## ABSTRACT

Title of Dissertation: SYNTHESIS OF FUNCTIONALIZED DIAZOACETOACETATES VIA MUKAIYAMA-TYPE CONDENSATIONS

Yu Liu, Doctor of Philosophy, 2012

Dissertation directed by: Professor Michael P. Doyle
Department of Chemistry and Biochemistry

Mukaiyama-type condensation reactions of 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate and different electrophiles are effective methods for the synthesis of highly substituted diazoacetoacetates. With 0.5-3 mol% of $Zn(OTf)_2$ as Lewis acid catalyst, Mukaiyama-Michael reactions of vinyldiazoacetates and α,β–unsaturated ketones proceed at ambient temperature to afford functionalized diazoacetoacetates in good yields. By carefully choosing the reaction conditions, both Mukaiyama-Michael adducts in either silyl enol ether form or in ketone form can be synthesized. Addition products obtained from these Mukaiyama-Michael reactions are investigated in dirhodium(II) catalyst induced dinitrogen extrusion reactions.

Enedione-diazoester derived from Mukaiyama-Michael reaction of 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate and 4-methoxy-3-bute-2-one can be

converted to resorcinol derivatives under base catalysis. This novel transformation was investigated and developed into a synthetic methodology for the preparation of poly-substituted resorcinol compounds.

Orthoesters also react with 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate in the presence of Lewis acid catalysts. Diazoacetoacetates that contain acetal functionality can be assembled by these reactions. Rhodium(II) acetate promoted dinitrogen extrusion reactions of these adducts can give β–alkoxycyclbutanone products, which are useful synthons in organic synthesis.

# SYNTHESIS OF FUNCTIONALIZED DIAZOACETOACETATES

# VIA MUKAIYAMA-TYPE CONDENSATIONS

by

Yu Liu

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park in partial fulfillment
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Doctor of Philosophy
2012

Advisory Committee:

Professor Jeffery Davis, Chair
Professor Michael Doyle
Professor Anderi Vedernikov
Professor Herman Sintim
Professor Srinivasa Raghavan

# DEDICATION

To my grandfather, Qingyun Liu,

and to my parents, Guangxing Liu and Anli Wang

# ACKNOWLEDGEMENTS

Now that I am at the finishing line of this journey to a PhD degree, looking back at what I have experienced during this five-year adventure, there are just so many people that I am truly grateful to. I wish I would be able express my deepest appreciation to all these people in this acknowledgement, but I would have to write another chapter in order to do so. Therefore, I will try my best to express my gratitude to those very special individuals in this short paragraph, although what they have done to help and support me in this pursue for a doctoral degree goes well beyond these simple words.

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I would like to thank the Chinese community in the Chemistry Department. I have already mentioned many of them, but there are still a few more to add: Dr Huan Wang, Dr Yang Liu, Jing Wu, Jia Liu, Sijia Qin, and Xiaoyu Wang. Chinese people would say it is *yuan fen* that we are able to get together in the U.S. far from our home country. I am really glad that I had the chance to know all of you. Since you are all here with me, I rarely feel lonely although I am far away from home.

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side of the earth, I know that your hearts are always here with me. It is your love that carries me through this adventure, and gives me confidence to continue moving forward from here on.

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF SCHEMES

# Chapter 1

# Mukaiyama-Michael Additions of Vinyldiazoacetate with α,β–Unsaturated ketones

## 1.1 Introduction

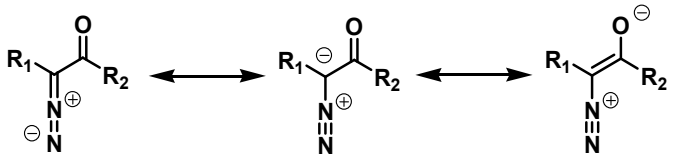
My graduate work is centered on the synthesis of functionalized diazoacetoacetates. Therefore, the first chapter of this thesis starts with a brief overview of diazocarbonyl compounds, and attention is directed to diazoacetoacetates since they can be conveniently prepared and readily functionalized. Then we go on to discuss different synthetic routes developed to make diazoacetoacetate derivatives and bring out our approach using Lewis acid catalyzed Mukaiyama-type condensations to make fuctionalized diazoacetoacetates.

### 1.1. 1 Structure and Reactivity of Diazocarbonyl Compounds

Diazocarbonyl compounds have the general structure depicted in Figure 1.1 This structure can be represented by three resonance hybrids.[1] A few interesting features of diazocarbonyl compounds can be noticed from these resonance structures: firstly, the two nitrogen atoms appear like a diazonium ion (triple bonded with formal positive charge on the internal nitrogen) in two of the resonance structures. Since dinitrogen is a good leaving group,[2] the two nitrogen atoms could be released as nitrogen gas under appropriate conditions. Secondly, the negative charge is delocalized by the adjacent carbonyl group, this could

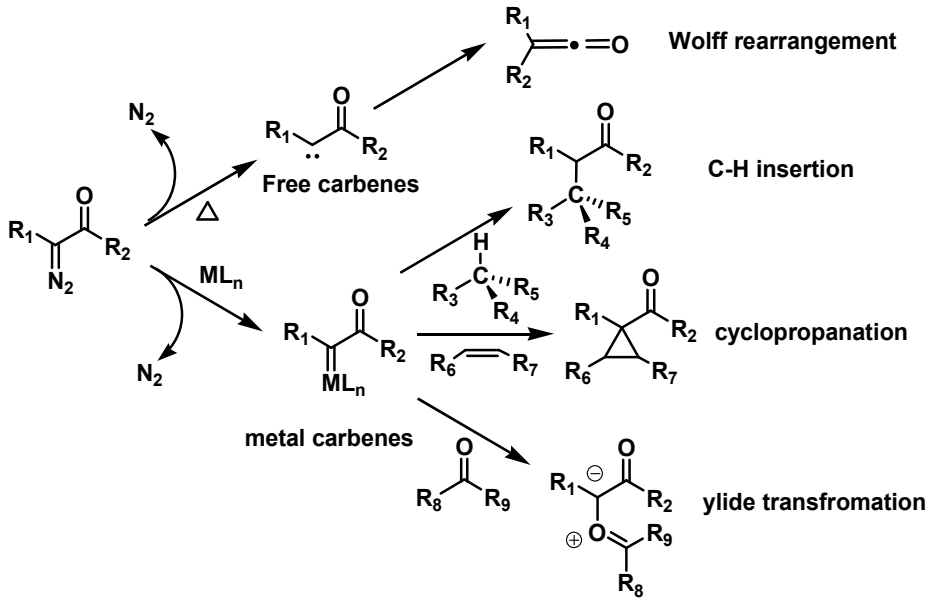
make the compound more stable compared to diazo compounds with no carbonyl group next to the diazo unit. What is more, the enolate-like structure could act as a nucleophile to react with electrophiles. Lastly, with separated charge in the molecule suggested by the resonance structures, diazocarbonyl compounds resemble zwitterions and are good dipolar compounds.[3] The structure of diazocarbonyl compounds dictates their reactivity in organic reactions. This becomes evident as we move on to discuss representative transformations of diazocarbonyl compounds.

**Figure 1.1** Resonance Structures of Diazocarbonyl Compounds.



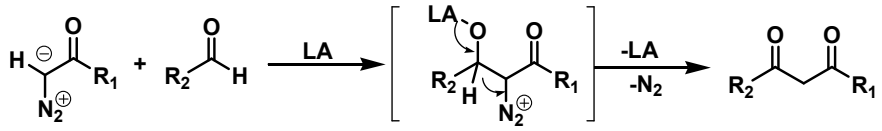
Loss of dinitrogen is known as the dinitrogen extrusion of diazocarbonyl compounds. Dinitrogen extrusion can be induced by heat, acids or metal catalysts. Decomposition of diazocarbonyl compounds leads to highly reactive carbene species, either free or metal stabilized, that undergo a wide array of transformations including cyclopropanation, C-H insertion, ylide reactions, and the Wolff rearrangement.[4] Numerous useful scaffolds such as cyclopropanes, cycloalkanones, and β-lactams could be synthesized from diazocarbonyl compounds via carbene reactions (Scheme 1.1).[4]

**Scheme 1.1** Carbene Reactions of Diazocarbonyl Compounds.



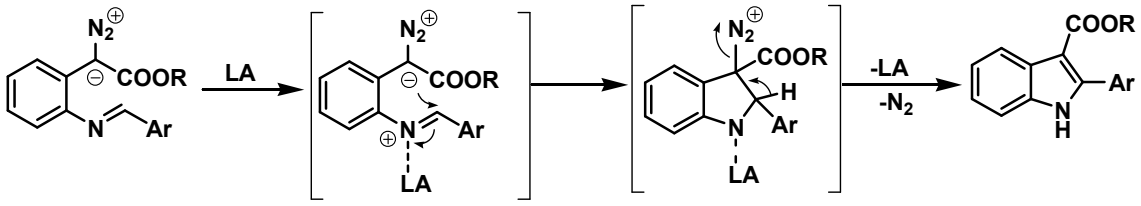

The diazo functionality can be recognized as the combination of a nucleophile (negatively charged carbon) and a good leaving group (dinitrogen). This character is demonstrated by two examples here: The reaction described in Scheme 1.2 is known as the Roskamp reaction.[5] In this reaction, Lewis acid activated aldehydes undergo nucleophilc attack by diazocarbonyl compounds to give the intermediated diazonium ions. With 1,2-hydride shift dinitrogen is released to afford β-keto-carbonyl compounds as products.

**Scheme1.2** Roskamp Reaction of Diazocarbonyl Compounds.




Another example is a reaction recently developed by Doyle and coworkers. Indole derivatives can be synthesized by a transformation of aryl diazoesters (Scheme 1.3).[6] Similar to the Roskamp reaction described in Scheme 1.2, this indole synthesis via diazocarbonyl compounds also takes advantage of the nucleophlicity of the diazo compounds to carry out an intramolecular addition to imines. Proton transfer and dinitrogen extrusion following the cyclization step afford the indole products. The idea of applying diazocarbonyl compounds as the combination of a nucleophile and a good leaving group can be noticed in other transformations in the literature.[5]

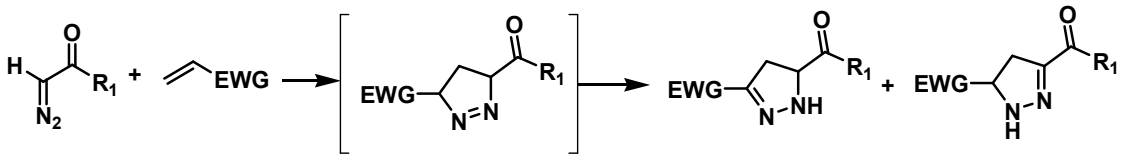
**Scheme 1.3** Indole Synthesis Applying Diazocarbonyl Compounds.




The dipolar nature of diazocarbonyl compounds makes them feasible for 1,3-dipolar cycloaddition reactions that produce heterocycles. Alkenes with electron-withdrawing groups can be used as dipolarophiles to react with diazo compounds,

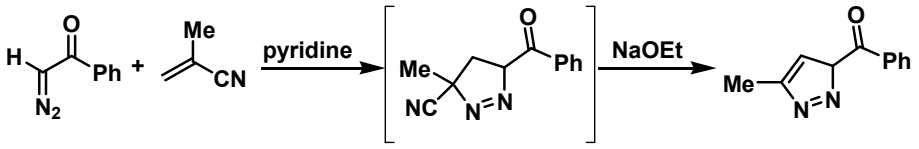
and pyrazoline derivatives are produced from these cycloaddition reactions (Scheme 1.4).[8]

**Scheme 1.4** Diploar Cycloadditions of Diazocarbonyl Compounds.



A representative example of 1,3-diploar cycloaddition reactions applying diazocarbonyl compounds was reported by Doyle (Scheme 1.5).[3b] α-Diazo acetophenone reacts with an α,β-unsaturated nitrile to give 5-cyano-2-pyrazolines. The pyrazoline intermediate can be further converted to pyrazoles through sodium ethoxide promoted HCN elimination.

**Scheme 1.5** Pyrazole Synthesis via 1,3-Dipolar Cyclization of Diazocarbonyl Compounds.

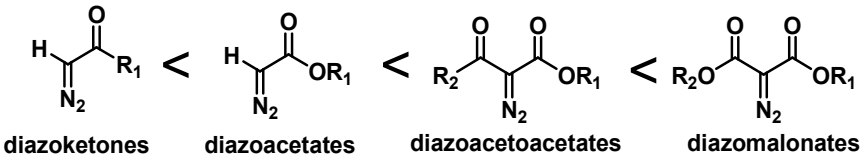


The unique structures of diazocarbonyl compounds give them versatile reactivity. With such reactivity, diazocarbonyl compounds are considered as useful synthetic reagents and they have been studied extensively by organic chemists.[1,3,4,5,9]

### 1.1.2 Different Categories of Diazocarbonyl Compounds.

The carbonyl groups adjacent to the diazo functionality play important roles in determining the properties of diazocarbonyl compounds.[1] Depending on the dfifrerent categories of carbonyl groups attached, diazocarbonyl compounds can be classified as diazoketones, diazoacetates, diazoacetoacetates and diazomalonates. These diazo compounds and their relative stability are shown in Figure 1.2.

**Figure 1.2**. Diazocarbonyl Compounds Classified by Adjacent Carbonyl Groups.




For each category of these diazocarbonyl compounds shown in Figure 1.2, a vast amount of research work has been conducted regarding their preparations, reactivity and applications in organic synthesis.[1,3,9] All of these diazocarbonyl compounds are established as useful building blocks in organic reactions.

Among these diazocarbonyl compounds, those that can be effectively synthesized and easily functionalized are ideal for the construction of structurally complex diazocarbonyl compounds which are of great importance in understanding the reactivity of diazo functionalities within molecules that are highly substituted. With this consideration in mind, we realize that diazoacetoacetates and their derivatives have an advantage compared to diazoketones and diazoacetates. In order to demonstrate this point, we will go

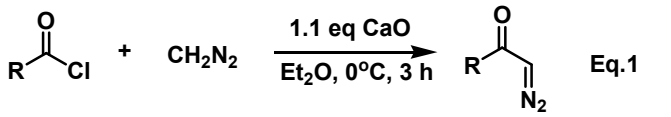
through prevailing methods for the synthesis of diazoketones, diazoacetates and diazoacetoacetates in the following sections. By comparing these methods and the diazocarbonyl compounds prepared by such methods, we will be able to show that diazoacetoacetates are preferable for the synthesis of various novel diazocarbonyl compounds.

#### 1.1.2.1 Diazoketones

Diazoketones have keto groups adjacent to the diazo functionality. They are used primarily as carbene precursors.[4a] Upon formation of highly reactive metal carbene intermediates by dinitrogen extrusion, a number of carbene reactions can be realized such as the Wolff rearrangement[10] and C-H insertion reactions.[11] Unsaturated diazoketones undergo acid-promoted cyclization[4a] which is a synthetically useful reaction and has been applied in total synthesis of natural products.[12]

Despite the great number of reactions applying diazokeones, there are only a few convenient methods for the synthesis of these compounds. For example, terminal diazo groups can be installed by reacting acid chlorides with diazomethane in presence of base. A recent example of this transformation is given in equation 1:[13] acid chlorides with different substituents (**1**) are converted to the corresponding diazoketones **2** by reactions with diazomethane using a stoichiometric amount of calcium oxide as base. Although this transformation is a useful method to prepare terminal diazoketones, diazomethane is a toxic reagent that needs to be handled with caution. Alternative methods for the synthesis of

diazoketones are available including reactions of anhydrides with trimethylsilyldiazomethane[14] or reacting bromoacetates with N,N'-ditosylhydrazine.[15] However, these methods haven't been widely applied as the reaction of acyl chlorides and diazomethane for the preparation of diazoketones.




1 2

R = alkyl, aryl, $CH_2OBn$, $CH_2CO_2Et$

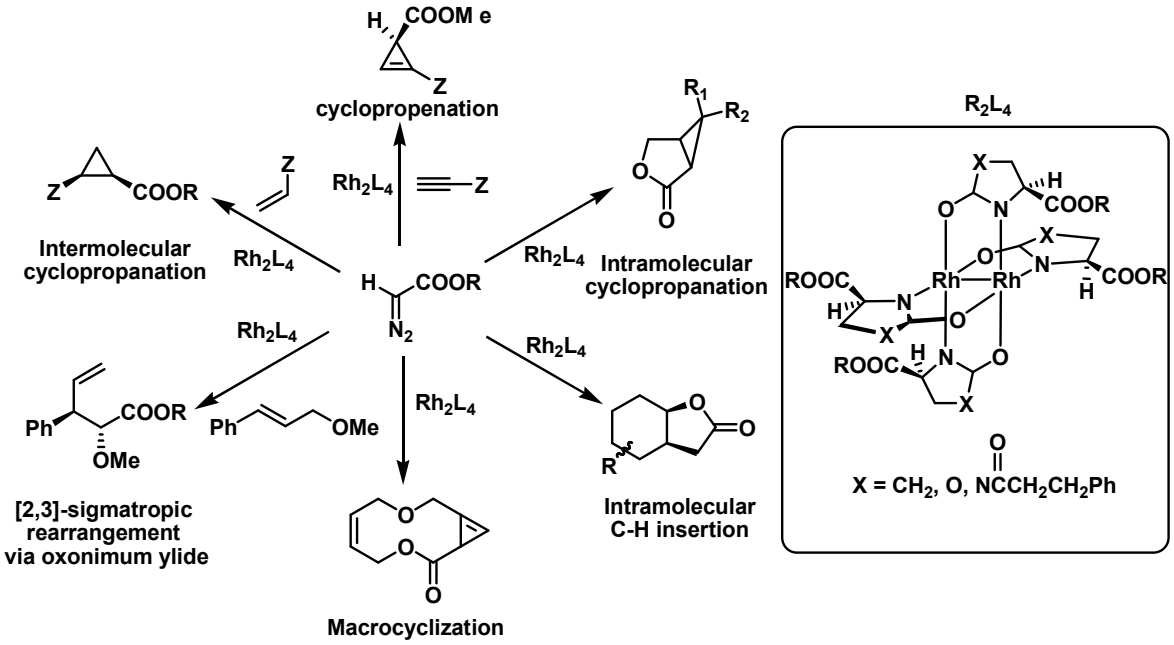
Moreover, acyclic internal diazoketones that have functional groups attached on both sides of the diazo functionality are rarely reported in the literature. This in part is due to the fact that there are few effective methods that can be employed to prepare this type of compound. As a result, diazoketones could only be modified through one side of the molecule most of the time which limited the scope of diazoketone compounds that could be explored.

### 1.1.2.2 Diazoacetates

Diazoacetates have an ester group next to the diazo functionality. Since the ester groups are more electron-withdrawing compared to ketone groups, diazoacetates are more effective in stabilizing the diazo group than diazoketones.[4a] Diazoacetates are commonly used as carbene precursors in catalytic reactions.[4] Dirhodium compounds are effective catalysts to induce dinitrogen extrusion of diazoacetates, and metal carbene intermediates are formed upon loss of nitrogen gas. Various metal carbene mediated

transformations can be realized. For example, using dirhodium carboxamidate catalysts developed by Doyle, α-diazoacetates can be transformed to cyclopropanes, cyclopropenes, and Ɣ-lacones in a stereoselective fashion. All of these products derived from diazo decomposition reactions are useful building blocks in organic synthesis (Scheme 1.6).[4a]

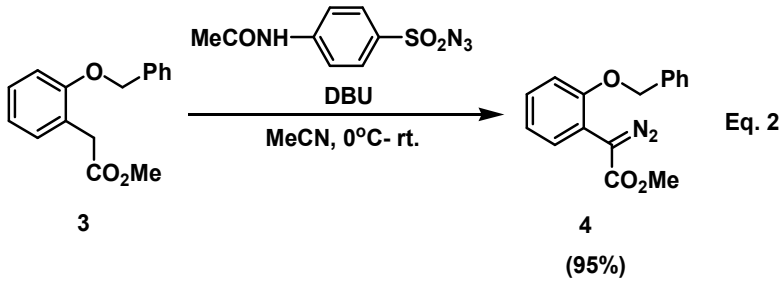
**Scheme 1.6** Dirhodium(II) Carboxamidates Catalyzed Diazo Decomposition of α-Diazoacetates.




Diazoacetates are widely applied in total synthesis and a number of compounds that are of biological interest can be prepared from diazoacetates[16] such as (-)-enterolactone,[17] *R*-baclofen[18] and *S*-imperanine.[19]

Since diazoacetates are useful synthetic reagents, a number of methods regarding the preparation of diazoacetates have been developed. Diazoacetates

are mainly prepared by diazo transfer reactions.[1,4a] When the α-position of the carbonyl group is sufficiently reactive to allow deprotonation by a mild base, direct diazo transfer by reactions of enolates and sulfonyl azides can be employed.[1,4] For instance, the methylene protons between the ester group and the aryl group in β–aryl ester **3** can be deprotonated by 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU). The resulted enolate undergoes direct diazo transfer reaction with 4-acetamidobenzenesulfonyl azide (*p*-ABSA), which is a commonly used diazo transfer reagent, to form the desired diazoacetate **4** (Eq.2).[20]

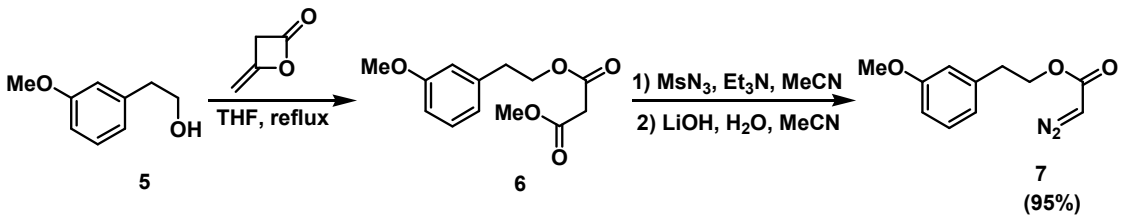



**3** **4** (95%) Eq. 2

In the cases where the methylene groups are activated by only one carbonyl group and not sufficiently acidic, a strong base is required to promote the diazo transfer reactions. However, the use of strong base such as lithium diisopropylamide (LDA) often results in the formation of side products. As a result, indirect methods for diazo transfer reactions have been developed to address this problem. For instance, 1,3-dicarbonyl compounds can be first assembled and then applied in direct diazo transfer reaction, and subsequent acyl cleavage will afford the corresponding diazoacetates.[1,4] Diazoacetate **7** can be prepared in this manner by the procedure described in Scheme 1.7.[21] In this transformation,

alcohol **5** was first reacted with diketene to form acetoacetate **6**. Intermediate **6** then underwent diazo transfer reaction followed by acyl cleavage in presence of lithium hydroxide to afford the desired diazoacetate product **7**.

**Scheme 1.7** Preparation of Diazoacetate **7** via Acetoacetate **6**




The Regitz deformylating diazo transfer protocol is another indirect method for the preparation of diazoacetates.[22] This transformation starts from Claisen condensations of carbonyl compounds and ethyl formate. The resulting 1,3-dicarbonyl compound is activated for diazo transfer and subsequent deformylation affords diazoacetate products.

Although there are quite a few indirect methods for the synthesis of diazoacetates,[1,4,21,22] all of them have to bring in extra steps and extended the synthesis to reach the targeted diazoacetate compounds and this appear to be a drawback for accessing this class of diazocarbonyl compounds.

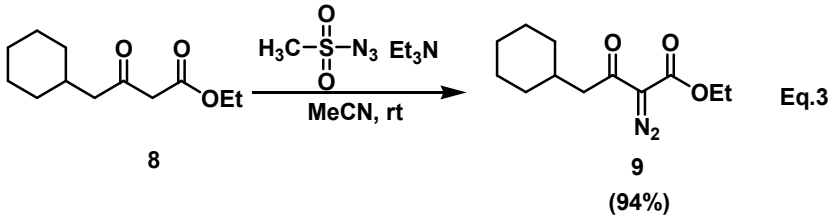
What is more, α-diazoacetates are the most commonly used diazoacetate compounds and, although there are a few transformations that can be used to make diazoacetate derivatives that have more substituents other than the ester groups,[23] there are not many effective methodologies for the synthesis of highly

functionalized diazoacetates and the development towards this direction is rather limited.

### 1.1.2.3 Diazoacetoacetates

Diazoacetoacetates are also widely used diazocarbonyl compounds.[4,9] Similar to diazoketones and diazoacetates that have been previously mentioned, They are also employed in both methodology development[24, 25,26] and synthesis of structurally complex molecules.[27,28]

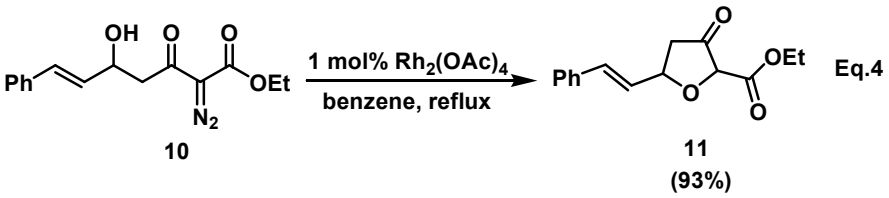
Compared to diazocarbonyl compounds that have been discussed previously, diazoaceoacetates have several advantageous attributes: First of all, the preparation of diazoaceoacetates is straightforward. Diazoacetoacetates are readily accessible from β-ketoesters. Since the methylene protons between the two carbonyl groups are fairly acidic ($pK_a$ =10.7 in water),[29] they can be easily removed under mild basic conditions. The enolates thus formed can obtain the dinitrogen group from the diazo transfer reagents. For instance, β-ketoester **8** reacts with mesyl azide in the presence of triehtylamine to give daizoester **9** as product in high yield (Eq.3).[30]




**8** **9** **(94%)** **Eq.3**

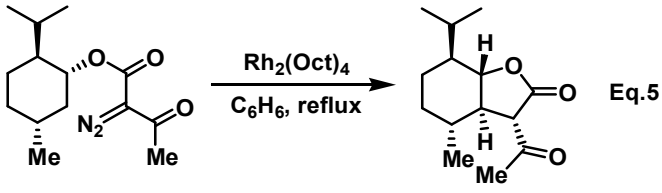
Secondly, diazoacetoacetates demonstrate a high level of selectivity in diazo decomposition reactions.[4a] For instance, Wang, *et. al*. reported a reaction in

which substituted diazoacetoacetate **10** was transformed to tetrahydrofuran derivative **11** in high yield (Eq.4).[31] Although there was an alkene group presented in the molecule, no cyclopropane product could be identified, and the O-H insertion product was the only compound observed after dirhodium catatlyst induced dinitrogen extrusion.




**10** **11** (93%) **Eq.4**

Another good example to demonstrate the high level of selectivity of diazoacetoacetate in catalytic dinitrogen extrusion reactions is a transformation reported by Doyle (**Eq.5**).[32] Diazoacetoacetate **12** was transformed to bicyclic lactone product **13** as a single diastereomer by insertion in to a secondary C-H bond catalyzed by dirhodium acetate. Although there were other reaction sites in the substrate that can possibly undergo C-H insertion of the metal carbene intermediate, γ-lactone **13** was the only product and no other insertion product could be observed.




**12** **13** (80%) **Eq.5**

These two examples show that diazoacetoacetates are able to react in a chemo-, regio- and stereoselective manner in catalytic diazo decomposition

reactions. This is a favorable character of diazoacetoacetate derivatives since the competition of different reaction pathways that would lead to multiple products can be avoided.

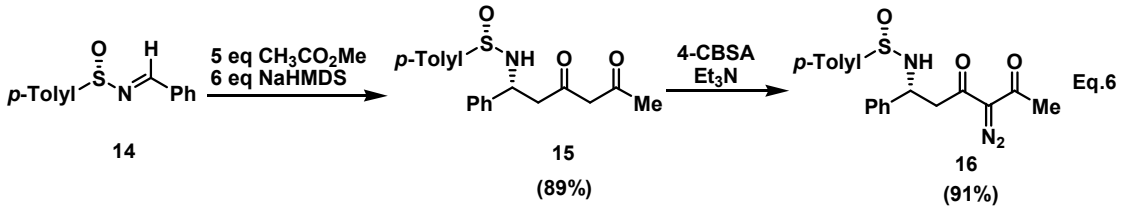
Lastly, what we think is the most important feature of diazoacetoacetates is that they are versatile compounds that can be readily functionalized. Unlike diazokeones or diazoacetates that are limited by the methods for further elaborations,[4a] functional groups can be readily incorporated into diazoacetoacetates. This offers diazoacetoacetates great potential for constructing highly functionalized diazocarbonyl compounds. Diazoacetoacetates and their derivatives that have been mentioned in the previous discussion are all good representatives for functionalized diazoacetoacetates[30 31 32] and these compounds lead to novel chemistry including diazo decomposition reactions[4, 9, 24,25,26] and applications in total synthesis.[4,16,27,28] With these plausible features of diazoacetoacetate derivatives being considered, we decided to focus on the chemistry related to this class of diazocarbonyl compounds.

### 1.1.3 Synthesis of Functionalized Diazoacetoacetates

In order to access functionalized diazoacetoacetates and study their reactivity, effective methods for the preparation of these compounds are of great importance. [1,4a] Therefore, methodologies that lead to functionalized diazoacetoacetates will be discussed in details in this section.

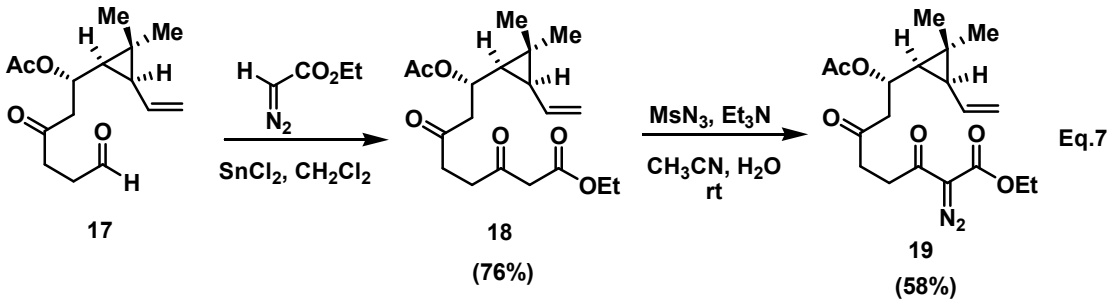
### 1.1.3.1 Synthesis of Functionalized Diazoacetoacetates from β-Ketoesters

A commonly applied strategy for the synthesis of functionalized diazoacetoacetates is to first prepare the precursor of the diazoacetoacetates, which is the corresponding β-ketoesters, followed by diazo transfer reactions to produce the intended diazo compounds. For example, β-ketosester **15** can be prepared from a reaction of sulfinimine **14** and 5 equivalent of sodium enolate of methyl acetate. Acetoacetate **15** can then be converted to diazoaceoacetate **16** via diazo transfer reaction with (4-carboxylbenzene)sulfonyl azide (4-CBSA) as diazo transfer reagent (Eq.6).[33]




Eq.6

Another example targeting a more structurally complex diazoacetoacetate derivative is shown in Equation 7. In the synthesis of a tigliane ring system reported by Dauben, functionalized diazoaceocate compound **19** was prepared from β-ketoester **18** by diazo transfer reaction.[34] The β-ketoester intermediate **18** was prepared by Roskamp reaction[5] of aldehyde **17** with ethyl diazoacetate catalyzed by Lewis acid.[35]

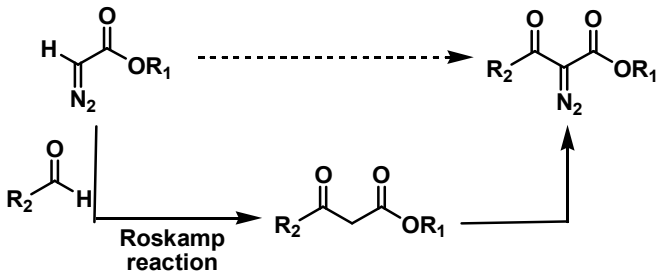



As is demonstrated by the two examples in equation 6 and equation 7, diazo transfer reactions using β–ketoesters are a straight forward synthetic route to prepare diazoacetoactates and their derivatives. However, in more complex systems, it could be difficult to assemble the desired ketoester functionality for diazo transfer reactions and the compatibility of reagents required for diazo transfer reaction (usually involve excess amount of base) with existing functional groups can be problematic.[36] Therefore, alternative strategies for the preparation of functionalized diazoacetoacetates have also been developed. Noticeably, there are methods that start from simple diazo compounds such as diazoacetates or diazoacetoacetates that are readily available[1,4a] and construct functionalized diazocarbonyl compounds. In these transformations, the diazo unit is not affected while the molecules are functionalized. Complementary to the conventional methods that apply β–ketoesters in diazo transfer reactions, these alternative approaches are important additions to the synthetic tools that afford functionalized diazoacetoacetates and representative examples of these methodologies are discussed in the following sections.

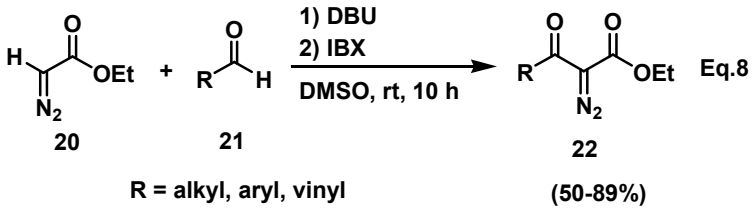
### 1.1.3.2 Synthesis of Functionalized Diazoacetoacetates from Diazoacetates

Diazoacetates can be used as electrophiles to react with nucleophiles such as aldehydes, followed by release of the diazo unit to give β-ketoesters as products (Scheme 1.2, Roskamp reaction).[5] The resulting ketoesters can then be converted to diazoacetoacetates by diazo transfer reactions. This transformation was employed in the synthesis of diazoester **19** in equation 7.[35] However, in this approach, the diazo compounds had to be first decomposed to afford the ketoester intermediate and the diazo unit was then reinstalled via diazo transfer reaction by an additoinal step. Therefore, this approach appears to be inefficient. It would be preferable if diazoacetates can be transformed to diazoacetoacetates without affecting the diazo groups (Scheme 1.8).

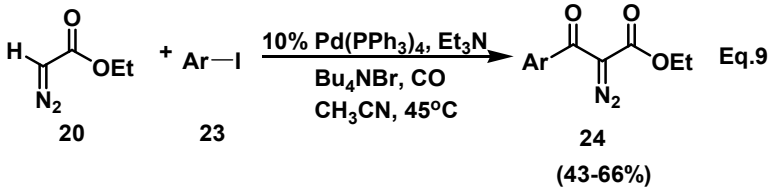
**Scheme 1.8** Different Approaches for Preparing Diazoacetoacetates via Diazoacetates.




A method that employs diazoacetates to prepare diazoacetoacetates without losing the diazo functionality is shown in equation 8. Reported by Erhumwunse and Steel, diazoacetoacetate derivatives **22** can be prepared by condensation of ethyl diazoacetate **20** and aldehydes **21** followed by in situ oxidation with 2-iodoxylbenzoic acid (IBX) in a one-pot manner.[37]



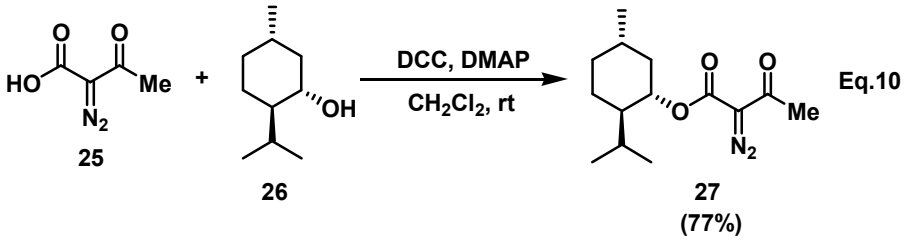

Wang discovered that palladium-catalyzed carbonylation of ethyl diazoacetate (**20**) followed by cross coupling with aryl iodides (**23**) afford β–keto α-diazocarbonyl compounds (**24**) in moderate yields (Eq. 9).[38] This is another example in which the diazo unit can be preserved in the synthesis of substitutied diazoacetoacetates via diazoacetates.




### 1.1.3.3 Synthesis of Functionalized Diazoacetoacetates from Diazoacetoacetic Acid

Stoltz and coworkers reported a method of preparing esters of α-diazoacetoacetates by direct coupling of 2-diazoacetoacetic acid (**25**) and alcohols, such as **26**, upon treatment with DCC and catalytic amount of 4-Dimethylaminopyridine (DMAP) (Eq. 10).[36] Diazoacetoacetic acid can be readily prepared by hydrogenolysis of benzyl diazoacetoacetate catalyzed by Pd/C. This reaction can be used to assemble diazoacetoacetates with a variety of different ester groups. The main advantage of this method compared to other prevalent

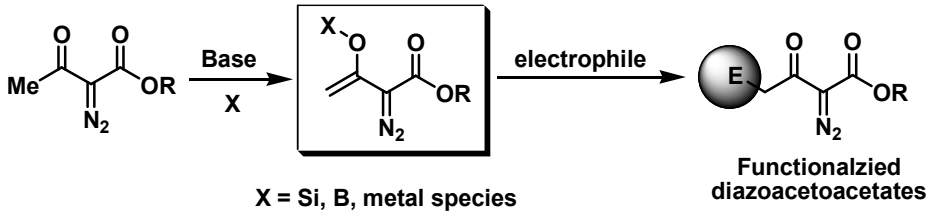
methods is that base-sensitive substrates are tolerated under this reaction condition.




### 1.1.3.4 Synthesis of Functionalized Diazoacetoacetates from Vinyldiazoacetates

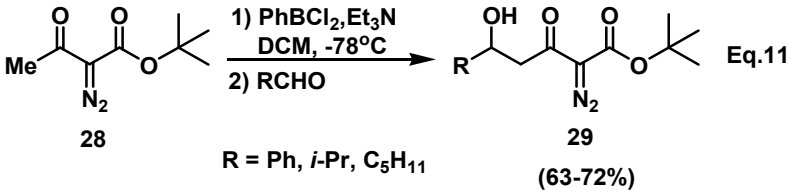
The acetyl groups in diazoacetoacetates are excellent entry points for functionalization. They could be transformed to the corresponding enol or enolate and the resulting vinyldiazoacetates can undergo nucleophilic additions to give functionalized diazoacetoacetates (Scheme 1.9).

**Scheme 1.9** Synthesis of Functionalized Diazoacetoacetates via Vnyldiazoacetates.



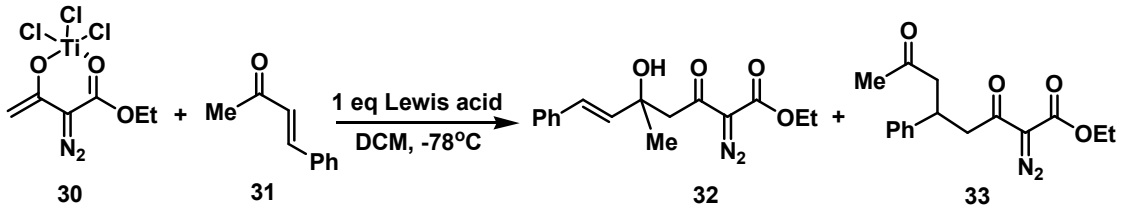

There is precedent for reactions that employ different types of vinyldiazoacetates to prepare functionalized diazoacetoacetates. For instance, Calter reported that stoichiometric amount of B(III) Lewis acid reacts with diazo ketoesters and forms boron enolates in situ. The intermediate vinyldiazoacetates

undergo nucleophilic additions with aldehydes to produce substituted *tert*-butyl 5-hydroxy-3-oxo-2-diazopentanoate (**29**) (Eq.11).[39]



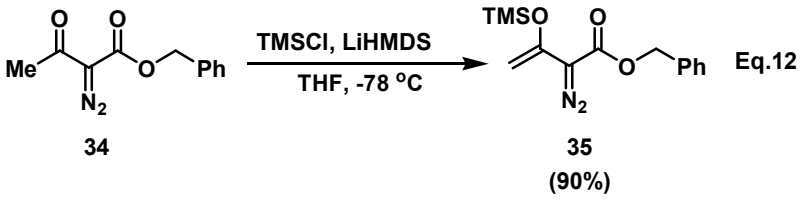

Titanium enolates of diazoacetoacetates have been reported by Wang's group.[40] Enolate **30** is pepared by reacting ethyl diazoacetoacetate with a stoichiometric amount of titanium chloride at -78°C. It is then used without isolation to react with α,β–unsaturated keone **31**. The regioselectivity of these reacions could be controlled by using different Lewis acids, as is demonstrated in Table 1.1 Depending on the Lewis acid involved, this vinyldiazoacetate can undergo either 1,2- or 1,4-additions with α,β–unsaturated carbonyl compounds.

**Table 1.1** Addition of Titanium Enolate of Diazoacetoacetate with α,β–Unsaturated Ketone.




| Lewis acid | 32:33 | yield of 32+33(%) |
|---|---|---|
| none | 60:40 | 63 |
| $Ti(OiPr)_4$ | 96:4 | 72 |
| $TiCl_4$ | 17:83 | 69 |

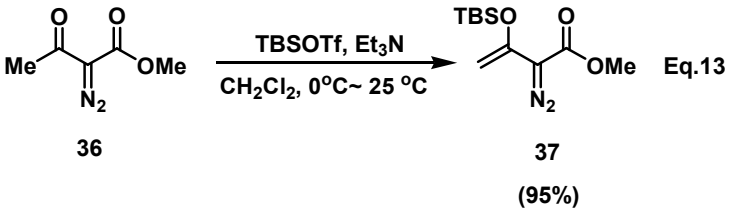
Although boron and titanium enolates are presumably formed as reactive intermediates in the two examples discussed above, they have not be separated and characterized. In contrast, silyl enol ether derivatives of vinyldiazoacetates are stable compounds that can be isolated and characterized. For example, Karady reported the preparation of silyl enol ether type of vinyldiazoacetate **35**. The reaction employs lithum hexamethyldisilazide (LiHMDS) to deprotonate benzyl diazoacetoacetate (**34**) and the enolate thus formed is trapped with trimethylsilyl chloride (Eq.12).[27] Problems associated with these conditions include the limited substrate scope due to the strong basic condition. What is more, this method only works for trimethylsilyl chloride, which gives labile silyl enol ether product while Switching to more stable silyl reagents such as *tert*-butyldimethylsilyl chloride failed to provide the expected vinyldiazoacetate under the same reaction conditions.




**34** **35** (90%) **Eq.12**

The methods for the preparation of vinyldiazoacetates mentioned so far all require harsh reaction conditions such as low temperature and strong base. Although vinyldiazoacetates are particularly useful reagents to construct highly substituted diazoacetoacetates, the reaction conditions involved for the perparation of vinyldiazoacetates appear to be a limiting factor for their wide application.

An improved method was reported by Ueda. *et.al*. In this reaction trialkylsilyl triflates are applied as the siylating reagent and trimethylamine is used to deprotonate the acyl proton (Eq. 19)[41] This method overcomes some of the difficulties in Karady's method: with increased reactivity of the silylation reagent, bulky silyl groups such as *tert*-butyldimethylsilyl group could be transferred to diazoacetoacetates which leads to silyl enol ethers with increased stability. Also, since the silyl reagents are very reactive, a mild base is sufficient to promote this transformation, therefore base sensitive substrates are tolerated under this condition. This method was adopted by Davies and the vinyldiazoacetates synthesized by this procedure were applied in his synthesis towards 8-Oxabicyclo[3.2.1]octane derivatives.[42] With such effective methods for the preparation of vinyldiazoacetates, the application of silyl enol ethers of diazoacetoacetates can be further extended.



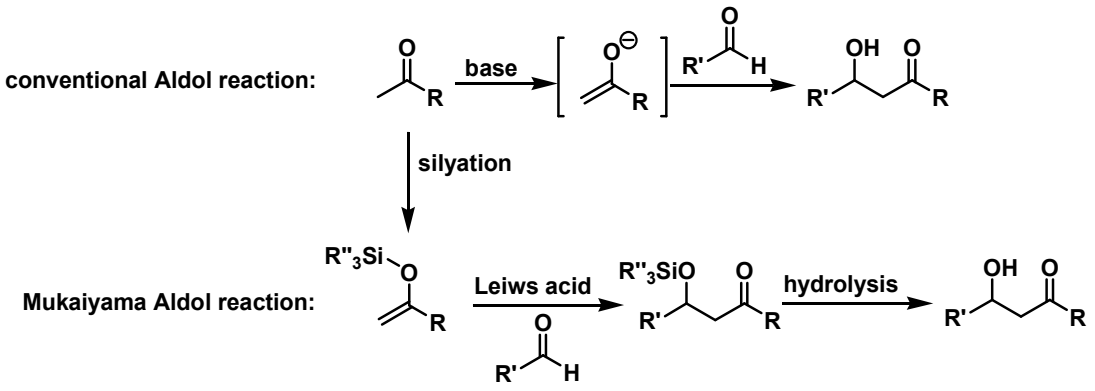

**36** **37** **(95%)** **Eq.13**

An important application of vinyldiazoacetates with enolsilane functional group is the Mukaiyama-type addition reactions. A number of highly functionalized diazoacetoacetate compounds can be synthesized by these reactions. Therefore, the Mukaiyama-aldol reaction of vinyldiazoacetates will be discussed separately in the following section.

### 1.1.4 Mukaiyama-aldol Reactions of Vinyldiazoacetates

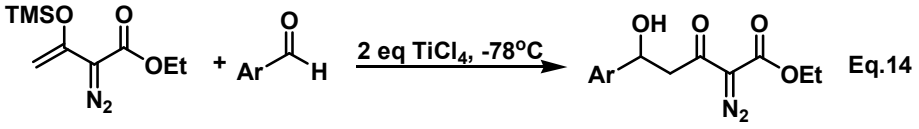
Aldol reaction is among the most powerful methods to build a carbon-carbon bond.[43] An important variant of aldol reactions is the Mukaiyama-aldol reaction.[44] As illustrated in Scheme 1.10, the Mukaiyama-adol reactions employ silyl enol ethers as nucleophile rather than enolates and the reaction is promoted by Lewis acids instead of bases. Titanium chloride was used as the Lewis acid by Mukaiyama initially, Other Lewis acids such as $BF_3Et_2O$, $AlCl_3$, $Sc(OTf)_3$, $Cu(OTf)_2$, Ag(OTf), $La(OTf)_3$ have also been evaluated for the Mukaiyama-aldol reactions through time.[45] Adducts formed in Mukaiyama-aldol reactions are usually in the alcohol form. However, silyl ether products have also been observed.[45] Therefore, the mechanism of the reaction probably involves a silyl transfer step, but since a strong Lewis acid is often involved, the intial silyl adducts are readily hydrolyzed to form products in alcohol form.

**Scheme 1.10** Conventional Aldol Reaction vs Mukaiyama-aldol Reaction.




In 1996, Karadi introduced the Mukaiyama-aldol reaction of vinyldiazoacetates: In the presence of stoichiometric $TiCl_4$, silyl enol ether **38** reacted with aromatic

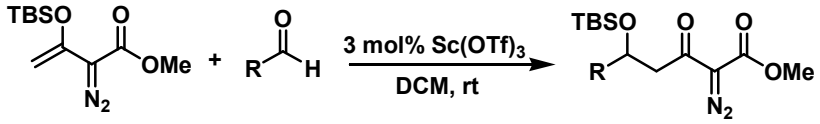
adehydes to yield the corresponding adducts in alcohol form (Eq.14).[46] This chemistry is an exciting development of transformations featuring vinyldiazoacetates. It opens the door for the synthesis of novel diazoester compounds by Mukaiyama-aldol condensations. However, this method suffers from the fact that an excess amount of strong Lewis acid had to be used to promote the reactions and the reactions had to be performed at -78°C. The yields of the reaction were not very high which could be the outcome of the harsh conditions applied. Therefore, an improved method with a catalytic amount of Lewis acid that can be performed under mild conditions would be more desirable.




38 29 40 (60-80%)

In 2005, Doyle reported an efficient Mukaiyama-aldol reaction of vinyldiazoacetate **37** with aldehydes catalyzed by $Sc(OTf)_3$ (Table 1.2).[47] Compared with previous work by Karadi, this new method has several advantages: first of all, the reaction is catalytic, only 3 mol% of Lewis acid is needed to catalyze this transformation. Second, the reaction is performed under mild conditions (room temperature instead of -78°C). Lastly, the yields are improved, and substrate scope is expended. Another interesting feature of this transformation is that since the reaction conditions are sufficiently mild, the silyl group is retained in products **42**.

**Table 1.2** Catalytic Mukaiyama-aldol Reaction of Vinyldiazoacetate **37b.**

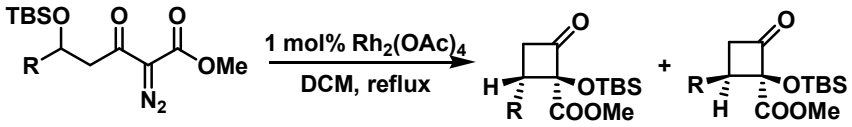



37 41 42

| R | yield of 43 (%) |
|---|---|
| Ph | 93 |
| 4-MeOC$_6$H$_4$ | 98 |
| 4-CF$_3$C$_6$H$_4$ | 94 |
| BnOCH$_2$ | 93 |
| *n*-heptyl | 94 |
| *n*-propyl | 92 |

The resulting diazo compounds **42** were subject to diazo decomposition reactions and poly- substituted cyclobutanone products (**43** and **44**) were produced in mainly one diastereomer (Table 1.3).

**Table 1.3** Diazo Decomposition of Mukaiyama-aldol Adduct **42**.

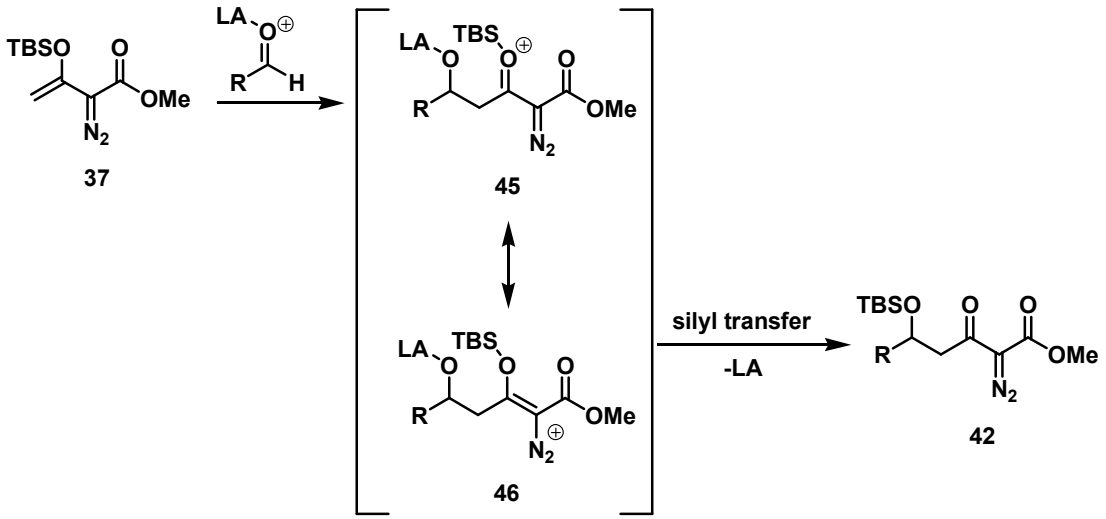



42 43 44

| R | yield of 80+81 (%) | 80:81 |
|---|---|---|
| Ph | 80 | 10:1 |
| 4-Me-C$_6$H$_4$ | 84 | 12:1 |
| 4-F-C$_6$H$_4$ | 84 | 10:1 |

From a mechanistic perspective, This Mukaiyama-aldol reaction starts with the nucleophilic attack of vinyl ether **37** on Lewis acid activated aldehydes to afford reaction intermediates **45.** Carbonyl oxonium ion **45** can then undergo silyl transfer to produce the observed addition products **42** (Scheme 1.11). It is worth mentioning that in this transformation, the diazo group could help stabilizing intermediate **45** by forming resonance contributing sturcutre **46**. This extra stabilization provided by the neighboring diazo functional group could be a crucial factor for being able to achieve this Mukaiyama-aldol reaction under such mild conditions.

**Scheme 1.11** Mechanism of the Mukaiyama-aldol Reaction of Vinyldiazoacetate.




As an extension of Mukaiyama-aldol reaction, Mukaiyama-Michael reaction uses α,β–unsaturated carbonyl compounds as electrophiles instead of aldehydes to react with silyl enol ethers.[44] However, to our best knowledge, the Mukaiyama-Michael reaction with vinyldiazoacetates had not been reported in the literature. The closest example we could find is the reaction reported by

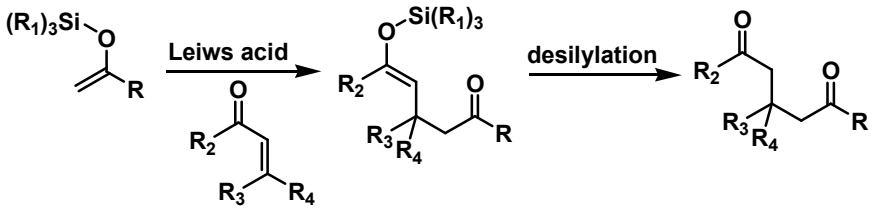
Wang in which titanium(IV) enolate derivatives of diazoacetoacetates were applied as nucleophiles (Table 1.1).[40] With success in Mukaiyama-aldol reaction, we envisioned the possibility to apply these reaction conditions to the Mukaiyama-Michael addition of vinyldiazoacetates. The Mukaiyma-Michael reactions of vinyldiazoacetates turned out to be feasible, and the results obtained from these investigations are discussed in details in the next section.

## 1.2 Results and Discussion

Encouraged by the success with Mukaiyama-aldol reaction of 3-*tert*-butyldimethyl siloxy-2-diazo-3-butenoate (**37**) and aldehydes (**41**) catalyzed by $Sc(OTf)_3$ (Table 1.2), we determined to further develop this chemistry. Conjugate additions of α,β–unsaturated carbonyl compounds with siloxy vinyldiazoacetates, which are known as Mukaiyama-Michael reactions seem suitable to explore. First reported by Mukaiyama, the Mukaiyama-Michael reactions refer to the condensations of enolsilanes and α,β–unsaturated carbonyl compounds (Scheme 1.12).[48] Strong Lewis acids such as $TiCl_4$ or $SnCl_4$ have been used in stoichiometric amount to promote these transformations,[49] examples with catalytic amount of Lewis acid could also be noticed in the literature.[50] Zinc(II) chloride[50a], indium(III) chloride[50c],lanthanide(III) iodides[50d] and samarium iodide[50e,50f] were applied as Lewis acid catalysts to promote the Mukaiyama-Michael reactions. The catalyst loading for these reactions are 10-20 mol%. Similar to the scenario in Mukaiyama-aldol reactions, with a few exceptions,[50e,50f] the disilylation products are obtained instead of the silyl transferred product due to the strong acidic conditions applied. Mechanistic wise, although a silyl transfer step is generally accepted, alternative mechanisms were also proposed. For example, Evans suggested the formation of a dihydropyran intermediate before hydrolyzed by an alcoholic additive.[51] Oteria and Fukuzumi have conducted a mechanistic study, based on which they proposed an electron transfer mechanism when less bulky ketene silyl acetals are employed in the Mukaiyama-Michael reactions.[52] Due to the acidic reaction conditions and labile silyl group (such as TMS group)

employed, the hydrolyzed products in ketone form are usually obtained from the Mukaiyama-Michael additions in previous examples therefore, limited information were obtained regarding the reaction mechanism. No previous report that involves vinyldiazoacetates in Mukaiyama-Michael reactions could be found in the literature.

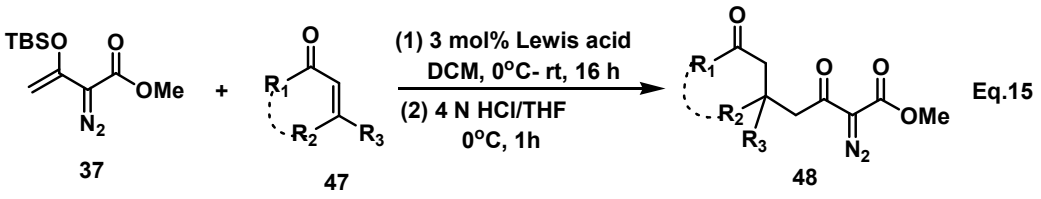
**Scheme 1.12** Mukaiyama-Michael Reactions.




### 1.2.1 Previous Results (work done by Dr Yu Zhang)

#### 1.2.1.1 General Information

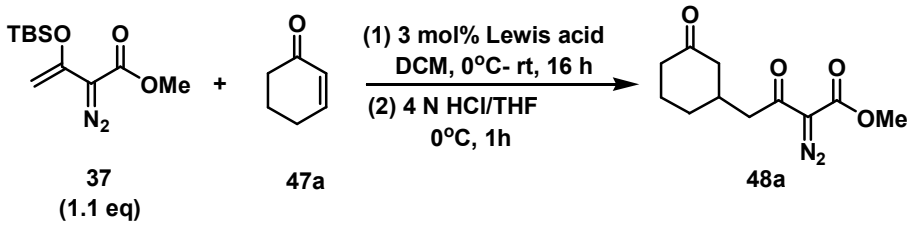
3-TBSO-Vinyldiazoacetate **37** was prepared by the method reported by Ueda[41] using *tert*-butyldimethylsilyl triflate as the silylation reagent and triethylamine as base. Diazoacetoacetate **36** can be converted to vinyldiazoacetate **37** in excellent yield (Eq. 13). Silyl enol ether **37** was then subjected to reaction with α,β–unsaturated ketones (**47**) catalyzed by 3 mol% Lewis acid catalyst. The reagents were mixed in dichloromethane and stirred at 0$^{o}$C then slowly warmed to room temperature. After 16 hours, the reaction mixture was concentrated followed by acid hydrolysis with 4 N HCl/THF at 0$^{o}$C to remove the silyl group (Eq.15). This reaction was optimized and examined.




### 1.2.1.2 Catalyst Screening

2-Cylcohexenone (47**a**) was chosen as the substrate for catalyst screening. At first, scandium triflate, which is the preferred catalyst for the Mukaiyama-aldol reaction reported by our research group previously,[47] was applied in the Mukaiyama-Michael reaction. The expected reaction indeed occurred and produced the corresponding adduct **48a**, but the yield is only moderate (43%) (Table 1.4, entry 1). Other metal triflates were then evaluated under the same reaction conditions. Lanthanum(III) triflate, silver(I) triflate and tin(II) triflate produced the product in moderate yields as well (entry 2-4); copper(II) triflate gave a lower yield of Mukaiyama-Michael adduct **48a** due to catalysis of dinitrogen extrusion (entry 5). Zinc(II) triflate, which is a mild, inexpensive Lewis acid, gave the best yield for this reaction at 79% (entry 6). With an increase in the amount of 3-TBSO-vinyldiazoacetate substrate **37** from 1.1 equivalents to 1.5 equivalents, the yield of the desired product could be further improved to 96% (Entry 7).

**Table 1.4** Optimization of the Mukaiyama-Michael Reaction.




37 (1.1 eq) 47a 48a

| Entry | Lewis acid | yield of 48a |
|---|---|---|
| 1 | $Sc(OTf)_3$ | 43 |
| 2 | $La(OTf)_3$ | 50 |
| 3 | $Sn(OTf)_2$ | 48 |
| 4 | AgOTf | 44 |
| 5 | $Cu(OTf)_2$ | 29 |
| 6 | $Zn(OTf)_2$ | 79 |
| 7[a] | $Zn(OTf)_2$ | 96 |

[a] 1.5 equivalent of 37 was used

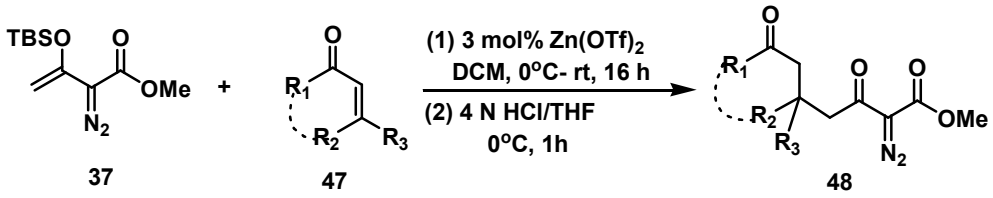
One possible explanation for the preference of mild Lewis acids for this Mukaiyama-Michael reaction is that since the silyl transfer is suggested to be the rate-limiting step of the Mukaiyama-type addition,[53] a mild Lewis acid that is loosely bound to the carbonyl oxgen in the α,β–unsaturated ketone moiety can be readily released in the silyl transfer step.[54] As a result, a mild, less oxophilc Lewis acid such as zinc(II) triflate appears to be a better catalyst in comparison with other stronger Lewis acids, such as scandium(III) triflate. In fact, zinc(II) triflate is extremely effective in catalyzing this reaction, and the catalyst loading can be further reduced: with only 0.1 mol% of $Zn(OTf)_2$, the intended Mukaiyama-Michael addition still proceeded and gave 94% isolated yield of **84a** with 24 hours reaction time. The mild, catalytic condition is a an advantageous feature of

this reaction especially compared to other reactions in which stoichiometric or even excess amount of strong Lewis acids are required.

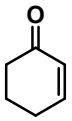
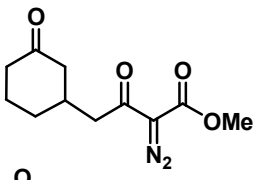
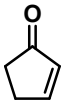
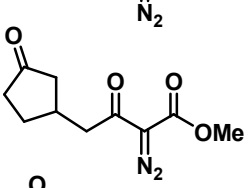
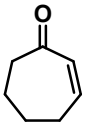
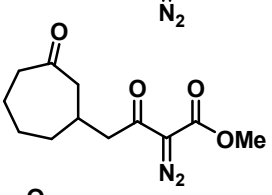
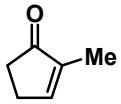
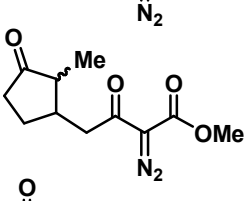
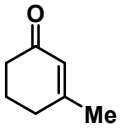
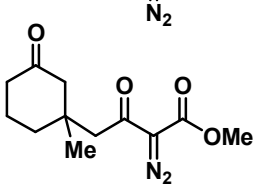
### 1.2.1.3 Substrate Scope of α,β–Unsaturated Ketones 47

Under the optimal conditions established in Table 1.4, different enone substrates **47** were investigated and the results are summarized in Table 1.5.

**Table 1.5** Mukaiyama-Michael Reactions with Representative Enones.

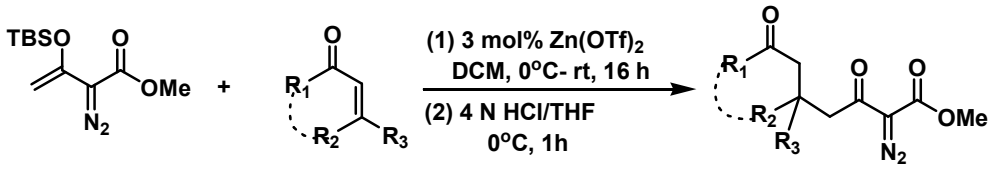



37 47 48

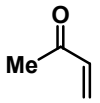
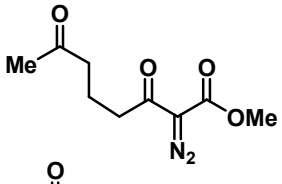
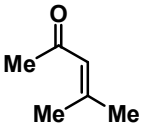
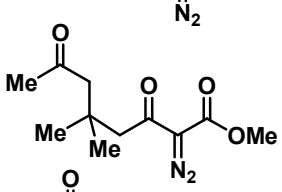
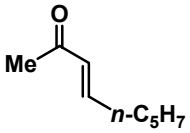
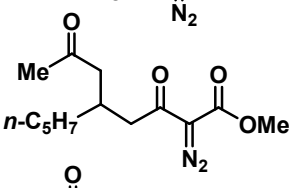
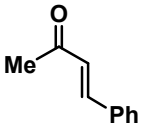
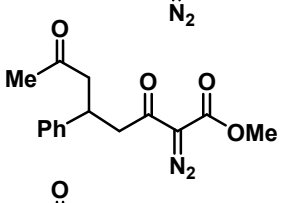
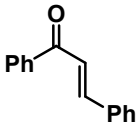
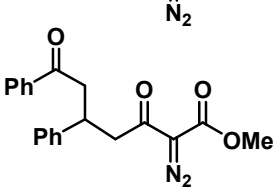
| Entry | | enone 47 | product 48 | yield % |
|---|---|---|---|---|
| 1 | a |  |  | 96 |
| 2 | b |  |  | 84 |
| 3 | c |  |  | 94 |
| 4 | d |  |  | 99 |
| 5 | e * |  |  | 68 |

* 2 equivalent of 37 was used and reaction time was 36 h

**Table 1.5**. Mukaiyama-Michael reactions with representative enones (continued).




37 47 48

| Entry | | enone 47 | product 48 | yield % |
|---|---|---|---|---|
| 6 | f |  |  | 74 |
| 7 | g* |  |  | 71 |
| 8 | h |  |  | 88 |
| 9 | i |  |  | 92 |
| 10 | j |  |  | 99 |

* 2 equivalent of 37 was used and reaction time was 36 h

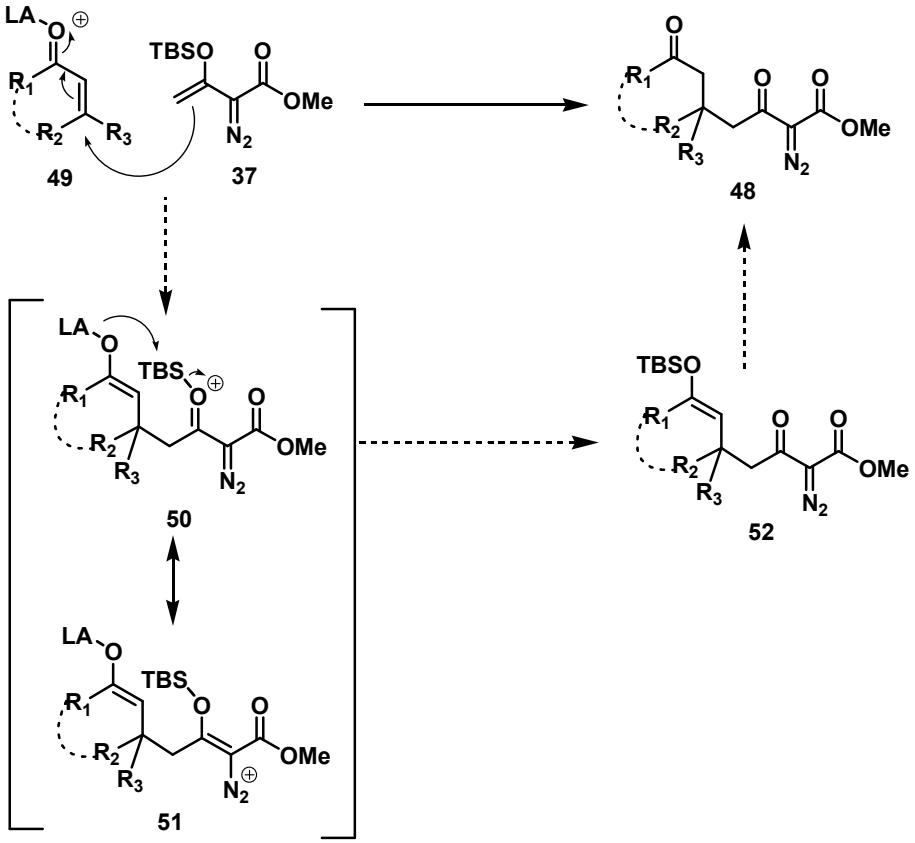
As is shown in Table 1.5, cyclic (entries 1-5) and acyclic (entries 6-10) α,β-unsaturated ketones (**47**) all gave good to excellent yields in this Mukaiyama-Michael reactions. Sterically hindered substrates such as **47e** and **47g** also worked with extended reaction times (36 hours) and an increased amount of 3-TBSO-vinyldiazoacetate **37** (2 equivalents instead of 1.5 equivalents). When

methyl vinyl ketone (**47f**) was used, a byproduct with a second addition of the enone substrate was also observed. We will come back to discuss the formation of this double addition product later on. In all cases, only 1,4-addition products were obtained, and no 1,2-addition products could be observed based on $^{1}H$ NMR spectrum of the crude reaction mixtures.

#### 1.2.1.4 Mechanistic Perspective

A possible mechanism of the Mukaiyama-Michael reaction is depicted in Scheme 1.13. Upon activation by the Lewis acid catalyst, α,β–unsaturated carbonyl compounds undergo nucleophilic addition with 3-TBSO-vinyldiazoacetate **37**. Reaction intermediates **50**, which could be stabilized by the neighboring diazo group through resonance contributing structure **51**, undergo silyl transfer that would release the catalyst and produce diazoesters **52**. It is anticipated that compounds **52** with sily enol ether functionality should be the initial Mukaiyama-Michael addition products before acid promoted hydrolysis. However, no evidence that could support the formation of diazoesters **52** was obtained at this point. Diazo compounds **52** possess different functional groups compared to their hydrolyzed form **48** (silyl enol ether instead of a ketone). We were interested in getting the silyl enol ether form of the Mukaiyama-Michael adducts **52** since they can be further elaborated via the silyl enol ether functional groups. What is more, the capability to provide products with different functionalities would add versatility to this methodology.

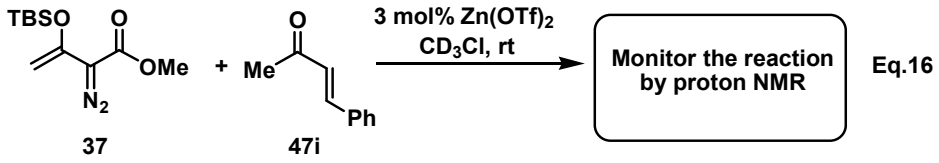
**Scheme 1.13** Proposed Mechanism for the Mukaiyama-Michael Reaction.




## 1.2. 2 Discovery and Synthesis of Diazoacetoacetate Derivatives with Vinyl Ether Functionality

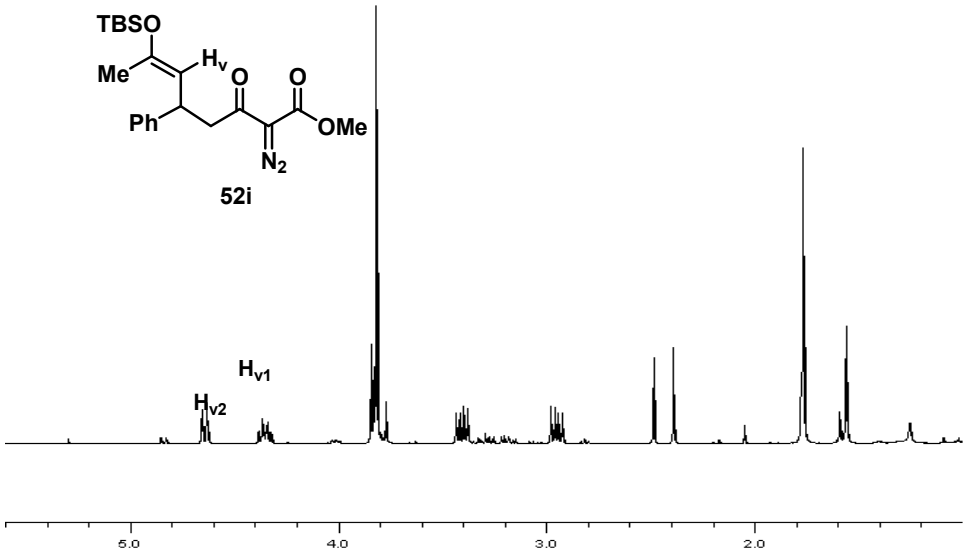
### 1.2. 2.1 NMR Experiments that Prove the Existence of Vinyl Ether Adducts 52

To prove the existence of the silyl transferred product **52**, we performed the reaction of vinyl diazoacetate **37** with α,β–unsaturated carbonyl compound **47i** in deuterated chloroform. The reaction was monitored by proton NMR through time to determine the composition of the reaction mixture (Eq.22).



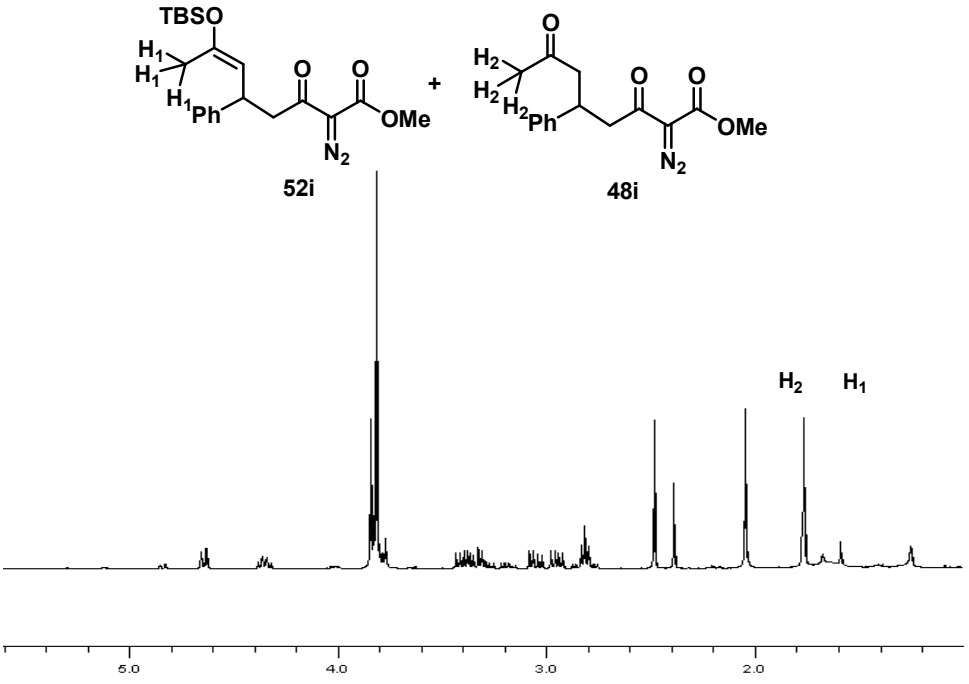

Adduct **52i** was visualized by NMR after reacting vinyldiazoacetate **37** with enone **47i** at room temperature for 2 hours, and it was the only product in the system besides a small amount of diazoacetoacetate from the hydrolysis of vinyl ether **37** (peaks at 3.8 ppm and 2.5 ppm)(Figure 1.3). The vinyl proton at 4.69 ppm is the most diagnostic peaks to support the structure of vinyl ether **52i** since no signal of Mukaiyama-Michael adduct in ketone form (**48**) would appear in this region for vinyl protons. The proton NMR spectrum also suggested that compound **52i** existed as two isomers resulting from the geometry of the double bond in approximately a 3 to 1 ratio.

**Figure 1.3** Proton NMR spectrum of the reaction mixture after 2 hours.



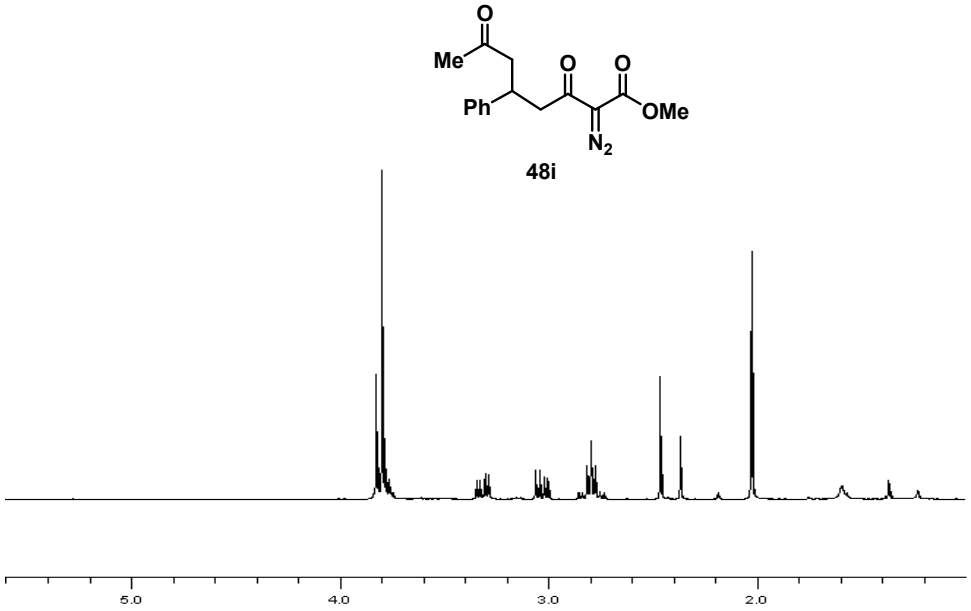
As the reaction proceeded, compound **52i** slowly hydrolyzed to give the corresponding ketone product 48**i**: a proton NMR spectrum after 8 hours (Figure 1.4) showed that the composition of the reaction became a mixture of the vinyl ether product **52i** and the ketone product **48i** which was clearly shown by the decrease of methyl proton signal of **52i** at 1.81 ppm and the appearance of methyl group in **48i** at 2.01 ppm.

**Figure 1.4** Proton NMR Spectrum of the Reaction Mixture after 8 Hours.




Finally, after 24 hours, the signals representing the vinyl protons in compound **52i** had completely disappeared which indicates that vinyl ether adduct **52i** completely decomposed and the hydrolyzed Mukaiyama-Michael adduct **48i** became the predominant product in the reaction mixture (Figure 1.5).

**Figure 1.5** Proton NMR Spectrum of the Reaction Mixture after 24 Hours.




Based on the results from these NMR experiments, we realized that the vinyl ether adduct **52i** was indeed produced during the reaction. However, it slowly decomposed to give the hydrolyzed product **48i**. We speculated that the hydroscopic character of the Lewis acid catalyst could be the reason for the decomposition of the vinyl ether adduct. Although the reaction was initiated under anhydrous conditions, the Lewis acid catalyst zinc triflate could slowly draw moisture from the atmosphere to the reaction. With water and Lewis acid catalyst presented in the system, hydrolysis of the vinyl ether becomes possible. If this would be the case, then the Lewis acid catalyst not only catalyzes the expected Mukaiyama-Michael addition but it also accelerate the hydrolysis of the silyl enol ether adduct. To gain evidence that can support this hypothesis, the reaction described in equation 16 was performed again, but this time under strict anhydrous condition: all reagents were added into a NMR tube in a glove box

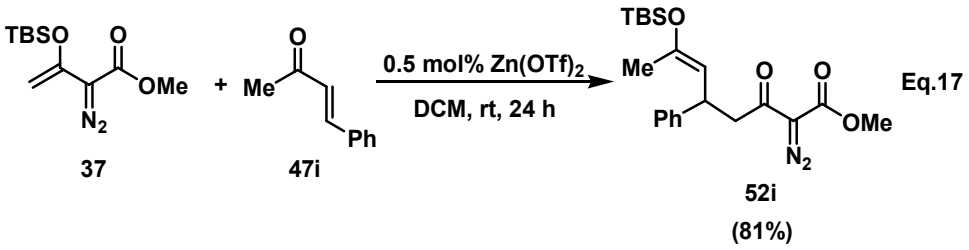
and the NMR tube is then carefully sealed to isolate the reaction from the outside environment. In this case, vinyl ether product **52i** remained intact even after 16 hours and only trace amount of hydrolyzed product was observed. This result proved that water from the environment caused the decomposition of the silyl enol ether product **52** produced from the Mukaiyama-Michael addition.

### 1.2. 2. 2 Reaction Conditions that Preserve Silyl Transferred Products 52

The presence of silyl transferred products **52** was confirmed by $^{1}$H NMR spectra. However, silyl enol ether compounds (**52**) are labile under acidic conditions in contact with the moisture from the environment. We have also demonstrated that vinyl ether adduct **52** can be obtained under very strict anhydrous conditions by carrying out the reaction in a glove box. However, we wanted to find out if this transformation could be achieved in a more convenient manner.

We realized that an important variable that affects hydrolysis of **52** is the amount of Lewis acid catalyst involved. The Lewis acid catalyst not only absorbs water from the atmosphere but also promotes the hydrolysis of vinyl ether adducts **52**. Therefore, by decreasing the catalyst loading we could slow down the unwanted hydrolysis of compound **52** while not affecting the desired Mukaiyama-Michael reaction significantly, since zinc(II) triflate was demonstrated to be very efficient in catalyzing this Mukaiyama-Michael addition. With this consideration in mind, we performed the Mukaiyama-Michael reaction of 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate (**52**) and 4-phenyl-3-buten-2-one (**47i**) using only 0.5 mol% of zinc triflate instead of 3 mol% that was previously applied.

Under this condition the hydrolysis of Mukaiyama-Michael adduct **52i** was prevented, and ketone product **48i** resulting from hydrolysis was eliminated. With the reaction time being extended from 16 hours to 24 hours, a good yield of diazoester **52i** was obtained despite the fact that the catalyst loading was reduced (Eq.17). In order to prevent potential decomposition of the vinyl ether product during chromatography on silica gel, 1 % triethylamine was added to the eluent to neutralize the acidity of silica during column chromatography of the crude product. An 81% isolated yield was obtained for Mukaiyama-Michael adduct **52i**.

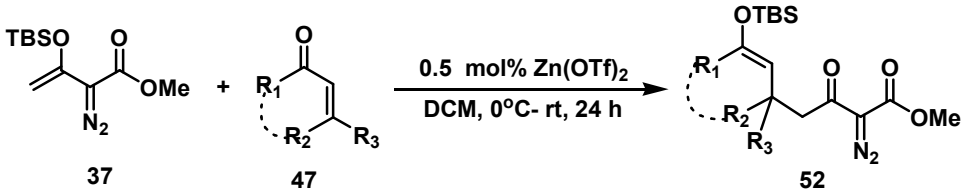


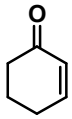
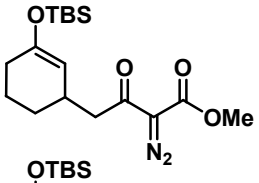
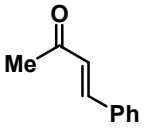
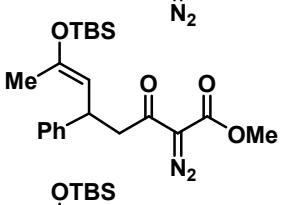
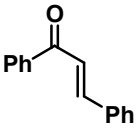
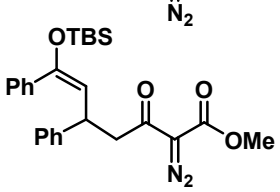

### 1.2. 2. 3 Selective Examples for the Synthesis of Silyl Enol Ether Compounds 87

With modified reaction conditions that afford silyl enol ether product **52**, we investigated a few representative α,β–unsaturated ketones, and the results are shown in Table 1.6. In all three cases, the silyl enol ether products **52** were produced in good yields. With acyclic enone substrates, the products were isolated as mixtures of Z and E isomers. In the case of Mukaiyama-Michael adduct **52i**, a 3/1 ratio for the two isomers is observed. The E isomer was determined to be the major isomer based on a selective NOE experiment that will

be discussed in detail in the experimental section. A larger isomeric ratio (10/1) was observed for compound **52j** which implies that the size of the substituent attached to the vinyl carbon affects the isomeric ratio.

**Table 1.6** Mukaiyama-Michael Reactions with 0.5 mol% of Catalyst that Afford Vinyl Ether Product **52**

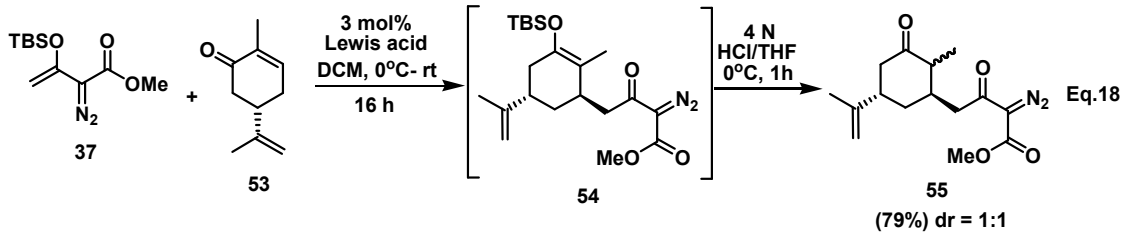



| Entry | | enone 47 | product 52 | yield % |
|---|---|---|---|---|
| 1 | a |  |  | 78 |
| 2 | i |  |  | 81 |
| 3 | j |  |  | 83 |

### 1.2. 2. 4 Diastereoselectivity in Mukaiyama-Michael Reaction of Vinyl Diazoacetate 37 and S-(-)-Carvone (53)

*S*-(-)-Carvone (**53**) is a naturally occurring α,β-unsaturated ketone with a stereogenic center. It is an interesting enone substrate for the Mukaiyama-Michael addition with vinyldiazoacetate **37** since it can offer information about the diastereoselectivity of this transformation. Therefore, S-(-)-carvone was

subjected to the Mukaiyama-Michael reaction with vinyl diazoester **37**. The silyl transferred product **54** was formed as a single diastereomer, as indicated by the $^1$H NMR of the reaction mixture. However, upon hydrolysis the desilylated ketone product **55** was obtained as a mixture of two diastereomer in 1:1 ratio (Eq.18). The Mukaiyama-Michael addition was shown to be diastereoselective by this example but the subsequent hydrolysis step was not selective at all.

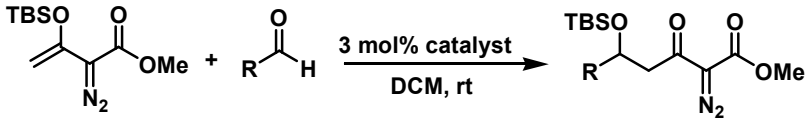



### 1.2.3 Reexamine the Mukaiyama-aldol Reaction with Zinc(II) Triflate as the Lewis Acid Catalyst

Zinc(II) triflate turned out to be a very effective catalyst for the Mukaiyama-Michael reaction. Therefore we decided to reexamine the Mukaiyama-aldol reaction[47] with zinc(II) triflate as the Lewis acid catalyst. A few representative substrates were investigated in comparison with the results obtained with scandium triflate as catalyst (Table 1.7). Zinc triflate works equally well comparing to scandium triflate in catalyzing Mukaiyama-aldol addition reactions with benzaldehyde (Entry 1) cinnamaldehyde (Entry 2). What is more, ortho and para ntirobenzaldehyde (Entry 3, Entry 4), which were unreactive in $Sc(OTf)_3$ catalyzed reactions, reacted with vinyldiazoacetate **37** when zinc triflate was

employed as catalyst. Based on these results from Table 1.7, zinc(II) triflate is concluded to be the superior catalyst for Mukaiyama-aldol reactions.

**Table 1.7** Zinc Triflate Catalyzed Mukaiyama-aldol Reactions with Selected Aldehyde substrates.

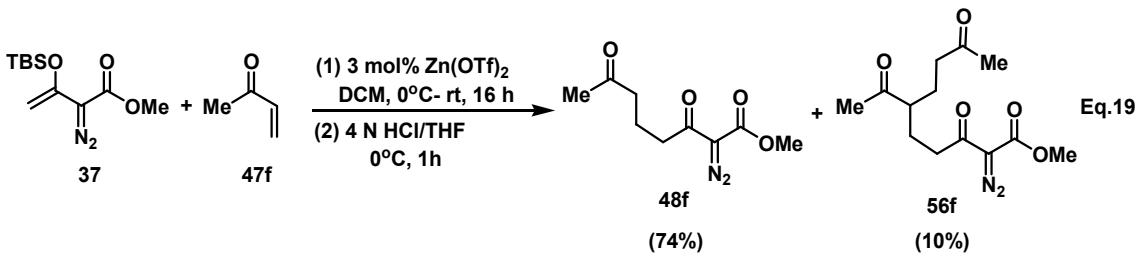



37 41 42

| Entry | R | yield of 42 (%) with $Sc(OTf)_3$ | yield of 42 (%) with $Zn(OTf)_2$ |
|---|---|---|---|
| 1 | Ph | 93 | 97 |
| 2 | trans-β-styryl | 89 | 91 |
| 3 | 4-$NO_2$-$C_6H_4$- | 0 | 80 |
| 4 | 2-$NO_2$-$C_6H_4$- | 0 | 61 |

### 1.2.4 Cascade Reaction of Diazoester 52

When methyl vinyl ketone (**47f**) was subject to reaction with vinyldiazoacetate **37** catalyzed by zinc triflate, besides the major product 48**f**, a minor product (**56f**) with two scaffords of the enone moiety was also isolated (10 % isolated yield)(Eq.19).

