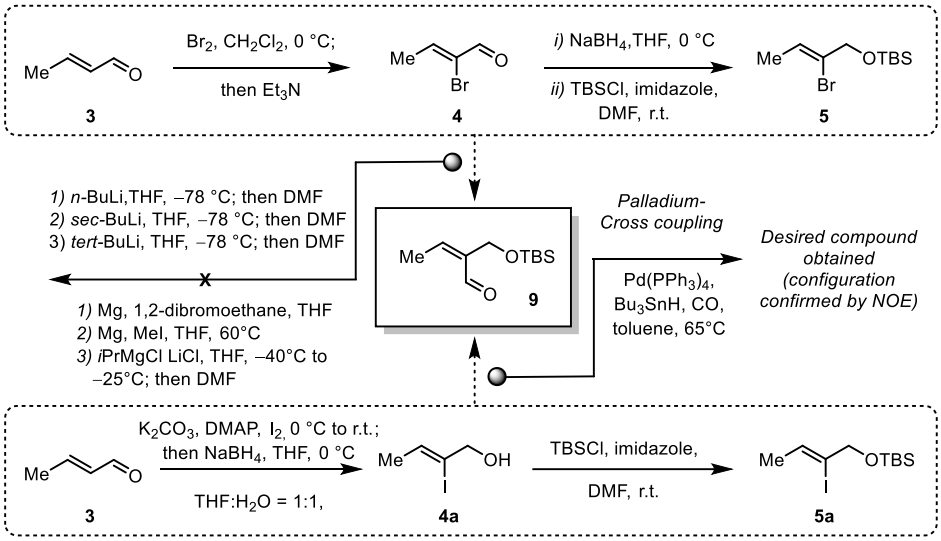


Scheme 4. Attempts on construction of coupling partner of Knoevenagel condensation (A) Bromination of crotonaldehyde; (B) Allylic functionalization of Baylis-Hillman adduct.

Alternative synthetic attempt has been made by utilizing Baylis-Hillman compound **6** (Scheme 4B). Allylic bromination and $S_N2`$ Mitsunobu reaction of 2-substituted methyl acrylate **6** were reported to furnish allylic bromide and allylic alcohol respectively, with (*E*) configuration in stereoselective manner. With allylic compound **7, 8a** in hand, a survey of simple oxidation was demonstrated to furnish aldehyde. Unexpectedly, all oxidation conditions with 4-Methylmorpholine N-oxide were not suitable for the substrate, while Dess-Martin reaction gave 1:1 ratio of *E/Z* isomers, presumably due to susceptive characteristic of α,β,γ-unsaturated formylbutenoate to isomerization.

2.2 Alternative Synthetic Pathway towards Aldehyde 9 and Preparation of α,β,γ-Unsaturated System 10

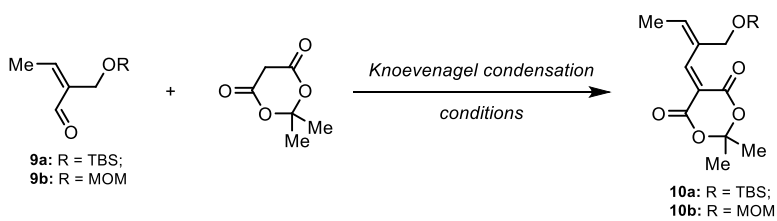
Revisiting previous trial, we decided to utilize previously obtained (*E*)-bromobutenal **4** by formylation of halide group (Scheme 5). Aldehyde **4** was reduced to alcohol, then protected with TBS group. Resulting protected alcohol was then treated with organolithium reagents for lithium-halogen exchange, to generate sp^2 anion. Finally, addition of N,N-Dimethylformamide was expected to give formylated compound. However, no formylation has been taken place. Subsequent quenching experiments revealed that organolithium reagents might induce further side reaction, which structure rearranged via elimination of OTBS group. To our delight, iodide **5a**, obtained from known three-step-procedure, resulted desired (*E*)-enal **9** via palladium-mediated carbonylation.[9]



Scheme 5. Altered Attempts on construction of coupling partner of Knoevenagel condensation.

Having two coupling partners in hand, Knoevenagel condensation was conducted following various conditions (Table 1).[10] Knoevenagel condensation with highly isomerizable aldehyde, however, was proved to be problematic. Not only configuration of aldehyde was easily mixed up, decreasing *E/Z* ratio down to 1:1 ratio since most conditions contained acid or base in catalytic or stoichiometric manner, but also it was confirmed that self-condensation of aldehyde was favored over coupling with Meldrum's acid.

Table 1. Knoevenagel Condensation Studies, Reagents and Conditions.



Entry	*Conditions*	*Result*
1	piperidine, benzene, r.t.	*Meldrum' acid remained unreacted, while aldehyde reacted.*
2	piperidine, EtOH, r.t.	
3	pyrrolidinium acetate, benzene, r.t.	
4	PPh_3, EtOH, r.t.	
5	DMAP, THF, r.t.	
6	$TiCl_4$, THF, 0 °C; then pyridine	
7	NaH, THF, 0 °C; then $TiCl(OiPr)_3$,	

From synthetic studies above, we realized that compound **10** was not suitable compound for practical material preparation. In fact, compound **10** embraced a few structural drawbacks (Figure 3). First, this highly activated diene system can undergo various side reactions. Closely related system was studied in 1988[11], and the study revealed that reaction conditions for Knoevenagel condensation can also be an appropriate condition for other side reactions (Figure 3A). Even if the diene system could be securely obtained, desired alkene configuration we aimed for is expected to give subtle distortion to the system due to 1,3 allylic strain between methyl C-H and C(sp^2)-H, and this, as we hypothesized, can boost isomerization to relieve the strain (Figure 3B). Also, the fact that no effective synthesis directly towards diene substituted Meldrum's acid is available so far is also a big obstacle.

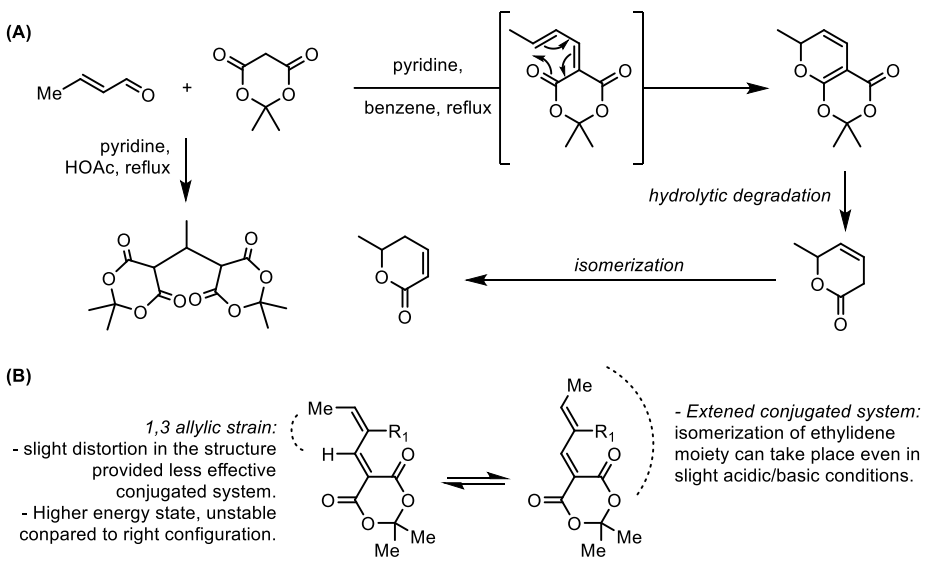


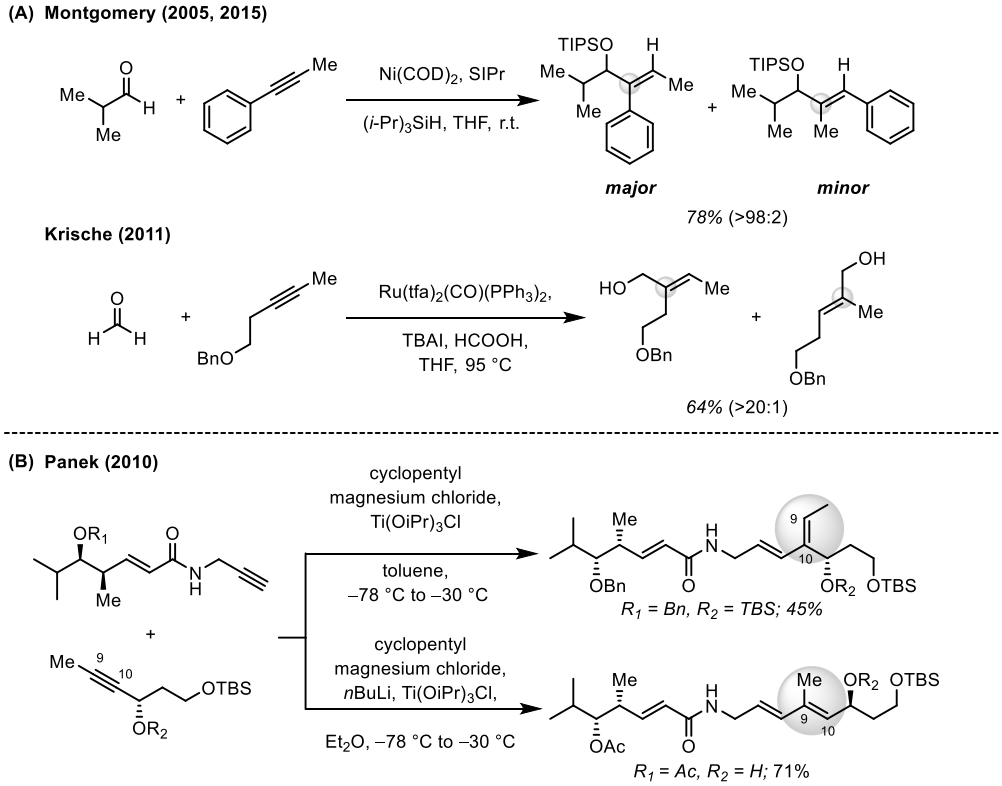
Figure 3. Hypothesis of compound susceptivity

2.3 Alternative Synthetic Pathway towards Intermediate via Alkyne-Aldehyde Reductive coupling

From the retrosynthetic point of view, utilizing crotonaldehyde as precursor of (*E*)-

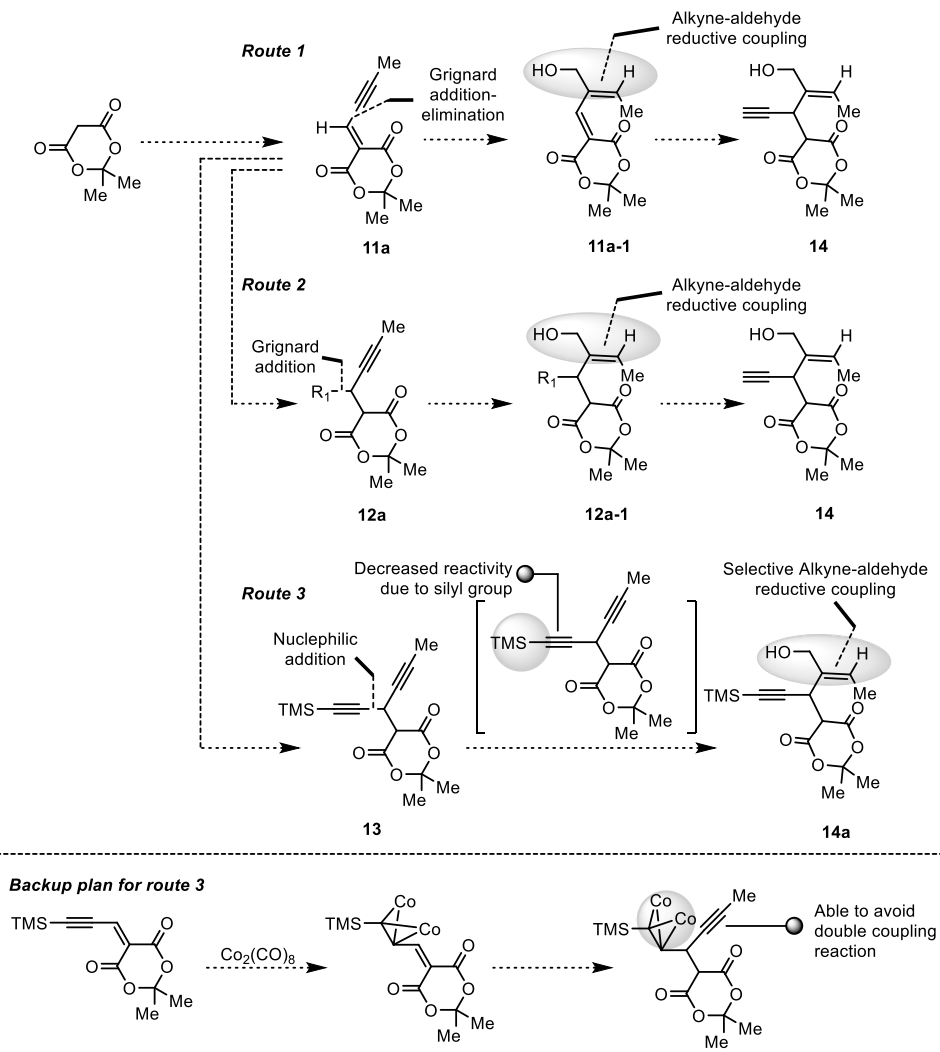
ethylidene was proved to be ineffective. Inspired by cis-constitution between methyl group and other functional group in the system we are aiming for, we conceived that alkyne-aldehyde reductive coupling would be able to give desired configuration in syn-addition manner. This strategy not only can provide functional group essential for later amination with tryptamine, but also can avoid isomerization we had difficulty in.

Alkyne-aldehyde reductive coupling has its rich history over the past few decades and has been a powerful tool for synthetic researches. However, one of the drawbacks is that regioisomers can be formed throughout the reaction, and in the vast majority of cases, regioselectivity is poorly controlled.



Scheme 6. Alkyne-Aldehyde Reductive Coupling (A) Prevously Developed Methods; (B) Application in Complex Molecule Synthesis

Extensive studies have revealed the solution for this problem (Scheme 6). Recently, Montgomery and coworkers[13a] developed regioselective alkyne-aldehyde reductive coupling. Under nickel(0) condition, excellent regio-control has been demonstrated by using sterically demanding NHC ligand and bulky silane. Also in 2011, Krische and coworkers[13b] developed regio- and stereoselective alkyne-formaldehyde coupling, and each Ruthenium and nickel provides different regioisomer. These methods presented the possibility of our new direction towards novel (*E*)-ethylidene moiety. This possibility was also supported by previously reported complex macromolecule synthesis paper.[12]



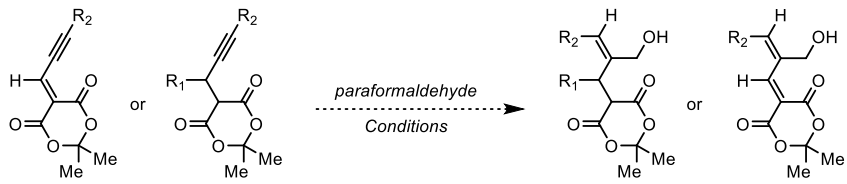
Scheme 7. Retorsynthesis towards intermediate via Alkyne-Aldehyde Reductive Coupling.

Based on these observations, the revised strategy of synthesis is described in Scheme 7. All three routes aimed for intermediate **14** and embraced same reductive coupling step throughout the sequences, but to slightly different substrates.

Route 1 is initiated from Meldrum's acid conjugated with 1-propynl group, and as desired reductive coupling occurs, previously mentioned extended conjugated dioxane-dione **11a-1** will be formed. In this case, isomerization is appeared to be inevitable. Route 2 is started with a substrate with functional group R_1 installed, which can be potentially transformed into alkyne moiety. By installing alkyne precursor in advance, extended conjugated system can be avoided as well as isomerization. In route 3, dual alkynyl compound will be utilized as the reductive coupling partner. Terminal alkyne moiety which will be further used for formal Pictet-Spengler reaction will be silyl-protected. Since a few examples have been reported that silylated terminal alkyne exhibited lower reactivity towards reductive coupling,[14] we anticipated that selective hydro-hydroxymethylation via intrinsic preference of the substrate might occur, thus giving allylic alcohol while TMS-alkyne remained unreacted. In case of unsated result, terminal alkyne can be protected in advance, and then propynl moiety can be introduced so to avoid unwanted double-coupling.

We started our investigation from synthesizing the series of alkynlated Meldrum's acids with both single alkyne and double alkyne moieties. Alkyne-aldehyde coupling conditions developed by Montgomery[12a] and Krische[12b] each were applied using formaldehyde as aldehyde coupling partner (Table 2).

Table 2. Various Alkynyl Meldrum's acid Substrates and Condition Screening.



11a, 11b | **12a, 12b:** R_1 = Me; **13:** R_1 = TMS-ethynyl, R_2 = Me | **12a-1, 12b-1:** R_1 = Me; **14a:** R_1 = TMS-ethynyl | **11a-1, 11b-1**

Entry	*Substrate*	*R_1*	*R_2*	*Conditions*	*Result*
1	13	TMS-ethynyl	Me	$Ru(tfa)_2(CO)(PPh_3)_2$,TBAI, HCOOH, THF, 95 °C	*Dimerized*
2	13	TMS-ethynyl	Me	$Ni(COD)_2$, PCy_3, Cs_2CO_3, H_2O, toluene, 75 °C	
3	13	TMS-ethynyl	Me	$Ni(COD)_2$, SIPr, *t*BuOK, $(i\text{-}Pr)_3SiH$, THF, r.t. to reflux	
4	12a	Me	Me	$Ru(tfa)_2(CO)(PPh_3)_2$,TBAI, HCOOH, THF, 95 °C	
5	12a	Me	Me	$Ni(COD)_2$, PCy_3, Cs_2CO_3, H_2O, toluene, 75 °C	
6	12a	Me	Me	$Ni(COD)_2$, SIPr, *t*BuOK, $(i\text{-}Pr)_3SiH$, THF, r.t. to reflux	
7	12b	Me	TMS	$Ru(tfa)_2(CO)(PPh_3)_2$,TBAI, HCOOH, THF, 95 °C	
8	12b	Me	TMS	$Ni(COD)_2$, PCy_3, Cs_2CO_3, H_2O, toluene, 75 °C	
9	12b	Me	TMS	$Ni(COD)_2$, SIPr, *t*BuOK, $(i\text{-}Pr)_3SiH$, THF, r.t. to reflux	
10	11a	H	Me	$Ru(tfa)_2(CO)(PPh_3)_2$,TBAI, HCOOH, THF, 95 °C	
11	11a	H	Me	$Ni(COD)_2$, PCy_3, Cs_2CO_3, H_2O, toluene, 75 °C	

To our disappointment, however, numerous trials of optimization proved to be unsuccessful. Notably, all reactions gave alkyne-alkyne coupling product without no alkyne-aldehyde coupling like expected product **11a-1**, **11b-1**, **12a-1**, **12b-1** or **14a**. The rationale of this outcome is described in Figure 4. We postulated that dimerized/trimerization prevailed over aldehyde coupling in the presence of Meldrum's acid moiety in system, presumably due to directing effect of dione closely placed near alkyne group.

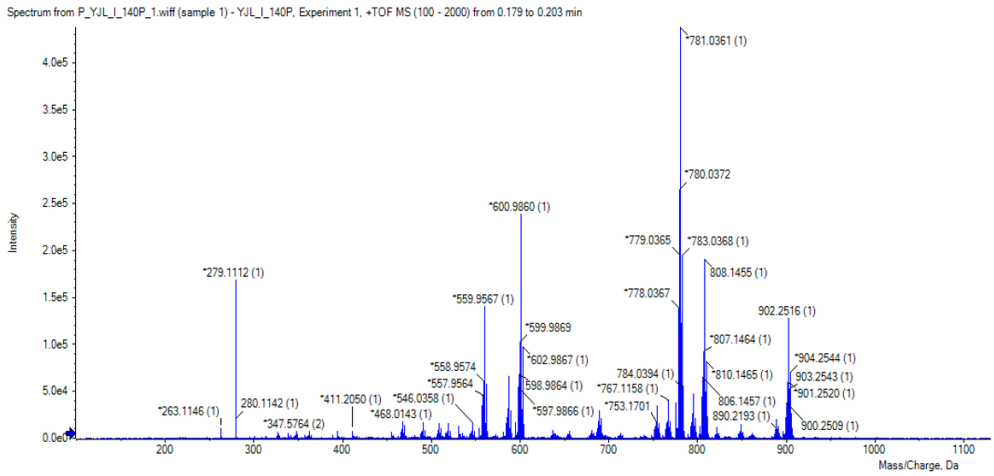
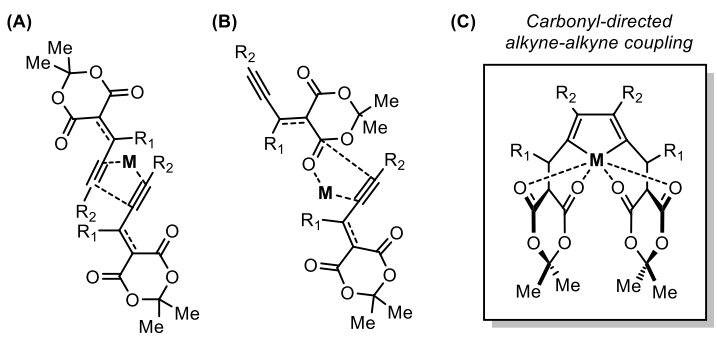


Figure 4. Plausible intermolecular side-reactions



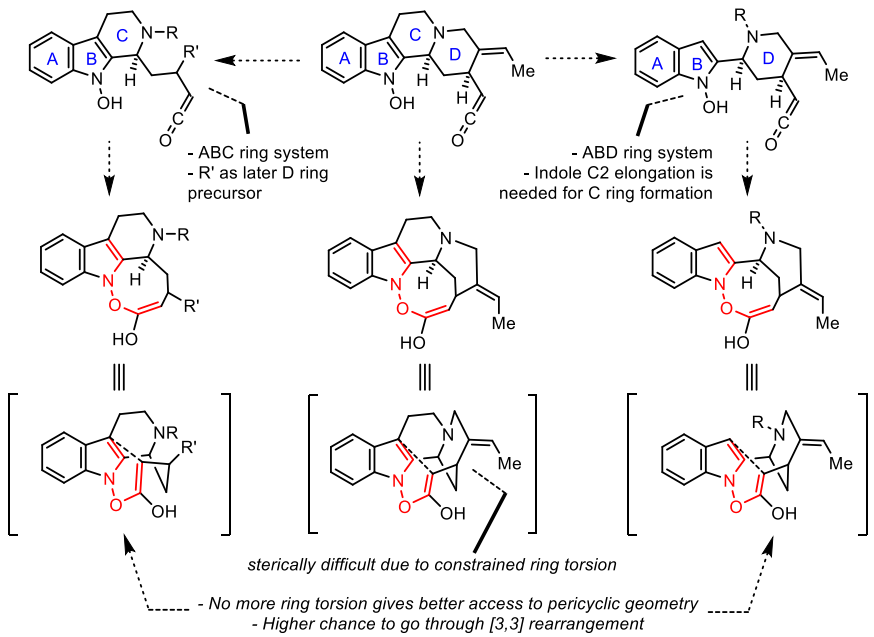
Synthetic effort above implied that dioxane-dione group is not pertinent for certain reactions, especially transition metal-catalyzed reactions presumably due to both reactivity and metal-directing effect, let alone with acidic α-proton and thermal instability. Unable to install functionalized D ring moiety successfully, it was obvious that we should put our attention to different part of the molecule. For this reason, we rearranged the order of functionalization and restructured the overall synthetic plan.

2.4 Examination in Rigidity Driven [3,3]-Ireland-Claisen Sigmatropic Rearrangement

Preliminary synthetic studies implied that Meldrum's acid moiety can be an impeding factor for certain functional group manipulations, especially transition-metal catalysis.

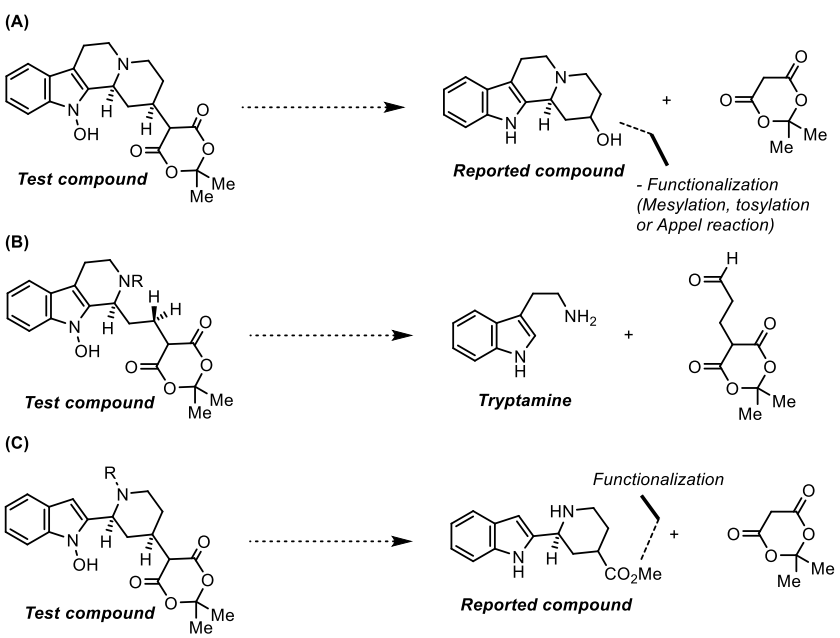
Our attention now is turned to an achievement of one of the key ideas, which is rigidity-dependent [3,3]-Ireland-Claisen type sigmatropic rearrangement. Although our aim is still developing an direct synthesis of rhazimal from geissoschizine core, previous studies alluded that ring strain in tetracyclic core might be critical for C7-C16 bond formation. Clearly there are positive factors that structural rigidity can also prohibit undesired [3,3]-sigmatropic rearrangement in indole C7 position, but at the same time we decided to consider insight from previous synthetic works, and study with tricyclic core system concurrently.

For this reason, we rearranged the order of functionalization and restructured the overall synthetic plan. We sought to demonstrate the key [3,3]-sigmatropic rearrangement in model substrates. Initial model studies were commenced with the preparation of three different types of tricyclic core and tetracyclic core for proof-of-concept study. Tetracyclic core system can be more attractive model as it can be a closer representative for direct access of rhazimal core structure from geissoschizine-core. Nevertheless, tricyclic systems should not be taken lightly, as according to postulation in Vincent's paper and related synthetic studies,[5c] high ring strain of core structure can be a major obstacle to establish $\pi-\pi$ stacking for [3,3]-rearrangement transition state due to its rigidity. Also, we conceived that different rigidity each model has will offer divergent reactivities towards key transformation step and starting from here, further studies towards optimization of key rearrangement relying on its constrained structure can be commenced (Scheme 8).



Scheme 8. Hypothesis of Rigidity-Dependent [3,3]-Rearrangement in Multi-cyclic Systems.

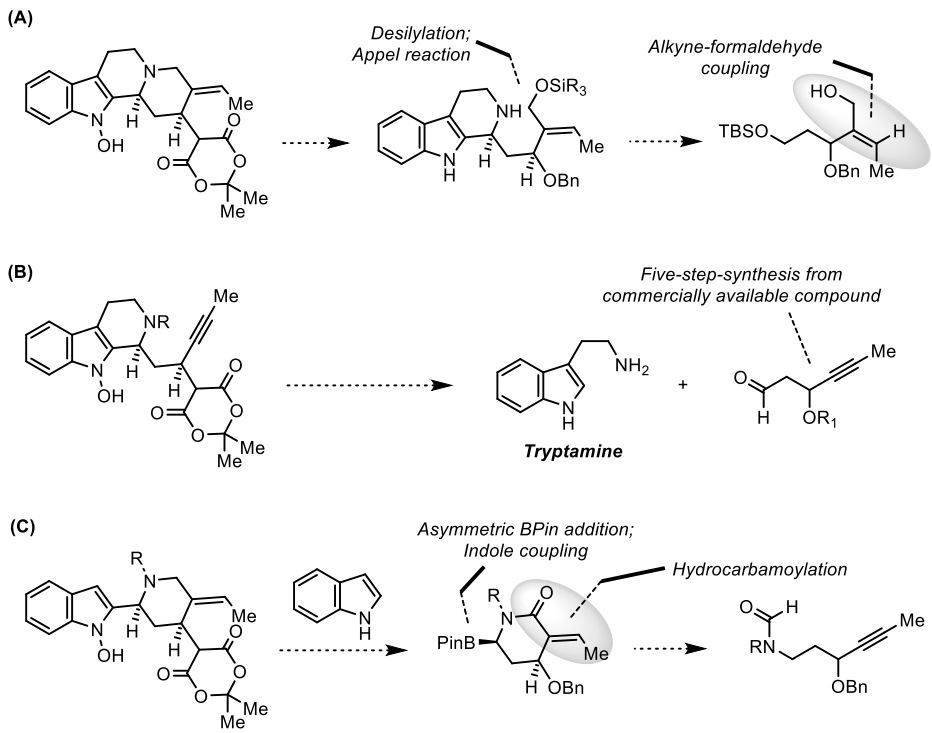
Synthetic strategies for ABCD ring system, ABC ring system, ABD ring system are outlined below (Scheme 9). Test substrates will be synthesized first, followed by real synthetic substrates depending on rearrangement results.



Scheme 9. Preparation of Model Substrates (A) ABCD ring system; (B) ABC ring system; (C) ABD ring system.

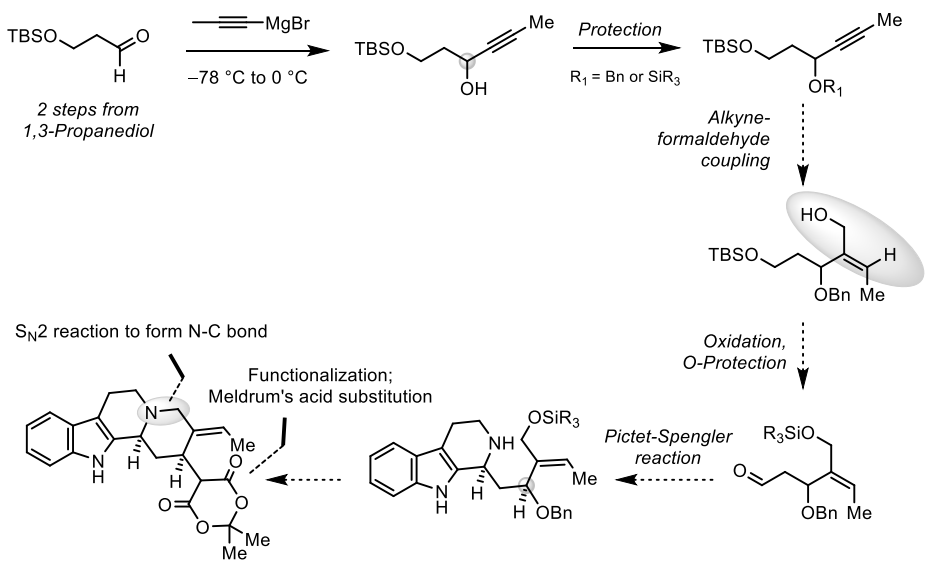
2.5 Future Plan

The goal we are aiming for can be summarized in three sections. First, revised intermediate approaching towards Rhazimal will be prepared, in parallel with model substrates. Retrosynthetic view is outlined in Scheme 10, and specific preparation steps are described through Scheme 11, 12, 13. All three routes are initiated with preparation of alkyne substrate, which shares highly similar reaction sequences with same or slightly different starting material.