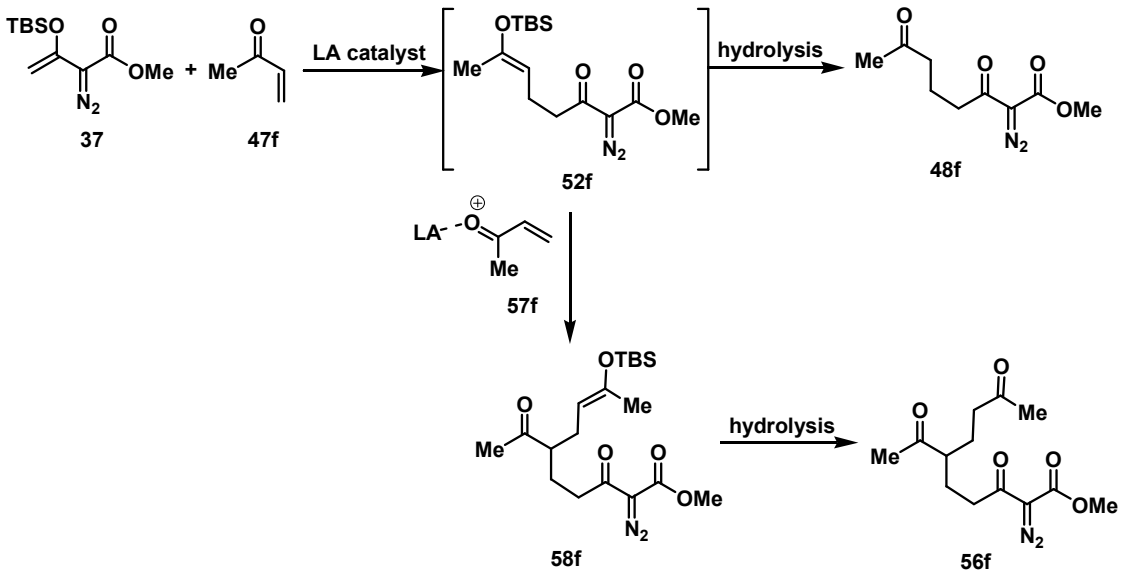



37 47f 48f (74%) 56f (10%) Eq.19

The formation of this double addition byproduct can be understood as follows: before hydrolysis of the silyl enol ether functional group, the initial Mukaiyama-

Michael addition product **52f** is a reactive nucleophile that is suitable to undergo a second Mukaiyama-type addition reaction with another mole of methyl vinyl ketone under the reaction conditions. The addition product **58f** then hydrolyzed to give **56f** as the product obtained after the reaction. This process is depicted in Scheme 1.14.

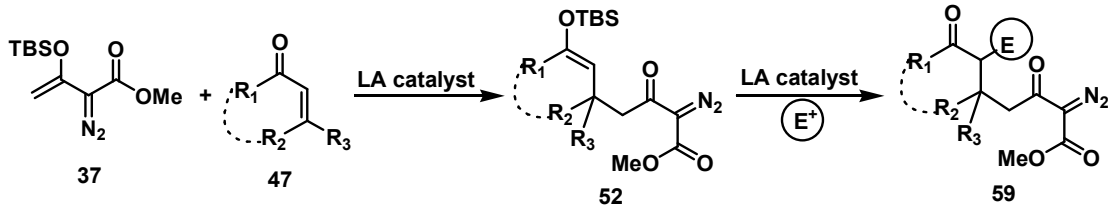
**Scheme 1.14** Reaction of Vinyldiazoacetate **37** with Methyl Vinyl Ketone.



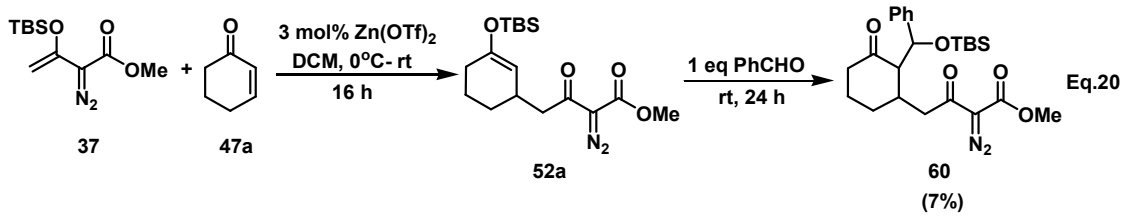

Based on the result obtained from the Mukaiyama-Michael reaction of 3-TBSO vinyldiazoacetate **37** with methyl vinyl ketone (**47f**), we realize the possibility of developing a cascade process. Once the Mukaiyama-Michael adduct **52** is produced, addition of another nucleophile that can react with this silyl enol ether might be able to induce a second addition. In this case, Instead of having the same electrophile attached to the resulting diazo compound (such as the reaction with methyl vinyl ketone), different functional groups could be incorporated and

highly fucntionalized diazoaceoacetate could be synthesized from this cascade reaction (Scheme 1.15).

**Scheme 1.15** Proposed Cascade Reaction.




To evaluate this possible cascade reaction, the Mukaiyama-Michael reaction of 3-TBSO-2-diazo-3-butenoate (**37**) and 2-cyclohexenone (**47a**) was reexamined (Eq.20). In this trial, once the reaction reached completion after 24 hours, 1 equivalent benzaldehyde was added to the reaction mixture. After stirring at room temperature for another 24 hours, diazoester **60** that derived from Mukaiyama-aldol reaction of silyl enol ether **52a** with benzaldehyde was produced. However, the isolated yield of compound **60** was very low (7%). Attempts to optimize this cascade reaction were not successful: Increasing the amount of benzaldehyde from 1 equivalent to 2 equivalents failed to improve the yield of compound **60**. Performing the reaction in a 40$^{o}$C oil bath or with additional Lewis acid catalyst (5 mol% zinc catalyst) added together with benzaldehyde only caused the hydrolysis of vinyl ether intermediate **52a** but did not facilitate the intended cascade reaction.



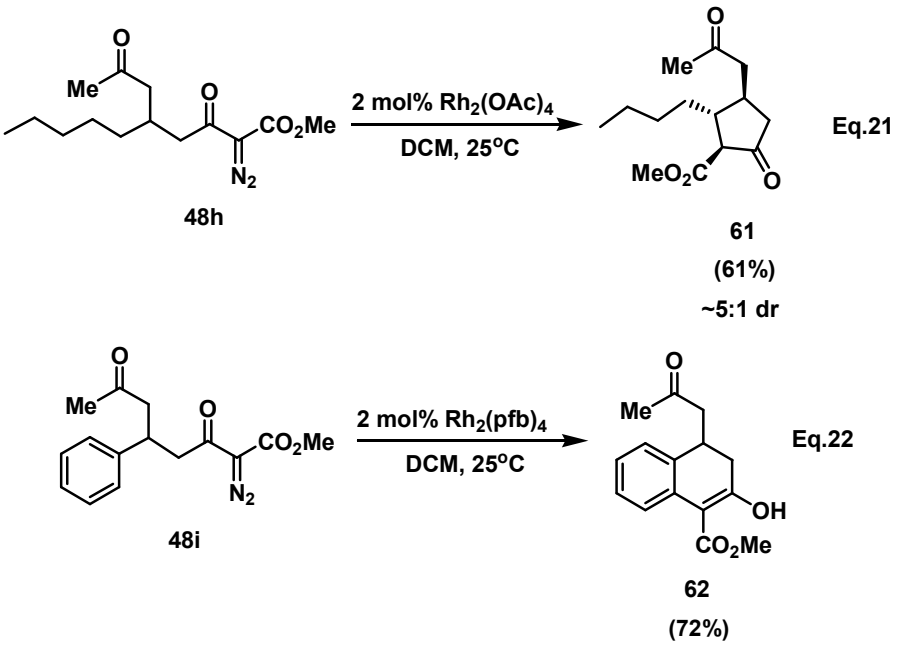

The difference of the silyl enol ether starting material **37a** and the silyl enol ether intermediate **52a** might account for the poor result of this cascade reaction. Due to the presence of a neighboring diazo group, vinyldiazoacetate **37** is more prone to nucleophilic attack on electrophiles since the intermediate resulting from these condensation reactions can be stabilized by the diazo group via resonance. We emphasized this character of vinyl diazoester **37** in our discussion about the reaction mechanisms of both the Mukaiyama-aldol reaction (Scheme 1.11) and the Mukaiyama-Michael reaction (Scheme 1.13). We believe this stabilization is an important factor for being able to achieve these Mukaiyama-type additions under mild conditions with very small amount of metal triflates as Lewis acid catalysts at ambient temperature. By contrast, the silyl enol ether intermediate **52a** no longer has an adjacent diazo group therefore this structural difference might render the second addition less likely to occur under the same mild reaction conditions.

### 1.2.5 Diazo Decomposition of the Mukaiyama-Michael Adducts

Mukaiyama-Michael condensations lead to diazoacetoacetates that are rich in functionalities (compounds **48** and **52**). The reactivity of these novel diazo

compounds in dirhodium(II) catalysts induced dinitrogen extrusion reactions are interesting topics to study.

Dirhodium(II) catalysts promoted dinitrogen extrusion reactions of diazoacetoacetate derivatives **48**, which are the hydrolyzed products from the Mukaiyama-Michael reactions, were studied by Dr Yu Zhang (former post doctoral fellow in Doyle research group).[55] Two representative examples from his work are shown in equation 21 and 22. α–Diazo-β-keto ester 48**h** was prepared by Mukaiyama-Michael addition of 3-TBSO-2-diazo-3-butenoate (**37**) and non-3-en-2-one (47**h**). This Mukaiyama-Michael adduct underwent C-H insertion reaction catalyzed by rhodium(II) acetate to afford highly substituted cyclopentane derivative **61** as a mixture of two diastereomers (indicated by $^{1}$H NMR spectrum) in 61% isolated yield (Eq. 21). Diazoacetoacetate derivative **48i** was also made by the Mukaiyama-Michael reaction. In contrast with the C-H insertion product **61** from diazo decomposition reaction of **48h**, the aromatic substitution product **62** was observed (Eq.22) Dirhodium(II) perfluoroacetate provided the highest yield (72%) compared to rhodium acetate (30%) and rhodium triphenylacetate (62%).

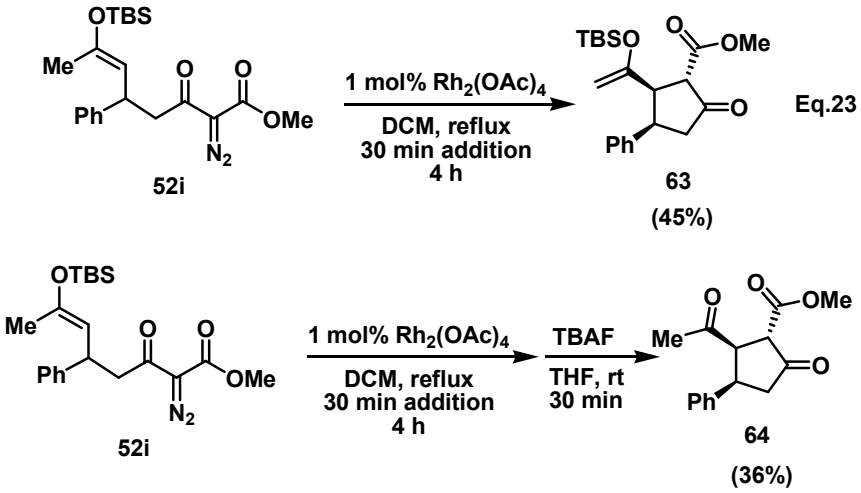



These two examples demonstrated that functionalized diazoacetoacetates (**48**) derived from the Mukiayma-Michael condensations of α–silyoxy-vinyldiazoacetate **37** and enones can undergo dirhodium(II)-catalyzed diazo decomposition reactions. Typical metal carbene mediated reactions, such as C-H insertion and aromatic substitution were observed and multifunctional organic compounds with relative complexity can be synthesized by these reactions.

In contrast with diazoesters **48**, The Mukaiyama-Michael adducts **52** possess different functional groups: the silyl enol ethers resulted from silyl transfer are preserved, rather than hydrolyzed to form the ketone groups in compounds **48.** As a result, diazoesters **52** are engaged in different transformations compared to diazoester **48** in dirhodium(II) catalyzed diazo decomposition reactions.

Diazoester **52i** derived from the Mukaiyama-Michael addition of 3-TBSO-2-diazo-3-butenoate (**37**) and 4-phenyl-3-buten-2-eone (**47i**) was subjected to

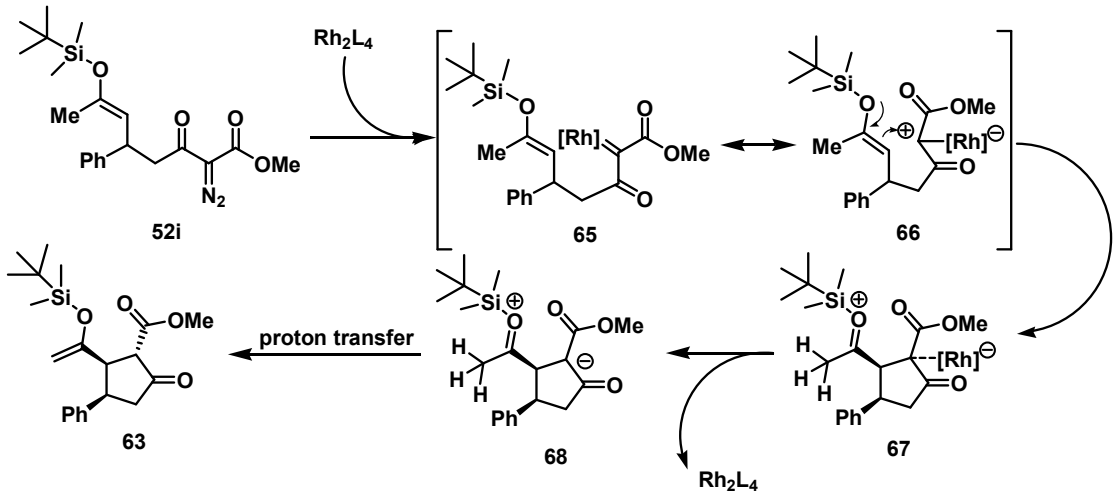
dirhodium(II) acetate catalyzed diazo decomposition reaction. Substrate **52i** was slowly added to a refluxing DCM solution with 1 mol% catalyst during 30 minutes. The reaction solution was under reflux for a total of 4 hours after the addition. Highly substituted cyclopentanone **63** was isolated in moderate yield after the reaction (Eq.23). The structure of diazo decomposition product **63** was illuminated by its $^{1}$H NMR spectrum: it has a silyl enol ether moiety which is suggested by the signals of the vinyl protons and protons from the TBS group. Proton NMR also revealed that product **63** is a single diastereomer, and the relative stereochemistry was assigned based on coupling constants. A 16 Hz coupling constant between the proton alpha to both carbonyl groups and the allylic proton indicates *trans* geometry in analogy to a similar cyclopentanone system,[56] and since there is no observable coupling between the benzylic proton and the allylic proton by $^{1}$H NMR, these two protons were assigned to be *cis*. The predicted structure of compound **63** based on its proton NMR spectrum is supported by an additional experiment where the crude reaction product was treated with tetra-*n*-butylammonium fluoride (TBAF) and in this case, the terminal silyl enol ether was decomposed and cyclopentanone **64** with a acetyl group was identified (Eq. 24).



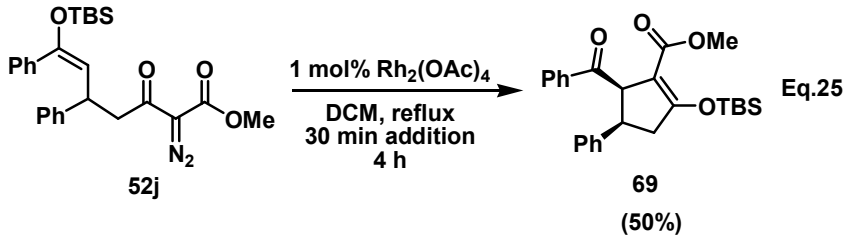

Although the $^{1}H$ NMR spectrum of the crude reaction mixture looked rather clean, and product other than **63** was not evident, the isolated yield of **63** was relatively low. Considering the sensitive character of a terminal silyl enol ether functional group, we suspected that product **63** was lost partially during purification on silica gel which is slightly acidic. However, using eluent that contains 1 % triethylamine to neutralize the acidity of silica gel or switching to column chromatograph with florisil failed to provide higher yield.

A possible mechanism for the diazo decomposition reaction of **52i** is depicted in Scheme 1.16. Extrusion of nitrogen gas gives metal carbene intermediate **65** which undergoes nulceophilc attack by the vinyl ether to give zwitterion **67**. Proton transfer from the α-methyl group of carbonyl oxonium ion to the enolate carbon after the metal catalyst dissociated affords the cyclopentanone product **63**.

**Scheme 1.16** Proposed Reaction Mechanism for Diazo Decomposition of Diazoester **52i**.

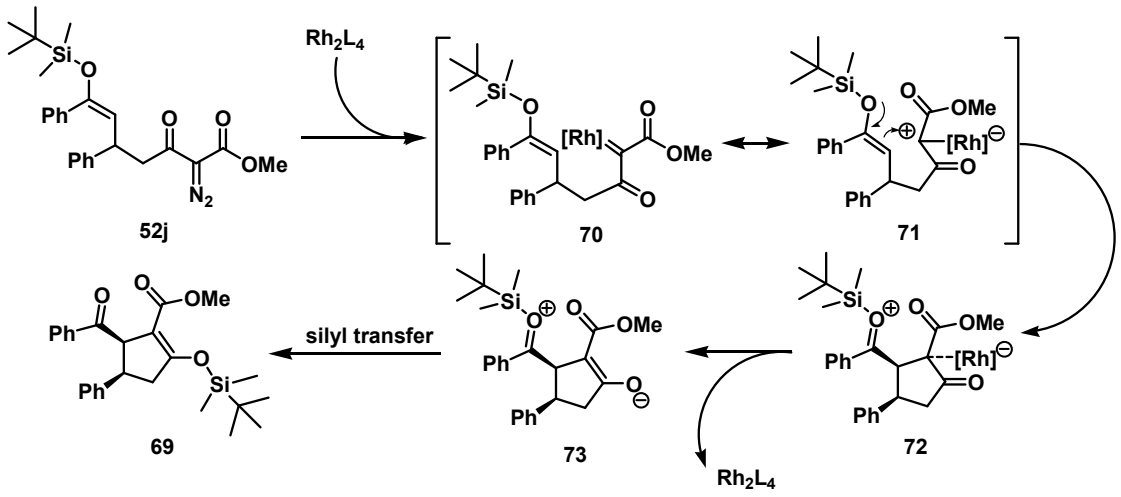



If the methyl group in starting material **52i** is replaced by a phenyl group, there won't be proton available at the last step to complete this transformation by proton transfer. We were curious about whether there would be an alternative reaction pathway that could afford a different product under this circumstance. Therefore, compound **52j** which was prepared by Mukaiyama-Michael reaction of vinyl diazoacetate **37** and chalcone (**47j**), was subject to diazo decomposition reaction under the same reaction conditions that was employed in diazo decomposition reaction of **52i**. Cyclopentene **69** was obtained in this reaction (Eq. 25). The relative stereochemistry was assigned to be *cis* in product **69** since there is almost no coupling between the benzylic proton and the proton at the tertiary carbon, and this is in consistent with the result obtained with cyclopentanone **63**.




The mechanism for diazo decomposition reaction of diazoester **52j** resembles the one described in Scheme 1.16. The only difference is that a silyl transfer to the enolate oxgen occurs instead of proton transfer to the enolate carbon towards the end of this transformation (Scheme 1.17).

**Scheme 1.17** Proposed Mechanism for Diazo Decomposition of Diazoester **52j**

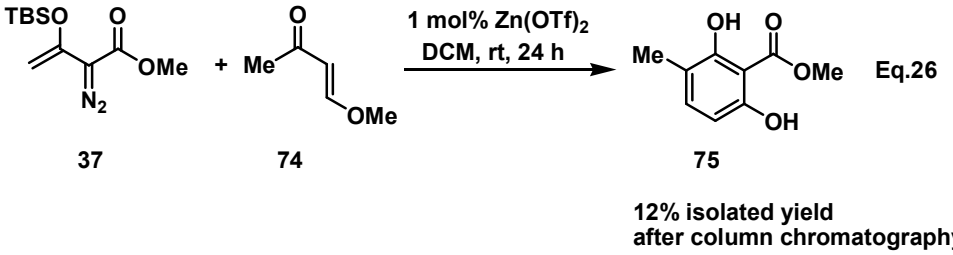



Diazo decomposition reactions of diazoesters **52i** and **52j** are potentially useful transformations for the preparation of multi-substituted cyclopentanone and cyclopentene products. More importantly, considering the fact that C-H insertion of metal carbenes does not generally occur at C-H bonds alpha to a carbonyl group,[4] these transformations that involve silyl enol ethers provide a way to

achieve a formal insertion at the carbon adjacent to a carbonyl group. Therefore, these reactions could be complementary to the established C-H insertion reactions of metal carbenes derived from diazocarbonyl compounds.

### 1.2.6 Mukaiyama Michael Reaction with 4-Methoxyl-3-bute-2-one

An unexpected transformation was discovered when substrate 4-methoxy-3-bute-2-one (**74**) was subjected to Mukaiyama-Michael addition with 3-TBSO-2-diazo-3-butenonate (**37**). 12% of resorcinol compound **75** was obtained after purification by silica gel chromatography (Eq.26). We studied this interesting transformation and we were able to establish this chemistry as applicable synthetic methodologies. The research work on this resorcinol formation will be the content of the second chapter.




### 1.2.7 Summary

We studied the Mukaiyama-Michael condensations of vinyl diazoacetate **37** and α,β–unsaturated carbonyl ketones (**47**) as an extension of the $Sc(OTf)_3$ catalyzed Mukaiyama-aldol reactions previously reported by our group. In this investigation we discovered that zinc triflate is a superior catalyst to scandium triflate in promoting the intended Mukaiyama-Michael reactions. The catalyst loading could be as low as 0.1 mol% without affecting the yield of the addition

product. A problem associated with Lewis acid catalysis was the hydroscopic nature of the metal triflate salt: water is drawn by the Lewis acid catalyst to the reaction solution, and the hydrolysis of the initial Mukaiyama-Michael adducts is accelerated by the metal triflate catalysts. We managed to shut down the hydrolysis reaction by controlling catalyst loading at a low level that is sufficient for the Muakiyama-Michael reaction to occur, but not too high to cause the decomposition of the adducts. A number of highly functionalized diazoacetoacetates, both in the silyl enol ether form and the ketone form, can be prepared by this zinc(II) triflate catalyzed Mukaiyama-Michael additions. We also reexamined the Muakiyama-aldol reactions with zinc (II) triflate, and zinc(II) triflate is effective in catalyzing these addition reactions as well. We subjected the Mukaiyama-Michael addition products to dirhodium(II) catalysts catalyzed diazo decomposition reactions. Classic metal carbene reactions can be achieved for diazoesters **48** while novel transformations that involve interaction of metal carbenes and silyl enol ether fuctional groups in dinitrogen extrusion of diazoester **52** were also observed. In conclusion, this efficient Mukaiyama-Michael reaction between a diazo-containning silyl enol ether and various enones is a practical methodology for the construction of highly substituted diazo acetoacetates. This Mukaiyama-Michael addition allows further investigations on novel diazo compounds that could be synthesized by this method.

## 1.3 Experimental Section

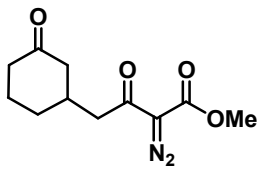
### 3.1. General information

Reactions were performed in oven-dried (140$^{o}$C) or flame-dried glassware. Dichloromethane (DCM) was passed through a solvent column prior to use and was not distilled. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 $F_{254}$ plates. The developed chromatogram was analyzed by UV lamp (254 nm) or ethanolate phosphomolybdic acid (PMA). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated system on silica gel (230-400 mesh). Metal triflate salts were purchased from Aldrich and used as received. All TBSO-substituted vinyldiazoesters were prepared by the method described by Ueda.[41] All other commercially available reagents were used as received unless otherwise mentioned.

NMR spectra were measured on Bruker AV-400 ($^{1}$H at 400 MHz, $^{13}$C at 100 MHz). $^{1}$H NMR spectra were recorded **with tetramethylsilane (TMS) at 0.00 ppm as the internal standard.** Data are reported as follows: chemical shift (in ppm, δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet, comp = composite) and coupling constants (in Hz). $^{13}$C NMR spectra were obtained **with complete proton decoupling. Chemical shifts are reported in ppm utilizing $CDCl_3$ peak as a reference (77.0 ppm).** High Resolution Mass Spectra (HRMS) were recorded by JEOL Accu TOF-CS (ESI, positive mode) spectrometer. Infrared (IR) spectra were measured on a JESCO FT/IR-4100 instrument.

### 1.3.2 General Procedure for Mukaiyama-Michael Reactions that Produce Diazoester 48 (Tables 1.4 and 1.5).

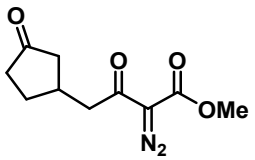
To a flame-dried 25-mL round bottom flask under nitrogen was added zinc triflate (5.5 mg, 0.015 mmol), followed by 2-cyclohexen-1-one (**47a**) (49 mg, 0.50 mmol) and 2 mL of dry DCM. The mixture was stirred at 0°C. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**37**) (202 mg, 0.750 mmol) was added via syringe all in once. The yellow solution was stirred at 0°C for 1 hour and then slowly warmed to room temperature. After 16 hours the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 5 mL of tetrahydrofuran (THF) and stirred at 0°C, and then 1.0 mL of 4N aqueous HCl solution was added dropwise. After 1h at 0°C the reaction was quenched by slow addition of 15 mL of saturated sodium bicarbonate solution until basic to pH paper. The resulting solution was extracted with three 10-mL portions of DCM, and the combined organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 1:2 EtOAc/hexane to give 114 mg of a light yellow oil as product **48a** (0.48 mmol, 96% yield).




**48a**

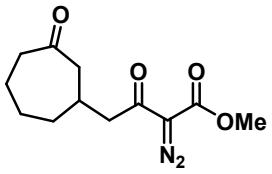
**48a:** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.75 (s, 3H), 2.86 (dd, *J* = 15.7 Hz, *J* = 6.5 Hz, 1H), 2.76 (dd, *J* = 15.7 Hz, *J* = 6.5 Hz, 1H), 2.37-2.13 (comp, 4H), 2.06-1.85

(comp, 3H), 1.65-1.55 (m, 1H), 1.39-1.29 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 210.5, 190.7, 161.6, 76.1, 52.17, 47.45, 46.01, 41.11, 35.03, 31.04, 24.86; IR (neat): 2137, 1712, 1652 cm$^{-1}$; HRMS (FAB) for $C_{11}H_{14}N_2O_4$ $[M+H]^+$ calcd: 239.1032; found: 239.1035; TLC $R_f$ = 0.25 (1:2 hexanes/EtOAc).




**48b**

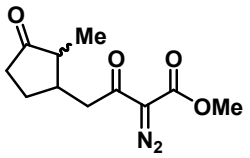
**48b:** 84% yield. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.76 (s, 3H), 2.97 (dd, *J* = 16.8 Hz, *J* = 6.6 Hz, 1H), 2.90 (dd, *J* = 16.8 Hz, *J* = 6.6 Hz, 1H), 2.63-2.55 (m, 1H), 2.39 (dd, *J* = 17.2 Hz, *J* = 7.5 Hz, 1H), 2.25-2.04 (comp, 3H), 1.78 (dd, *J* = 18.3 Hz, *J* = 10.2 Hz, 1H), 1.55-1.48 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 218.3, 190.8, 161.5, 75.8, 52.0, 45.1, 44.4, 38.0, 32.6, 29.0; IR (neat): 2134, 1741, 1718, 1650 cm$^{-1}$; HRMS (FAB) for $C_{10}H_{12}N_2O_4$ $[M+H]^+$ calcd: 225.0875; found: 225.0879; TLC $R_f$ = 0.23 (1:2 hexanes/EtOAc).




**48c**

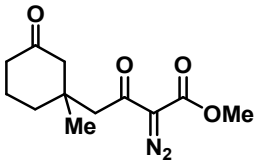
**48c:** 94% yield. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.72 (s, 1H), 2.74 (dd, *J* = 14.8 Hz, *J* = 7.8 Hz, 1H); 2.69 (*J* = 14.8 Hz, *J* = 7.8 Hz, 1H), 2.43-2.29 (comp, 4H), 2.27-2.20 (m, 1H), 1.78-1.75 (comp, 3H), 1.50-1.33 (comp, 2H), 1.28-1.20 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 213.1, 190.8, 161.4, 76.0, 52.0, 49.2, 46.4, 43.6, 36.5,

32.0, 28.3, 24.1; IR (neat): 2141, 1720, 1698, 1650 $cm^{-1}$; HRMS (FAB) for $C_{12}H_{16}N_2O_4$ $[M+H]^+$ calcd: 253.1188; found: 253.1193; TLC $R_f$ = 0.23 (1:2.5 hexanes/EtOAc).



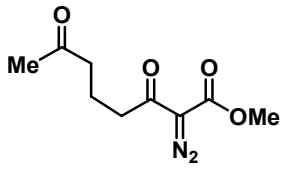

**48d**

**48d:** 84% yield. **48d** was isolated as a mixture of diastereomers in a ~3:1 ratio favoring what we presume to be the trans isomer. For the major isomer: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.73 (s, 3H), 3.06 (dd, *J* = 16.2 Hz, *J* = 3.8 Hz, 1H), 2.84-2.76 (m, 1H), 2.30-1.93 (comp, 4H), 1.71 (dd, *J* = 10.7 Hz, *J* = 6.7 Hz, 1H), 1.33-1.38 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 219.4, 191.0, 161.4, 75.9, 52.0, 49.4, 44.2, 40.3, 36.9, 27.1, 12.2; IR (neat): 2139, 1736, 1723, 1654 $cm^{-1}$; HRMS (FAB) for $C_{11}H_{14}N_2O_4$ $[M+H]^+$ calcd: 239.1032; found: 239.1037; TLC $R_f$ = 0.25 (1:2.5 hexanes/EtOAc). Visible signals for the minor isomer: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.66-2.60 (m, 1H), 1.62 (dd, *J* = 13.1 Hz, *J* = 7.1 Hz), 0.86 (d, *J* = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 202.5, 191.2, 46.2, 39.8, 35.8, 35.7, 25.6, 9.9.




**48e**

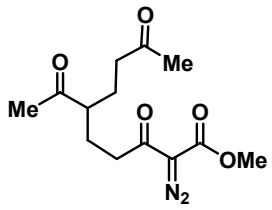
**48e:** 68% yield. The general procedure was followed except that the reaction time was 36 h at room temperature. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.76 (s, 3H), 2.95 (d, *J* = 14.8 Hz, 1H), 2.71 (d, *J* = 14.8 Hz, 1H), 2.44 (d, *J* = 14.6 Hz, 1H), 2.21 (s, 2H), 2.13 (d, *J* = 13.5 Hz, 1H), 1.77-1.86 (m, 3H), 1.62 (d, *J* = 6.2 Hz, 1H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 210.9, 190.6, 161.5, 77.1, 52.8, 52.0, 48.7, 40.6, 39.2, 35.6, 24.7, 21.6; IR (neat): 2138, 1710, 1647 $cm^{-1}$; HRMS (FAB) for $C_{12}H_{16}N_2O_4$ $[M+H]^+$ calcd: 253.1188; found: 253.1193; TLC $R_f$ = 0.24 (1:3 hexanes/EtOAc).



**48f**

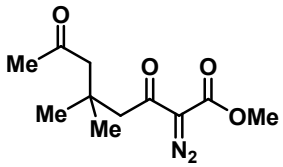
**48f:** 74% yield. The general procedure was followed except that 2.0 equiv of **1** was used. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.79 (s, 3H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 3H), 2.12 (s, 3H), 1.86-1.93 (m, 2H) ; $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 208.0, 191.9, 161.6, 75.7, 52.0, 42.4, 39.0, 29.7, 18.1; IR (neat): 2138, 1714, 1654 $cm^{-1}$; HRMS (FAB) for $C_9H_{12}N_2O_4$ $[M+H]^+$ calcd: 213.0875; found: 213.0879; TLC $R_f$ = 0.25 (1:2 hexanes/EtOAc).

A product from a second Mukaiyama-Michael reaction with methyl vinyl ketone was also isolated in 10% isolated yield besides the expected Mukaiyama-Michael adduct **48f**.



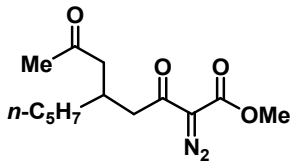
**56f**

**56f:** $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.80 (s, 3H), 2.82-2.74 (comp, 2H), 2.52-2.45 (m, 1H), 2.43-2.31 (comp, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 1.98-1.88 (m, 1H), 1.88-1.81 (m, 1H), 1.75-1.65 (comp, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 211.11, 207.70, 191.67, 161.45, 75.72, 52.10, 50.81, 40.40, 37.40, 29.84, 28.71, 24.91, 24.28; IR (neat): 2133, 1708, 1656 cm$^{-1}$; HRMS (FAB) for $C_{13}H_{18}N_2O_5$ $[M+H]^+$ calcd: 283.1294; found: 283.1290; TLC $R_f$ = 0.27 (1:1 hexanes/EtOAc).



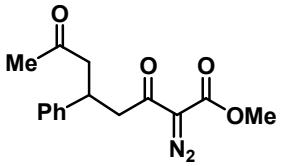
**48g**

**48g:** 71% yield. The general procedure was followed except that the concentration of the enone **5g** was 0.5M, and the reaction time was 36 hours at room temperature. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.77 (s, 3H), 2.99 (s, 2H), 2.59 (s, 2H), 2.05 (s, 2H), 1.04 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 208.3, 191.9, 161.6, 52.49, 52.0, 47.66, 33.34, 31.78, 28.11 (the diazo carbon not located); IR (neat): 2137, 1714, 1648 cm$^{-1}$; HRMS (FAB) for $C_{11}H_{16}N_2O_4$ $[M+H]^+$ calcd: 241.1188; found: 241.1196; TLC $R_f$ = 0.23 (1:5 hexanes/EtOAc).



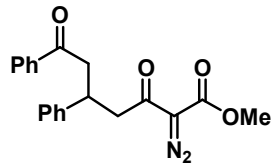

**48h**

**48h:** 88% yield. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.76 (s, 3H), 2.90 (dd, *J* = 16 Hz, *J* = 4.9 Hz, 1H), 2.62 (dd, *J* = 12.9 Hz, *J* = 7.1 Hz, 1H), 2.43-2.34 (comp, 3H), 2.05 (s, 3H), 1.24-1.19 (comp, 8H), 0.80 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 208.1, 191.9, 161.5, 75.9, 52.0, 47.9, 44.2, 34.5, 31.7, 30.3, 30.1, 26.2, 22.4, 13.8; IR (neat): 2136, 1718, 1652 cm$^{-1}$; HRMS (FAB) for $C_{14}H_{22}N_2O_4$ $[M+H]^+$ calcd: 283.1658; found: 283.1656; TLC $R_f$ = 0.25 (1:5 hexanes/EtOAc).




**48i**

**48i:** 92% yield. The general procedure was followed except that the hydrolysis time was 1 hour at 0$^{o}$C and then 3 hours at room temperature. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.24-7.17 (comp, 5H), 3.75 (s, 3H), 3.29 (dd, *J* = 16.3 Hz, *J* = 7.2 Hz, 1H), 3.00 (dd, *J* = 16.3, *J* = 7.2 Hz, 1H), 2.81-2.70 (comp, 2H), 1.99 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 206.7, 190.6, 161.4, 143.4, 128.4, 127.2, 126.5, 76.0, 52.0, 49.3, 45.8, 36.3, 30.2; IR (neat): 2136, 1716, 1653 cm$^{-1}$; HRMS (FAB) for $C_{15}H_{16}N_2O_4$ $[M+H]^+$ calcd: 289.1188; found: 289.1193; TLC $R_f$ = 0.25 (1:3 hexanes/EtOAc).



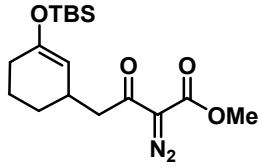

48j

**48j:** 89% yield. The general procedure was followed except that the hydrolysis time was 1 hour at 0°C and then 2 hours at room temperature. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.88 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30-7.23 (comp, 4H), 7.15 (t, *J* = 6.8 Hz, 1H), 4.02-3.98 (m, 1H), 3.77 (s, 3H), 3.44-3.28 (comp, 3H), 3.19 (dd, *J* = 17.1 Hz, *J* = 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 198.1, 190.6, 161.5, 143.7, 136.8, 132.8, 128.4, 127.9, 127.3, 126.4, 76.0, 52.0, 45.9, 44.5, 36.5; IR (neat): 2139, 1721, 1650 $cm^{-1}$; HRMS (FAB) for $C_{20}H_{18}N_2O_4$ $[M+H]^+$ calcd: 351.1345; found: 351.1342; TLC $R_f$ = 0.25 (1:5 hexanes/EtOAc).

### 1.3.3 General Procedure for Mukaiyama-Michael Reactions that Produce diazoester 52 (Tables 1.6).

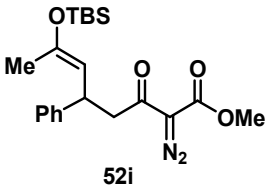
To a flame-dried 25-mL round bottom flask under nitrogen was added zinc triflate (1 mg, 0.0025 mmol), followed by 2-cyclohexen-1-one (49 mg, 0.5 mmol) and 2 mL of dry DCM. The mixture was stirred at 0°C. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (154mg, 0.6mmol) was added by syringe all in once. The yellow solution was stirred at 0°C and slowly warmed to room temperature. After 24 hours, the crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography with 1% (volume percentage) triethylamine added to the eluting solvent (10:1

hexanes/EtOAc) to give 130 mg of a light yellow oil as product **52a** (0.39 mmol, 78% yield).



**52a**

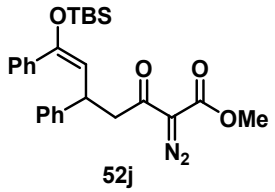
**52a:** 78% yield. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 4.71 (s, 1H), 3.75 (s, 3H), 2.81~2.61(comp, 3H), 1.89(m, 2H), 1.66 (m, 2H), 1.51 (m, 1H), 1.13 (m, 1H), 0.83 (s, 10H), 0.04 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 192.4, 162.4, 152.2, 108.6, 52.8, 47.4, 32.0, 30.6, 29.3, 26.4, 22.0, 18.7, -3.7, -3.7; IR (neat): 2132, 1724, 1658 cm$^{-1}$; HRMS (ESI) for $C_{17}H_{28}N_2O_4$ Si $[M]^+$ calcd: 353.1897; found: 353.1880; TLC $R_f$ = 0.50 (10:1 hexanes/EtOAc)



**52i**

**52i:** 81% yield. **52i** was isolated as a mixture of diastereomers (*E/Z* isomers) in a ~3:1 ratio. For the major isomer: $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.36-7.25 (comp, 5H), 4.69 (d, *J* = 10 Hz, 1H), 4.40 (q, *J* = 17 Hz, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 3.45 (dd, *J* = 15 Hz, *J* = 7Hz, 1H), 2.99 (dd, *J* = 15 Hz, *J* = 7.5 Hz, 1H), 1.81 (s, 3H), 0.98 (s, 10H), 0.11(s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 191.7, 162.6, 147.9, 145.8, 129.1, 128.1, 126.7, 111.0, 52.9, 47.9, 38.4, 26.6, 23.6, -2.9, -3.0; IR (neat): 2132, 1720, 1658 cm$^{-1}$; HRMS (ESI) for $C_{21}H_{30}N_2O_4$ Si $[M+Na]^+$ calcd:

425.1873; found: 425.1861;TLC $R_f$ = 0.30 (10:1 hexanes/EtOAc). Visible signals of minor isomer: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.21-7.16 (comp, 5H), 4.88 (d, *J* = 10 Hz, 1H), 4.08-4.02 (comp,1 H), 3.86 (s, 3H), 3.37-3.30 (comp 1H), 3.25~3.20 (comp, 1H), 1.82 (s, 3H), 0.93 (s, 10H), 0.16 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.0, 137.1, 129.3, 129.2, 127.9, 127.3, 126.9, 111.4, 52.9, 52.6, 47.7, 40.7, 26.4, 19.0, 18.8.



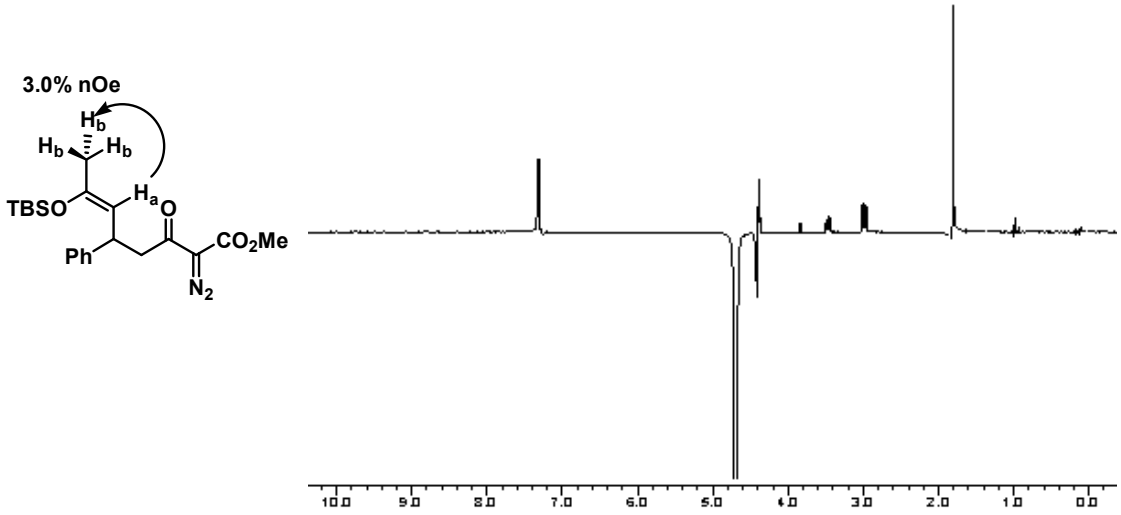
**52j**

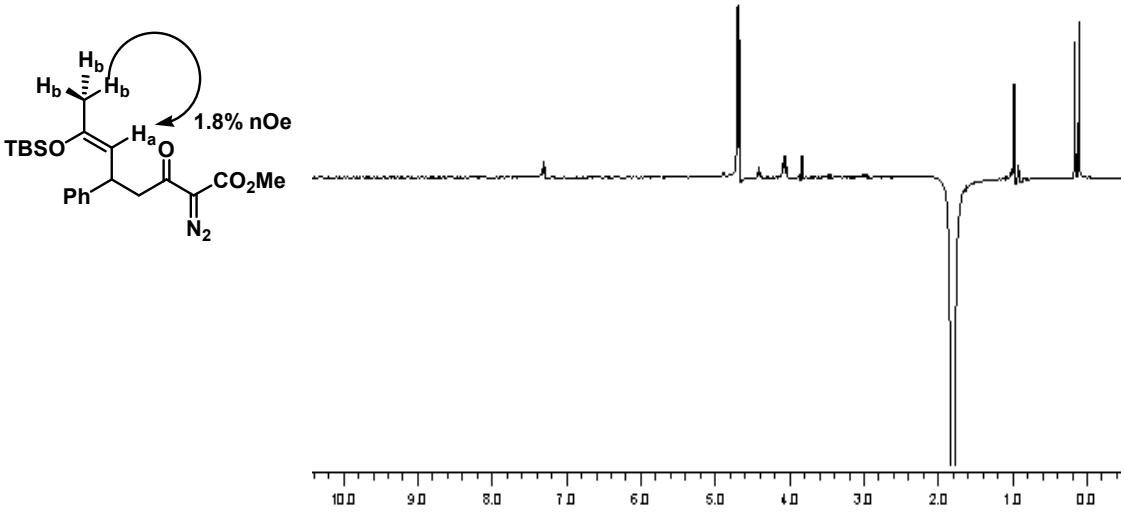
**52j:** 83% yield. Only a trace amount of the minor diastereomer could be observed by NMR. Signals of major isomer: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.48-7.22 (comp, 10H), 5.41 (d, *J* = 10 Hz, 1H), 4.60 (q, *J* = 17.5 Hz, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.60 (dd, *J* = 15.5 Hz, *J* = 7.5Hz, 1H), 3.19 (dd, *J* = 15.5 Hz, *J* = 7.5 Hz, 1H), 1.07 (s, 10H), 0.08 (d, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 191.5, 162.6, 150.7, 140.3, 129.3, 128.7, 128.7, 128.3, 127.3, 127.0, 114.3, 52.8, 47.9, 39.0, 26.7, 19.1, -3.1, -3.6; IR (neat): 2119, 1720, 1645 cm$^{-1}$; TLC $R_f$ = 0.30 (10:1 hexanes/EtOAc). Compound **8i** was hydrolyzed to **48j**.

### 1.3.4 Determination of Relative Stereochemistry in Methyl 7-*tert*-butyldimethylsiloxy-3-oxo-5-phenyl-2-diazo-oct-6-enoate (52i)

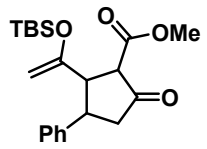
The relative stereochemistry of substituents in **52i** was determined by nOe experiment. Upon irradiation of the doublets at δ 4.69 ppm ($H_a$) 3.0%

enhancement was observed for the singlet at δ 1.81ppm ($H_b$), which is the most significant. Similarly, upon irradiation of the singlet at δ 1.81ppm ($H_b$) 1.5% enhancement was observed for doublets at δ 4.69 ppm ($H_a$), which is the most significant. This observation is reconciled with the *Z* isomer. Indirectly, this indicates the *Z* isomer is the major product.



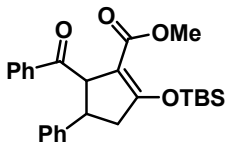



### 1.3.5 Dinitrogen Extrusion Reactions of Methyl 7-*tert*butyldimethylsiloxy-3-oxo-5-phenyl-2-diazo-oct-6-enoate (52i) and Methyl 7-tertbutyldimethylsiloxy-3-oxo-5,7-diphenyl-2-diazo-hept-6-enoate (52j)




63

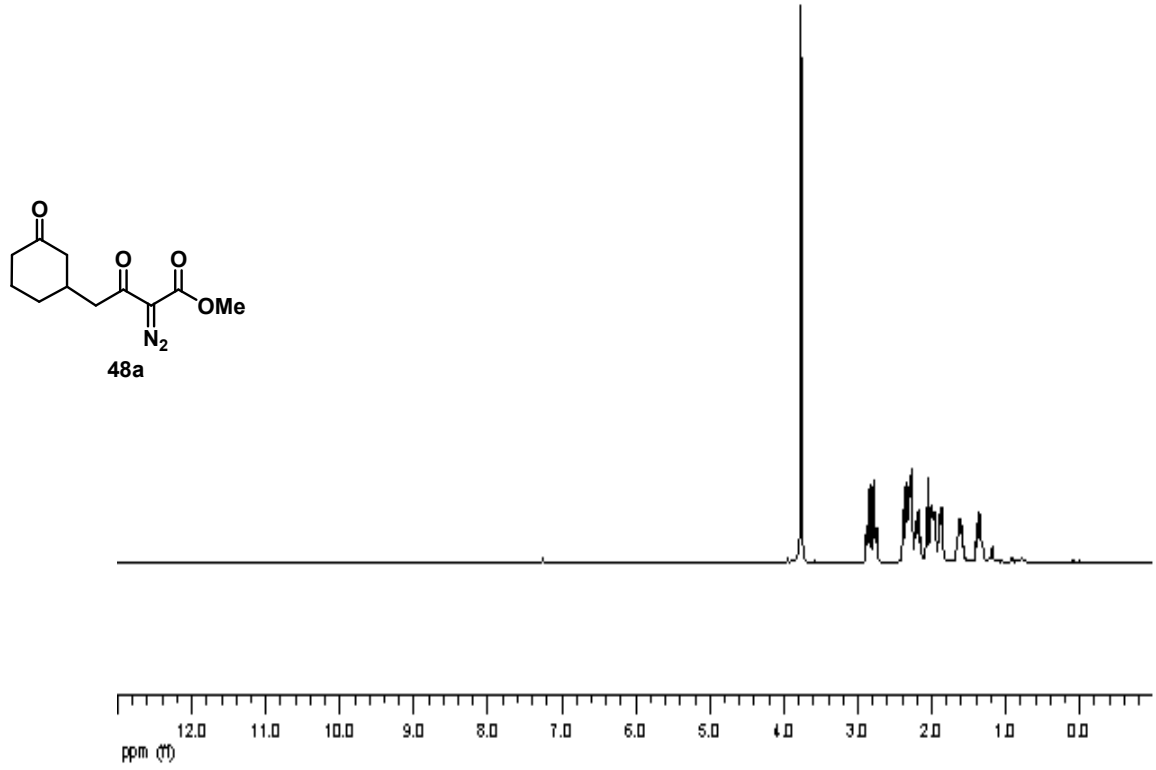
**Synthesis of methyl 2-(1-tertbutyldimethylsiloxyvinyl)-5-oxo-3-phenylcyclo pentane-carboxylate (63)** A solution of the Mukaiyama-Michael adduct **52i** (402 mg, 1 mmol) in 8.0 mL of anhydrous $CH_2Cl_2$ was added via syringe pump over 30 minutes to a solution of $Rh_2(OAc)_4$ (4 mg 0.01 mmol) in 4.0 mL of refluxing $CH_2Cl_2$ in a 25 mL RB flask. The reaction was stirred in refluxing $CH_2Cl_2$ for 4 hours after addition was finished. The catalyst was then removed by passing the resulting solution through a short plug of silica and the solvent was removed under reduced pressure. The crude reaction mixture was purified by silica gel chromatography, eluting with 1:7 EtOAc/hexane to give 168 mg of a light yellow oil as product **62** (0.45 mmol, 45% yield). **62:** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.34-7.22 (comp, 5H), 3.93 (d, *J* = 8 Hz, 2H), 3.55 (d, *J* = 16 Hz, 1H), 3.40 (dd, *J* = 18 Hz, *J* =16 Hz, 2H), 3.43-3.35 (comp,1H), 3.30 (dd, *J* = 16 Hz, *J* =4 Hz, 1H), 2.80 (dd, *J* = 4 Hz, *J* =16 Hz), 2.56 (dd, *J* = 18 Hz, *J* =12 Hz), 0.94 (s, 9H), 0.13 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 208.7, 168.8, 153.5, 140.1, 128.6, 127.3, 127.1, 92.4, 59.6, 55.0, 52.4, 46.1, 43.0, 25.8, 18.2, -4.71, -5.11; IR (neat): 1730, 1759 cm$^{-1}$. HRMS for $C_{21}H_{31}O_4Si$ $[M+H]^+$ calcd: 374.1913; found: 374.1894.

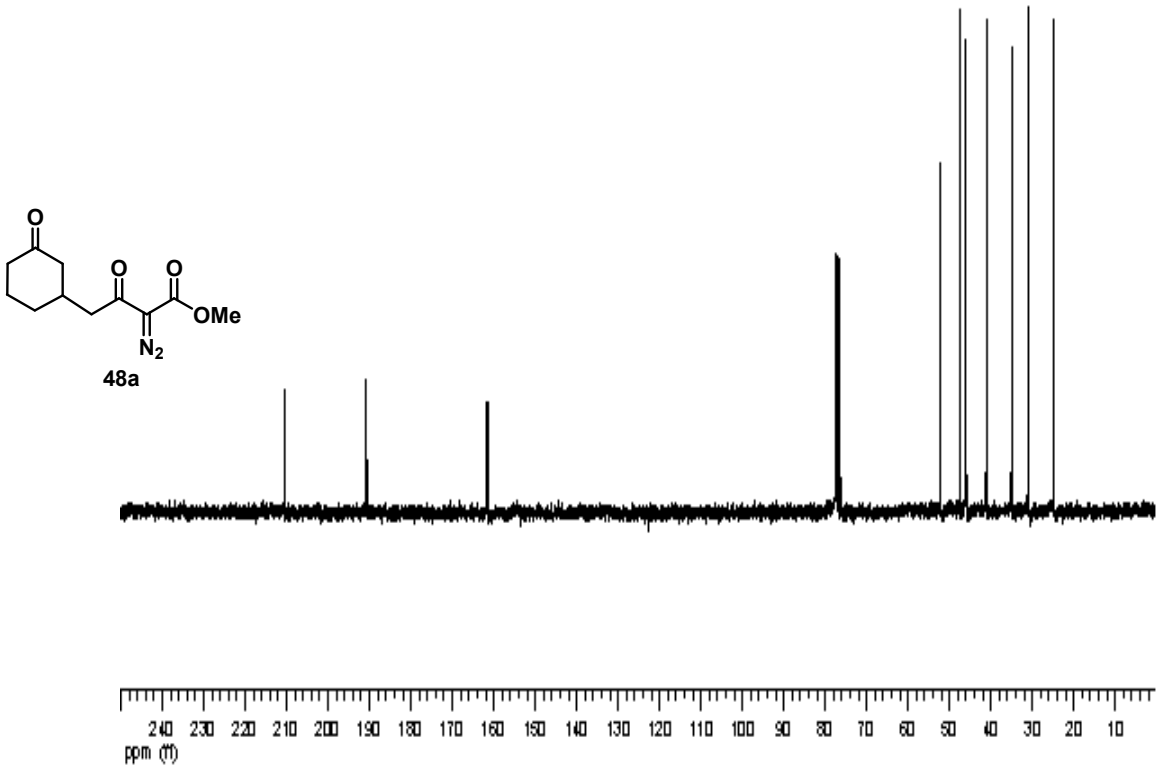


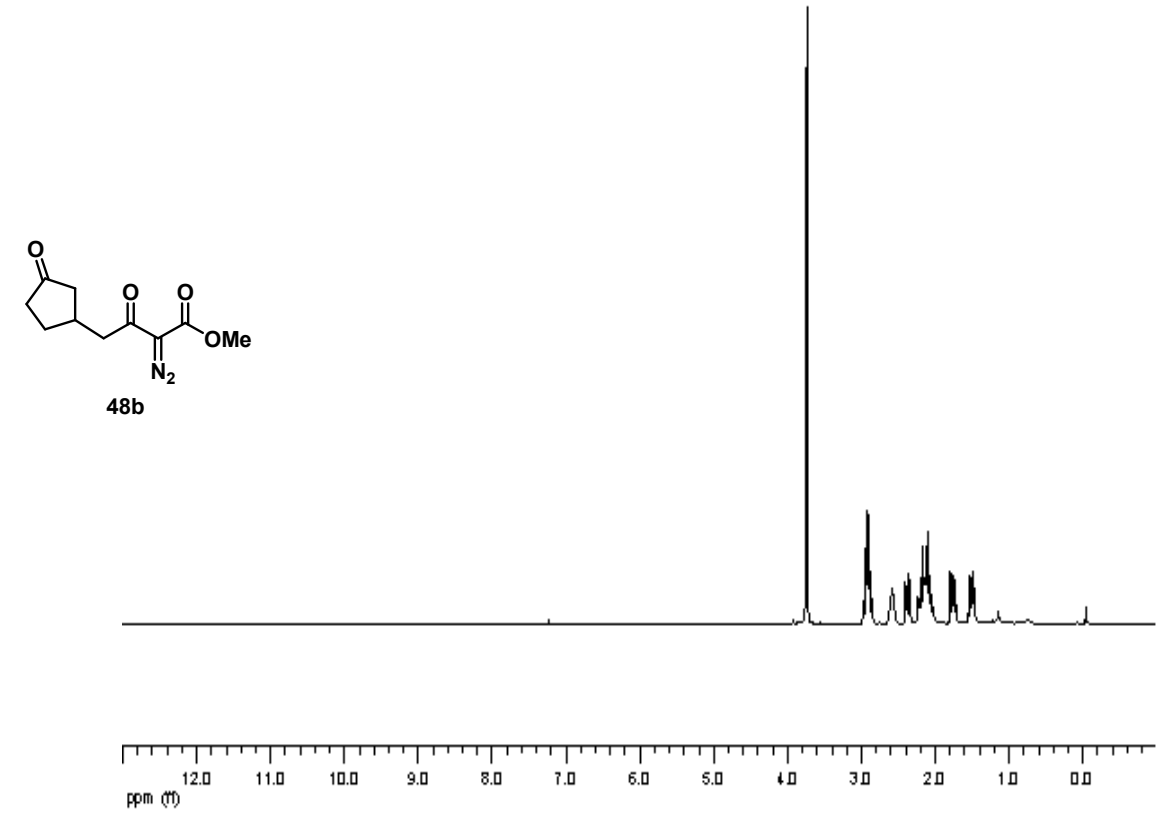

**69**

**Synthesis of methyl 2-tertbutyldimethylsiloxy-4-phenyl-5-benzoyl-cyclopent-1-enecarboxylate (69)** A solution of the Mukaiyama-Michael adduct **52j** (232 mg, 0.5 mmol) in 8.0 mL of anhydrous $CH_2Cl_2$ was added via syringe pump over 30 minutes to a solution of $Rh_2(OAc)_4$ (2 mg 0.005 mmol) in 4.0 mL of refluxing $CH_2Cl_2$ in a 25 mL RB flask. The reaction was stirred in refluxing $CH_2Cl_2$ for 4 hours after addition of **52j**. The catalyst was then removed by passing the resulting solution through a short plug of silica and the solvent was removed under reduced pressure. The crude reaction mixture was purified by florisil, eluting with 1:7 EtOAc/hexane to give 110 mg of a light yellow oil as product **62** (0.25 mmol, 50% yield). **69:** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.85 (d, *J* = 8 Hz, 2H), 7.52 (t, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 2H), 7.35 (t, *J* = 8 Hz, 2H), 7.29 (t, *J* = 8 Hz, 1H), 7.27 (d, *J* = 8 Hz, 2H), 4.86 (d, *J* = 4 Hz, 1H), 3.65 (s, 3H), 3.34 (dd, *J* = 4 Hz, *J* = 8 Hz, 1H), 3.18 (dd, *J* = 8 Hz, *J* = 12 Hz, 1H), 2.62 (dd, *J* = 4 Hz, *J* = 12 Hz, 1H), 1.06 (s, 9H), 0.34 (s, 3H), 0.32 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 202.1, 166.7, 165.2, 146.0, 137.4, 133.6, 129.7, 129.4, 129.3, 129.2, 127.9, 127.5,109.2, 58.2, 51.4, 45.0, 44.1, 26.3, 19.1, -3.15, -3.31; IR (neat): 3027, 2950, 1716, 1685, 1632 cm$^{-1}$; HRMS for $C_{26}H_{33}O_4Si$ $[M+H]^+$ calcd: 436.2070; found: 436.2050.

### 1.3.6 $^{1}$H NMR and $^{13}$C NMR Spectra

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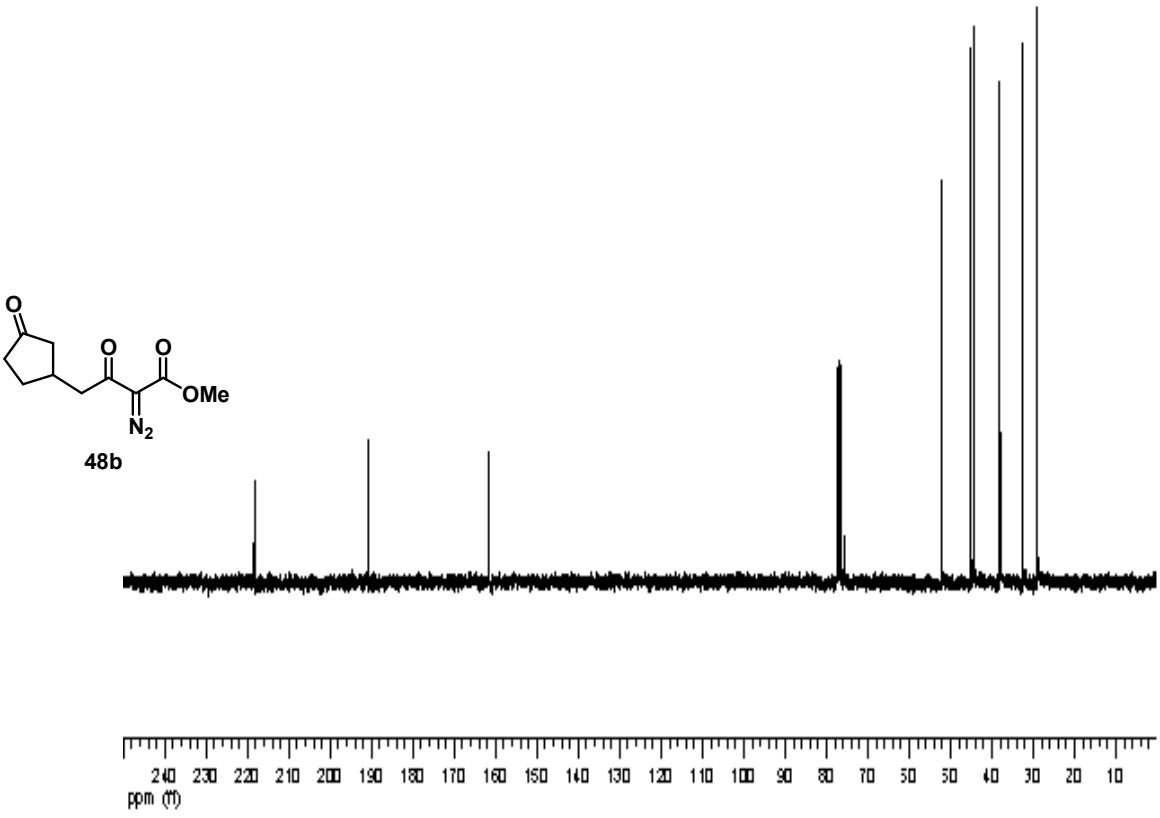
**48b**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ppm (f1)

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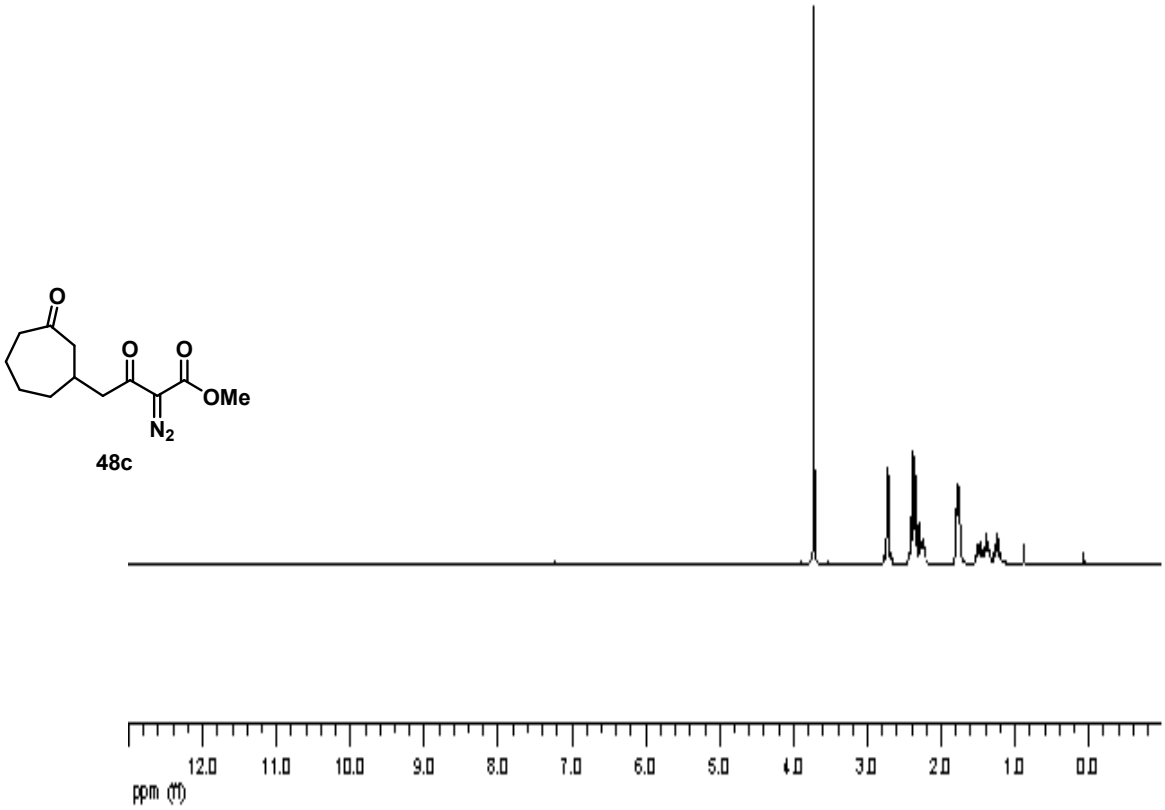
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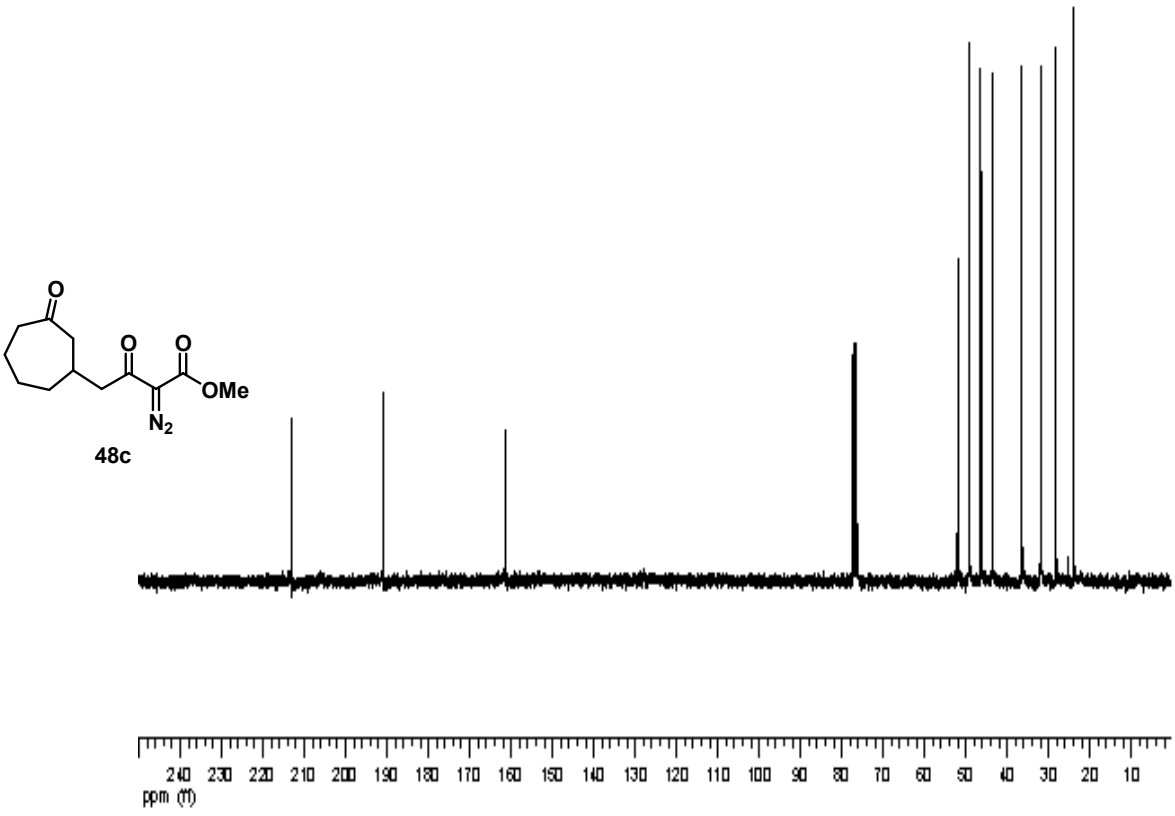
48c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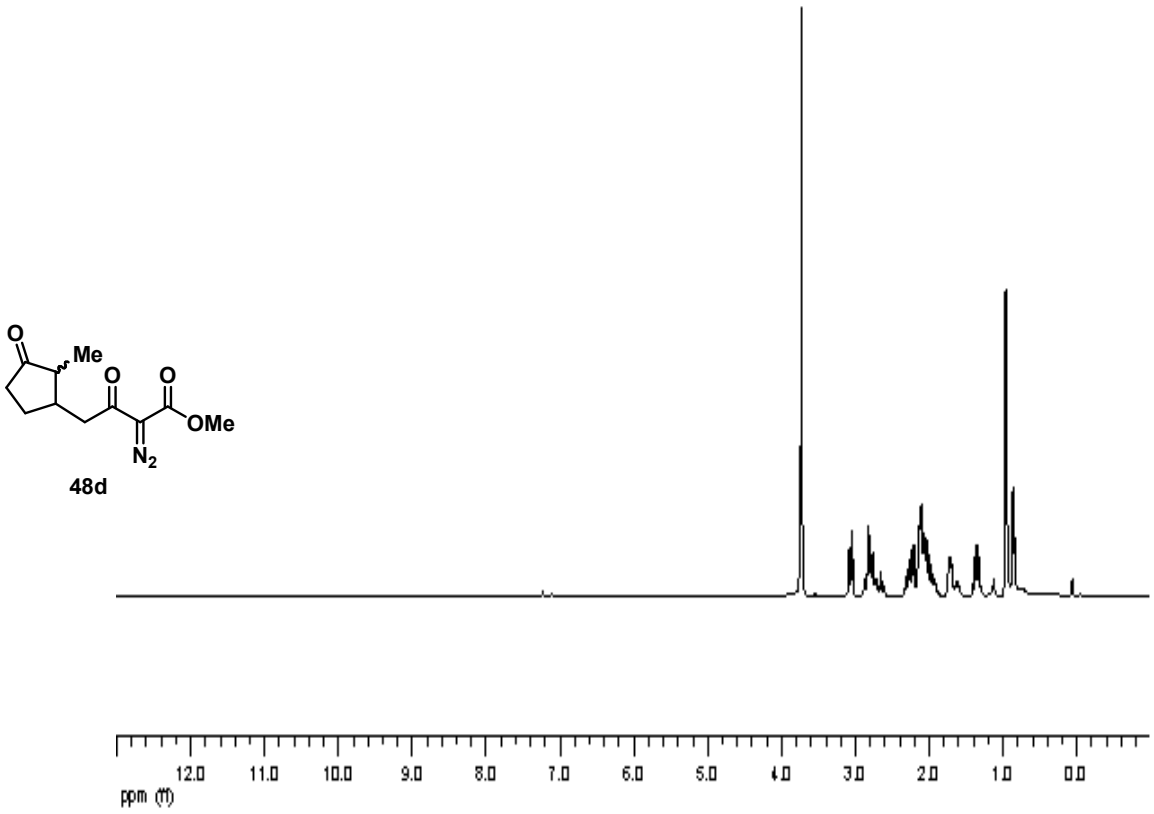
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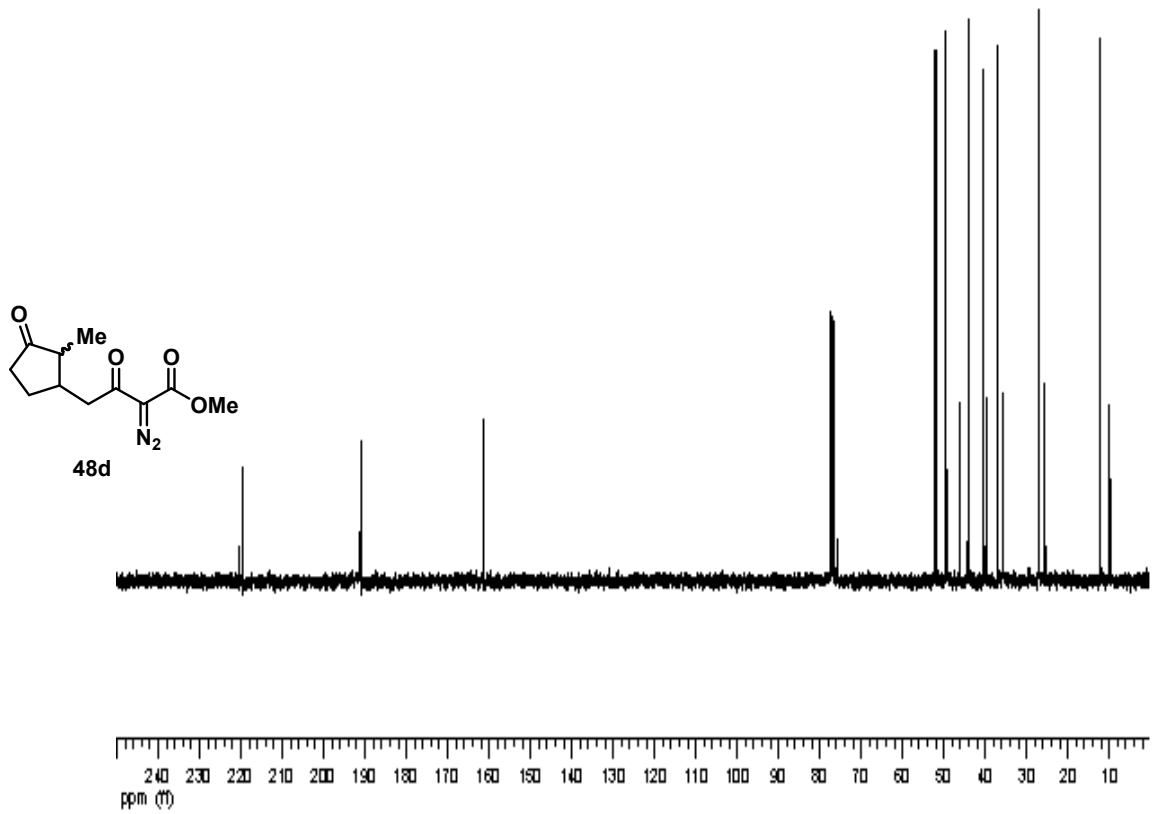
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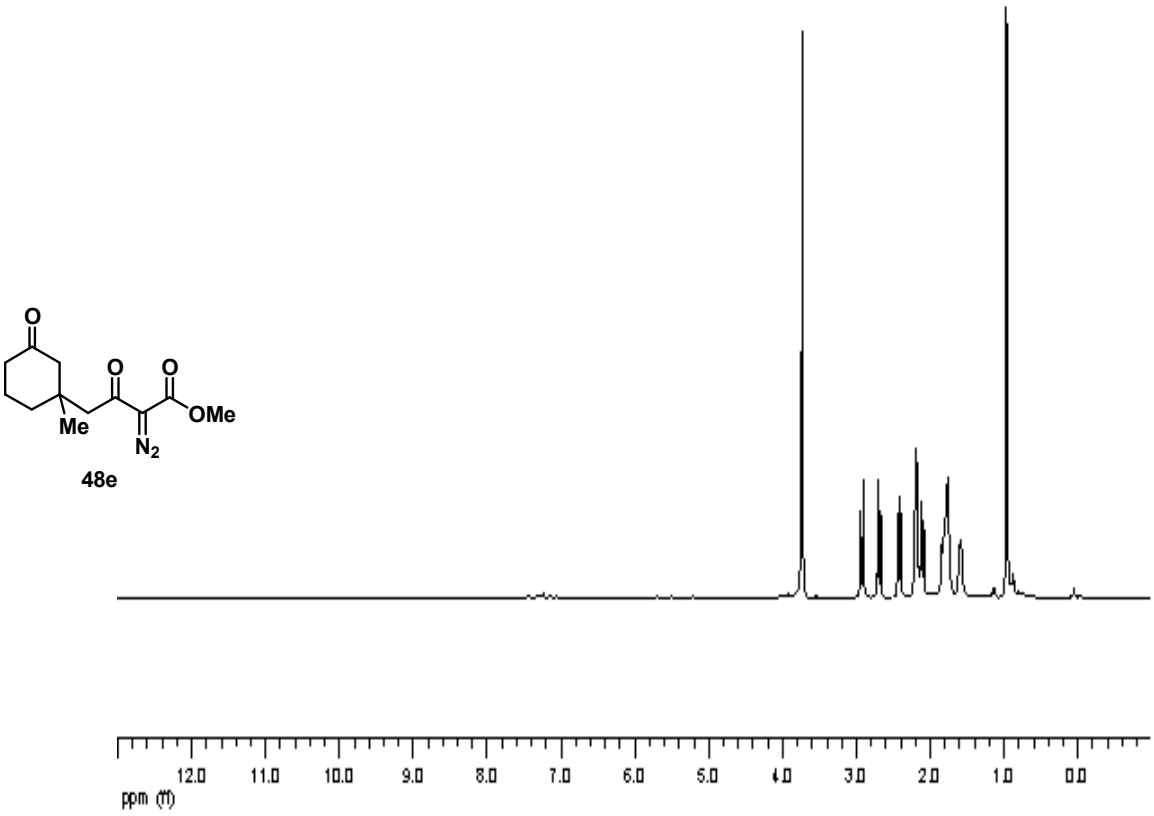
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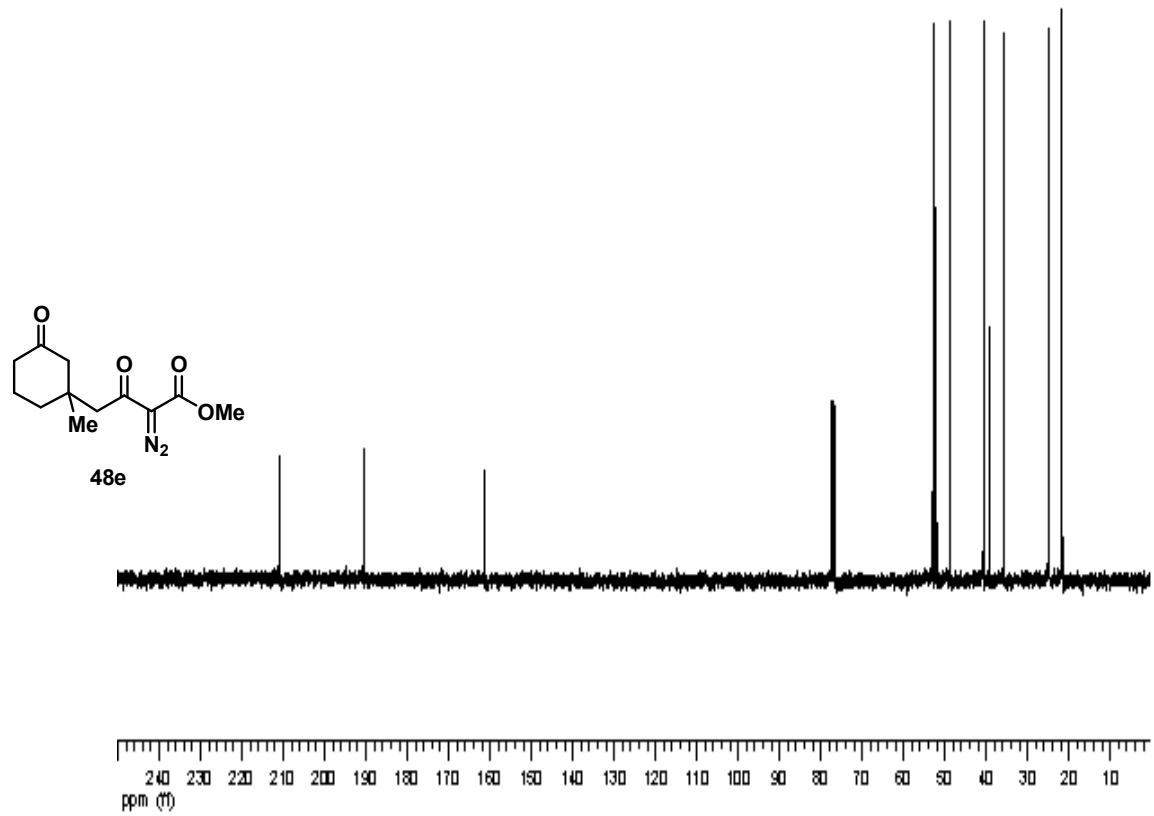
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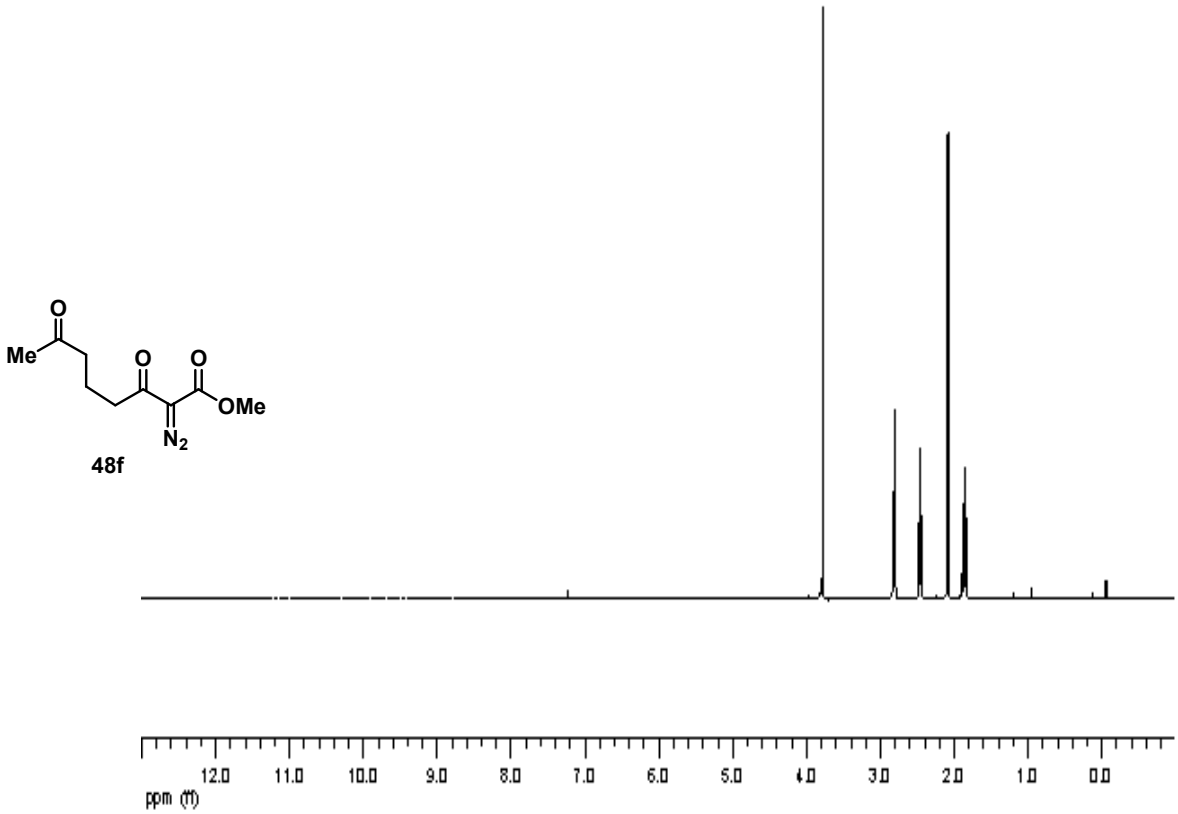
48e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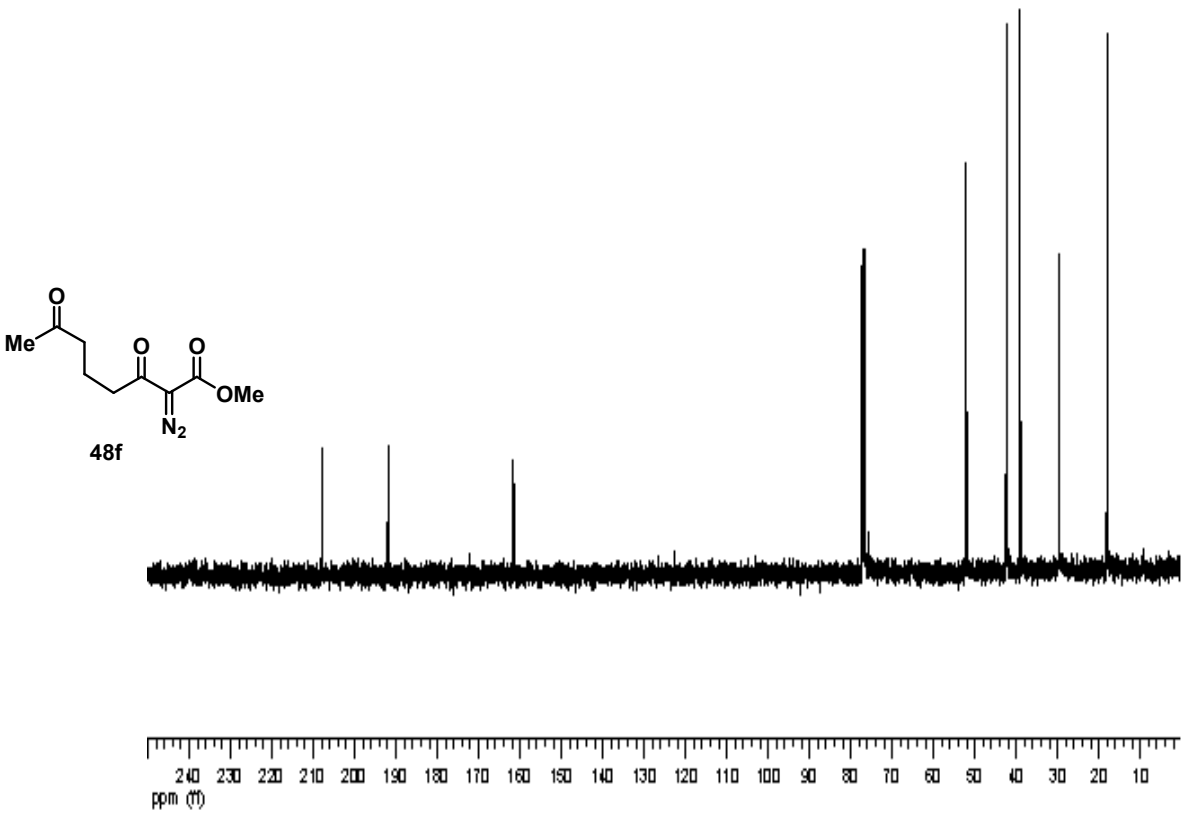
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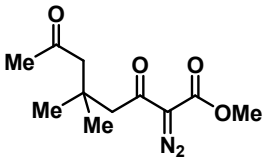
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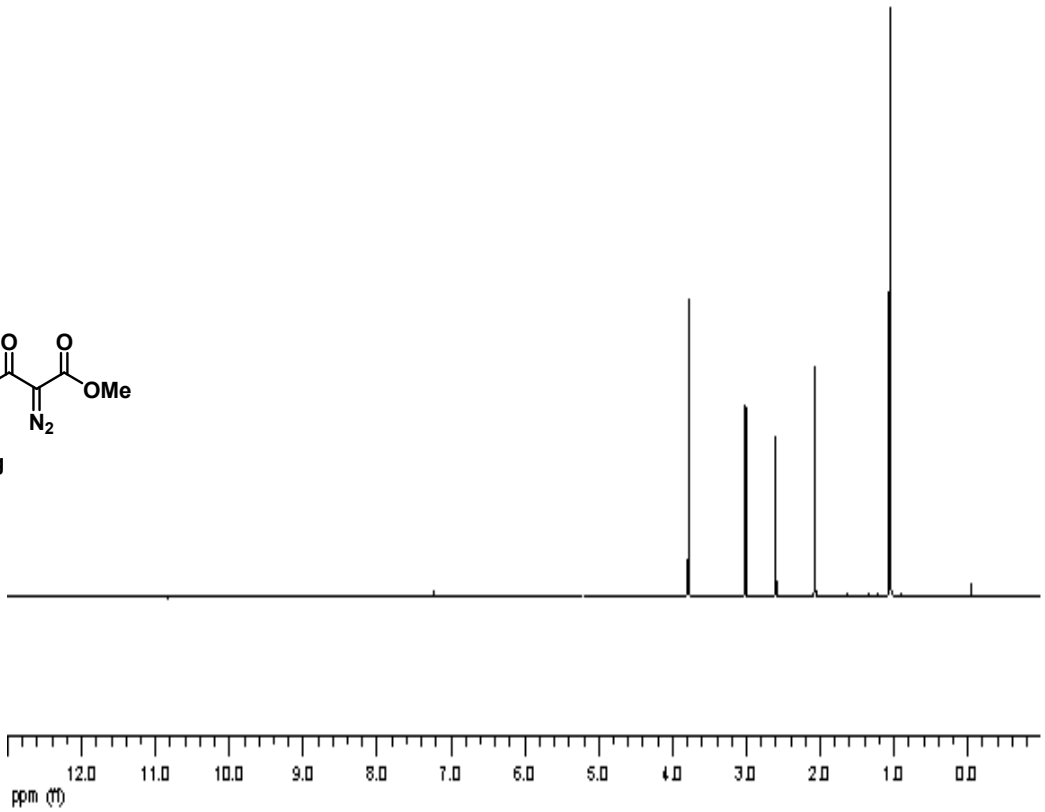
**48g**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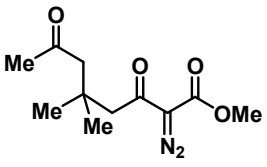
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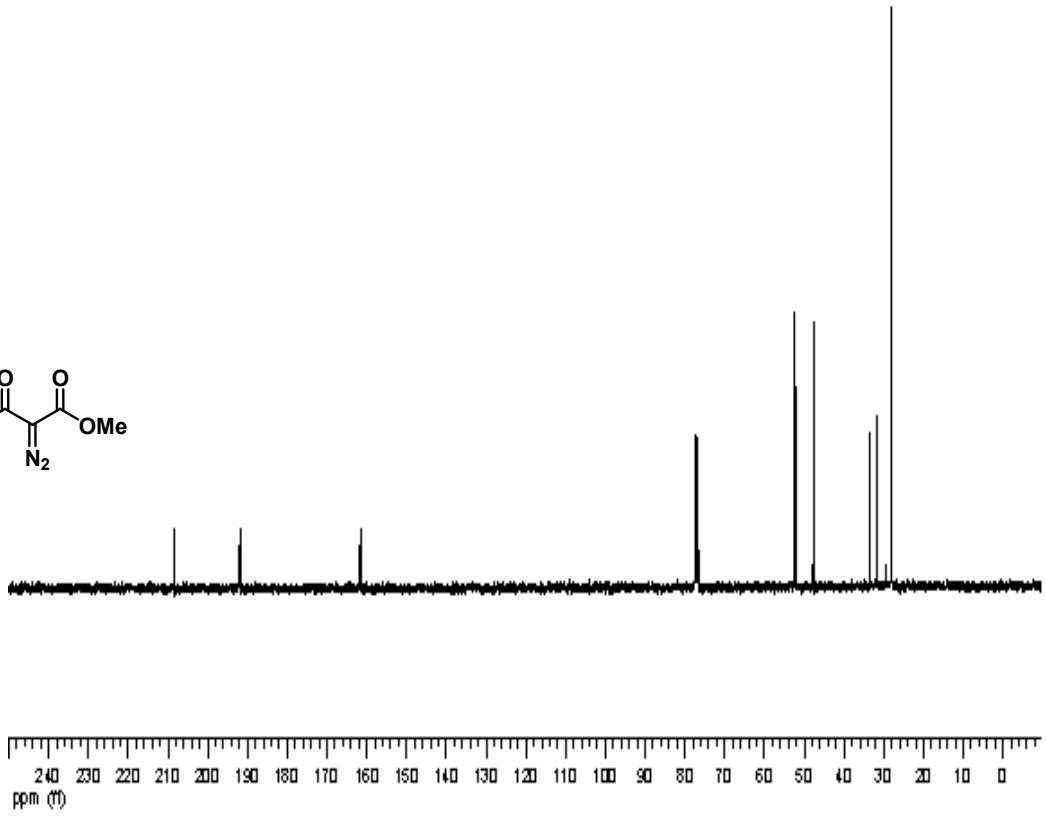
Me
OMe
N2