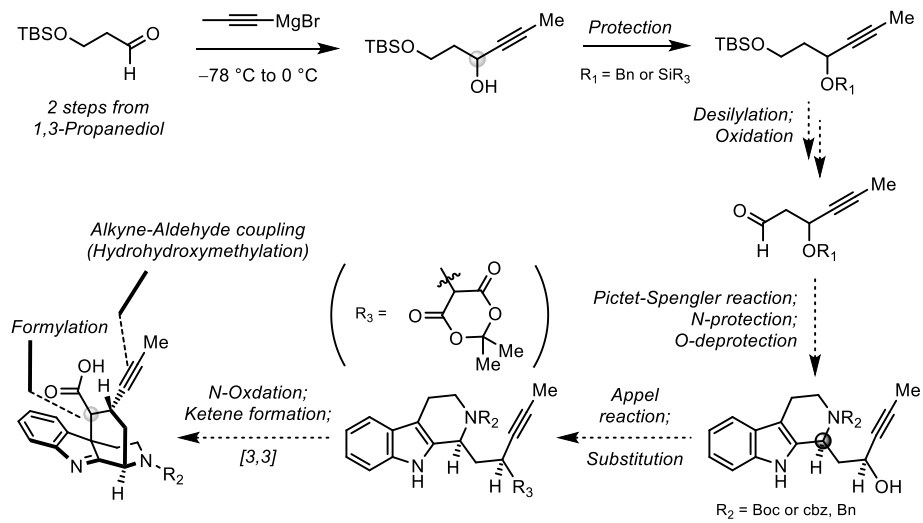
Scheme 10. Retrosynthetic route of multi-cyclic systems (A) ABCD ring system; (B) ABC ring system; (C) ABD ring system.

The synthetic route for tetracyclic core system is described in Scheme 11. Silyl-protected hydroxyl propanal will be undergone Grignard addition to obtain alkynl moiety. Alkyne coupling with formaldehyde will give allylic alcohol, which will become aldehyde partner for Pictet-Spengler reaction after a few transformations. Silyl protected alcohol will be deprotected, then halogenated to form C-N bond as a closure for last D ring moiety. N-oxidation, ketene formation and [3,3] Ireland-Claisen rearrangement will be attempt in completed tetracyclic skeleton substrate.



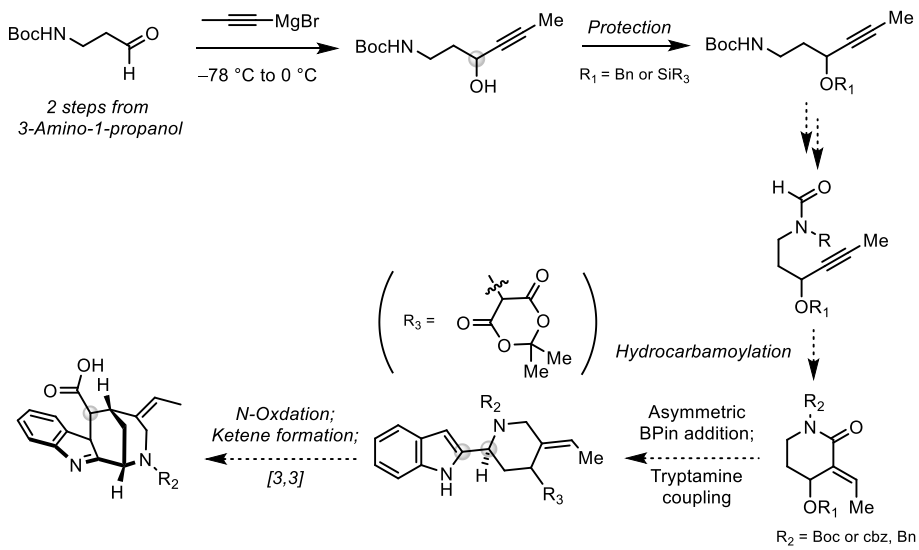
Scheme 11. Synthetic Plan of Rhazimal via ABCD ring system intermediate.

The synthetic route for ABC tricyclic core system is described in Scheme 12. Identical sequence of previous tetracyclic core synthesis will be followed to get silyl protected alkyne substrate. Alkyne, however, will remain untouched until we get tricyclic core through Pictet-Spengler reaction. After successful [3,3] Ireland-Claisen rearrangement, last ring closure will be imposed via hydrohydroxymethylation.



Scheme 12. Synthetic Plan of rhazimal via ABC ring core intermediate.

The synthetic route for ABD tricyclic core system is described in Scheme 13. Identical sequence of previous tetracyclic core synthesis will be used, but with 3-amino-1-propanal. This additional nitrogen will become the corresponding trialkylamine in D ring. After installing formamide moiety, hydrocarbamoylation will be done to get D ring moiety with (*E*)-ethylidene group After amide reduction, asymmetric BPin addition in carbon adjacent to nitrogen will be able to couple D ring with indole, thus achieve ABD ring skeleton. After key [3,3] rearrangement, 6-membered ring cyclization between indole C7 and N4 will be the last ring closure to complete rhazimal.



Scheme 13. Synthetic Plan of Rhazimal via ABD ring system intermediae.

Secondly, key [3,3] Ireland-Claisen rearrangement in indole N-oxide substrate should be well studied. Even though there are a few experimental proofs that support the possibility of the reaction, investigation of reaction conditions, reactivity of N-oxide and silyl enol ether etc. using model substrate will give vague idea of how to success the reactions in real system.

Lastly, investigation of later stage selective functionalizations cannot be underrated. This effort can be directly connected to collective syntheses of relevant natural products, consummating bioinspired syntheses of akuammiline.

3. CONCLUSION

In summary, a synthetic endeavor towards total synthesis of rhazimal has been demonstrated. One of key intermediate α,β,γ-unsaturated substrate **10** which we initially considered as easily affordable, was found to be wrong. Not only limited scope of Knoevenagel condensation was problematic, but also structural property which is highly susceptible to either acidic, basic conditions was critical. Based on these observations, an improved and practical solution has been proposed.

Firstly, alkyne-aldehyde coupling on functionalized Meldrum's acid substrates were examined. Unfortunately, it showed undesired dimerization under metal-mediated conditions. Assumption is that has directing effect, along with electron-withdrawing effect of Meldrum's acid have boosted dimerization/trimerization.

Secondly, rigidity-dependent [3,3]-Ireland-Claisen type sigmatropic rearrangement should be investigated using differently designed structures based on their number of rings. Overall three core systems are under synthesizing, and from these substrates, better system for key rearrangement will be determined.

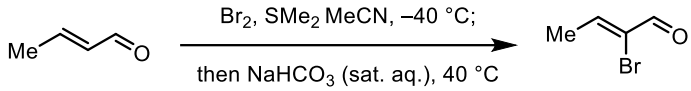
In parallel, synthetic endeavor towards real substrate preparation also will be organized in near future. As three possible routes branch out from same reaction sequence, intermediate can be easily synthesized simultaneously and be devoted to one of the three sequences depending on the result of model study.

4. EXPERIMENTAL SECTION

General Procedures

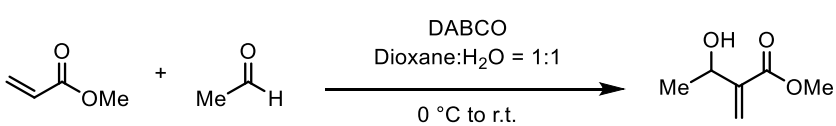
Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2) and toluene were dried and distilled according to the standard protocols. Benzene and acetonitrile (CH_3CN) were purchased in anhydrous form and used without further purification. Acetone, ethyl acetate (EtOAc), Et_2O, CH_2Cl_2, hexanes and water were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F−254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, anisaldehyde or potassium permanganate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on an Agilent 400-MR DD2 Magnetic Resonance System or Varian/Oxford As-500 instrument and calibrated using residue undeuterated solvent as internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Scientific Nicolet 6700 spectrometer and IRTracer-100 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker (compact) Ultra High Resolution ESI Q-TOF mass spectrometer. Optical rotation ([α]) was recorded on a Jasco P-1030 polarimeter.

(*Z*)-2-bromobut-2-enal 4



To a stirred solution of dimethyl sulfide (1.67 mL, 22.6 mmol) in acetonitrile (20 mL) at –40 ℃ was added bromine (0.77 mL, 15.1 mmol) in CH_2Cl_2 (4 mL) dropwise. The resulting mixture was stirred for 10 min before crotonaldehyde (1.0 mL, 12.1 mmol) was added. The resulting mixture was slowly warmed up to 0 °C and stirred for 30 min. The precipitate was filtered, washed with hexane (1 × 20 mL) and CH_2Cl_2 (1 × 20 mL), and dissolved in $NaHCO_3$ (30 mL, sat. aq.) and stirred for additional 15 min at 35 °C before CH_2Cl_2 (20 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 8:2) to afford (*Z*)-2-bromobut-2-enal (0.68 g, 38 %) as a colorless oil. **(*Z*)-2-bromobut-2-enal 4:** R_f= 0.52 (silica gel, hexanes:EtOAc 8:2); IR (film) ν_{max} 2928, 1698, 1624, 1172, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.22 (q, J = 7.0 Hz, 1H), 2.12 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.9, 150.8, 130.1, 17.9 ppm.

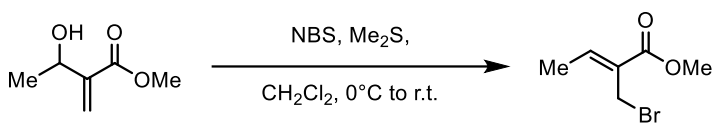
Hydroxyester 6



To a stirred solution of methyl acrylate (16.0 mL, 178.9 mmol) in 1,4-dioxane: H_2O (1:1, 20 mL) at 0 °C was added acetaldehyde (5.0 mL, 89.4 mmol) followed by DABCO (10.0 g, 89.4 mmol). The resulting mixture was stirred for 3 days at room temperature before it was quenched with H_2O (30 mL). The layers were separated and the aqueous layer was extracted

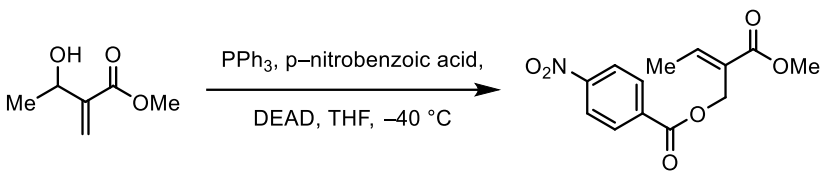
with EtOAc (3 × 30 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 8:2) to afford hydroxyester **5** (6.28 g, 54 %) as a colorless oil. **6:** R_f = 0.27 (silica gel, hexanes:EtOAc 8:2); IR (film) ν_{max} 3411, 1715, 1439, 1279, 1099, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.20 (s, 1H), 5.81 (d, J = 1.4 Hz, 1H), 4.60 (t, J = 5.8 Hz, 1H), 3.77 (s, 3H), 2.62 (d, J = 4.8 Hz, 1H), 1.37 ppm (dd, J = 6.5, 0.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 143.3, 124.2, 67.2, 51.9, 22.0 ppm; HRMS calcd. For $C_6H_{10}O_3Na^+$ $[M + Na]^+$ 153.0529, found 153.0522.

Bromoester 7



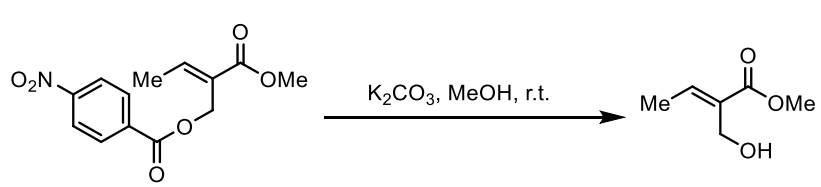
To a stirred solution of *N*-Bromosuccinimide (8.68 g, 48.8 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added dimethyl sulfide (4.32 mL, 58.4 mmol) dropwise. The resulting mixture was stirred for 10 min before a solution of **6** (6.28 g, 48.3 mmol) in CH_2Cl_2 (63 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 16 h before it was quenched with water (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 7:3) to afford bromoester **6** (6.6 g, 71 %) as a pale yellow oil. **7:** R_f = 0.75 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 2316, 1724, 1434, 1264, 1099, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.06 (q, J = 7.3 Hz, 1H), 4.22 (s, 2H), 3.77 (s, 3H), 1.90 ppm (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 150.8, 130.1, 17.9 ppm.

Nitrobenzoate 7a



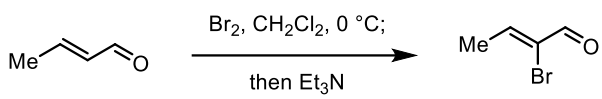
To a stirred solution of **6** (2.85 g, 21.9 mmol) in THF (44 mL) was added PPh_3 (7.47 g, 28.5 mmol) and p-nitrobenzoic acid (4.76 g, 28.5 mmol). The resulting mixture was cooled to at –40 °C and DEAD (4.51 mL, 28.5 mmol) was added dropwise, slowly warmed up to –30 °C over 1 h and stirred for additional 1 h before solution was warmed up to 0 °C. The resulting mixture was stirred for additional 15 min before it was concentrated under reduced pressure. The residue was dissolved in Et_2O (30 mL) and H_2O (50 mL). The layers were separated and the aqueous layer was washed with H_2O (1 × 50 mL), NaOH (20 mL, sat. aq.), extracted with Et_2O (3 × 30 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 7:3) to afford nitrobenzoate **7a** (5.08 g, 83 %) as a white solid. **7a:** R_f = 0.82 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 2924, 1717, 1520, 1293, 1124, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 – 8.22 (m, 2H), 8.18 – 8.13 (m, 2H), 7.23 (q, J = 7.2 Hz, 1H), 5.14 (s, 2H), 3.77 (s, 3H), 1.99 ppm (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 164.5, 150.5, 145.4, 135.4, 130.8, 127.5, 123.5, 59.0, 52.0, 14.8 ppm; HRMS calcd. For $C_{13}H_{13}NO_6Na^+$ $[M + Na]^+$ 302.0638, found 302.0635.

Hydroxyester 8a



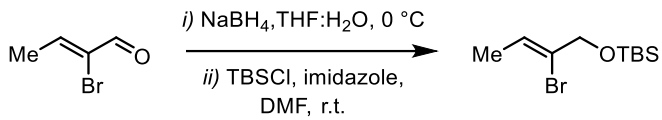
To a stirred solution of **7a** (5.08 g, 18.2 mmol) in MeOH (30 mL) at room temperature was added K_2CO_3 (2.515 g, 18.2 mmol). The resulting mixture was stirred for 1 h before it was quenched with H_2O (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 7:3) to afford hydroxyester **8a** (1.50 g, 63 %) as a colorless oil. **8a:** R_f = 0.29 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 3420, 1713, 1437, 1284, 1140, 1006, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.96 (q, J = 7.3 Hz, 1H), , 4.33 (s, 2H), 3.75 (s, 3H), 1.88 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 140.4, 131.39, 56.6, 51.5, 13.8 ppm; HRMS calcd. For $C_6H_{10}O_3Na^+$ $[M + Na]^+$ 153.0530, found 153.0522.

(Z)-2-bromobut-2-enal 4



To a stirred solution of crotonaldehyde (1.0 mL, 12.07 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added bromine (0.63 mL, 12.2 mmol). The resulting mixture was stirred for 1 h before Et_3N (2.0 mL, 14.5 mmol) was added. The resulting mixture was stirred for 1 h, warmed to room temperature and stirred for additional 1 h before it was quenched with NH_4Cl (20 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. All physical properties of bromoaldehyde are identical to those obtained from Pictet-Spengler reaction of (*Z*)-2-bromobut-2-enal.

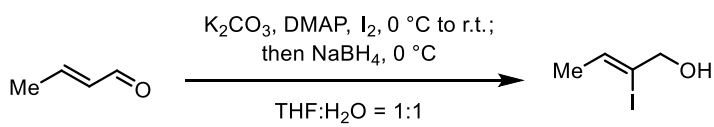
TBS ether 5



i) To a stirred solution of (*Z*)-2-bromobut-2-enal 4 (1.80 g, 12.1 mmol) in THF: H_2O (9:1, 10 mL) at 0 °C was added $NaBH_4$ (0.69 g, 18.1 mmol). The resulting mixture was stirred for 1 h before it was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was used directly without further purification.

ii) To a stirred solution of compound above (crude, 1.82 g, 12.07 mmol) in DMF (13 mL) at room temperature was added imidazole (2.47 g, 36.2 mmol) followed by TBSCl (3.68 g, 24.1 mmol). The resulting mixture was stirred for 16 h before it was quenched with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL), washed with brine (3 × 50 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 9:1) to afford TBS ether **5** (2.18 g, 68 %) as a colorless oil. **5:** R_f = 0.80 (silica gel, hexanes:EtOAc 9:1); IR (film) ν_{max} 2961, 2863, 1259, 1099, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.05 (q, *J* = 6.8 Hz, 1H), 4.23 (s, 2H), 1.75 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.0, 122.7, 68.1, 25.8, 25.7, 18.4, 18.1, 16.1, –3.0, –5.3 ppm.

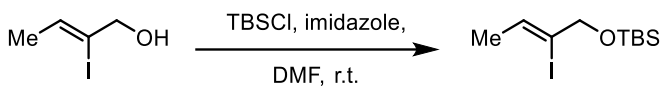
(Z)-2-iodobut-2-en-1-ol 4a



To a stirred solution of crotonaldehyde (3.55 mL, 42.8 mmol) in THF:H_2O (1:1, 86 mL) at

0 °C was added K_2CO_3 (7.20 g, 52.1 mmol) followed by DMAP (1.05 g, 8.56 mmol) and iodine (16.43 g, 64.8 mmol). The resulting mixture was warmed up to room temperature and stirred for 3 h. The reaction mixture was again cooled to 0 °C before $NaBH_4$ (1.62 g, 42.8 mmol) was added. The resulting mixture was stirred 2 h before it was quenched with H_2O (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 7:3) to afford (*Z*)-2-iodobut-2-en-1-ol **4a** (6.35 g, 75 %) as a pale yellow oil. **4a:** R_f= 0.32 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 3327, 2937, 1646, 1296, 1078, 897, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.95 (dt, *J* = 6.3, 1.2 Hz, 1H), 4.23 (s, 2H), 1.87 (s, 1H), 1.78 ppm (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.3, 109.6, 71.5, 21.4 ppm.

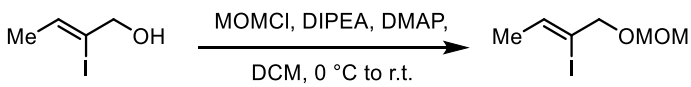
TBS ether 5a



To a stirred solution of (*Z*)-2-iodobut-2-en-1-ol 4a (1.40 g, 7.12 mmol) in DMF (14 mL) was added imidazole (1.46 g, 21.4 mmol) followed by TBSCl (2.15 g, 14.2 mmol). The resulting mixture was stirred for 16 h before it was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL), washed with brine (3 × 20 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 9:1) to afford TBS ether **5a** (1.91 g, 86 %) as a pale pink oil **5a:** R_f= 0.89 (silica gel, hexanes:EtOAc 9:1); IR (film) ν_{max} 2998, 1773, 1379, 1245, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.96 (dt, *J* = 6.5, 1.7 Hz, 1H), 4.24 (s, 2H), 1.77 (d, *J* =

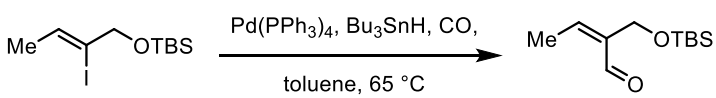
6.3 Hz, 3H), 0.9 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.7, 108.8, 71.5, 25.9, 21.2, 18.4, –5.2 ppm.

MOM ether 5b



To a stirred solution of (*Z*)-2-iodobut-2-en-1-ol 4a (1.80 g, 9.09 mmol) in CH_2Cl_2 (18 mL) at 0 °C was added MOMCl (2.76 mL, 36.4 mmol) followed by DIPEA (6.30 mL, 14.2 mmol) and DMAP (0.11 g, 0.91 mmol). The resulting mixture was warmed up to room temperature and stirred for 16 h before it was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 9:1) to afford MOM ether **5b** (1.93 g, 88 %) as a pale yellow oil **5b:** R_f = 0.89 (silica gel, hexanes:EtOAc 9:1); IR (film) ν_{max} 2998, 1771, 1379, 1245, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (tdt, *J* = 6.3, 5.2, 1.2 Hz, 1H), 4.63 (s, 2H), 4.22 (s, 2H), 3.38 (s, 3H), 1.78 ppm (dd, *J* = 6.4, 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 104.8, 94.9, 75.1, 55.6, 21.5 ppm.

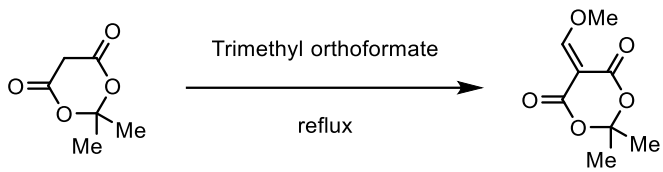
Aldehyde 9a



To a stirred solution of TBS ether **5a** (227 mg, 0.73 mmol) in degassed, CO bubbled toluene (7.3 mL) was added $Pd(PPh_3)_4$ (59.0 mg, 51 μmol). The resulting mixture was warmed up to 65 °C and a solution of Bu_3SnH (0.23 mL, 0.95 mmol) in toluene (3 mL) was added dropwise

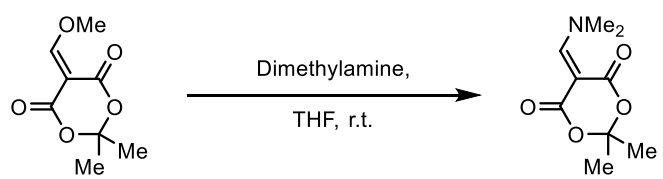
via syringe pump over 1 h. The resulting mixture was stirred for additional 1 h before cooled to room temperature. The resulting mixture was concentrated under reduced pressure and purified directly by flash column chromatography (silica gel, hexanes:EtOAc 1:0 → 8:2) to afford aldehyde **9a** (87.5 mg, 56 %) as a pale yellow oil. **9a:** R_f= 0.67 (silica gel, hexanes:EtOAc 8:2).

5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione



To a stirred solution of Meldrum's acid (7.00 g, 48.6 mmol) was dissolved in trimethylorthoformate (50 mL). The resulting mixture was refluxed for 4 h before it was concentrated under reduced pressure. The resulting mixture was dissolved in THF (8 mL) and then hexanes (40 mL) for recrystallization to afford 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.26 g, 58 %) as a white crystal. **5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione:** R_f= 0.19 (silica gel, EtOAc:MeOH 7:3); IR (film) ν_{max} 1731, 1437, 1247, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.24 (s, 3H), 1.66 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 163.1, 158.6, 104.7, 96.8, 66.3, 27.2 ppm; HRMS calcd. For $C_8H_{10}O_5Na^+$ $[M + Na]^+$ 209.0422, found 209.0420.

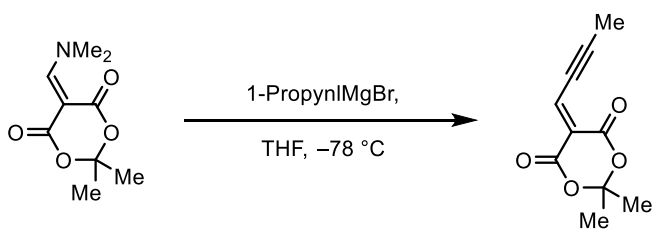
5-((dimethylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione



To a stirred solution of 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.00 g,

10.7 mmol) in acetonitrile (50 mL) was added dimethylamine (2.0 M in THF, 5.91 mL, 11.8 mmol). The resulting mixture was stirred for 1 h before it was concentrated under reduced pressure. The resulting mixture was dissolved in EtOAc (5 mL) and then hexanes (50 mL) for recrystallization to afford 5-((dimethylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.03 g, 95 %) as a pale yellow crystal. **5-((dimethylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione:** R_f = 0.11 (silica gel, EtOAc:MeOH 7:3); IR (film) ν_{max} 1722, 1676, 1377, 1203, 1113, 932, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.34 (s, 3H), 3.23 (s, 3H), 1.64 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 102.8, 83.9, 48.6, 43.8, 26.4 ppm; HRMS calcd. For $C_9H_{13}NO_4Na^+$ $[M + Na]^+$ 222.0740, found 222.0737.

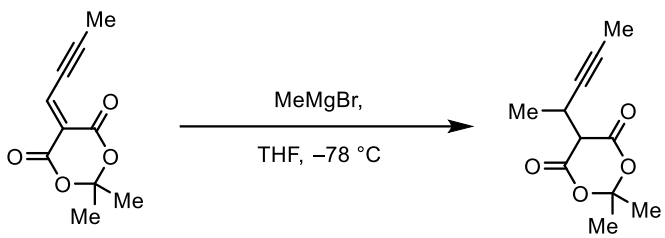
Alkyne 11a



To a stirred solution of 5-((dimethylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.20 g, 1.00 mmol) in THF (10 mL) at −78 °C was added 1-propynl magnesium bromide (0.5 M in THF, 2.2 mL, 1.10 mmol). The resulting mixture was stirred for 2 h before it was quenched with NH_4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 →6:4) to afford Alkyne **11a** (0.14 g, 72 %) as a pale yellow solid. **11a:** R_f = 0.43 (silica gel, hexanes:EtOAc 3:7); IR (film) ν_{max} 2218, 1734, 1597, 1284, 1177, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (q, J = 2.8 Hz, 1H), 2.28 (d, J = 2.8 Hz, 3H), 1.72 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 158.5,

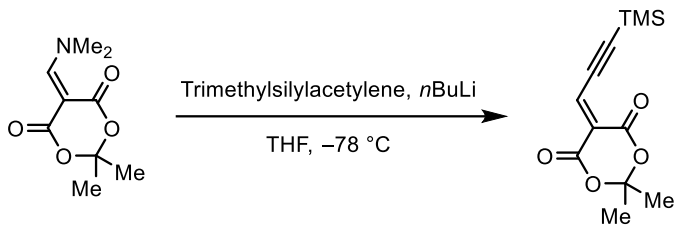
139.0, 123.0, 118.7, 105.0, 78.8, 27.7, 6.4 ppm; HRMS calcd. For $C_9H_{13}NO_4Na^+$ $[M + Na]^+$ 249.0741, found 222.0737.

Alkyne 12a



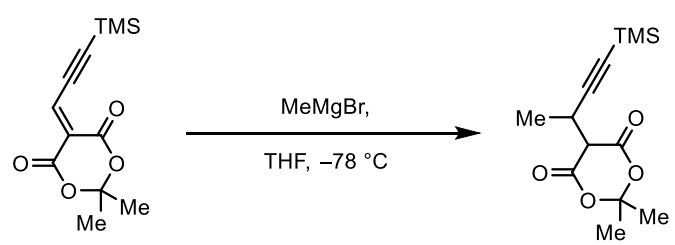
To a stirred solution of alkyne **11a** (0.14 g, 0.72 mmol) in THF (8 mL) at −78 ℃ was added methyl magnesium bromide (3.0 M in diethyl ether, 0.36 mL, 1.08 mmol). The resulting mixture was stirred for 2 h before it was quenched with NH_4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 →6:4) to afford alkyne **12a** (0.10g, 66 %) as a pale yellow solid **12a:** R_f= 0.16 (silica gel, hexanes:EtOAc 3:7); IR (film) ν_{max} 2923, 1789, 1752, 1300, 1205, 987 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (s, 1H), 3.50 (s, 1H), 1.76 (s, 9H), 1.43 ppm (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 163.7, 105.1, 78.6, 78.2, 51.0, 29.7, 28.5, 27.4, 25.8, 18.8, 3.6 ppm; HRMS calcd. For $C_{11}H_{14}O_4Na^+$ $[M + Na]^+$ 233.0787, found 233.0784.

TMS Alkyne 11b



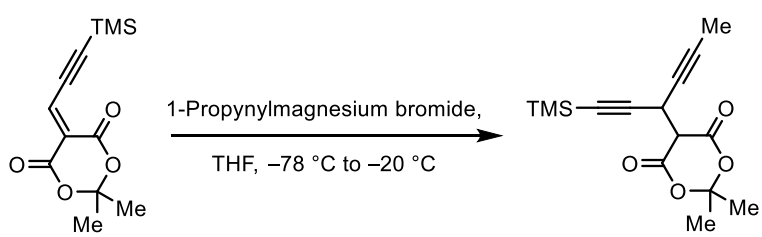
To a stirred solution of trimethylsilylacetylene (5.47 mL, 39.5 mmol) in THF (30 mL) at −78 °C was added *n*BuLi (2.5 M in hexanes, 13.5 mL, 33.8 mmol). The resulting mixture was stirred for 1 h before a solution of 5-((dimethylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.62 g, 28.2 mmol) in THF (20 mL) was added. The reaction mixture was stirred for additional 1 h before it was quenched with NH_4Cl (50 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 →6:4) to afford TMS alkyne **11b** (5.23 g, 74 %) as a pale yellow solid. **11b:** R_f = 0.66 (silica gel, hexanes:EtOAc 3:7); IR (film) ν_{max} 1794, 1752, 1298, 1203, 987, 878, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (dt, J = 4.5, 1.7 Hz, 1H), 1.71 (s, 6H), 0.26 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 158.0, 136.7, 127.4, 124.3, 105.1, 100.7, 27.8,−1.1 ppm; HRMS calcd. For $C_{12}H_{16}O_4SiNa^+$ $[M + Na]^+$ 275.0714, found 275.0710.