**48g**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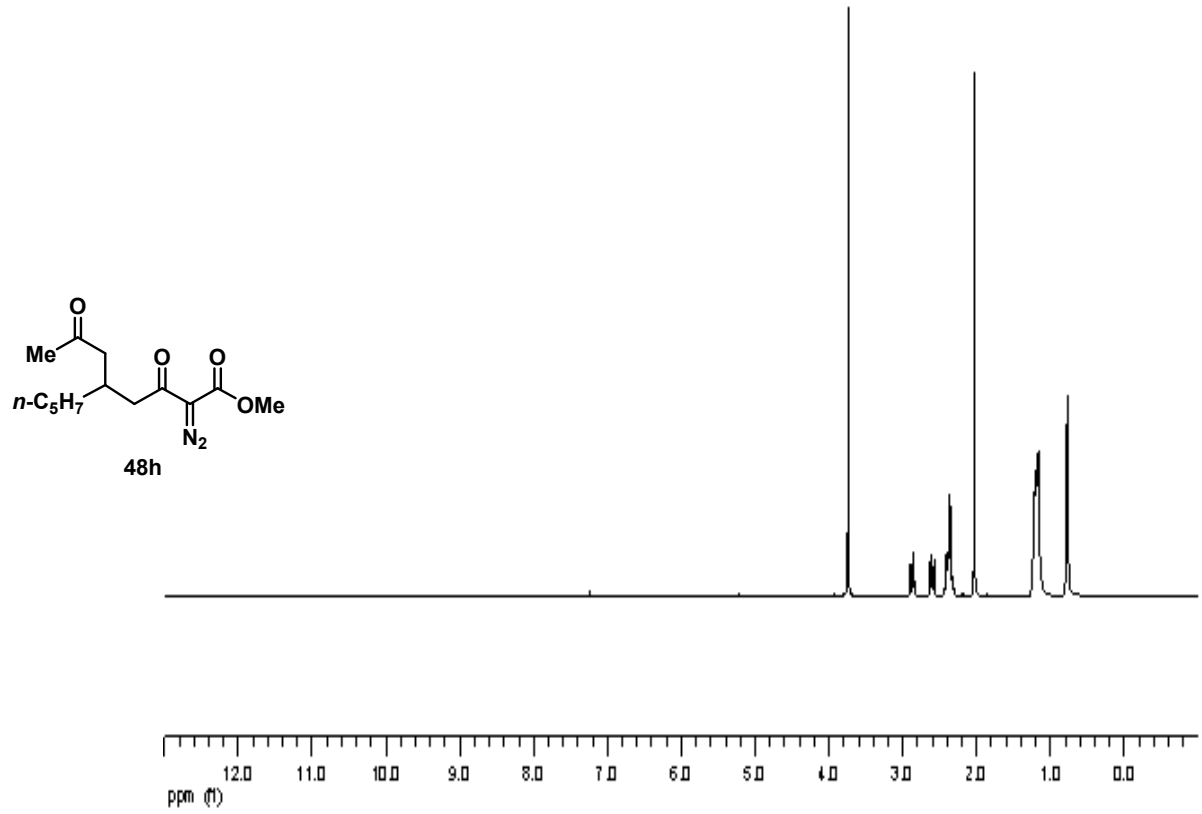
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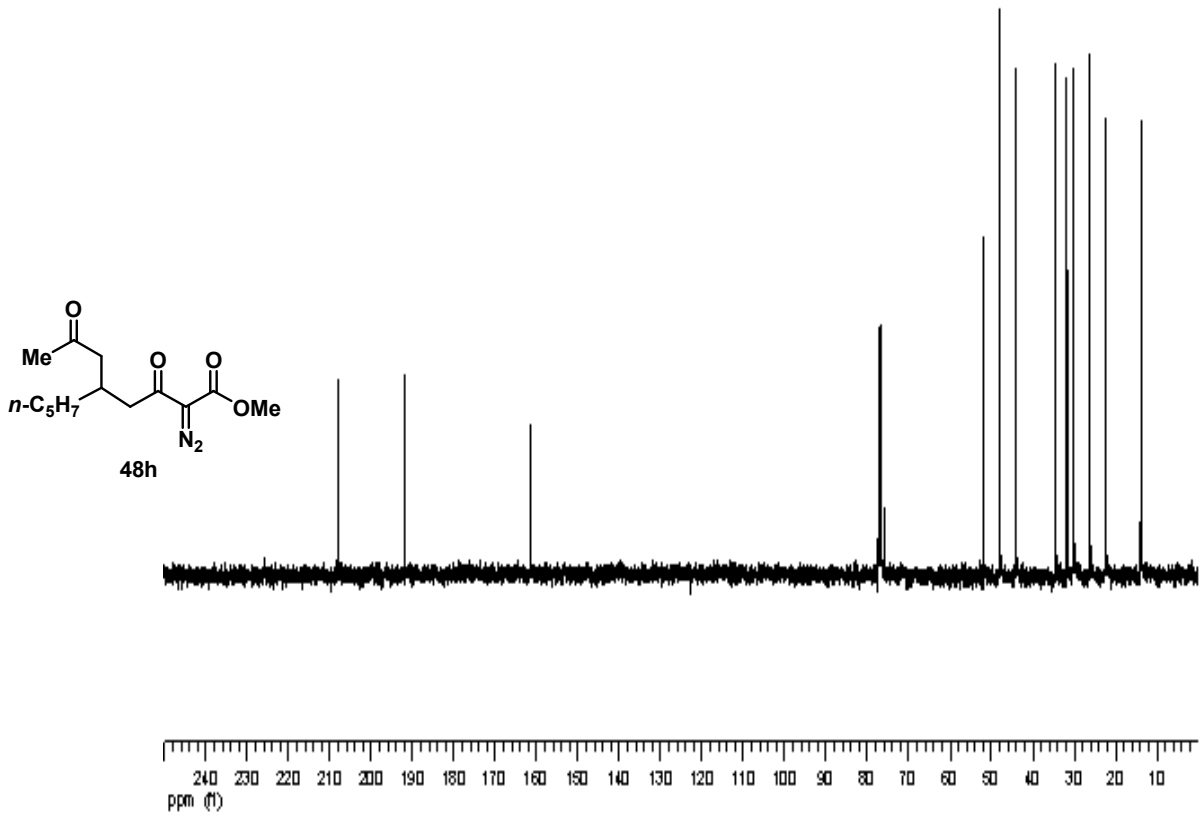
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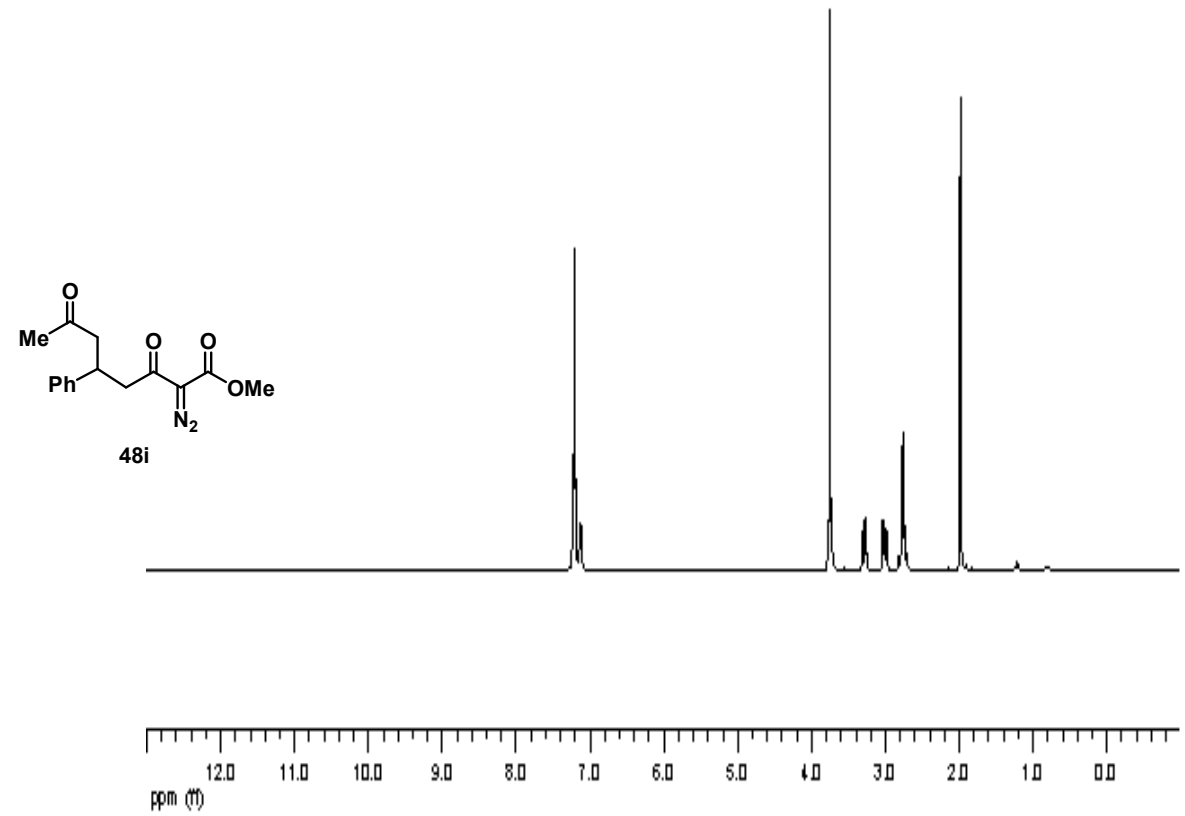
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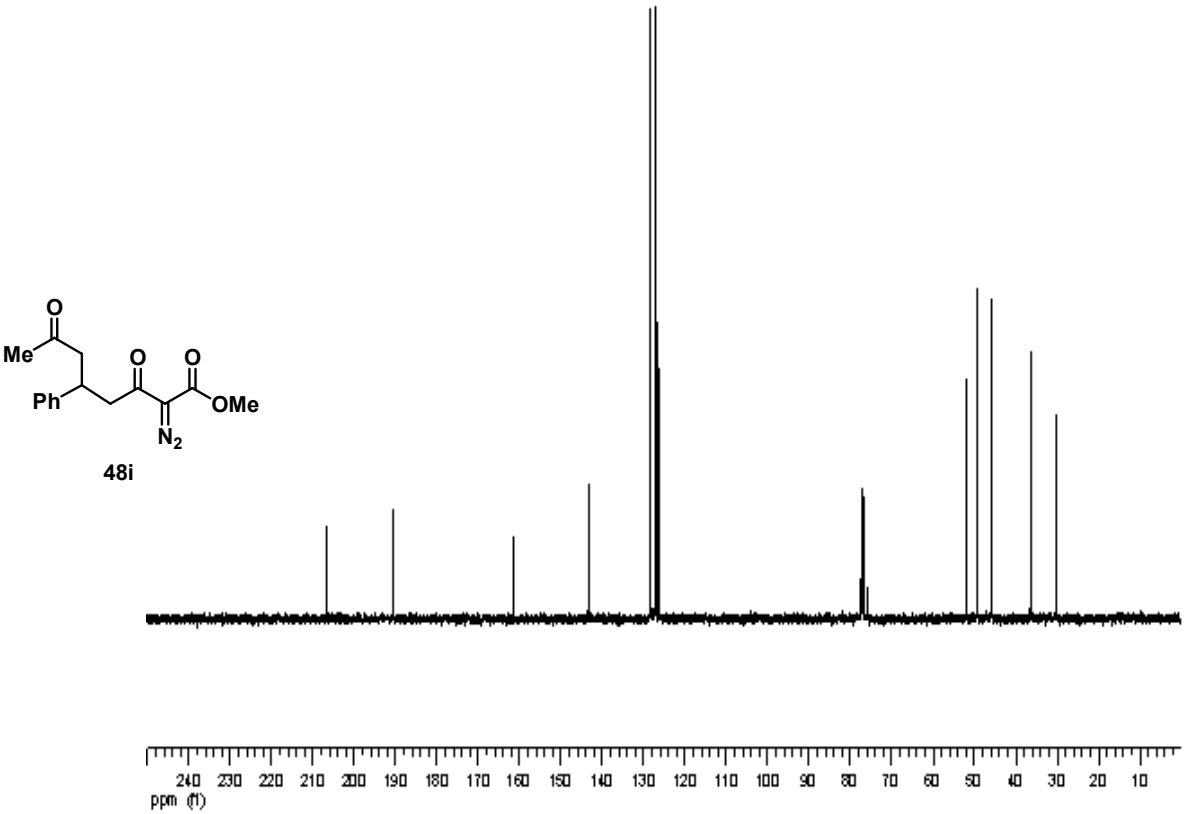
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ppm (f1)

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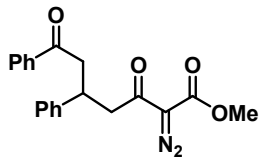
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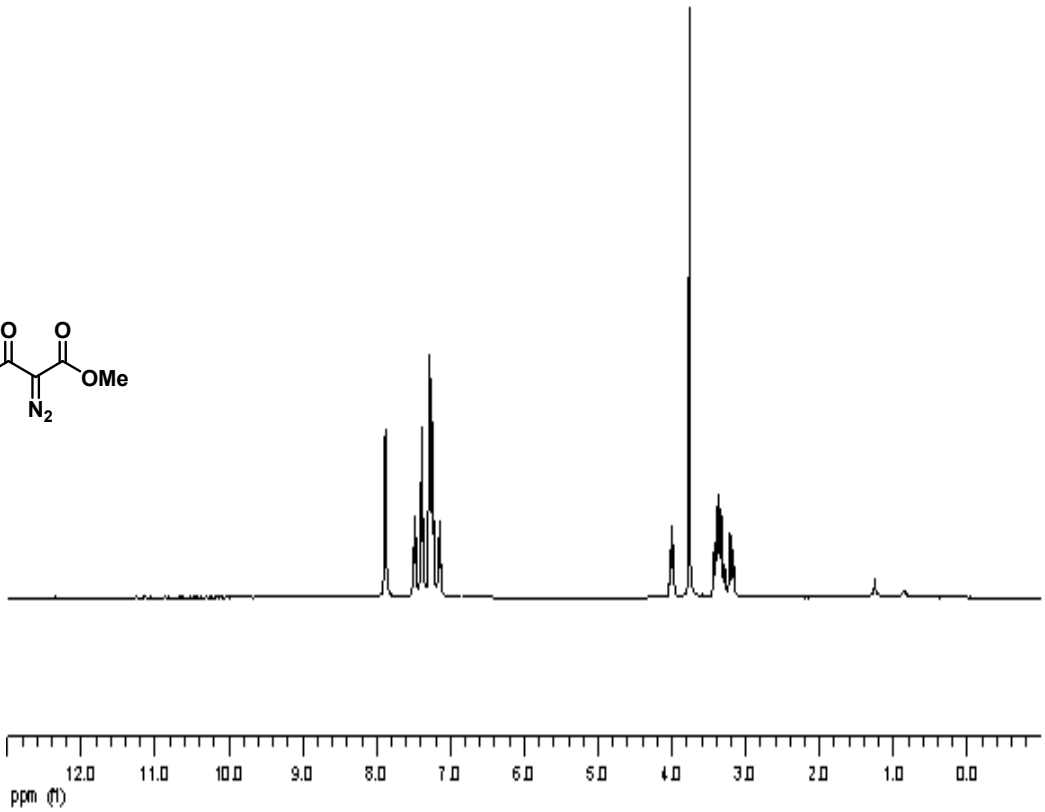
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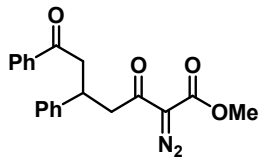
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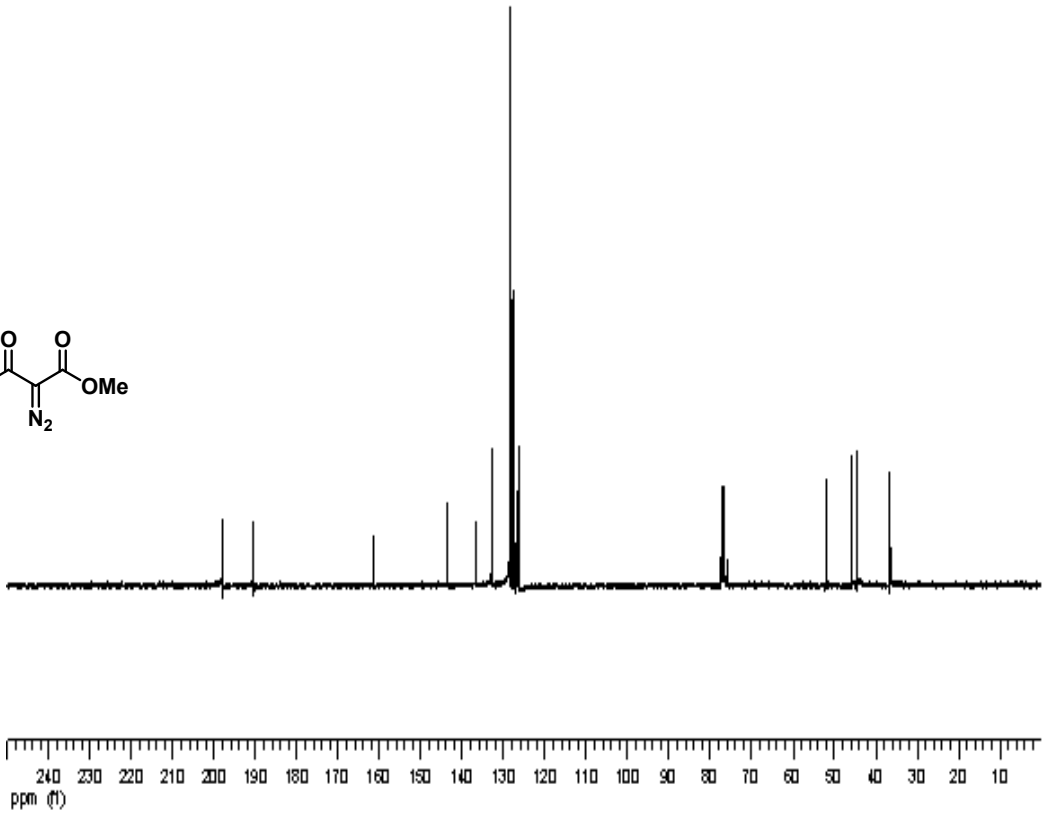
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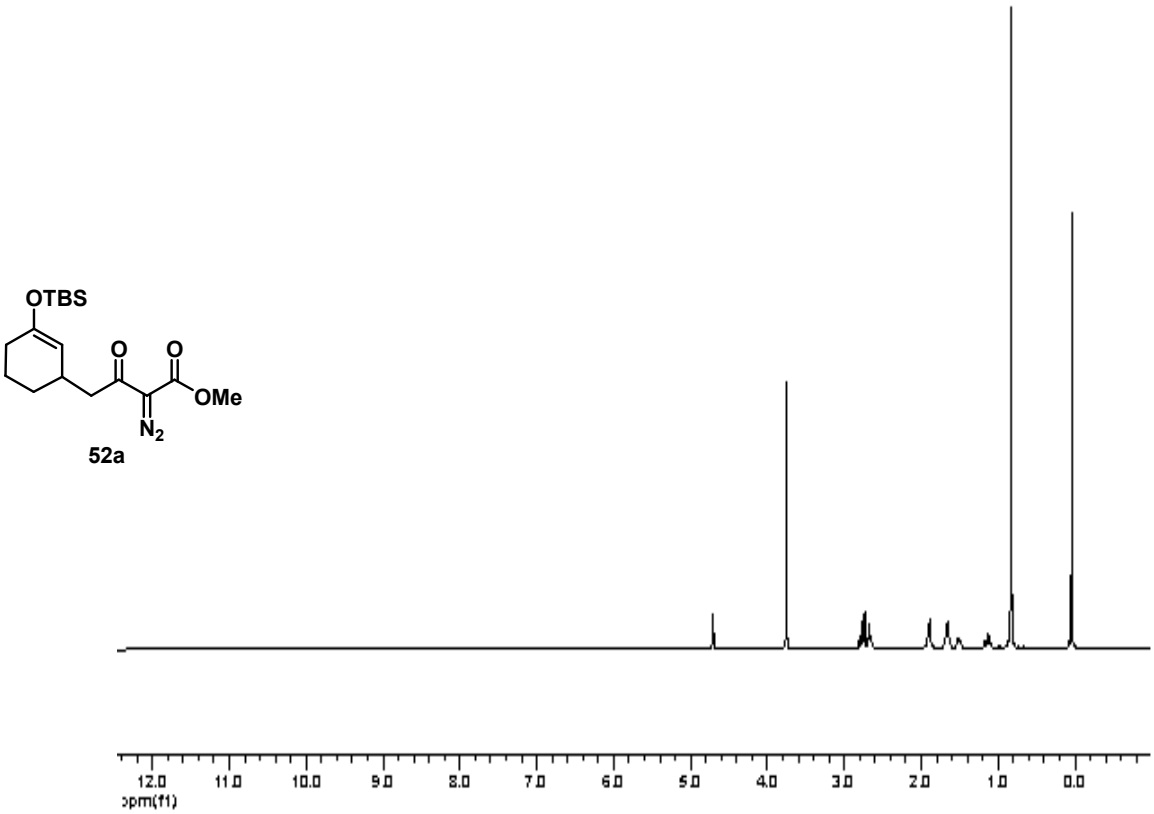
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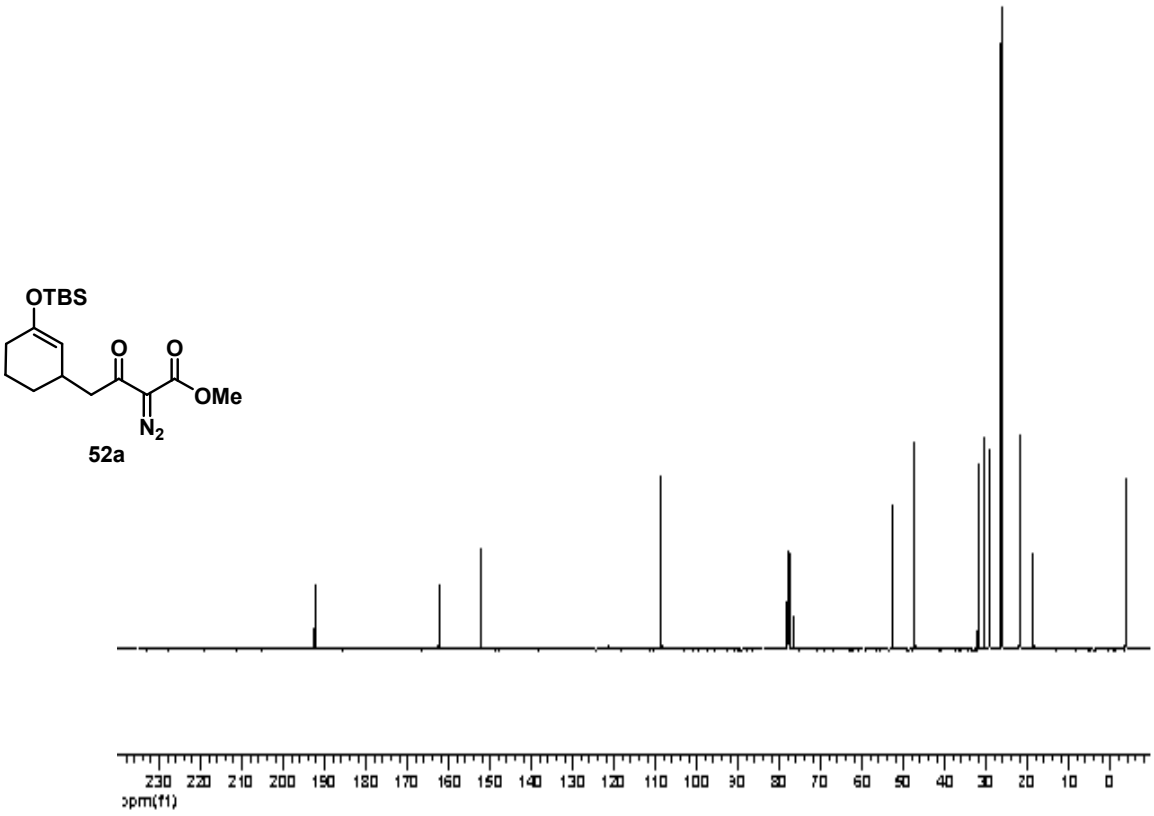
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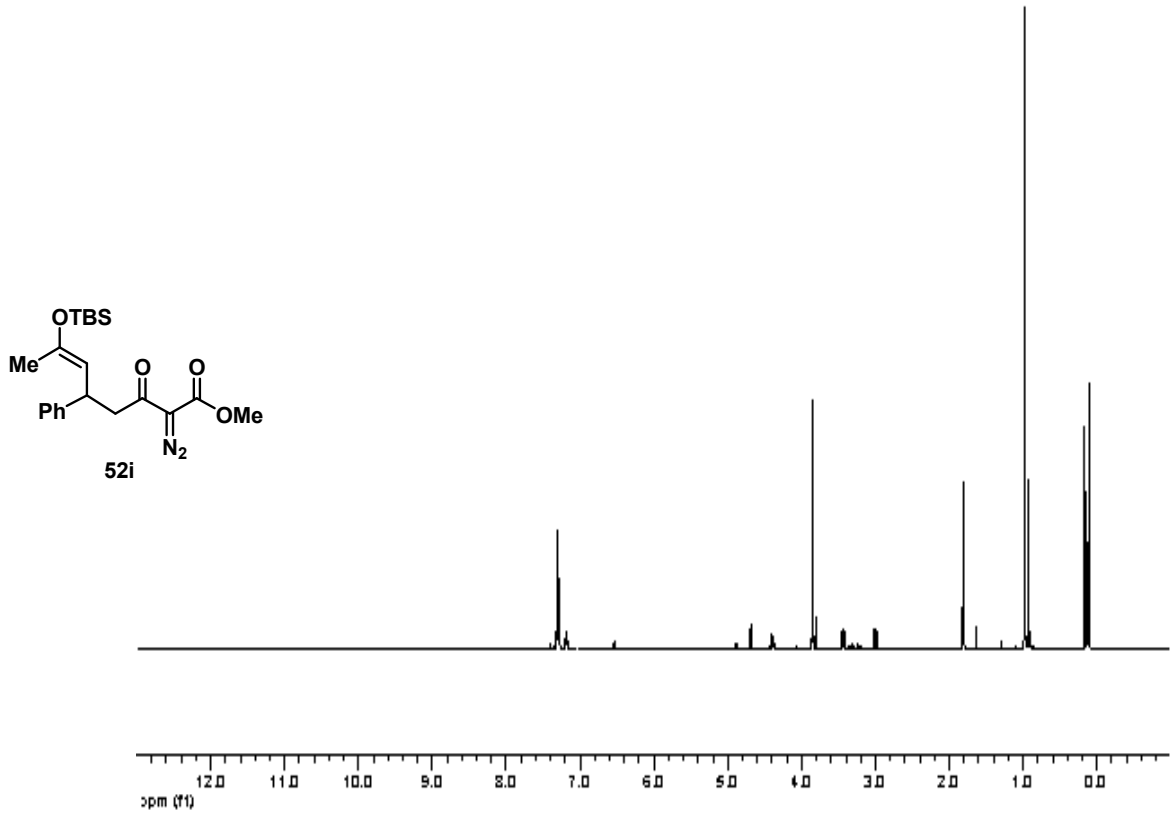
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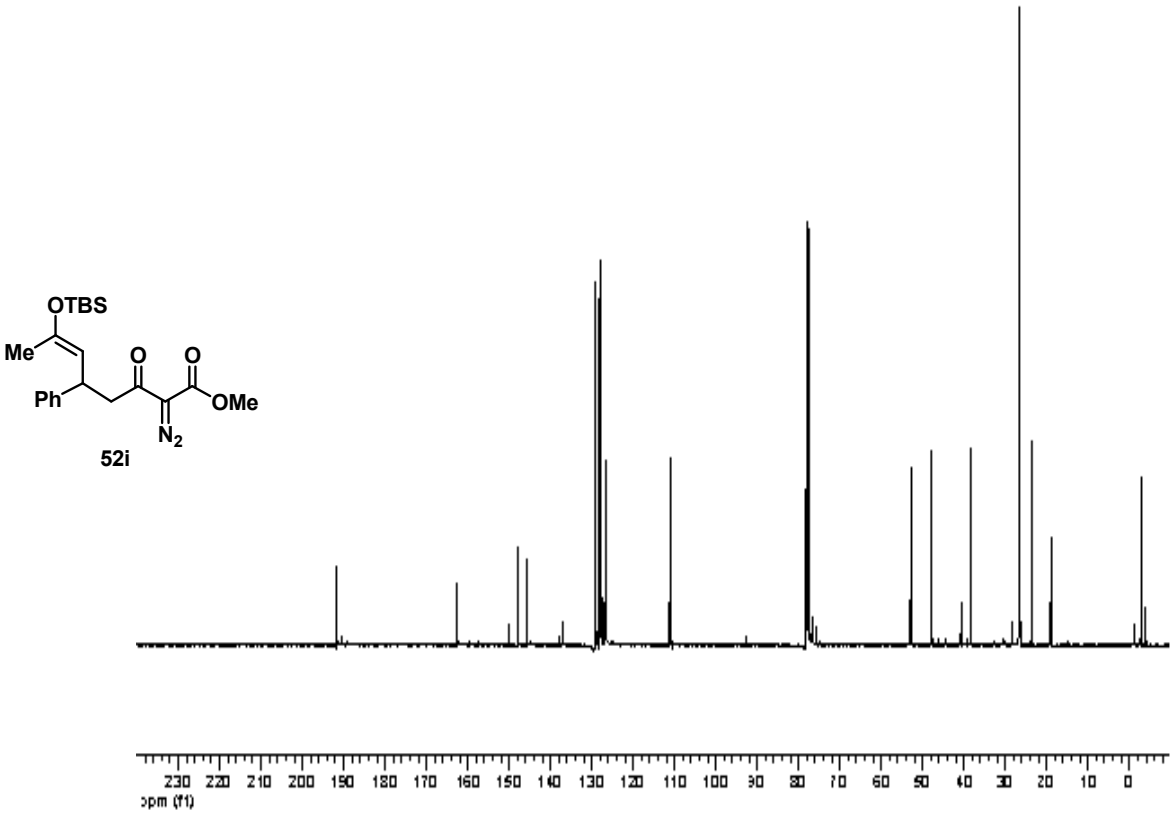
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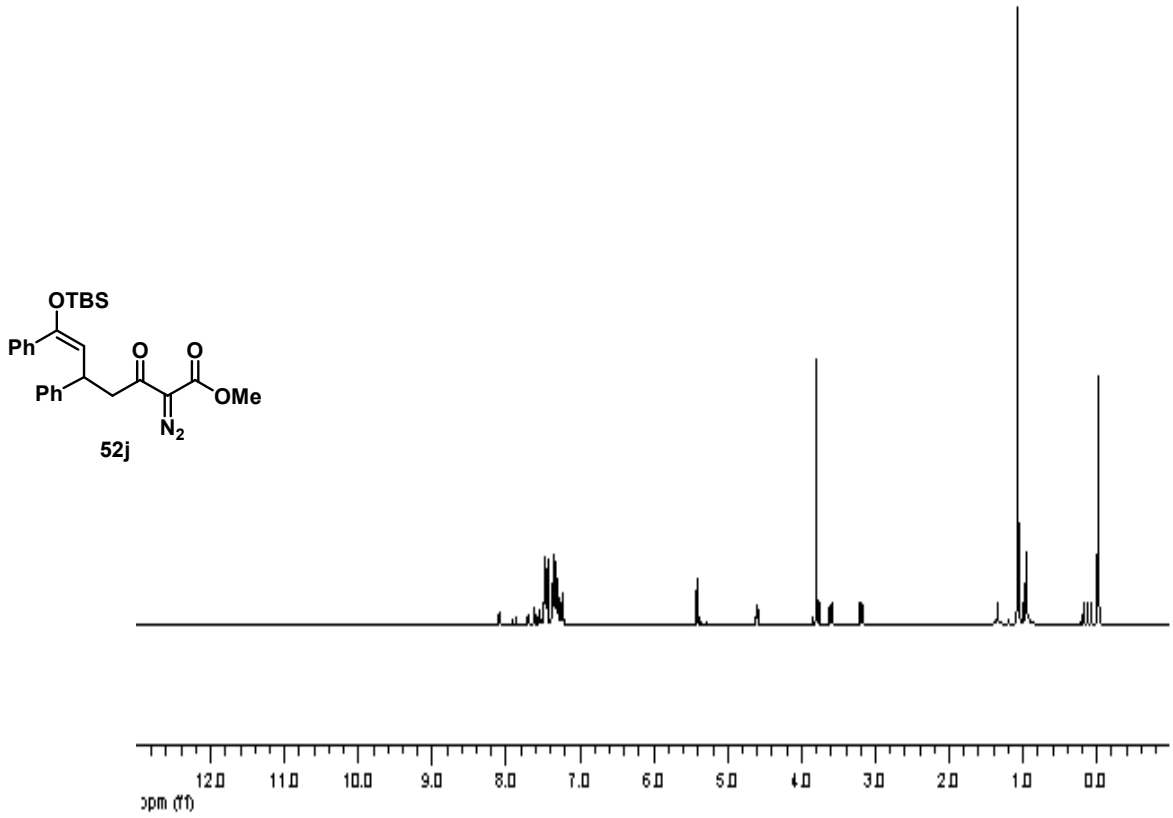
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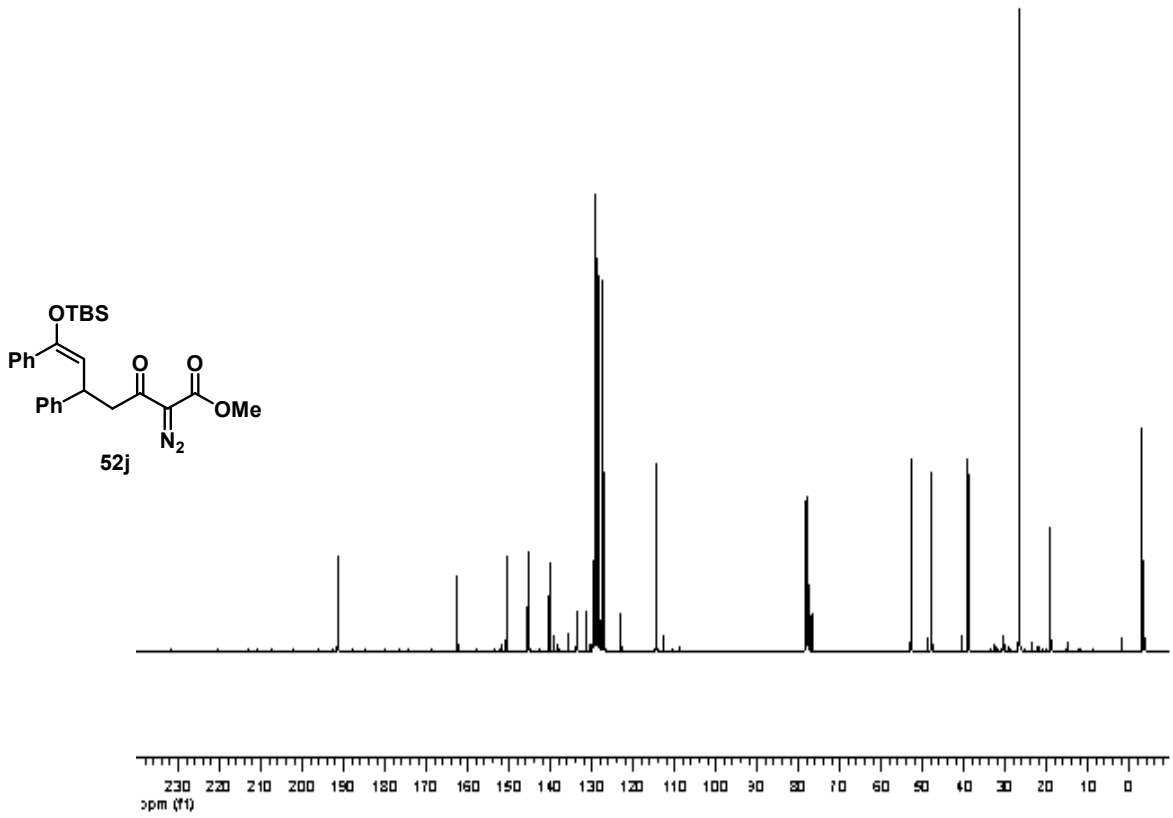
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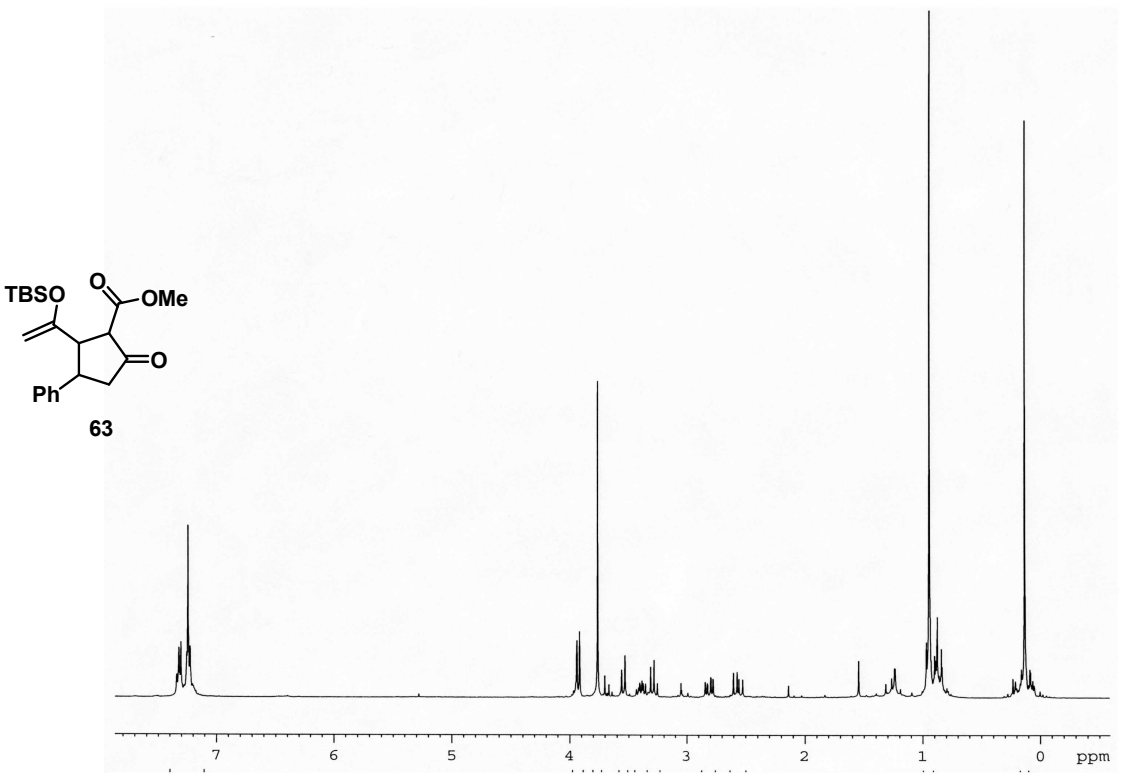
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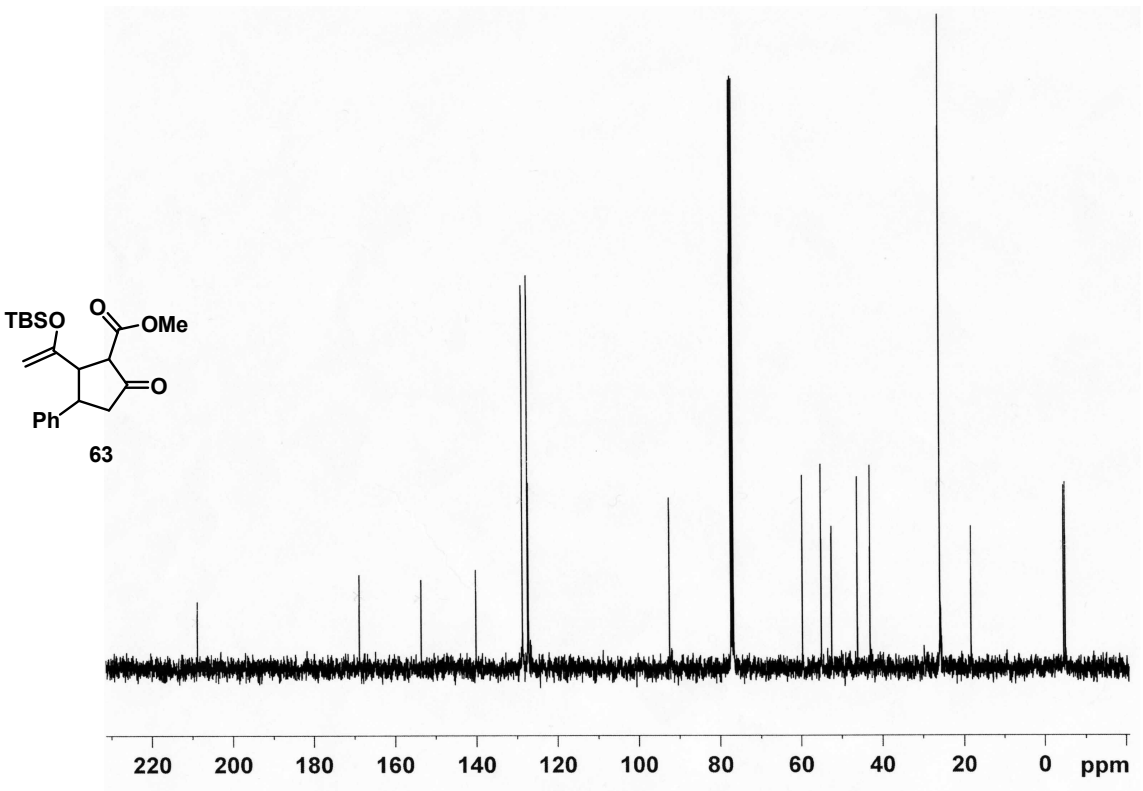
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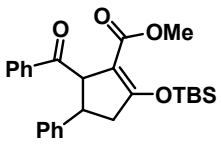
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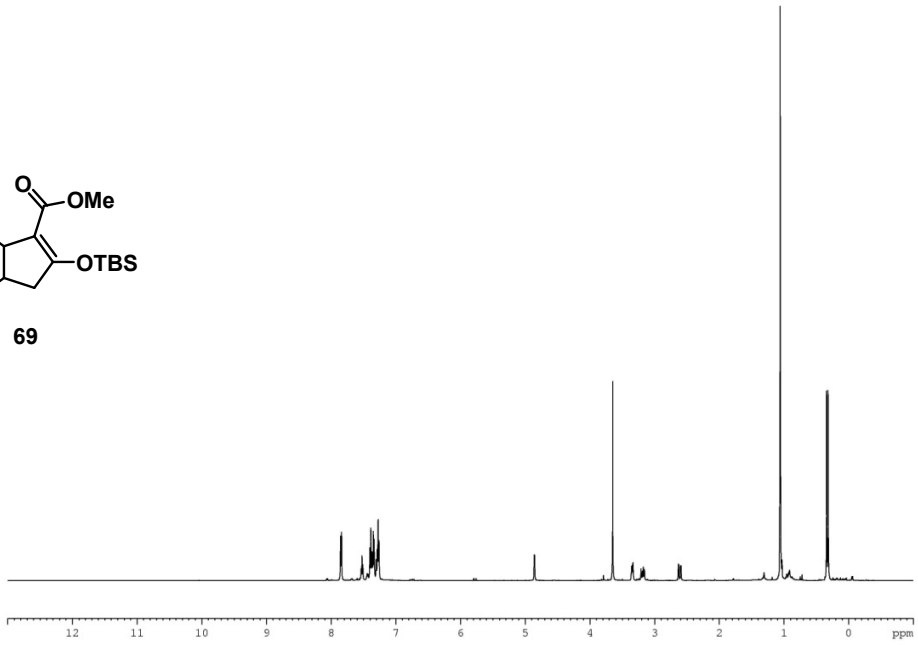
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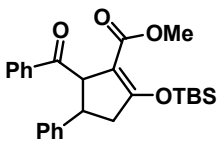
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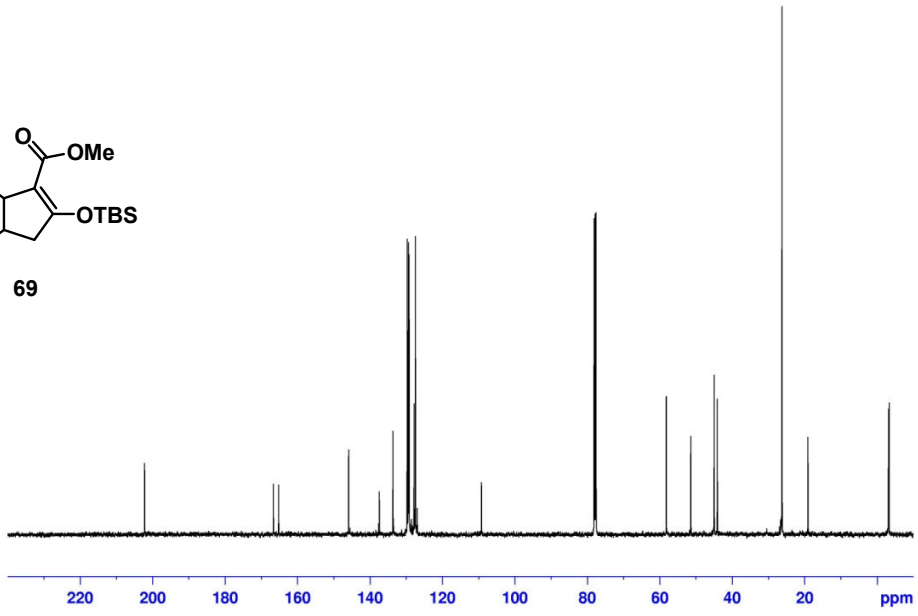
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# Chapter 2

# Synthesis of Poly-substituted Resorcinols via Enedione-diazoesters Derived from the Mukaiyama-Michael Reactions

## 2.1 Introduction

With the discovery of an intriguing transformation that converts a α–diazo-β-ketoester to a resorcinol derivative, we decided to explore this chemistry as a potential method for resorcinol synthesis. To demonstrate the importance of resorcinol compounds in a broader view, a brief review of resorcinol compounds and their derivatives, both naturally occurred and synthetically prepared, is presented at the beginning of this section, followed by the discussion of concurrent methods for the preparation of resorcinol compounds. Within this framework, one could better understand how our work on resorcinol synthesis fits in the big picture.

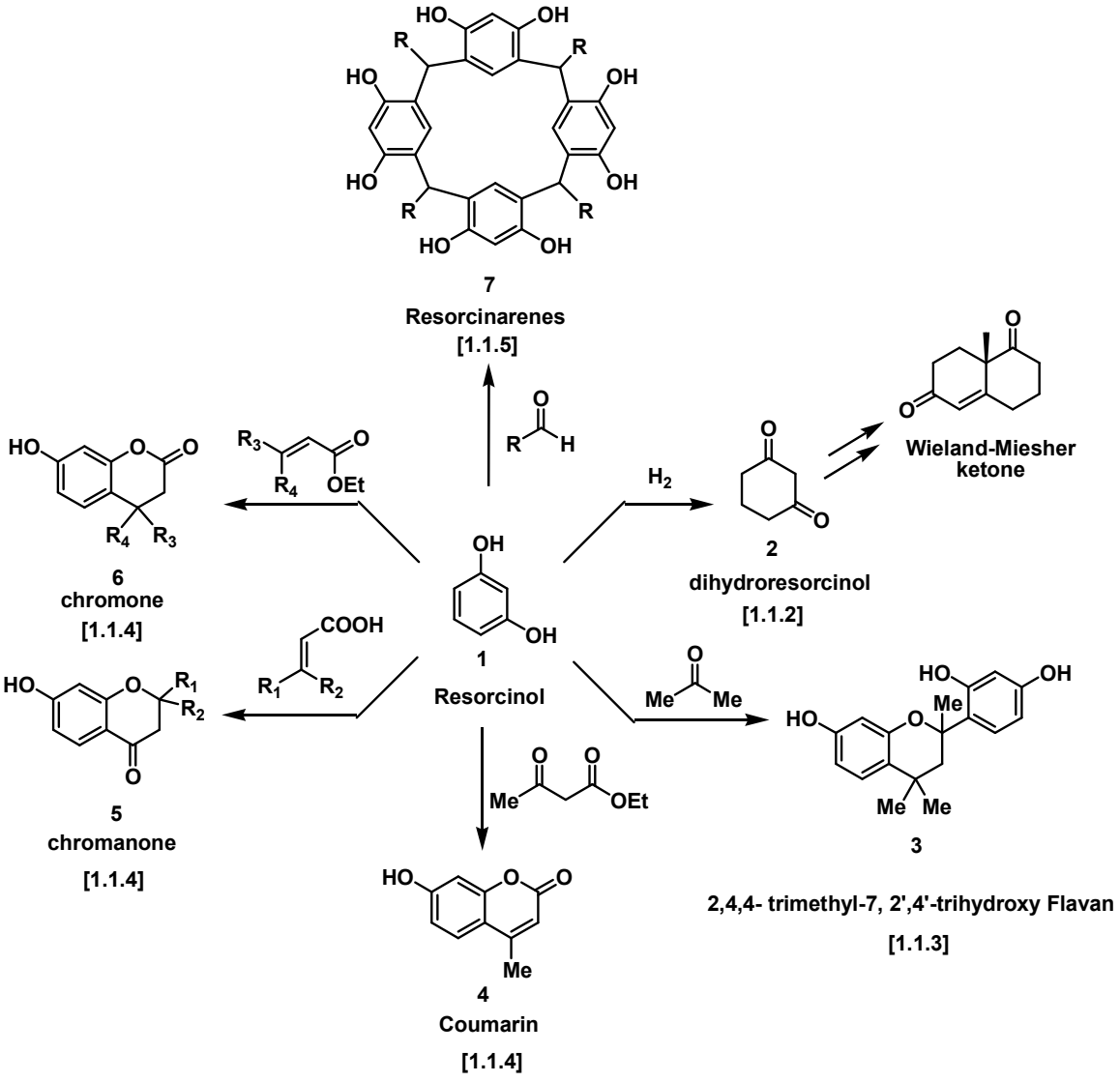
### 2.1.1 Resorcinol Compounds and Their Importance

#### 2.1.1.1 General Information

Resorcinol (**1**), which is also known as resorsin, meta-dihydroxybenzene, and 1,3-benzenediol,[1] has two hydroxyl groups on the *meta*-position of a benzene ring. Resorcinol and its derivatives are valuable materials in the rubber industry, polymer science, agricultural chemicals, pharmaceuticals and many other fields.[1,2] From the perspective of organic chemistry, resorcinol compounds are

useful synthetic motifs since the activated aromatic ring readily undergoes various transformations, and a number of different products can be prepared from resorcinols. As is indicated in Scheme 2.1, dihydroresorcinols (**2**), flavans (**3**), coumarin (**4**), chromanones (**5**), chromones (**6**) and resorcinarenes (**7**)[3] can all be prepared from resorcinol compounds. Many of these products made from resorcinols are either valuable building blocks in synthesis or have practical applications. [1,2] The chemistry regarding these resorcinol derived compounds will be discussed in detail in the following sections.

**Scheme 2.1** Resorcinol and Its Derivatives.

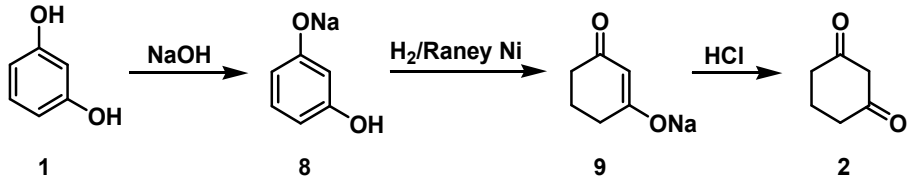



### 2.1.1.2 Dihydroresocinols and Weiland-Miesher Ketones

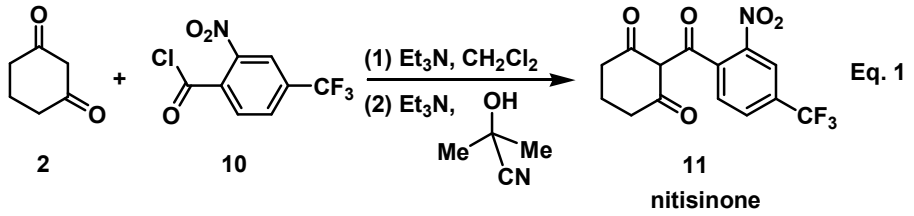
1,3-cyclohexanedione (**2**) (also known as dihydroresorcinol) is an important building block in organic synthesis. Dihydroresorcinol (**2**) can be readily synthesized by treating resorcinol with sodium hydroxide followed by hydrogenation reaction catalyzed by Raney nickel (Scheme 2.2).[4] Substituted

resoricnols can also be used in catalytic hydrogenation reaction to prepare the corresponding dihydroresorcinols.[5]

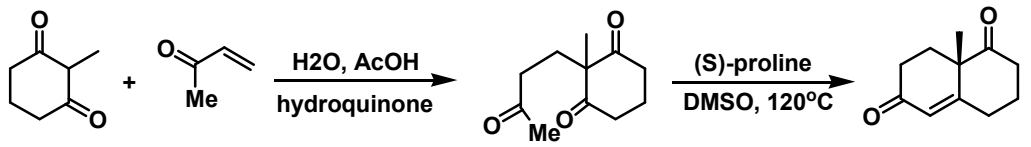
**Scheme 2.2** Preparation of Dihydroresorcinol from Resorcinol.




The 1,3-diketo structure of 1,3-cyclohexandione renders the methylene group between the two carbonyls acidic with a $pK_a$ of 4.8; it is as strong an acid as acetic acid. Therefore, it can easily react with base to give the corresponding enolate which is capable to undergo nucleophilc addtion with halogens, alkyl halides, anhydrides, aldehydes, ketones and many other electrophilic reagents.[2] Various useful compunds can be derived from dihydroresorcinol; an example is given in Equation 1: dihydroresorcinol reacts with 2-nitro-4-trifluoromethyl benzoyl chloride (**10**) under basic condition to give nitisinone (**11**). Nitisinone is an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD), and it is the active component in the drug Orfadin that is used for treatment of tyrosinemia.[6]



Dihydroresorcinols are used as starting materials to prepare the Wieland-Miesher ketones (Eq.2). Wieland-Miesher ketones are versatile synthons in the total synthesis of many natural products, especially steroids and terpenoids since it contains the AB ring structure of the steroid skeleton. For instance, Wieland-Miesher ketone **15** is utilized in K. J. Shea's total synthesis of adrenosterone [7] and the total synthesis of Taxol reported by Danishefsky [8]




**12** **13** **14** **15**

**(57%)**

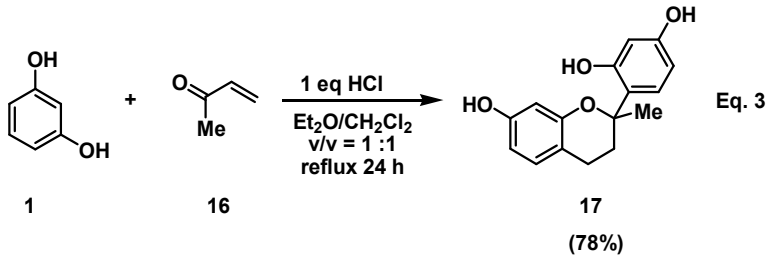
**Wieland-Miesher ketone**

**Eq. 2**

Considering the wide applications of dihydroresorcinols such as compound **2** and compound **12**, effective methods for the preparation of resorcinol derivatives which are precursors of dihydroresorcinols are of great importance.

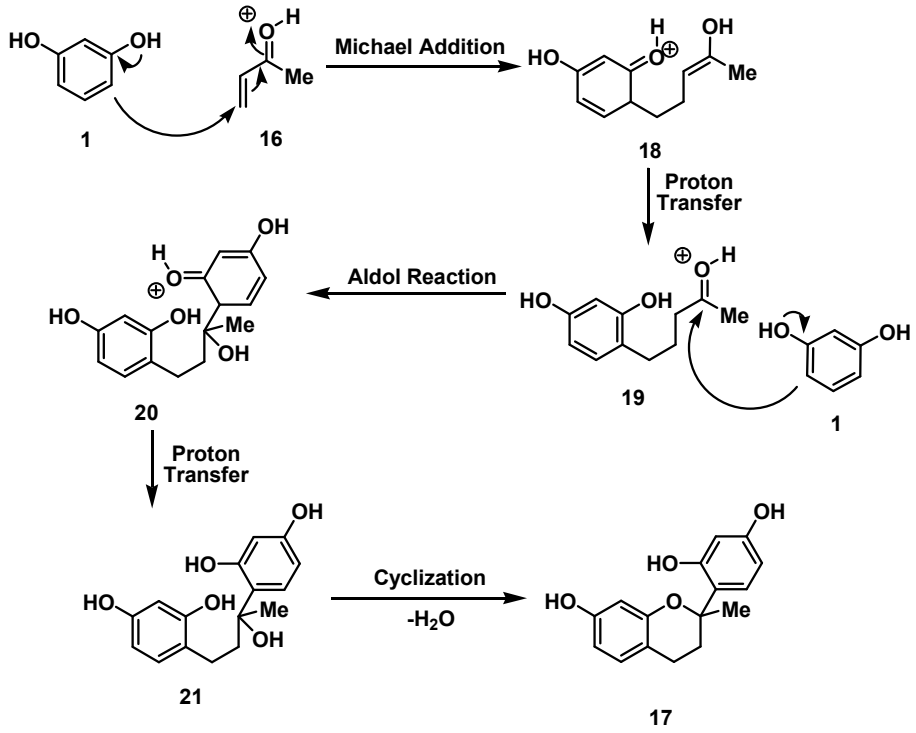
### 2.1.1.3 Flavan Compounds

Resrocinols undergo reactions with α,β-unsaturated ketones in presence of acids. With excess resorcinol substrates, flavan-type structures can result from these reactions. For example, resorcinol reacts with methyl vinyl ketone to give a trihydroxy flavan compound (Eq. 3).[9]



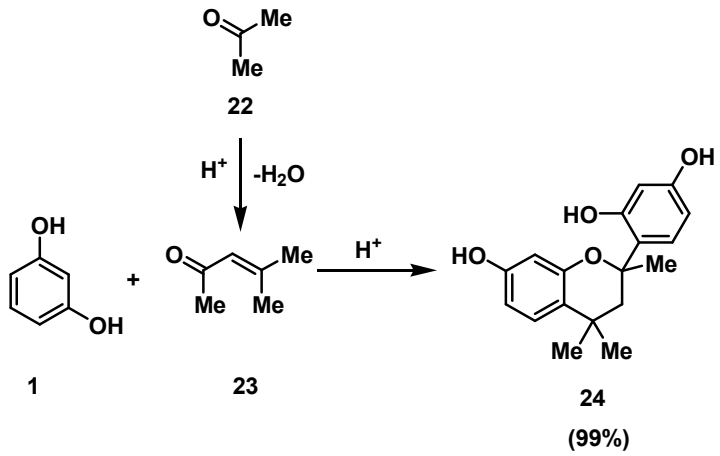

In this transformation, a Michael addition reaction first occurs between the unsaturated ketone and resorcinol at the 4 position of the aromatic ring followed by an aldol condensation of the intermediate Michael adduct and another mole of resorcinol substrate. Finally, an intramolecular cyclization leads to the heterocyclic ring structure in the product. The mechanism of this process is described in Scheme 2.3.

**Scheme 2.3** Mechanism of Reaction between Resorcinol and Methyl Vinyl Ketone.



Simple acyclic ketones such as acetone, and cyclic ketones such as cyclopentanone and cyclohexanone, can first undergo self-condensation to give α,β-unsaturated ketone under acidic conditions; the unsaturated ketone thus formed will then react with resorcinol to afford flavan-type compound. For instance, acetone reacts with resorcinol to afford 2,4,4-trimethyl-7,2',4'-trihydroxy flavan (**24**) (Scheme 2.4).

**Scheme 2.4** Reaction of Resorcinol and Acetone under Acidic Conditions.

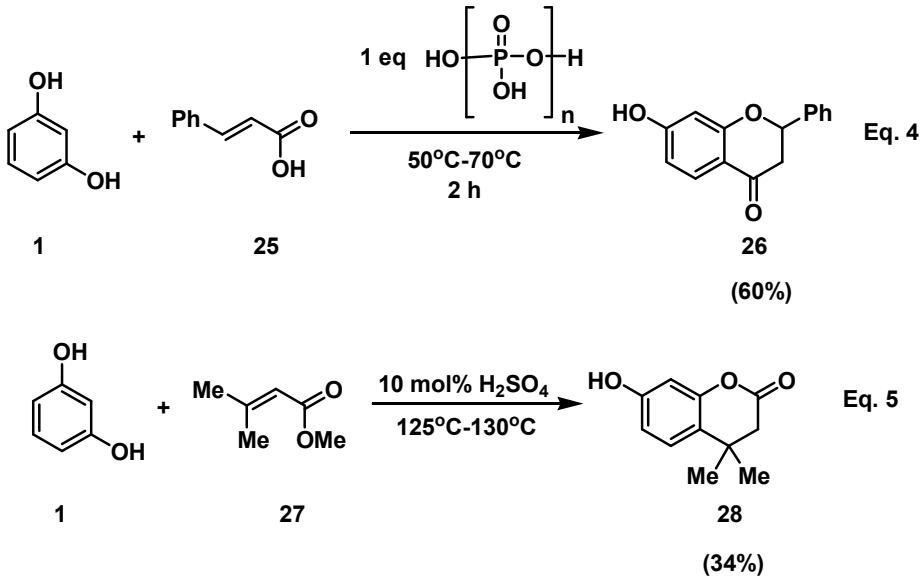



Flavan compounds resulting from these reactions are applied in rubber industry[10] and in the manufacture of circuits.[11]

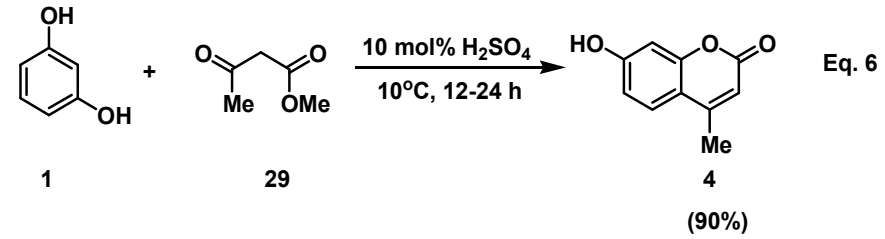
### 2.1.1.4 Chromanones, Chromones and Coumarins

Resorcinols react with α,β-unsaturated carboxylic acids and esters under acidic conditions. Interestingly, although they seem rather similar, α,β-unsaturated carboxylic acids and α,β-unsaturated esters react differently with resorcinols: in the case of α,β-unsaturated carboxylic acids, they first undergo Friedel-Crafts-type alkylation followed by intramolecular cyclization to give chromanone type

compounds as products. For example, 3-phenylacrylic acid (**25**) reacts with resorcinol in presence of a stoichometric amount of polyphosphoric acid (PPA) to afford 7-hydroxy-2-phenylchromanone (Eq. 4).[12] In contrast, when an α,β-unsaturated ester is applied, nucleophilic acyl substitution first occurs followed by cyclization to afford chromone (dihyrdrocourmarin) structure. An example is given in Eq.5 where 7-hydroxy-4,4-dimethyl-3,4-dihydrocourmarin (**28**) is prepared by reacting resorcinol with 3,3-dimethylacrylate (**27**).[13]

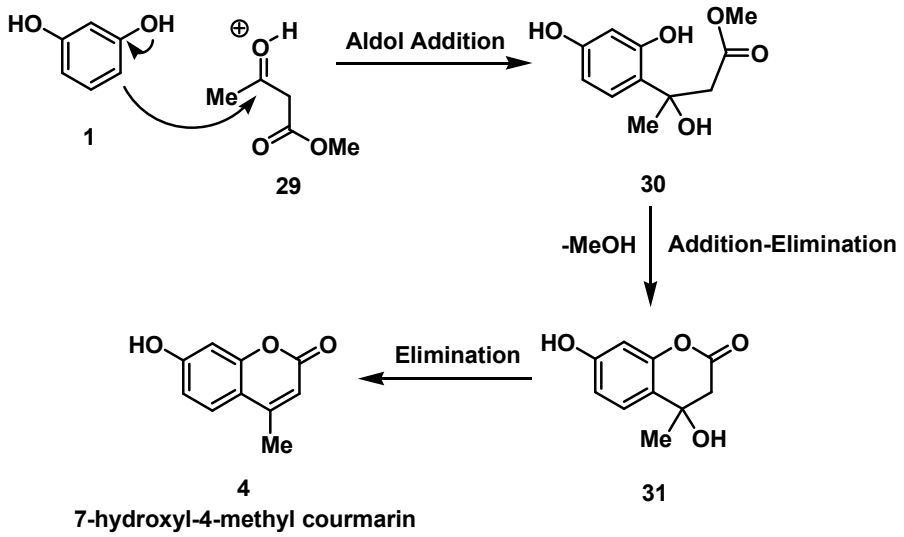



Resorcinols react with keto esters to give coumarin compounds. This transformation is known as the Pechmann reaction,[14] and it is widely used for the synthesis of courmarin compounds. For instance, resorcinol reacts with methyl acetoacetate to yield 7-hydroxy-4-methylcoumarin (Eq. 6).[15]




The reaction mechanism for the synthesis of courmains via resorcinols involves an aldol condensation between the resorcinol and the acetyl group in the ketoester substrate, followed by cyclization to afford the lactone ring. Elimination of the hydroxyl group derived from the aldol reaction will lead to the courmarin product (Scheme 2.5).

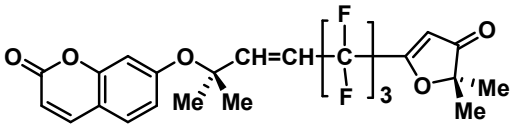
**Scheme 2.5**. Mechanism of Reaction of Resorcinol and Methyl Acetoacetate.




Chromanone and courmarin compounds that could be synthesized from resorcinols have been applied in the synthesis of various important compounds for different applications.[1,2] For instance, compound **32**, which contains

courmarin moiety, is a Geipavarin analogue that possesses significant tumor-inhibiting properties (Figure 2.1).[16]

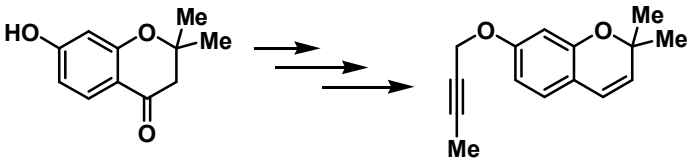
**Figure 2.1.** Geiparvarin Analogue.



**32**

Another example is shown in Scheme 2.6. Butylnoxychromene (**34**) can be synthesized from hydroxychromanone (**33**)[17] and it is utilized as an insect control agent.

**Scheme 2.6** Butylnoxychromene Derived from Hydroxychromanone.



**33**

**2,2-dimethyl-7-hydroxy-chromanone**

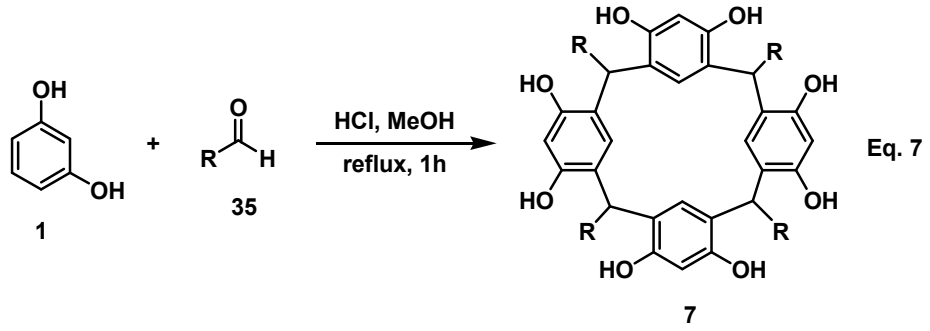
**34**

**2,2-dimethyl-7-(2-butynoxy)-3-chromene**

### 2.1.1.5 Resrocinarene

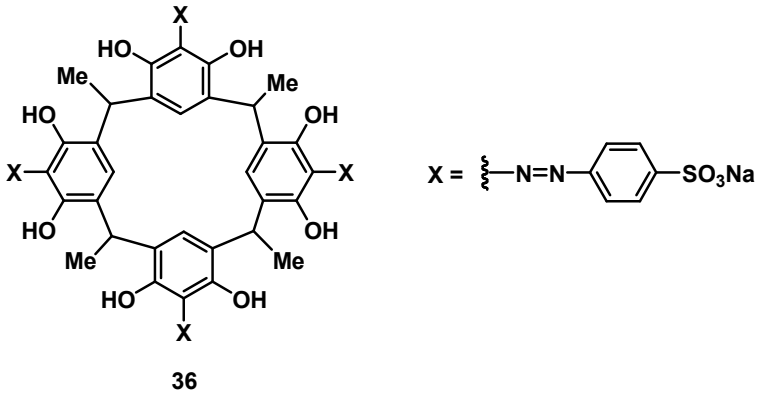
Resrocinearene (calix[4]resorcinearene) (**7**) is a marcrocylcic tetramer that is prepared by condensation of equmolar of resorcinols and aldehydes (Eq. 7). It has a half-bowl shape and functions as a molecular container that is suitable for host and guest interaction with many species such as metal cations, ammonium ion, and organic molecules with polar functional groups. Because of its

interesting structure and properties, resorcinarenes have been extensively studied by supramolecular chemists.[3,18,19]




Resorcinols are essential ingredients to construct resorcinearenes. What is more, the property of resorinarenes can be tuned by changing the substituents on the aromatic ring of resorcinols. For instance, attaching an arylsufonate group on the aryl ring of the resorcinol (X= -N=N-$C_6H_4SO_3Na$) leads to resorcinarene **36** that are soluble in water and are able to bind hydrophobic molecules in water (Figure 2.2).[17]

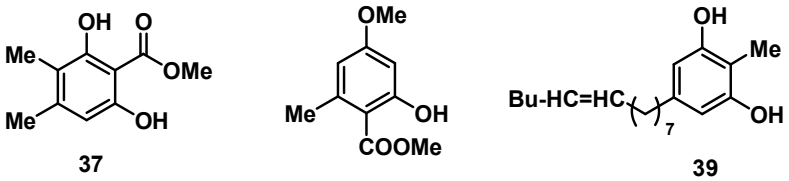
**Figure 2.2** Resorinarene Derived from Substituted Resorcinol.



### 2.1.2 Natural Products Containing the Resorcinol Structure

The core structure of resorcinol compounds, the meta-dihydroxylbenzene ring, occurs in many naturally occurred compounds, many of which have biological activity.[1,2] Some of these natural products are simply substituted resorcinols. A few examples of these resorcinol compounds are illustrated in Figure 2.3: 2,6-dihydroxy-3,4-dimethylbenzoic acid methyl ester (**37**) is identified as one of the constituents from *Picea morrisonicola*.[21] Methyl 6-hydroxy-4-methoxy-2-methylbenzoate (**38**), is an antibiotic substance isolated from fungus *sparassis raamosa*.[22] The 5-tridecenylresorcinols (**39**) were obtained from *Ardisia japonica* Blume and had antitubercular activity.[23]

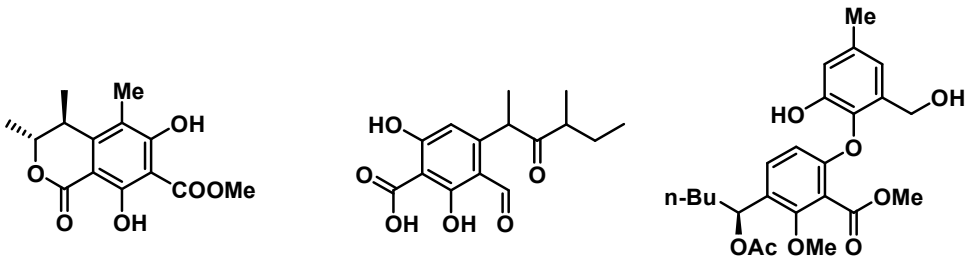
**Figure 2.3** Naturally Occurred Resorcinol Derivatives.




**37** **38** **39**

There are also many structurally complex natural products that contain resorcinol skeleton (Figure 2.4).[1,2] Dihydrocitrinone (**40**) is an isocourmarin derivative that is identified as metabolite of aspergilus carneus.[24] Ascochital (**41**) is isolated from marine fungus Kirschsteiniothelia maritima and has antibacterial activity.[25] Secopenicillide A (**42**) is a new penicillide derivative isolated from *Penicillium simplicissimum*.[26]

**Figure 2.4.** Complex Natural Products with Resorcinol Skeleton.



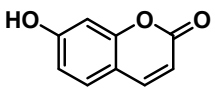

**40**
**dihydrocitrinone**

**41**
**ascochital**

**42**
**secopenicillide A**

Compounds that are readily derived from resorcinols are also identified in natural products.[1,2] For instance, courmarins are commonly present as secondary metabolities in seeds, roots and leaves of many plants.[1] For example, 7-hydroxylcourmairn (**43**) which can be prepared by Pechmann condensation of resorcinol and formylacetate is a natural product by the name umbelliferone that occurs in many plants. It also demonstrates antioxidant properties.

**Figure 2.5**. Natural Product 7-Hydroxylcourmarin (Umbelliferone).




**43**
**Umbelliferone**

### 2.1.3 Synthesis of Resorcinol Compounds

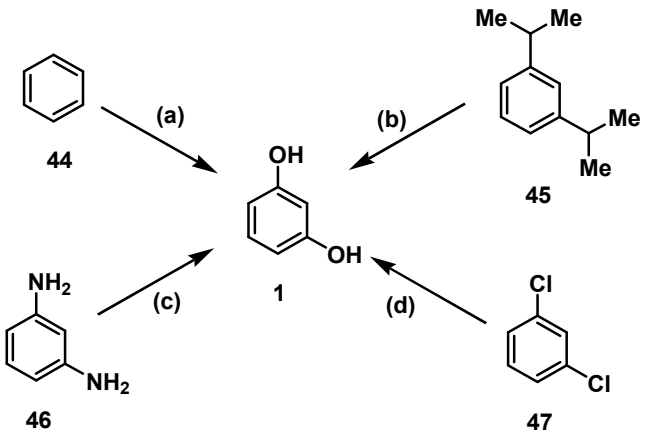
Resorcinol compounds are important ingredients for a variety of structures that are useful in both industrial application and academic research.[1,2] They are identified as essential component of a number of natural products and phenolic compounds of pharmaceutical interest.[21-26] Therefore, effective synthetic

methods that lead to resorcinol compounds are highly desirable. A survey of established methods will be discussed under this section.

### 2.1.3.1 Synthesis of Unsubstituted Resorcinol

Unsubstituted resorcinol is made primarily by disulfonation/caustic fusion of benzene (Scheme 2.7,a). Other approaches such as hydroperoxidation/cleavage of *m*-diisopropylbenzene (**b**), acid hydrolysis of *m*-phenylenediamine (**c**), alkaline hydrolysis of haloaromatic compounds (**d**) have also be reported and applied. [1, 2]

**Scheme 2.7** Methods Used for the synthesis of Resorcinol.




**(a): 1) $H_2SO_4$, 25°C-200°C; 2) NaOH, 300°C-360°C; 3)$H^+$.**
**(b): 1)$O_2$, peroxide; 2)$H^+$. (c): $H_2O$, $NH_4SO_4$, 220°C.**
**(d): NaOH, 180°C-200°C**

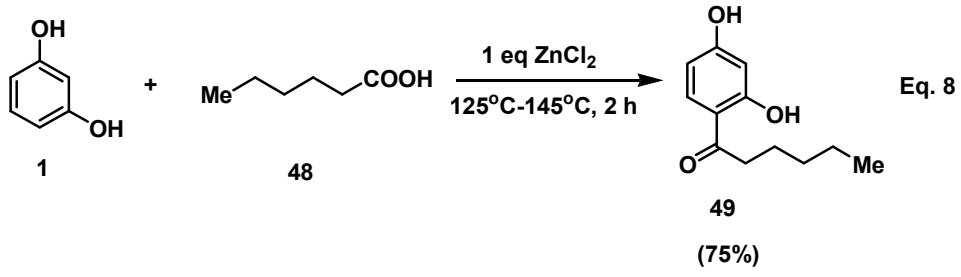
### 2.1.3.2 Synthesis of Substituted Resorcinols

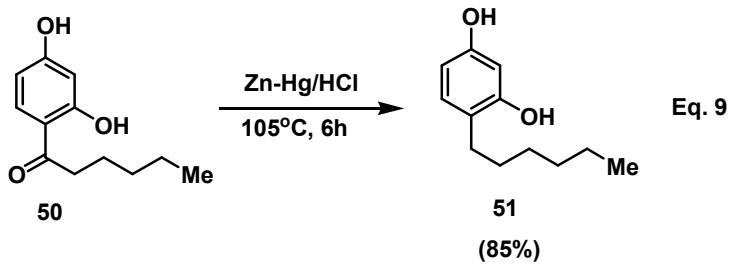
#### 2.1.3.2.1 Eletrophilic Substitution Reactions

Substituted reorcinols are accessible via eletrophilc substitution reactions. The electron donating effect of the two hydroxyl groups makes the aromatic ring

electron rich and, therefore, enables resorcinols to undergo eletrophilic aromatic substitution reactions with electrophilc reagents such as alkyl halides, alcohols and unsaturated aliphatic hydrocarbons. The rate of electrophilic substitution on resorcinol is faster than on phenol and its derivatives. The 2,4,6-positions on the benzene ring are activated by the OH group via resonance. *Para* positions (4,6-positions) are the most reactive sites. The *ortho* position (2-position) is less preferred since it has two adjacent hydroxyl groups and is therefore, more sterically hindered compared to the 4- and 6-positions; The *meta*-position (5-position) is less reactive due to electronic distribution by resonance and does not undergo eletrophilic substitution reactions like other positions on the aromatic ring.

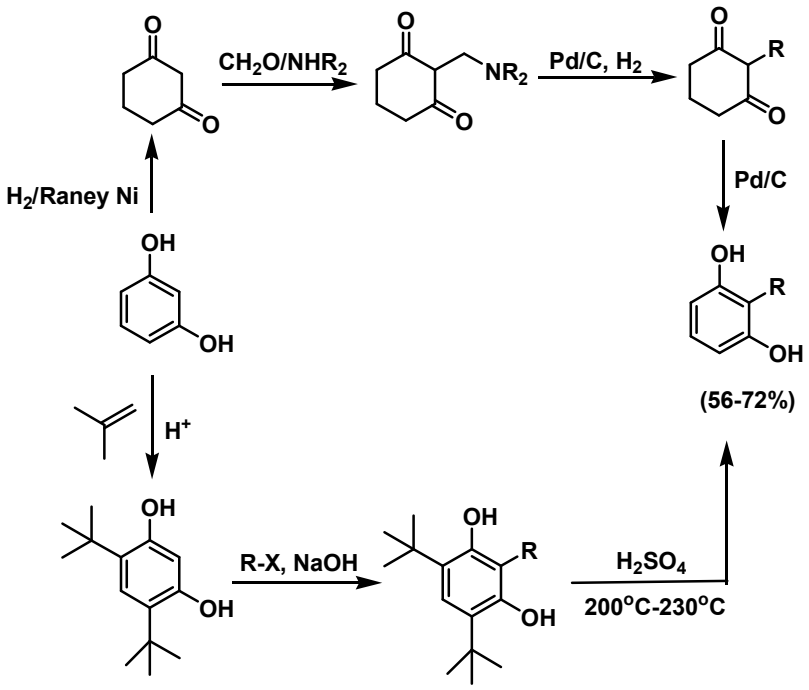
4-Alkyl substituted resorcinols can be made by Fredel-Craft alkylation reactions of carboxylic acids and resorcinol to give the acyl substituted intermediates (Eq. 8), followed by reduction of the carbonyl group (Eq. 9).[27]



A major problem of this approach is the regioselectivity on the aromatic ring: the 4-and 6-positions are readily accessible and easily functionalized, however, the 2-position, although activated, is difficult to access without affecting the 4-and 6-position. A mixture of products is usually obtained when 2-substituted resorcinols are the intended products. This problem can be circumvented by taking an indirect approach. For instance, reduction of resorcinols gives the corresponding dihyroresoricnols which readily react with electrophiles at the methylene group between the two carbonyls; The substituted dihyroresoricnols are then oxidized to form 2-substitued resorcinols (Scheme 2.8).[28] Another approach is to occupy the 4,6-positions with protecting groups. In this case, the 2-position becomes the only reactive site for electrophilic substitutions so the reactions will take place at this position. The protecting groups are removed after the substitution reactions[29] (Scheme 2.8). Although these methods could solve the selectivity issue, they would also extend the synthetic steps and therefore be less efficient.

**Scheme 2.8** Methods for Synthesis of 2-Substituted Resorcinols.



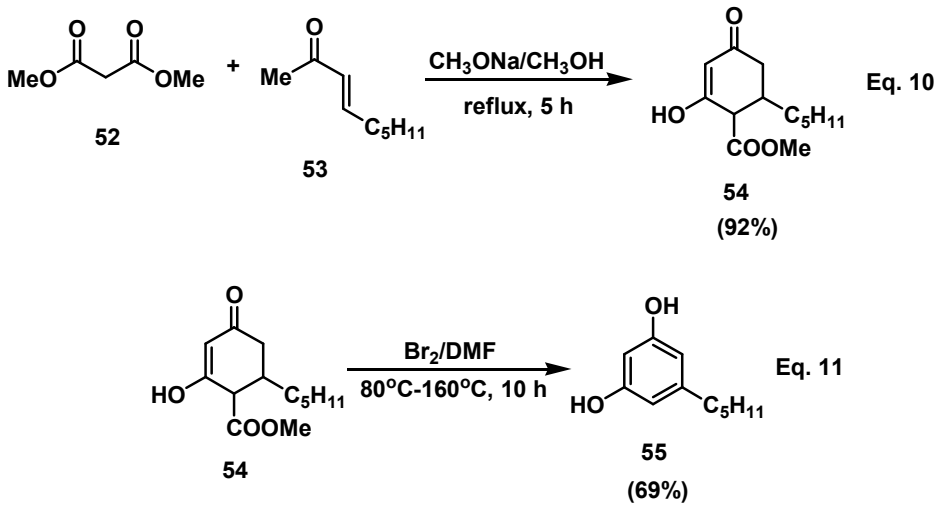

Another drawback of eletrophilic substitution reactions is that they cannot access the 5-position of the aromatic ring. Although the aromatic rings in resorcinols are strongly activated by the two hydroxyl groups, the 5-position of resorcinols is much less reactive than other positions duet to the directing effect of the hydroxyl groups. As a result, no electrophilic substitution would occur at the 5-position, so 5-substituted resorcinols have to be made by other means.

Eletrophilic substitution reactions are commonly applied for the synthesis of resorcinol derivatives. However, this conventional method suffers mainly from the poor regioselectivity on the aromatic ring. Due to this limitation, it is rather difficult to assemble polysubstituted resorcinol compounds with different substituents on the aromatic ring by this method. Another disadvantage of this approach is the

harsh conditions involved: high temperature and strong acid are usually required to perform these reactions.

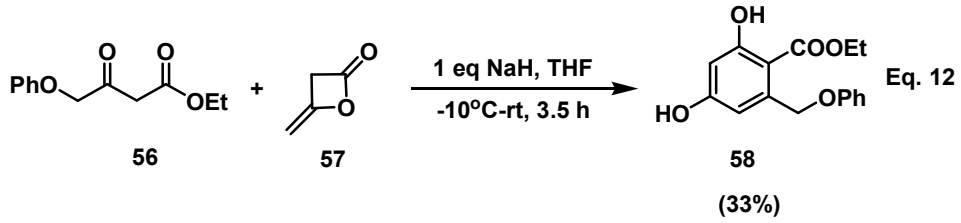
#### 2.1.3.2.2 Cyclization of Acyclic Compounds

Resorcinol derivatives can be prepared through condensation/ cyclization/dehydrogenation of acyclic compounds. For example, Focella and coworkers reported a synthesis of olivetol (**55**), which is a 5-alkylsubstituted resorcinol compound, from dimethyl malonate and 3-none-2-none.[30] Under basic conditions these two substrates condensed and cyclized to form intermediate **54** (Eq. 10). The cyclic enone intermediate was then converted to olivetol (**55**) when heated with a stoichometric amount of bromine at high tempertature (Eq. 11). One advantage of this approach is that it can incorporate functional groups onto the aromatic ring at the 5-position of the resorcinol, which is difficult to achieve by electrophilic substitution. However, similar to the electrophilic substitution reactions, these methods that prepare resorcinols from acyclic starting materials also require harsh reaction conditions, such as the condition employed in equation 11.




### 2.1.2.2.3 Ketene Reactions

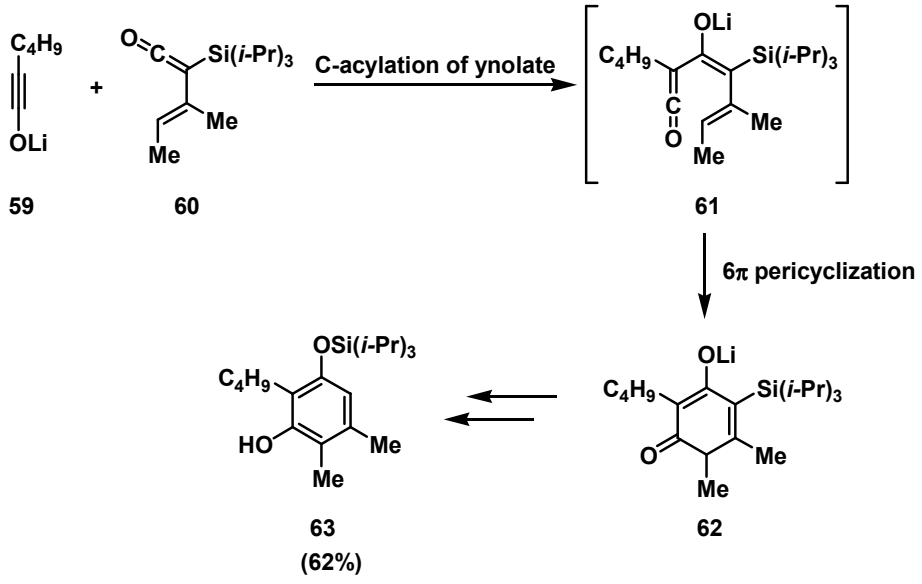
Ketenes are highly reactive species that are widely applied as reaction intermediates in organic synthesis.[31] They have been utilized for the synthesis of resorcinol compounds in a few cases. Diketene (**57**) is applied to construct resorcinol derivatives. Kato, *et. al*.[32] reported that diketene reacts with β-ketoesters promoted by base to afford resprocinol derivatives (Eq.12). The reaction can be performed at -10°C which is rather mild compared to reaction conditions in electronphilic substitutions. But the yield of this transformation is low in all cases.




In 2005, Danheiser at MIT reported a novel reaction of (trialkysilyl)vinylketenes (**60**) with lithum ynolates (**59**) to produce highly substituted resorcinol

compounds.[33] The mechanism of this transformation (which is described in Scheme 2.9) starts with C-acylation of the ynolate. The intermediate thus formed undergoes 6π-electrocyclic ring closure to give the cylcohexadienone **62** which will then tautomerize into the resorcinol product **63**. This is a recent example of resorcinol synthesis from ketenes. This reaction occurs at ambient temperature and it leads to resorcinol derivatives with multiple substituents in moderate to good yields. A problem associated with this chemistry is the availability of the vinylketene substrate: it has to be prepared from diazoketones via a photochemical Wolff rearrangement.[34] A lack of convenient procedure to access the vinylketene substrates hinders this chemistry from practical application.

**Scheme 2.9** Reaction Mechanism of Vinylketene with Lithium Ynolate.



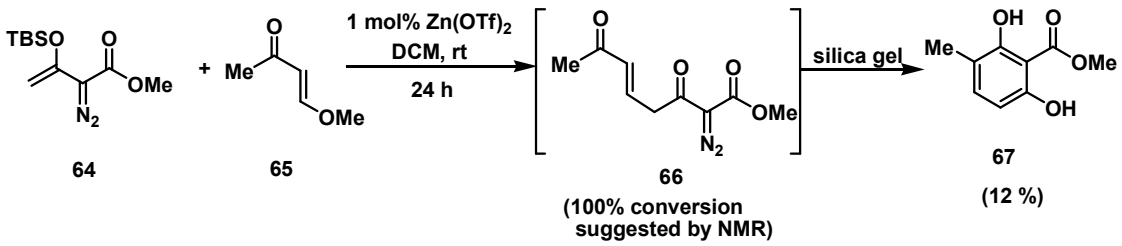

Despite the importance and wide application of resorcinol compounds, only a limited number of methods are available for the synthesis of resorcinol derivatives, and they suffer from problems including multiple synthetic steps, low

yield and harsh reaction conditions. Therefore, novel methods that employ simple, readily available starting materials to prepare resorcinol compounds under mild conditions are highly desirable.

### 2.1.3 An Unexpected Process that Provides Resorcinol Compounds

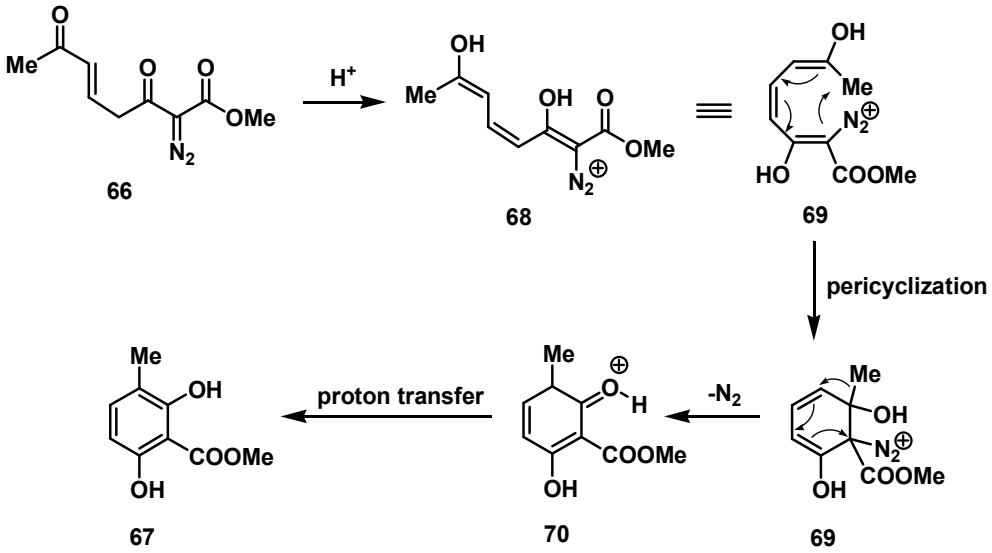
During our investigation of the Mukaiyama-Michael reaction of 3-*tert*-butylsilyloxy-substituted vinyl diazoacetates (**64**) and α,β–unsaturated carbonyl compounds we discovered an interesting transformation. When 4-methoxyl-3-buten-2-one (**65**) was applied to react with vinyl diazoester **64**, enedione-diazoester intermediate **66** was observed by proton NMR of the reaction mixture. This intermediate is formed by eliminating *tert*-butyldimethylsilylmethyl ether from the initial adduct of the Mukaiyama-Michael reaction. The initial Mukaiyama-Michael adduct, however, is not observed under this conditions. What is more interesting is that compound **66** decomposed during column chromatography on silica gel and, instead of the expected enedione-diazoester, a small amount of 6-methyl-2-carboalkoxyresourcinol (**67**) was isolated after purification (Scheme 2.10).

**Scheme 2.10** An Unexpected Transformation.



A proposed mechanism for this unexpected reaction is depicted in Scheme 2.11. In an acidic environment (the acidity of the silica gel), the enedione-diazoester (**66**) enolized to form intermediate **68** which is capable to undergo pericyclization to form the six-memembered ring structure in compound **69**. Then 1,2-migration of the methyl group coupled with release of nitrogen gas to give intermediate **70**. Finally proton transfer affords the resorcinol product **67**.

**Scheme 2.11** Proposed Mechanism for the Formation of Resorcinol 67.




We realized that this is an unprecedent transformation that has no prior equivalent in the literature before. Moreover, we envisioned that it could be developed into a practical synthetic method for the preparation of resorcinol derivatives that would have several advantages. First of all, the starting materials for this reaction are readily accessible: the α,β–unsaturated carbonyl compound is commercially available, and the vinyl diazoacetate can be conveniently prepared by standard procedure. Secondly, the reaction conditions are mild.

Reaction occurs at room temperature and no harsh reagents have to be used. Lastly, although we were not certain about the efficiency of this process at that point, no other reaction intermediates or byproducts were identified indicating that this could be a clean reaction. Therefore, we decided to investigate this novel transformation, and the results we obtained thus far will be discussed in detail in the rest of this chapter.

## 2.2 Results and Discussion

### 2.2.1 Synthesis of 2, 6-dihydroxyl-3-methylbenzoate

#### 2.2.1.1 Optimization of Reaction Conditions

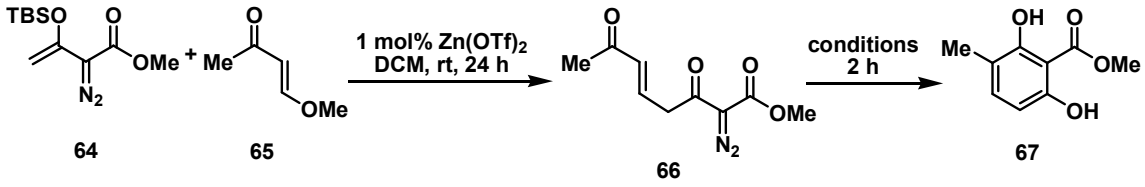
The reaction of 3-*tert*-butylsilyloxy-substituted vinyl diazoacetate **64** and 4-methoxyl-3-butene-2-one (**65**) afforded 4-methy-2-carboalkoxyresorcinol **67** after column chromatography on silica gel instead of the expected enedione-diazoester **66** that was indicated by the $^{1}$H NMR spectrum of the reaction mixture before purification. Based on the mechanism proposed in Scheme 2.11, enol intermediate **66** probably triggered the rearrangement to **67** with silica gel serving as an acid catalyst to induce the enolization of the enedione-diazoester **66** during column chromatography. Although the resorcinol compound can be obtained in this way, chromatography on silica gel does not serve as a practical means to synthesize this compound because only 12 % of the original mass was recovered, and the majority of the enedione-diazoester was lost during chromatography. To optimize this reaction, various conditions were investigated, and the results of this study are summarized in Table 2. 1.

We first tried to promote this reaction by adding silica gel to the reaction mixture when the Mukaiyama-Michael addition reached completion (Entry 1). However, rearrangement to **67** did not occur even in refluxing dichloromethane (Entry 2). Only migration of the enone double bond occurred with 36% conversion as determined by a $^{1}$H NMR spectrum of the reaction mixture.

We then turned to more acidic conditions: with an excess molar amount of glacial acetic acid, similar result was obtained: double bond migration occurs under this condition, but resorcinol **67** was not found (Entry 3). With 2 equivalents of 4 N aqueous HCl, resorcinol **67** was produced, however, only a 21% isolated yield of this compound was obtained (Entry 4).

Based on the mechanism proposed in Scheme 2.11, we speculated that instead of Brønsted acids that could lead to enol intermediate **68**, Lewis acids might also be able to promote this transformation by forming enolate complexes. Therefore, a number of Lewis acids were evaluated. Strong Lewis acids such as titanium chloride (Entry 5) and boron trifuoride etherate (Entry 6) lead to the decomposition of enedione-diazoester (**66**). After reacting these strong Lewis acids with compound **66** at ambient temperature for 2 hours, the $^{1}$H NMR spectrum of the reaction mixture suggested that **66** had been fully consumed, however, none of the diagnostic peaks for resorcinol **67** could be identified. The mild Lewis acids, scandium triflate (Entry 7) and ytterbium triflate (Entry 8), failed to promote any reaction. Compound **66** remained intact in the reaction mixture, and no other compound was noticed after conducting the reaction at room temperature overnight.

**Table 2.1** Optimization of Reaction Conditions.




64 65 66 67

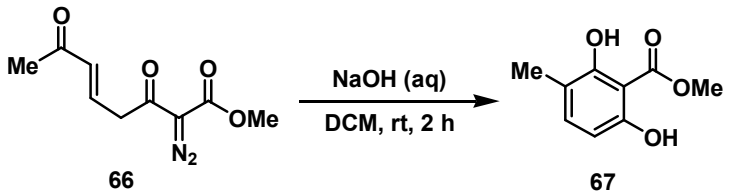
| Entry | reagent | amount | solvent | temperature | yield (%) |
|---|---|---|---|---|---|
| 1 | silica | 100 mg | DCM | rt | NR |
| 2 | silica | 100 mg | DCM | 40°C (reflux) | NR |
| 3 | acetic acid | 5 equiv | DCM | rt | NR |
| 4 | 4 N HCl (aq) | 2 equiv | THF | rt | 21 |
| 5 | $TiCl_4$ | 1 equiv | DCM | rt | decomp |
| 6 | $BF_3$ $EtO_2$ | 2 equiv | DCM | rt | decomp |
| 7 | $Sc(OTf)_3$ | 0.5 equiv | DCM | rt | NR |
| 8 | $Yb(OTf)_3$ | 0.5 equiv | DCM | rt | NR |
| 9 | $Et_3N$ | 5 equiv | DCM | rt | 45 |
| 10 | NaOH (aq) | 0.1 equiv | DCM | rt | 83 |

With limited success under acidic conditions, we turned to the use of basic conditions with the rationale that instead of acid induced enolization of intermediate **66**, deprotonation of the enedione-diazoester by a base would lead to the corresponding enolate that might be able to form the resorcinol compound as well (a more detailed discussion on the reaction mechanism is presented in the following section). The rearrangement reaction indeed occurred with addition of a base. When 5 equivalents of triethylamine was added to the reaction solution with enedione-diazoester **66**, the expected resorcinol product **67** was produced and isolated in 45% yield (Entry 9). However, we were not able to further improve the yield of the resorcinol product using triethylamine as base. Varying the amount of triethylamine or performing the reaction at higher temperature (40°C

oil bath) gave mediocre yields that were less than 50%. We then switched to other basic reagents and found that sodium hydroxide aqueous solution catalyzed this transformation effectively. With catalytic amount of sodium hydroxide, the yield of **67** was improved to 83% (Entry 10).

It is worth mentioning that the concentration of the sodium hydroxide aqueous solution plays an important role in this reaction. The yields of **67** as a function of different concentrations of the base are summarized in Table 2.2. A comparison can be drawn between the results from Entry 1 and Entry 2: With the same amount of sodium hydroxide (0.1 equiv), if the base solution is dilute (0.01 mol/L, 5 mL), only a moderate yield was obtained (Entry 1); By contrast, applying sodium hydroxide as 0.5 mL of a 0.1 mol/L aqueous solution afforded the resorcinol product **67** in high yield (Entry 2). A further increase of the concentration (Entry 3) had shown a detrimental effect on the reaction yield.

**Table 2.2**. Resorcinol Formation with Sodium Hydroxide (aq) at Different Concentrations.

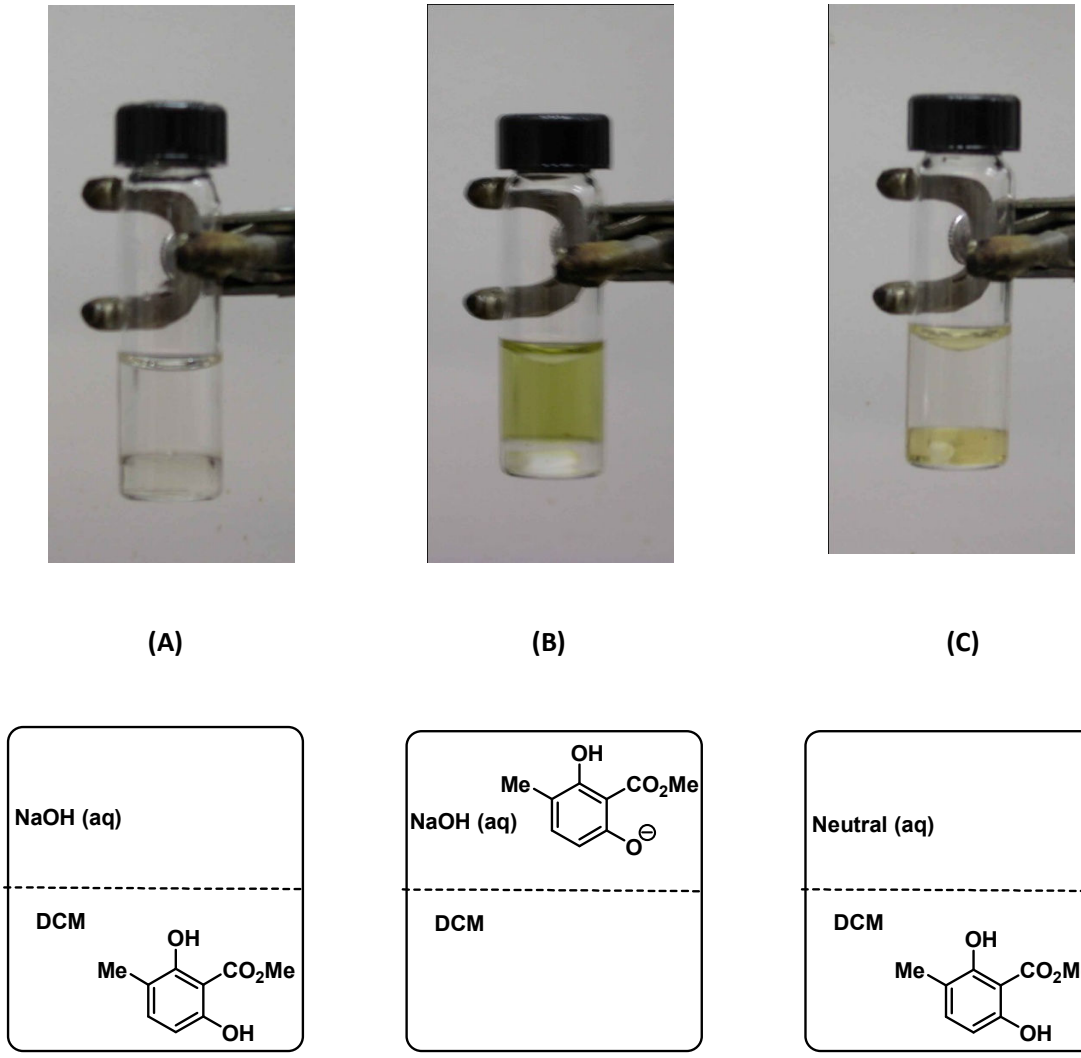



66 67

| Entry | concentration of NaOH (aq) | volume of NaOH (aq) | equiv of NaOH | yield of 67 (%) |
|---|---|---|---|---|
| 1 | 0.01 mol/L | 5 mL | 0.1 eq | 67 |
| 2 | 0.1 mol/L | 0.5 mL | 0.1 eq | 83 |
| 3 | 0.2 mol/L | 0.5 mL | 0.2 eq | 72 |

We speculate that the solubility of resorcinol **67** in water could be a reason for the different results observed for Entry 1 and Entry 2 in Table 2.2. Since unsubstituted resorcinol is very soluble in water (717 g/L),[2] we suspect that resorcinol derivative **67** would have similar water solubility. Therefore when a large amount of water is involved in the reaction, a portion of the product could be lost in the aqueous phase. This argument is supported by a liquid-liquid extraction experiment (Figure 2.6): A solution of 1.0 mmol resorcinol **67** in 1 mL dichloromethane was prepared, followed by addition of 2 mL sodium hydroxide aqueous solution that contained excess amount of NaOH (1.5 equiv) (A). After mixing the two phases by shaking the vial vigorously, compound **67** was transferred to the aqueous phase by forming the corresponding phenolate, and this is evident by the color change of the upper water layer (B). Neutralizing the basic solution with 4 N HCl converted the phenolate to resorcinol **67** again and released the neutral compound back to the organic solution (C). Only 75% of the resorcinol compound could be recovered after this simple treatment. This result suggests that a considerable amount of resorcinol **67** could be lost in contact with water.

**Figure 2.6** Liquid-liquid Extraction Experiment.



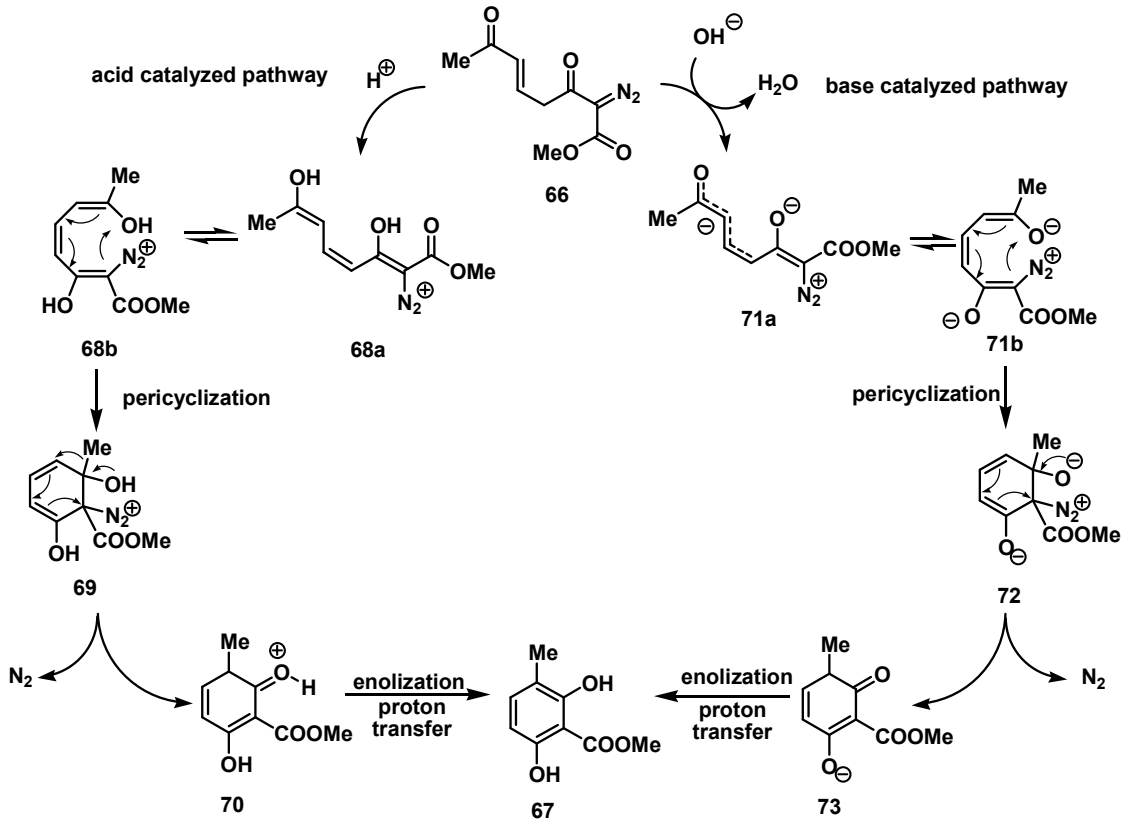

The influence of excess amount of base was also investigated: When the reaction reached completion under the optimum conditions (Table 2.1, Entry 10), an additional 1 equivalent of sodium hydroxide in 0.5 mL aqueous solution was added to the reaction mixture. The reaction product **67** was transferred to the aqueous layer under this condition. However, less than 20% of resorcinol **67** could be recovered after neutralizing the water layer with 4 N HCl followed by back extraction with DCM. Although there was an increase in the volume of water

involved, it should not affect the result dramatically based on the liquid-liquid extraction experiment mentioned before. Therefore, this experiment suggests that a significant amount of product could be lost in presence of an excess amount of base, and this result is consistent with what has been obtained earlier (Table 2.2, Entry 3).

#### 2.2.1.2 Mechanism for Resorcinol Formation from Enedione-diazoester 66

The mechanism for the formation of resorcinol **67** via ene-dione diazoester **66** is not self-evident, and it arises as an interesting subject to explore. Based on the experimental results we obtained, reaction mechanisms for both acid-catalyzed and base-catalyzed pathways were proposed, and they are depicted in Scheme 2. 12.

**Scheme 2.12** Proposed Reaction Mechanism under Acid and Base Catalysis




This transformation starts from acid-base reactions of enedione-diazoester **66**. The methlyene proton in **66** should be rather acidic due to the presence of the adjacent carbonyl group and acylvinyl group. An analogy between **66** and a 1,3-dicarbonyl compound can further illuminate this point: the structure of **66** can be recognized as a 1,3-dicarbonyl system extended by a conjugated double bond. The $pK_a$ of acetylacetone, a representative 1,3-dicarbonyl compound, is around 9 at 25$^{o}$C,[35] so we expect compound **66** to have similar $pK_a$ value. Therefore, under acidic conditions, ene-dione diazoester **66** is capable for tautomerization to give

enol intermediate **68a**, while under basic conditions the methylene proton can be removed by base to form the corresponding enolate **71a**.

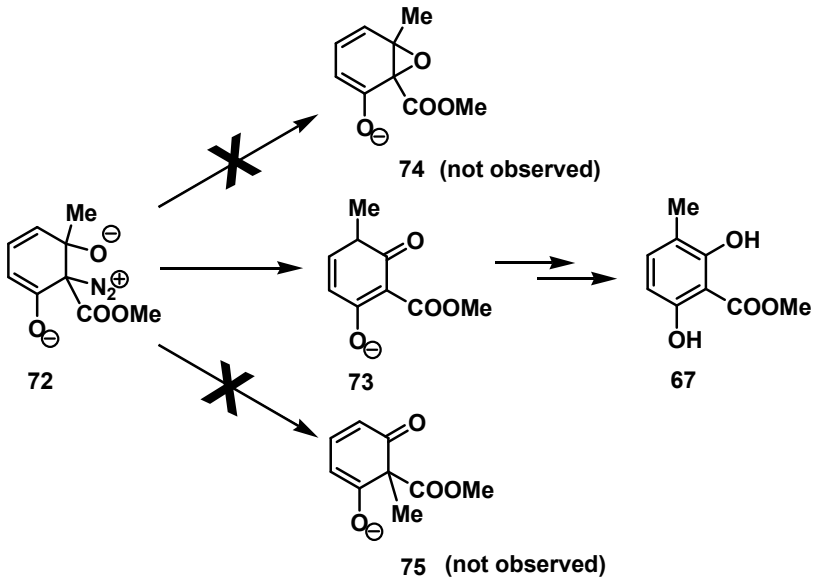
With the conjugated triene structures, both enol **68a** and enolate **71a** can undergo pericyclization to afford the six-membered ring when they adopt appropriate conformations (**68b** and **71b**). Similar 6-π electrocyclizations involving enolate derivatives can be found in the literature.[33, 36] For example, in a transformation we have mentioned previously (2.9), lithium enolate specie **61** undergoes 6π- pericyclization to afford resorcinol derivative **63** as the product. However, highly reactive reagents such as lithium ynolate or organolithium compounds are required in stoichiometric amount to form the enolate-triene structure in previous reported examples while enolate **71** is produced under relatively mild conditions with catalytic amount of sodium hydroxide. Compared to enol intermediate **68**, enolate **71** does have an advantage in this step. The polar attraction between the negative charge that resides on the carbonyl oxygen of the methyl keone and the formal positive charge on the diazo group favors conformer **71b** since it brings those two oppositely charged groups into proximity. By contrast, this effect is not presented in the acid catalyzed pathway. This difference in the mechanistic detail could account for the fact that resorcinol **67** can be prepared in higher yield under base catalysis compared to acid catalysis.

Upon formation of either intermediate **69** or **72**, a 1,2-methyl shift coupled with the loss of the dinitrogen as nitrogen gas would afford the cyclic diene intermediate (**70** and **73**). Finally, proton transfer and enolization of the ketone lead to the aromatic ring structure in product **67**.

There are a few fascinating details in this mechanism that are worth further discussion. First of all, isomerization of the double bond from *trans* to *cis* in either the enol intermediate **68** or enolate anion **71** is critical for the overall transformation because only in the Z-geometry is it possible for the two ends of the molecule to come close to each other and carry out the cyclization process. Starting with the E-isomer of compound **66**, the formation or the enol/enolate intermediate under acidic or basic conditions makes it possible for the isomerizaion of the double bond and the transformation that follows.

Secondly, the diazonium ion (**69 and 72**) is set up for dinitrogen loss in concert with methyl migration to give intermediate **70** or **73**, and in this step, the methyl group migrates in the reverse direction to that of the dinitrogen extrusion. Interestingly, although other possible reaction pathways exist, such as a semipinacol rearrangement[37] in which the methyl group would migrate to the carbon bearing the diazonium ion (**75**); or epoxide formation by a SN2-like displacement of the dinitrogen by the neighboring oxygen to give **74**[38] (Scheme 2.13), these alternative transformations do not occur. Resorcinol **67** is the sole product obtained in this reaction, and no evidence for the formation of other by-products was noticed.

**Scheme 2.13** Possible Reaction Pathways for Intermediate **72**.

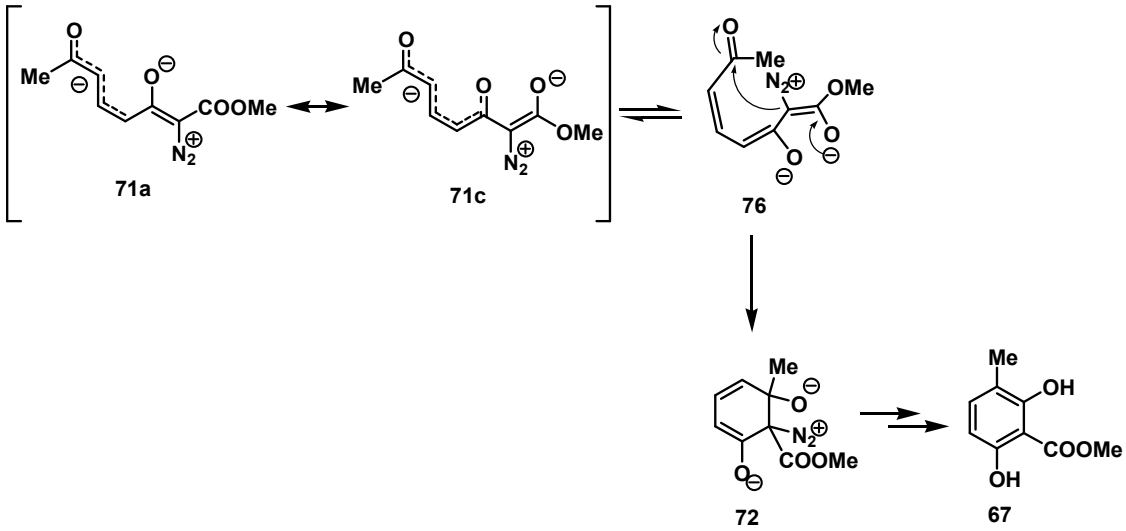



Lastly, in the base-catalyzed reaction pathway, the phenolate form of **67** should be produced prior to the resorcinol product. The $pK_a$ of unsubstituted resorcinol is 9.8,[2] therefore the phenolate intermediate should be basic enough to continue proton removal from enedione-diazoester **66** that has a $pK_a$ about 9, As a result, only a catalytic amount of base is required to promote this reaction. Once the reaction is initiated, it becomes self-sustained.

The formation of the 6-memebered ring could be understood from another mechanistic perspective. Instead of the resonance hybrid **71a**, the structure of the enolate anion can also be visualized as that of **71c**. In this resonance structure the ester carbonyl group is polarized, and the negative charge is delocalized in the conjugated system between the methyl ketone group and the β–keto group of the diazoacetoacetate. In this system, the negative charge resides mainly on the β–keto group since it benefits from proximity to the

diazonium ion. Therefore, a nucleophilic attack of the ketal enolate to the methyl ketone will have a greater tendency to lead to the ring closure and give rise to intermediate **72** (Scheme 2.14).

**Scheme 2.14** Alternative Mechanism for Cyclization.

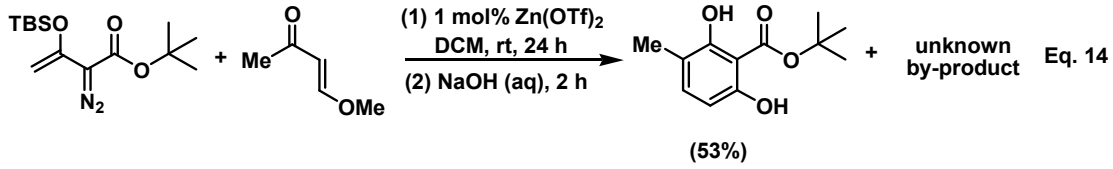



### 2.2.1.3 Substrate Scope of the Resorcinol Synthesis

We investigated the substrate scope of this resorcinol synthesis by subjecting different vinyl diazo compounds and α, β–unsaturated ketones to the optimized reaction conditions that employs zinc(II) triflate catalyzed Mukaiyama-Michael addition followed by base promoted cyclization/rearrangement. The results from these investigations are discussed in this section.

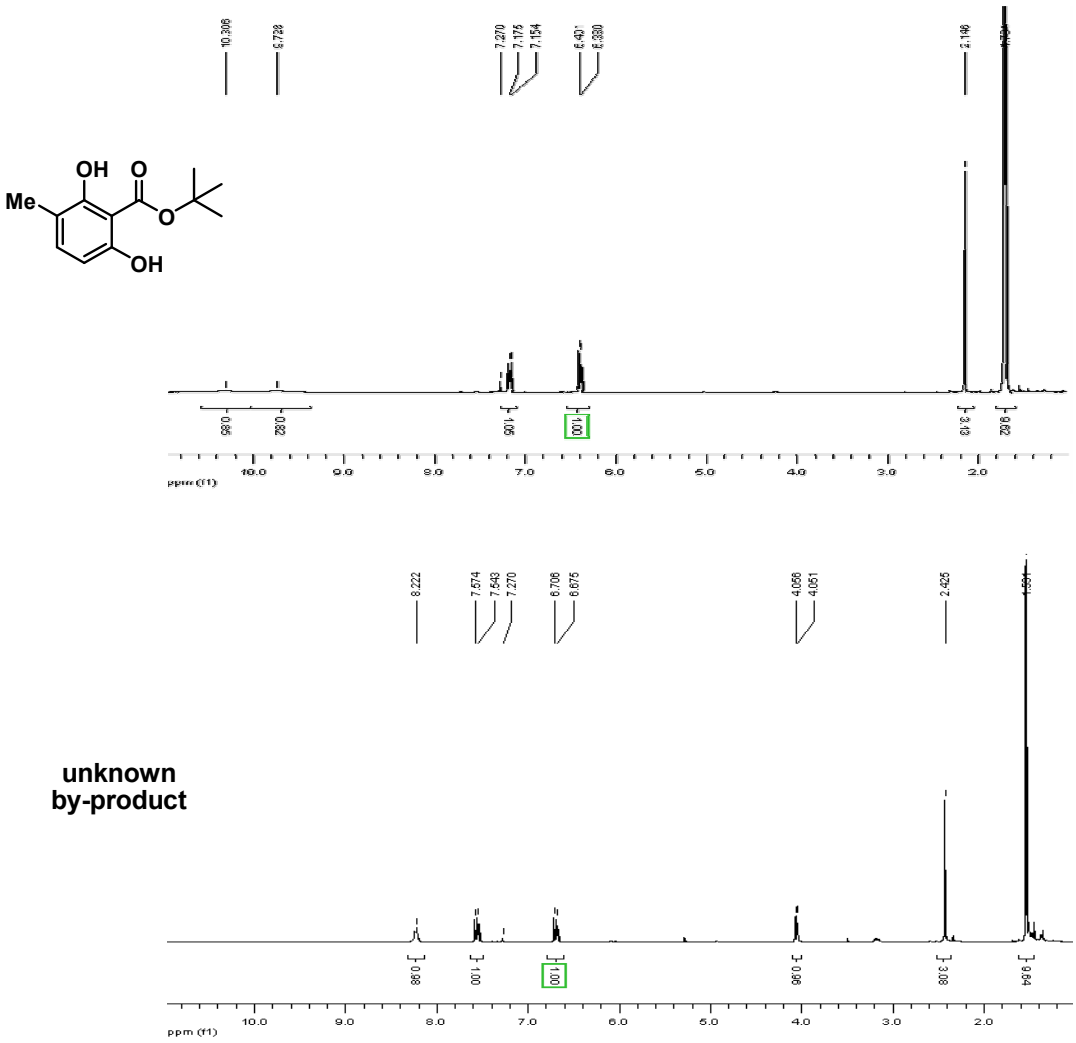
#### 2.2.1.3.1 Vinyldiazoacetates with Various Ester Groups and By-product Associated with These Substrates

By switching the ester group in 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate from a methyl group to a bulkier *tert*-butyl group we noticed that the yield of the resorcinol product decrease from 83% to 53%. Meanwhile, a minor product was obtained (Eq.13).



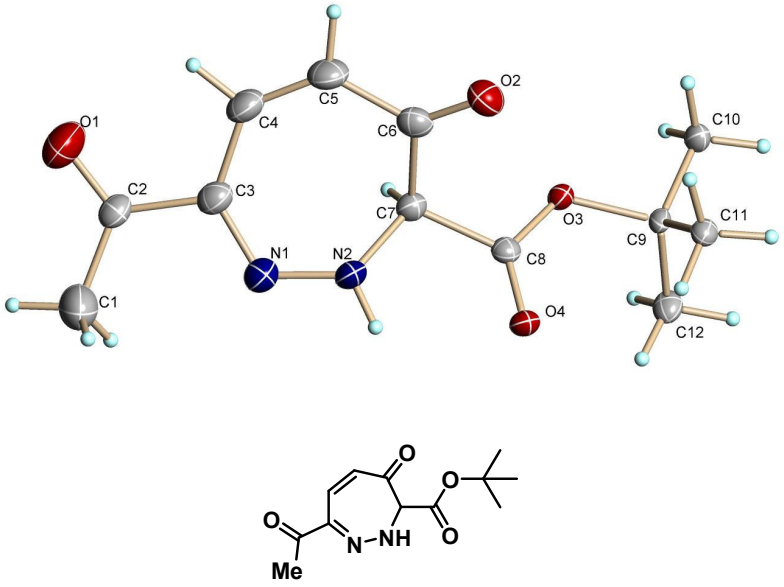

The $^{1}$H NMR spectrum of this by-product suggests that it has the same number of protons as the major product but it is difficult to come up with the exact structure of this by-product based on proton NMR spectrum (Figure 2.7). Other spectroscopic data ($^{13}$C, IR) of this by-product was also obtained. However, we were not able to determine the structure of this compound based on these spectra.

**Figure 2.7** $^{1}$H spectra of the major resorcinol product and the unknown by product.



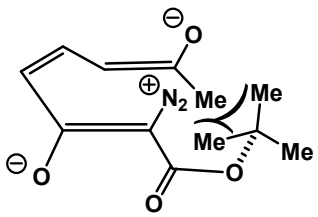

It was not until a single crystal was obtained for this minor product could we confirm the 1,2-diazepine structure of this compound: a seven-membered ring that contains the two nitrogen atom from the diazo group. The crystal structure is shown in Figure 2.8.

**Figure 2.8** X-ray structure of 1,2-diazepine.



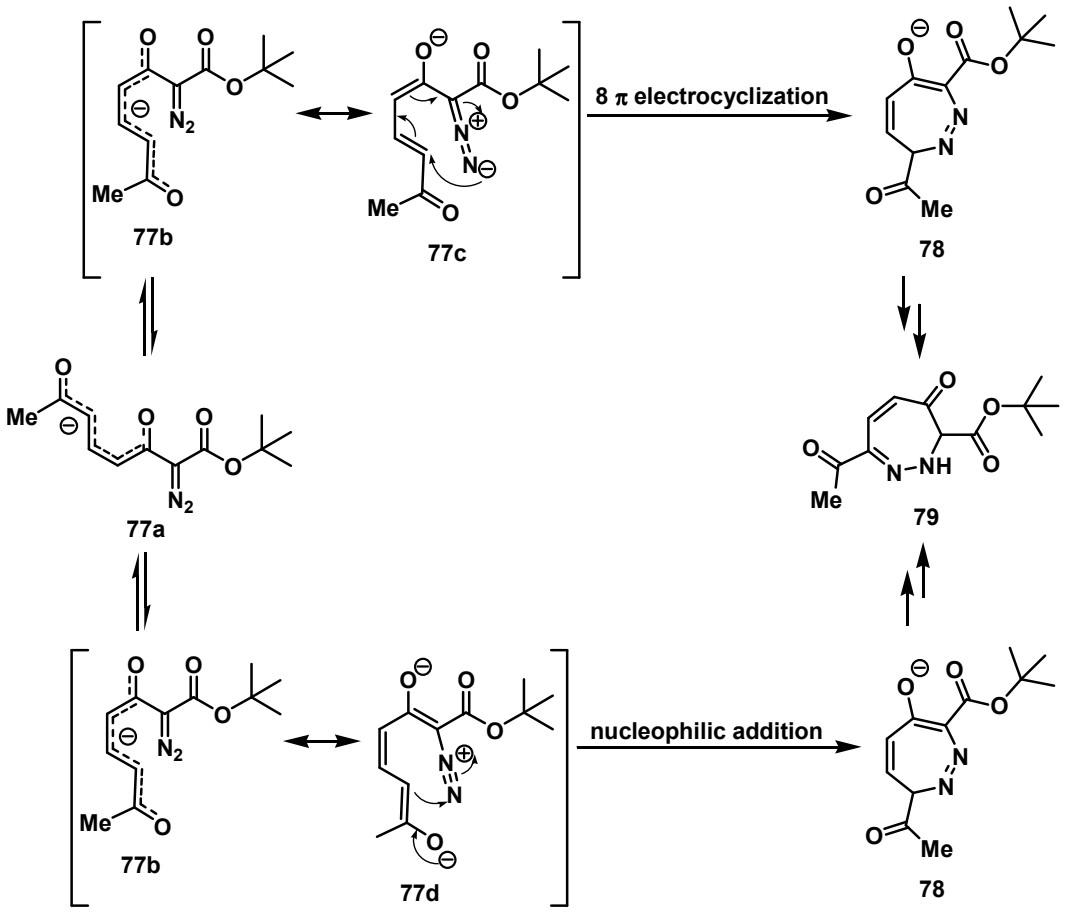

The formation of this by-product could be attributed to steric effects of the bulky ester groups: based on the mechanism proposed, the formation of the resorcinol requires the enol/enolate (**68**/**73**) intermediate to wrap up the two ends of the molecule then undergo cyclization. However, with bulky ester group, it becomes difficult to coiling up the molecule due to the steric repulsion of the ester group and the methyl group on the other end of the molecule (Figure 2.9). As a result, the 1,2-diazepine by-product arises.

**Figure 2.9.** Steric Interaction of the Enolate Intermediate.



The mechanism for the formation of the diazepine by-product is described in Scheme 2.15. Once the enolate intermediate **77a** is produced, similar to the resorcinol formation, the isomerization of the double bond first occurs. However, the diene enolate does not adopt *cis* geometry for both double bonds to undergo pericyclization. Instead, the methyl enolate double bond uses a *trans* geometry (**77b**) to avoid the unfavorable steric interaction of the bulky ester group and the enolate methyl group that has been demonstrated in Figure 2.9. In this case an alternative approach for cyclization arises. If this enolate intermediate is recognized as a resonance hybrid **77c**, a 8π-electrocyclization is feasible and this cyclization would afford intermediate **78**. There has been previous example of 8π-electrocyclization involving diazo functionality that we found in the literature: Nemoto *et.al*. reported a 8π electrocyclic reaction of *o*-quinodimethane inlvoving a diazo group that affords 2,3-benzodiazepine derivatives.[39] Alternatively, the formation of **78** could be viewed as a nucleophilc addition of another resonance contributing structure (**77d)**. In this scenario, nucleophilic attack of the enolate to the terminal nitrogen of the diazo group would lead to ring closure. In either case, intermediate **78** would be produced which upon isomerization gives diazepine product **79**.

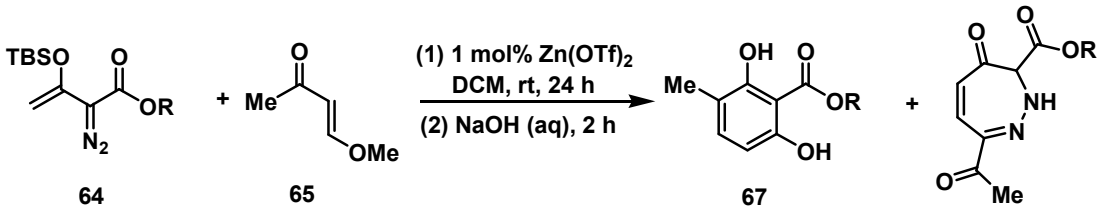
**Scheme 2.15** Proposed Mechanism for the Formation of 1,2-Diazepine By-products.




Other vinyl diazoacetates with bulky ester groups were also evaluated and the results are summarized in Table 2.3. As expected, resorcinol **67** was produced as the major product while diazepines **79** appeared as the minor product in all cases. The amount of sodium hydroxide required to achieve optimum yield varies: when isopropyl ester is involved, 0.1 equivalent of sodium hydroxide is sufficient, and an increase of sodium hydroxide to 0.2 equivalent causes the yield to decrease slightly (Entry 2 and Entry 3). In contrast, when *tert*-butyl or benzyl esters are used, 0.2 equivalent of sodium hydroxide instead of 0.1 equivalent

turned out to be more effective and gives higher yields (Entry 4 to Entry 7). However, the influence of the amount of sodium hydroxide is modest.

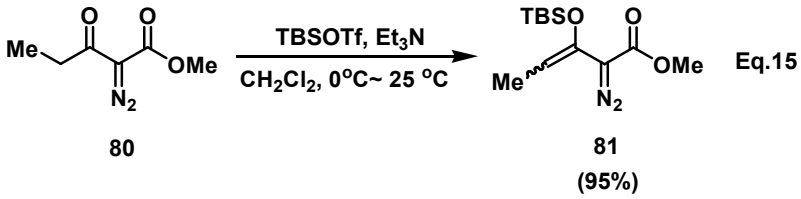
**Table 2.3** Resorcinol Synthesis with Various 3-*tert*-Butyldimethylsiloxy-2-diazo-3-butenoate.




| Entry | | R | equivalents of NaOH | yield of 67+79 (%) | 67:79 |
|---|---|---|---|---|---|
| 1 | a | Me | 0.1 equiv | 83 | - |
| 2 | b | *i*-Pr | 0.1 equiv | 73 | 81:19 |
| 3 | | *i*-Pr | 0.2 equiv | 67 | 79:21 |
| 4 | c | *t*-Bu | 0.1equiv | 68 | 79:22 |
| 5 | | *t*-Bu | 0.2 equiv | 72 | 73:27 |
| 6 | d | Bn | 0.1 equiv | 66 | 71:29 |
| 7 | | Bn | 0.2 equiv | 73 | 67:33 |

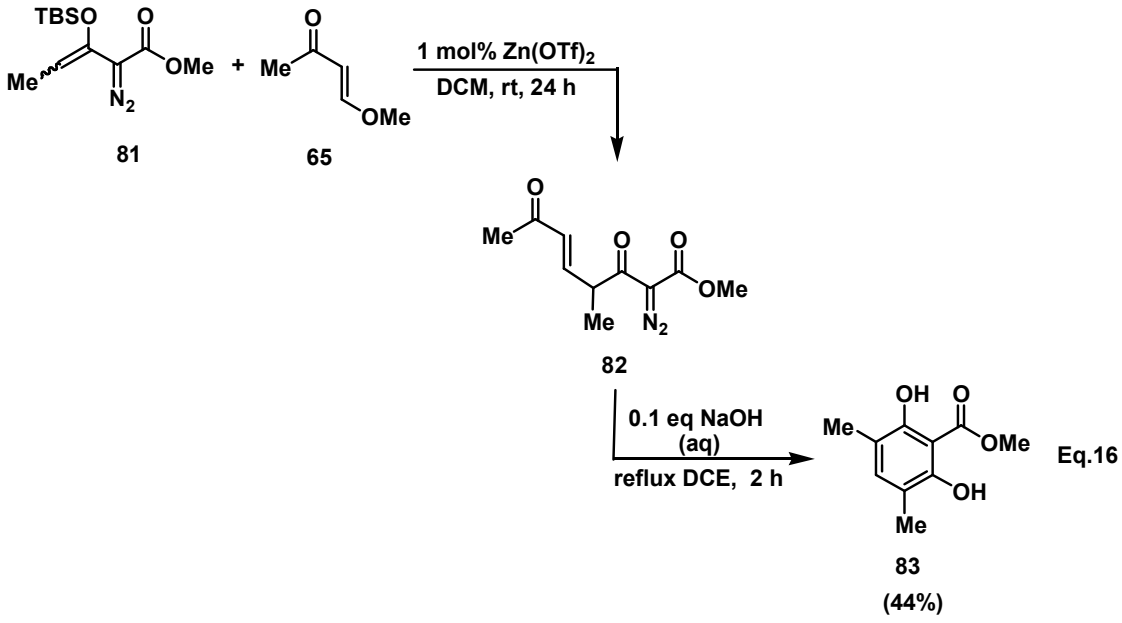
### 2.2.1.3.2 Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazopent-3-enoate and Its Application in Synthesis of Atraric Acid Analog

Methyl 2-diazo-3-oxopentanoate (**80**) was employed to prepare the corresponding vinyldiazoacetate under the reaction conditions described in equation 15. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazopent-3-enoate (**81**) was obtained in good yield. It was obtained as a mixture of two isomers due to the geometry of the double bond and the ratio of these two isomers is about 10:1 based on the integration of the methoxy groups in the products indicated by $^1$H NMR spectroscopy.




80 81 (95%) Eq.15

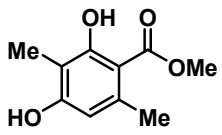
Compound **81** was subjected to reaction with α,β–unsaturated ketone **65**. With 1 mol% $Zn(OTf)_2$ catalyst, the reaction proceeded smoothly at ambient temperature and the starting materials were fully consumed to yield the intended ene-dione diazoester **82** after reacting overnight (observed by $^1H$ NMR). However, the conversion of intermediate **82** to the resorcinol product **83** was sluggish at room temperature, therefore the temperature was raised to 80°C by performing the reaction in refluxing 1,2-dichloroethane. Under these conditions reaction intermediate **82** was able to reach full conversion, and the intended resorcinol product **83** could be produced in moderate yield (Eq. 16).




81 65 82 83 (44%) Eq.16

Resorcinol **83** is a regio-isomer of the natural product atraric acid (**84**) which has the structure illustrated in Figure 2.10. Atraric acid can be extracted from the plant *Pygeum africanum* and it is widely used in the therapy of benign prostate hyperplasia and in combinational therapy for prostate cancer.[40] As a analog of atraric acid, resorcinol **83** also demonstrates similar biological activity and it is applied in the treatment of benign prostate hyperplasia, prostate carcinoma and spinobulbar muscular atrophy.[41]

**Figure 2.10** Natural Product Atraric Acid.

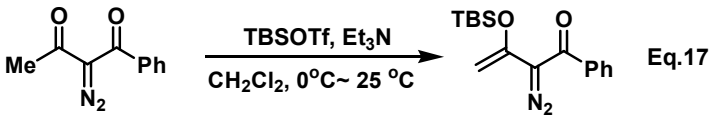



**84**

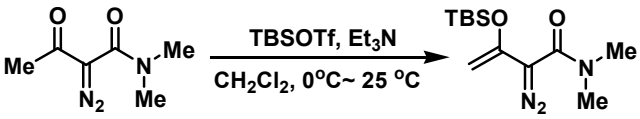
**atraric acid**

### 2.2.1.3.3 Vinyldiazoketone and Vinyldiazoacetamide

Vinyldiazoketone **86** and vinyldiazoacetamide **88** can be prepared by the same protocol that we employed in the synthesis of 3-TBSO-2-diazo-3-butenoate (**64**): Treated with *ter*t-butyldimethylsilyl triflate under basic condtions, 1-phenyl-2-diazo-1,3-butanedione (**85**) and N,N-dimethyl-diazoacetoacetamide (**87**) were converted to the corresponding vinyl diazo compounds in good yields (Eq. 17 and Eq. 18).

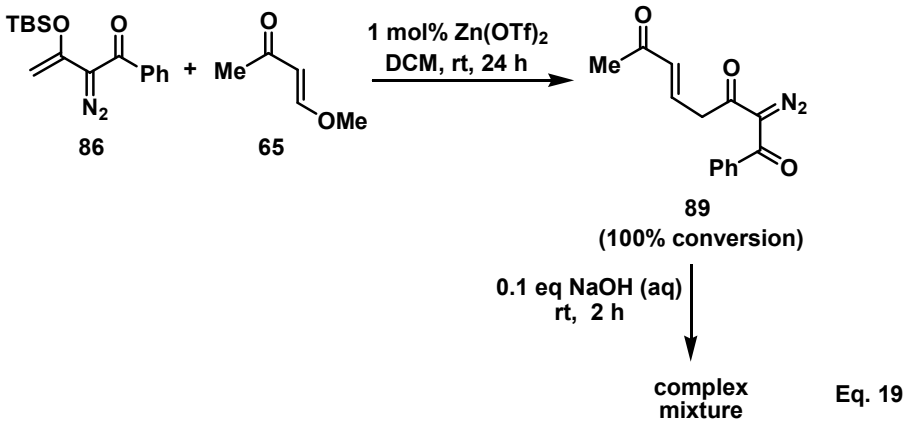



85 86 (77%) Eq.17



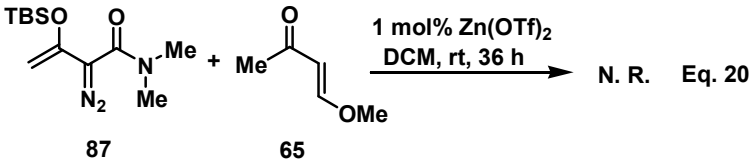

87 88 (86%) Eq.18

When diazo ketone **86** was subjected to reaction with enone **65** catalyzed by zinc(II) triflate, the expected adduct **89** was observed by $^{1}$H NMR spectrum with good conversion. However, this intermediate failed to give any resorcinol product with the addition of catalytic amount of aqueous sodium hydroxide. Based on the proton NMR spectrum of the reaction solution, a complex mixture of products was resulted, and no major product could be identified (Eq.19). This reaction was repeated a couple more times, and the same results were produced, therefore the pericyclization/rearrangement of enedione-diazoketone was not further pursued.




Eq. 19

Vinyldiazoacetamide **88** failed to undergo Mukiayama-Michael addition with substrate **65.** Both substrates remained intact in the reaction mixture even with extended reaction times (Eq.20).

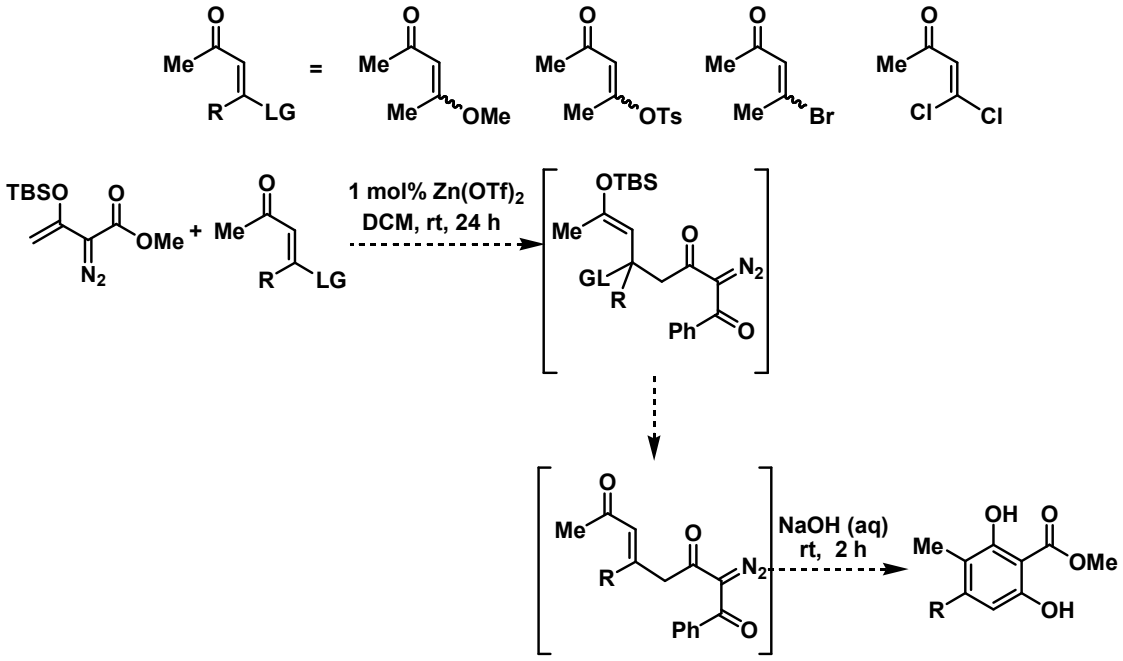



### 2.2.1.3.4 α,β-Unsaturated Ketones

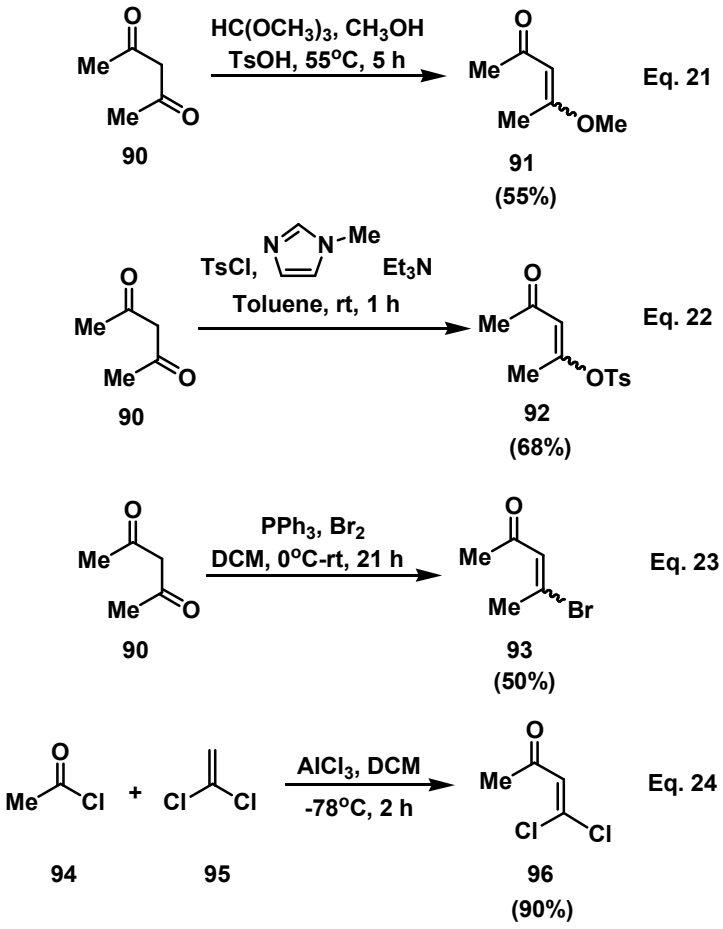
To explore the scope of the reaction with enone substrates, several α,β-undsaturated ketones other than 4-methoxy-3-butene-2-one (**65**) were prepared and subjected to reactions with 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate (**64**) in zinc(II) triflate catalyzed Mukaiyma-Michael reactions.

A few candidate compounds are illustrated in Scheme 2.16. All of these compounds have functional groups that appear as leaving groups (alkoxy, tosylate and halides) attached to the vinyl carbon. Therefore, once the Mukaiyama-Michael adducts are formed with these enone substrates, they would be set up for elimination in the same manner as 4-methoxy-3-butene-2-one (**65**) that is previous employed. What is different from the reaction with substrate **65** is that additional R groups (R = methyl or chloro) would be incorporated to the enedione diazoester intermediates. As a result, if the following cyclization/rearrangement reactions catalyzed by base turn out to be applicable to these enedione diazoesters, resorcinol products with substitutents at the 5-positon on the aromatic ring would be prepared from these reactions.

**Scheme 2.16** Proposed Reaction of α, β-Unsaturated Ketones with Trisubstituted Alkenes.

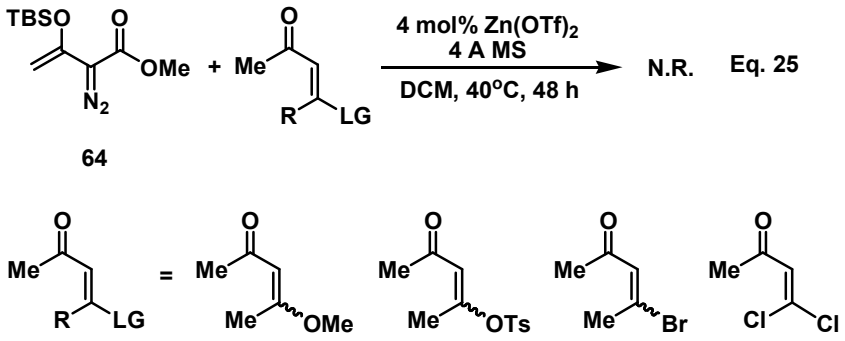



All the enone compounds that are shown in Scheme 2.16 can be accessed by procedures reported in the literature: 4-methoxy-3-penten-2-one (**91**) was made from 2,4-pentadione (**90**) by reaction with trimethyl orthoformate in methanol catalyzed by *p*-toluenesulfonic acid (Eq. 21).[42] Enol tosylate was prepared by coupling acetylacetone (**90**) with tosyl chloride in presence of N-methylimidazole and base (Eq.22).[43] 2-Bromo-4-oxo-pent-2-ene (**93**) was prepared by reacting 2,4-pentadione (**90**) with bromine in presence of triphenyl phosphine (Eq.23).[44] 4,4-dichloro-3-buten-2-one (**96**) was made by reaction of acetic acid chloride (**94**) and 1,1-dichloroethylene (**95**) promoted by aluminum trichloride (Eq. 20).[45]



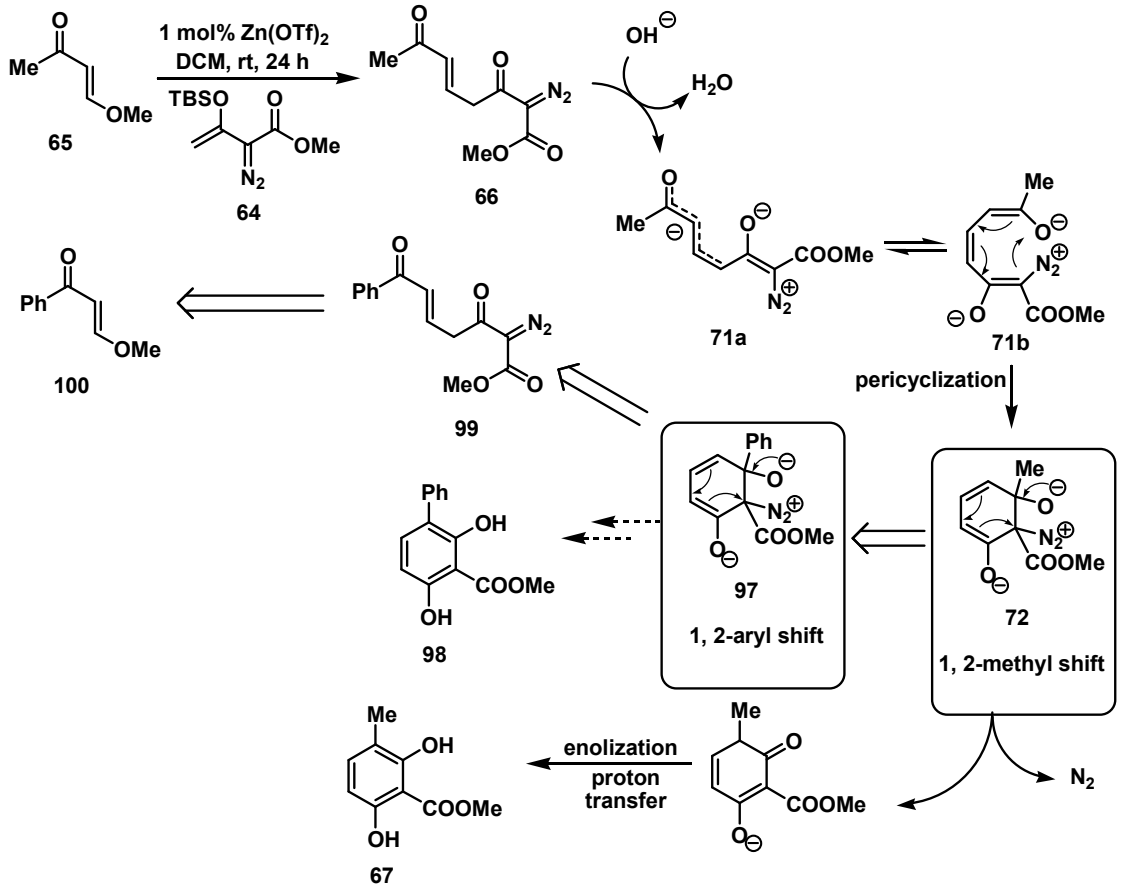

These enone compounds were subjected to reactions with 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate **64** in zinc triflate(II) catalyzed Mukaiyama-Michael reaction but, to our disappointment, in all cases, no addition product could be identified after mixing these reagents and stirring at ambient temperature overnight. Only hydrolysis of the silyl enol ether induced by the hydroscopic Lewis acid catalyst was observed given longer reaction times (24 hours). Replacing the Lewis acid catalyst with $Sc(OTf)_3$ or changing the TBS group to a less bulky TMS group showed no influence to the reaction and no desired product could be observed. Performing these reactions with higher catalyst loading (4 mol%) or at higher temperature (40°C oil bath) only

accelerated the decomposition of the vinyl ether substrate **64** and no intended addition products were produced under these conditions. We were able to prevent the hydrolysis of the silyl enol ether by adding 4 Å molecular sieves to the reaction so the vinyldiazoacetate would not decompose significantly when a large amount of zinc(II) trilfate catalyst is applied or higher temperature is involved. In our last attempt, the reactions of vinyldiazoacetate **64** and these enone compounds were performed with 4 mol% of zinc triflate catalyst and 100 mg 4 Å molecular sieves and then heated with 40$^{o}$C oil-bath for 2 days. $^{1}$H NMR spectra of the reaction mixture at that point still showed no sign of the intended adduct. Both vinyldiazoacetate **64** and the enone substrates remained in the reaction mixture (Eq. 25).




Without success with this type of β,β- disubstituted methyl vinyl ketone as substrates, we turned to other α,β–unsaturated ketones that could potentially be involved in the Muakiyama addition followed by the pericyclizaiton/rearrangement. In the reaction mechanism we proposed(Scheme 2.12), one key step is the 1,2-methyl shift coupled with nitrogen extrusion. We would like to see if we replace the methyl ketone motif with a phenyl ketone, whether a 1,2-aryl shift would also be feasible to afford the corresponding resorcinol product (Scheme 2.17).

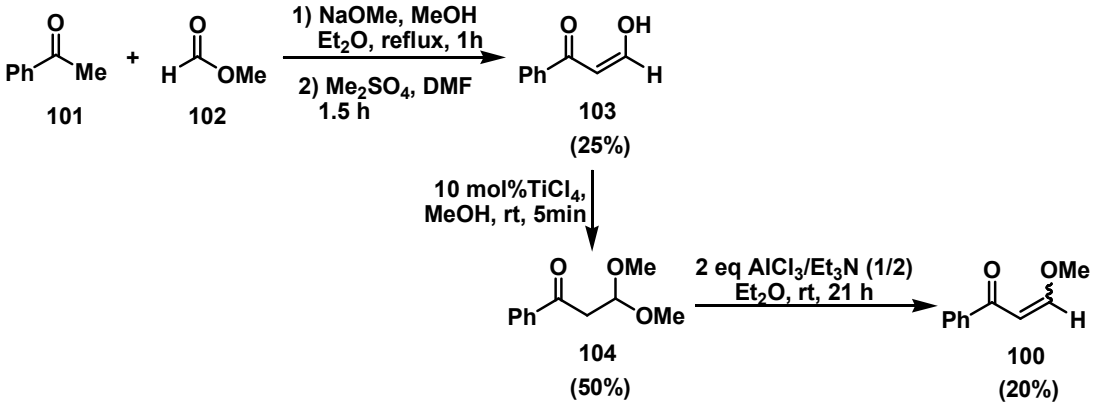
**Scheme 2.17**. Proposed Mechanism Using Enone Substrate (**100**) for 1,2-aryl shift.



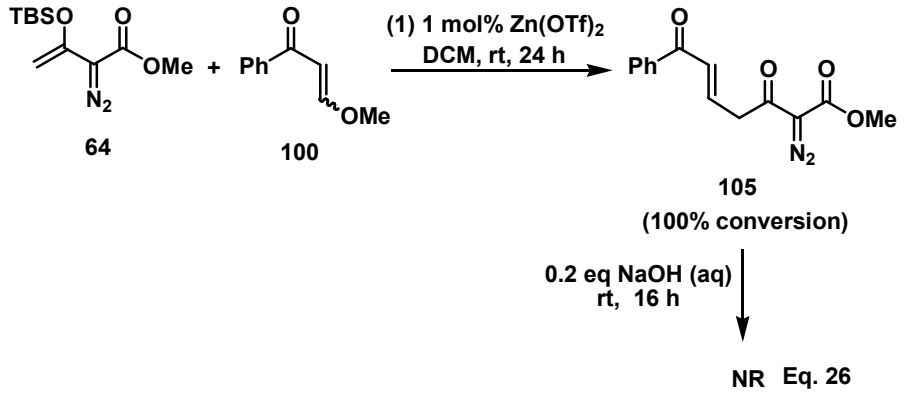

To test this idea described in Scheme 2.17, 3-methoxy-1-phenylprop-2-en-1-one (**100**) needed to be employed in the Mukaiyama-Michael reaction. Enone **100** was not commercially available but it could be prepared by a three-step synthesis described in Scheme 2.18: reaction of acetophenone and methyl formate gave 1,3-dicarbonyl compound **101** in enol form. [46] Intermeidate **102** was then treated with 10 mol% of $TiCl_4$ to afford formylacetophenone dimethyl acetal **103**[47] which, upon elimination in the presence of a mixture of aluminum

trichloride and triethylamine in excess amount, gave the intended enone product **100**.[48]

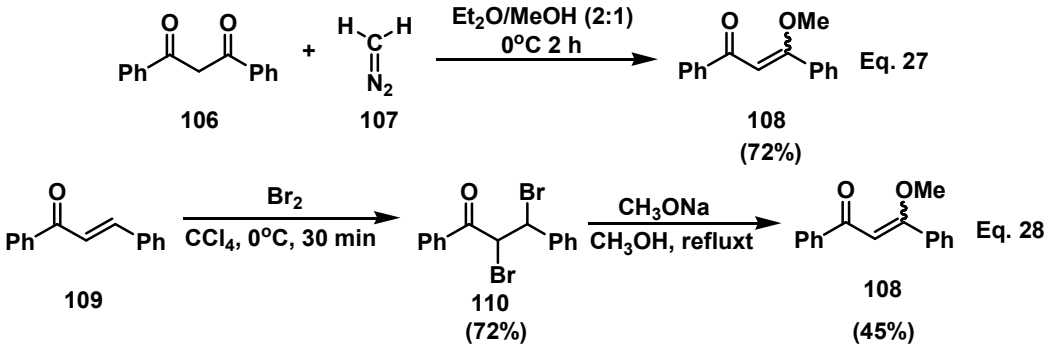
**Scheme 2.18** Synthesis of 3-Methoxy-1-phenylprop-2-en-1-one (**100**).




With enone substrate **100**, the Mukaiyama addition and subsequent elimination worked, and the expected imtermediate **105** was observed by $^{1}$H NMR spectroscopic analysis of the reaction mixture. Compound **100** was fully consumed according to the same proton NMR spectrum. However, when the intermediate thus formed was treated with aqueous sodium hydroxide (0.1 equiv) and stirred at room temperature for two hours, no cyclization product was formed. With extended reaction time (16 hours) and an increased amount of base (0.2 equiv), the $^{1}$H NMR of the reaction mixture after reacting overnight showed that intermediate **105** still existed in large amount and no diagnostic signals that would suggest the formation of the resorcinol products can be observed (Eq.26). Since no indication of reaction was obtained, this reaction was not further investigated.



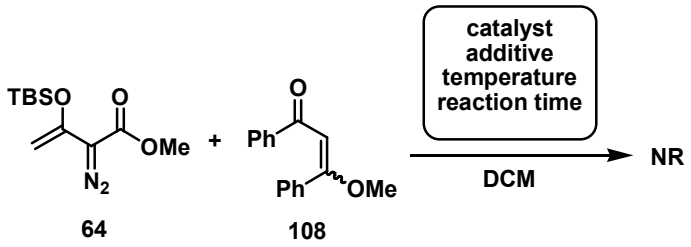

β–Methoxychalcone (**108**) was also considered as a candidate to react with 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate. This enone compound can be prepared by methylation of dibenzoylmethane (**106**) with an excess amount of diazomethane (Eq.22).[49] This method was employed to make one batch of β–methoxychalcone on small scale (4 mmol). In order to avoid the usage of hazardous reagent diazomethane on a large scale, compound **108** was prepared by an alternative method. As is shown in equation 28, bromination of chalcone followed by reaction with sodium methoxide in refluxing methanol afforded β–methoxychalcone in moderate yield.[50]




We were disappointed to find that β–methoxychalcone (**108**) failed to react with vinyl 3-*tert*-butyldimethylsiloxy-2-diazo-butenoate (**64**). Just like the β,β-

disubstituted methyl vinyl ketones (**91-93**) that have been discussed earlier, no Mukaiyama adduct was produced under various conditions (Table 2.4).

**Table 2.4** Various Reaction Conditions Evaluated for Mukaiyama-Michael Reaction of Vinyldiazoacetate **64** and β–Methoxychalcone.




64 108

| Entry | catalyst | additive | temperature | reaction time |
|---|---|---|---|---|
| 1 | 1 mol% $Zn(OTf)_2$ | - | rt | 24 h |
| 2 | 1 mol% $Sc(OTf)_3$ | - | rt | 24 h |
| 3 | 4 mol% $Zn(OTf)_2$ | - | rt | 24 h |
| 4 | 4 mol% $Zn(OTf)_2$ | - | 40°C | 24 h |
| 5 | 4 mol% $Zn(OTf)_2$ | 4 A MS | 40°C | 48 h |

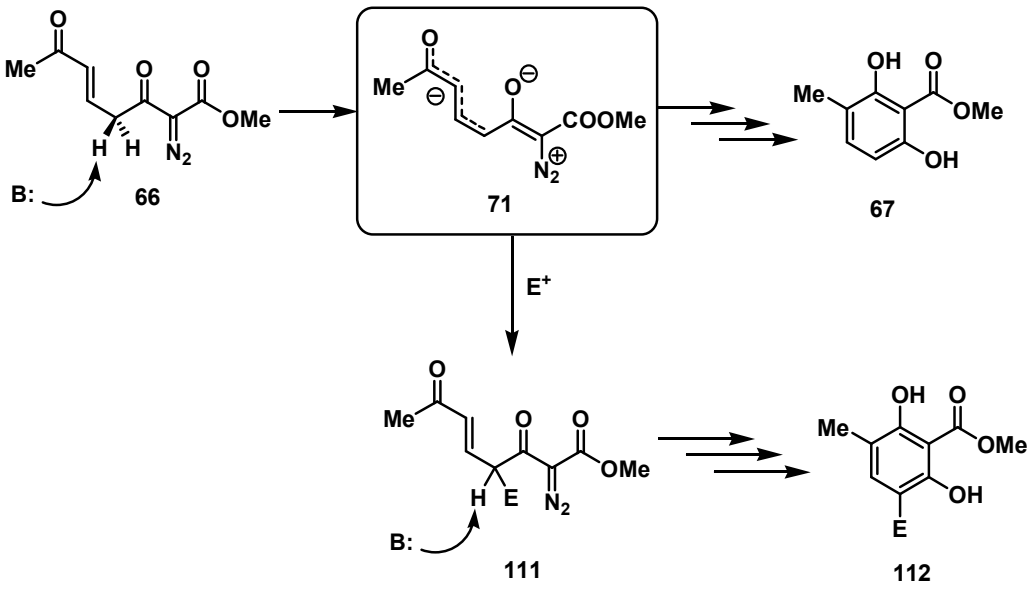
Efforts have been made to explore the substrate scope of α,β–unsaturated ketones in the resorcinol synthesis. Unfortunately, all the enone compounds that have been investigated thus far failed to undergo the expected transformation. Either the Mukaiyama-Michael addition catalyzed by triflate salt or the pericyclization/rearrangement promoted by base is problematic for these enone substrates. 4-methoxy-3-buten-2-one is the only substrate suitable to carry out this reaction we have discovered at this stage. The limited substrate scope of the enone substrate is a limitation of this methodology.

### 2.2.2 Synthesis of 2,6-Dihydroxyl-4-substituted-5-methylbenzoate

#### 2.2.2.1 Opportunity for Extension of the Resorcinol Synthesis Based on Mechanistic Analysis

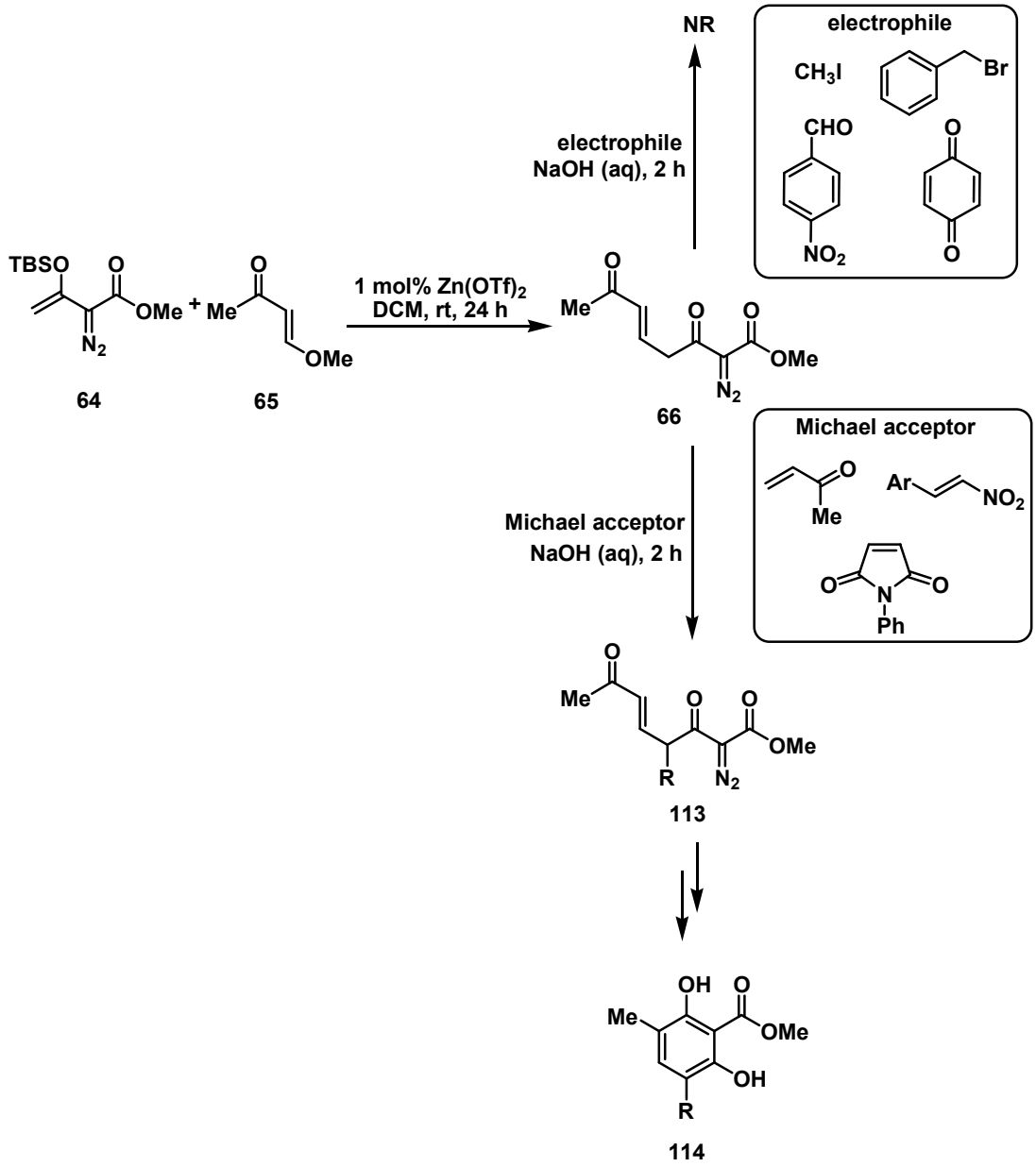
Since we were not able to extend this resorcinol synthesis simply by switching to other α,β–unsaturated ketones as substrates, we decided to seek other means to advance this chemistry. We reexamined the reaction mechanism for the resorcinol formation depicted in Scheme 2.12 and came up with an idea to elaborate this transformation by reacting enolate intermediate **71** derived from enedione-diazoester **66** with electrophiles (Scheme 2.19). Enolate intermediate **77** should be relatively stable due to conjugation but it should also be nucleophilic, similar to acetylacetonate which has been reported to react with methyl acrylate as eletrophile under basic conditions.[51] Therefore, we thought it may be possible to intercept enolate intermediate **77** with electrophilic reagents ($E^+$ in Scheme 2.19). Adduct **111** derived from this reaction would suggest the exsitence of the enolate intermediate. Moreover, this reaction would lead to enedione diazoester compounds that contain additional functional group compared to diazoester **66** that was previously used in the resorcinol synthesis. If the follow-up pericyclization reaction would also occur under the same basic conditions, the overall transformation could produce poly-substituted resorcinol **112**.

**Scheme 2.19** Proposed Transformation by Intercepting Enolate **71**.




We introduced different electrophilic reagents with a catalytic amount of sodium hydroxide (aq) to the reaction solution after enedione-diazoester (**66**) was produced from the Mukaiyama-Michael reaction (Scheme 2.20). A number of commonly used electrophiic reagents such as methyl iodide, benzyl bromide, *p*-nitrobenzaldehyde and 1,4-benzoquinone failed to provide the expected adduct resulting from the addition of enolate intermediate **71**, and resorcinol **67** was the sole product after reacting at room temperature for 2 hours. However, when methyl vinyl ketone (MVK) was employed, compound **113** that is resulted from the Michael addition of enolate **71** to methyl vinyl ketone was observed.

**Scheme 2.20** Attempts for Intercepting Enolate Intermediate in the Resorcinol Synthesis with Different Electrophiles.




The formation of diazoester **113** suggests that it is indeed possible to intercept reaction imtermediate enolate **71** with appropriate electrophiles, and this

observation therefore opened the door for further elaboration of this chemistry. We have discovered other Michael acceptors such as *N*-phenylmaleimide and β-nitrostyrenes react with enolate **71** as well**.** The results from these reactions are discussed in the following sections in detail.

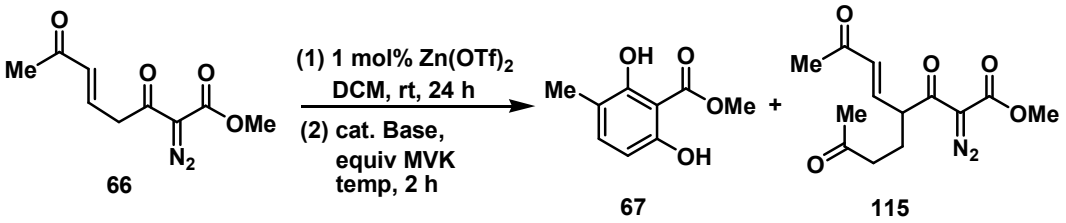
### 2.2.2.2 Methyl Vinyl Ketone as Electrophile

Methyl vinyl ketone is able to trap the enolate intermediate that is present during the formation of resorcinol. After the formation of the enedione-diazoester **66**, addition of methyl vinyl ketone followed by a catalytic amount of base (0.1 equiv sodium hydroxide in aqueous solution) produced the Michael addition product **115** at room temperature for 2 hours. Unlike diazoester **66** which decomposes in contact with silica gel, the Michael addition product **115** was sufficiently robust to survive silica gel purification. However, a small amount (2%) of 2,6-dihydroxyl-4-(2-oxo)-butyl-5-methylbenzoate (**116**) that is derived from diazoester **115** was also isolated after column chromatography, indicating that a small portion of enedione diazoester **115** might also be lost during purification by silica gel chromatography.

Reaction of enedione diazoester **66** (which was made by Mukaiyama-Michael addition of vinyl diazoaceate **64** and enone **65**) and MVK is optimized under various conditions, and the results are summarized in Table 2.5. In most cases, the intramolecular pericyclization/rearrangement appeared to be a competitive reaction pathway to the intended intermolecular Michael addition with methyl vinyl ketone. As a result, resorcinol **67** was produced as by-product after these

reactions. With 0.1 equivalent sodium hydroxide (aq) and 2 equivalents of MVK, enedione-diazoester **66** produced resorcinol **67** and diazoester **115** in 60:40 ratio (Entry 1). Increasing the amount of sodium hydroxide to 0.2 equivalent favors the formation of resorcinol **67** rather than the desired Michael adduct **115** (Entry 2). The ratio of the Michael adduct and resorcinol by-product is also influenced by the amount of MVK involved: Using 4 equivalents of MVK (Entry 3) instead of 2 equivalents (Entry 1) improved the product ratio from 60: 40 in favor of the resorcinol product to 41:59, where the Michael adduct **115** became the major product. A further increase in the amount of MVK however, did not alter the ratio any further (Entry 4). The most important discovery made during the optimization is that there is a dramatic temperature effect associated with this reaction: performing the reaction in a $0^{o}C$ ice-bath gave the Michael addition product almost exclusively (Entry 5). By contrast, when the reaction was carried out in an oil bath at $40^{o}C$, the ratio of adduct **115** to resorcinol decreased significantly (Entry 6).

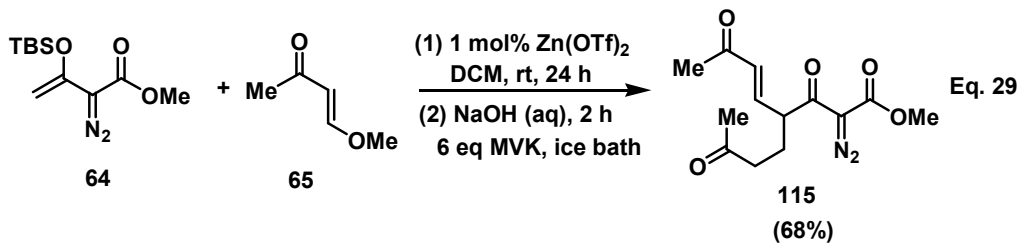
**Table 2.5** Reacitons of Enedione-diazoeser **66** with Methyl Vinyl Ketone (MVK) under Various Conditions.



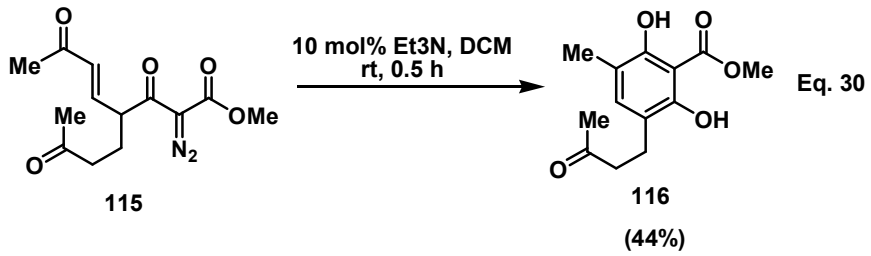

| Entry | base | equiv MVK | temp | yield of 67(%) | yield of 115(%) | ratio 67 : 115 |
|---|---|---|---|---|---|---|
| 1 | 0.1 eq NaOH (aq) | 2 | rt | 38 | 25 | 60: 40 |
| 2 | 0.2 eq NaOH (aq) | 2 | rt | 54 | 18 | 75 : 25 |
| 3 | 0.1 eq NaOH (aq) | 4 | rt | 22 | 32 | 41 : 59 |
| 4 | 0.1 eq NaOH (aq) | 6 | rt | 24 | 34 | 42 : 58 |
| 5 | 0.1 eq NaOH (aq) | 6 | 0°C | 4 | 69 | 5 : 95 |
| 6 | 0.1 eq NaOH (aq) | 6 | 40°C | 49 | 19 | 72 : 28 |

*** Yields and product ratio are determined based on internal standard in the reaction mixture**

Employing the optimum conditions from Table 2.5, Entry 5, we reacted enedione diazoester **66** with 6 equivalents of MVK under base catalysis. After reacting in a 0°C ice-bath for 2 hours, the reaction mixture was concentrated and purified by flash column chromatography with fast air flow on a small column to minimize exposure of the desired product to silica gel. In this way, the Michael addition product was obtained in 68% isolated yield (Eq. 29).