TMS Alkyne 12b



To a stirred solution of TMS alkyne **11b** (0.50 g, 1.98 mmol) in THF (10 mL) at −78 ℃ was added methyl magnesium bromide (3.0 M in diethyl ether, 1.0 mL, 2.97 mmol). The resulting mixture was stirred for 2 h before it was quenched with NH_4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 →6:4) to afford TMS alkyne **12b** (0.38 g, 72 %) as a pale yellow solid **12b:** R_f = 0.30 (silica gel, hexanes:EtOAc 3:7); IR (film) ν_{max} 1794, 1752, 1298, 1203, 987, 878, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.60 (qd, J = 7.1, 2.7 Hz, 1H), 3.52 (d, J = 2.9 Hz, 1H), 1.75 (s, 6H), 1.44 (d, J = 7.1 Hz, 3H), 0.09 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 163.6m 105.7, 105.1, 87.0, 50.7, 28.6, 27.5, 26.8, 18.5, −0.1 ppm; HRMS calcd. For $C_{13}H_{20}O_4SiNa^+$ $[M + Na]^+$ 291.1026, found 291.1023.

TMS Alkyne 13



To a stirred solution of TMS alkyne **11b** (52.0 mg, 0.21 mmol) in THF (6.2 mL) at −78 ℃ was added 1-propynl magnesium bromide (0.5 M in THF, 0.62 mL, 0.31 mmol) dropwise. The resulting mixture was stirred for 1h and warmed up to −20 ℃, stirred for 16 h before it was quenched with 1N HCl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 1:0 →6:4) to afford TMS alkyne **13** (41.2

mg, 68 %) as a pale yellow solid. **13:** R_f= 0.18 (silica gel, hexanes:EtOAc 3:7); IR (film) ν_{max} 1793, 1335, 1293, 1201, 1013, 897, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.53 (t, J = 2.6 Hz, 1H), 3.77 (d, J = 2.7 Hz, 1H), 1.77 (d, J = 3.6 Hz, 9H), 0.13 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 162.3, 105.2, 99.8, 87.3, 79.1, 72.7, 51.4, 28.4, 27.3, 23.3, 3.8, -0.3 ppm; HRMS calcd. For $C_{15}H_{20}O_4SiNa^+$ $[M + Na]^+$ 315.1025, found 315.1023.

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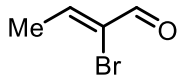
6. LIST OF ABBREVIATIONS

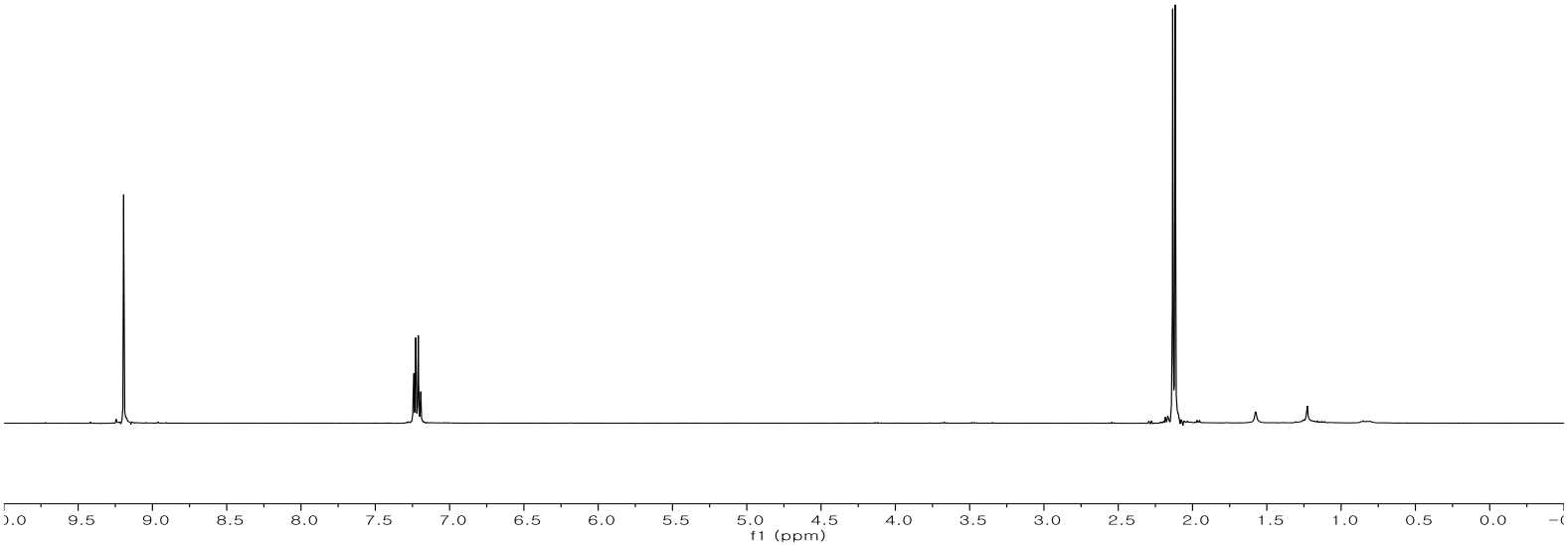
Ac	acetate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEAD	Diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
Et_3N	Triethylamine
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
Me	methyl
MOM	methoxymethyl
MS	molecular sieves
NBS	*N*-bromosuccinimide
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
PPh_3	Triphenylphosphine
SIPr	1,3-Bis-(2,6-diisopropylphenyl)imidazolinium chloride
TBAI	Tetrabutylammonium iodide
TBS	tert-butyldimethylsilyl

tfa	CF_3COO^-
THF	tetrahydrofuran
TMS	trimethylsilyl

7. ^{1}H and ^{13}C NMR Spectra for Compounds

^{1}H NMR (400 MHz, $CDCl_3$)





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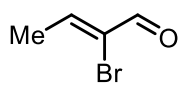

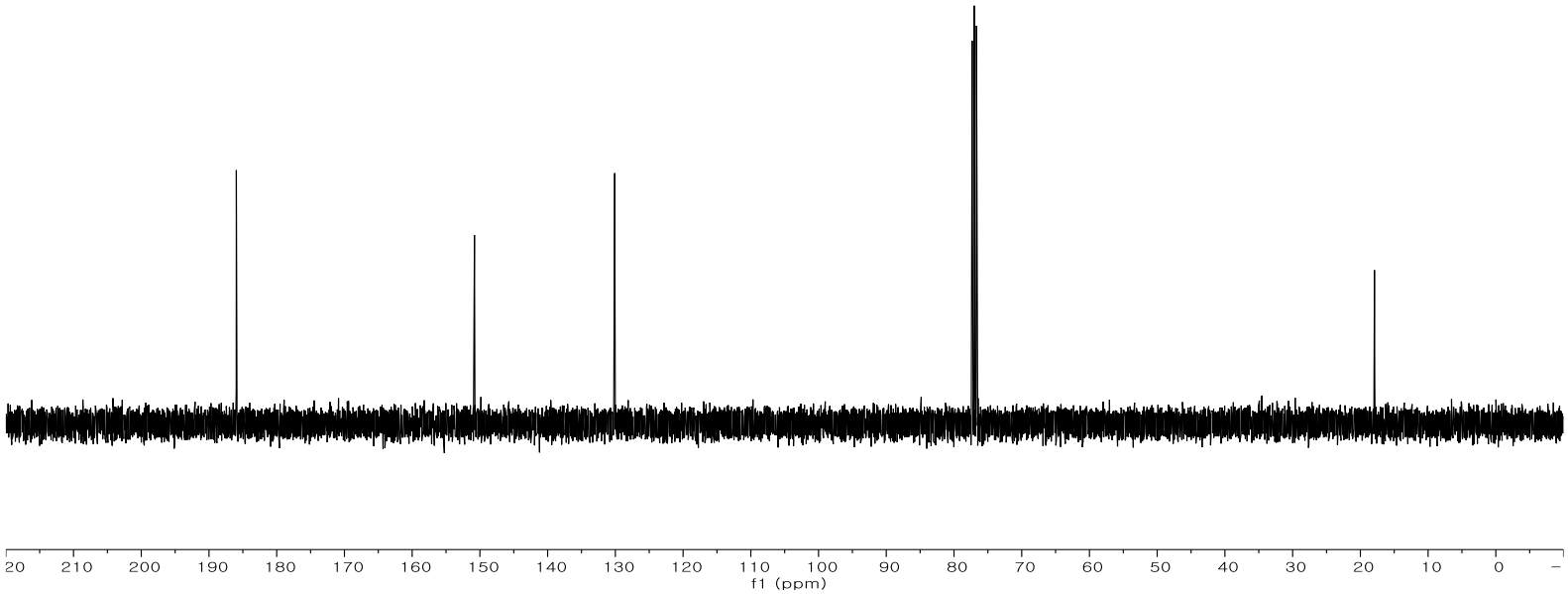

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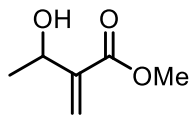

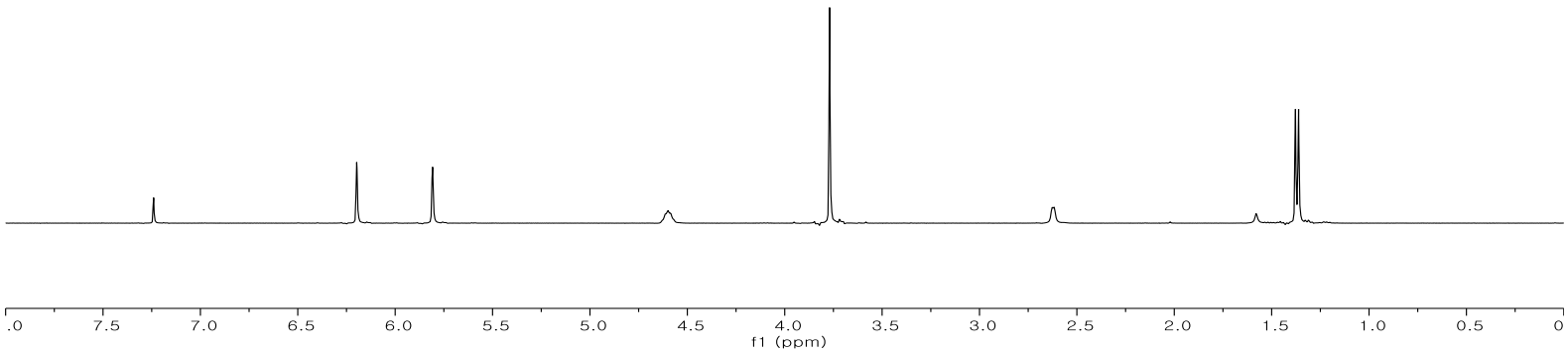

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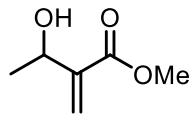

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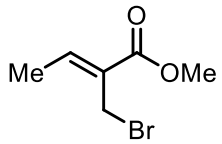

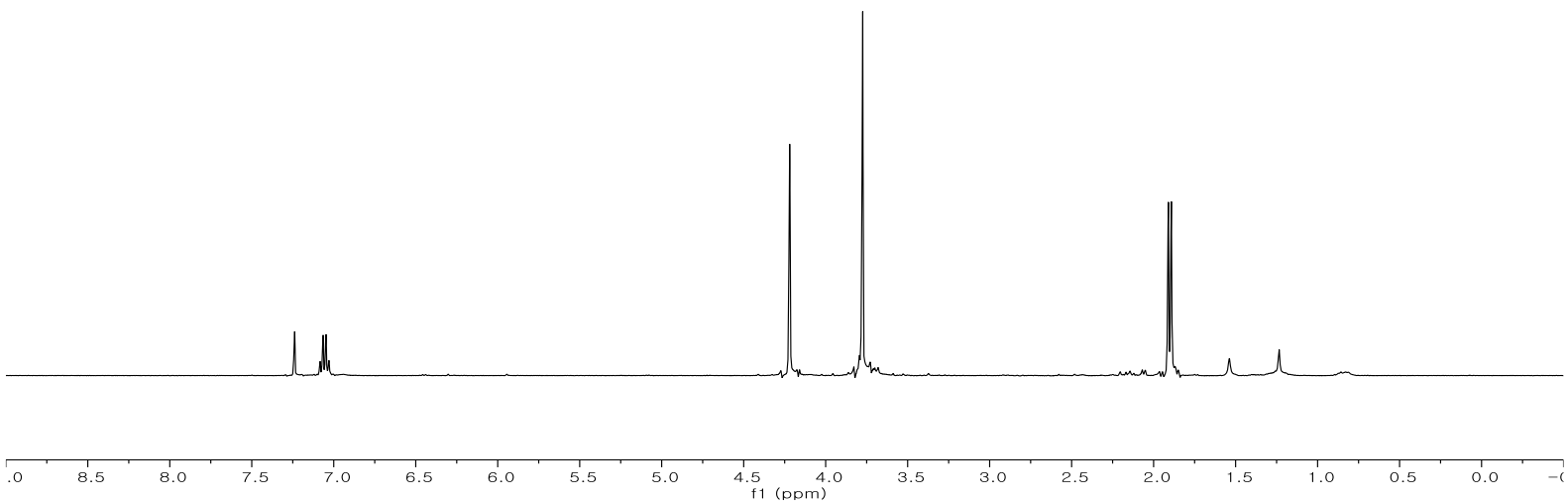

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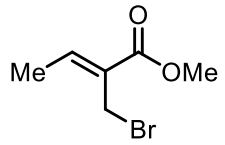

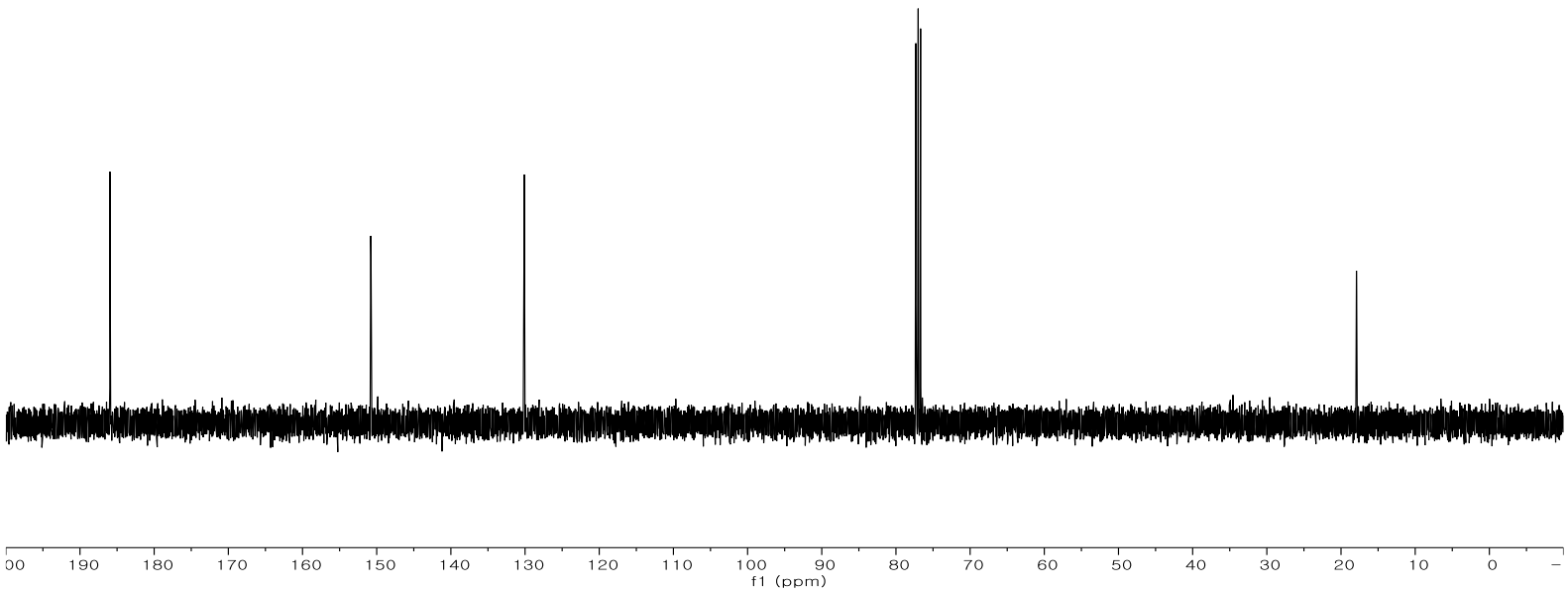

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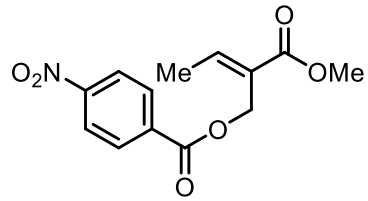