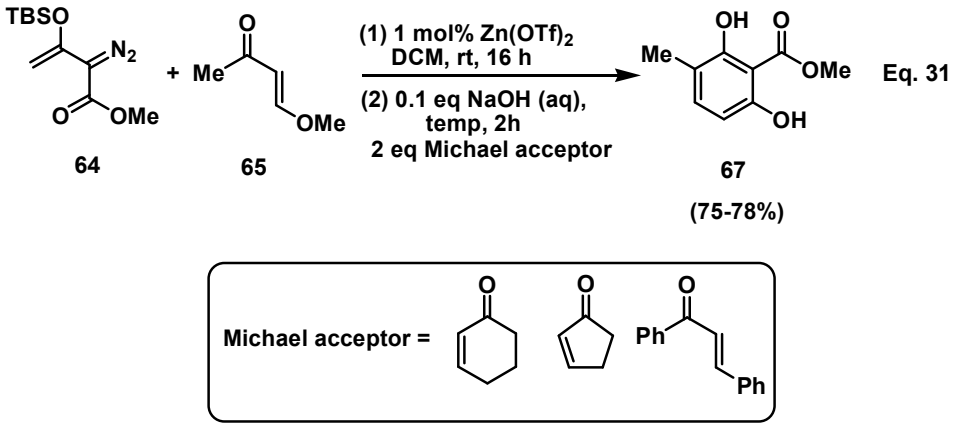


When treated with 5 mol% triethylamine in DCM, compound **115** was converted to resorcinol **116** in 45% isolated yield (Eq. 30). Besides the desired resorcinol product **116**, the $^{1}$H NMR spectrum of the reaction mixture suggested that by-products were also produced under this reaction condition. However, no other material could be isolated other than compound **116** after purification by chromatography on silica gel. Meanwhile, in another experiment, the reaction mixture was concentrated and dissolved in deuterated chloroform. Upon addition of small amount (10 mol%) of trifluoroacetic acid to the solution, $^{1}$H NMR spectrum showed that signals of the by-products disappeared completely in a short period (30 minutes). These results suggest that the by-products might be rather sensitive therefore they could have decomposed during purification.




Eq. 30

Other α,β–unsaturated ketones that are widely used as Michael acceptors such as cyclohexenone, cyclopentenone or chalcone failed to react with enedione diazoester **66** in presence of 0.1 equivalent of sodium hydroxide (aq), and resorcinol **67** was the only product obtained in all three cases (Eq.31).

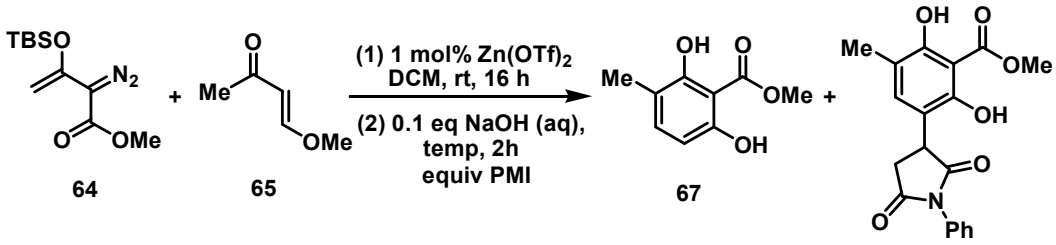



### 2.2.2.3 *N*-Phenylmaleimide as Wlectrophile

*N*-Phenylmaledimide (PMI) is a good electrophile due to the presence of two electron withdrawing carbonyl groups on both sides of the double bond.[52,53] Therefore, PMI was subjected to reaction with enedione-diazoester **66** catalyzed by aqueous sodium hydroxide. The Michael addition between enolate **71** derived from diazoester **66** and *N*-phenylmaleimide indeed occurred. However, the result is different from what we have observed with methyl vinyl ketone as Michael acceptor: the direct Michael adduct that would be a counterpart of compound **115** was not observed and the corresponding resorcinol product **116** was identified instead. What is similar to the reaction with methyl vinyl ketone is that resorcinol **67** was also produced as by-product. Variaous conditions were investigated and the results are summarized in Table 2.6. Increasing the amount of PMI from one equvialent to two improved the ratio of product **116** dramatically (Entry1, Entry 2). However, a further increase of the PMI to 4 equivalents did not alter the ratio of the two products but decreased the yields of the two product combined from 82% to 53% (Entry 3). Unlike the scenario with methyl vinyl ketone, reaction

temperature did not affect the product ratio when PMI was applied (Entry 4, Entry 5): the reaction was performed in both 0°C ice-bath and 40°C oil bath but similar yields and product ratios were obtained in these cases compared to the reaction at room temperature. Increasing the amount of sodium hydroxide (Entry 6) did increase the ratio of product **116** but the yield of the reaction dropped significantly (only 27% combined yield). Switching to triethyamine as base (Entry 7) and perform the reaction under homogeneous condition failed to improve the results.

**Table 2.6** Reacitons with *N*-Phenylmaleimide as Michael Acceptor under Various Conditions.




| Entry | base | equiv PMI | temp | yield of 67(%) | yield of 117(%) | ratio 67 : 117 |
|---|---|---|---|---|---|---|
| 1 | 0.1 eq NaOH (aq) | 1 | rt | 63 | 20 | 75 : 25 |
| 2 | 0.1 eq NaOH (aq) | 2 | rt | 42 | 40 | 52 : 48 |
| 3 | 0.1 eq NaOH (aq) | 4 | rt | 26 | 27 | 49 : 51 |
| 4 | 0.1 eq NaOH (aq) | 2 | 0°C | 39 | 39 | 50 : 50 |
| 5 | 0.1 eq NaOH (aq) | 2 | 40°C | 28 | 26 | 57 : 43 |
| 6 | 0.2 eq NaOH (aq) | 2 | rt | 9 | 18 | 32 : 68 |
| 7 | 5 mol% $Et_3N$ | 2 | rt | - | 26 | - |

*** Yields and product ratio are determined based on internal standard in the reaction mixture**

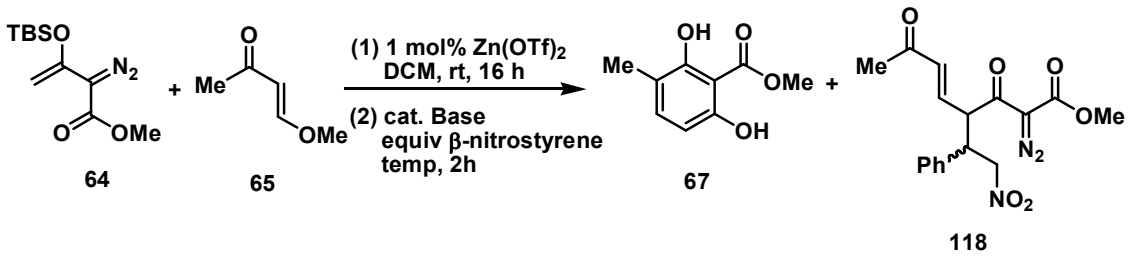
PMI is known to undergo anionic polymerization under basic conditions.[54] Therefore, we suspect that PMI might polymerize under reaction conditions described in Table 2.6 since it was applied in excess amount at high concentration in presence of base. Due to this possible side-reaction that consumes PMI, the intended intermolecular Michael addition would become less efficient, so it could not compete with the intramolecular pericyclization of enedione-diazoester **66**. Therefore, polymerization of PMI might be the problem that renders the Michael addition of PMI and enedione-diazoester **66** not be able to overcome the intramolecular pericyclization reaction of enedione-diazoester **66.**

#### 2.2.2.4 β-Nitrostyrene as Electrophile

β-Nitrostyrenes are good electronphiles due to the strong electron-withdrawing nature of the nitro group.[55] They appear to be more reactive than α,β-unsaturated carbonyl compound in Michael additions.[56] We subjected β-nitrostyrene to reactions with enedione-diazoester **66** derived from the Mukaiyama Michael addition. Upon addition of aqueous sodium hydroxide, the Michael adduct **118** was produced together with resorcinol **67** as by-product. We went on to optimize the reaction conditions, and the results are shown in Table 2.7. Under heterogeneous conditions where sodium hydroxide was employed as base, an increase of β-nitrostyrene from 2 equivalents to 4 equivalents increased the yield of the Michael adduct and its percentage in the product ratio (Entry1, Entry2); but a further increase to 8 equivalents decimated the yield of both product (Entry 3). Temperature showed little influence on the reaction. Similar yields and product ratios were observed when reactions were performed in ice-bath (Entry 4) or

40$^{o}$C oil bath (Entry 5) was applied; Increasing the amount of sodium hydroxide from 0.1 equivalent to 0.2 equivalent led to less resorcinol product; however Michael adduct **118** was produced in a yield that is comparable to what was obtained with 0.1 equivalent of sodium hydroxide (Entry 6). These results with β-nitrostyrene are similar to those that were obtained with *N*-phenylmaleimide: the yield of adduct **118** is only moderate and the resorcinol by-product is always produced. However, when switching from heterogeneous conditions to homogeneous conditions where triethylamine instead of sodium hydroxide was used as the catalyst, a rather different result was obtained: the Michael addition product **118** was isolated in 61% isolated yield and resorcinol **67** was no longer observed (Entry 7). This is very different from what was observed from the reaction with *N*-phenylmaeimde where the reaction under homogeneous condition produced very poor yield of the Michael addition product. What is more, the reaction under homogenous conditions are more economical comparing to reactions under heterogenous conditions since 2 equivalents of β-nitrostyrene is sufficient to afford the Michael adduct in good yield.

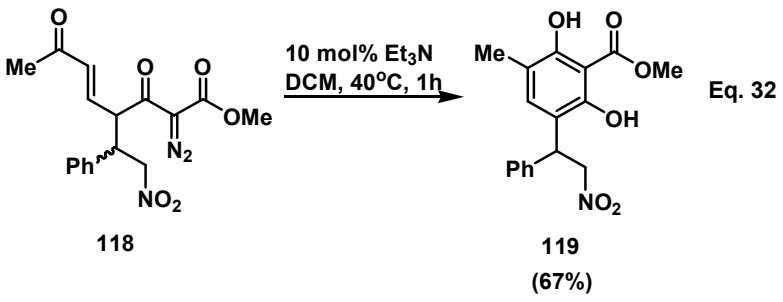
**Table 2.7** Reacitons with β-Nitrostyrene under various conditions.




| Entry | base | equiv | β-nitrostyrene | temp | yield of 67(%) | yield of 118(%) | ratio 67 : 118 |
|---|---|---|---|---|---|---|---|
| 1 | 0.1 eq NaOH (aq) | 2 | | rt | 53 | 27 | 67 : 33 |
| 2 | 0.1 eq NaOH (aq) | 4 | | rt | 44 | 37 | 54 : 46 |
| 3 | 0.1 eq NaOH (aq) | 8 | | rt | 26 | 21 | 55 : 45 |
| 4 | 0.1 eq NaOH (aq) | 4 | | 0°C | 38 | 35 | 52 : 48 |
| 5 | 0.1 eq NaOH (aq) | 4 | | 40°C | 39 | 31 | 55 : 45 |
| 6 | 0.2 eq NaOH (aq) | 4 | | rt | 12 | 38 | 24 : 76 |
| 7 | 5 mol% $Et_3N$ | 2 | | rt | - | 61 | - |

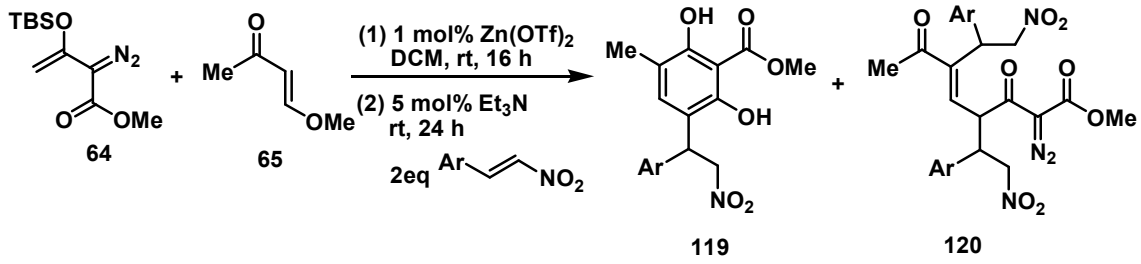
*** Yields and product ratio are determined based on internal standard in the reaction mixture**

The Michael adduct **118** formed with β-nitrostyrene could be converted to the corresponding resorcinol compound **119** when treated with 10 mol% triethylamine (Eq.31). The reaction was sluggish and could not reach full conversion at room temperature. Therefore we raised the reaction temperature, and in $40^0$C oil bath substrate **118** was complete consumed to give **119** in 67% isolated yield.



We then evaluated the substrate scope by changing the aryl group in the nitrostyrene substrate (Table 2.8). Interestingly, In all cases, Michael adducts **118** were partially converted to the corresponding resorcinol **119** after reacting with 5 mol% triethylamine at room temperature. This resorcinol product was not observed when β-nitrostyrene with no substitutent on the aryl group was employed. Furthermore, when the reaction was allowed to run for 24 hours, the Michael adduct were fully consumed and resorcinol **119** became the major product of the reactions. By-product **120** was also isolated at this point. The structure of this by-product is illuminated by 1D and 2 D NMR experiments. (See Experimental Section for details). Nitrostyrenes with electron-withdrawing substituents favor the double addition by-product more compared to those have electron-donating group on the aromatic ring but the difference is rather subtle (Entry 1-Entry 4). At this stage, we reexamined the reaction with β-nitrostyrene with no substituent on the aromatic ring which only gave Michael adduct **118** in 2 hours reaction time (Table 2.7). Given longer reaction time, compound **118b** could also be directly converted to resorcinol **119b** (Table 2.8, Entry 2). What is more, the one-pot reaction provided better yield of resorcinol product **119b** compared the stepwise approach (50% yield compared to 41% combined yield in two steps). Nitrostyrene with heterocycle also gives the corresponding resorcinol product (Entry 5).

**Table 2.8.** Synthesis of 4-(1´-aryl -2´-nitroethyl)-Resorcinols.

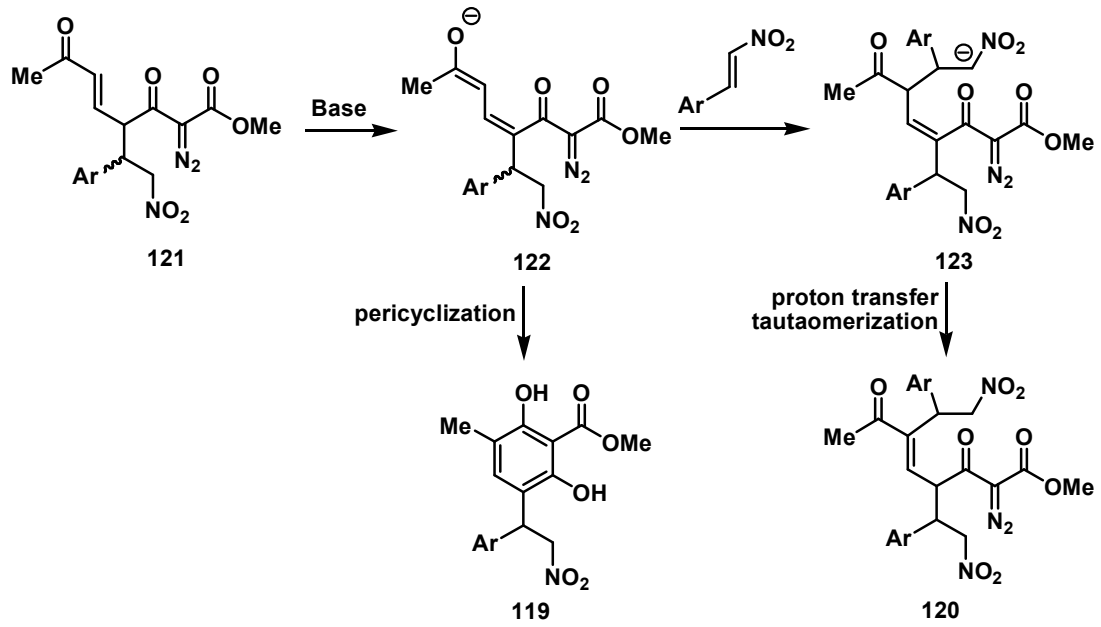



| Entry | Ar | | yield of 119 (%) | yield of 120 (%) | yield of 119+120 (%) | 119:120 |
|---|---|---|---|---|---|---|
| 1 | 4-methoxy-phenyl | a | 56 | 8 | 64 | 87:13 |
| 2 | phenyl | b | 50 | 11* | 61 | 82:18 |
| 3 | 4-fluoro-phenyl | c | 56 | 16 | 72 | 78:22 |
| 4 | 4-trifluoromethyl-phenyl | d | 57 | 17 | 74 | 77:23 |
| 5 | Furyl | e | 63 | 26* | 89 | 71:29 |

*** obtained as a complicated mixture of several isomers**

A reaction mechanism that explains the formation of by-products **120** is depicted in Scheme 2.21. After addition of the first nitrostyrene molecule, reaction intermediate **121** is produced (we were able to isolate this compound when Ar equals to phenyl group). Diazoester **121** can be deprotonated again to give enolate **122** which can undergo pericyclization to afford resorcinol **119** as the major product of this transformation. Meanwhile, aldol condensation of enolate **122** with another molar of nitryostyrene can afford reaction intermediate **123**. Upon tautaomerization and proton transfer, reaction intermediate **123** can be converted to diazoester **120**.

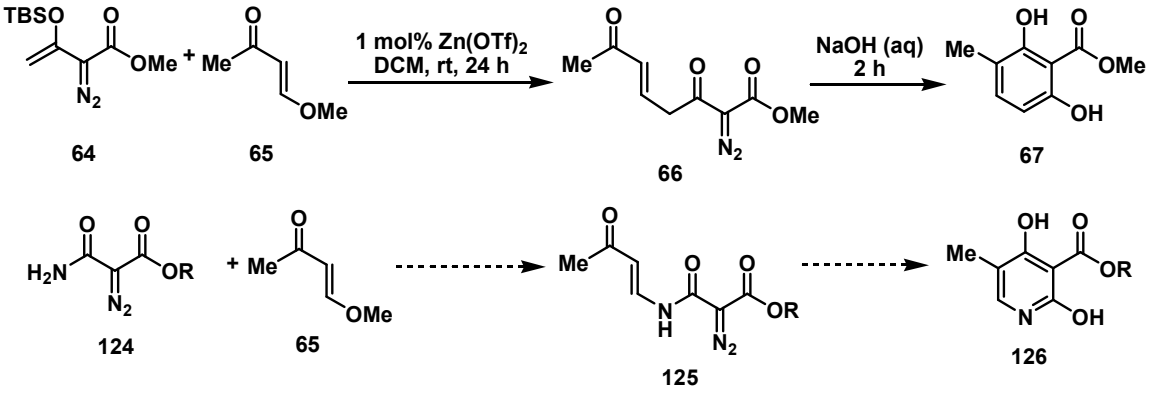
**Scheme 2.21**. Formation of Double Addition By-product **120.**



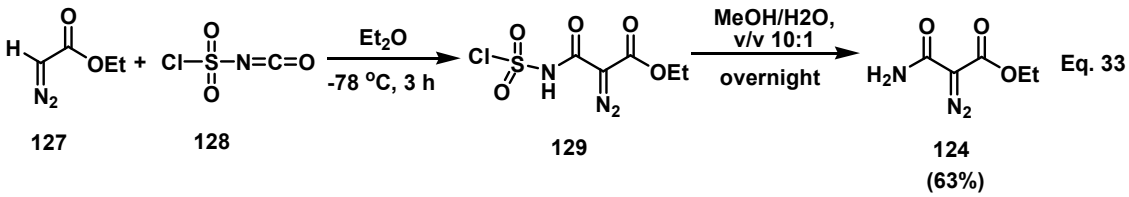

### 2.2.3 Attempt to Synthesize Heterocyclic Compound by Percyclization of Heteroatom Substituted Enedione-diazoester

A heterocycle synthesis inspired by the resorcinol formation from 3-*tert*-butyldimethylsiloxy-2-diazobutanoate (**64**) and 4-methoxy-3-buten-2-one (**65**) is proposed in Scheme 2.22. Replacing the $CH_2$ group in diazoester **66** with a NH group could potentially lead to formation of poly-substituted pyridines given that the pericyclization/rearrangement is applicable to diazoester **125**.

**Scheme 2.22**. Proposed Synthesis of Substituted Pyridine Applying the Pericyclization/ rearrangement of Diazoester **125**.

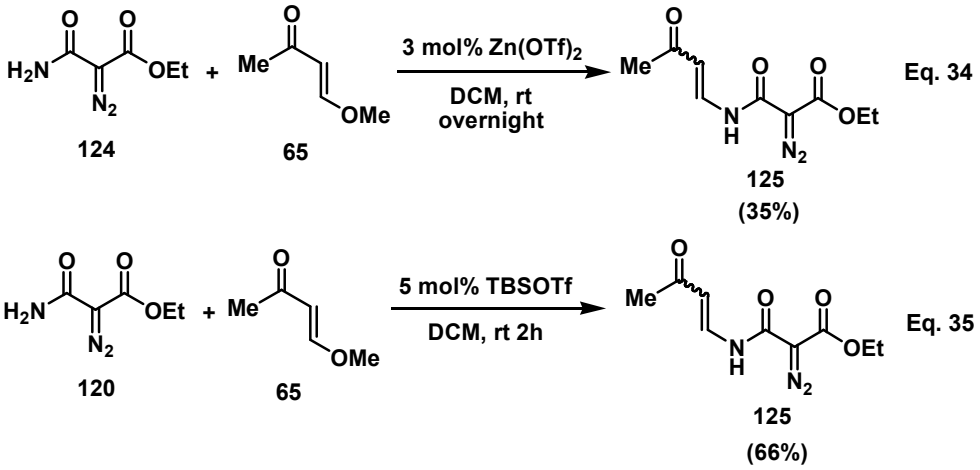



In order to explore this transformation proposed in Scheme 2.22, Ethyl carbamoyl diazoacetate (**124**) need to be synthesized. A procedure reported in the literature[57] employs ethy ldiazoacetate (**127**) to react with chlorosulfonyl isocyanate(**128**) in ether at -78$^{o}$C, and intermediate **129** thus produced is stirred in a methanol/water (10/1) solution overnight to afford the desired diazo compound. We tried this reaction and we were able to prepare β–carbamoyl diazoester **124** in 63% isolated yield by this method (Eq.33).




We subjected diazo ester **124** and 4-methoxy-3-buten-2-one (**65**) to the conditions developed for the Mukaiyama-Michael addition: with 3 mol% zinc triflate as Lewis acid catalyst, these two reagents were stirred at room

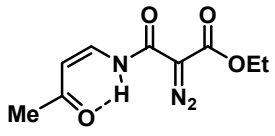
temperature over night. Enone substrate **65** was fully consumed at this point according to $^1$H NMR spectrum. However, the intended adduct **125** was obtained only in 35% yield (Eq.34). We looked for alternative method to prepare the targeted diazoester **125** and discovered a method in the literature in which trialkylsiyl triflate was used to promote an aza-Michael addition of 1$^o$-amide and α,β-unsaturated ketones.[58] We applied the reaction conditions established in this work and to the addition of carbamoyl diazoester **124** and enone **65**. Using this method we were able to synthesize diazoester **125** in 66% yield (Eq.35), which is significantly improved compared to the reaction catalyzed by $Zn(OTf)_2$.




Different from enedione-diazoester **66**, which is a sensitive material that we were not able to obtain after chromatography on silica gel, ethyl 2-(3-oxobut-1-enylcarbamoyl) diazoacetate (**125**) is stable enough to go through silica gel purification without a significant loss of material. What is more, the $^1$H NMR spectrum of compound **125** shows a coupling constant of 8 Hz between the two vinyl protons indicating a *cis* geometry of the alkene double bond. By contrast, a 16 Hz coupling constant between the vinyl protons was observed in the $^1$H NMR

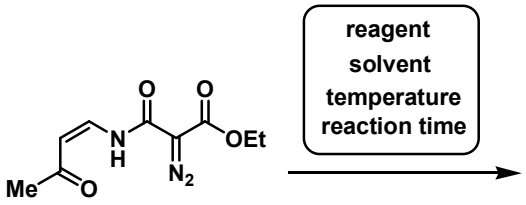
spectrum of compound **66** which predicts the *trans* geometry. One possible explanation for this difference is that in compound **125** takes a *cis* geometry so it can benefit from an intramolecular hydrogen bond (Figure 2.11) while formation of a hydrogen bond is not an option in structure of **66**.

**Figure 2.11** Possible Intramolecular Hydrogen Bond Formation of Diazoester **125**.




We were disappointed to find out that ethyl 2-(3-oxobut-1-enylcarbamoyl) diazoacetate (**125**) was unable to undergo the desired cyclization/rearrangement reaction under various reaction conditions we have tried (Table 2.9). A number of bases such as triethylamine (Entry 1), DBU (Entry 2), sodium hydride (Entry 3) sodium methoxide (Entry 4) were used. However essentially no reaction could be promoted in all cases and the starting material remained in the reaction solution even after mixing for a long periods of time (16 hours overnight). Under acidic conditions (Entry 5-Entry 7), the *trans* isomer of diazoester **125** was formed in various ratios to the *cis* isomer that we started with, but no other product could be identified in the reaction mixture according to $^{1}$H NMR of the reaction mixture.

**Table 2.9**. Various Conditions Attempted to Promote Pericyclization/rearrangement of Diazoester **125**.




**125**

| Entry | reagent | solvent | temperature | Reaction time | result | *cis*:*trans* |
|---|---|---|---|---|---|---|
| 1 | 2eq $Et_3N$ | DCM | 40°C | 2 h | NR | - |
| 2 | 2eq DBU | DCM | 40°C | 16 h | NR | - |
| 3 | 0.5 eq NaH | THF | rt | 16 h | NR | - |
| 4 | 0.5 eq $CH_3ONa$ | $CH_3OH$ | rt | 16 h | NR | - |
| 5 | 2eq $CF_3COOH$ | DCM | 40°C | 2 h | NR * | 79:21 |
| 6 | 0.5 eq 1 N HCl | THF | rt | 16 h | NR * | 83:17 |
| 7 | 0.5 eq *p*-TsOH | DCM | 40°C | 16 h | NR * | 72:28 |

*** isomerization of the alkene double bond was observed.**

## 2.2.4 Summary

We discovered a novel reaction that transforms α–diazo-β-ketoesters to 2-carboalkoxylresorcinols by serendipity. This interesting transformation is unprecedented in the previous literature. We were able to develop this transformation into a synthetic methodology for the preparation of multi-substituted resorcinol compounds. Compared to other concurrent methods for the synthesis of substituted resorcinols, readily accessible starting material and mild reaction conditions are the advantangeous features of this new method. The mechanism for the formation of these resorcinol products, which features a pericyclic reaction of a conjugated enolate and 1,2-migaration of methyl group in

concert with loss of nitrogen, is really fascinating because, although the overall transformation is very complicated, the reaction occurs with high efficiency and provides the resorcinol products in good yields. An unexpected 1,2-diazpine by-product derived from vinyldiazoacetate substrates with bulky ester groups was also identified and characterized. The presence of this by-product deomonstrates the versatility of this reaction: with simple modification of the ester groups in one of the substrate, the reaction is able to provide a very different type of product. We further extended this chemistry by trapping the enolate intermediate with different Michael acceptors and the Michael adduct thus formed were then converted to the corresponding resorcinol compounds. Noticeably, when β-nitrostyrenes were employed as Michael acceptor, a highly efficient one-pot synthesis of poly-substituted resorcinol compounds was achieved by sequential addition of reagents. One limitation of this methodology is the scope of the enone substrate. Among all the compounds that were tried, only 4-methoxy-3-butene-2-one was able to undergo this transformation. Efforts have been made to explore the possibility of a heterocyclic version of this transformation but diazoester **125** prepared for this purpose failed to undergo the desired transformation. Despite these limitations, this method is a valuable addition to existing methods for construction of resorcinol derivatives.

## 2.3. Experimental Section

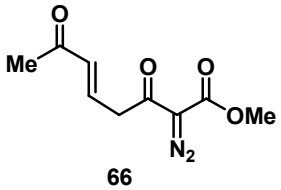
### 2.3.1. General Information

Reactions were performed in oven-dried (140$^{o}$C) or flame-dried glassware. Dichloromethane (DCM) was passed through a solvent column prior to use and was not distilled. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 $F_{254}$ plates. The developed chromatogram was analyzed by UV lamp (254 nm) or bys staining of phosphomolybdic acid (PMA) ethanol solution. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated system on silica gel (230-400 mesh). Metal triflate salts were purchased from Aldrich and used as received. *trans*-4-Methoxy-3-buten-2-one (90%) was purchased from Acros or Aldrich and used as received. All TBSO-substituted vinyldiazoesters were prepared by the method described by Ueda.[59] All other commercially available reagents were used as received unless otherwise mentioned.

NMR spectra were measured on Bruker AV-400 ($^{1}$H at 400 MHz, $^{13}$C at 100 MHz). $^{1}$H NMR spectra were recorded **with tetramethylsilane (TMS) (0.00 ppm) as the internal standard.** Data are reported as follows: chemical shift (in ppm, δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet, comp = composite) and coupling constants (in Hz). $^{13}$C NMR spectra were obtained **with complete proton decoupling. Chemical shifts are reported in ppm utilizing $CDCl_3$ peak as a reference (77.0 ppm).** High resolution mass spectra (HRMS) were recorded by JEOL Accu

TOF-CS (ESI, positive mode). Infrared (IR) spectra were measured on a JESCO FT/IR-4100 instrument.

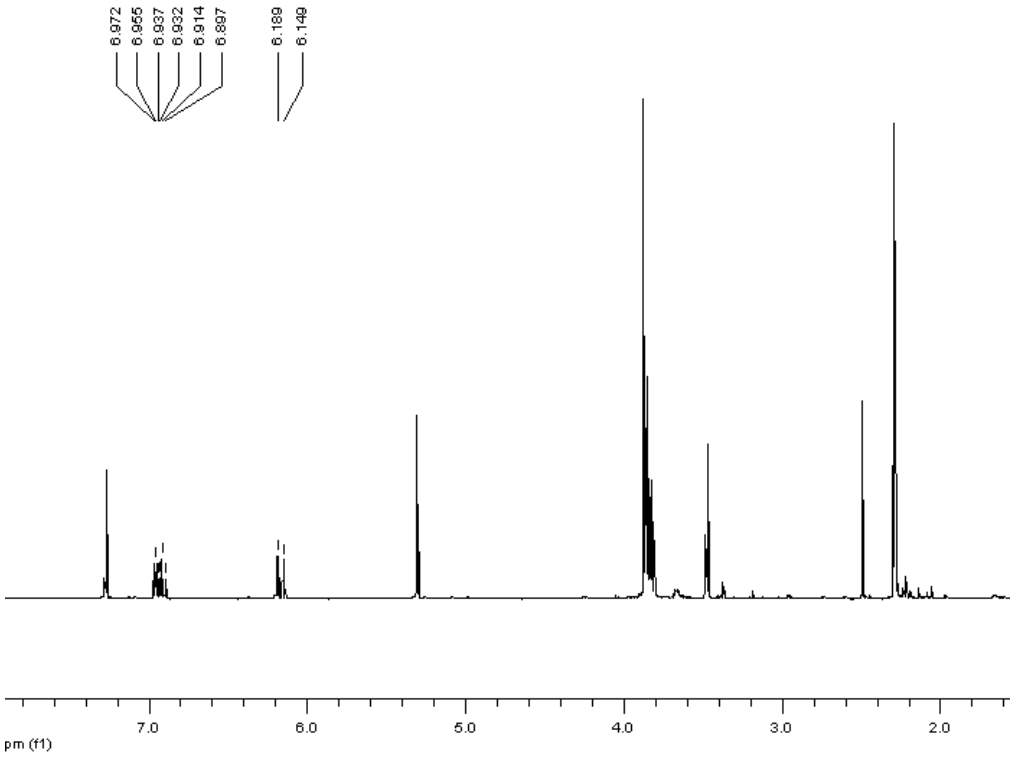
### 2.3.2 Procedure for Mukaiyama-Michael Addition and In-situ Elimination that Affords methyl 3,7-dioxo-2-diazo-(*E*)-oct-5-enoate (66)



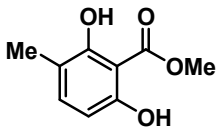

**66**

To an oven-dried 4 dr vial under nitrogen was added zinc triflate (4 mg, 0.01 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (103 mg, 0.930mmol) and 4 mL of dry DCM. The mixture was stirred at 0$^{o}$C. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64**) (307 mg, 1.20 mmol) was added via syringe all at once. The yellow solution was stirred vigorously and slowly warmed to room temperature. After 16 hours the crude reaction mixture was concentrated under reduced pressure. At this point substrate **64** was fully consumed and methyl 3,7-dioxo-2-diazo-(*E*)-oct-5-enoate (**66**) was produced, as indicated by a $^{1}$H NMR spectrum of the reaction mixture (Figure 2.12). The E-geometry was also established by NMR: a 16 Hz coupling constant of the vinyl protons indicates *trans* geometry of the double bond.

**Figure 2.12** $^{1}$H NMR Spectrum of Reaction Mixture with Enedione-diazoester 66 as the Major Specie.



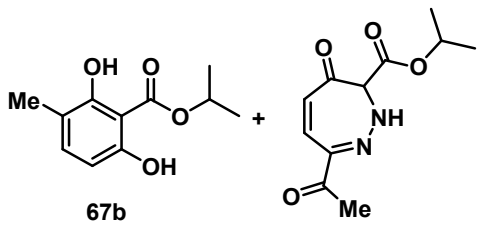

### 2.3.3 Procedure for the Synthesis of 2,6-Dihydroxy-3-methylbenzoate (67) and 7-Acetyl-3,4-dihydro-4-oxo-2H-1,2-diazepine-3-carboxylate(79)




**67a**

**Synthesis of methyl 2,6-dihydroxy-3-methylbenzoate(67a).** To a 4 dr vial was added methyl 3,7-dioxo-2-diazo-(*E*)-oct-5-enoate(**66**) from the Mukaiyama-Michael addition and in-situ elimination step without purification, followed by 2 mL of DCM and 1.0 mL 0.10 mol/L NaOH aqueous solution (0.10 mmol). The

reaction mixture was stirred vigorously at room temperature. After stirring for two hours, a deep red aqueous phase and a yellow organic phase was formed. The organic phase was removed by pipette and was flashed through a short silica plug to remove water. The resulting solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give 141 mg of a pale yellow liquid as product **67a** (0.77 mmol, 83% yield). **67a:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.06 (br, 1H), 9.30 (br, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 4.07 (s, 1H), 2.14 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 158.6, 158.5, 137.4, 116.6, 107.2, 99.5, 52.7, 15.2; IR (neat): 3430, 3129 (br), 2960, 2922, 1674, 1634, 1599 cm$^{-1}$; HRMS (ESI) for $C_9H_{11}O_4$ $[M+H]^+$ calcd 183.0658; found 183.0666.




67b 79b

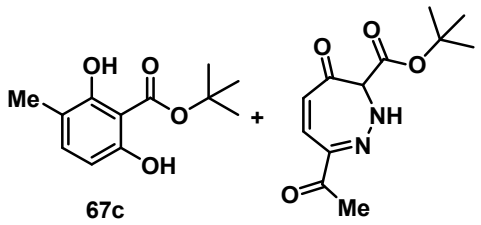
**Synthesis of isopropyl 2,6-dihydroxy-3-methylbenzoate(67b) and isopropyl (1E,5Z)-7-acetyl-3,4-dihydro-4-oxo-2H-1,2-diazepine-3-carboxylate(79b).** To an oven-dried 4 dr vial under nitrogen was added zinc triflate (4 mg, 0.01 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (103 mg, 0.930mmol) and 4 mL of dry DCM. The mixture was stirred at 0$^{o}$C. Isopropyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64b**) (341 mg, 1.20 mmol), which was prepared according to the procedure previously reported by Ueda,[59] was

added via syringe all at once. The yellow solution was stirred vigorously and slowly warmed to room temperature. After 16 hours the crude reaction mixture was concentrated under reduced pressure. At this point substrate **65** was fully consumed and intermediate isopropyl 3,7-dioxo-2-diazo-(*E*)-oct-5-enoate(**66b**) was produced, as indicated by a $^{1}$H NMR spectrum of the reaction mixture. To a 4 dr vial was added **66b** and 2.0 mL DCM, followed by 1.0 mL 0.20 mol/L NaOH aqueous solution (0.20 mmol). The reaction mixture was allowed to react at room temperature and was stirred vigorously. After stirring for 2.0 hours, a deep red aqueous phase and a yellow organic phase was formed. The organic phase was removed by pipette and filtered through a short silica plug to remove small amount of water. The resulting solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give a pale yellow liquid as product **67b** (59% yield). Then the eluent was switched to 1:4 EtOAc/hexane to elute product **79b** (14% yield) as a reddish yellow oil.

**67b:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.19 (br, 1H), 9.57 (br, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.46 (sept, *J* = 4.0 Hz, 1H), 2.14 (s, 3H), 1.48 (d, *J* = 4.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.6, 158.7, 158.6, 137.5, 116.4, 107.1, 99.8, 71.3, 22.0, 15.2; IR (neat): 3436, 3139 (br), 2983, 2929, 1666, 1632, 1599 $cm^{-1}$; HRMS (ESI) for $C_{11}H_{15}O_4$ $[M+H]^+$ calcd 211.0971; found.211.0980.

**79b:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.14(br, 1H), 7.60 (d, *J* = 12.0 Hz, 1H), 6.74(d, *J* = 12.0 Hz, 1H), 5.27 (sept, *J* = 4.0 Hz, 1H), 4.12 (d, *J* = 4.0 Hz, 1H), 2.45 (s,

3H), 1.38 (d, *J* = 4.0 Hz, 3H), 1.32 (d, *J* = 4.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.5, 176.2, 165.0, 140.2, 133.4, 130.0, 71.5, 68.3, 25.0, 21.7, 21.7; IR (neat): 3288(br), 2982, 2939, 1737, 1669 cm$^{-1}$; HRMS (ESI) for $C_{11}H_{15}N_2O_4$ $[M+H]^+$ calcd 239.1032; found 239.1029.



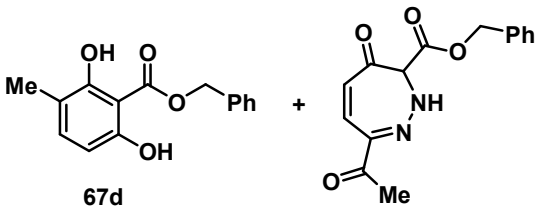

67c 79c

**Synthesis of *tert*-butyl 2,6-dihydroxy-3-methylbenzoate(67c) and *tert*-butyl (1*E*,5*Z*)-7-acetyl-3,4-dihydro-4-oxo-2H-1,2-diazepine-3-carboxylate(79c).** To an oven-dried 4 dr vial under nitrogen was added zinc triflate (4 mg, 0.01 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (103 mg, 0.930mmol) and 4 mL of dry DCM. The mixture was stirred at 0$^o$C. *tert*-butyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64c**) (358 mg, 1.20 mmol), which was prepared according to procedure previously reported by Ueda,[59] was added via syringe all at once. The yellow solution was stirred vigorously and slowly warmed to room temperature. After 16 hours the crude reaction mixture was concentrated under reduced pressure. At this point substrate **65** was fully consumed and intermediate *tert*-butyl 3,7-dioxo-2-diazo-(*E*)-oct-5-enoate(**66c**) was produced, as indicated by a $^1$H NMR spectrum of the reaction mixture. To a 4 dr vial was added **66c** from the Mukaiyama-Michael addition and in-situ elimination step without purification and 2.0 mL DCM, followed by 1.0 mL 0.20

mol/L NaOH aqueous solution (0.20 mmol). The vigorously stirred reaction mixture was allowed to react at room temperature. After 2.0 hours a deep red aqueous phase and a yellow organic phase was formed. The organic phase was removed by pipette and filtered through a short silica plug to remove the small amount of water. The resulting solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:15 EtOAc/hexane to give 94 mg of a pale yellow liquid as product **67c** (0.47 mmol, 52% yield). Then the eluent was switched to 1:4 EtOAc/hexane to elute product **79c** (0.18 mmol, 20% yield) as a yellow oil.

**67c:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.27 (br, 1H), 9.71 (br, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 8.0 Hz, 1H), 2.13 (s, 1H), 1.69 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.0, 158.7, 158.6, 137.1, 116.3, 107.1, 100.6, 86.5, 28.4, 15.2; IR (neat): 3395, 3114 (br), 2927, 1665, 1633, 1600 $cm^{-1}$; HRMS (ESI) for $C_{12}H_{17}O_4$ $[M+H]^+$ calcd 225.1128; found 225.1138.

**79c:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.20 (br, 1H), 7.59 (d, *J* = 12.0 Hz, 1H), 6.72 (d, *J* = 12.0 Hz, 1H), 4.02 (d, *J* = 4.0 Hz,1H), 2.45 (s, 3H), 1.56 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.5, 176.4, 164.5, 140.2, 133.4, 130.0, 85.1, 68.4, 28.0, 25.0; IR (neat): 3295, 2980, 2927, 2137, 1739, 1715, 1682, 1662 $cm^{-1}$; HRMS (ESI) for $C_{12}H_{17}N_2O_4[M+H]^+$ calcd 253.1188; found 253.1190.




67d 79d

**Synthesis of benzyl 2,6-dihydroxy-3-methylbenzoate (67d) and benzyl (1*E*,5*Z*)-7-acetyl-3,4-dihydro-4-oxo-2H-1,2-diazepine-3-carboxylate (79d).** To an oven-dried 4 dr vial under nitrogen was added zinc triflate (4 mg, 0.01 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (103 mg, 0.930 mmol) and 4 mL of dry DCM. The mixture was stirred at 0$^{o}$C. Benzyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64d**) (398 mg, 1.20 mmol), which was prepared according to the procedure previously reported by Ueda,[59] was added via syringe all at once. The yellow solution was stirred vigorously and slowly warmed to room temperature. After 16 hours the crude reaction mixture was concentrated under reduced pressure. At this point substrate **65** was fully consumed, and intermediate benzyl 3,7-dioxo-2-diazo-(*E*)-oct-5-enoate(**66d**) was produced as indicated by a $^{1}$H NMR spectrum of the reaction mixture. To a 4 dr vial was added **66d** from the Mukaiyama-Michael addition and in-situ elimination step without purification, followed by 4.0 mL DCE and 1.0 mL 0.20 mol/L NaOH aqueous solution (0.20 mmol). The reaction mixture was heated to reflux and was stirred at the maximum speed of the stirrer. After stirring for 2.0 hours, the stirrer was turned down and the reaction was left alone for a few minutes. At this point, a deep red aqueous phase and a yellow organic phase was formed. The organic phase was then removed by pipet and run through a short silica plug to

remove the small amount of water. The resulting solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give 113 mg of a yellow liquid as product **67d** (0.44 mmol, 49% yield). Then the eluent was switched to 1:4 EtOAc/hexane to elute product **79d** (0.22 mmol, 24% yield) as a yellow oil.

**67d:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.04 (br, 1H), 9.42 (br, 1H), 7.46~7.38 (comp, 5H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.39 (d, *J* = 8.0 Hz, 1H), 5.49 (s, 2H), 2.13 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.7, 158.7, 158.6, 137.8, 133.9, 129.3, 129.1, 128.8, 116.6, 107.3, 99.6, 68.1, 15.2; IR (neat): 3424, 3124(br), 2921, 2850, 1667, 1631, 1588 $cm^{-1}$; HRMS (FAB) for $C_{15}H_{15}O_4$ $[M+H]^+$ calcd 259.0971; found 259.0978.

**79d:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.22 (br, 1H), 7.57 (d, *J* = 12.0 Hz, 1H), 7.35-7.40 (comp, 5H), 6.71 (d, *J* = 12.0 Hz, 1H), 5.35 (d, *J* = 4.0 Hz, 2H), 4.22 (s,1H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 196.4, 176.2, 165.5, 140.3, 134.3, 133.3, 130.1, 128.9, 128.7, 128.6, 69.0, 25.0; IR (neat): 3302(br), 3065, 3035, 2956, 2926, 2140, 1744, 1715, 1669 $cm^{-1}$; HRMS (ESI) for $C_{15}H_{15}N_2O_4[M+H]^+$ calcd 287.1032; found.287.1041.

### 2.3.4. Crystal Structure Information for *tert*-Butyl (1*E*,5*Z*)- 7-acetyl-3,4-dihydro-4-oxo -2H -1,2-diazepine-3-carboxylate(79c)

A yellow plate of C12H16N2O4, approximate dimensions 0.035 X 0.25 X 0.50 $mm^3$, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 150(2)$^{o}$ K on a three-circle diffractometer system equipped

with Bruker Smart Apex II CCD area detector using a graphite monochromator and a MoK fine-focus sealed tube (= 0.71073 Å) . The detector was placed at a distance of 6.000 cm from the crystal.

A total of 1223 frames was collected with a scan width of -0.5° and exposure time of 60 sec/frame using Apex2 (Bruker, 2005). The total data collection time was 22.4 hours. The frames were integrated with Apex2 software package using a narrow-frame integration algorithm. The integration of the data using a triclinic unit cell yielded a total of 4914 reflections to a maximum q angle of 24.99°, of which 2202 were independent (completeness = 99.7%, Rint = 1.80%, Rsig = 2.26%) and 1867 were greater than 2 (I). The final cell dimensions of a = 5.9230(13) Å, b = 10.189(2) Å, c = 11.365(3) Å, = 106.520(3)°, = 104.950(3)°, = 94.331(3)°, V = 627.1(2) Å3, are based upon the refinement of the XYZ-centroids of 2779 reflections with 2.4 < q < 28.5° using Apex2 software. Analysis of the data showed 0 % decay during data collection. Data were corrected for absorption effects with the semi-empirical from equivalent method using SADABS (Sheldrick, 1996). The minimum and maximum transmission coefficients were 0.868 and 0.996.

The structure was solved and refined using the SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997) software in the space group P-1 with Z = 2 for the formula unit. The final anisotropic full-matrix least-squares refinement on F2 with 186 variables converged at R1 = 3.20 % for the observed data and wR2 = 6.52 % for all data. The goodness-of-fit was 1.000. The largest peak on the final difference map was 0.193 e/Å3 and the largest hole was -0.172e/Å3. On the

basis of the final model, the calculated density was 1.336 g/cm3 and F(000),268 e.

**Table 2.10** Crystal Data and Structure Refinement for **79c**.

| | |
|---|---|
| X-ray lab book No. | 1935 |
| Crystal ID | Doyle/Yu Liu 05/13/2010 $C_{12}H_{16}O_4$ 150K |
| Empirical formula | $C_{12}H_{16}N_2O_4$ |
| Formula weight | 252.27 |
| Temperature | 150(2) K |
| Wavelength | 0.71073 Å |
| Crystal size | 0.50 0.25 0.035 $mm^3$ |
| Crystal habit | yellow plates |
| Crystal system | Triclinic |
| Space group | P-1 |
| Unit cell dimensions | *a* = 5.9230(13) Å = 106.520(3)° |
| | *b* = 10.189(2) Å = 104.950(3)° |
| | *c* = 11.365(3) Å = 94.331(3)° |
| Volume | 627.1(2) $Å^3$ |
| Z | 2 |
| Density, $\rho_{calc}$ | 1.336 $g/cm^3$ |
| Absorption coefficient, | 0.101 $mm^{-1}$ |
| F(000) | 268 e |
| Diffractometer | Bruker Smart Apex II CCD area detector |
| Radiation source | fine-focus sealed tube, MoK |
| Detector distance | 6.000 cm |
| Data collection method | ω and φ scans |
| Total frames | 1223 |
| Frame size | 512 pixels |
| Frame width | -0.5° |

| | |
|---|---|
| Exposure per frame | 60 sec |
| Total measurement time | 22.4 hours |
| | |
| θ range for data collection | 1.95 to 24.99° |
| Index ranges | $-7 \leq h \leq 7$, $-12 \leq k \leq 12$, $-13 \leq l \leq 13$ |
| Reflections collected | 4914 |
| Independent reflections | 2202 |
| Observed reflection, I>2 (I) | 1867 |
| Coverage of independent reflections | 99.7 % |
| Variation in check reflections | 0 % |
| Absorption correction | Semi-empirical from equivalents |
| | SADABS (Sheldrick, 1996) |
| Max. and min. transmission | 0.996 and 0.868 |
| Structure solution technique | direct |
| Structure solution program | SHELXS-97 (Sheldrick, 1990) |
| Refinement technique | Full-matrix least-squares on $F^2$ |
| Refinement program | SHELXL-97 (Sheldrick, 1997) |
| Function minimized | $\Sigma w(F_o^2 - F_c^2)^2$ |
| Data / restraints / parameters | 2202 / 0 / 186 |
| Goodness-of-fit on $F^2$ | 1.000 |
| $\Delta/\sigma_{max}$ | 0.001 |
| Final R indices: $R_1$, I>2 (I) | 0.0320 |
| $wR_2$, all data | 0.0652 |
| $R_{int}$ | 0.0180 |
| $R_{sig}$ | 0.0226 |
| Weighting scheme | $w = 1/[\sigma^2(F_o^2)+ (0.01P)^2 + 0.334P]$, |
| | $P = [\max(F_o^2 ,0) + 2F_o^2]/3$ |
| Largest diff. peak and hole | 0.193 and -0.172 e/Å$^3$ |

---

$R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$

**Table 2.11.** Atomic Coordinates and Equivalent* Isotropic Atomic Displacement Parameters ($Å^2$) for **79c**

| Atom | *x/a* | *y/b* | *z/c* | $U_{eq}$ |
|---|---|---|---|---|
| O1 | -0.19105(18) | 0.30470(11) | 0.39987(9) | 0.0351(3) |
| C1 | 0.1414(3) | 0.21241(16) | 0.49244(15) | 0.0358(4) |
| C2 | -0.0422(2) | 0.30634(15) | 0.49793(13) | 0.0262(3) |
| C3 | -0.0385(2) | 0.40195(14) | 0.62460(13) | 0.0220(3) |
| N1 | 0.1289(2) | 0.39033(12) | 0.72184(11) | 0.0240(3) |
| N2 | 0.1674(2) | 0.47589(12) | 0.83800(11) | 0.0258(3) |
| C4 | -0.2388(2) | 0.47410(15) | 0.62899(14) | 0.0253(3) |
| C5 | -0.2976(2) | 0.55503(15) | 0.72911(14) | 0.0275(3) |
| C6 | -0.1406(2) | 0.61939(14) | 0.85876(13) | 0.0229(3) |
| O2 | -0.20794(17) | 0.67289(10) | 0.95126(10) | 0.0295(2) |
| C7 | 0.1245(2) | 0.61844(14) | 0.87017(13) | 0.0216(3) |
| C8 | 0.2779(2) | 0.69456(14) | 1.00714(13) | 0.0215(3) |
| O3 | 0.27433(16) | 0.82904(9) | 1.03539(9) | 0.0242(2) |
| O4 | 0.38182(16) | 0.63402(10) | 1.07649(9) | 0.0262(2) |
| C9 | 0.3927(2) | 0.92393(14) | 1.16872(13) | 0.0239(3) |
| C10 | 0.3227(3) | 1.06184(15) | 1.16104(15) | 0.0327(4) |
| C11 | 0.2974(3) | 0.87617(16) | 1.26407(14) | 0.0301(3) |
| C12 | 0.6587(2) | 0.92861(16) | 1.19724(15) | 0.0319(4) |

* $U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

**Table 2.12** Anisotropic Atomic Displacement Parameters* ($Å^2$) for **79c**.

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| O1 | 0.0316(6) | 0.0433(7) | 0.0224(5) | 0.0069(5) | -0.0014(5) | 0.0045(5) |
| C1 | 0.0321(9) | 0.0362(9) | 0.0286(8) | -0.0016(7) | 0.0035(7) | 0.0082(7) |
| C2 | 0.0225(7) | 0.0264(8) | 0.0248(8) | 0.0068(6) | 0.0021(6) | -0.0025(6) |
| C3 | 0.0186(7) | 0.0215(7) | 0.0231(7) | 0.0077(6) | 0.0015(6) | 0.0004(5) |
| N1 | 0.0223(6) | 0.0236(6) | 0.0215(6) | 0.0042(5) | 0.0015(5) | 0.0043(5) |
| N2 | 0.0257(6) | 0.0251(6) | 0.0206(6) | 0.0046(5) | -0.0020(5) | 0.0092(5) |
| C4 | 0.0196(7) | 0.0276(8) | 0.0239(8) | 0.0084(6) | -0.0015(6) | 0.0017(6) |
| C5 | 0.0172(7) | 0.0306(8) | 0.0322(8) | 0.0100(7) | 0.0026(6) | 0.0056(6) |
| C6 | 0.0231(7) | 0.0195(7) | 0.0277(8) | 0.0101(6) | 0.0066(6) | 0.0058(6) |
| O2 | 0.0292(6) | 0.0289(6) | 0.0313(6) | 0.0076(5) | 0.0120(5) | 0.0072(4) |
| C7 | 0.0214(7) | 0.0216(7) | 0.0206(7) | 0.0071(6) | 0.0035(6) | 0.0045(5) |
| C8 | 0.0177(7) | 0.0229(7) | 0.0239(7) | 0.0069(6) | 0.0060(5) | 0.0047(5) |
| O3 | 0.0242(5) | 0.0212(5) | 0.0222(5) | 0.0048(4) | 0.0007(4) | |

| | | | | | |
|---|---|---|---|---|---|
| | 0.0038(4) | | | | |
| O4 | 0.0254(5) | 0.0257(5) | 0.0245(5) | 0.0075(4) | 0.0012(4) |
| | 0.0082(4) | | | | |
| C9 | 0.0213(7) | 0.0235(7) | 0.0207(7) | 0.0017(6) | 0.0017(6) |
| | 0.0020(6) | | | | |
| C10 | 0.0355(9) | 0.0246(8) | 0.0315(8) | 0.0045(6) | 0.0035(7) |
| | 0.0045(6) | | | | |
| C11 | 0.0277(8) | 0.0329(8) | 0.0284(8) | 0.0068(7) | 0.0086(6) |
| | 0.0069(6) | | | | |
| C12 | 0.0215(8) | 0.0346(9) | 0.0327(8) | 0.0040(7) | 0.0045(6) |
| | 0.0001(6) | | | | |

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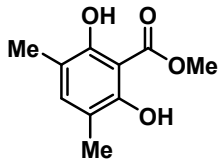
* The anisotropic atomic displacement factor exponent takes the form:-2 $^{2}$ [ $h^2a^{*2}U_{11}$ +... + 2hka*b*$U_{12}$ ]

**Table 2.13.** Hydrogen Atom Coordinates and Isotropic Atomic Displacement Parameters ($Å^2$) for **79c**.

| Atom | *x/a* | *y/b* | *z/c* | $U_{iso}$ |
|---|---|---|---|---|
| H1A | 0.1232 | 0.1600 | 0.4028 | 0.068(4) |
| H1B | 0.1209 | 0.1478 | 0.5398 | 0.068(4) |
| H1C | 0.2997 | 0.2682 | 0.5311 | 0.068(4) |
| H2 | 0.269(3) | 0.4562(17) | 0.8972(16) | 0.042(5) |
| H4 | -0.354(3) | 0.4448(15) | 0.5453(14) | 0.026(4) |
| H5 | -0.451(3) | 0.5828(15) | 0.7157(14) | 0.032(4) |
| H7 | 0.167(3) | 0.6596(15) | 0.8117(14) | 0.026 |
| H10A | 0.3812 | 1.0879 | 1.0963 | 0.039(3) |
| H10B | 0.3919 | 1.1330 | 1.2447 | 0.039(3) |
| H10C | 0.1498 | 1.0539 | 1.1371 | 0.039(3) |
| H11A | 0.1239 | 0.8607 | 1.2350 | 0.040(3) |
| H11B | 0.3536 | 0.9475 | 1.3484 | 0.040(3) |
| H11C | 0.3530 | 0.7896 | 1.2704 | 0.040(3) |
| H12A | 0.6981 | 0.8376 | 1.1999 | 0.042(3) |
| H12B | 0.7385 | 0.9986 | 1.2804 | 0.042(3) |
| H12C | 0.7112 | 0.9526 | 1.1299 | 0.042(3) |

### 2.3.5 Procedure for the Synthesis of Methyl 2,6-dihydroxy-3,5-dimethylbenzoate (83).

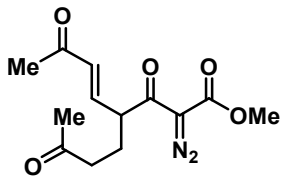



**83**

To an oven-dried 4 dr vial under nitrogen was added zinc triflate (4 mg, 0.0 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (100 mg, 0.900 mmol) and 4 mL of dry DCM. The mixture was stirred at 0$^{o}$C. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazopent-3-enoate (**81**) (405 mg, 1.50 mmol), which was prepared according to procedure previously reported by Ueda,[59] was added via syringe all at once. The yellow solution was stirred vigorously and slowly warmed to room temperature. After 16 hours the crude reaction mixture was concentrated under reduced pressure. At this point substrate **65** was fully consumed, and intermediate methyl 3,7-dioxo-2-diazo-4-methyl-(*E*)-oct-5-enoate (**82**) was produced as indicated by a $^{1}$H NMR spectrum of the reaction mixture. To a 25 mL round bottom flask was added **82** from the Mukaiyama-Michael addition and in-situ elimination step without purification, followed by 4mL DCE and 0.50 mL 0.20 mol/L NaOH aqueous solution (0.10 mmol). The vigorously stirred reaction mixture was heated to reflux. After 2 hours a deep red aqueous phase and a yellow organic phase was formed. The organic phase was removed by pipette and filtered through a short silica plug to remove the small amount of water. The resulting solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:15

EtOAc/hexane to give 76 mg of a yellow liquid as product **83**(0.39 mmol, 43% yield). **83:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.70 (br, 2H), 7.08 (s, 1H), 4.07 (s, 3H), 2.13 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 156.2, 139.3, 115.5, 99.1, 52.7, 15.1; IR (neat): 3429, 3132, 2955, 2925, 2857, 1666, 1626, 1607 $cm^{-1}$;HRMS (FAB) for $C_{10}H_{13}O_4$ $[M+H]^+$. calcd 197.0814; found 197.0822.

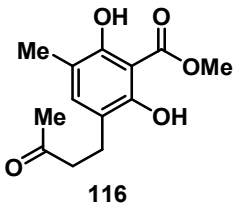
### 2.3.6 Procedures for Intercepting Enolate Intermediate 71 with Methyl Vinly Ketone and Synthesis of Methyl 2,6-dihydroxy-3-methyl-5-(3-oxobutyl)-benzoate (116)




115

**Synthesis of methyl 3,7-dioxo-4-(3-oxo-butyl)-2-diazo-(*E*)-oct-5-enoate (115).** To a 4 dr vial was added zinc triflate (4 mg, 0.01 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (103 mg, 0.930 mmol) and 4.0 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (307 mg, 1.20 mmol) was added via syringe all at once. After 16 h the crude reaction mixture was concentrated under reduced pressure. To the reaction mixture in a 4 dr vial was then added 4.0 mmol methyl vinyl ketone and 2.0 mL DCM. The solution was cooled down to 0$^{o}$C with ice bath and was stirred at the maximum speed of the stirrer. 1.0 mL 0.10 mol/L NaOH aqueous solution (0.10 mmol) was then added to the reaction. After stirring for 2.0 hours, yellow precipitate was accumulated in the aqueous phase and a

reddish yellow organic phase was formed. The organic phase was then removed by pipette and run through a short silica plug to remove small amount of water. The resulting solution was concentrated under reduced pressure the residue was purified by silica gel chromatography, eluting with 1:2 EtOAc/hexane using short column and fast air flow to minimize decomposition of the product. After chromatography, 173 mg (65%) product was isolated **115:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.69 (dd, $J_1$= 8.0 Hz, $J_2$= 16.0 Hz, 1H), 6.07 (d, $J$ = 16.0 Hz, 1H), 4.31 (q, $J$ = 8.0 Hz, 1H), 3.78 (s, 3H); 2.41-2.35 (comp, 2H), 2.19 (s, 3H), 2.05 (s, 3H), 2.08-2.03 (comp, 1H), 1.89-1.82 (comp, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 207.2, 198.0, 191.0, 161.0, 143.6, 133.2, 52.3, 49.3, 40.5, 29.9, 26.9, 25.1; IR (neat): 2956, 2921, 2852, 2340, 2359, 2141, 1712, 1675, 1651cm$^{-1}$; HRMS (ESI) for $C_{13}H_{17}N_2O_5$ $[M+H]^+$ calcd 281.1137; found: 281.1121

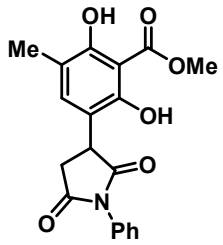



**116**

**Synthesis of methyl 2,6-dihydroxy-3-methyl-5-(3-oxobutyl)-benzoate (116).** To a 4 dr vial was added 151 mg methyl-3,7-dioxo-4-(3-oxo-butyl)-2-diazo-(*E*)-oct-5-enoate (**115**) (0.5 mmol) and 1.0 mL DCM. 6 mg of triethylamine (0.05mmol) was then added to the solution. Within a minute, a lot of bubbles were formed from the solution and the color of the reaction turned from bright yellow to brownish yellow. The reaction mixture was stirred at room temperature for 30 minutes. The resulting yellow solution was concentrated under reduced pressure

and the residue was purified by silica gel chromatography, eluting with 1:2 EtOAc/hexane to yield 65 mg (45%) yellow oil as product. **116:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.73 (br, 2H), 7.09 (s, 1H), 4.07 (s, 3H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 2.13 (s, 3H), 2.12 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 208.7, 170.4, 156.8, 156.1, 138.8, 118.4, 115.9, 99.2, 52.7, 43.4, 29.9, 24.1, 15.1; IR (neat): 3437, 3141, 2959, 2921, 2849, 1713, 1669, 1625cm$^{-1}$; HRMS (ESI) for $C_{13}H_{17}O_5$ $[M+H]^+$ calcd 253.1076; found 253.1072.

### 2.3.7. Procedures for Intercepting enolate Intermediate 71 with *N*-Phenylmaleimide and Synthesis of 2,6-Dihydroxy-3-methyl-5-(2,5-dioxo-1-phenylpyrrolidin-3-yl)benzoate (117)

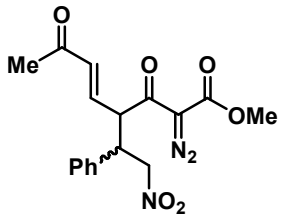



**117**

To a 4 dr vial was added zinc triflate (4 mg, 0.01 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (103 mg, 0.930 mmol) and 4.0 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (307 mg, 1.20 mmol) was added via syringe all at once. After 16 h the crude reaction mixture was concentrated under reduced pressure. To the reaction mixture in a 4 dr vial was then added 2.0 mmol *N*-phenylmaleimide and 2.0 mL DCM, followed by 1.0 mL of 0.1 mol/L aqueous NaOH (0.1 mmol). After rapid stirring for 2 h, the stirrer was discontinued

whereupon a deep red aqueous phase separated from a yellow organic phase. The organic phase was then removed by pipet and run through a short silica plug to remove the small amount of water. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1:2 EtOAc/hexane to give 129 mg (0.363 mmol) yellow solid (39%) as product. **117**: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.88 (br, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 4.0 Hz, 2H), 7.20 (s, 1H), 4.09 (s, 3H), 3.98 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.23 (dd, *J* = 8.0, 12.0 Hz, 1H), 2.97 (dd, *J* = 4.0, 16.0 Hz, 1H), 2.17 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.6, 175.7, 170.0, 139.3, 132.4, 137.4, 129.1, 128.5, 126.6, 117.0, 115.1, 100.0, 53.1, 43.6, 36.1, 15.1; IR (neat): 3369, 3068 (br), 2926, 2854, 1706, 1667, 1625 1600 cm-1; HRMS (ESI) for $C_{19}H_{18}NO_6$ $[M+H]^+$ calcd 356.1135; found 356.1111.

### 2.3.8 Procedures for Intercepting Enolate Intermediate 71 with β-nitrostyrenes and Synthesis of Methyl 2,6-Dihydroxy-3-methyl-5-(1-aryl-2-nitroethyl)benzoate (119) and Methyl 3,7-Dioxo-4,6-(1-(4-aryl-2-nitroethyl)-2-diazo-oct-5-enoate (120).

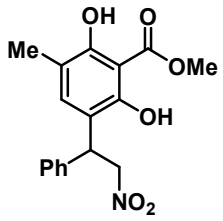



**118**

**Synthesis of Methyl 3,7-Dioxo-4-(1-phenyl-2-nitroethyl)-2-diazo-(*E*)-oct-5-enoate (118)** To a 4 dr vial was added zinc triflate (4 mg, 0.01 mmol), followed

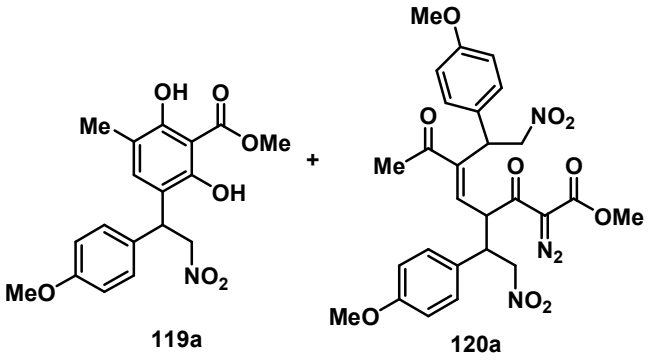
by *trans*-4-methoxy-3-buten-2-one (**65**) (103 mg, 0.930mmol) and 2.0 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (281 mg, 1.10 mmol) was added all at once. After 16 hours 2 equiv. of solid β–nitrostyrene (298 mg, 2.00 mmol) was added to the reaction solution. When the yellow solid (β–nitrostyrene) was fully dissolved 5.0 mol% of triethylamine (5 mg, 0.05 mmol) was added causing the color of the solution to turn from yellow to deep red. The reaction was stirred at room temperature for 2 h during which the color of the solution became darker. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1:2 EtOAc/hexane, using a short column and fast airflow to minimize decomposition of the product. The product was isolated as a yellow syrup in 204 mg (0.567 mmol, 61%) as a mixture of two diastereomers that could not be separated by chromatography. NMR analysis showed a 2:1 diastereomeric ratio. **118**: major isomer: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33-7.18 (comp, 5H), 6.69 (dd, *J* = 8.0, 16.0 Hz, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.14 (t, *J* = 8.0 Hz, 1H), 4.68-4.57 (comp, 2H), 4.20-4.05 (comp, 1H), 3.79 (s, 3H); 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 188.7, 160.8, 140.2, 136.6, 135.8, 128.9, 128.3, 128.0, 78.3, 52.8, 52.4, 45.0, 27.3; minor isomer: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.40 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H), 5.98 (d, *J* = 16.0 Hz, 1H), 4.94 (t, *J* = 8.0 Hz, 1H), 4.76 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.68-4.57 (comp, 1H), 4.20-4.05 (comp, 1H), 3.85 (s, 3H); 2.04 (s, 3H); $^{13}$C NMR (100 MHz, CDCl3) $\delta$ 197.5, 189.6, 161.0, 141.1, 136.0, 134.5, 129.0, 128.8, 128.1, 77.8, 52.6, 52.2, 45.6,26.8; IR (neat): 2955, 2924, 2856,

2361, 2336, 2143, 1717, 1677, 1651cm-1; HRMS (ESI) for $C_{17}H_{18}N_3O_6$ $[M+H]^+$ calcd 360.1195; found: 310.1197.




**119**

**Synthesis of Methyl 2,6-Dihydroxy-3-methyl-5-(1-phenyl-2-nitroethyl)benzoate (119)** To a 4 dr vial was added 33 mg of methyl-3,7-dioxo-4-(1-phenyl-2-nitroethyl)-2-diazo-(*E*)-oct-5-enoate **118** (0.10 mmol) and 0.5 mL DCM, then 1 mg of triethylamine (0.01 mmol). The reaction mixture was heated with stirring at 40°C in oil bath for 1 h. The resulting solution was concentrated under reduced pressure. The crude reaction mixture was purified with a short silica plug, eluting with DCM to give 20 mg (0.067 mmol, 67%) of a yellow oil. **119**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.92 (br, 2H), 7.34-7.22 (comp, 5H), 7.03 (s, 1H), 5.16 (t, *J* = 8.0 Hz, 1H), 5.06 (dd, *J* = 8.0, 12.0 Hz, 1H), 4.96 (dd, *J* = 8.0, 12.0 Hz, 1H), 4.05 (s, 3H), 2.10 (s, 3H); $^{13}$C NMR (100 MHz, CDCl3) $\delta$ 170.1, 158.0, 155.9, 138.9, 136.9, 128.8, 127.8, 127.3, 116.8, 116.7, 99.7, 77.7, 53.0, 43.1, 15.4; IR (neat): 3427, 3121, 3026, 2959, 2921, 2849, 2358, 2329, 1673, 1624, 1549 cm-1; HRMS (ESI) for $C_{17}H_{18}NO_6$ $[M+H]^+$ calcd 332.1134; found 332.1128.

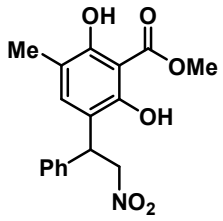



**Synthesis of Methyl 2,6-Dihydroxy-3-methyl-5-(1-(4-methoxyphenyl)-2-nitroethyl)benzoate (119a) and Methyl 3,7-Dioxo-4,6-(1-(4-methoxyphenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (120a).** To a 4 dr vial was added zinc triflate (2 mg, 0.005 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (50 mg, 0.45mmol) and 2 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (180 mg, 0.70 mmol) was added all at once. The yellow solution was allowed to react overnight. After 16 hours, 2.0 equivalents of 4-methoxy-β–nitrostyrene (179 mg, 1.0 mmol) was added to the solution, followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) when 4-methoxy-β–nitrostyrene was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction was stirred at room temperature for 24 h during which time the solution became cloudy and the color got darker. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1: 4 EtOAc/hexane, to give 90 mg (0.25 mmol, 56%) of a pale yellow solid as methyl 2,6-dihydroxy-3-methyl-5-(1-(4-methoxyphenyl)-2-nitroethyl)benzoate (**119a**). Switching the eluent to 1: 2 EtOAc/hexane allowed the isolation of 21 mg (0.036 mmol, 8%) of methyl 3,7-dioxo-4,6-(1-(4-

methoxyphenyl)-2-nitroethyl)-2-diazooct-5-enoate (**120a**) as a yellow syrup. It is a mixture of two diastereomers which could not be separated by chromatography. NMR analysis showed a 6:1 diastereomeric ratio.

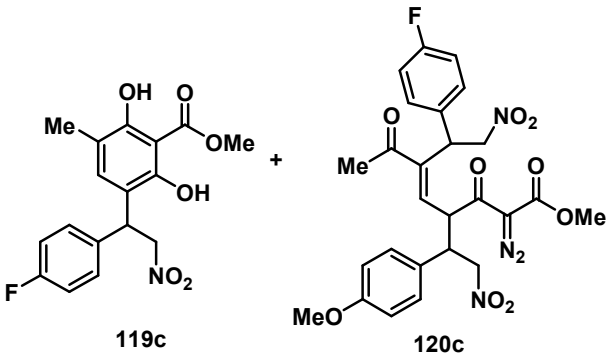
**Methyl 2,6-Dihydroxy-3-methyl-5-(1-(4-methoxyphenyl)-2-nitroethyl)benzoate (119a)**: $^{1}$H NMR (400 MHz, CDCl3) $\delta$ 9.86 (br, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 5.10 (t, *J* =8.0 Hz, 1H), 5.02 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.90 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.04 (s, 3H), 3.76 (s, 3H), 2.10 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.2, 158.8, 157.9, 155.8, 136.8, 130.8, 128.9, 117.1, 116.7, 114.2, 77.9, 55.2, 53.0, 42.4, 15.4; IR (neat): 3381, 3167, 2957, 2838, 1676, 1613, 1549, 1436 cm-1; HRMS (ESI) for $C_{18}H_{20}NO_7$ $[M+H]^+$ calcd 362.1240; found 362.1224.

**Methyl 3,7-Dioxo-4,6-(1-(4-methoxyphenyl)-2-nitroethyl)-2-diazooct-5-enoate (120a)** (major isomer): $^{1}$H NMR (400 MHz, CDCl3) $\delta$ 7.44 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 5.51 (t, *J* = 12.0 Hz, 1H), 5.26 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.87 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 4.74 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H), 3.95 (comp,1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.74 (comp, 1H), 3.52 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 2.41 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.5, 189.0, 161.2, 159.6, 159.3, 144.4, 140.6, 130.8, 129.7, 129.1, 127.9, 114.8, 114.4, 77.6, 77.5, 55.4, 55.2, 52.6, 48.9, 45.6, 43.0, 27.6; IR (neat): 2957, 2923, 2145, 1711, 1673, 1649, 1610, 1549, 1512, 1437 cm-1; HRMS (ESI) for $C_{27}H_{29}N4O_{10}$ $[M+H]^+$ calcd 569.1874; found 569.1874.




**119b**

**Synthesis of Methyl 2,6-Dihydroxy-3-methyl-5-(1-phenyl-2-nitroethyl)benzoate (119b) (one-pot method)** To a 4 dr vial was added zinc triflate (2 mg, 0.005 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (50 mg, 0.45mmol) and 2 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (180 mg, 0.70 mmol) was added all at once. The yellow solution was allowed to react overnight. After 16 hours, 2 equivalents of β–nitrostyrene (150 mg, 1.00 mmol) was added to the solution, followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) when β–nitrostyrene was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction was stirred at room temperature for 24 h during which time the solution became cloudy and the red color got darker. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1: 6 EtOAc/hexane, to give 76 mg (0.23 mmol, 50%) of a pale yellow syrup as methyl 2,6-dihydroxy-3-methyl-5-(1-phenyl-2-nitroethyl)benzoate (**119b**). Switching the eluent to 1: 2 EtOAc/hexane allowed the isolation of 25 mg (0.049 mmol, 11%) double addition by-product as a mixture of multiple isomers which could not be separated by chromatography.

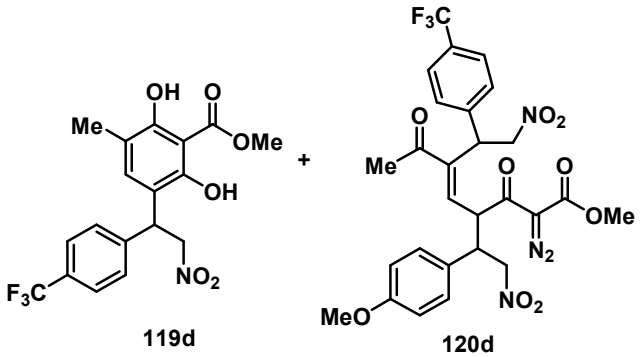



**Synthesis of Methyl 2,6-Dihydroxy-3-methyl-5-(1-(4-fluorophenyl)-2-nitroethyl)benzoate (119c) and Methyl 3,7-Dioxo-4,6-(1-(4-fuorophenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (120c).** To a 4 dr vial was added zinc triflate (2 mg, 0.005 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (50 mg, 0.45 mmol) and 2.0 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (180 mg, 0.70 mmol) was added all at once. The yellow solution was allowed to react overnight. After 16 hours, 2.0 equivalents of solid 4-fluoro-β–nitrostyrene (167 mg, 1.00 mmol) was added to the solution followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) when 4-fluoro-β–nitrostyrene was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction was stirred at room temperature for 24 hours during which time the color of the solution became darker and the solution became cloudy. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1:6 EtOAc/hexane, to give 88 mg (0.25 mmol, 56%) of **119c** as pale yellow liquid then 40 mg (0.072 mmol, 16%) **120c** as a yellow syrup. It is a mixture of two diastereomers which could not be separated by chromatography. NMR analysis showed a 2:1 diastereomeric ratio.

**Methyl 2,6-Dihydroxy-3-methyl-5-(1-(4-fluorophenyl)-2-nitroethyl)benzoate (119c)**: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.99 (br, 1H), 9.86 (br, 1H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 8.0 Hz, 2H), 7.00 (s, 1H), 5.12 (t, *J* =8.0 Hz, 1H) 5.05 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H), 4.92 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H), 4.06 (s, 3H), 2.10 (s, 3H); $^{13}$C NMR (100 MHz, CDCl3) $\delta$ 170.1, 163.1, 160.7, 158.0, 158.9, 136.7, 134.6, 129.4, 129.3, 116.9, 116.5, 115.8, 115.6, 99.8, 77.7, 53.0, 42.6, 15.4; IR (neat): 3432, 3117, 2962, 1673, 1625, 1551, 1510, 1437 cm-1; HRMS (ESI) for $C_{17}H_{17}FNO_6$ $[M+H]^+$ calcd 350.1040; found 350.1019.

**Methyl 3,7-Dioxo-4,6-(1-(4-fuorophenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (120c)** major isomer: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (dd, *J* = 4.0 Hz, 8.0 Hz, 2H), 7.14-7.10 (comp, 2H), 7.02-6.94 (comp, 4H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.53 (t, *J* = 8.0 Hz, 1H), 5.22 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.91(dd, *J* = 4.0 Hz, 12.0 Hz, 1H), 4.76(dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 4.04 (ddd, *J* = 4.0 Hz, 8.0 Hz, 12.0 Hz, 1H), 3.86 (s, 3 H), 3.83 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H) 3.66 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H); 2.41 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.0, 188.9, 163.4, 161.3, 144.0, 140.8, 134.4 (d, $J_{CF}$ = 0.3 Hz), 131.8 (d, $J_{CF}$ = 0.3 Hz), 130.2 (d, $J_{CF}$ = 10 Hz), 129.8 (d, $J_{CF}$ = 10 Hz), 116.4 (d, *J* = 18 Hz), 116.0 (d, *J* = 18 Hz), 77.5, 77.2, 52.7, 48.9, 45.5, 42.9, 27.5; minor isomer: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (dd, *J* = 4.0 Hz, 8.0 Hz, 2H), 7.12-7.10 (comp, 4H), 7.07 (dd, *J* = 4.0 Hz, 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.52 (comp, 1H), 4.99 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H), 4.56 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.48 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 4.15-4.09 (comp, 1H), 3.86-3.81 (1H), 3.63-3.68 (1H), 2.37 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.1, 188.9, 161.5, 160.6, 143.4, 141.0, 131.8 (d, $J_{CF}$ = 0.3 Hz), 130.0

(d, $J_{CF}$ = 7 Hz), 129.0 (d, $J_{CF}$ = 7 Hz), 115.8 (d, $J_{CF}$ = 17 Hz), 115.5 (d, $J_{CF}$ = 17 Hz), 77.5, 77.3, 52.4, 49.0, 46.3, 41.6, 27.1; IR (neat): 2148, 1711, 1675, 1649, 1550, 1510, 1437 cm-1; HRMS (ESI) for $C_{25}H_{23}F_2N4O_8$ $[M+H]^+$ calcd 544.1484; found 544.1492.



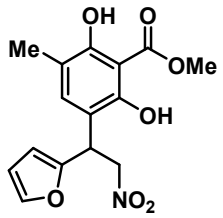

**Synthesis of Methyl 2,6-Dihydroxy-3-methyl-5-(1-(4-trifluoromethylphenyl)-2-nitroethyl)benzoate (119d) and Methyl 3,7-Dioxo-4,6-(1-(4-trifuoromethylphenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (120d).** To a 4 dr vial was added zinc triflate (2 mg, 0.005 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (50 mg, 0.45 mmol) and 2.0 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (180 mg, 0.70 mmol) was added all at once. The yellow solution was allowed to react overnight. After 16 hours, 2.0 equivalents of solid 4-trifluoromethyl-β–nitrostyrene (216 mg, 1.00 mmol) was added to the solution followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) when 4-trifluoromethyl-β–nitrostyrene was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction was stirred at room temperature for 24 hours during which time the color of the solution became

darker and the solution became cloudy. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1:6 EtOAc/hexane, to give 87 mg (0.26 mmol, 57%) of **119d** as pale yellow oil then 48 mg (0.075 mmol, 17%) **120d** as a yellow syrup. It is a mixture of two diastereomers which could not be separated by chromatography. NMR analysis showed a 3:1 diastereomeric ratio.

**Methyl 2,6-Dihydroxy-3-methyl-5-(1-(4-trifluoromethylphenyl)-2-nitroethyl)-benzoate (119d)**: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.02 (br, 1H), 9.87 (br, 1H), 7.57 (d, *J* = 8.0 Hz), 7.42 (d, *J* = 8.0 Hz), 7.02 (s, 1H), 5.19 (t, *J* =8.0 Hz) 5.09 (dd, *J* = 8.0 Hz, 12.0 Hz), 5.02 (dd, *J* = 8.0 Hz, 12.0 Hz), 4.07 (s, 3H), 2.11 (s, 3H); $^{13}$C NMR (100 MHz, CDCl3) $\delta$ 170.1, 158.3, 155.9, 143.1, 136.7, 134.6, 129.6 (d, $J_{CF}$ = 30 Hz), 129.4, 128.2, 125.7(d, $J_{CF}$ = 3 Hz), 124.0 (q, $J_{CF}$ = 270 Hz) 99.8, 77.2, 53.1, 43.2, 15.3; IR (neat): 3435, 3110, 2965, 2924, 1674, 1621, 1553, 1439 cm-1; HRMS (ESI) for $C_{18}H_{17}F_3NO_6$ $[M+H]^+$ calcd 400.1008; found. 400.1014.

**Methyl 3,7-Dioxo-4,6-(1-(4-fuorophenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (120d)** major isomer: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 5.60 (t, *J* = 8.0 Hz, 1H), 5.23 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 5.07 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H), 5.06 (comp, 1H), 4.65 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.56 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H), 4.27 (ddd, *J* = 4.0 Hz, 8.0 Hz, 12.0 Hz, 1H), 3.56 (s, 3 H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 198.7, 188.4, 170.2, 141.6, 139.9, 137.1, 128.7, 127.6, 126.3, 126.0 (d, $J_{CF}$ = 3 Hz), 125.6 (d, $J_{CF}$ = 3 Hz), 77.1, 77.1, 52.5, 49.0, 46.4, 42.07, 27.1; visible signals of the minor isomer:

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.13 (d, $J$ = 8.0 Hz, 2H), 7.11 (d, $J$ = 8.0 Hz, 2H), 5.76 (t, $J$ = 8.0 Hz, 1H), 4.12 (s, 3H), 2.19 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 143.0, 142.4, 137.4, 129.9, 127.4, 125.4 (d, $J_{CF}$ = 3 Hz), 125.2 (d, $J_{CF}$ = 3 Hz), 53.1, 48.7, 44.1, 40.8, 15.3; IR (neat): 2960, 2923, 2853, 2154, 1714, 1679, 1651, 1621, 1554, 1439 cm-1; HRMS (ESI) for $C_{27}H_{22}F_6N_4O_8$ $[M+H]^+$ calcd 645.1419; found 645.1425.



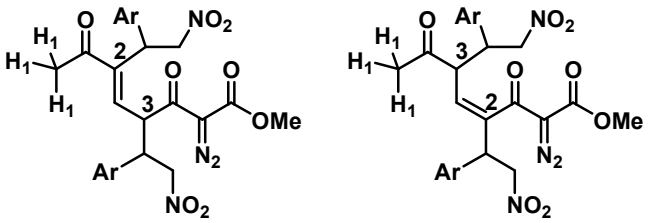

**119e**

**Synthesis of Methyl 2,6-Dihydroxy-3-methyl-5-(1-(1-furyl)-2-nitroethyl)benzoate (119e)** To a 4 dr vial was added zinc triflate (2 mg, 0.005 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**65**) (50 mg, 0.45 mmol) and 2.0 mL of dry DCM. With stirring at room temperature methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**64a**) (180 mg, 0.70 mmol) was added all at once, and the yellow solution was allowed to react overnight. After 16 hours, 2.0 equivalents of 2-(2-nitrovinyl)furan (150 mg, 1.00 mmol) was added, followed by 5 mol% triethylamine (3 mg, 0.03 mmol) when 2-(2-nitrovinyl)furan was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction solution was stirred at room temperature for 24 h during which time the color of the solution became darker. The resulting solution was concentrated under reduced pressure, and the crude residue was purified by silica gel chromatography, eluting with 1:6 EtOAc/hexane, to give 90

mg (0.28 mmol, 63%) of a yellow solid as major product **119e**. In addition, 58 mg (0.12 mmol, 26%) double addition by-product was obtained as a mixture of multiple isomers which could not be separated by chromatography. **119e**: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.94 (br, 2H), 7.37 (s, 1H), 7.02 (s, 1H), 6.32 (d, *J* = 4.0 Hz), 6.18 (*J* = 4.0 Hz), 5.25 (t, *J* = 8.0 Hz), 4.91 (sept, *J* = 8.0 Hz), 4.07 (s, 3H), 2.10 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.1, 158.4, 155.7, 142.4, 137.1, 117.0, 114.4, 110.5, 107.3, 99.6, 76.3, 53.0, 37.2, 15.3; IR (neat): 3392, 3125, 2967, 2923, 1669, 1626, 1545, 1437 cm-1; HRMS (ESI) for $C_{15}H_{16}NO_7$ $[M+H]^+$ calcd 322.0927; found 322.0906.

### 2.3.9 HMBC Experiments to Support the Structure of Methyl 3,7-Dioxo-4,6-(1-(4-fuorophenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (120c)

Compound **120c** could have two possible structures (**120c$_1$** and **120c$_2$**) which are difficult to differentiate only by H1 and C13 NMR. Therefore a HMBC experiment is performed on this compound to illuminate the structure. With structure **120c$_1$**, one would expect to see correlation between **H$_1$** and alkene carbon **C$_2$** through a 3 bond coupling. By comparison, there should be no coupling between these two signals in structure **120c$_2$** since they would be 5 bonds between thesetwo atoms. Meanwhile, there should be no correlation between **H$_1$** and alkyl carbon **C$_3$** with structure **120c$_1$** but it should be evident if the structure would be **120c$_2$**




**120c$_1$** **120c$_2$**

**Ar = 4-fluoro-phenyl**

The result is depicted in Figure 2.13 and an enlargement of the key region is shown in Figure 2.13.