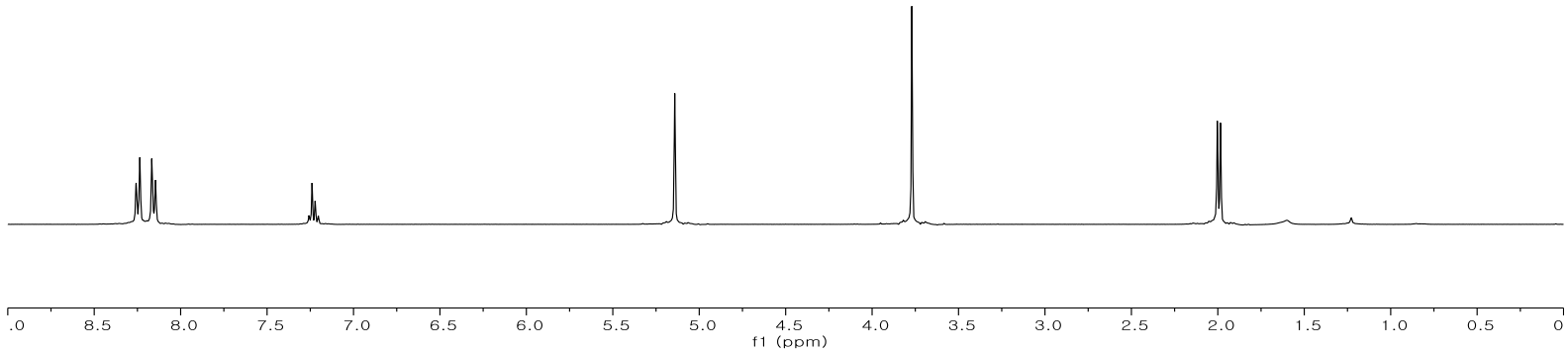

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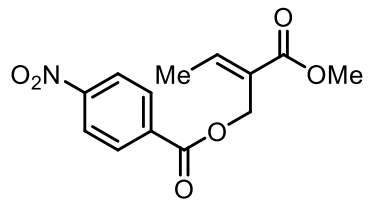

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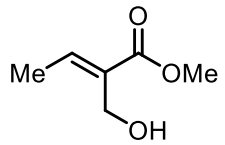
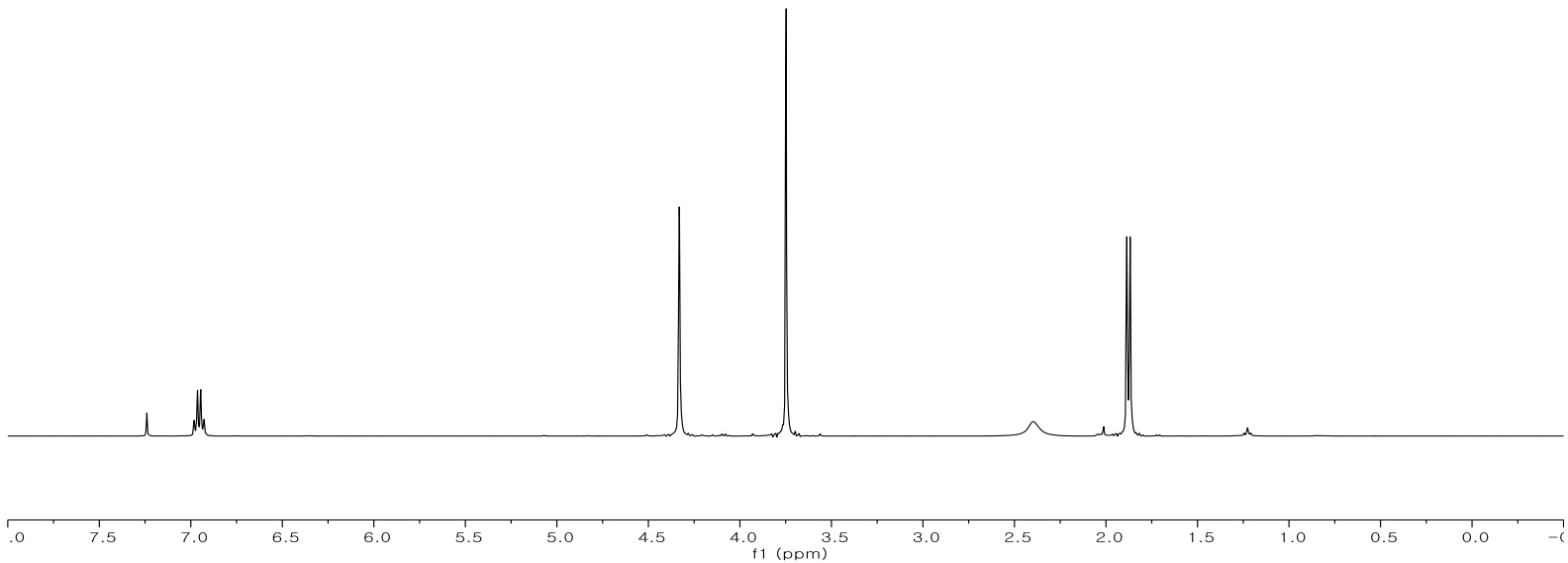
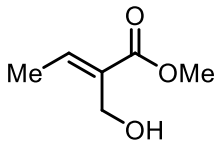
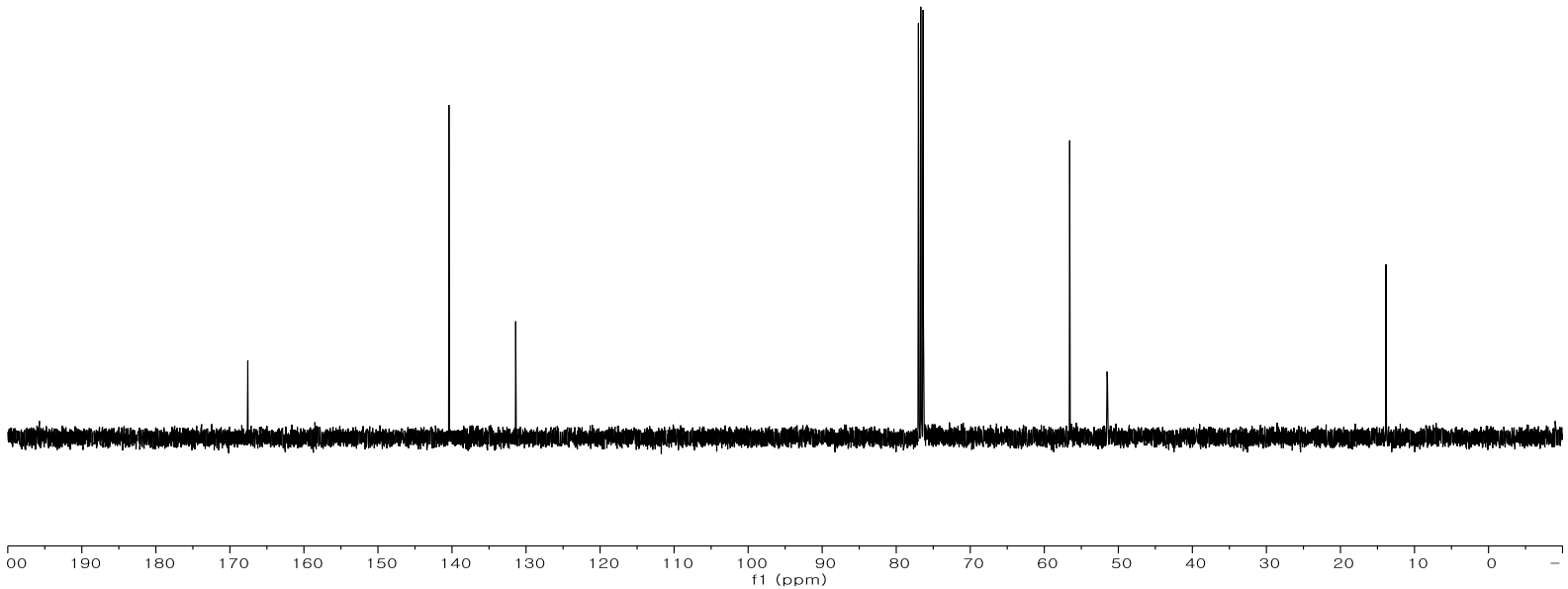




^{13}C NMR (100 MHz, $CDCl_3$)





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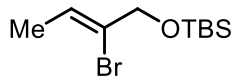

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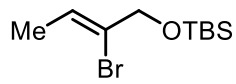

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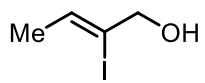

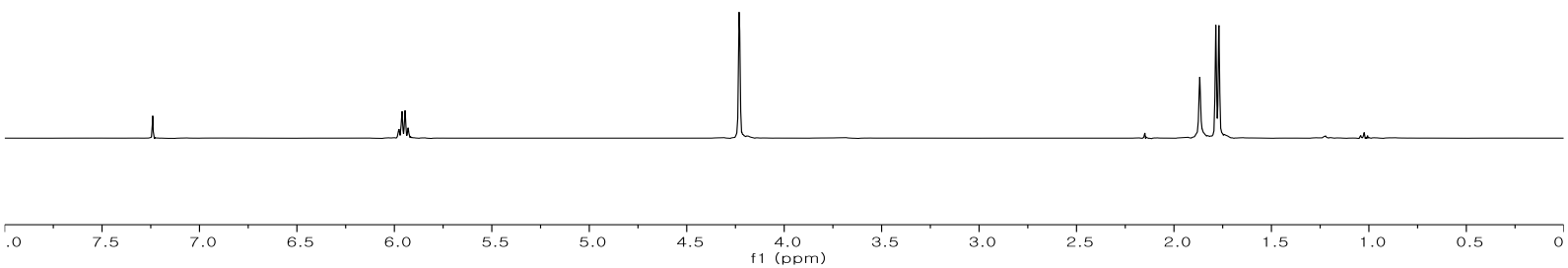

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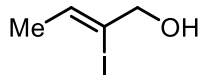

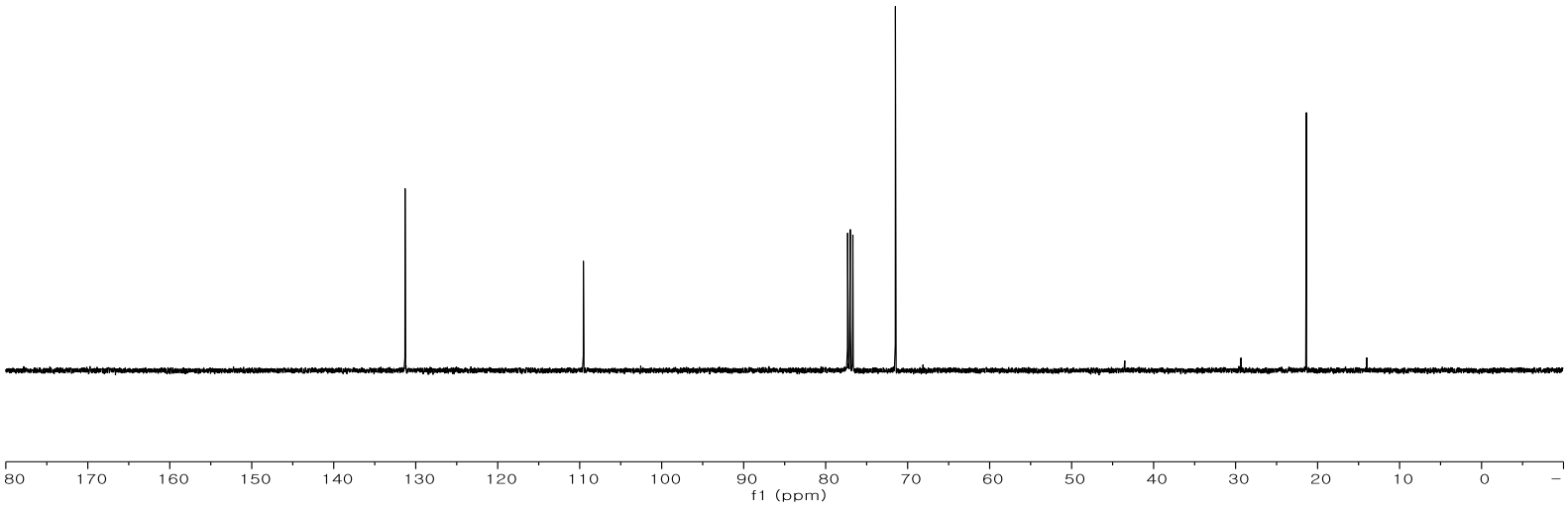

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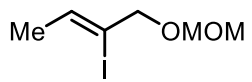

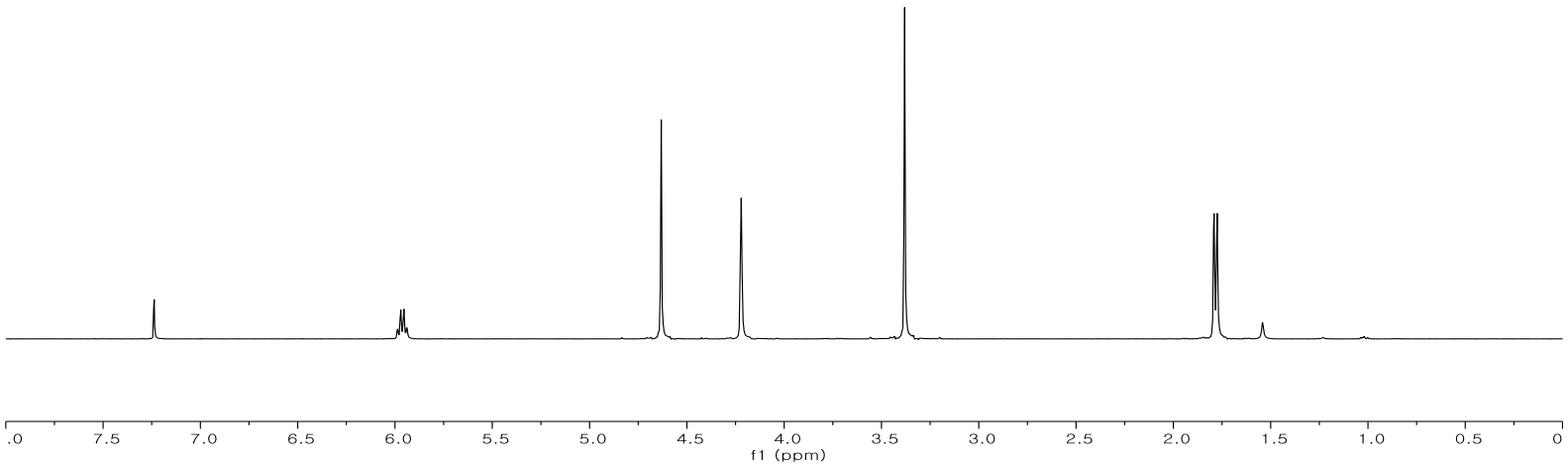

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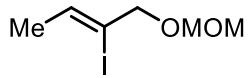

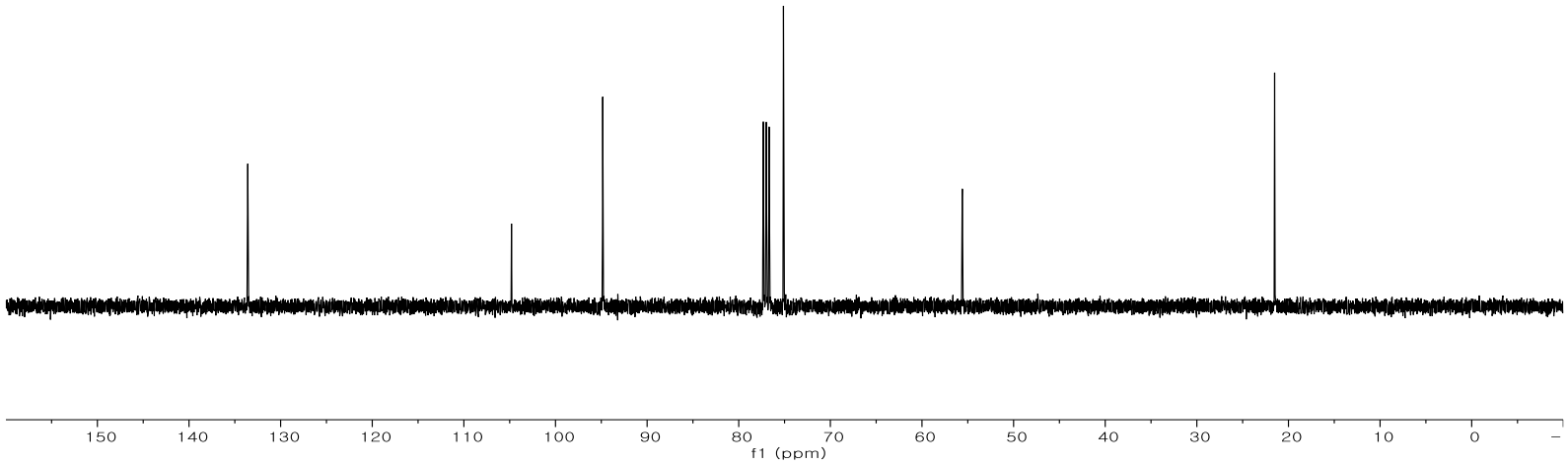

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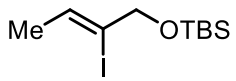

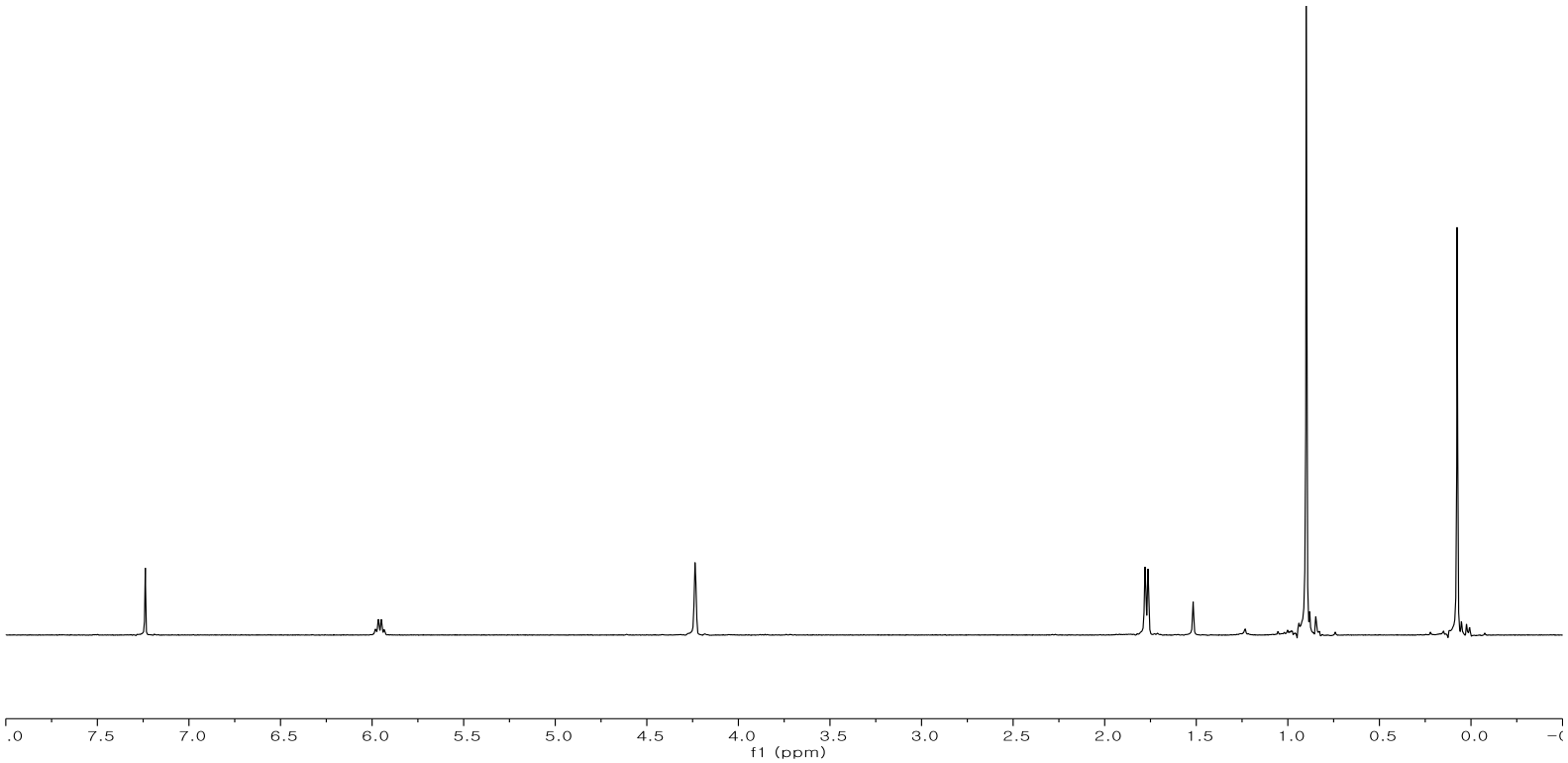

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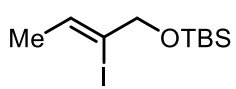

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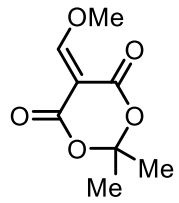

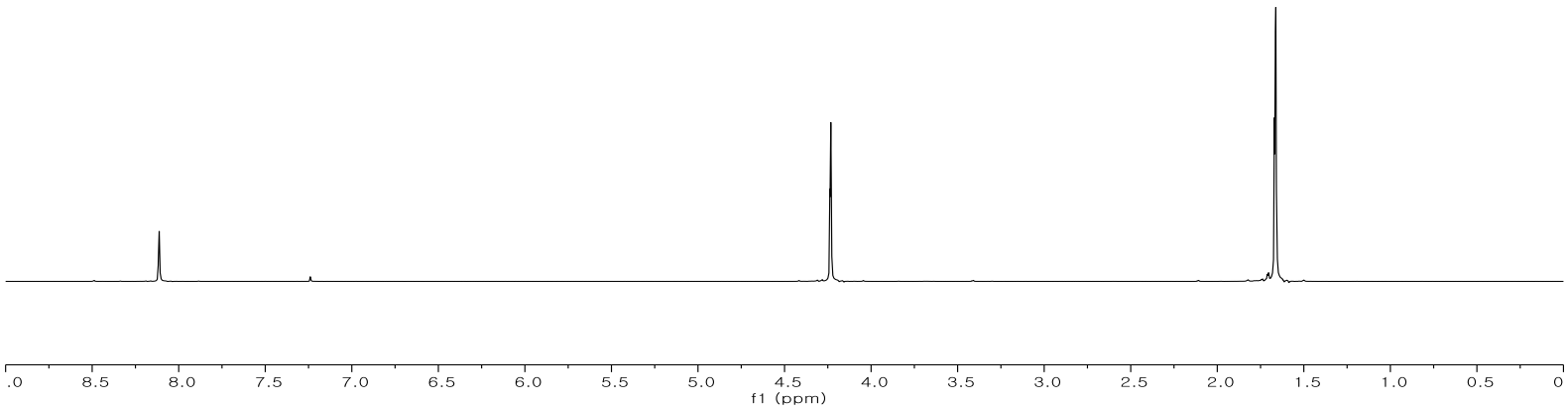

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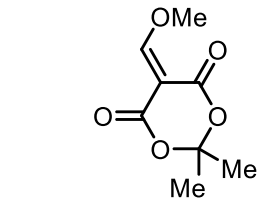

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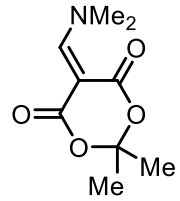

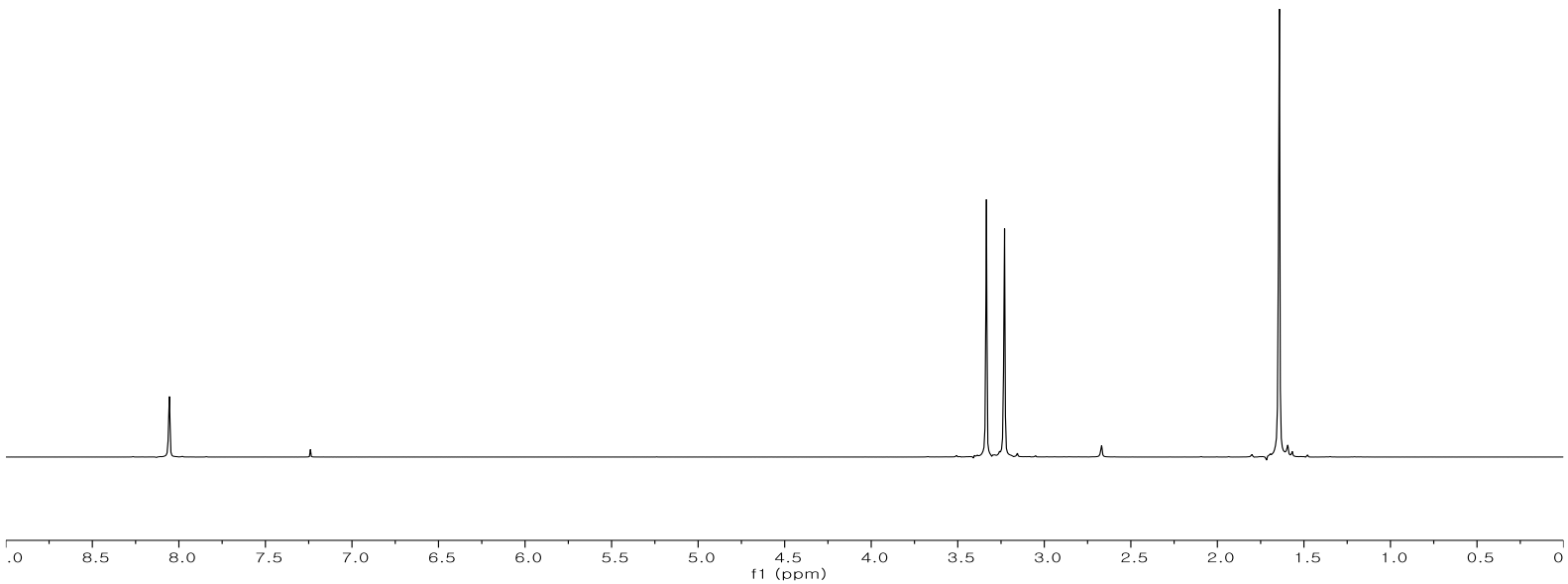

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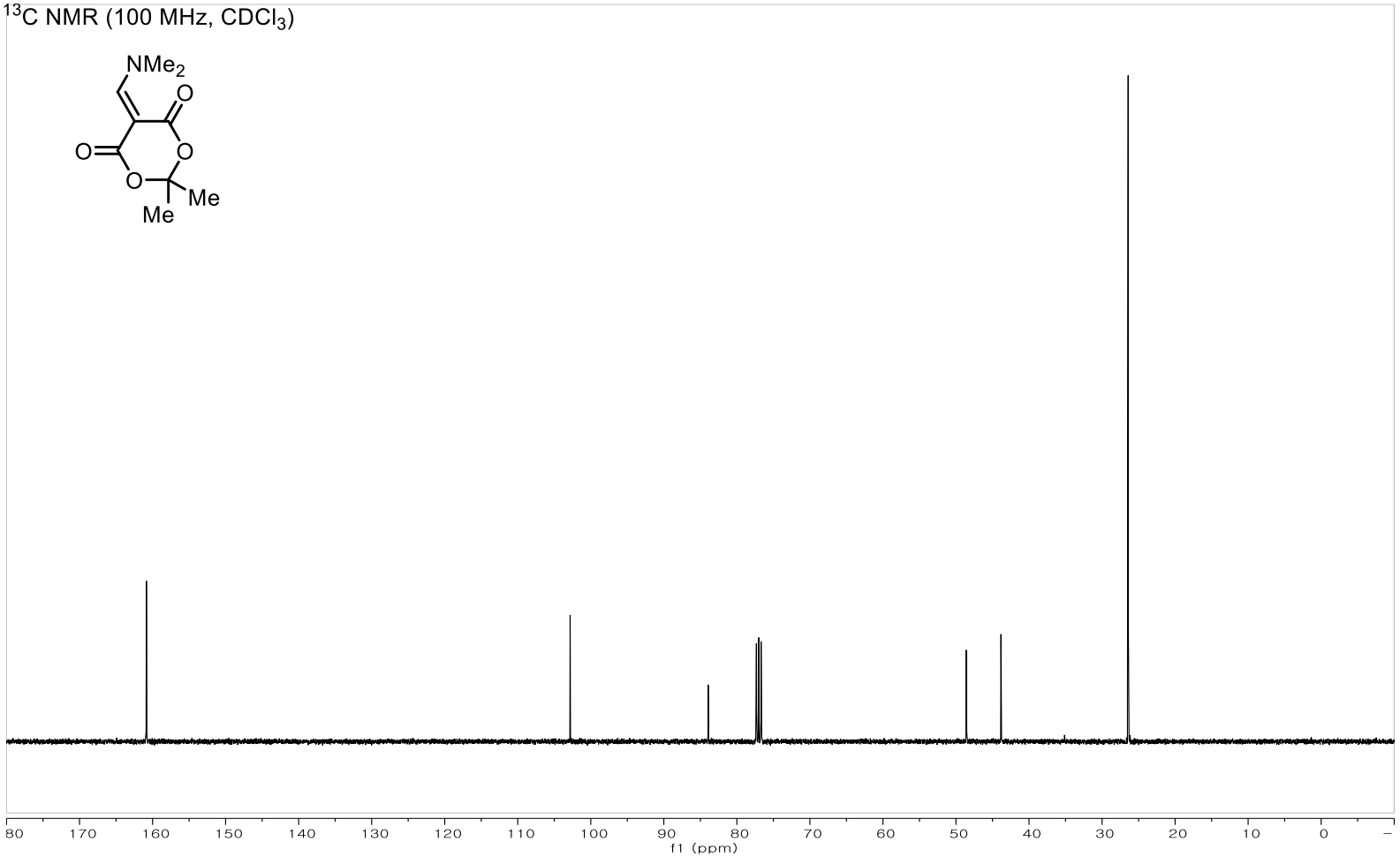