**Figure 2.13**. HMBC Spectrum of Methyl 3,7-Dioxo-4,6-(1-(4-fuorophenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (**120c**)

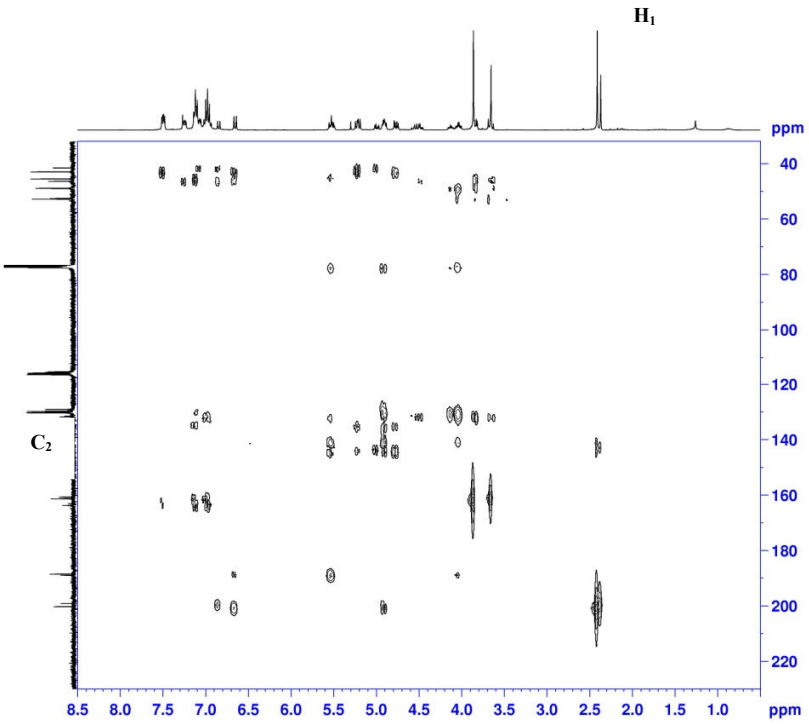
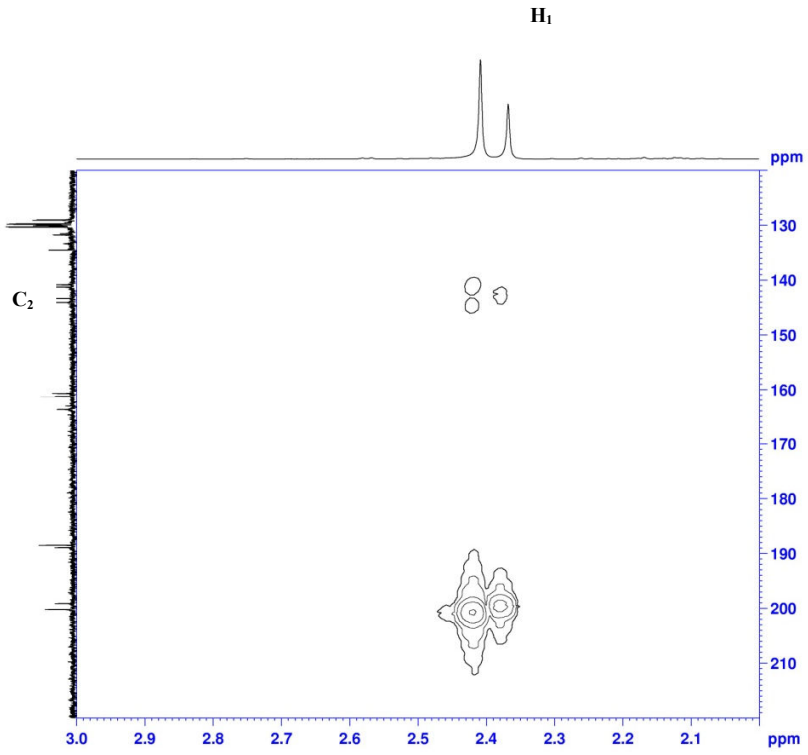
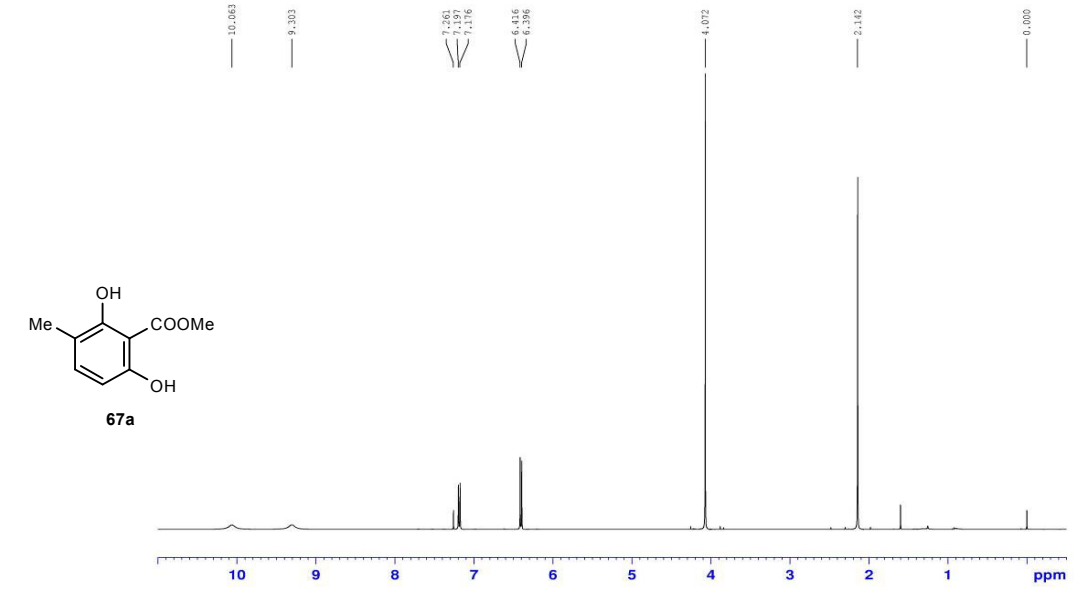


**Figure 2.14**. Enlarged HMBC Spectrum of Methyl 3,7-Dioxo-4,6-(1-(4-fuorophenyl)-2-nitroethyl)-2-diazo-oct-5-enoate (**120c**)

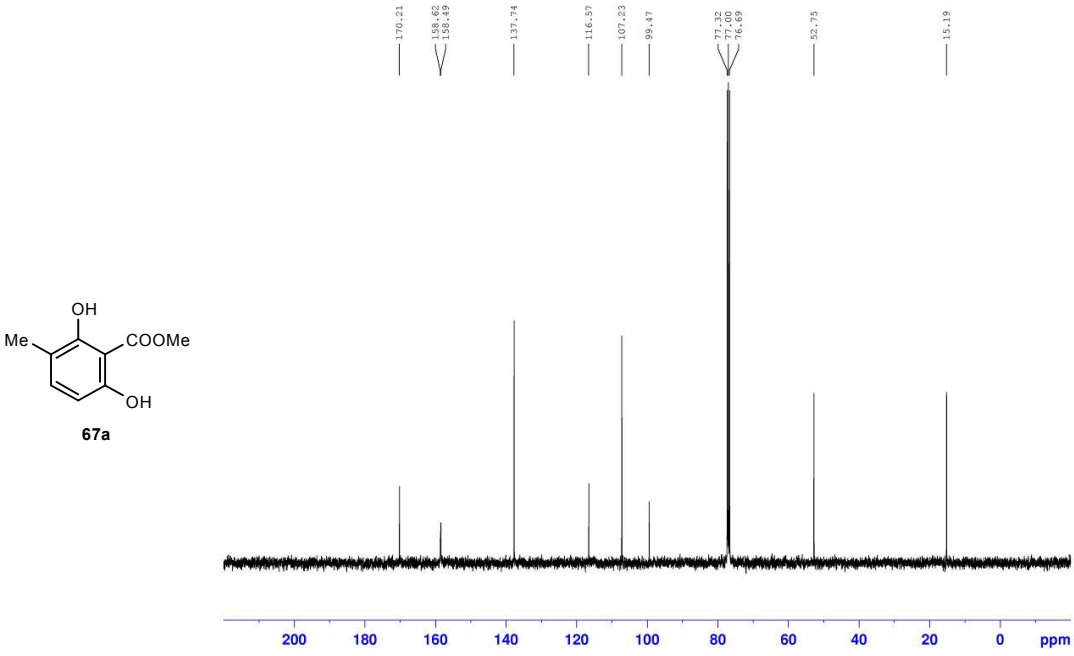



These experimental results showed that other than the carbonyl carbon at 200 ppm, $\mathbf{H_1}$ is coupled with the alkene carbon $\mathbf{C_2}$ at 140.8 ppm (possibly the other alkene carbon at 144.0 ppm as well) but not the alkyl carbon $\mathbf{C_3}$ which appears in the range between 42.9 ppm and 52.7 ppm. What is more, since the same correlation is shown for both isomers, it suggests that these two isomers are diastereomers rather than isomers caused by different position of the double bond in the molecule.

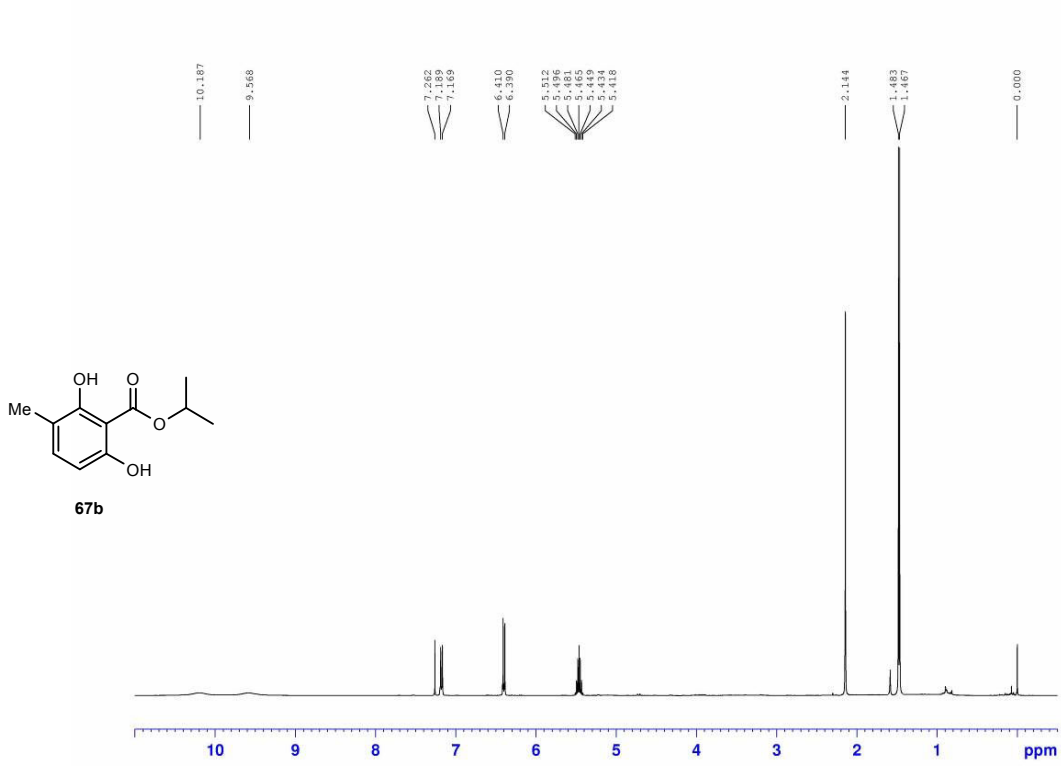
## 2.3.10 $^{1}$H NMR and $^{13}$C NMR Spectra



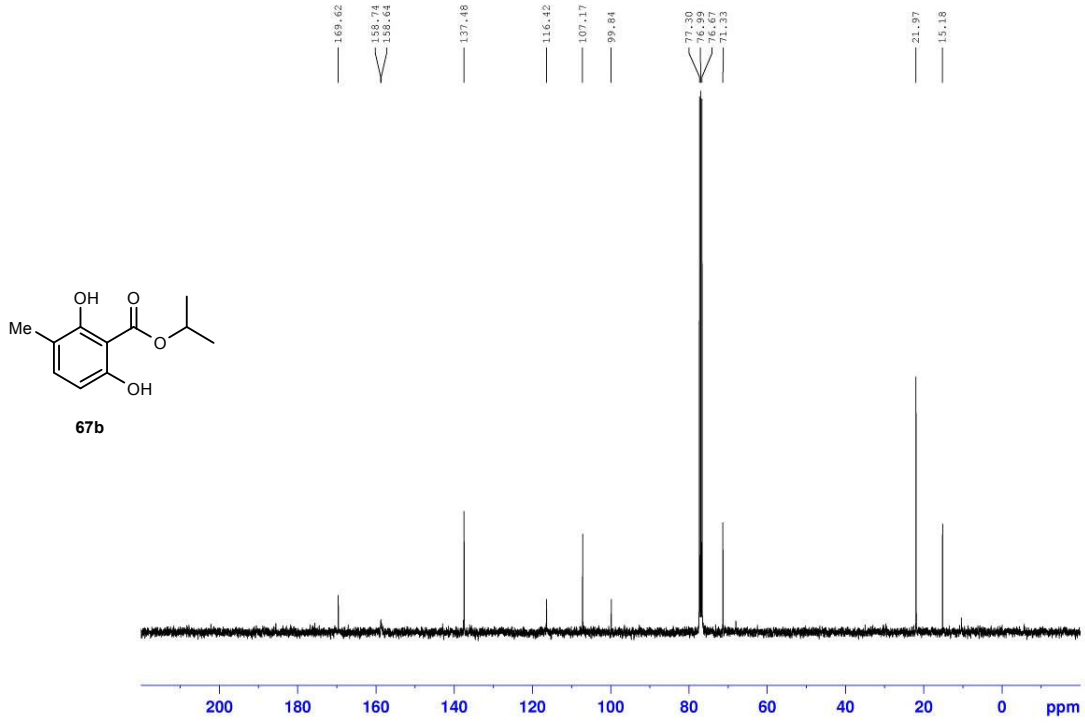

**67a**



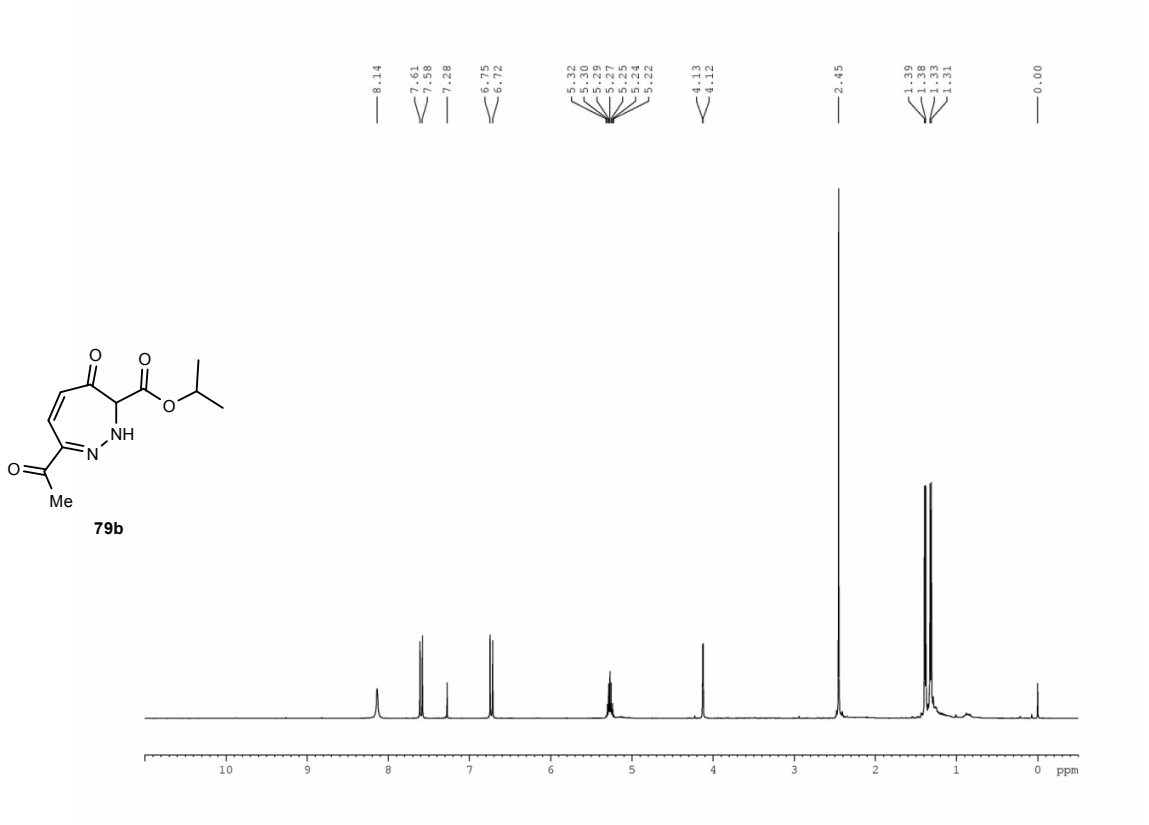

**67a**


10.187
9.568
7.262
7.189
7.169
6.410
6.390
5.512
5.496
5.481
5.465
5.449
5.434
5.418
2.144
1.483
1.467
0.000
OH
O
Me
O
OH
10
9
8
7
6
5
4
3
2
1
ppm

**67b**

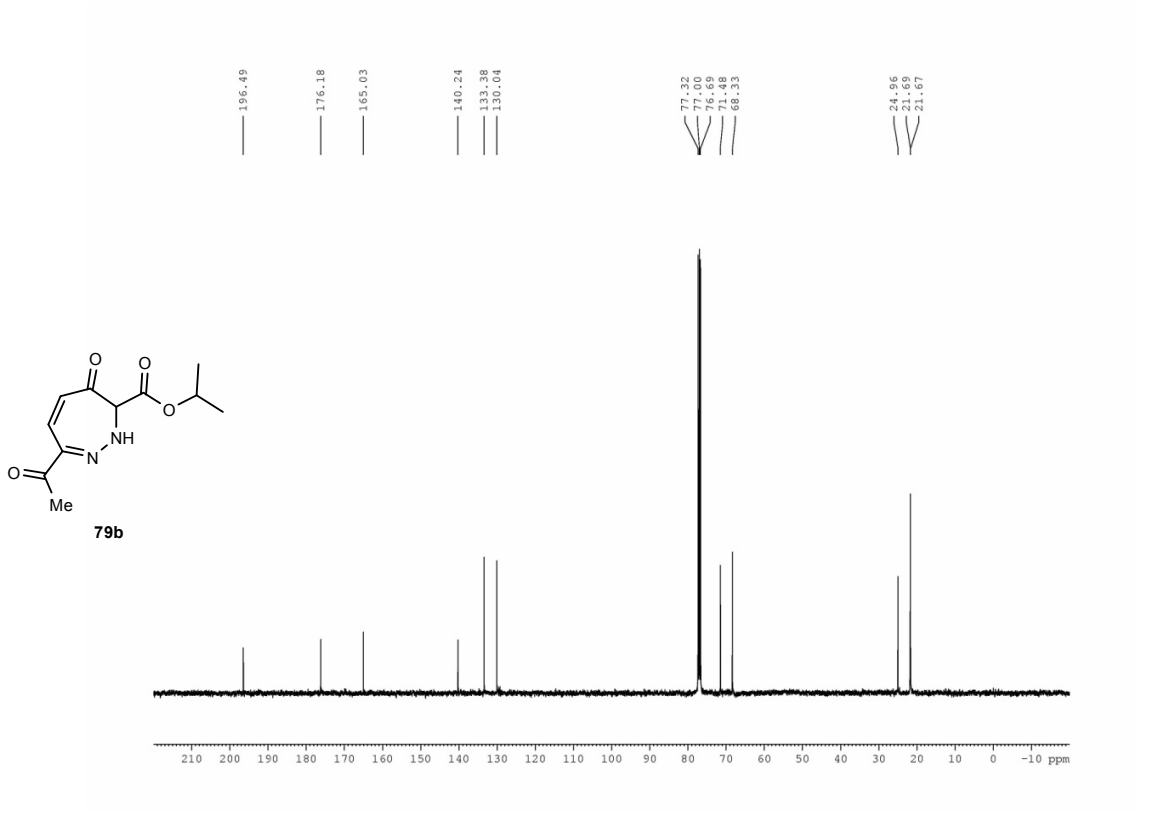

169.62
158.74
158.64
137.48
116.42
107.17
99.84
77.30
76.99
76.67
71.33
21.97
15.18
OH
O
Me
O
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

**67b**


8.14
7.61
7.58
7.28
6.75
6.72
5.32
5.30
5.29
5.27
5.25
5.24
5.22
4.13
4.12
2.45
1.39
1.38
1.33
1.31
0.00
10
9
8
7
6
5
4
3
2
1
0
ppm

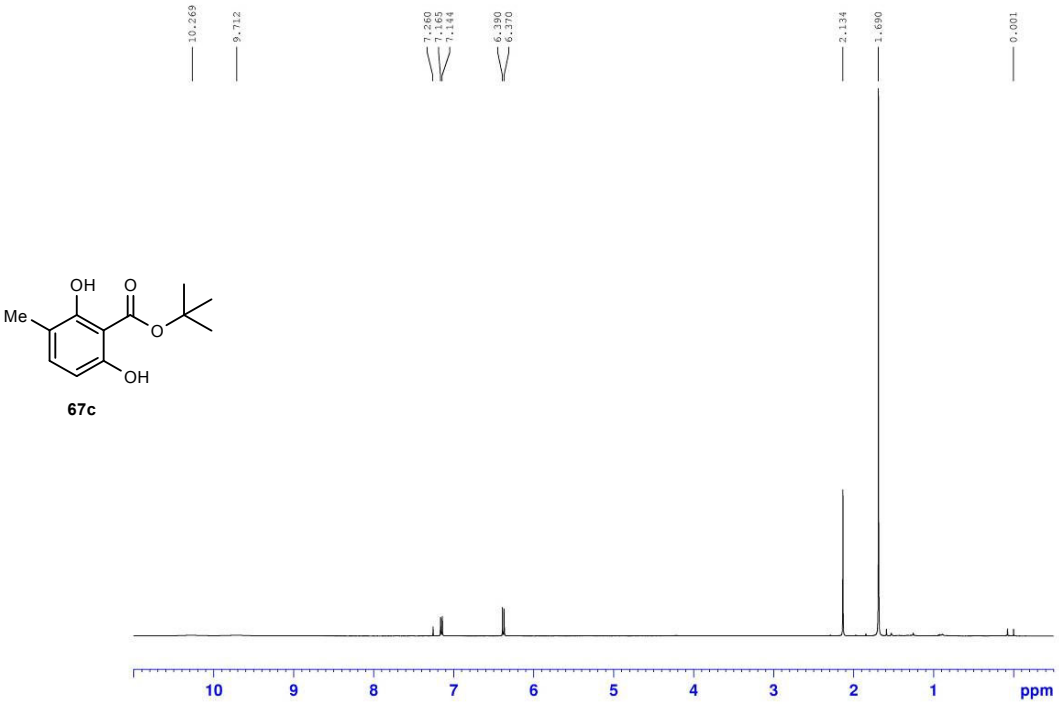

O
O
O
NH
N
O
Me

**79b**

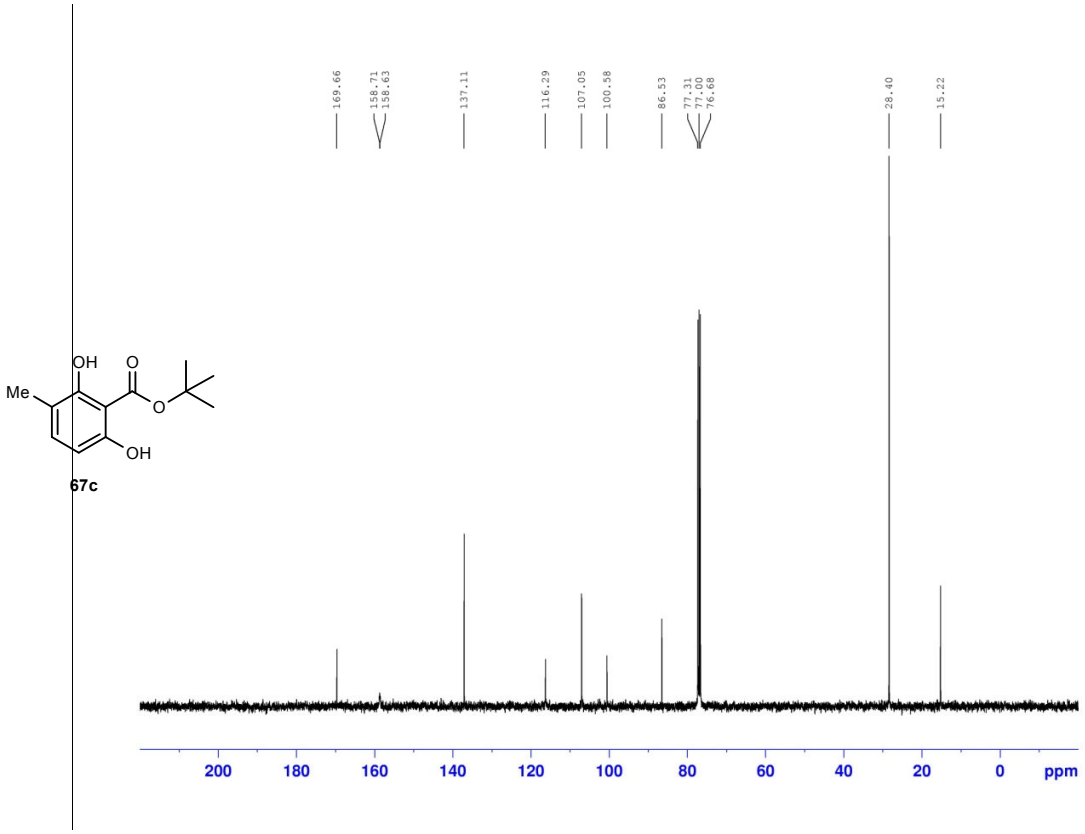

196.49
176.18
165.03
140.24
133.38
130.04
77.32
77.00
76.69
71.48
68.33
24.96
21.69
21.67
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm


O
O
O
NH
N
O
Me

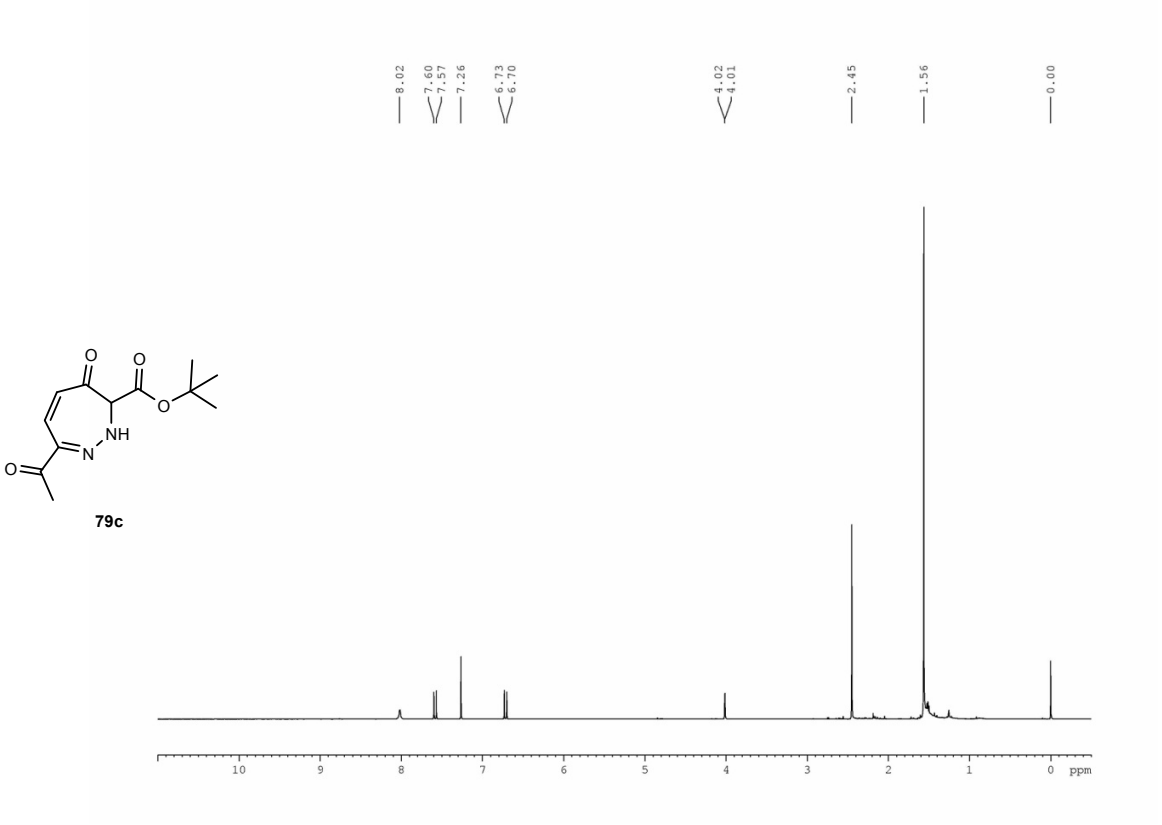
**79b**


10.269
9.712
7.260
7.165
7.144
6.390
6.370
2.134
1.690
0.001
OH
O
Me
O
OH
10
9
8
7
6
5
4
3
2
1
ppm

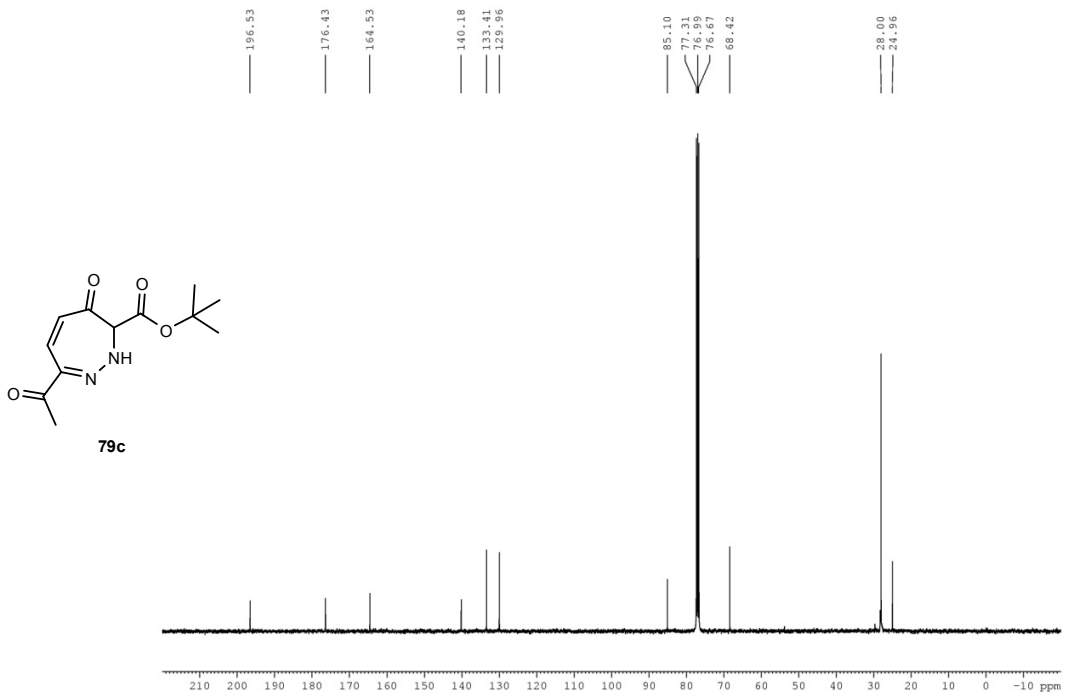
**67c**


169.66
158.71
158.63
137.11
116.29
107.05
100.58
86.53
77.31
77.00
76.68
28.40
15.22
OH
O
Me
O
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

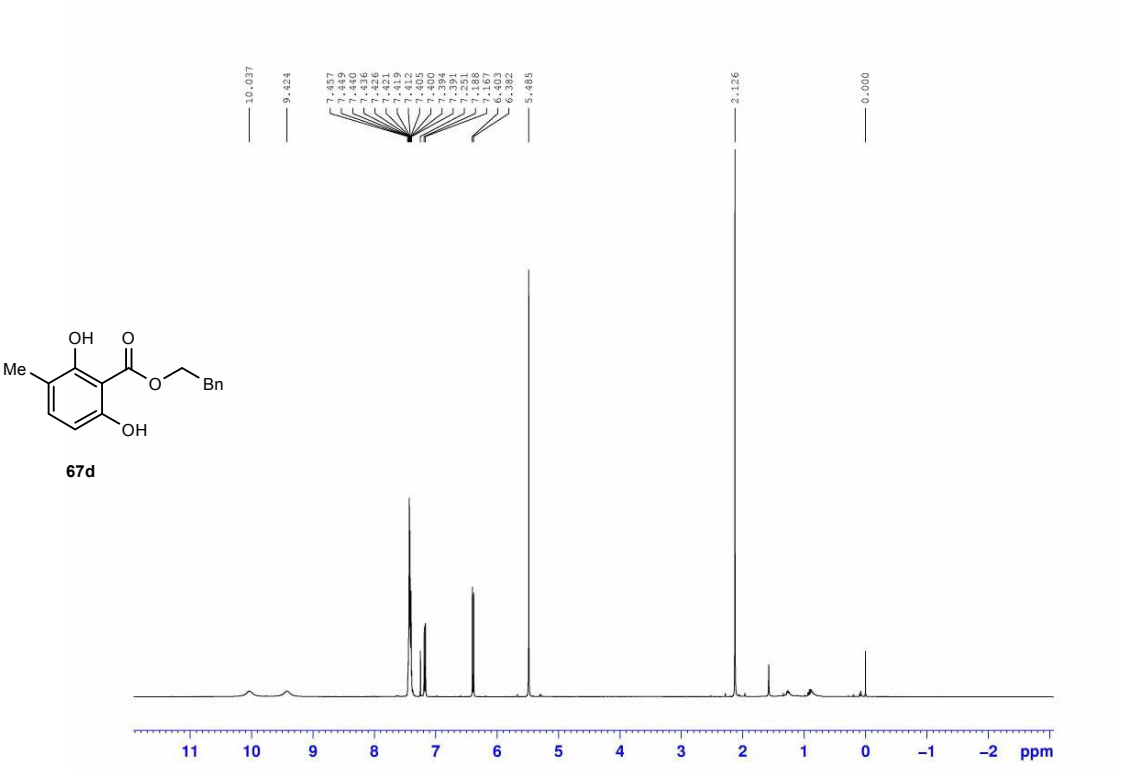
**67c**


8.02
7.60
7.57
7.26
6.73
6.70
4.02
4.01
2.45
1.56
0.00
O
O
O
NH
N
O
10
9
8
7
6
5
4
3
2
1
0
ppm

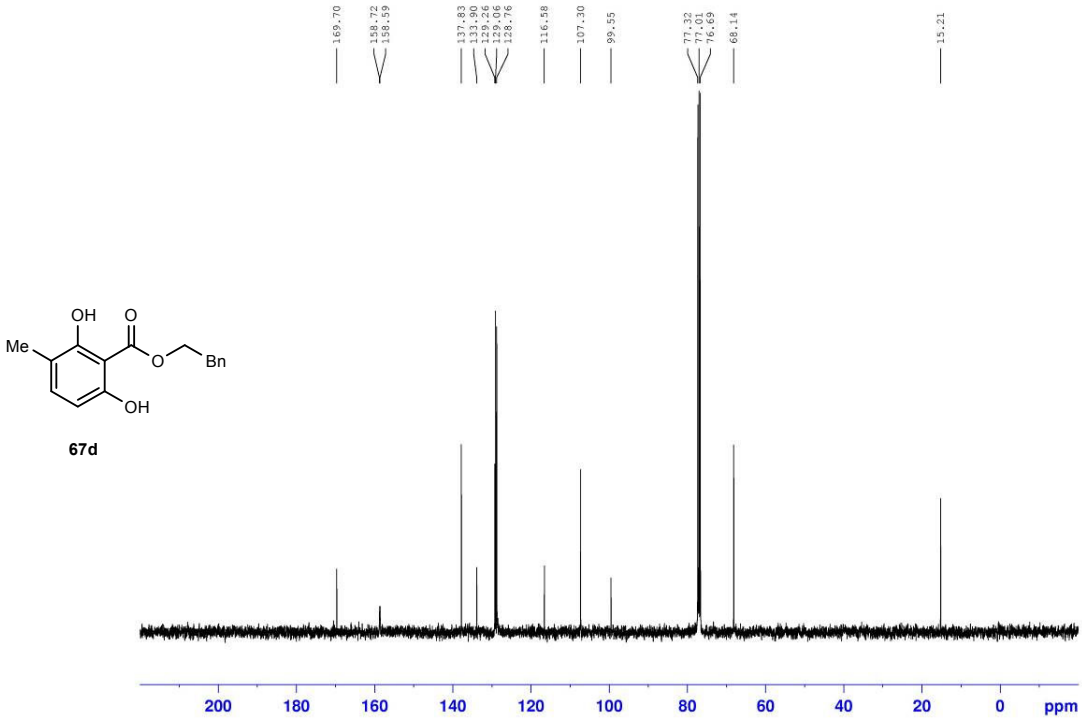
**79c**


196.53
176.43
164.53
140.18
133.41
129.96
85.10
77.31
76.99
76.67
68.42
28.00
24.96
O
O
O
NH
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10 ppm

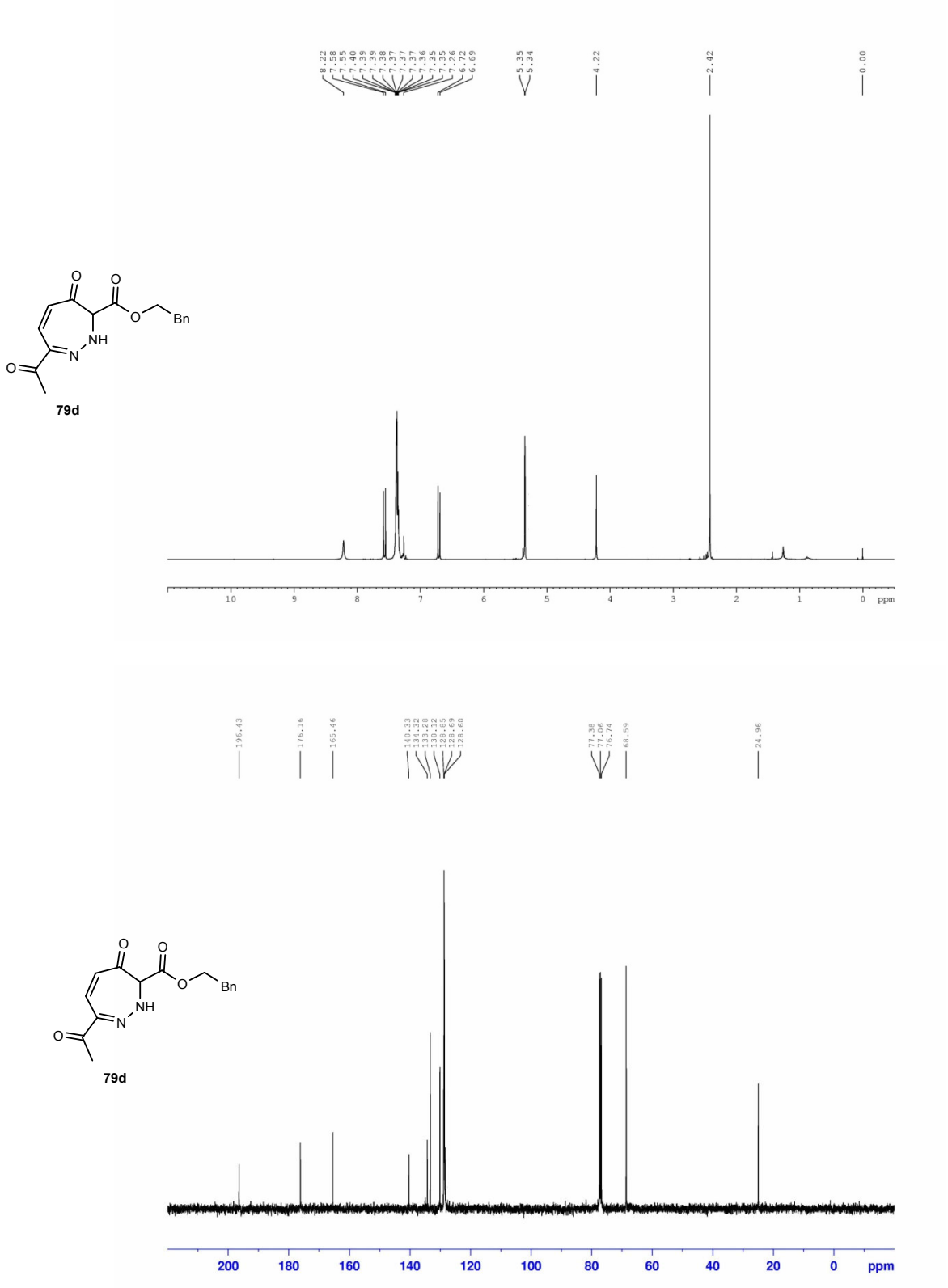
**79c**

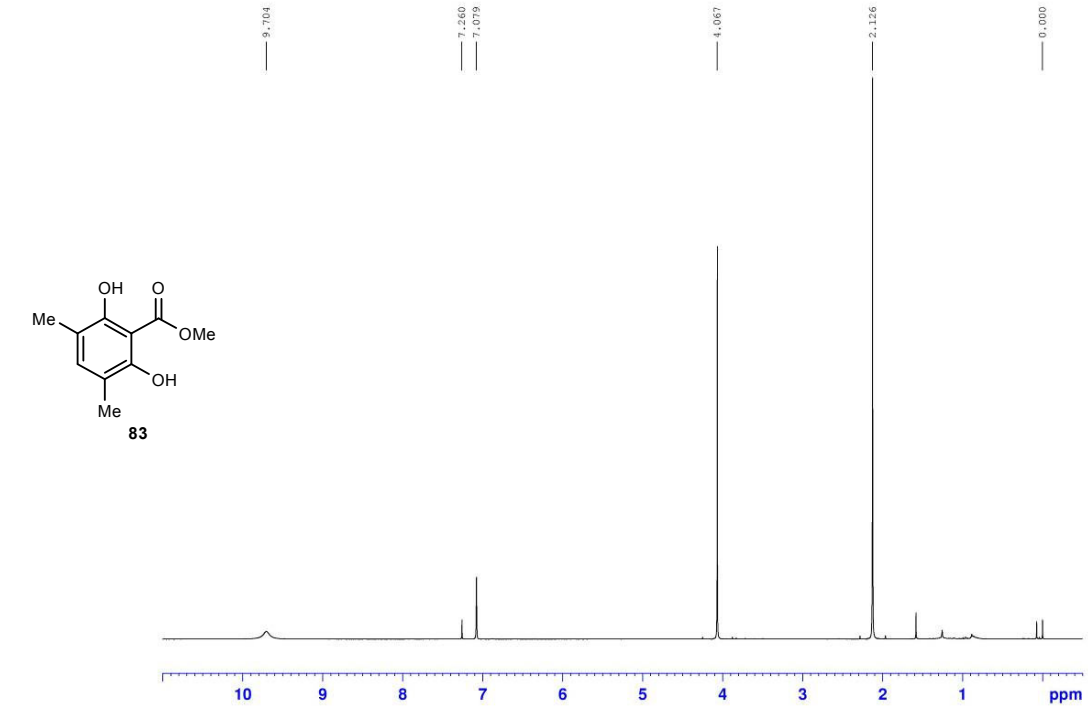

10.037
9.424
7.457
7.449
7.440
7.436
7.426
7.421
7.419
7.412
7.405
7.400
7.394
7.391
7.251
7.188
7.167
6.401
6.382
5.485
2.126
0.000
OH
O
Me
O
Bn
OH
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
ppm

**67d**

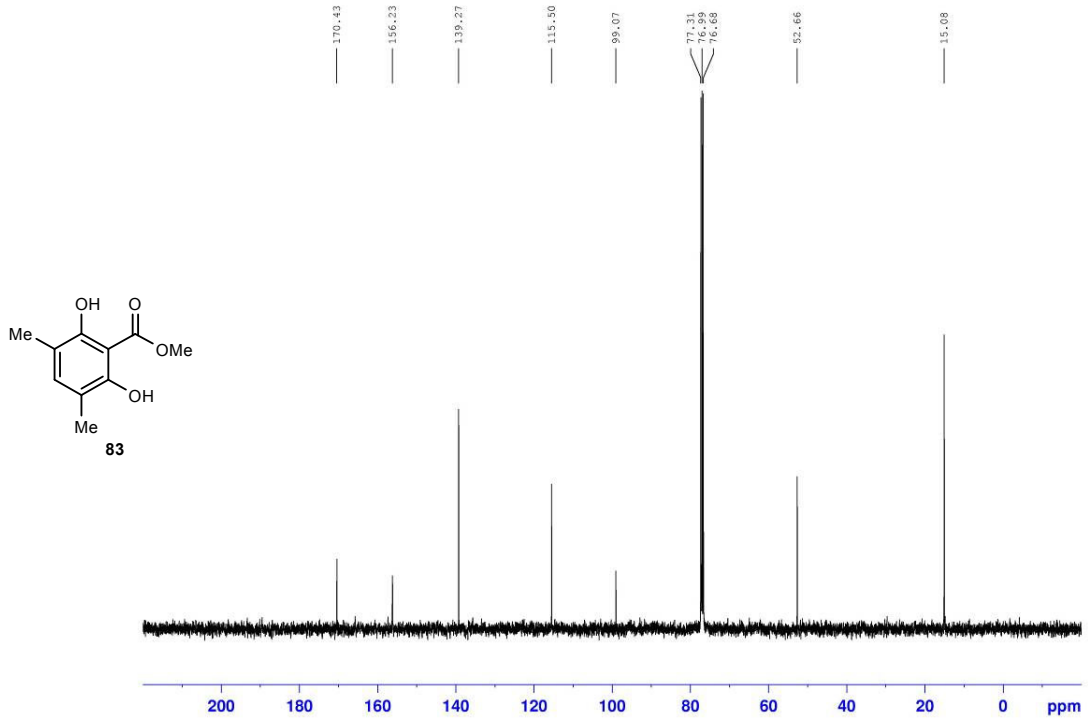

169.70
158.72
158.59
137.83
133.90
129.66
129.06
128.76
116.58
107.30
99.55
77.32
77.01
76.69
68.14
15.21
OH
O
Me
O
Bn
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

**67d**

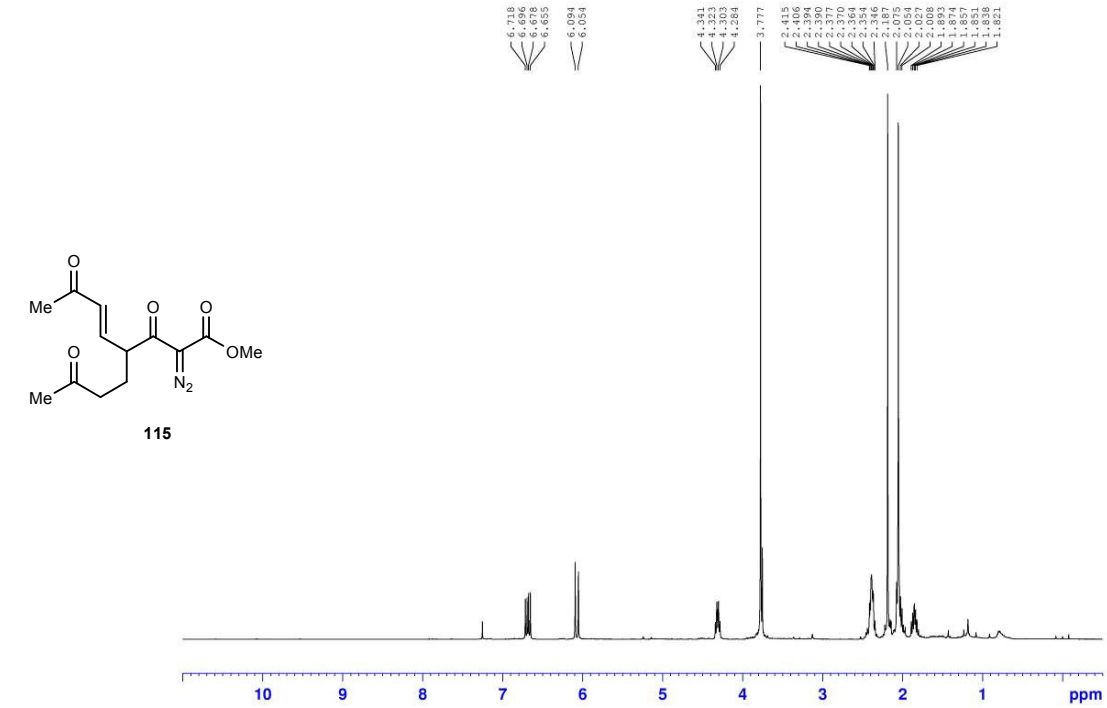

8.22
7.58
7.55
7.40
7.39
7.39
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.26
6.72
6.69
5.35
5.34
4.22
2.42
0.00
O
O
O
Bn
NH
N
O
79d
10
9
8
7
6
5
4
3
2
1
0
ppm
196.43
176.16
165.46
140.33
134.32
133.28
130.22
128.80
128.69
128.60
77.38
77.06
76.74
68.59
24.96
O
O
O
Bn
NH
N
O
79d
200
180
160
140
120
100
80
60
40
20
0
ppm

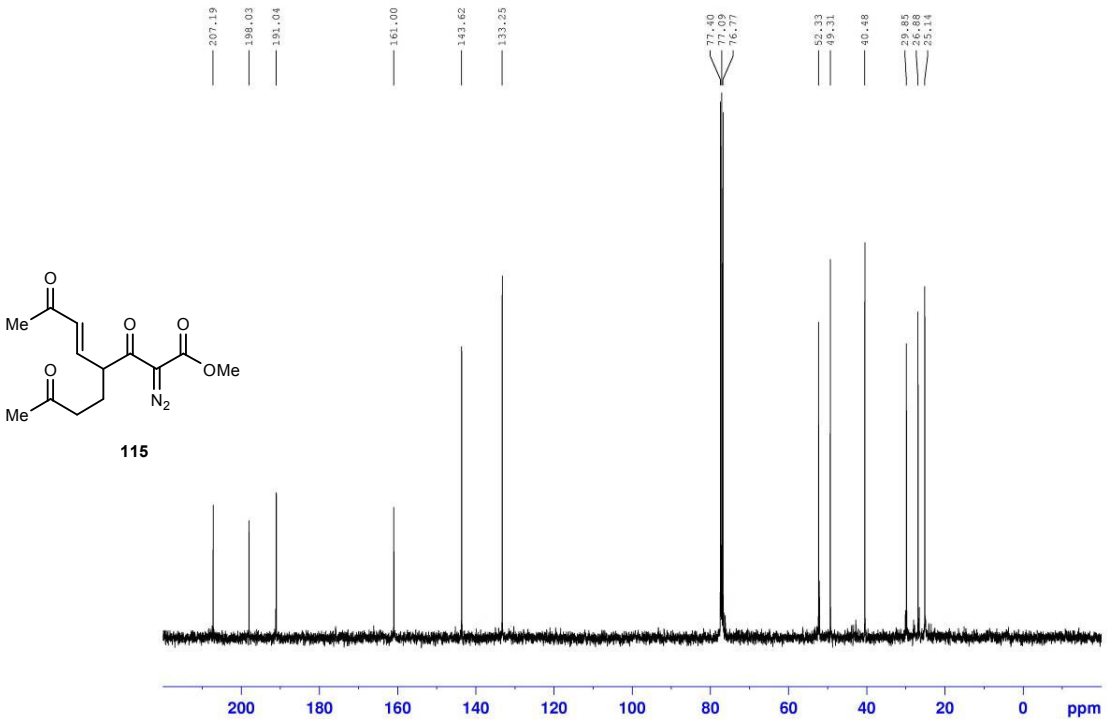

9.704
7.260
7.079
4.067
2.126
0.000
OH
O
Me
OMe
OH
Me
10
9
8
7
6
5
4
3
2
1
ppm

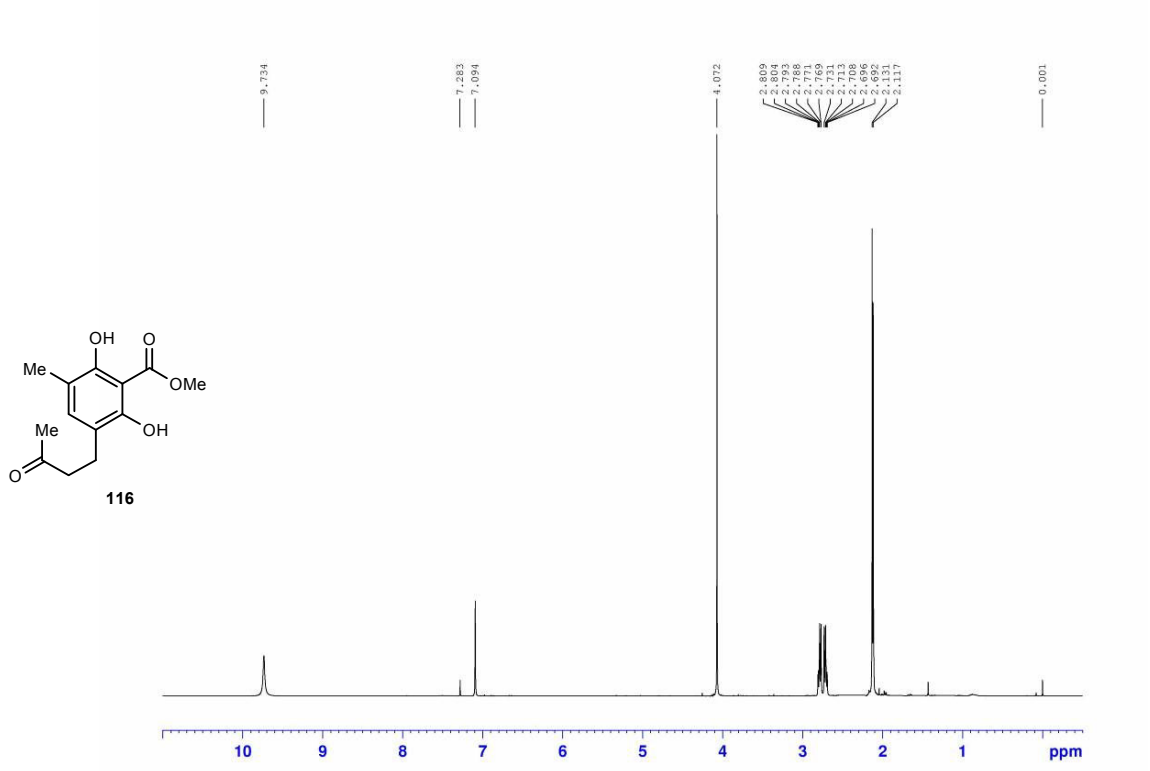
**83**

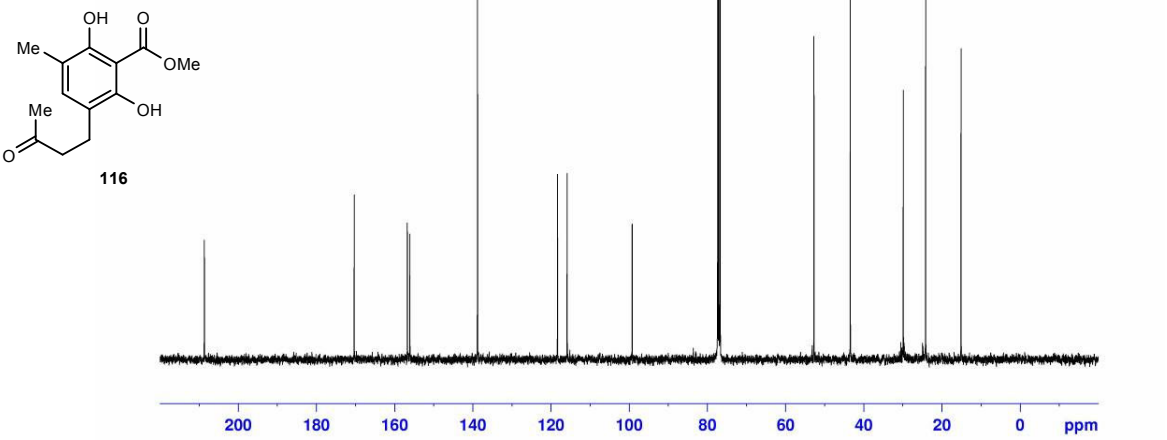

170.43
156.23
139.27
115.50
99.07
77.31
76.99
76.68
52.66
15.08
OH
O
Me
OMe
OH
Me
200
180
160
140
120
100
80
60
40
20
0
ppm

**83**


6.718
6.696
6.678
6.655
6.094
6.054
4.341
4.323
4.303
4.284
3.777
2.415
2.406
2.394
2.390
2.377
2.370
2.364
2.354
2.346
2.057
2.055
2.054
2.027
2.008
1.893
1.874
1.857
1.851
1.838
1.821
Me
O
O
O
OMe
O
Me
N2
115
10
9
8
7
6
5
4
3
2
1
ppm

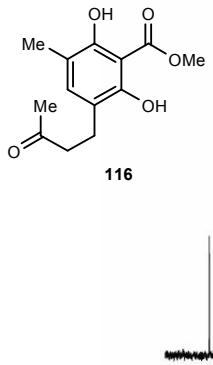

207.19
198.03
191.04
161.00
143.62
133.25
77.40
77.09
76.77
52.33
49.31
40.48
29.85
26.88
25.14
Me
O
O
O
OMe
O
Me
N2
115
200
180
160
140
120
100
80
60
40
20
0
ppm


9.734
7.283
7.094
4.072
2.809
2.804
2.793
2.788
2.771
2.769
2.731
2.713
2.708
2.696
2.692
2.131
2.117
0.001
10
9
8
7
6
5
4
3
2
1
ppm

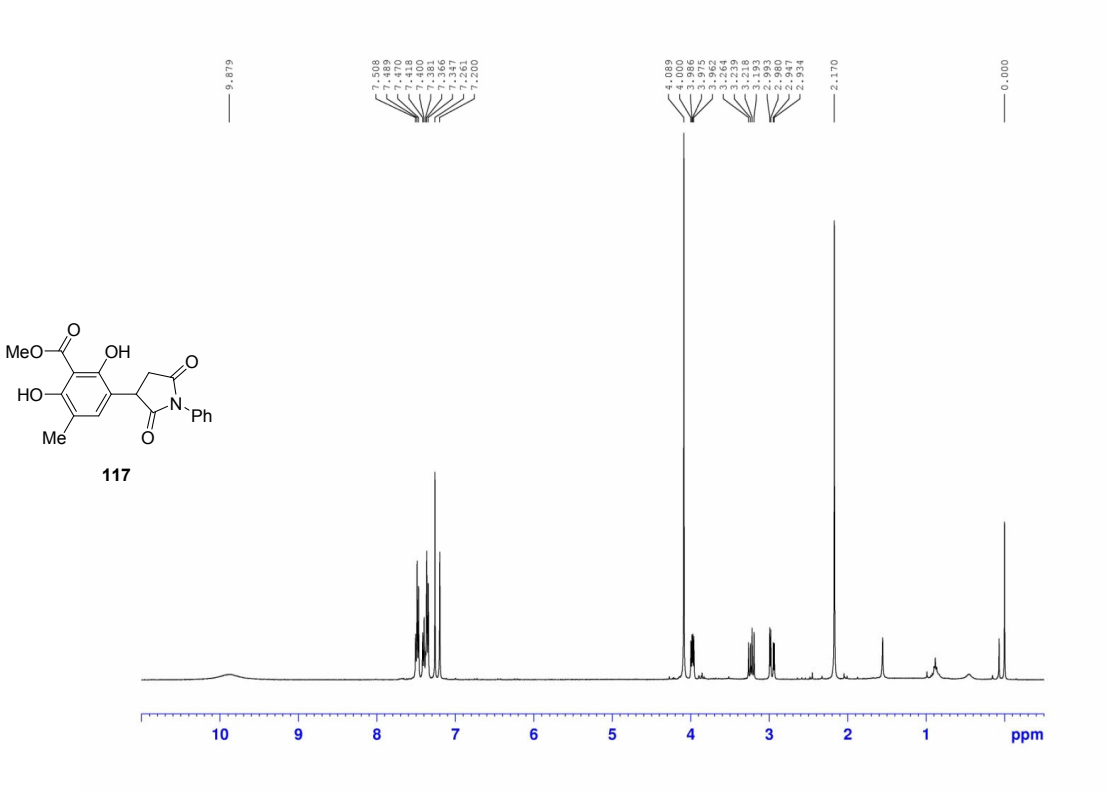

208.68
170.35
156.76
156.11
138.81
118.35
115.87
99.24
77.36
77.04
76.72
52.73
43.43
29.89
24.16
15.10
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
O
Me
OMe
Me
OH
O

**116**

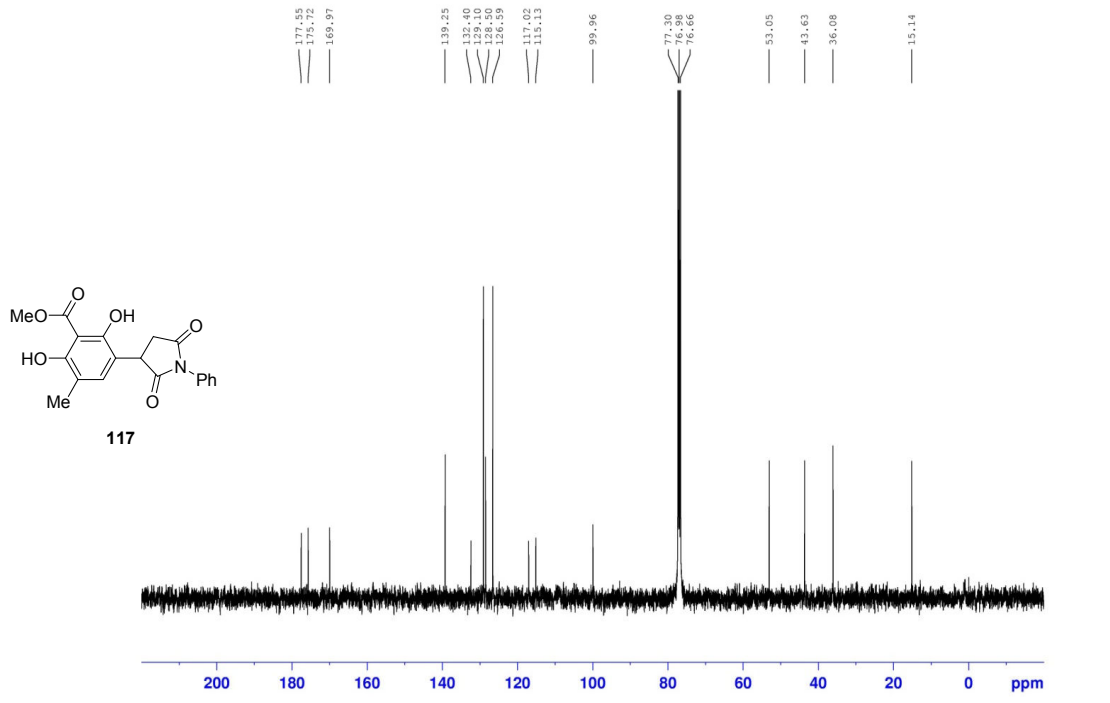

OH
O
Me
OMe
Me
OH
O

**116**


9.879
7.508
7.489
7.470
7.418
7.400
7.381
7.366
7.347
7.261
7.200
4.089
4.000
3.986
3.975
3.962
3.264
3.239
3.218
3.193
3.183
2.980
2.947
2.934
2.170
0.000
10
9
8
7
6
5
4
3
2
1
ppm

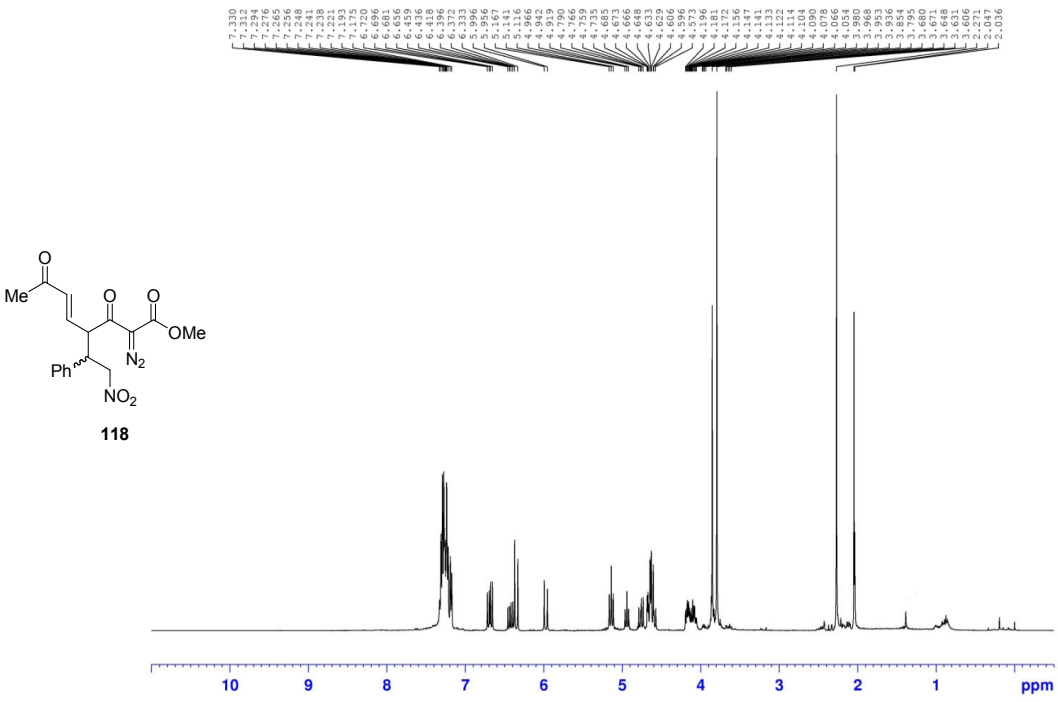

MeO
OH
HO
Me
O
N
Ph

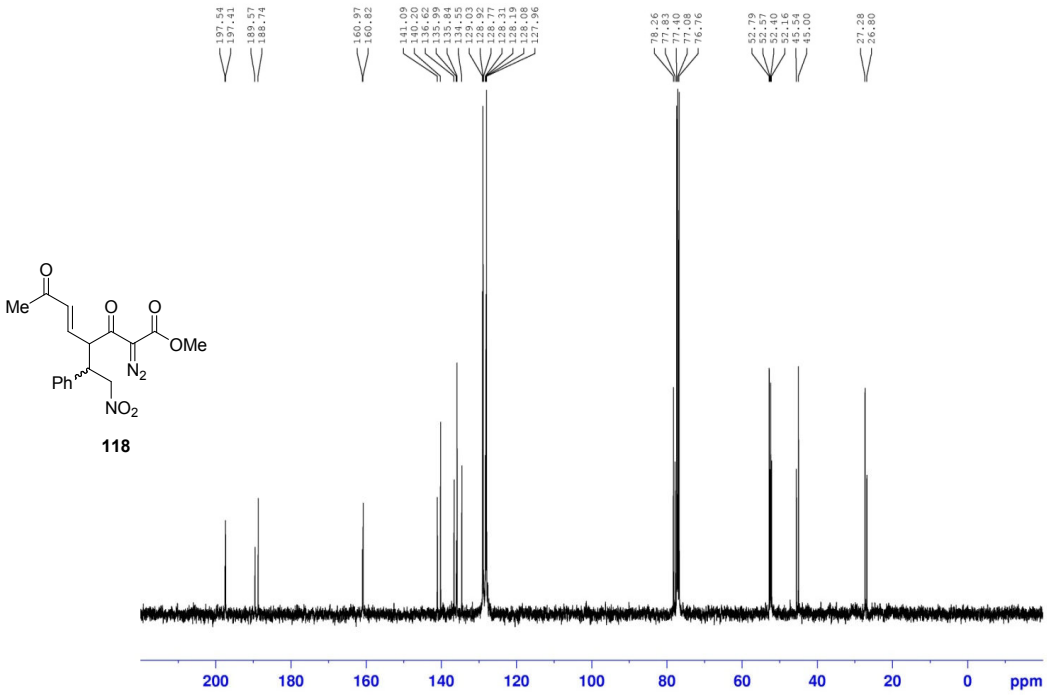
**117**

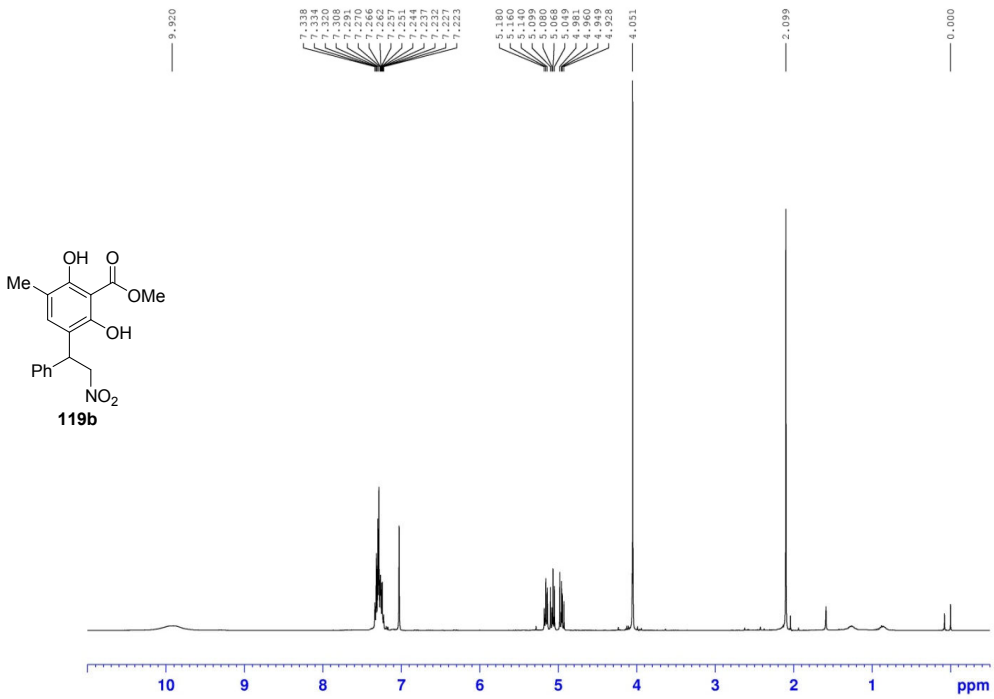

177.55
175.72
169.97
139.25
132.40
129.10
128.50
126.59
117.02
115.13
99.96
77.30
76.98
76.66
53.05
43.63
36.08
15.14
200
180
160
140
120
100
80
60
40
20
0
ppm

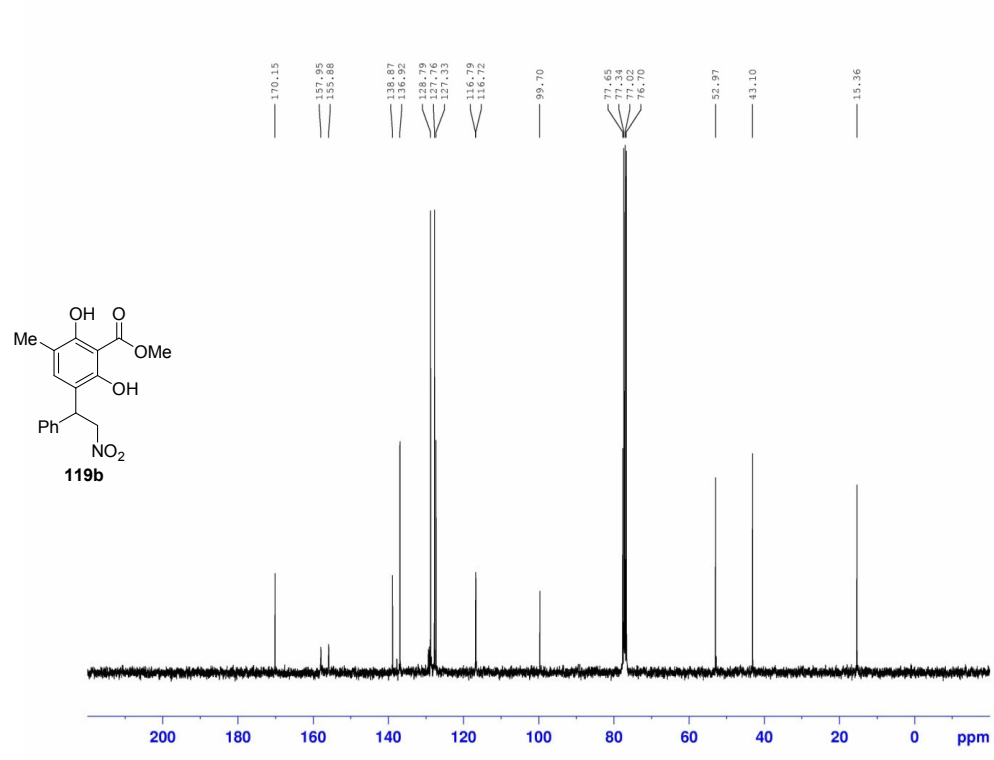

MeO
OH
HO
Me
O
N
Ph

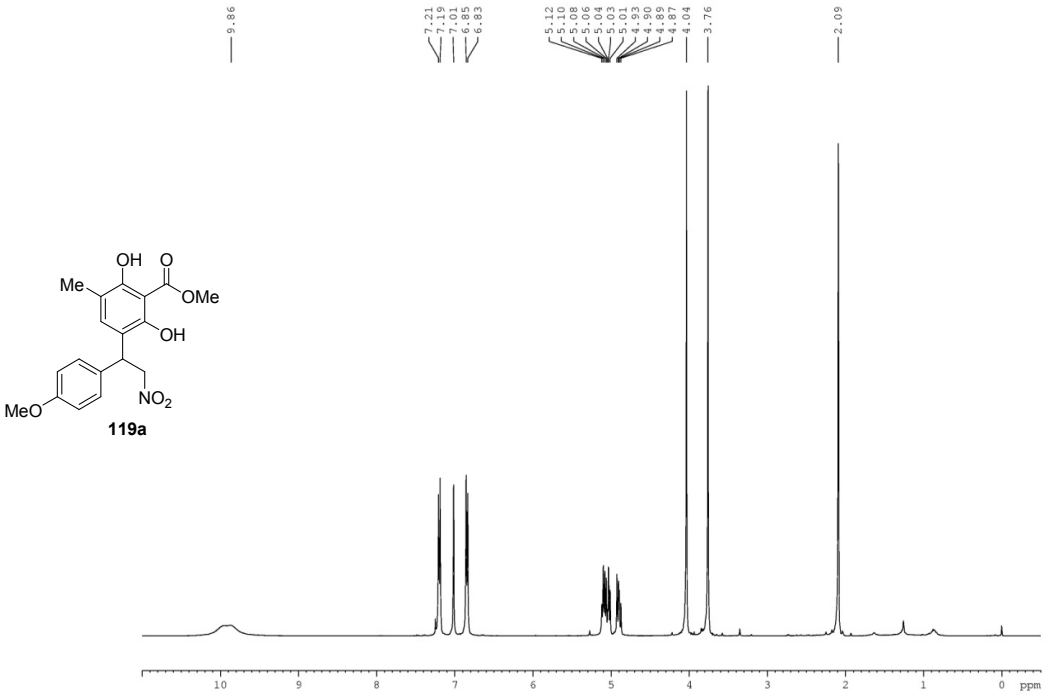
**117**

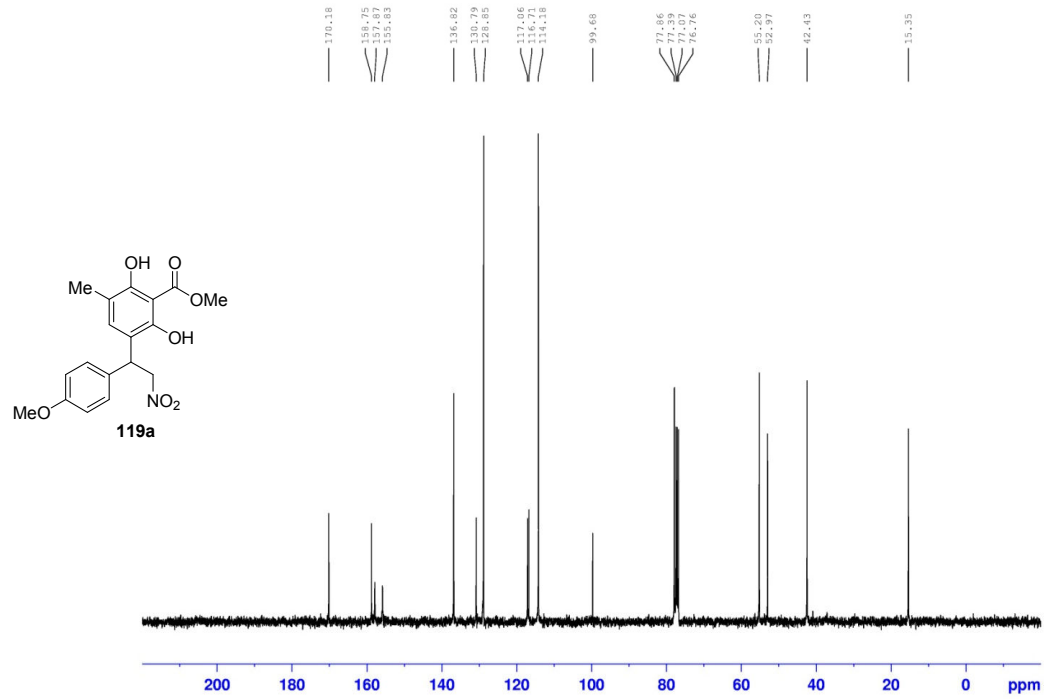

Me
O
O
O
OMe
N2
Ph
NO2
118
10
9
8
7
6
5
4
3
2
1
ppm

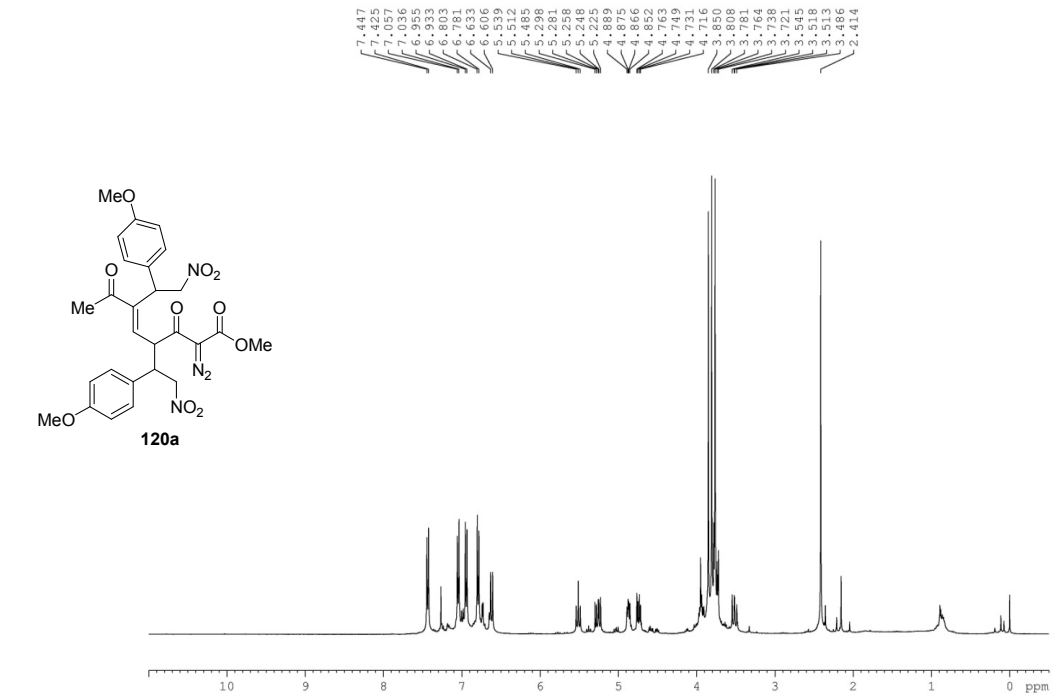

Me
O
O
O
OMe
N2
Ph
NO2
118
200
180
160
140
120
100
80
60
40
20
0
ppm

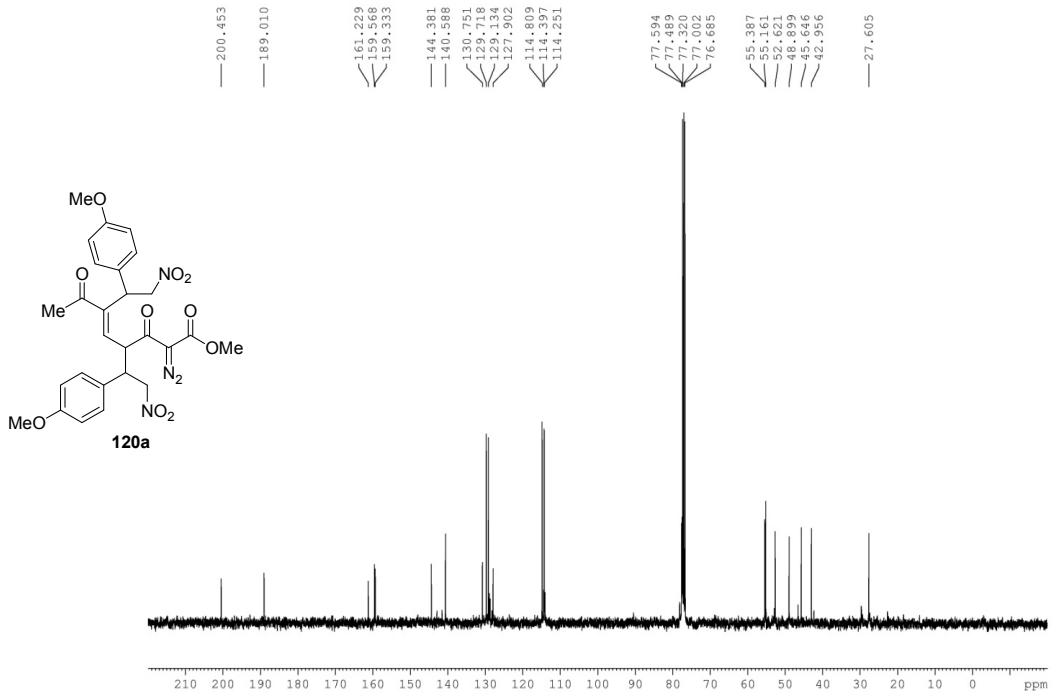

9.920
7.338
7.334
7.320
7.308
7.291
7.270
7.266
7.262
7.257
7.251
7.244
7.237
7.230
7.227
7.223
5.180
5.160
5.140
5.109
5.080
5.068
5.049
4.981
4.960
4.949
4.928
4.051
2.099
0.000
OH
O
Me
OMe
OH
Ph
NO2
119b
10
9
8
7
6
5
4
3
2
1
ppm


170.15
157.95
155.88
138.87
136.92
128.79
127.76
127.33
116.79
116.72
99.70
77.65
77.34
77.02
76.70
52.97
43.10
15.36
OH
O
Me
OMe
OH
Ph
NO2
119b
200
180
160
140
120
100
80
60
40
20
0
ppm


9.86
7.21
7.19
7.01
6.85
6.83
5.12
5.10
5.08
5.06
5.04
5.03
5.01
4.93
4.90
4.89
4.87
4.04
3.76
2.09
OH
O
Me
OMe
OH
MeO
NO2
119a
10
9
8
7
6
5
4
3
2
1
0
ppm


170.18
158.75
157.87
155.83
136.82
130.79
128.85
117.06
116.71
114.18
99.68
77.86
77.39
77.23
76.76
55.20
52.97
42.43
15.35
OH
O
Me
OMe
OH
MeO
NO2
119a
200
180
160
140
120
100
80
60
40
20
0
ppm


7.447
7.425
7.057
7.036
6.955
6.933
6.803
6.781
6.633
6.606
5.539
5.512
5.485
5.298
5.281
5.258
5.248
5.225
4.889
4.875
4.866
4.852
4.763
4.749
4.731
4.716
3.850
3.808
3.781
3.764
3.738
3.721
3.545
3.518
3.513
3.486
2.414
MeO
NO2
O
Me
O
O
OMe
N2
NO2
MeO
120a
10
9
8
7
6
5
4
3
2
1
0 ppm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114.397
114.251
77.594
77.489
77.320
77.002
76.685
55.387
55.161
52.621
48.899
45.646
42.956
27.605
MeO
NO2
O
Me
O
O
OMe
N2
NO2
MeO
120a
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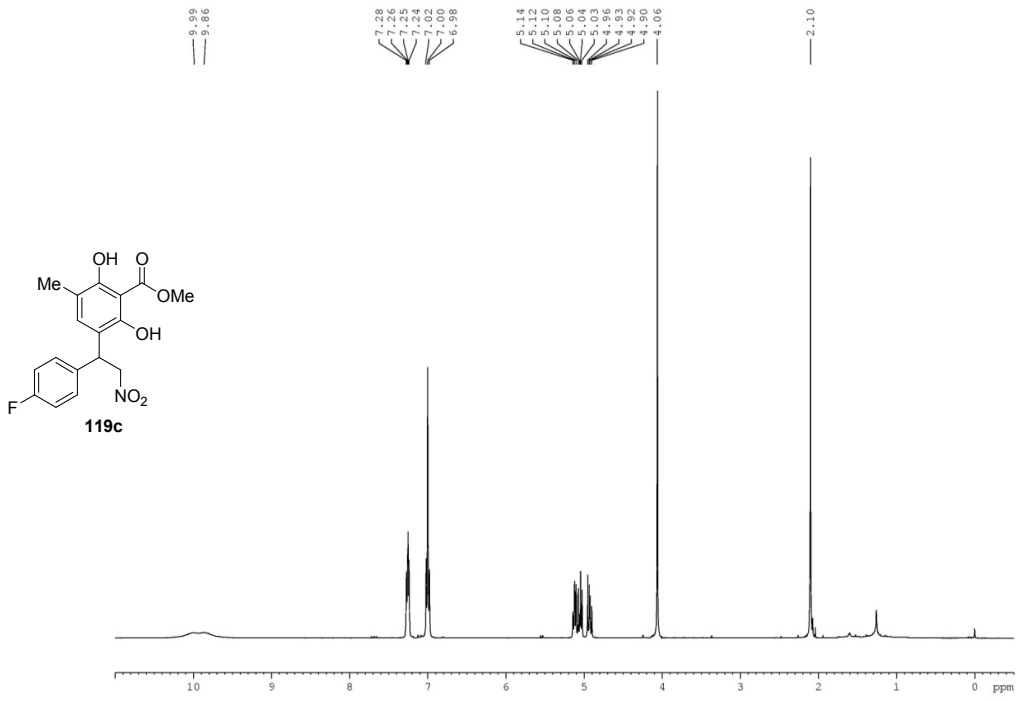
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4.06
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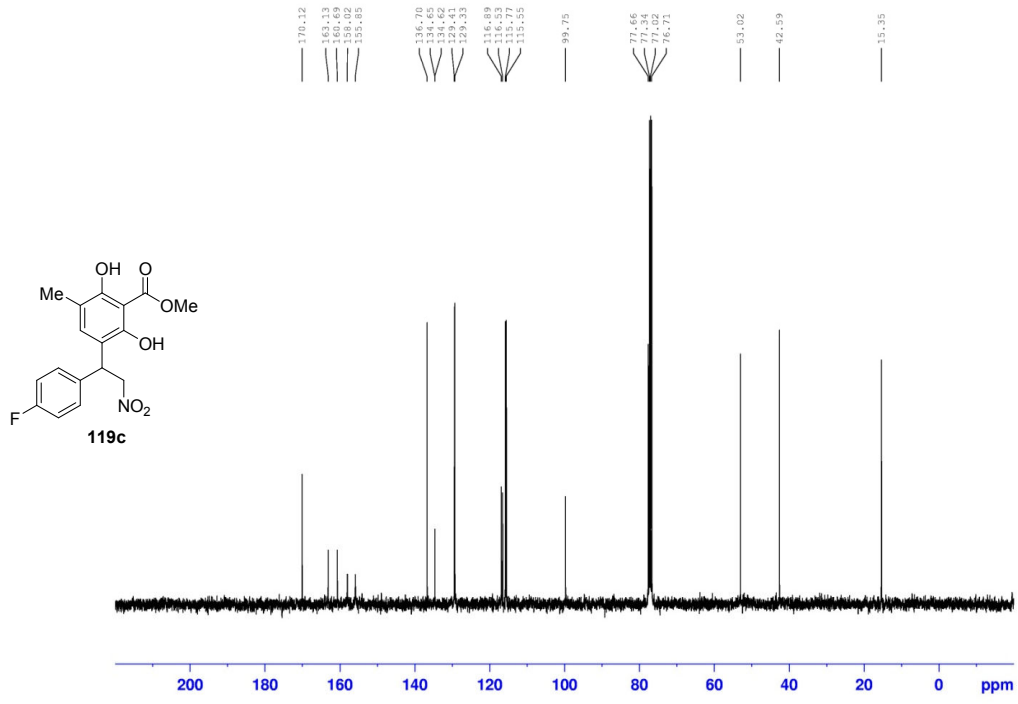
**119c**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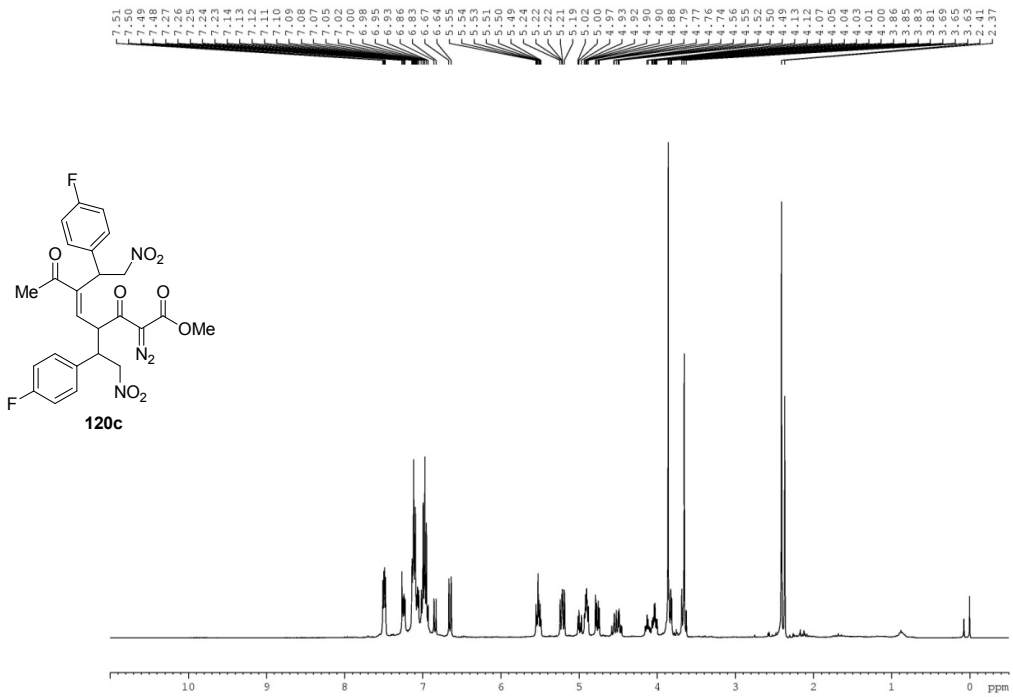
**119c**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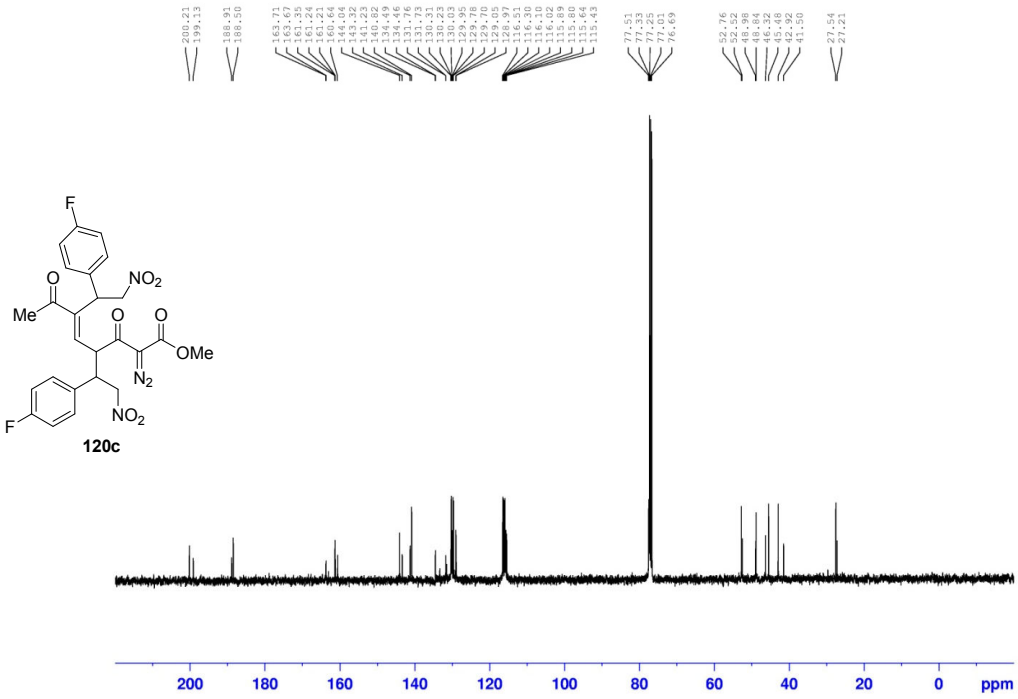
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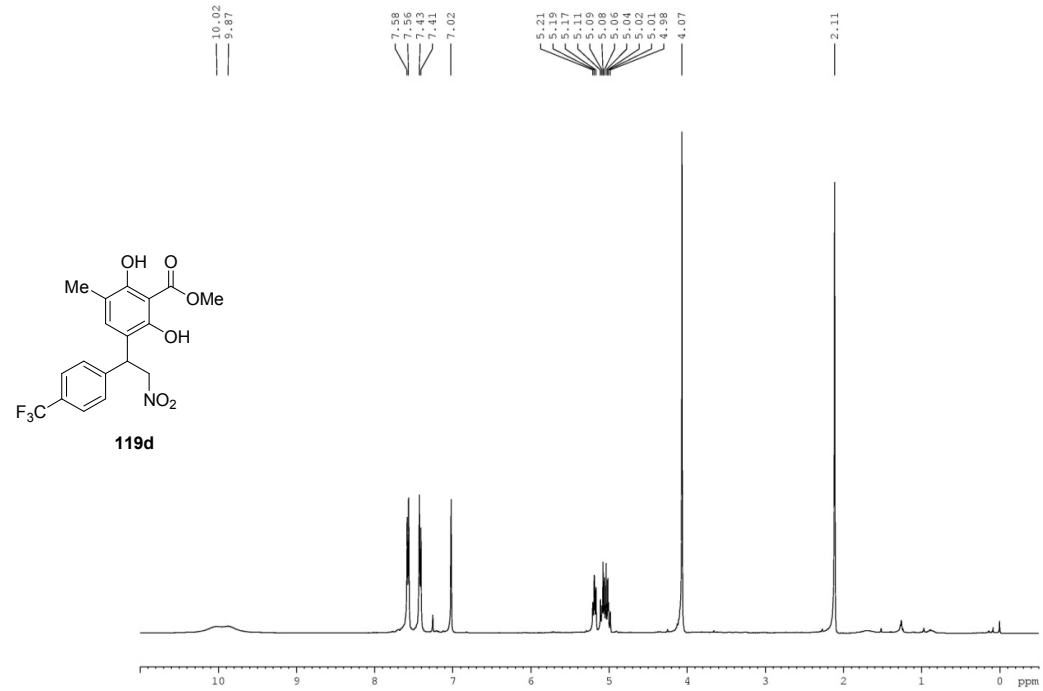
ppm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5.08
5.06
5.04
5.02
5.01
4.98
4.07
2.11
OH
O
Me
OMe
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NO2
10
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8
7
6
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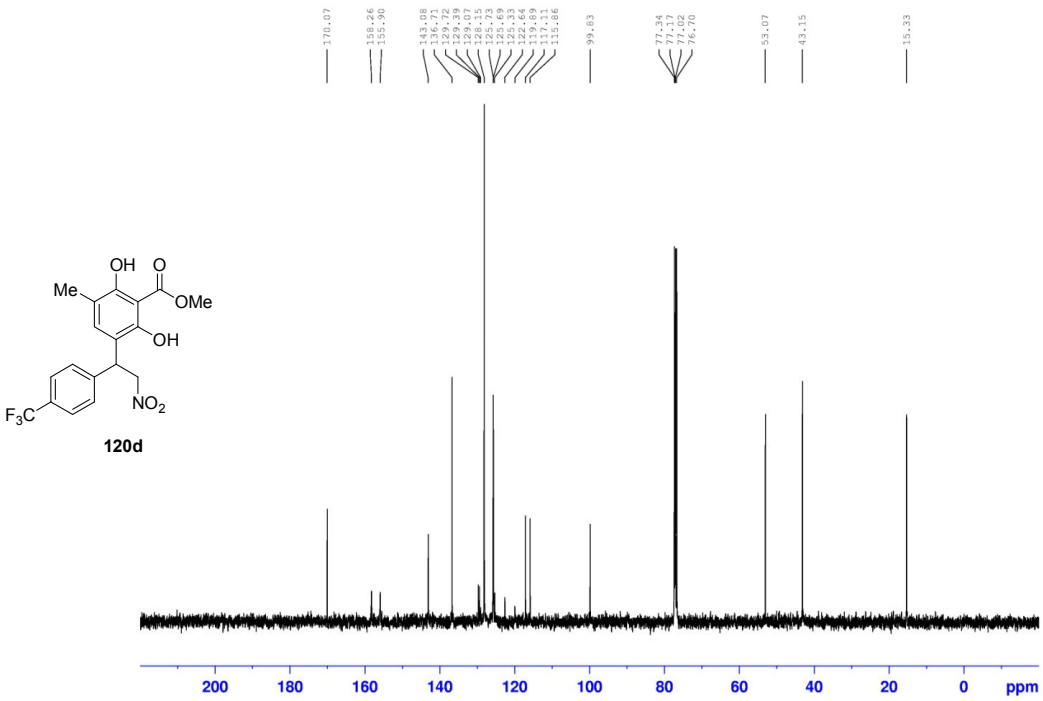
4
3
2
1
0
ppm