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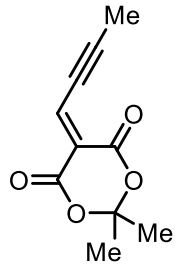

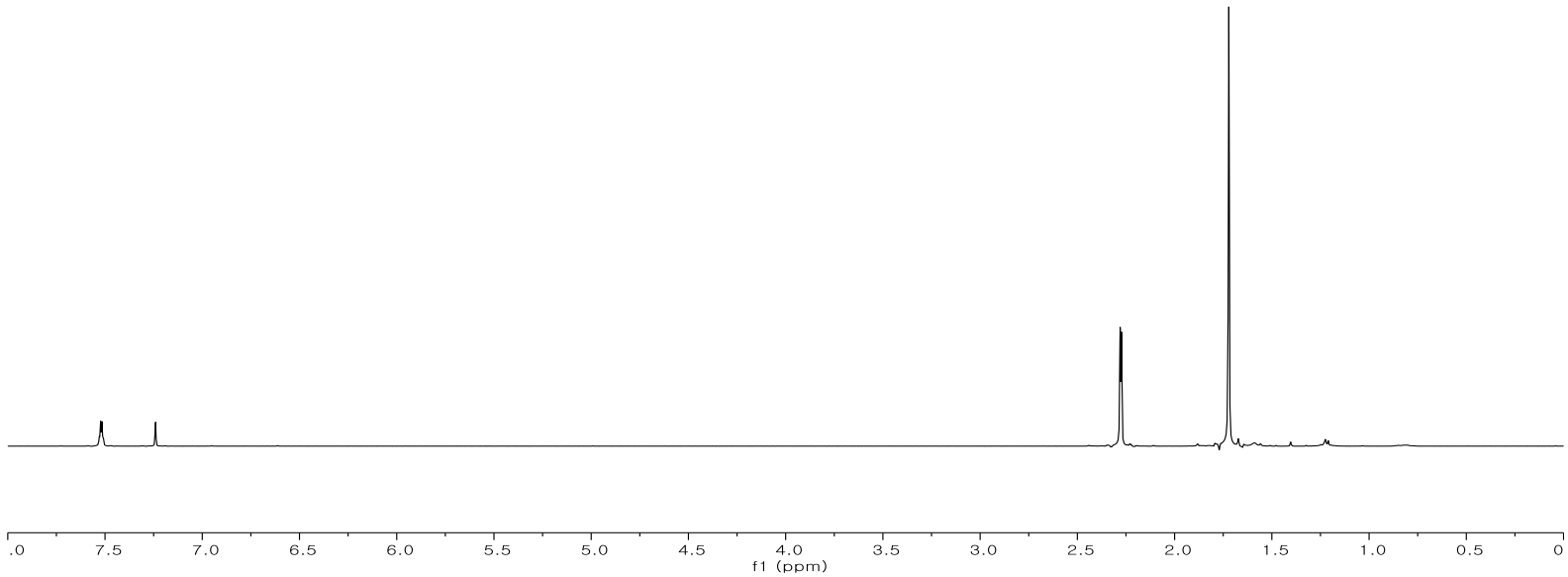

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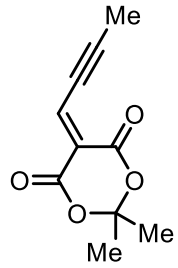

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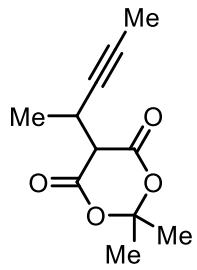

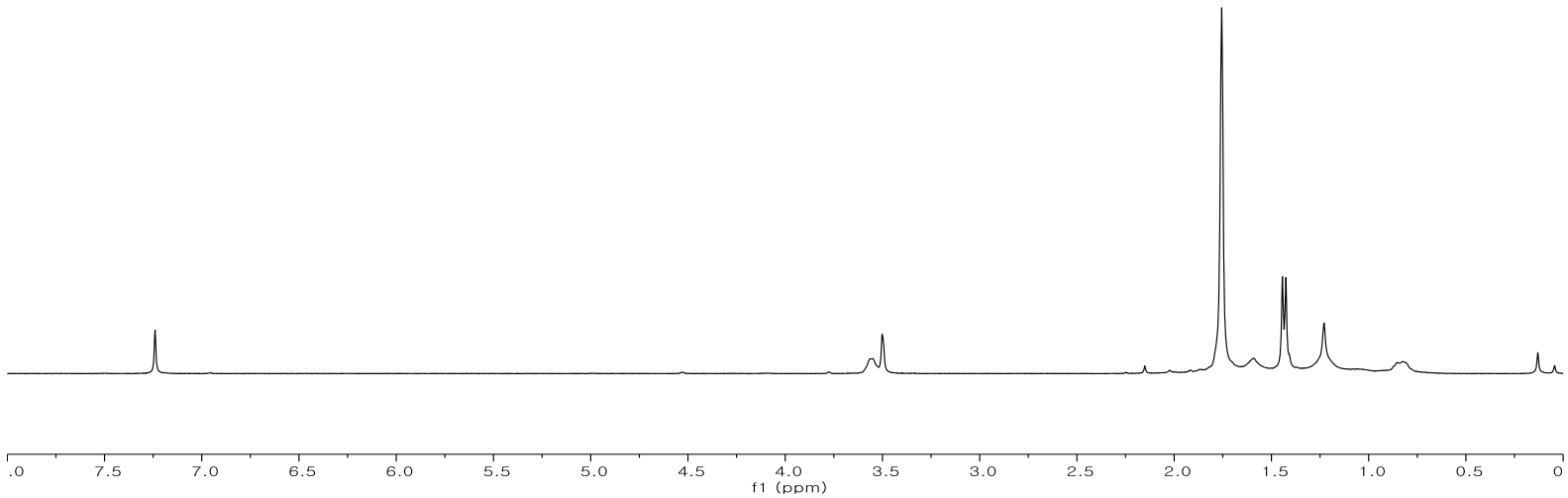

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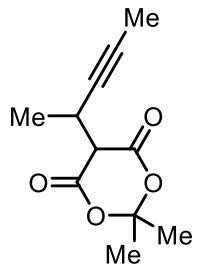

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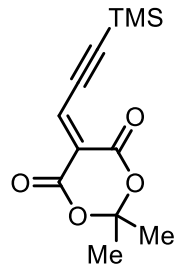

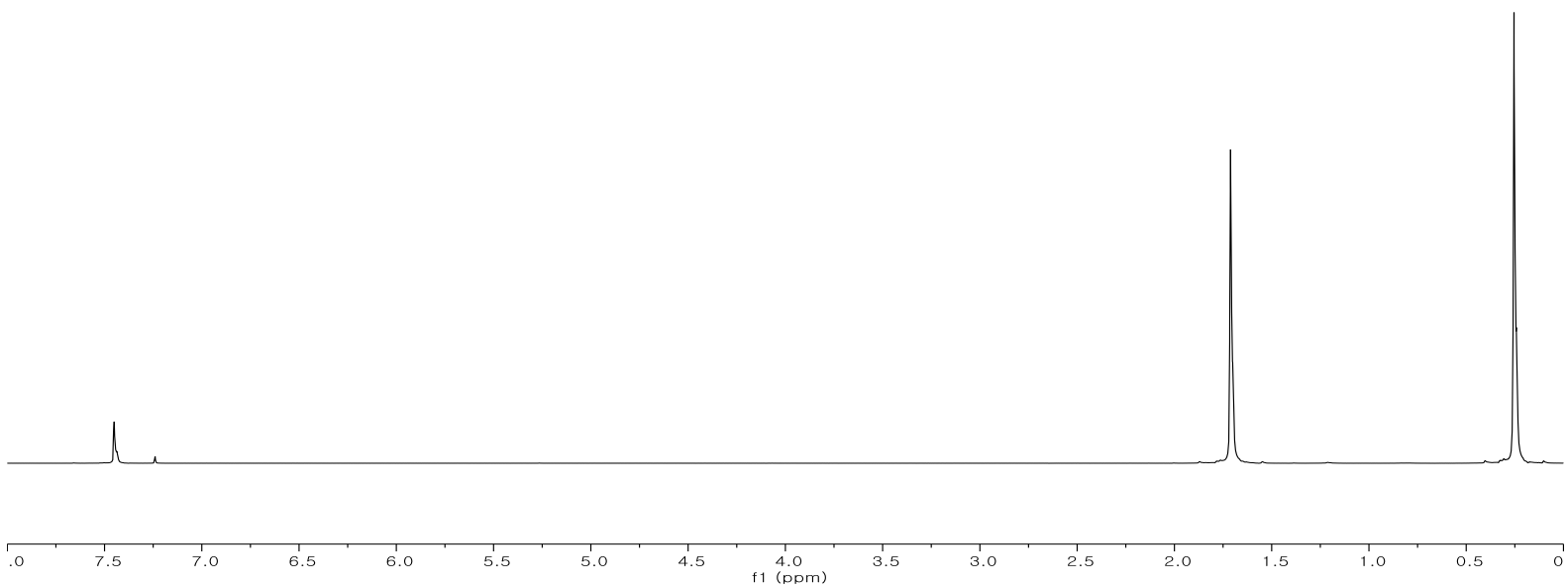

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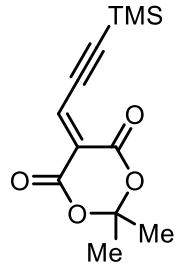

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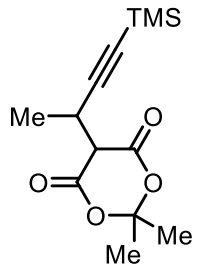

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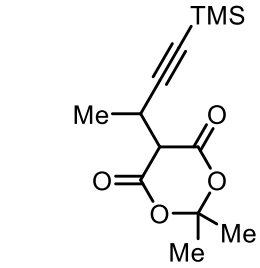

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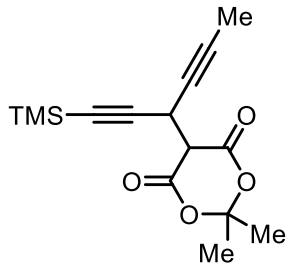

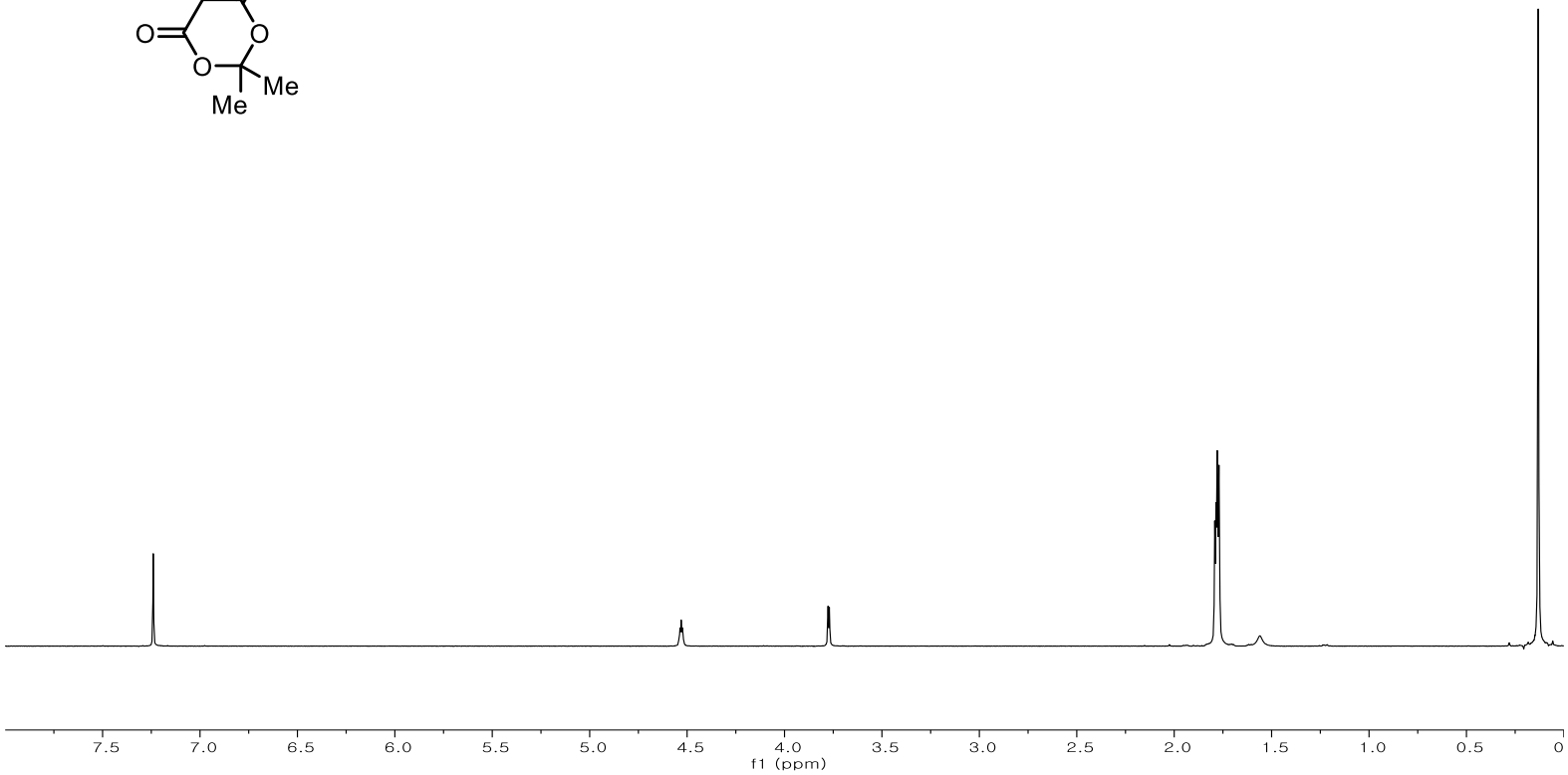

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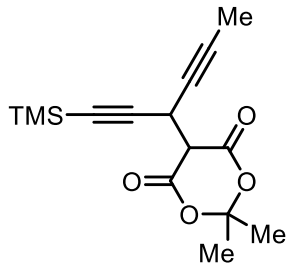

국문 초록

본문에서는 라지말을 합성하기 위한 전략으로 가이소스키진을 반응 중간체로 하여 생화학적 과정을 모방한 합성 전략을 소개한다. 크뇌베나겔 축합 반응에서 이어지는 비대칭 1,4 첨가 반응, 금 촉매를 이용한 픽텟 슈펭글러 고리화 반응은 기존의 가이소스키진 합성 방법과의 차별성을 확보한다. 이를 위한 연구의 일환으로 복합 파이 계를 갖는 반응 중간체 10을 대량생산하기 위한 방법을 모색하였으며, 여기서 발견한 전반적 전략의 중요 결점들을 분석하고 이에 따라 기존 합성 전략의 수정방향을 제시한다. 다양한 다중 고리 전구체들의 [3,3]-시그마 결합 자리옮김을 통한 산화적 고리화 반응은 기존에 없었던 라지말의 전합성을 가능케 하고 이로부터 다양한 아큐아밀린 알칼로이드들의 합성을 이끌어낼 수 있다.

주요어: 전합성, 천연물, 생체모방적 합성, 라지말, 가이소스키진, 아큐아밀린, 산화적 고리화 반응, [3,3]-시그마 결합 자리옮김.

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