**119d**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119.89
117.11
115.86
99.83
77.34
77.17
77.02
76.70
53.07
43.15
15.33
OH
O
Me
OMe
OH
F3C
NO2
200
180
160
140
120
100
80
60
40
20
0
ppm

**120d**


7.596
7.575
7.542
7.521
7.443
7.425
7.406
7.376
7.209
7.188
7.139
7.121
7.103
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6.878
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5.760
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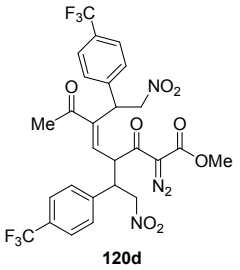
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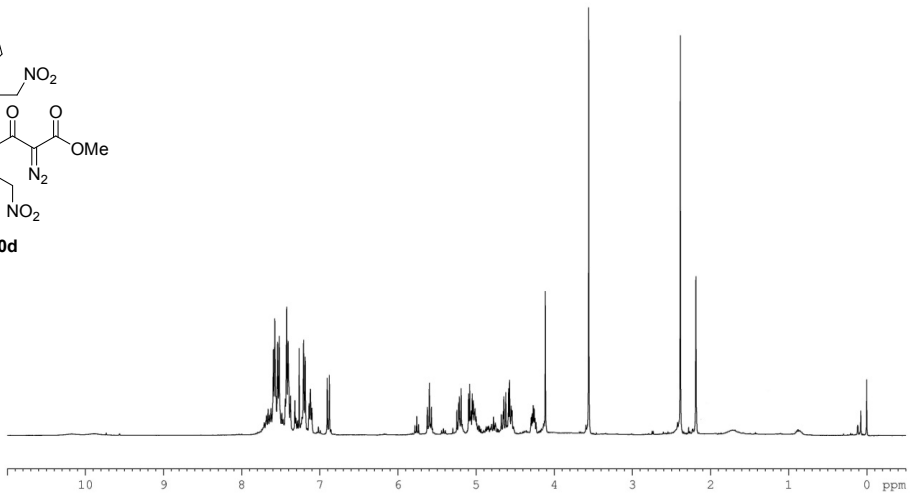
Me
O
O
OMe
N2
NO2
F3C

**120d**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9
8
7
6
5
4
3
2
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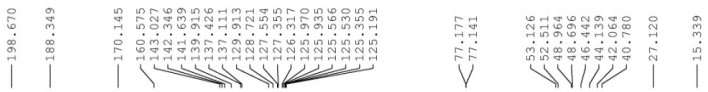
0
ppm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125.970
125.955
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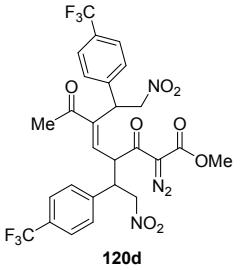
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NO2
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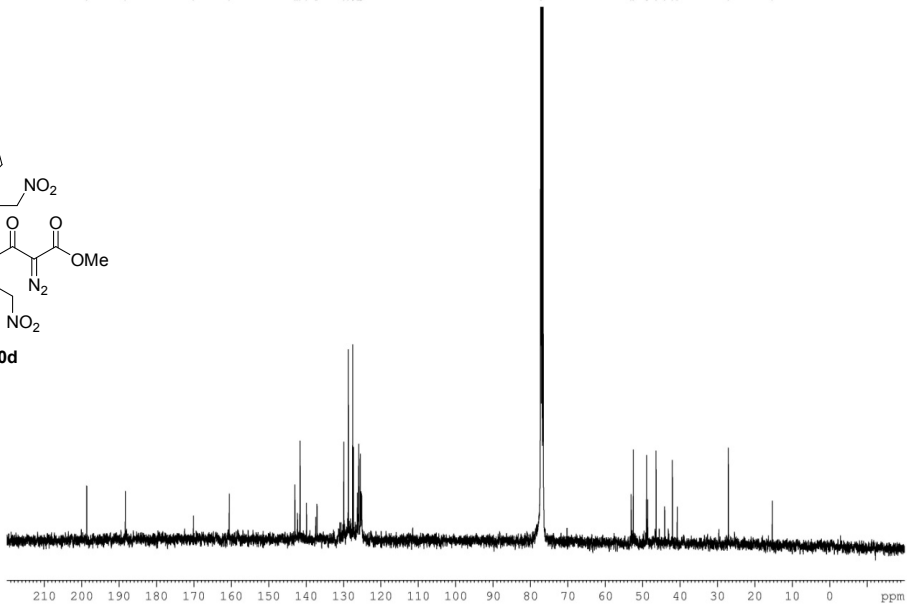
Me
O
O
OMe
N2
NO2
F3C

**120d**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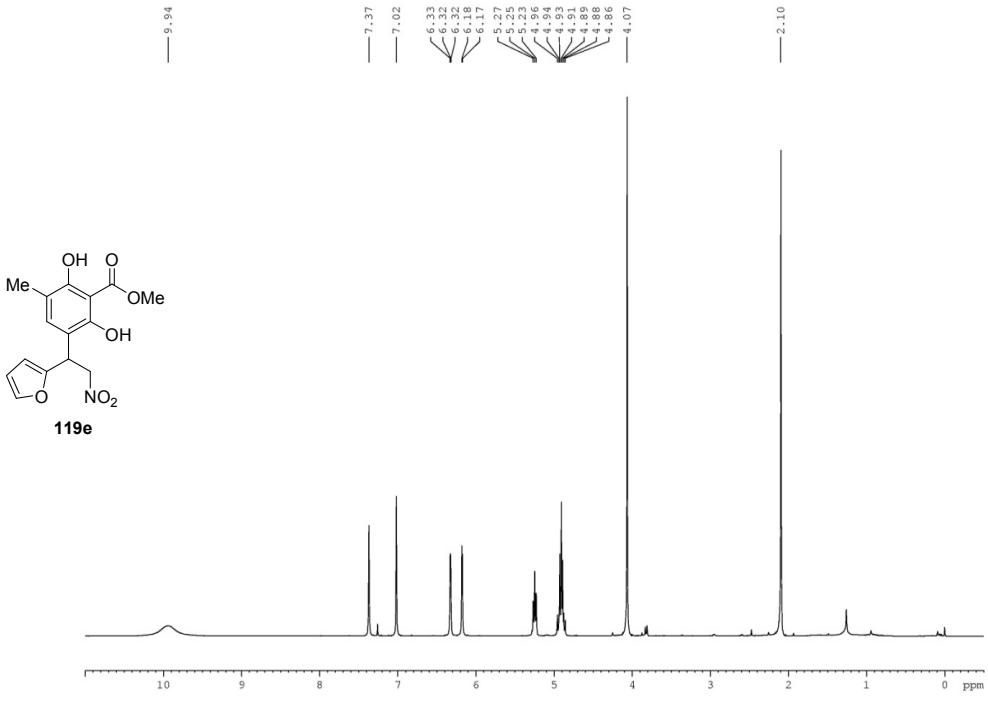
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2.10
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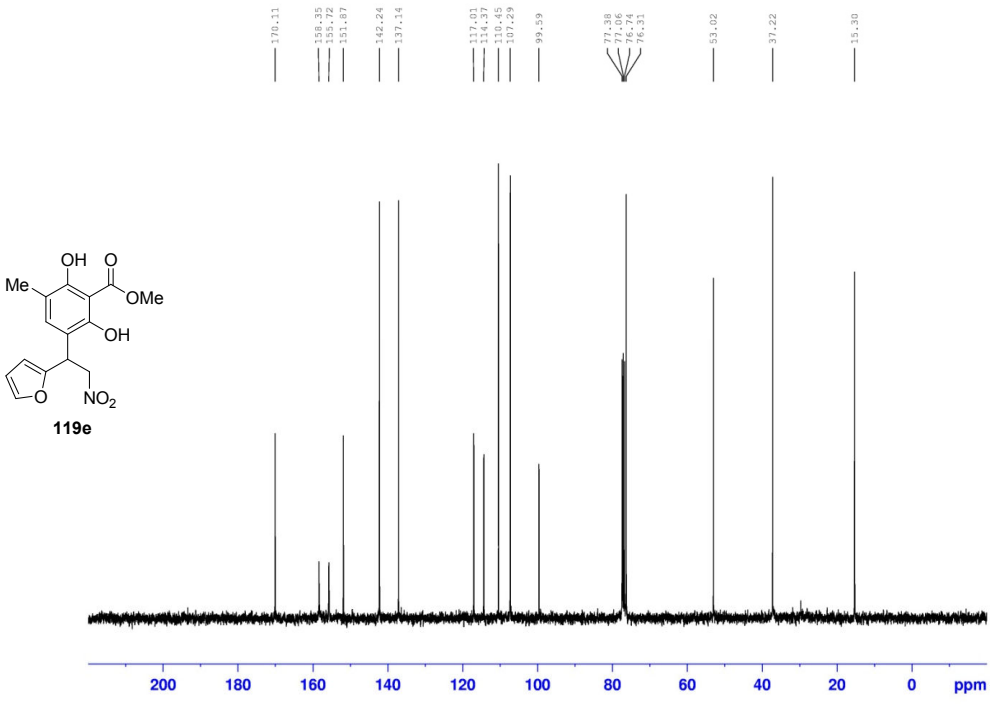
ppm

**119e**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53.02
37.22
15.30
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O
Me
OMe
OH
O
NO2
200
180
160
140
120
100
80
60
40
20
0
ppm

**119e**

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# Chapter 3

# Condensations of Vinyldiazoacetates and Orthoesters Catalyzed by Lewis Acids

## 3.1 Introduction

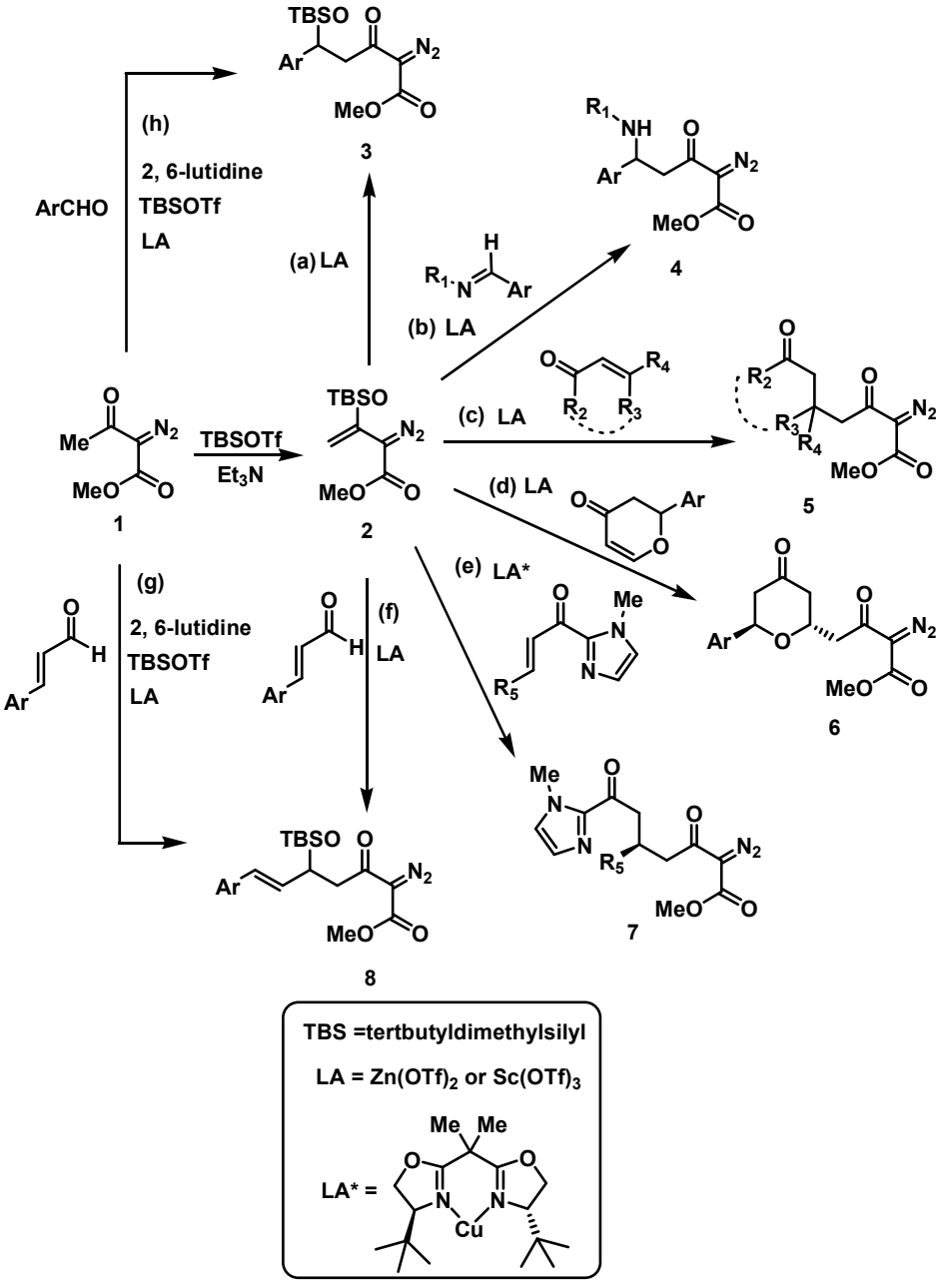
The Mukaiyama-type condensations of 3-(trialkylsilanoxy)-2-diazo-3-butenoate with various electrophiles are pivotal reactions around which our discussion revolves. The chemistry that we have developed depends on Mukaiyama-type additions with TBSO-vinyldiazoacetate as core reactions. We have discussed the Mukaiyama-Michael reaction of 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoates with different α,β-unsaturated ketones in Chapter 1, and a unique transformation involves the same vinyldiazoester and 4-methoxy-3-butene-2-one, and eventually leads to the formation of functionalized resorcinol compounds in chapter 2. Besides those that have been covered in the last two chapters, there is more exciting chemistry that has been developed based on the Mukaiyama-type condensations of the TBSO-vinyldiazoacetates, most of which is established by our own research group. We give here a brief review on the new work that also contributes to the synthesis of functionalized diazoacetoacetates by Mukaiyama-aldol /Michael reactions and applications of the addition products. From this survey one can see further growth of this chemistry into productive research areas.

Inspired by chemistry centered on Mukaiyama-type reactions of vinyldiazoacetates, we are determined to provide further extension by searching for other electrophiles that could react with TBSO-vinyldiazoacetates. We have discovered that orthoesters are suitable candidates for this purpose, and the reactions of orthoformates and orthoacetates with TBSO-vinyldiazoacetates will be the focus of this third chapter.

### 3.1.1 Construction of Functionalized Diazoacetoacetates via Mukaiyama-type Addition Reactions

Diazocarbonyl compounds are useful synthetic reagents and diazoacetoaceates, especially functionalized diazoacetoacetates, are an important subset. This point has been emphasized at the beginning of this thesis. As a result, effective synthetic methods for preparing diazoacetoacetate derivatives are of great importance, and the Mukaiyama-aldol and Mukaiyama-Michael reactions of vinyldiazoacetates are good examples of such methodologies. 3-*tert*-Butyldimethylsiloxy-2-diazo-3-butenoate (**2**) can be conveniently prepared from diazoacetoacetate (**1**) by a method reported by Ueda.[1] Upon formation, the vinyl diazo compound **2** can be applied in Mukaiyama-type condensations which react silyl enol ether with various electrophiles such as Lewias acid catalyst activated aldehydes and α,β –unsaturated carbonyl compounds. A number of electrophiles including aldehydes (pathway a), imines (pathway b), α,β-unsaturated ketones

**Scheme 3.1** Mukaiyama-type Condensations of Vinyldiazoacetate **2** that Lead to Diverse Products.

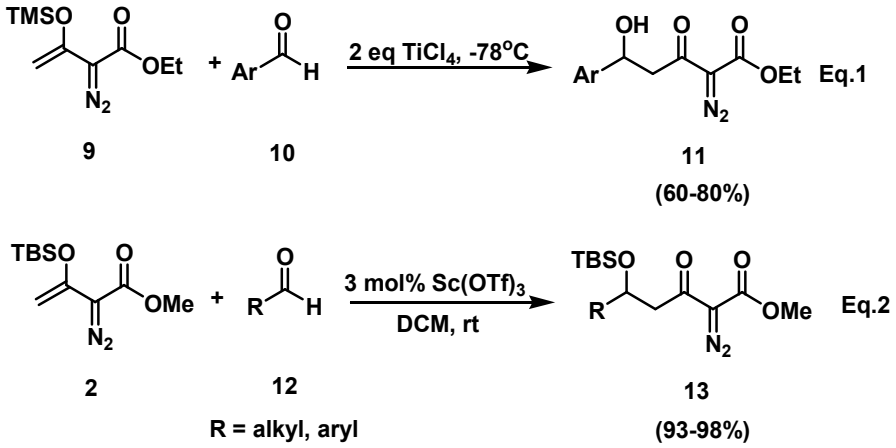



(pathway c), dihydropyranones (pathway d), α,β-unsaturated aldehydes (pathway f) have been treated with vinyldiazoacetate **2**, and the corresponding adducts,

which are diazoacetoacetates rich in functionalities (compound **3**-**8**) are prepared by these reactions (Scheme 3.1). Efforts have also been made to apply the diazo compounds resulting from these transformations in transition metal catalyzed dinitrogen extrusion reactions. Some of these functionalized diazoacetoacetates can also be accessed by a one-pot synthesis directly from diazoacetoacetates **1** (pathway g, h). An asymmetric version of the Mukaiyama-Michael reaction has also been investigated (pathway e).

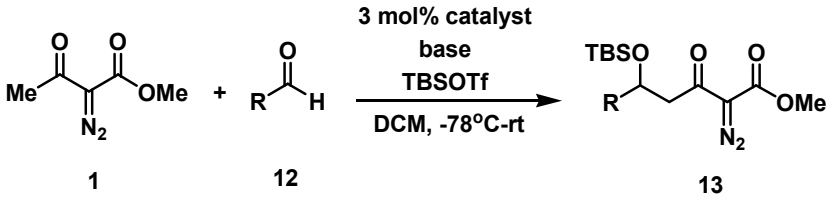
### 3.1.1.1 Synthesis of Diazoesters via Mukaiyama-aldol Reactions

As is mentioned in chapter 1, early attempts to effect Mukaiyama-aldol reactions of vinyldiazoacetate were reported by Karady.[2] In his method, a stoichiometric amount of $TiCl_4$ was employed as Lewis acid to promote the addition of ethyl 3-(trimethylsiloxy)-2-diazo-3-butenoate (**9**) with aromatic aldehydes at -78$^{o}$C (Eq.1). An improved method was later reported by Doyle in which $Sc(OTf)_3$ was applied in catalytic amount (3 mol%) to promote the Mukaiyama-aldol reaction of 3-*tert*-butyldimethylsiloxy-2-diazo-3-butenoate (**2**) with both aromatic and aliphatic aldehydes (Eq.2).[3] The mild reaction conditions and extended substrate scope are major advantages of this method. However, scadium(III) triflate failed to catalyze the intended Mukaiyama-aldol reaction when 4-nitro- and 2-nitrobenzaldehydes were employed as substrates. This problem were solved later by replacing $Sc(OTf)_3$ with $Zn(OTf)_2$ as the Lewis acid catalyst.[4]

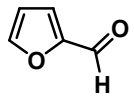
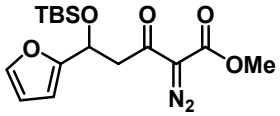
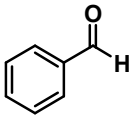
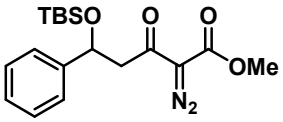
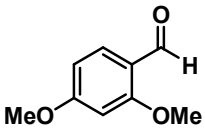
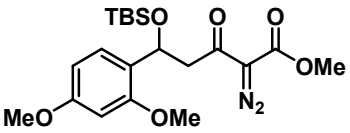
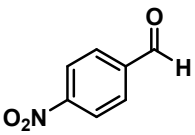
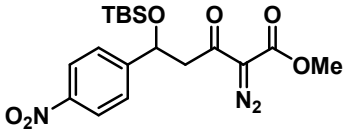
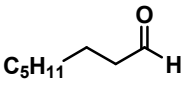
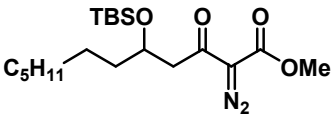
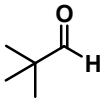
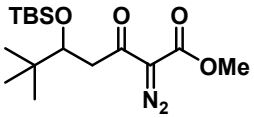



A further extension of the Mukaiyama-aldol reaction of vinyldiazoesters came out in 2010: a one-pot reaction that involves multiple reagents was reported by Zhou and Doyle.[5] Instead of preparing the vinyl diazo compound **2** by a separate step, this one-pot synthesis starts directly from diazoacetoacetate **1**. In presence of Lewis acid catalyst $Zn(OTf)_2$ (3 mol%), silylation regent TBS triflate (1.2 equiv) and a mild base 2,6-lutidine (3 equiv), diazoacetoacetate **1** reacts with aldehydes at -78$^{o}$C to afford the Mukaiyama-aldol adduct **13**. The results from these reactions are summarized in Table 3.1. One obvious advantage of this one-pot approach is that it avoids the preparation of the intermediate vinyldiazoacetate **2** therefore shortens the synthetic steps required. Zinc(II) triflate works well for aromatic aldehyde substrates (Entries 1-4); however, it is less effective when dealing with aliphatic aldehydes: the reactions failed to reach full conversion over 16 hours reaction time. A revised condition that employs scadium(III) trilfate as Lewis acid catalyst and triethylamine as base was applied to aliphatic aldehyde substrates and allowed the reaction to reach full conversion with the intended products obtained in good yields ( Entry 5, Entry 6).

**Table 3.1** One-pot Mukaiyama-aldol Reactions of Methyl diazoacetoaceate (**1**) and Various aldehydes.

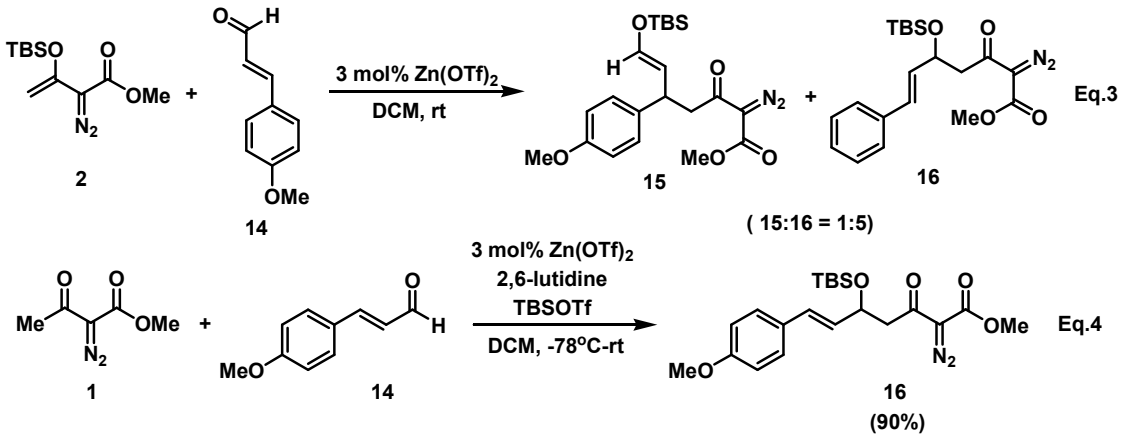



1 12 13

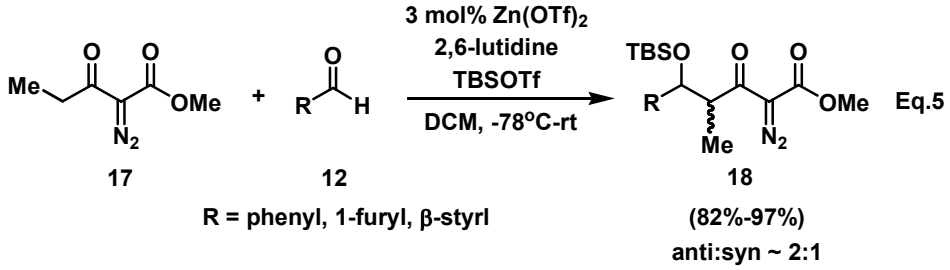
| Entry | catalyst | base | aldehyde 12 | 13 | yield of 13 |
|---|---|---|---|---|---|
| 1 | $Zn(OTf)_2$ | 2,6-lutidine |  |  | 82 |
| 2 | $Zn(OTf)_2$ | 2,6-lutidine |  |  | 93 |
| 3 | $Zn(OTf)_2$ | 2,6-lutidine |  |  | 95 |
| 4 | $Zn(OTf)_2$ | 2,6-lutidine |  |  | 96 |
| 5 | $Sc(OTf)_3$ | $Et_3N$ |  |  | 90 |
| 6 | $Sc(OTf)_3$ | $Et_3N$ |  |  | 89 |

The one-pot protocol was also applied to Mukaiyama-aldol reaction of diazoacetoacetate **1** and α,β–unsaturated aldehydes. Regarding these α,β–unsaturated aldehydes substrates, an important feature worth noticing is that the one-pot reaction provides better chemoselectivty for 1,2-addition over 1,4-

addition. For example, when 4-methoxycinamaldehyde (**14**) was used in the stepwise approach, the 1,2-addition product **16** and the 1,4-addition product **15** were obtained in a 5 : 1 molar ratio (Eq. 3); by contrast, with the same substrate under one-pot reaction conditions, the 1,2-addition product **16** became the only product observed, and it was obtained in 90% isolated yield (Eq. 4).



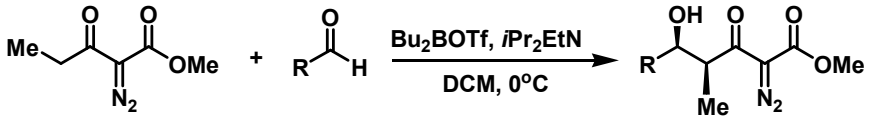

Methyl 2-diazo-3-oxo-pentanoate (**17**) was subjected to one-pot Mukaiyama-aldol reaction and under the conditions described in equation 5, the expected adduct **18** was produced in good yields but as a mixture of two diastereomers in about 2 : 1 *anti/cis* ratio.



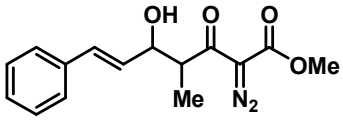
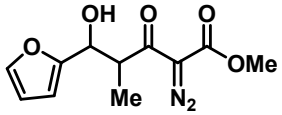
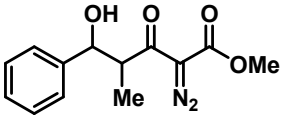
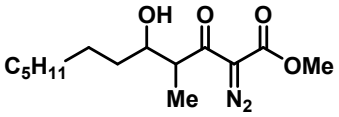
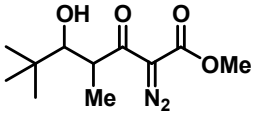

In pursuit of better diastereocontrol, other reaction conditions were investigated and ($n$-Bu)$_2$BOTf together with Hunig's Base turned out to be able to provide high

diastereoslectivity in one-pot Mukaiyama-aldol reactions with methyl 2-diazo-3-oxo-pentanoate (**17**) (Table 3.2).

**Table 3.2** One-pot Mukaiyama-aldol Reactions of Methyl 2-diazo-3-oxo-pentanoate (**17**) and Various Aldehydes.



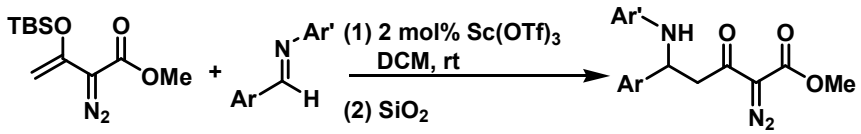

17 12 18

| Entry | 18 | syn:anti | yield of 18 |
|---|---|---|---|
| 1 |  | 99:1 | 73 |
| 2 |  | 99:1 | 77 |
| 3 |  | 96:4 | 75 |
| 4 |  | 97:3 | 69 |
| 5 |  | 97:3 | 69 |

The reaction conditions used for catalytic Mukaiyama-aldol reaction also work for imines in Mannich-type additions with 3-TBSO-2-diazo-3-butenoate **2** (Table 3.3).[3] Imine substrates **19** with different aryl substitutents were evaluated and high yields were obtained. The amount of catalyst required for this reaction

remained at 2 mol% which is the same amount used for reactions with aldehydes. This is a bit surprising considering the basic nature of imines. What is different from the Mukaiyama-aldol reaction is that instead of transferring to an oxygen atom to form a stable silyl ether, the silyl group came off nitrogen while the reaction mixtures were passed through a short silica plug to remove the Lewis acid catalyst.

**Table 3.3** Mannich Addition of Vinyldiazoaceatate **2** with Imines.

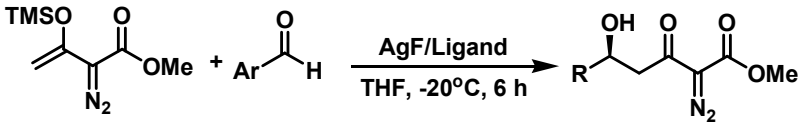



**2** **19** **20**

| Entry | Ar | Ar | yield of 20 |
|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | 4-$NO_2C_6H_4$ | 95 |
| 2 | 4-$ClC_6H_4$ | Ph | 90 |
| 3 | Ph | 4-$NO_2C_6H_4$ | 93 |
| 4 | Ph | Ph | 88 |

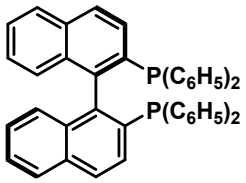
An asymmetric version of the Mukaiyama-aldol reaction with diazoester **2** was also reported.[6] AgF/(*R*)-BINAP was applied as the chiral catalyst to promote this transformation. High enantioselectivity was achieved by this method but the substrates were only limited to aromatic aldehydes (Table 3.4).

**Table 3.4** Asymmetric Mukaiyama-aldol Reactions with Vinyldiazoacetate **2**.




9 10 21

Ligand =

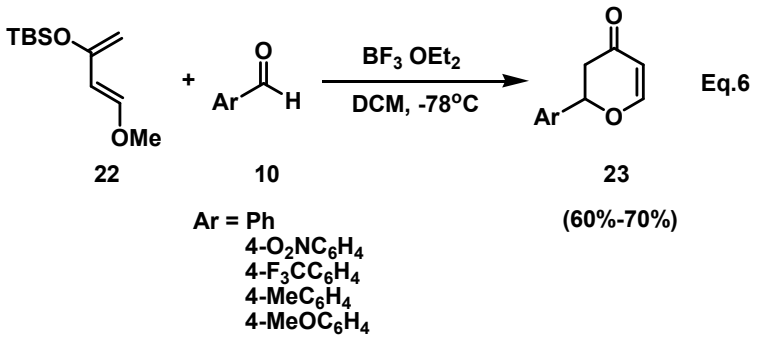



| Entry | Ar | yield of 21 | ee% 21 |
|---|---|---|---|
| 1 | Ph | 80 | 91 |
| 2 | 4-$MeOC_6H_4$ | 82 | 87 |
| 3 | 4-$MeC_6H_4$ | 80 | 88 |
| 4 | 4-$ClC_6H_4$ | 78 | 92 |
| 5 | β-styryl | 74 | 88 |

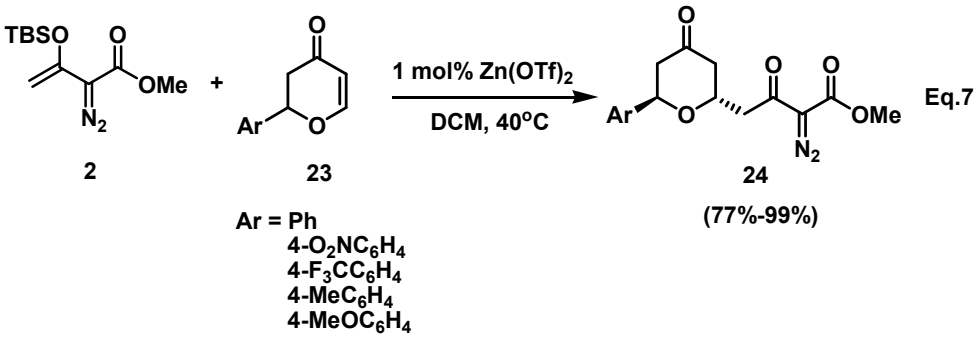
### 3.1.1.2 Synthesis of Diazoesters via Mukaiyama-Michael Reactions

Vast amount of information regarding the Mukaiyama-Michael reaction of vinyldiazoacetates **2** has been covered in the first chapter of this thesis. However, there has been more progress in the development of this transformation.

Dihydropyranones **23** were demonstrated to be applicable substrates for conjugated additions with vinyldiazoacetate **2**.[7] These dihydropyranone compounds can be prepared by hetero Diels-Alder reactions between aromatic aldehydes and Danishefsky's deine (**21**) (Eq. 6).[8]

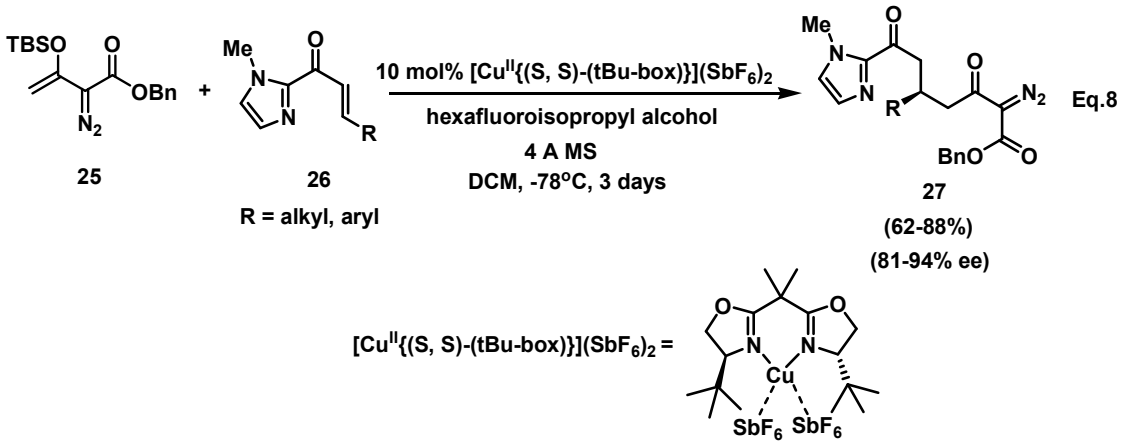



The reactions of vinyldiazoacetate **2** and dihydropyranones **23** failed to reach completion at room temperature but, by carrying out these reactions in 40°C oil bath, full conversion of the pyranone substrates was achieved, and the expected addition products were obtained in good to excellent yields (Eq.7). High diastereoselectivity was observed in all examples: only the *trans* isomer of products **24** (established by selective NOE experiments) were produced. These Mukaiyama-Michael reactions with dihydropyranones provide access to diazoacetoacetates that contain heterocycles, and the diazo decomposition of these novel diazo compounds derived from the Mukaiyama-Michael additions will be discussed in the section that follows.




An enantioselective Mukaiyama–Michael addition of vinyldiazoacetate **25** and α,β–unsaturated 2-acrylimmidazoles (**26**) catalyzed by chiral copper(II) Lewis

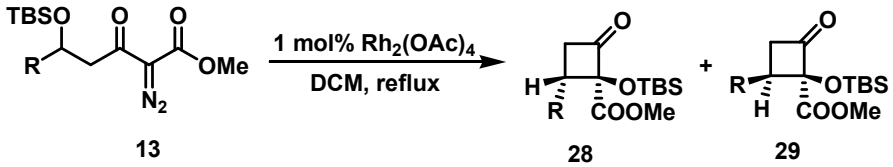
acid was reported earlier this year.[9] As an important extension of the established Mukaiyama-type addition reactions using vinyl diazocarbonyl compounds, this reaction provides chiral, multifunctional diazoacetoacetates in good yields and high enatioselectivity.




### 3.1.2 Application of Functionalized Diazoacetoacetate Derived from the Mukaiyama-type Condensations

δ-Siloxy-α-diazo-β-ketoalkanoates **13** obtained from Mukaiyama-aldol reactions were subjected to dirhodium(II) acetate catalyzed diazo decomposition reaction. In presence of 1 mol% dirhodium(II) acetate, compound **13** was transformed to highly substituted cyclobutanones (**28** and **29**) in refluxing dichloromethane (Table 3.5).[3] High yields and high diastereoselectivities were obtained from these reactions. The relative stereochemistry of the cyclobutanone products was determined by a selective NOE experiment.

**Table 3.5**. Diazo Decompositions of Mukaiyama-Aldol Adducts **13**.

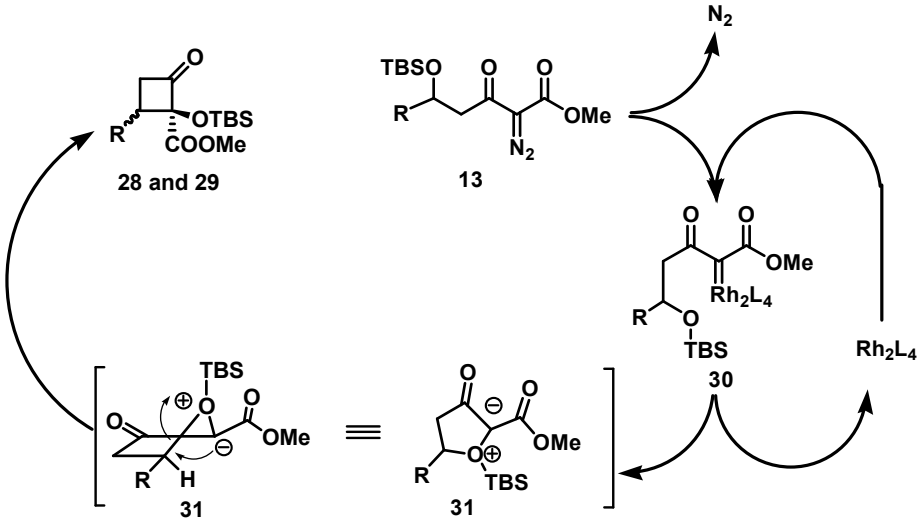



13 28 29

| R | yield of 28+29(%) | 28:29 |
|---|---|---|
| Ph | 80 | 10:1 |
| 4-Me-$C_6H_4$ | 84 | 12:1 |
| 4-F-$C_6H_4$ | 84 | 10:1 |

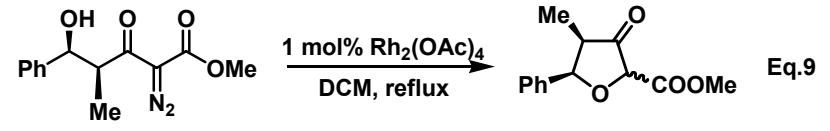
The mechanism of these diazo decomposition reactions (Scheme 3.2) starts from the loss of dinitrogen from diazoesters **13** upon their interaction with the dirhodium(II) catalyst. Once metal carbene intermediates **30** are produced, they can transform to the corresponding oxonium ylides (**31**) by the siloxy oxygen donating a lone pair electrons. Finally, migration of the the TBSO group and ring closure afford the observed cyclobutanone products (**28** and **29**).

**Scheme 3.2** Mecahanism of the Diazo Decomposition of Mukaiyma-aldol Adduct **13**.

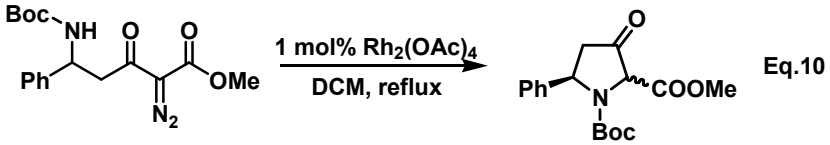


Small ring compounds are useful building blocks while the synthesis of strained ring systems has always been a challenge for synthetic chemists.[10] Therefore, diazo decomposition reaction of δ-siloxy-α-diazo-β-ketoalkanoates **13** appears to be a useful method for the preparation of four-membered ring structure with multiple functional groups.

δ-Hydroxy-γ-methyl-α-diazo-β-ketoalkanoate **32** that can be readily prepared by one-pot synthesis from 2-diao-3-oxo-pentanoate (**17**) and benzaldehydes[5] undergoes dirhodium(II) acetate catalyzed dinitrogen extrusion to give the corresponding O-H insertion product (Eq.9).[11] Tetrahydrofuran derivatives that are densely functionalized are produced with excellent yields. Similar to this reaction, δ-amino-α-diazo-β-ketoalkanoate **34**, which can be made by the Mannich-type addition of vinyldiazoacetate **2** and imine[3], undergoes intramolecular N-H insertion catalyzed by $Rh_2(OAc)_4$ to afford terahedropyroles in high yield (Eq.10).[12]



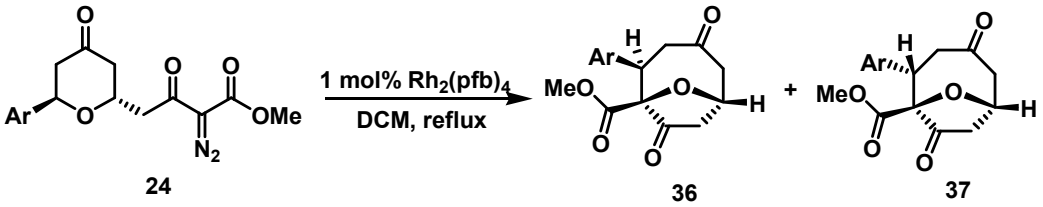

**32** **33** **(96%)** **dr = 5:3** **Eq.9**




**34** **35** **(94%)** **dr = 3:2** **Eq.10**

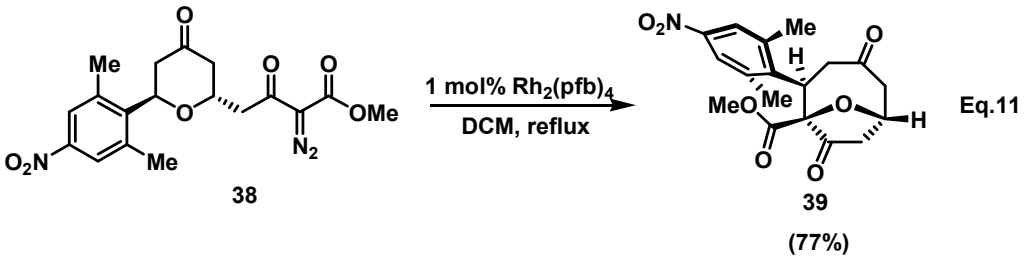
Aryl substituted tetrahydropyranone diazoacetoacetates **24** which are derived from the Mukaiyama-Michael addition of vinyldiazoacetate **2** and aryl substituted dihydropyranones **23** were also evaluated in dirhodium(II) catalyst promoted diazo decomposition reactions.[8] Dinitrogen extrusion induced by 1 mol% of dirhodium(II) perfluorobutyrate in refluxing dichloromethane led to a 8-membered ring structure,and compounds **36** and **37** were obtained as a mixture of these two diastereomers in about 7 : 3 ratio. Dihydropyranones **23** with different substituents at the 4 position on the aromatic rings were evaluated (Table 3.6).

**Table 3.6** Diazo Decomposition Reactions of Diazoaceatates **24.**




| Ar | yield of 36+37(%) | 36:37 |
|---|---|---|
| Ph | 77 | 71:29 |
| 4-$NO_2$-$C_6H_4$ | 94 | 74:26 |
| 4-$CF_3$-$C_6H_4$ | 92 | 74:26 |
| 4-Me-$C_6H_4$ | 55 | 69:31 |
| 4-MeO-$C_6H_4$ | 22 | 69:31 |

Further investigation revealed that the diastereomeric ratio of the diazo decomposition products can be tuned by the substituents on the aryl group in the starting material. For instance, diazo compound **38** with two *ortho* methyl substituents and a *para* nitro substituent on the benzene ring was applied and in this case, only diastereomer **39** was obtained in good yield.

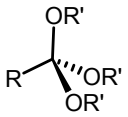



In summary, numerous novel diazoester compounds are assembled by the Mukaiyama-type condensations from 3-TBSO-2-diazo-3-butenoates which can be conveniently prepared from diazoacetoacetates. Electrophiles such as aldehydes, imines, α,β-unsaturated carbonyl compounds and dihydropyranones have been employed, and the diazoesters produced from these reactions were studied in diazo decomposition reactions catalyzed by dirhodium(II) catalysts. Highly substituted cyclobutanone, tetrahydrofuran, and terahydropyrole derivatives can be synthesized from these diazo decomposition reactions. In our effort to further extend this chemistry we examined other electrophilic compounds that can potentially react with the vinyl diazoesters.

### 3.1.3 Orthoesters

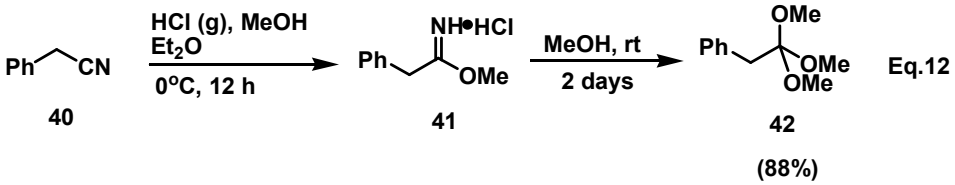
Orthoesters have the general structure depicted in Figure 3.1. They have three alkoxy groups attached to one carbon atom. The last substitutent on the quaternary carbon can be hydrogen (orthoformates in this case), alkyl or aryl groups.

**Figure 3.1**. Structure of Orthoformates/esters.




R = H, alkyl, aryl
R' = alkyl

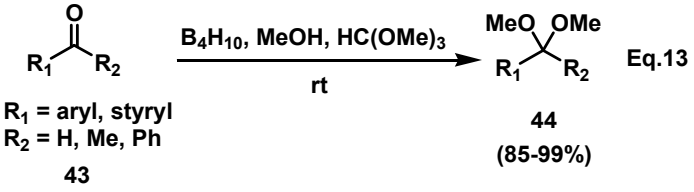
These compounds can be readily prepared by reacting nitriles with alcohols under acid catalysis.[13] For instance, triethyl orthophenylacetate was made from the condensation of benzyl cyanide and ethyl alcohol promoted by hydrogen chloride. The intermediate ethyl phenyliminoacetate hydrochloride (**41**) could be converted to the desired product **42** by treating it with additional ethyl alcohol (Eq. 12).[14]



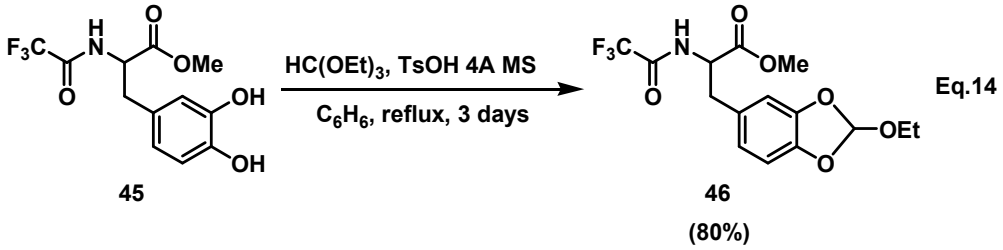

Orthoesters are stable under basic conditions but readily hydrolyze under mild acidic conditions in presence of water to give the corresponding esters.[15] Detailed mechanistic studies have been conducted, [15, 16, 17], and these works on the hydrolysis of orthoesters suggested that it occurs via an $A_{SE}2$ mechanism that involves proton transfer concerted in some sense with carbon-oxygen bond cleavage.[15]

Orthoesters are useful reagents in protecting carbonyl functional groups. For example, in a reaction described in equation 13, trimethyl orthoformate is

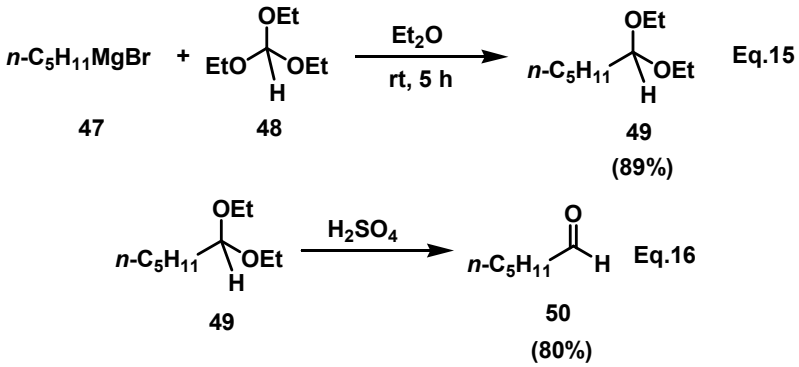
employed as water scavenger to comsume water produced in the reaction and shifts the reaction equilibrium to the side of the protected acetal product **44**.[18]




Orthoesters can be used as protecting groups for 1,2-diol structures. For example, cylclic ethyl orthoformate was utilized as a protecting group to protect the catechol hydroxyl groups of 3,4-dihydroxyphenylalamine **45** (Eq.14).[19] This protecting group is stable towards strong bases and nucleophiles, and can be removed efficiently by 1 M trimethylsilyl bromide in trifluoroacetic acid.

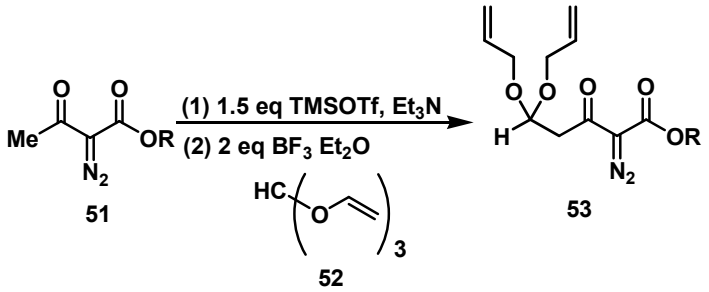



Orthoesters are also eletrophilic species since the carbon connected with three strong electron-withdrawing alkoxy groups readily undergoes nuclephilic attack by nuclephiles. The Bodroux-Chichibabin aldehyde synthesis can be used to demonstrate this point: a Gringnard reagent reacts with triethyl orthofomate to give acetal **49** (Eq.15). Upon hydrolysis of intermediate **49**, *n*-hexanal (**50**) is resulted as the product of this synthesis (Eq.16).[20]



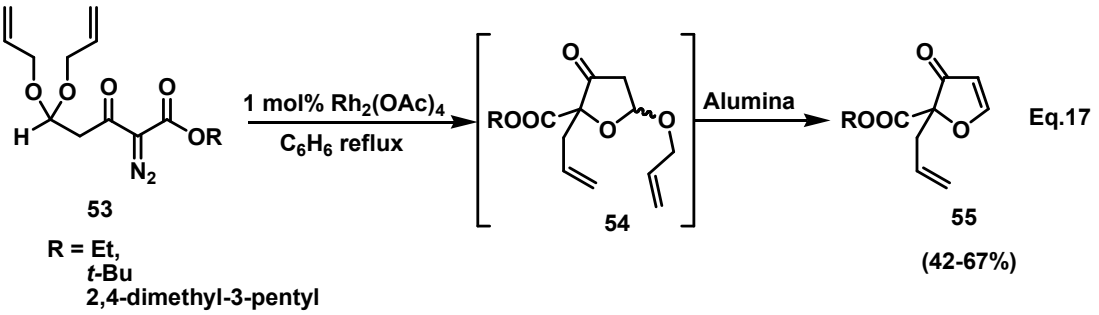

We propose that orthoesters could be candidates for reactions with 3-(trialkylsiloxy)-2-diazo-3-butenoate **2** as electrophiles since they are nuclephilic and can be activated by Lewis acids via chelation to the oxygens in the alkoxy groups. This speculation is supported by the work done by Calter.[21] In his paper, a Lewis acid-mediated condensation of orthoesters with vinyldiazoacetates that were generated in-situ from diazoacetoaceteates yielded diazoesters **52** with allylic acetals functionality (Table 3.7).

**Table 3.7** Condensation of Diazoacetoacetates **51** with Triallylorthoformate (**52**).




| R | yield of 52(%) |
|---|---|
| Et | 94 |
| *t*-Bu | 40 |
| 2,4-dimethyl-3-pentyl | 76 |

The diazo compounds **52** produced by these reactions were subjected to dirhodium(II) acetate catalyzed O-H insertion reactions, and dihydrofuran derivatives **55** were isolated as products from these decomposition reactions (Eq. 17).




These results suggested that it is feasible to react orthoesters with vinyldiazoacetates. However, regarding this reaction reported by Calter, there are a couple of disadvantages: first, an excess amount of strong Lewis acid (2 equiv) has to be used and the reaction has to be carried out at low temperature; what is more, the substrates that have been investigated are limited: only variation of the ester group in the diazoacetoacetate was conducted. Therefore, we are determined to investigate the scope of the condensation reactions between orthoesters and 3-TBSO-2-diazobutenoates using the reaction conditions we have established for the Mukaiyama-aldol/Michael additions. Two major advantages of our method would be the high efficiency of a catalytic reaction and the mild reaction conditions involved. The conditions we have established for Mukaiyama-type additions previously turned out to be applicable to the orthoester substrates. We continued to investigate the substrate scope of this reaction and studied the diazo decomposition reactions of the diazocarbonyl

compounds derived from these addition reactions. The results we have obtained so far will be discussed in the rest of this chapter.

## 3.2 Results and Discussion

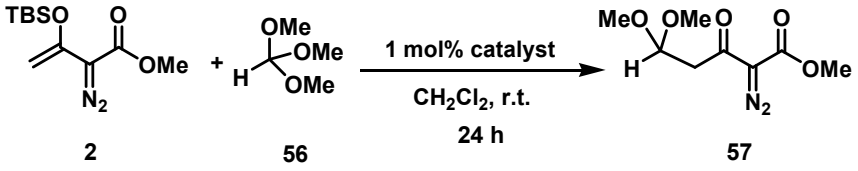
### 3.2.1 Addition of Orthoformates and Orthoacetates with 3-*tert*-butyldimethylsilyl 2-diazo-butanoate (2)

#### 3.2.1.1 Screening of Reaction Conditions

Trimethyl orthoformate (**56**) was treated with 3-TBSO-substituted vinyldiazoacetate **2** under Lewis acid catalysis. A number of metal triflate salts were evaluated as Lewis acid catalysts for this transformation, and the results from these reactions are shown in Table 3.8. For those Lewis acids that we have tested, $Mg(OTf)_2$ and $La(OTf)_3$ only gave a trace amount of the addition product **57** that is barely visible by $^1H$ NMR spectroscopy (Entry 1, Entry 2). In both cases, the majority of silyl enol ether **2** hydrolyzed eventually due to water absorbed by the Lewis acid catalyst from the environment. $Sn(OTf)_3$ (Entry 3) and $Yb(OTf)_3$ (Entry 4) promoted the addition reaction but the yields of methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate (**57**) were rather low; the yield of this reaction was improved to 35% when $Sc(OTf)_3$ was used (Entry 4). The copper based Lewis acids [such as $Cu(OTf)_2$ and $CuPF_6(CH_3CN)_4$] induced diazo decomposition of vinyldiazoacetate **2** and therefore were not suitable to promote the intended addition reaction (Entry 5 and Entry 6). $Zn(OTf)_2$, which is the preferred Lewis acid catalyst for Mukaiyama-aldol and Mukaiyama-Michael addition, was able to provide the intended diazoester product **57** in 52% isolated yield. Although the yield for the zinc(II) triflate catalyzed addition in this case is not as high as the Mukaiyama-aldol or Mukaiyama-Michael additions that we previously reported, it

is still considerably higher in comparison with other metal triflate salts we have evaluated. Therefore, we decided to choose $Zn(OTf)_2$ as the Lewis acid catalyst to further investigate the reaction of orthoesters and TBSO-vinyldiazoacetate.

**Table 3.8** Screening of Lewis Acid Catalysts.




**2** **56** **57**

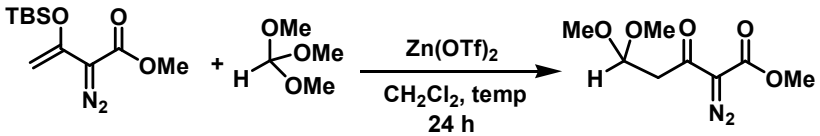
| Entry | catalyst | yield of 59 |
|---|---|---|
| 1 | $Mg(OTf)_2$ | NR * |
| 2 | $La(OTf)_3$ | NR * |
| 3 | $Sn(OTf)_2$ | 16 |
| 4 | $Yb(OTf)_3$ | 16 |
| 5 | $Sc(OTf)_3$ | 34 |
| 6 | $Cu(OTf)_2$ | - |
| 7 | $[Cu(CH_3CN)_4]PF_6$ | - |
| 8 | $Zn(OTf)_2$ | 52 |

*hydrolysis of vinyldiazoacetate 2 is observed

With zinc(II) triflate as the catalyst, the reaction of vinyldiazoacetate **2** and trimethyl orthoformate **56** was investigated under various conditions and the results from these reactions are summarized in Table 3.9. With 0.1 mol % catalyst loading (Entry 1), the reaction was very sluggish, and after 24 hours only trace amount (less than 10% based on $^1H$ NMR of the crude reaction mixture) was observed. Increasing the catalyst loading to 0.5 mol% $Zn(OTf)_2$ afforded 55% isolated yield of adduct **57** (Entry 2). This result is comparable to the one reported in Table 1.1 where 1 mol% of $Zn(OTf)_2$ was applied. However, a further

increase of the catalyst loading to 3 mol% failed to improve the yield and a 41% isolated yield was obtained (Entry 3). Therefore, we fixed the catalyst loading at 0.5 mol% for our investigations. Using 2 equivalents of trimethylorthoformate (**56**) benefits the reaction and improves the yield to 65% (Entry 4) but, when 4 equivalents of substrate **56** was applied, the yield decreased to 49% (Entry 5). Performing the reaction in a 40$^{o}$C oil bath showed no influence on the reaction in terms of yield (Entry 6). We also applied molecular sieves in the reaction (Entry 7). Since hydrolysis of vinyldiazoacetate **2** due to water absorbed by Lewis acid catalyst is expected to happen given longer reaction times, we thought that molecular sieves could remove the small amounts of water in the reaction. But, to our surprise, the reaction with molecular sieve as additive failed to provide adduct **57** after reacting at room temperature for 24 hours. Vinyldiazoacetate completely decomposed to afford diazoacetoacetate **1** as the only product in the reaction mixture. The acidity of molecular sieves might be problematic for this reaction.

**Table 3.9** Reactions under Various Conditions with $Zn(OTf)_2$ as Catalyst.




2 56 57

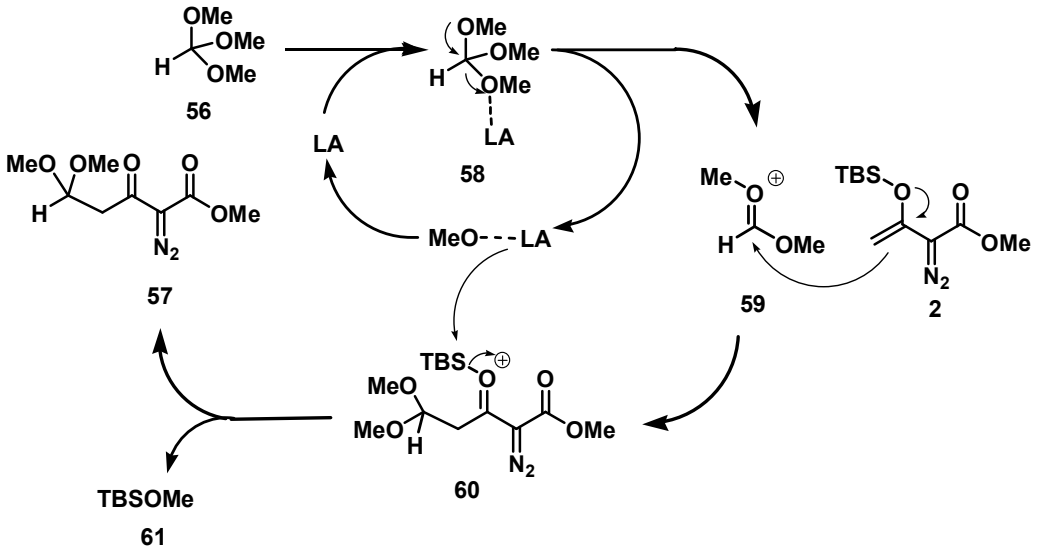
| Entry | catalyst loading | equivalent of 56 | temperature | additive | yield of 57 |
|---|---|---|---|---|---|
| 1 | 0.1 mol% | 1 equiv | rt | - | trace |
| 2 | 0.5 mol% | 1 equiv | rt | - | 55 |
| 3 | 3 mol% | 1 equiv | rt | - | 41 |
| 4 | 0.5 mol% | 2 equiv | rt | - | 65 |
| 5 | 0.5 mol% | 4 equiv | rt | - | 49 |
| 6 | 0.5 mol% | 2 equiv | 40°C | - | 66 |
| 7 | 0.5 mol% | 2 equiv | rt | 4 A MS | decomp |

### 3.2.1.2 Discussion on the Reaction Mechanism

A possible mechanism for the addition of 3-TBSO-2-diazo-3-butenoate (**2**) and trimethyl orthoformate (**56**) is proposed (Scheme

3.3). The Lewis acid catalyst activated orthoester **58** gives oxonium ion **59** upon loss of one methoxy group. Intermediate **59** is susceptible to nuclephilic attack by the silyl enol ether substrate **2**. Addition of vinyldiazoacetate **2** to intermediate **59** leads to adduct **60**. Finally, removal of the TBS group affords the reaction product **57** and *tert*-butyldimethylsilyl methyl ether (**61**) as by-product of this reaction.

**Scheme 3.3** Proposed Mechanism for the Addition of Vinyldiazoacetate and Trimethyl orthoformate.

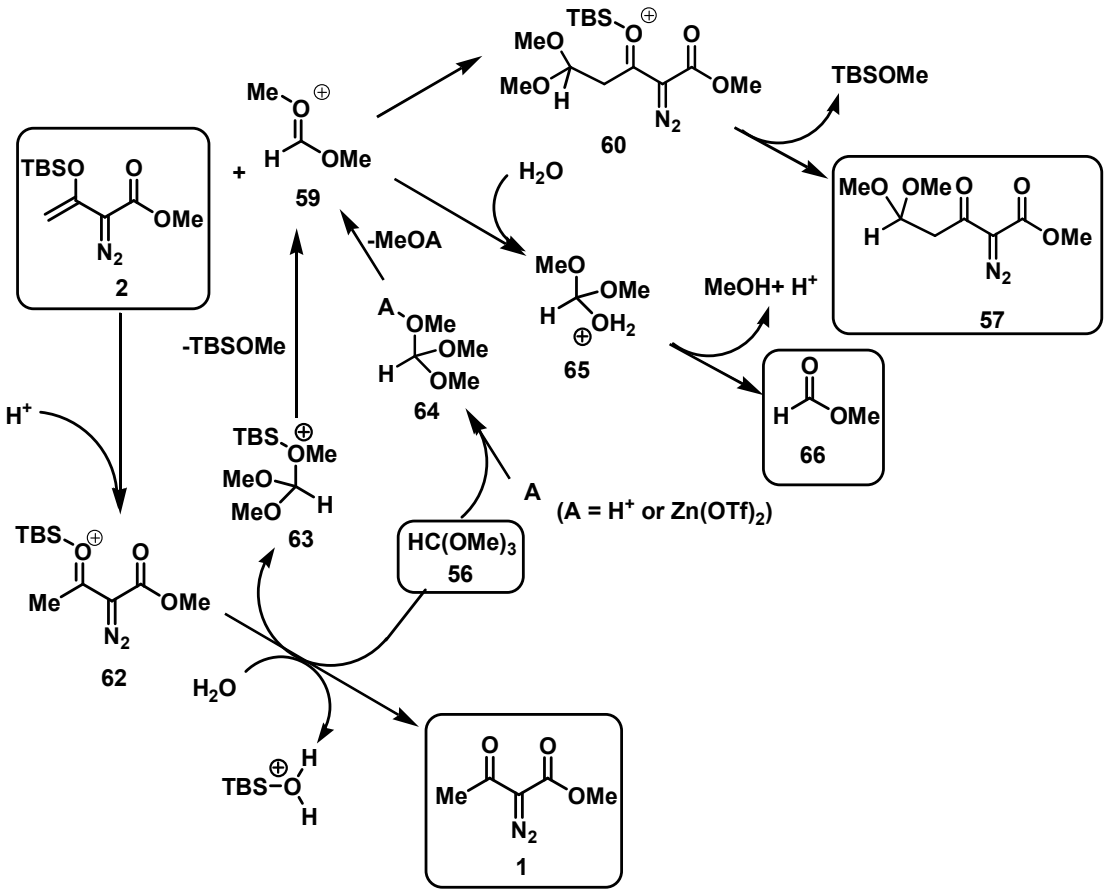



We have demonstrated in chapter 1 that the hydroscopic Lewis acid catalyst $Zn(OTf)_2$ is able to bring in water from the environment to the reaction solution. Protonic acid is then generated from the water absorbed in presence of the Lewis acid. In the reaction of 3-TBSO-2-diazo-3-butenoate (**2**) and trimethyl orthoformate (**58**), the presence of $H_2O$ and $H^+$ in the system makes the reaction scheme more complicated since both substrates are now susceptible to acid promoted hydrolysis (Scheme 3.4).

Decomposition of vinyldiazoacetate **2** to diazoacetoacetate **1** via intermediate **62** in the presence of $H^+$ is a side reaction that competes with the intended addition reactions. Previously, we circumvented this problem by using an excess amount of vinyl diazoester **2** (1.2 to 1.5 equivalents). Under these conditions, a portion of the silyl enol ether was sacrificed so that the electrophiles in these reactions

could be fully converted to the desired products. The electrophiles we employed before included aldehydes and α,β–unsaturated carbonyl compounds. However, trimethyl orthoformate (**56**) is different since it is prone to hydrolysis under the reaction conditions we employed. As is shown in Scheme 3.4, upon formation from either intermediate **63** or intermediate **64**, oxonium ion **59** can hydrolyze to give methanol and methyl formate (**66**), This is evident by an experiment in which excess amount of 3-TBSO-2-diazo-3-butenoate (**2**) was used (2 equivalents) to react with trimethyl orthoformate catalyzed by 0.5 mol% zinc trilflate in deuterated chloroform: The reaction was allowed to run overnight, and at that point, methyl formate was observed in $^{1}$H NMR spectrum of the crude reaction mixture. Based on the integrations from $^{1}$H NMR, 20% of the trimethyl orthoformate starting material was decomposed to give the methyl formate by-product (**66**). We tried to prevent the hydrolysis of the substrates by adding molecular sieves to the reaction (Table 3.2, Entry 7), however, vinyldiazoacetate **2** decomposed significantly under this condition. Although molecular sieves is able to remove moisture in the reaction, it is also known to be acidic, therefore oxonium ion **62** can still be produced with addition of molecular sieves. Instead of water from the enviroment, trimethyl orthoformate can also participate in the silyl transfer process and therefore induce the decomposition of **62** to give diazoacetoacetate **1**. Since both substrates (vinyldiazoacetate **2** and trimethyl orthoformate **56**) are sensitive to the acidic condition involved, it seems difficult to obtain the addition product without any decomposition of either starting material.

**Scheme 3.4** Possible Reaction Pathways in Presence of $H^+$ and $H_2O$.

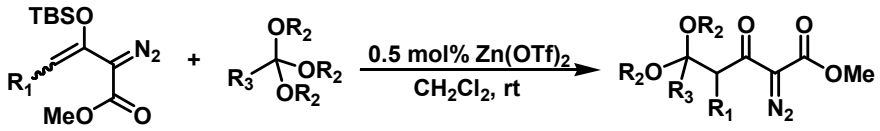



### 3.2.1.3 Substrate Scope

Among all the conditions we have examined, reacting 3-TBSO-2-diazo-3-butenoate (**2**) with 2 equivalents of trimethyl orthoformate (**56**) at room temperature for one day (Table 3.2, Entry 4) gives good yield of adduct **57** (65%). Therefore we continued to evaluate other substrates using this condition (Table 3.10). Triethyl orthoformate (Entry 2) and trimethyl orthoaceate (Entry 3) were readily converted to the expected adduct in moderate yields. Methyl 3-*tert*-butyl-dimethylsilanyloxy-2-diazopent-3-enoate was employed to react with trimethyl

orthoformate (Entry 4), and a 52% isolated yield was obtained for the addition product that has a methyl substituent adjacent to the acetal group. For orthoformate that has bulky alkoxy groups, such as triisopropyl orthoformate (Entry 5), the reaction became sluggish and low conversion of the orthoformate substrate was observed, so we performed the reaction in a 40$^{o}$C oil bath instead of at room temperature, and the addition product was produced in moderate yield (56%). Similarly, the reaction of trimethyl orthoacetate with a chloride substituent on the acetyl group also required higher reaction temperature to proceed (Entry 6), and a slightly lower yield (46%) of adduct **57f** was produced in this case. Trimethyl orthobenzoate (Entry 7) and tribenzyl orthoformate (Entry 8) failed to undergo addition with methyl 3-*tert*-butyl-dimethylsiloxy-2-diazo-3-butenoate (**2**) even at an elevated temperature (performing the reaction in a 40$^{o}$C oil bath). The orthoester substrates remained unchanged while the vinyl diazo compound **2** slowly hydrolyzed.

**Table 3.10** Substrate Scope for the Addition of Vinyldiazoesters and Orthoesters.




2 56 57

| Entry | | temp | $R_1$ | $R_2$ | $R_3$ | yield,% |
|---|---|---|---|---|---|---|
| 1 | a | rt | H | Me | H | 65 |
| 2 | b | rt | H | Et | H | 62 |
| 3 | c | rt | H | Me | Me | 56 |
| 4 | d | rt | Me | Me | H | 52 |
| 5 | e | 40°C | H | *i*-Pr | H | 56 |
| 6 | f | 40°C | H | Me | $ClCH_2$ | 46 |
| 7 | g | 40°C | H | Me | Ph | NR |
| 8 | h | 40°C | H | Bn | H | NR |

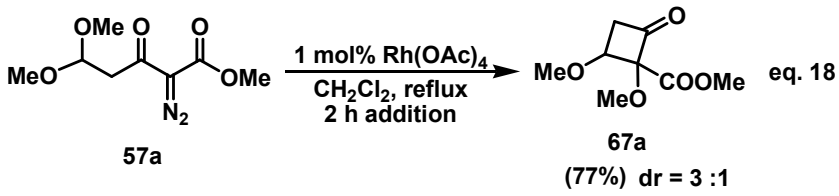
Since a number of δ,δ-dialkoxy-β-keto-α-diazoesters became available via addition reactions of vinyldiazoacetates and orthoesters, we went on to investigate the reactions of these novel diazo compounds(II) in dirhodium catalyzed dinitrogen extrusion.

### 3.2.2 Diazo Decomposition Reactions of δ,δ-Dialkoxy-β-keto-α-diazoesters (57)

#### 3.2.2.1 Formation of β–Alkoxy- cyclobutanone Catalyzed by Dirhodium(II) Catalyst

We applied methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate (**57a**) in a dirhodium(II) acetate catalyzed diazo decomposition reaction (Eq. 24). Diazoester **57a** was slowly added to a refluxing dichloromethane solution that

contained 1 mol% dirhdodium(II) acetate over 2 hours by syringe pump. Once the addition was complete, starting material **57a** had decomposed completely, and substituted cyclobutanone **67a** appeared as the only product according to $^1$H NMR spectrum of the crude reaction mixture. Removing the dirhodium(II) catalyst by a short silica plug afforded methyl 1,2-dimethoxy-4-oxocyclo butanecarboxylate (**67a**) in 77% isolated yield.




57a

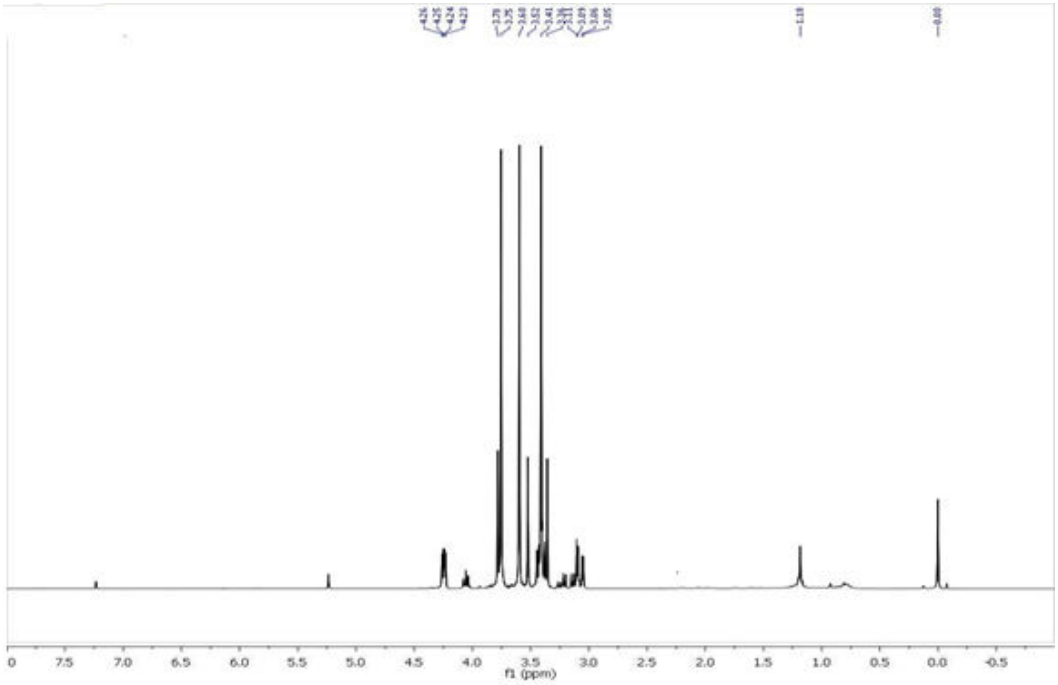
67a

(77%) dr = 3 :1

eq. 18

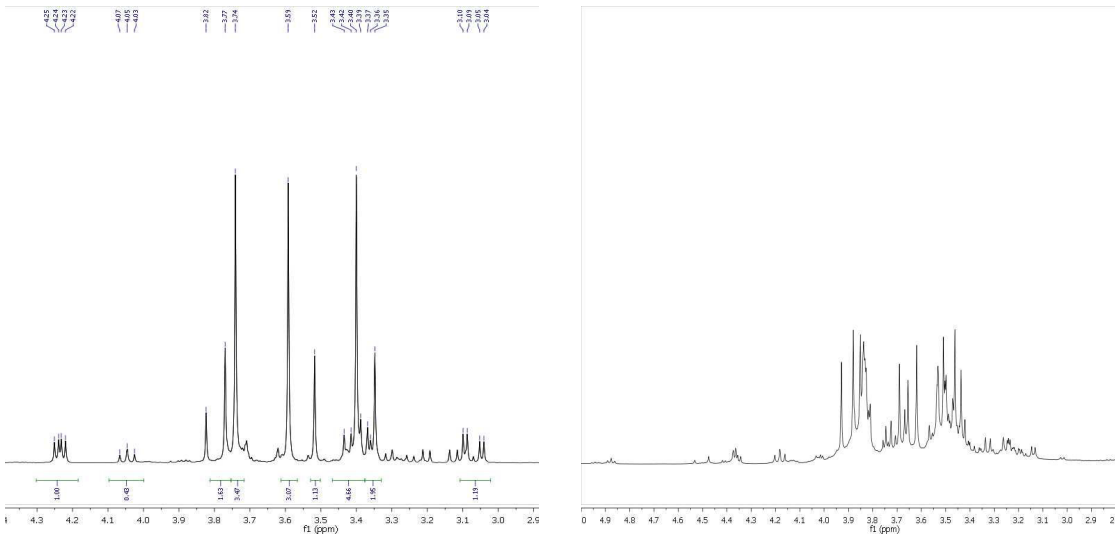
Good purity of diazo decomposition product **67a** was suggested by the proton NMR spectrum obtained after removing the dirhodium(II) catalyst (Figure 3.2). No signal of other compounds could be observed in this spectrum. The $^1$H NMR spectrum of the reaction product also suggested that cyclobutanone **67a** consist two diastereomers. The dr ratio was calculated to be 3:1 based on intergrations of corresponding signals of the two diastereomers. We tried to apply selective NOE experiment to determine the major diastereomer. However, due to the proximity of the signals in the NMR spectrum, we were not able to obtain clear NOE signals that could differentiate the two diastereomers.

**Figure 3.2** Proton NMR of Methyl 1, 2-dimethoxy-4-oxocyclo butanecarboxylate (**67a**).




We tried to further separate the two diastereomers of the diazo decomposition product **67a** by column chromatography. However, neither cyclobutanone **67a** nor any decomposition product could be recovered after column chromatography. The acidity of silica could be the reason for the loss of compound **67a.** An NMR experiment demonstrating the sensitive nature of compound **67a** towards acid is illustrated in Figure 3.3 Methyl 1,2-dimethoxy-4-oxo-cyclo-butanecarboxylate (**67a**) was dissolved in deuterated chloroform (Figure3.3, A), followed by small amount of trifluoroacetic acid (approximately 10 mol%) Severe decomposition of **67** was then observed: after 1 hour, the $^{1}H$ NMR spectrum of the solution became very messy and cyclobutanone compound **67a** could no longer be identified at this point (Figure 3.3, B).

**Figure 3.3** Decomposition of Methyl 1, 2-dimethoxy-4-oxo-cyclo-butanecarboxylate (**67a**) under Acidic Condition



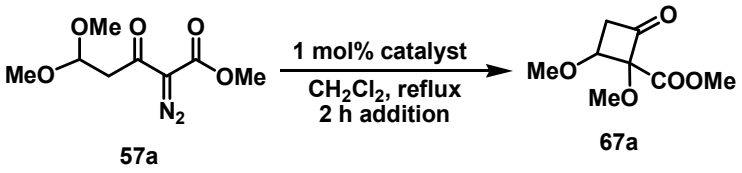
(**A**) cyclobutanone **67a** in $CD_3Cl$ (**B**) cyclobutanone **67a** treated with TFA

Other attempts using florisil or neutral alumina to purify cyclobutanone **67a** provided the same result: compound **67a** failed to survive chromatography in all cases. These results suggested that cyclobutanone **67a** is a highly sensitive compound that easily degenerates.

We also investigated other dirhodium(II) catalysts in diazo decomposition reaction of methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate (**57a**) (Table 3.11). Dirhodium(II) triphenylacetate ($Rh_2(OOCCPh_3)_4$) provided slightly lower yield and diasteromeric ratio comparable to dirhodium(II) acetate (Entry 2). When dirhodium(II) perfluorobutarate ($Rh_2(pfb)_4$) was employed (Entry 3), the $^1H$ NMR spectrum of the crude reaction mixture became messy compared to the reaction catalyzed by dirhodium(II) acetate and both the yield and dr ratio dropped in this

case as evidenced by $^1$H NMR spectrum. Dirhodium carprolactamate ($Rh_2(cap)_4$) failed to induce the intended diazo decomposition reaction; diazoester **57a** remained unchanged after slowly added to the catalyst solution (Entry 4).

**Table 3.11** Diazo Decomposition of Diazoester **57a** Catalyzed by Different Dirhodium(II) Catalysts.




57a 67a

| Entry | catalyst | yield of 67a * | dr of 67a * |
|---|---|---|---|
| 1 | $Rh_2(OAc)_4$ | 77 | 75:25 |
| 2 | $Rh_2(OOCCPh_3)_4$ | 73 | 70:30 |
| 3 | $Rh_2(pfb)_4$ | 46 | 58:42 |
| 4 | $Rh_2(cap)_4$ | NR | - |

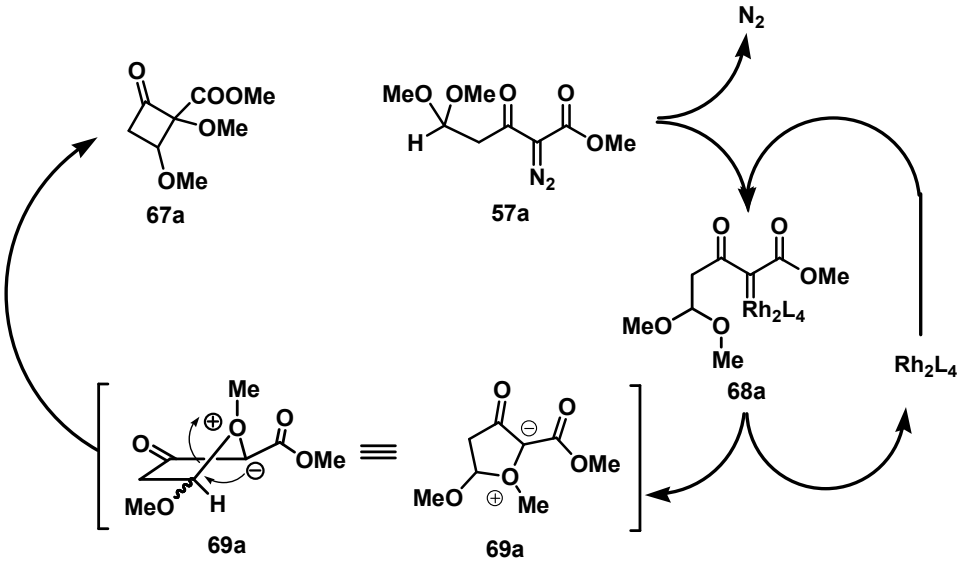
* Determined by $^1$H NMR of the reaction mixture with internal standard

### 3.2.2.2 Discussion on the Mechanism of the Diazo Decomposition Reaction that Leads to β–Alkoxy- cyclobutanones

A plausible reaction mechanism is depicted in Scheme 3.5. Upon interaction of methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate (**57a**) with the dirhodium(II) catalyst, the diazo group is released as nitrogen gas and metal carbene intermediate **68a** is produced. Metal carbene **68a** thus formed can undergo nucleophilic attack by the lone pair electrons of the oxygen from the methoxy group to give oxonium ylide intermediate **69a**. intramolecular nucleophilic attack

by the enolate coupled with migration of the methoxy group affords the four-memebered ring in product **67a**.

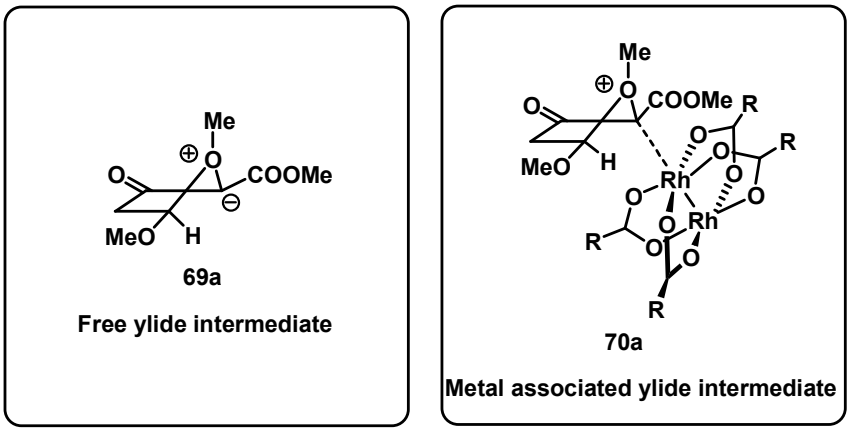
**Scheme 3.5** Proposed Reaction Mechanism of the Diazo Decomposition Reaction.




Oxonium ylide intermediate **69a** can be either a free ylide as illustrated in Scheme 3.5 or alternatively, a metal associated ylide (**70a** in Figure 3.4). If the reaction goes through a metal associated ylide intermediate, we would expect the electronic or steric character of the dirhodium(II) catalysts to have some impact on the outcome of the reaction such as yield or diastereoselectivity. However, Based on the experimental results from table 3.11, dirhodium(II) catalysts with bulky ligand ($(Rh_2(OOCCPh_3)_4$) or strong electron withdrawing ligand ($Rh_2(pfb)_4$) did not affect the diastereomeric ratio of the product significantly. Therefore, we think the diazo decomposition of diazoester **57a** is

more likely to go through a free ylide intermediate rather than one with metal catalyst attached.

**Figure 3.4**. Free Ylide Intermediate versus Metal Associated Ylide Intermediate.

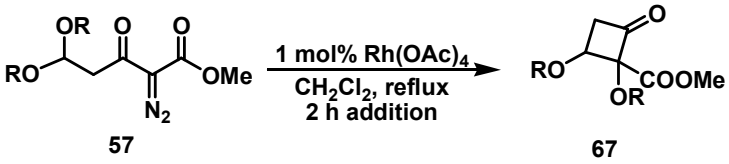



A Lower yield was obtained in the diazo decomposition reaction catalyzed by dirhodium(II) perfluorobutarate compared to the results obtained with other dirhodium catalysts (Table 11, Entries 1-3). Since the ligands in $Rh_2(pfb)_4$ is strongly electron-withdrawing due to the fluoride substituents, this catalyst has enhanced Lewis acidity compared to rhodium(II) acetate and rhodium(II) tripehylacetate. We have shown that cyclobutanone **67a** is susceptible to acid induced degradation (Figure 3.3) so we suspect that the strong Lewis acidity of $Rh_2(pfb)_4$ might be responsible for the decrease in the yield of the diazo decomposition reaction. Therefore, although dirhodium(II) perfluorobutarate provided a lower yield, it is more likely due to the decomposition of the cyclobutanone product rather than the influence of the catalyst on the ylide intermediate.

### 3.2.2.3 Substrate Scope for the Preparation of 1, 2-Dialkoxy-4-oxocyclobutanecarboxylate 67 by Diazo Decomposition Reaction of δ, δ-Dialkoxy-β-keto-α-diazoesters 59

δ,δ-Dialkoxy-β-keto-α-diazoesters **57** that had been prepared by reacting vinyldiazoacetates **2** and orthoesters (**56**) (summarized in table 3.10) were subjected to diazo decomposition catalyzed by dirhodium(II) acetate. When diazoesters derived from orthoformates (**57a, 57b, 57e**) were applied, β–alkoxy-cyclobutanone products were produced as expected (Table 3.12). Proton NMR spectra of the reaction mixtures looked very clean, and only the cyclobutanone products were observed. The products were purified by filtration through a short silica plug, and good yields were obtained. As the size of the alkoxy group increased from methyl group to isopropyl (Entry 1-Entry 3), the diastereomeric ratio decreased from 3:1 to about 1:1.

**Table 3.12** Rhodium(II) Acetate Catalyzed Diazo Decomposition of δ,δ-Dialkoxy-β-keto-α-diazoesters **57**.



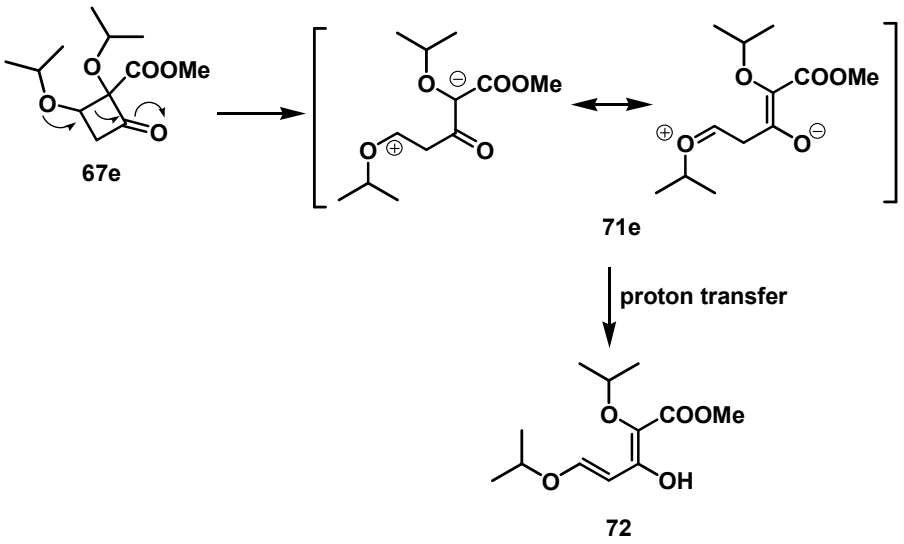

57 67

| Entry | | R | yield% | dr |
|---|---|---|---|---|
| 1 | a | Me | 77 | 75:25 |
| 2 | b | Et | 75 | 72:28 |
| 3 | e | *i*-Pr | 72 | 53:47 |

During our study of the substrate scope for this diazo decomposition reaction (Table 3.12), we discovered that cyclobutanone **67e** which contains large

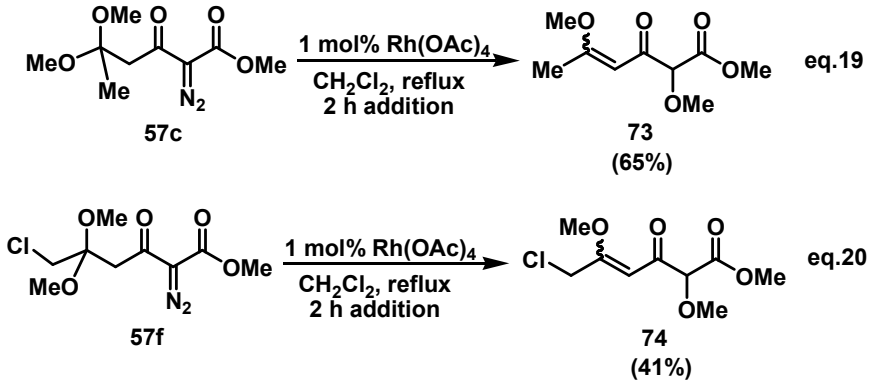
isopropyl groups is not stable even in deuterated chloroform solution at ambient temperature. It slowly decomposed, and after 2 days signals corresponding to cyclobutanone **67e** in proton NMR spectrum could no longer be observed. TLC of the solution at this point showed multiple spots. We were able to isolate one of the major spot in small amount (15%). A diene structure (**72**) was assigned to this decomposition product according to $^{1}H$ and $^{13}C$ NMR spectra. The mechanism for the formation of this ring-opening product **72** is depicted in Scheme 3.6. Zwitterionic intermediate **71** which is produced by cleavage of the C-C bond between the quaternary carbon and the tertiary carbon, can be stabilized by forming the oxonium ion and by delocalizing the negative charge to the carbonyl oxgen. Tautomerization of intermediate **71** by proton transfer will afford the observed decomposition product **72**. Cyclobutanones are known to undergo ring-opening reactions due to the inherent strain of the 4-membered rings.[22] The presence of a trace amount of DCl generated by deuterated chloroform[23] might have induced this ring-opening process.

**Scheme 3.6** Decomposition of Cyclobutanone **76e** to Diene **72** via Ring-opening.



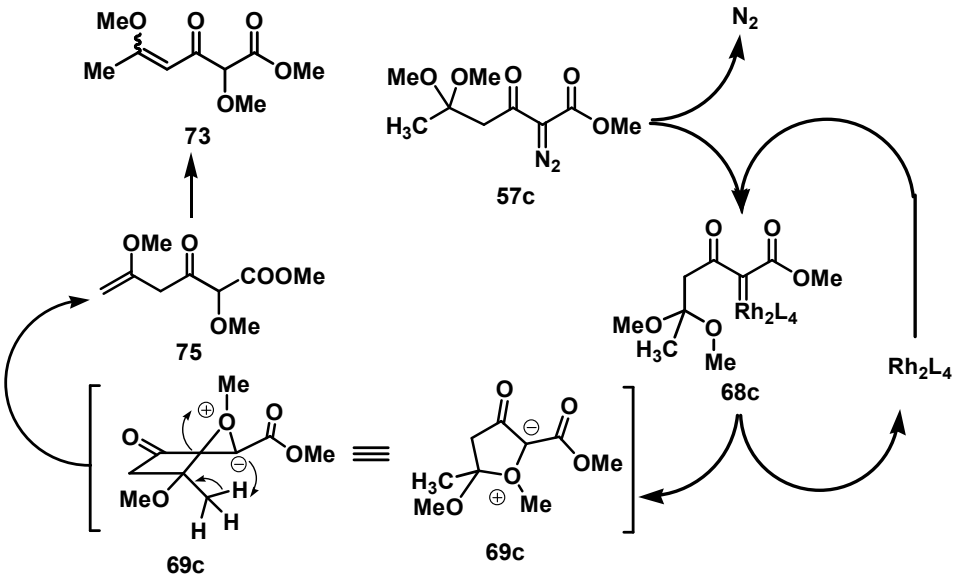

### 3.2.2.4 Diazo Decomposition of δ,δ-Dialkoxy-β-keto-α-diazoesters 57 that Afford Functionalized β-Ketoesters

Methyl 5,5-dimethoxy-3-oxo-2-diazohexanoate (**57c**) and methyl 6-chloro-5,5-dimethoxy-3-oxo-2-diazohexanoate (**57f**) are derived from addition of 3-TBSO-2-diazo-3-butenoate (**2**) and orthoacetates instead of orthoformates. When these two diazoesters were subjected to diazo decomposition catalyzed by dirhodium(II) acetate in refluxing DCM, functionalized β–ketoesters (**73** and **74**) were produced in moderate yields instead of substituted cyclobutanone products **67** (Eq. 26 and Eq. 27). In either cases, only one geometric isomer was obtained based on $^{1}$H NMR spectra.




A reaction mechanism that describes the transformation of diazoester **57c** to β–ketoester **73** is depicted in Scheme 3.7. Similar to what was proposed in the mechanism for converting diazoester **57** to cyclobutanone **67** (Scheme 3.6), oxonium ylide (**69c**) is formed via metal carbene intermediate **68c**. What is different from the mechanism in scheme 3.6 is that the enolate anion in the ylide intermediate now deprotonates from the terminal methyl group instead of performing nucleophilic attack to kick off the methoxy group as is shown in scheme 3.6. A terminal alkene is formed after migration of the methoxy group, and intermediate **75** thus formed was observed in the crude reaction mixture by $^{1}$H NMR. It was isolated in 44% yield after the reaction. However, compound **75** readily tautomerized to β–ketoester **73** in solution upon proton transfer. Since methyl 2,5-dimethoxy-3-oxohex-4-enoate (**73**) possesses a trisubstituted alkene which is in conjugation with the carbonyl group, it should be thermodynamically more favorable than methyl 2,5-dimethoxy-3-oxohex-5-enoate (**75**) that has non-conjugated, terminal alkene functionality.

**Scheme 3.7**. Mechanism for the Formation of Functionalized β–Ketoester **73b.**




### 3.2.3 Application of Functionalized β–Alkoxy-cyclobutanone

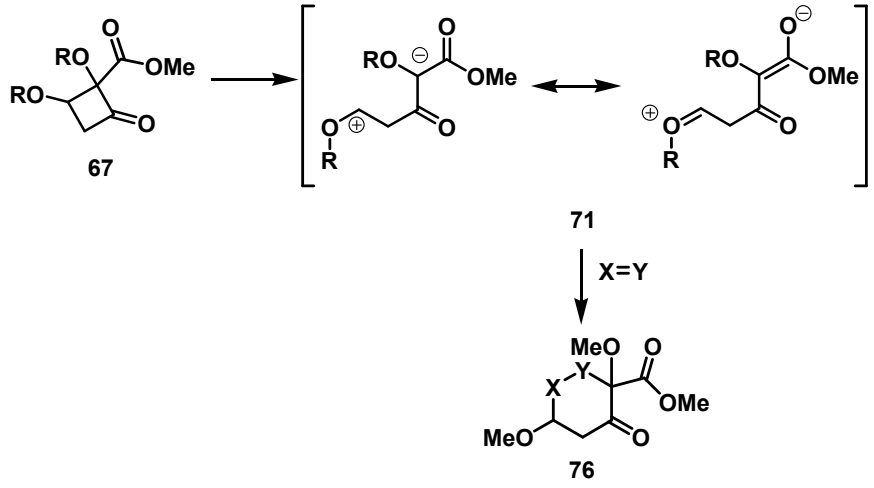
We are interested in functionalized β-alkoxycyclobutanones **67** which can be conveniently prepared by dirhodium(II) acetate catalyzed diazo decomposition reactions of δ,δ-dialkoxy-β-keto-α-diazoesters **57**. The decomposition of 1,2-diisopropoxy-4-oxocyclobutanecarboxylate (**67e**) to methyl 3-hydroxy-2,5-diisopropoxypenta-2,4-dienoate (**72**) (Scheme 3.6) implied that β-alkoxycyclobutanone **67** readily undergoes a ring-opening reaction to release the strain of the four-membered ring. Moreover, zwitterionic species **71** which is the proposed reaction intermediate seems to be applicable in further transformations such as dipolar cycloadditions. Therefore, we thought it is possible to take advantage of this decomposition reaction of 1,2-dialkoxy-4-oxocyclobutanecarboxylates **67** via ring-opening and apply these cyclobutanone compounds as reactive synthons to synthesize other functionalized molecules.

We were able to apply this strategy in the synthesis of substituted cyclohexenones and pyrazole derivatives using β-alkoxycyclobutanones **67** as reaction intermediates. The results from these investigations are discussed in this section.

### 3.2.3.1 Synthesis of Substituted Dihydro-Ɣ-pyrone via 1, 2-Dialkoxy-4-oxocyclobutane- carboxylates 67

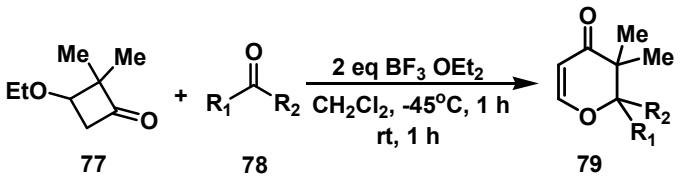
Cycloaddition using dipolar species **71** that derives from compound **67** and a dipolarphile is a potential application of β-alkoxycyclobutanones **67** (Scheme 3.8). Highly substituted cyclohexanone-type structures could be produced by this cycloaddition reaction.

**Scheme 3.8** Proposed Dipolar Cycloaddition Reaction.

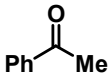
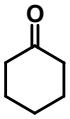


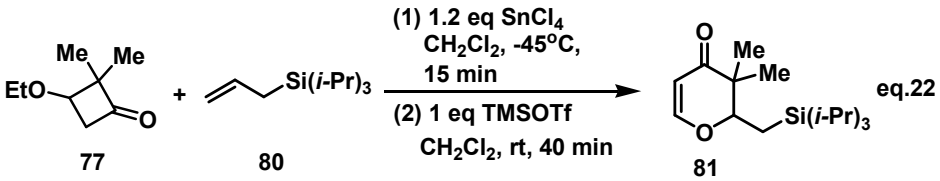

We were able to find precedent for cycloaddition reactions with other β–alkoxy-cyclobutanones in the literature. A paper published in 2008 described a Lewis acid-catalyzed intermolecular [4+2] cycloaddition of 3-alkoxycyclobutanone (**77**)

with aldehydes and ketones (eq.21).[24] As an extension of this reaction, the same cyclobutanone compounds were applied in cycloaddition reactions with allysilanes catalyzed by tin(IV) chloride (eq. 22).[25]




77 78 79

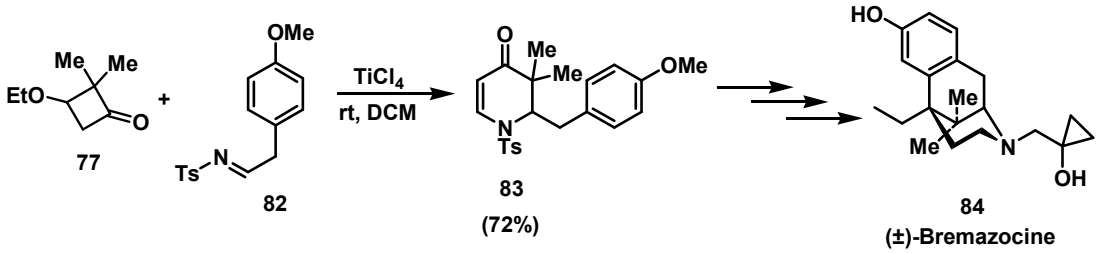
| Entry | 78 | yield of 79 (%) |
|---|---|---|
| 1 |  | 92 |
| 2 |  | 83 |
| 3 |  | 90 |




77 80 81 (78%)

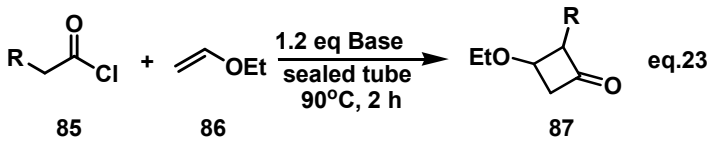
Cycloaddition reactions of 3-alkoxycyclobutanones with imines were also developed and applied in synthesis of (±)-Bremazocine (Scheme 3.9).[26]

**Scheme 3.9** Synthesis of (±)-Bremazocine from 3-Alkoxycyclobutanones.




77 82 83 (72%) 84 (±)-Bremazocine

We recognized that although cycloaddition reactions of β-alkoxycyclobutanones have been widely studied, methods for the preparation of β-alkoxycyclobutanones are rather limited. A commonly used method is to react ethyl vinyl ether with substituted ketenes, which are generated in situ from acetyl chloride using sterically hindered amines as base (Eq.30).[27] This reaction is performed with 10 equivalent of ethyl vinyl ether **86** in a sealed tube at 90$^{o}$C under solvent-free conditions. In order to intercept the reactive ketene derivatives, a large excess of ethyl vinyl ether is required, and the reaction has to be performed at high temperature with a stoichiometric amount of base. These conditions appear to be limitations of this method. More importantly, the substitutent (R group in **87**) in the β-alkoxycyclobutanone **87** products is confined by the acyl chloride **85** involved. Only cyclobutanone products with simple alkyl or aryl substituents at the α-position were prepared by this method. Since the conventional method has several drawbacks, new methods that employ mild conditions and have broad substrate scope are desirable.




eq.23

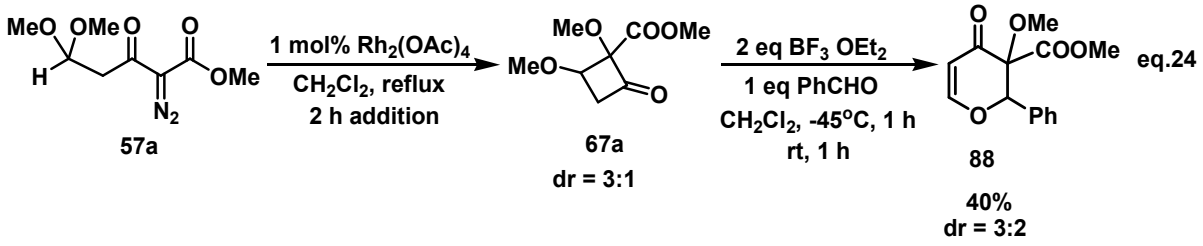
85 86 87

Base = *i*-$Pr_2$NEt or 2, 6-lutidine

| Entry | $R_2$ | yield% |
|---|---|---|
| 1 | H | 37 |
| 2 | Me | 77 |
| 3 | hex | 77 |
| 4 | *t*-Bu | 48 |
| 5 | Ph | 75 |
| 6 | 4-$MeOC_6H_4$ | 74 |
| 7 | 1-Naph | 83 |

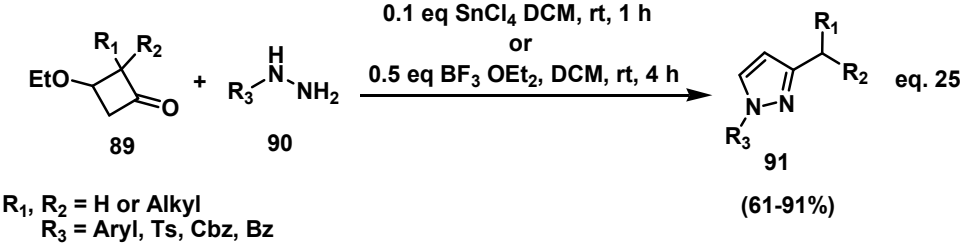
Consideration of the synthetic applications of functionalized β-alkoxycyclobutanones and the scarceness of effective method to prepare this kind of compound leads us to conclude that our approach to functionalized β-alkoxycyclobutanones by diazo decomposition reactions of δ,δ-dialkoxy-β-keto-α-diazoesters can be a useful method for the synthesis of highly substituted β-alkoxycyclobutanones.

We were able to apply methyl 1,2-dimethoxy-4-oxocyclobutanecarboxylate (**67a**) prepared by diazo decomposition of methyl 5,5-dimethoxy-3-oxo-2-diazopentanoate (**57a**) in cycloaddition reaction with benzaldehyde (Eq.24). The expected dihydropyranone product (**88**) (resulting from in situ elimination of methanol) was obtained in morderate yield.



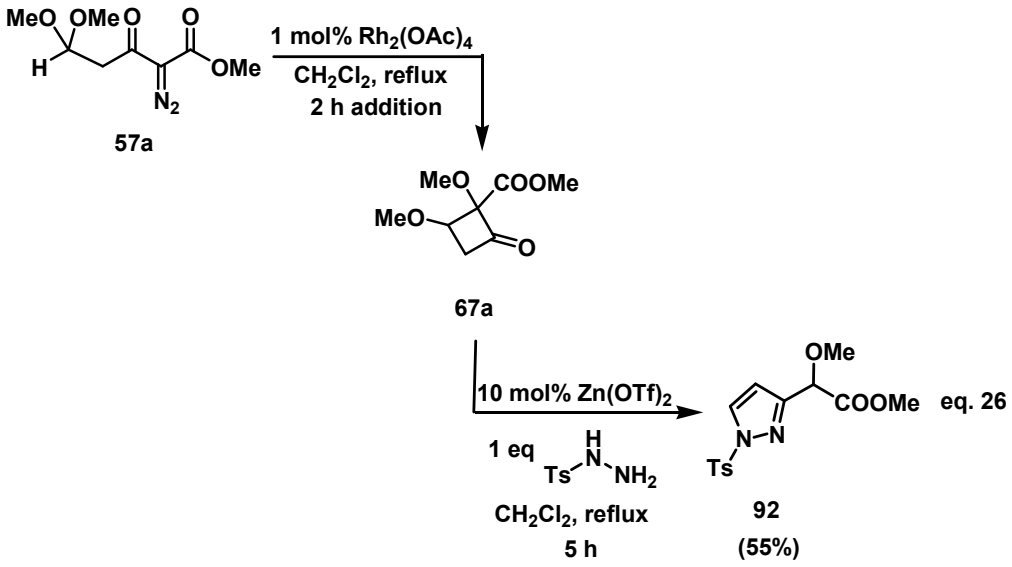

### 3.2.3.2 Synthesis of Pyrazole Derivatives via 1,2-Dialkoxy-4-oxocyclobutane- carboxylates 67

Another application for β-alkoxycyclobutanone compounds that we were able to found in the literature is the synthesis of pyrazoles by reacting β-alkoxycyclobutanone with monosubstituted hydrazine **87** (Eq.32).[28] Catalyzed by either tin(IV) chloride or boron trifluoride etherate, this transformation proceeds at room temperature to afford pyrazole products **88** in good yields.




An issue with this transformation is that the scope of the β-alkoxycyclobutanone substrate **89** is limited. The method described in equation 23 was employed; therefore, only alkyl substituents could be incorporated to the α–position on the cyclobutanone ring. We should be able to extend this chemistry by applying β-alkoxycyclobutanones **67** that can be prepared by diazo decomposition reactions of diazoester **57** in this pyrazole synthesis.

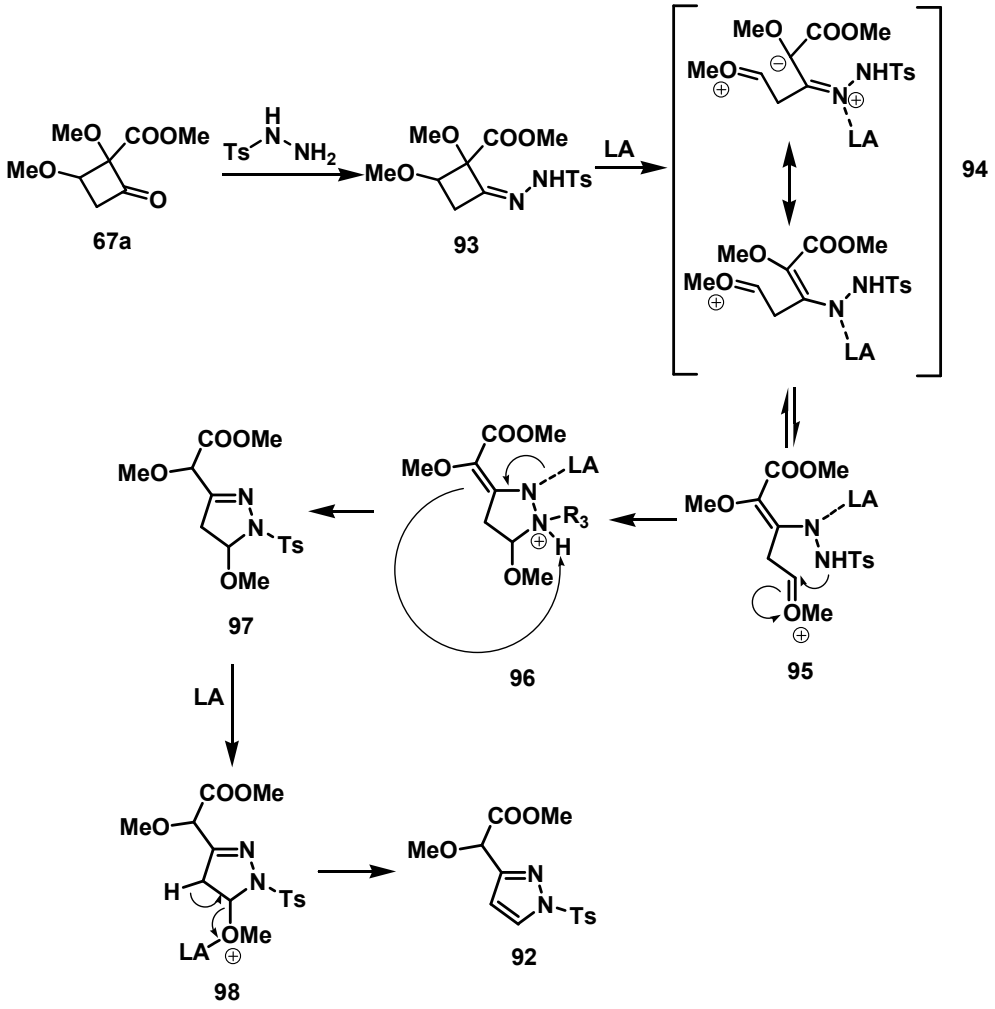
We employed methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate (**57a**) in diazo decomposition reaction catalyzed by dirhodium(II) acetate. After reacting for 2 hours in refluxing dichloromethane, methyl 1,2-dimethoxy-4-oxo-cyclo-butanecarboxylate (**67a**) was formed. Without isolation of intermediate **67a**, 1 equivalent of tosylhydrazine and 5 mol% zinc(II) triflate as Lewis acid catalyst were added to the reaction solution. The reaction was run in refluxing DCM for another 5 hours and the desired pyrazole product **92** was produced in 55% isolated yield after purification (Eq.26). We were able to achieve this one-pot synthesis of pyrazole compound **93** from diazoeser **57a** by sequential addition of reagents. Only 5 mol% of mild Lewis acid catalyst is required to promote this transformation, and these two features are the advantages of this pyrazole synthesis in comparison with the method described in equation 25.




A possible mechanism for this transformation is proposed in Scheme 3.10. Hydrazone intermediate **93** is first generated, then Lewis acid induced ring-

openning occurs to give dipolar specie **94**. Intramolecular nucleophilic attack on the oxonium carbonyl group by the secondary amine affords the five membered ring in intermediate **96**. Proton transfer after cyclization leads to intermediate **97** which upon elimination of methanol gives the observed pyrazole product **93**.

**Scheme 3.10**. Proposed Mechanism for the Synthesis of Pyrazole **92**.




β-Alkoxycyclobutanones **67** we made by diazo decomposition of δ,δ-dialkoxy-β-keto-α-diazoesters **57** could be a potentially useful synthons in organic synthesis. They can be readily converted to other functionalized organic compounds such

as substituted γ–dihydropyrones or pyrazole derivatives by established methods. The ease of functionalization of β-alkoxycyclobutanones **67** by modification of the diazoester precursor **57** is a major advantage compared to other concurrent methods.

### 3.2.4 Summary

To summarize this chapter, we have developed a reaction of 3-TBSO-2-diazo-3-butenoate (**2**) and orthoesters as an extension of the Mukaiyama-type addition reactions we previously established. This addition reaction of diazoester **2** and different orthoesters has the advantage of low catalyst loading and mild reaction conditions. One limitation for this methodology is that due to the acid sensitive nature of both silyl enol ether group in substrate **2** and the orthoesters, the yields of these transformations are generally moderate. δ,δ-Dialkoxy-β-keto-α-diazoesters **57** produced from this Mukaiyama-type condensations undergo diazo decomposition and give functionalized β-cyclobutanones which are versatile reaction intermediate that can be readily applied in the synthesis of substituted γ–dihydropyrones or pyrazole derivatives.

## 3.3 Experimental Section

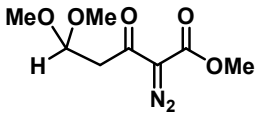
### 3.3.1 General Information

Reactions were performed in oven-dried (140$^{o}$C) or flame-dried glassware. Dichloromethane (DCM) was passed through a solvent column prior to use and was not distilled. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 $F_{254}$ plates. The developed chromatogram was analyzed by UV lamp (254 nm) or by staining with phosphomolybdic acid (PMA) ethanol solution. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated system on silica gel (230-400 mesh). Metal triflate salts were purchased from Aldrich and used as received. Dirhdodium(II) acetate was purchased from Pressure Chemical Co. and used as received. Other dirhodium(II) catalysts were prepared by method described in the literature.[29] l All TBSO-substituted vinyldiazoesters were prepared by the method described by Ueda.[1] All other commercially available reagents were used as received unless otherwise mentioned.

NMR spectra were measured on Bruker AV-400 ($^{1}$H at 400 MHz, $^{13}$C at 100 MHz). $^{1}$H NMR spectra were recorded **with tetramethylsilane (TMS) (0.00 ppm) as the internal standard.** Data are reported as follows: chemical shift (in ppm, δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet, comp = composite) and coupling constants (in Hz). $^{13}$C NMR spectra were obtained **with complete proton decoupling. Chemical shifts are reported in ppm utilizing $CDCl_3$ peak as a reference (77.0 ppm).** High resolution mass spectra (HRMS) were recorded by a JEOL

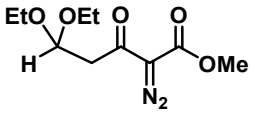
Accu TOF-CS (ESI, positive mode). Infrared (IR) spectra were measured on a JESCO FT/IR-4100 instrument.

### 3.3.2. Procedure for the Synthesis of Methyl 5, 5-dialkoxy-3-oxo-2diazo-pentanoate (57)



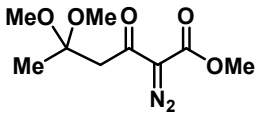

**57a**

**Synthesis of methyl 5, 5-dimethoxy-3-oxo-2-diazopentanoate (57a)** To an oven-dried 4 dr vial under nitrogen was added zinc triflate (2 mg, 0.005 mmol), followed by trimethyl orthoformate (**56a**) (212 mg, 1.96 mmol) and 4 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**2**) (256 mg, 1.00 mmol) was added via syringe all at once. The bright yellow solution was stirred vigorously at room temperature. After 16 hours the reaction mixture was concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give 140 mg of a pale yellow liquid as product **57a** (0.65 mmol, 65% yield). **57a:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.91 (t, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.35 (s, 6H), 3.20 (d, *J* = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.7, 161.5, 101.0, 53.4, 52.2, 43.3; IR (neat): 3018, 2135, 1721, 1656 cm$^{-1}$; HRMS (ESI) for $C_8H_{13}N_2O_5$ $[M+H]^+$ calcd 217.0824; found 217.0836.




57b

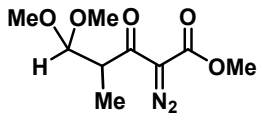
**Synthesis of methyl 5, 5-diethoxy-3-oxo-2-diazo-pentanoate (57b)** To an oven-dried 4 dr vial under nitrogen was added zinc triflate (2 mg, 0.005 mmol), followed by triethyl orthoformate (**56b**) (296 mg, 1.96 mmol) and 4 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**2**) (256 mg, 1.00 mmol) was added via syringe all at once. The bright yellow solution was stirred vigorously at room temperature. After 16 hours the reaction mixture was concentrated under reduced pressure to give the crude product as yellow oil. The crude product was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give 151 mg of a pale yellow liquid as product **57b** (0.62 mmol, 62% yield). **57b:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.89 (t, *J* = 8.0 Hz, 1H), 3.52 (dt, *J* = 8.0 Hz, *J* = 16.0 Hz 2H), 3.41 (dt, *J* = 8.0 Hz, *J* = 16.0 Hz 2H),3.70 (s, 3H), 3.07 (d, *J* = 8.0 Hz, 2H), 1.04 (t, *J* = 8.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.6, 161.3, 99.0, 76.2, 61.6, 52.0, 44.3, 15.0; IR (neat): 2979, 2135, 1718, 1657 cm$^{-1}$; HRMS (ESI) for $C_{10}H_{16}N_2O_5$ $[M+H]^+$ calcd 245.1137; found 245.1146.




57c

**Synthesis of methyl 5, 5-dimethoxy-3-oxo-2-diazohexanoate (57c)** To an oven-dried 4 dr vial under nitrogen was added zinc triflate (2 mg, 0.005 mmol),

followed by trimethyl orthoacetate (**56c**) (240 mg, 1.98 mmol) and 4 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**2**) (256 mg, 1.00 mmol) was added via syringe all at once. The bright yellow solution was stirred vigorously at room temperature. After 16 hours the reaction mixture was concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give 140 mg of a bright yellow liquid as product **57c** (0.52 mmol, 52% yield). **57a:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.84 (s, 3H), 3.29 (s, 2H), 3.23 (s, 6H), 1.46 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.5, 161.4, 100.3, 52.0, 48.2, 44.4, 21.7; IR (neat): 2956, 2833, 2132, 1717, 1652 cm$^{-1}$;HRMS (ESI) for $C_9H_{14}N_2O_5$ $[M+H]^+$ calcd 231.0981; found 231.0975.

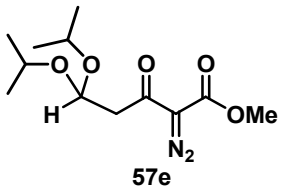


**57d**

**Synthesis of methyl 5, 5-dimethoxy-4-methyl-3-oxo-2-diazo-pentanoate (57d)**

To an oven-dried 4 dr vial under nitrogen was added zinc triflate (2 mg, 0.005 mmol), followed by trimethyl orthoformate (**56a**) (212 mg, 1.96 mmol) and 4 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazopent-3-enoate (**2d**) (280 mg, 1.00 mmol) was added via syringe all at once. The bright yellow solution was stirred vigorously at room temperature. After 16 hours the reaction mixture was concentrated under reduced pressure to give the crude product as a yellow oil. The crude product

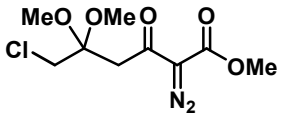
was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give 120 mg of a pale yellow liquid as product **57d** (0.52 mmol, 52% yield). **57d:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.57 (d, *J* = 8.0 Hz, 1H), 4.01 (quintet, *J* = 8.0 Hz 1H), 3.81 (s, 3H), 3.31 (s, 6H), 1.10 (d, *J* = 8.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 193.6, 161.4, 105.4, 76.1, 55.4, 52.1, 51.8, 44.0, 13.0; IR (neat): 2958, 2835, 2142, 1719, 1653 cm$^{-1}$; HRMS (ESI) for $C_9H_{14}N_2O_5$ $[M+H]^+$ calcd 231.0981; found 231.0972.



**57e**

**Synthesis of methyl 5, 5-diisopropoxy-3-oxo-2-diazopentanoate (57e)** To a 15 mL 2 neck round bottom flask connected with a condenser was added 2 mg zinc triflate (0.005 mmol). The apparatus was flame dried and then cooled under nitrogen. Triisopropyl orthoformate (**56e**) (380 mg, 1.96 mmol) was mixed with methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**2**) (256 mg, 1.00 mmol) and 4 mL of dry DCM, and this solution was added to the flame-dried flask with syringe. The bright yellow solution was heated in a 40$^{o}$C oil bath and stirred vigorously. After 16 hours the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by silica gel chromatography, eluting with 1:2 EtOAc/hexane to give 154 mg of a pale yellow liquid as product **57e** (0.56 mmol, 56% yield). **57e:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.06 (t, *J* = 8.0 Hz,

1H), 3.85 (sept, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 3.14 (d, *J* = 8.0 Hz, 2H), 1.14 (d, *J* = 6.0 Hz, 6H), 1.10 (d, *J* = 6.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.9, 161.5, 96.7, 76.4, 52.2, 46.0, 23.2, 22.3; IR (neat): 2974, 2835, 2132, 1720, 1657 $cm^{-1}$; HRMS (ESI) for $C_{12}H_{20}N_2O_5$ $[M+H]^+$ calcd 273.1450; found 273.1461.

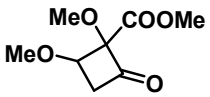



**57f**

**Synthesis of methyl 6-chloro-5, 5-dimethoxy-3-oxo-2-diazo-hexanoate (57f)**

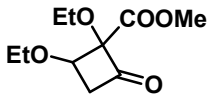
To a 15 mL 2 neck round bottom flask connected with a condenser was added 2 mg zinc triflate (0.005 mmol). The apparatus was flame dried and then cooled under nitrogen. 2-Chloro-1,1,1-trimethoxyethane (**56f**) (308 mg, 2.00 mmol) was mixed with methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**2**) (256 mg, 1.00 mmol) and 4 mL of dry DCM, and this solution was added to the fame-dried flask with syringe. The bright yellow solution was heated in a 40$^o$C oil bath and stirred vigorously. After 16 hours the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to give the crude product as yellow oil. The crude product was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give 121 mg of a pale yellow liquid as product **57f** (0.46 mmol, 46% yield). **57f:** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.84 (s, 2H), 3.81 (s, 3H), 3.42 (s, 2H), 3.21 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.8, 161.4, 101.0, 77.2, 52.2, 48.6, 43.9, 39.6; IR (neat): 2958, 2136, 1714, 1653 $cm^{-1}$; HRMS (ESI) for $C_9H_{14}ClN_2O_5$ $[M+H]^+$ calcd 265.0591; found 265.0596.

### 3.3.3. Procedure for Rhodium(II) Acetate Catalyzed Dinitrogen extrusion of Methyl 5,5-dialkoxy-3-oxo-2-diazo-pentanoate (57)



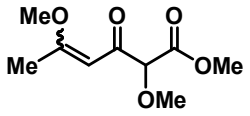

67a

**Synthesis of 1, 2-dimethoxy-4-oxocyclobutanecarboxylate (67a)** A solution of 106 mg methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate (**57a**) (0.50 mmol) in 4.0 mL of anhydrous $CH_2Cl_2$ was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 6.0 mL of anhydrous $CH_2Cl_2$. The catalyst was removed by passing the resulting solution through a short plug of silica after addition of the diazo compound. The solvent was removed under reduced pressure to give 72 mg of a pale yellow liquid as product (0.39 mmol, 77% yield). It is a mixture of two diastereomers which could not be separated by chromatography. NMR analysis showed a 3.0:1 diastereomeric ratio. major isomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.27 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 3.40-3.47 (comp, 1H), 3.43 (s, 3H), 3.05 (dd, *J* = 4 Hz, *J* = 18 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.7, 168.3, 96.1, 73.3, 58.4, 56.5, 52.4, 48.8; minor isomer: : $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.08 (t, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 3.55 (s, 3H), 3.38 (s, 3H), 3.26 (dd, *J* = 8 Hz, *J* = 18 Hz, 1H), 3.17-3.12 (comp, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 200.0, 167.0, 99.6, 75.1, 58.5, 55.4, 52.6; IR (neat): 1650, 1579, 1486 $cm_{-1}$; HRMS (ESI) for $C_8H_{13}O_5$ $[M+H]^+$ calcd 189.0762; found 189.0763.



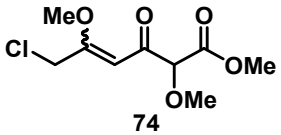

**67b**

**Synthesis of 1,2-diethoxy-4-oxocyclobutanecarboxylate (67b)** A solution of 122 mg methyl 5, 5-dimethoxy-3-oxo-2-diazopentanoate (**57b**) (0.50 mmol) in 4.0 mL of anhydrous $CH_2Cl_2$ was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 6.0 mL of anhydrous $CH_2Cl_2$. The catalyst was removed by passing the resulting solution through a short plug of silica after addition of the diazo compound. The solvent was removed under reduced pressure to give 72 mg of a pale yellow liquid as product (0.38 mmol, 75% yield). It is a mixture of two diastereomers which could not be separated by chromatography. NMR analysis showed a 2.6:1 diastereomeric ratio. major isomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.27 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H), 3.85 (q, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 3.74-3.69 (comp, 1H), 3.55 (dt, *J* = 8.0 Hz, *J* = 16.0 Hz, 1H), 3.46 (dd, *J* = 8.0 Hz, *J* = 18 Hz, 1H), 3.11 (dd, *J* = 4.0 Hz, *J* = 18 Hz, 1H); 1.25 (t, *J* = 7.2 Hz), 1.23 (t, *J* = 7.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.5, 168.9, 96.4, 71.7, 66.5, 64.7, 52.6, 52.5, 15.5, 15.0; visible signals for the minor isomer: 4.20 (t, *J* = 6.0 Hz), 3.79 (s, 3H), 3.30 (dd, *J* = 8.0 Hz, *J* = 18 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 73.8, 67.0, 63.7, 52.3, 48.9, 15.5, 14.9; IR (neat): 2980, 1731 cm$^{-1}$; HRMS (ESI) for $C_{10}H_{17}O_5$ $[M+H]^+$ calcd 217.1076; found 217.1089.




73

**Synthesis of methyl 2,5-dimethoxy-3-oxohex-4-enoate (73)** A solution of 116 mg methyl 5,5-dimethoxy-3-oxo-2-diazohexanoate (**57c**) (0.50 mmol) in 4.0 mL of anhydrous $CH_2Cl_2$ was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 6.0 mL of anhydrous $CH_2Cl_2$. The catalyst was removed by passing the resulting solution through a short plug of silica after the reaction, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography, eluting with 1:2 EtOAc/hexane to give 65 mg of a pale yellow liquid as product (0.33 mmol, 65% yield). **73:** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.84 (s, 1H), 4.30 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.48 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 191.1, 177.2, 168.3, 94.0, 87.3, 58.2, 56.0, 52.6, 20.4; IR (neat): 2958, 1748, 1682, 1575 cm$^{-1}$; HRMS (ESI) for $C_9H_{15}O_5$ $[M+H]^+$ calcd 203.0919; found 203.0909.

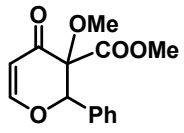



74

**Synthesis of methyl 6-chloro-2,5-dimethoxy-3-oxohex-5-enoate (74)** A solution of 132 mg methyl 5,5-dimethoxy-3-oxo-2-diazohexanoate (**57f**) (0.50 mmol) in 4.0 mL of anhydrous $CH_2Cl_2$ was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 6.0 mL of anhydrous $CH_2Cl_2$. The catalyst was removed by passing the resulting solution through a short plug of silica after the reaction, and the solvent was removed under reduced pressure.

The crude product was purified by flash column chromatography, eluting with 1:2 EtOAc/hexane to give 50 mg of a pale yellow liquid as product (0.21 mmol, 41% yield). **73:** $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.89 (s, 1H), 4.62 (d, d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.28 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.44 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 190.9, 171.5, 167.8, 95.6, 87.0, 58.4, 56.7, 52.7, 40.1; IR (neat): 2957, 1748, 1686, 1589 cm-1;HRMS (ESI) for $C_9H_{14}ClO_5$ $[M+H]^+$ calcd 237.0529; found 237.0533.

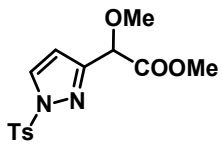
### 3.3.4. Procedure for the Synthesis of Substituted Dihydro-Ɣ-pyrone and Pyrazole derivative via 1,2-Dimethoxy-4-oxocyclobutanecarboxylate (67a)




88

**Synthesis of methyl 3,4-dihydro-3-methoxy-4-oxo-2-phenyl-2H-pyran-3-carboxylate (88)** A solution of 106 mg methyl 5,5-dimethoxy-3-oxo-2-diazopentanoate (**57a**) (0.50 mmol) in 4.0 mL of anhydrous $CH_2Cl_2$ was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 6.0 mL of anhydrous $CH_2Cl_2$. The catalyst was removed by passing the resulting solution through a short plug of silica after the reaction, and the solvent was removed under reduced pressure. The residue which was primarily 1, 2-dimethoxy-4-oxocyclobutanecarboxylate (**67a**), was dissolved in 3 mL $CH_2Cl_2$, followed by addition of 53 mg benzaldehyde (0.5 mmol, 1 equiv). The stirred solution was cooled to -45$^{o}$C with an acetonitrile-dry ice bath. Boron trifluoride etherate (126 µL, 1.00 mmol, 2 equiv) was then added to the reaction solution.

The reaction mixture was stirred at -45°C for 1 hour and then at room temperature for 1 hour. After the acetonitrile-dry ice bath was removed, the color of the reaction slowly turned from pale yellow to reddish brown. The reaction was quenched with saturated aqueous sodium bicarbonate solution and washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography, eluting with 1:3 EtOAc/hexane to give 51 mg of a pale yellow liquid as product **88** (0.20 mmol, 40% yield) as a mixture of two diastereomers which could not be separated by chromatography. NMR analysis showed a 3:2 diastereomeric ratio. **88**: major isomer: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, *J* = 8.0 Hz, 1H), 7.37-7.44 (comp, 5H), 5.65 (s, 1H), 5.60 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 3.43 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.5, 168.0, 164.1, 132.6, 129.5, 128.3, 128.2, 104.7, 84.9, 83.4, 54.7, 52.3; minor isomer: (400 MHz, $CDCl_3$) $\delta$ 7.53 (d, *J* = 8.0 Hz, 1H), 7.37-7.44 (comp, 5H), 5.44 (s, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.56 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.8, 166.7, 163.4, 134.0, 129.0, 128.1, 127.0, 107.1, 83.8, 83.8, 82.7, 55.6, 52.3; IR (neat): 3097, 3067, 2942, 2843, 1753, 1662, 1598 cm$^{-1}$; HRMS (ESI) for $C_{14}H_{14}O_5$ $[M+H]^+$ calcd 263.0919; found 263.0931.

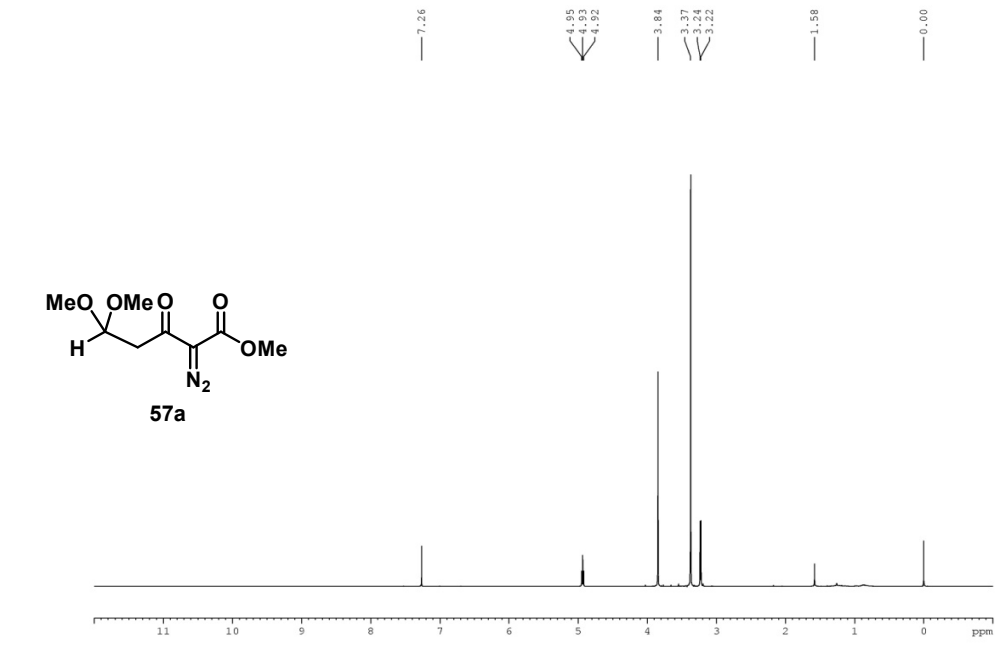


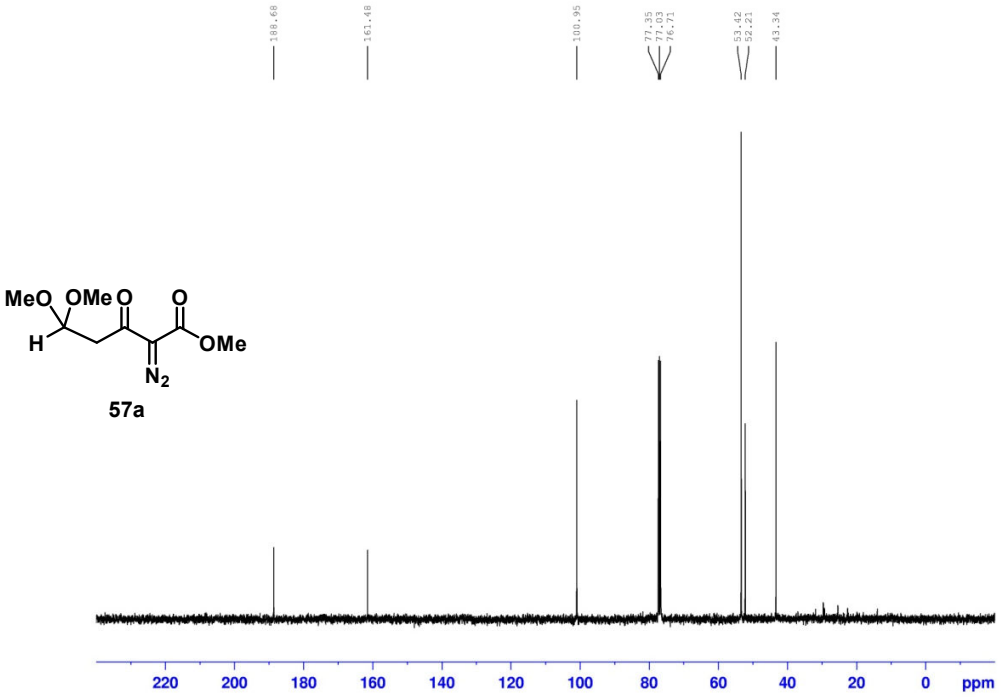

**93**

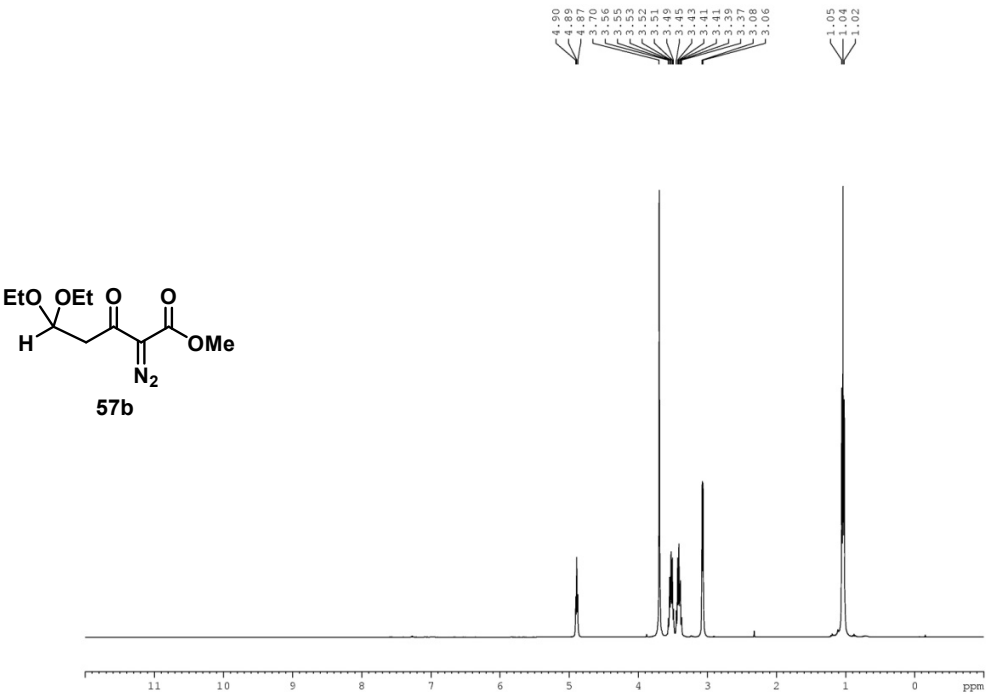
**Synthesis of methyl 2-methoxy-2-(1-tosyl-1H-pyrazol-3-yl)acetate (93)** A solution of 106 mg methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate (**57a**) (0.50

mmol) in 4.0 mL of anhydrous $CH_2Cl_2$ was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 6.0 mL of anhydrous $CH_2Cl_2$. *p*-Toluenesulfonyl hydrazide (93 mg, 0.50 mmol, 1.0 equiv) and zinc triflate (18 mg, 0.05 mmol, 0.10 equiv) was added to the reaction solution after the addition of diazoester **57a** was finished. The color of the reaction turned from yellow to reddish brown upon addition of the aryl hydrazine. The reaction was allowed to reflux for 6 hours. The catalyst was then removed by passing the resulting solution through a short plug of silica, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography, eluting with 1:2 EtOAc/hexane to give 90 mg of a pale yellow crystalline as product **93** (0.28 mmol, 55% yield). **93**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, *J* = 4.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.48 (d, *J* = 4.0 Hz, 1H), 4.92 (s, 1H), 3.71 (s, 3H), 3.34 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.4, 153.8, 146.0, 133.9, 132.5, 130.0, 128.1, 107.3, 76.8, 57.6, 52.5, 21.7; IR (neat): 3111, 2961, 2927, 2830, 1750 cm$^{-1}$;HRMS (ESI) for $C_{14}H_{16}N_2O_5S$ $[M+H]^+$ calcd 325.0858; found 325.0850.

### 3.3.5 $^{1}$H NMR and $^{13}$C NMR Spectra

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3.49
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3.41
3.39
3.37
3.08
3.06
1.05
1.04
1.02
EtO
OEt
O
O
H
OMe
N2
57b
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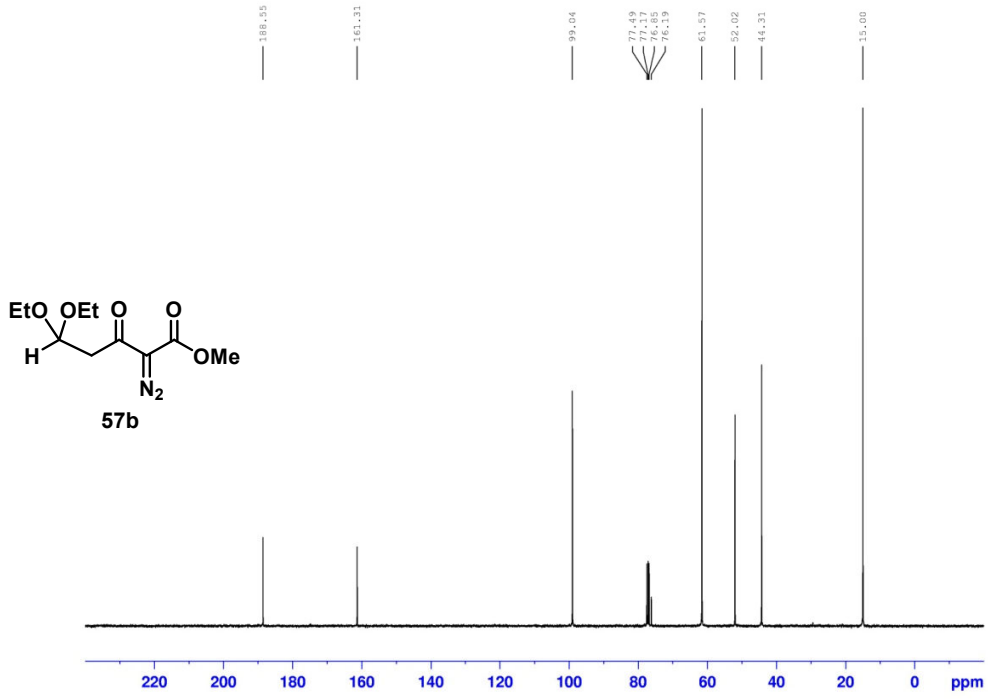
10
9
8
7
6
5
4
3
2
1
0
ppm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OEt
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H
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20
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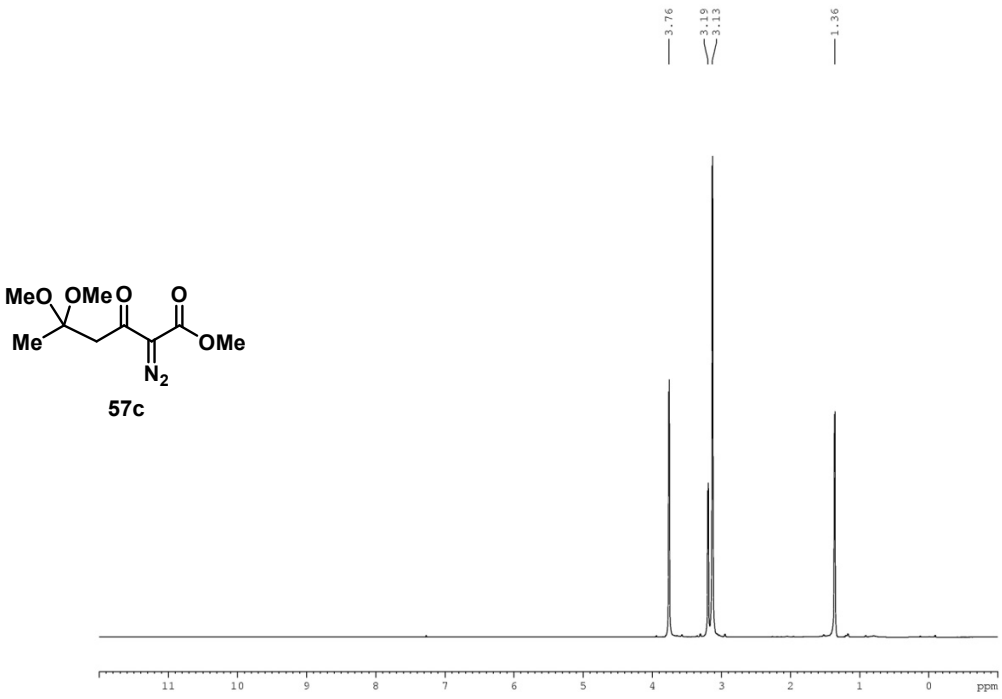
ppm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5
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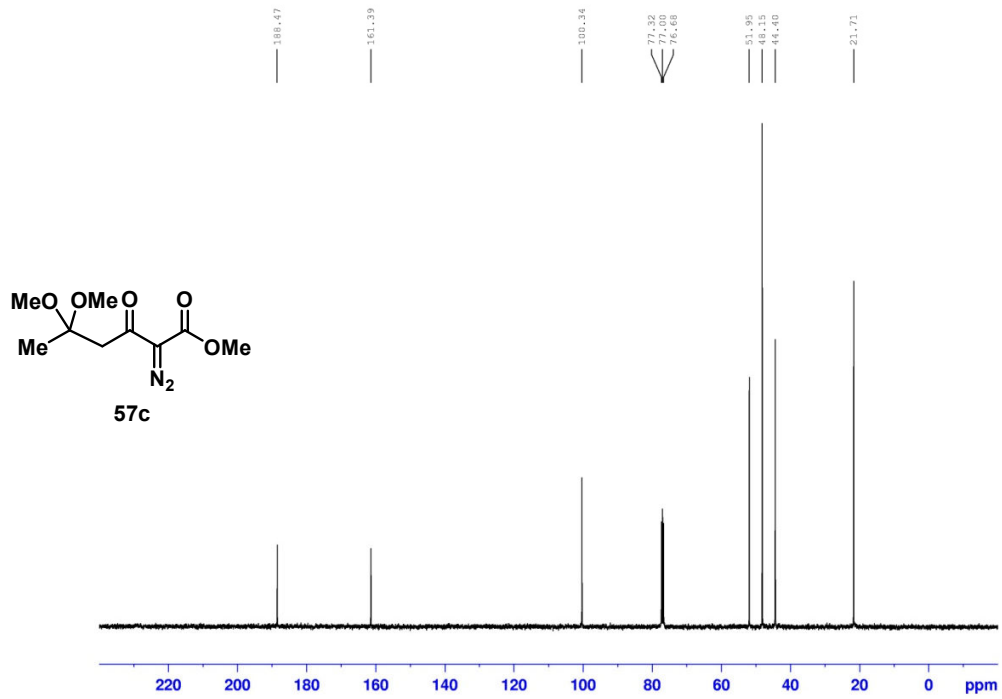
ppm

57c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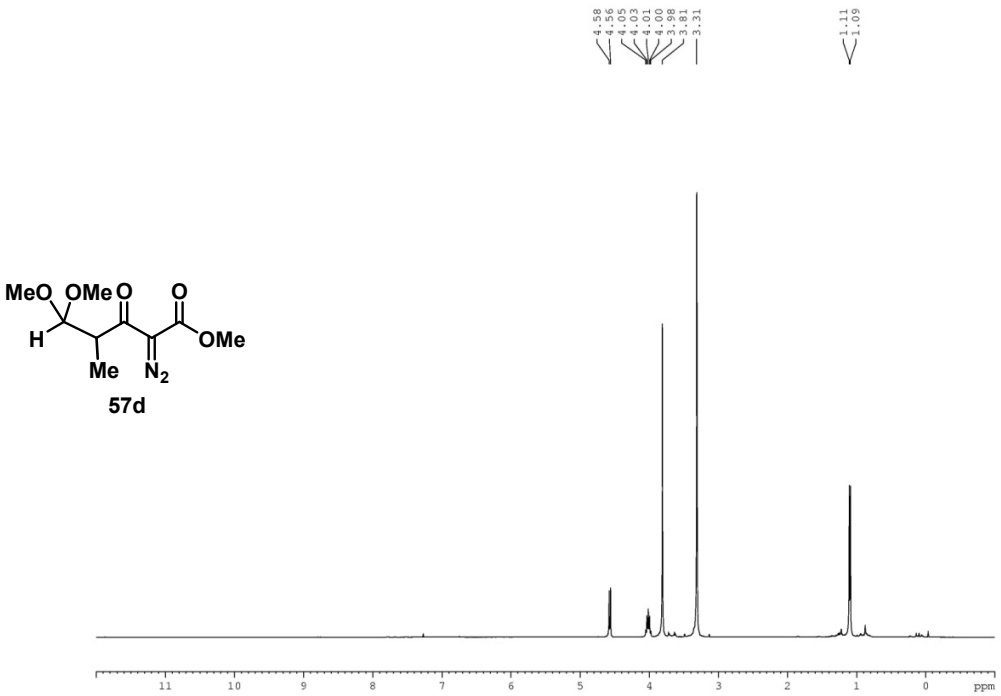
ppm

57c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1.09
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1
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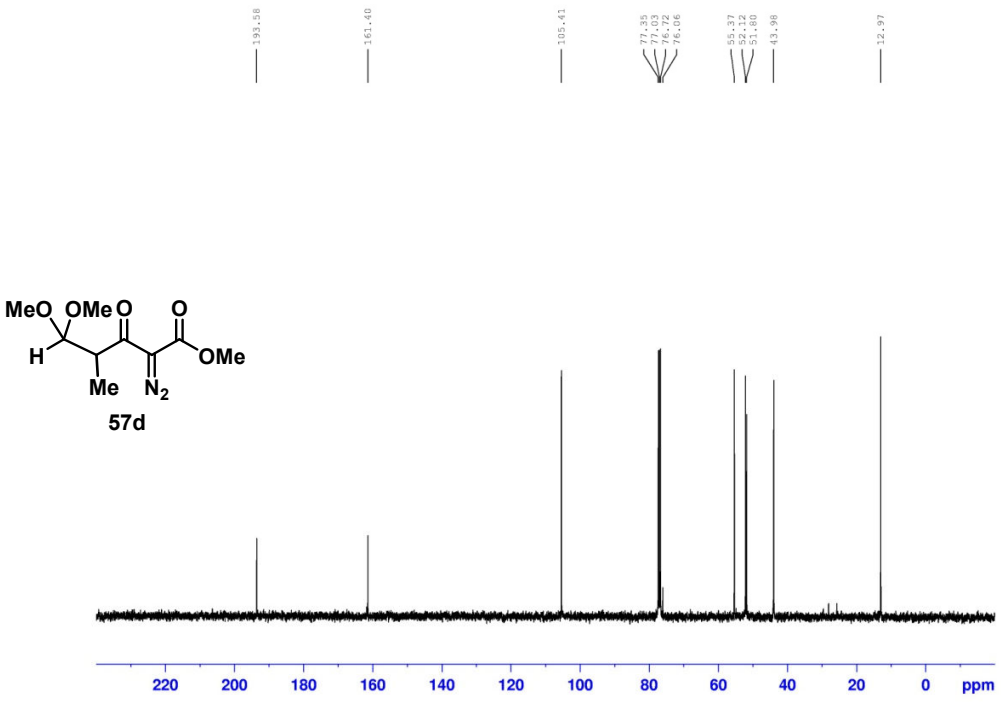
ppm

57d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76.06
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OMe
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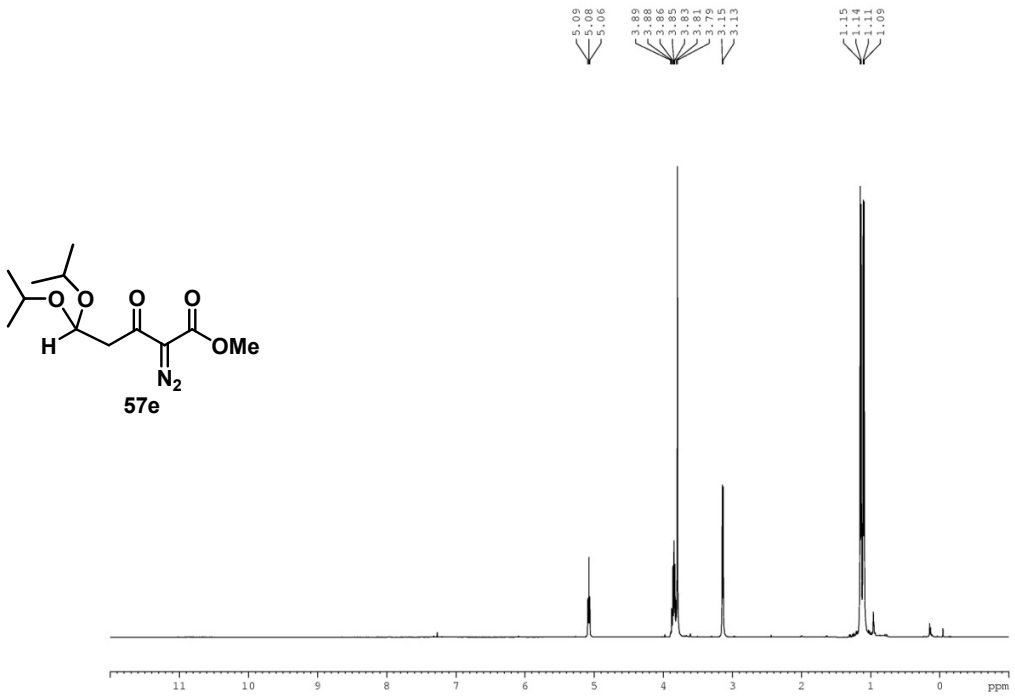
57d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O
O
O
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57e
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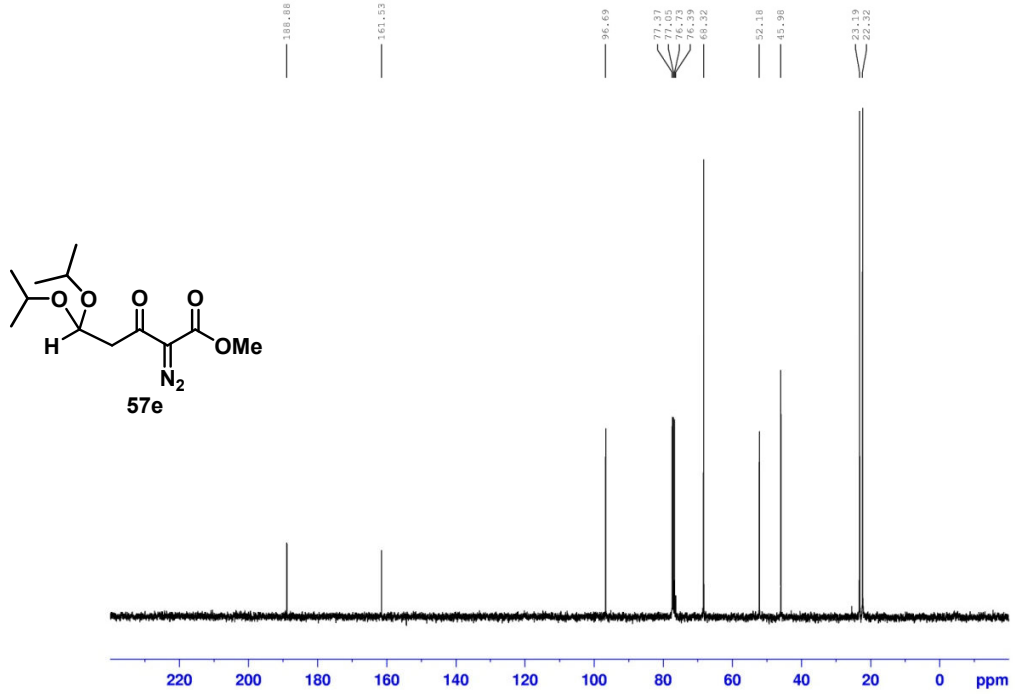
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23.19
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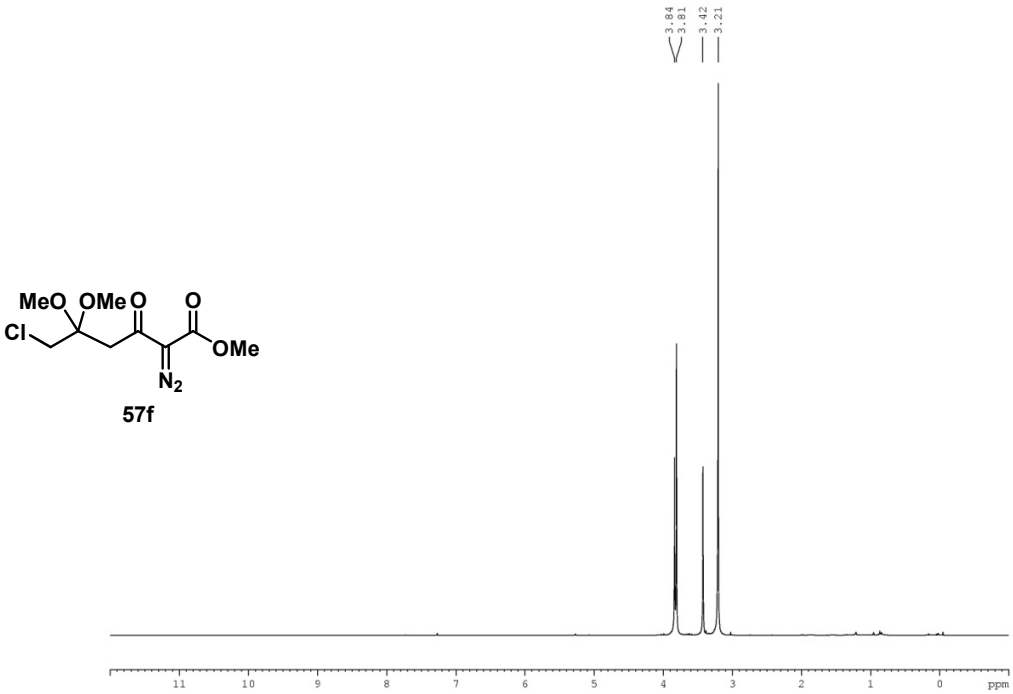
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Cl
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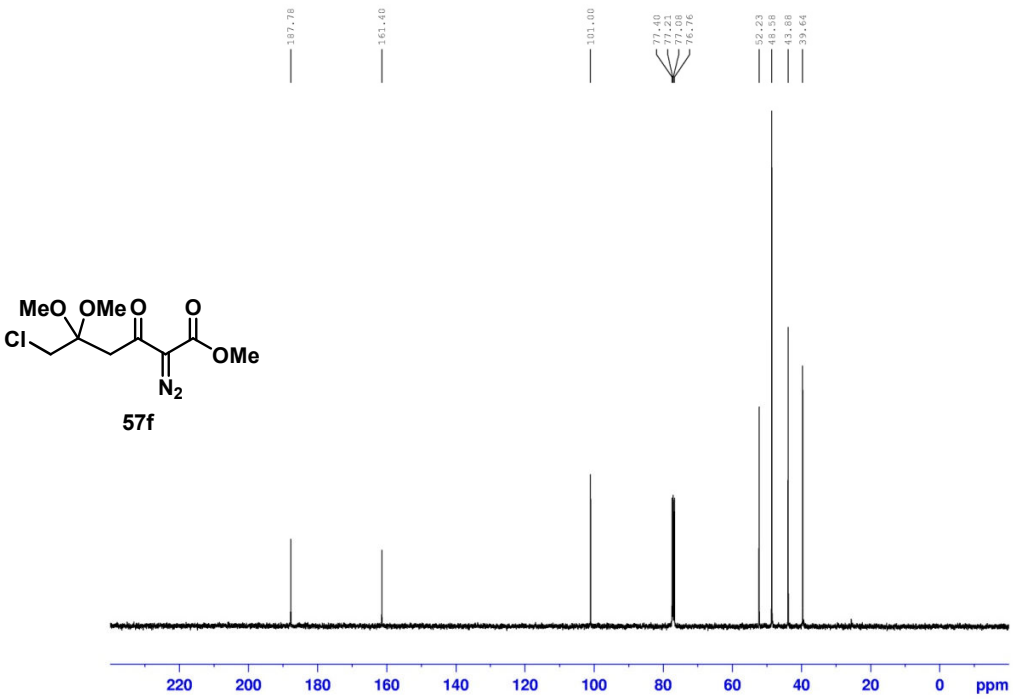
0
ppm

57f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60
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20
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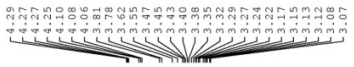
ppm

57f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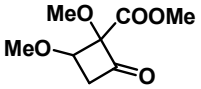
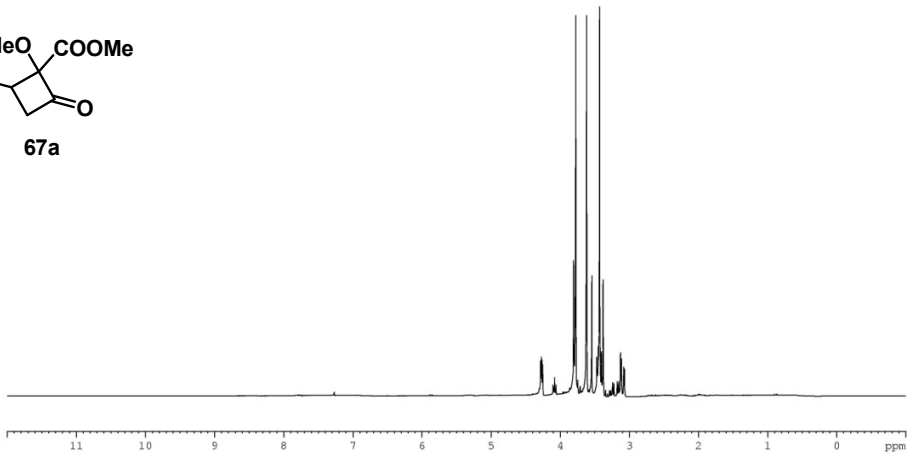
3.17
3.15
3.13
3.12
3.08
3.07


MeO
COOMe
MeO
O

67a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10
9
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7
6
5
4
3
2
1
0
ppm


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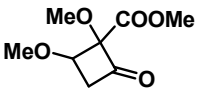
99.60
96.19
77.40
77.08
76.76
75.11
73.26
58.45
58.38
56.52
55.35
52.62
52.39
48.77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MeO
O

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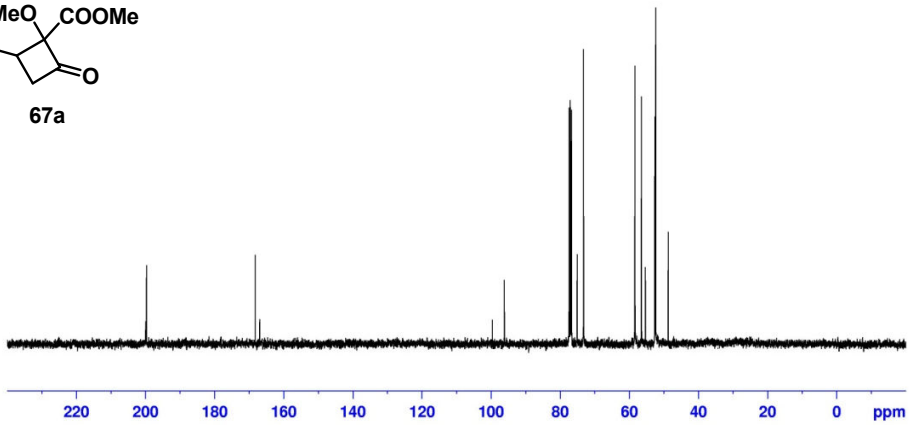
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3.88
3.86
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3.83
3.79
3.72
3.70
3.59
3.57
3.55
3.53
3.52
3.49
3.47
3.44
3.42
3.33
3.31
3.28
3.26
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3.13
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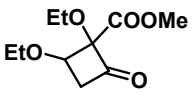
1.16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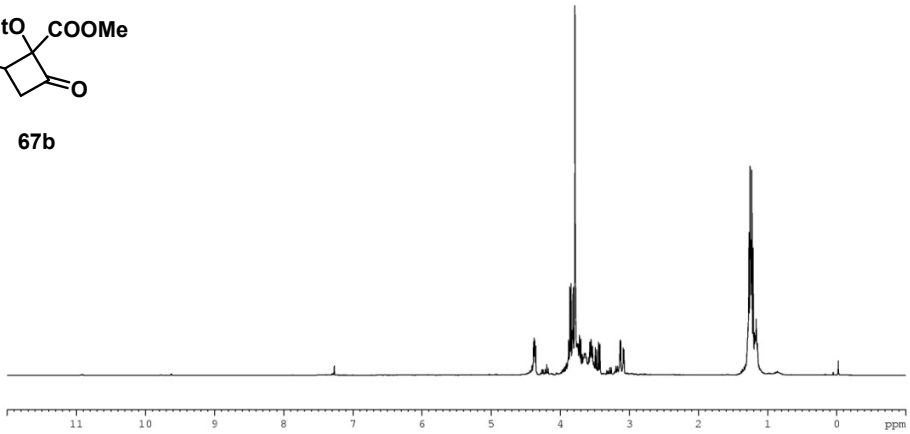
O

67b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76.70
73.78
71.70
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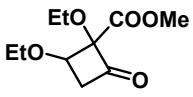
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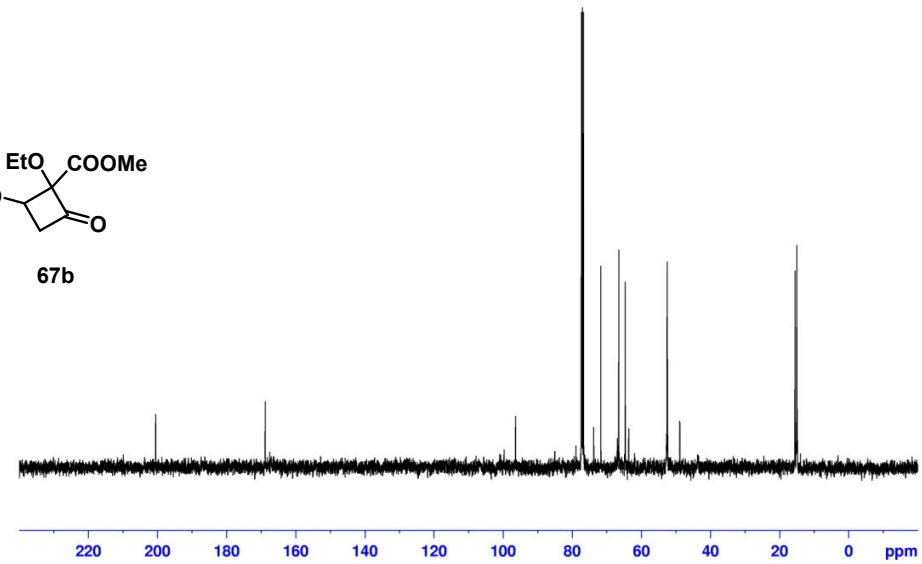
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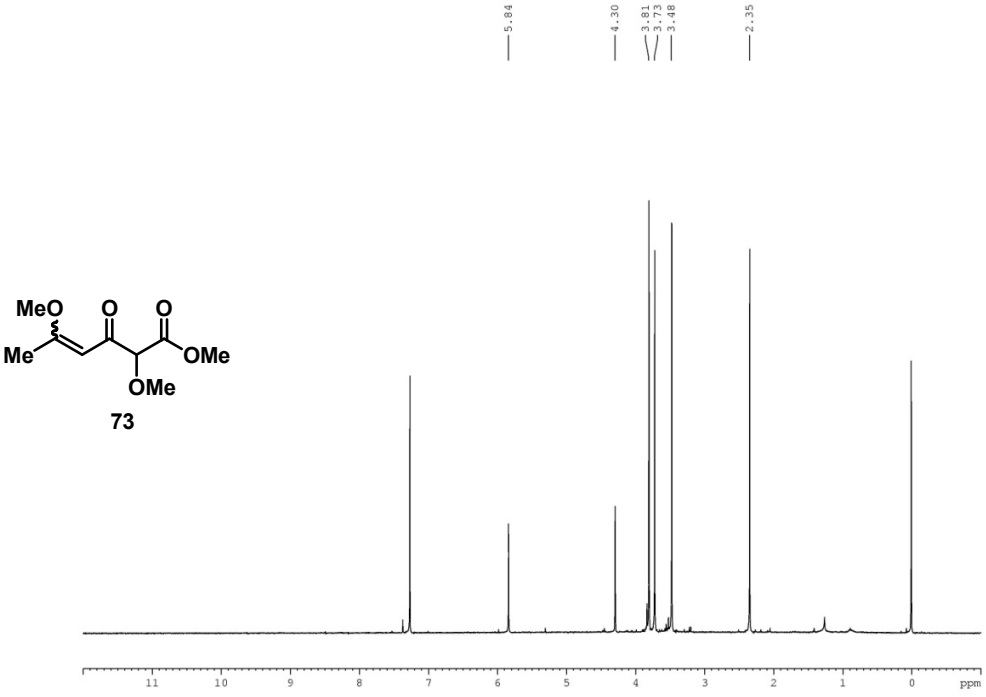
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2
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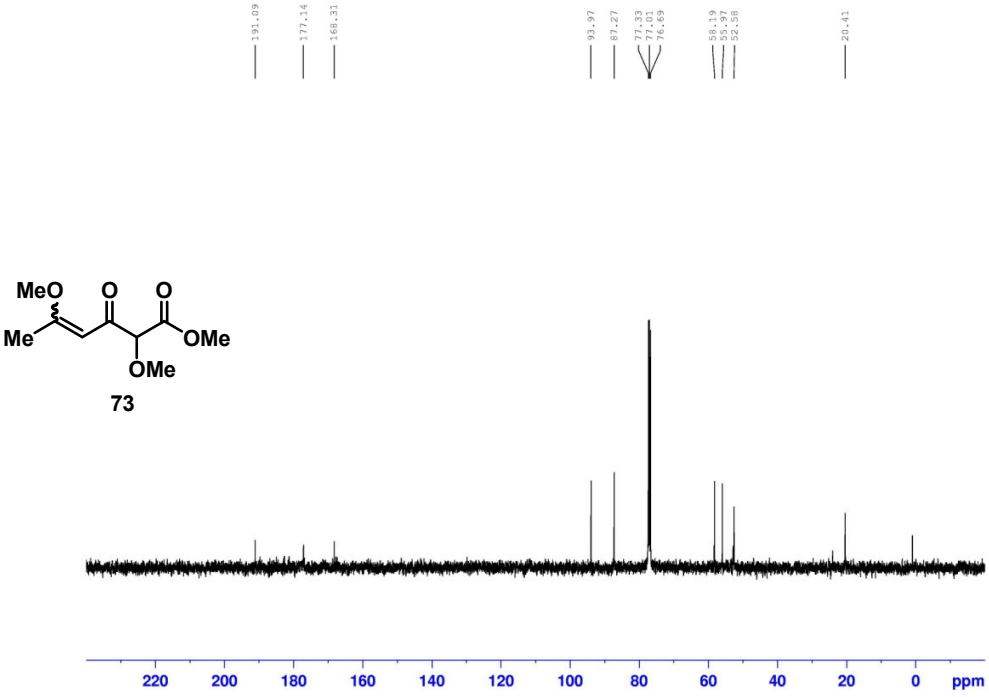
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OMe
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40
20
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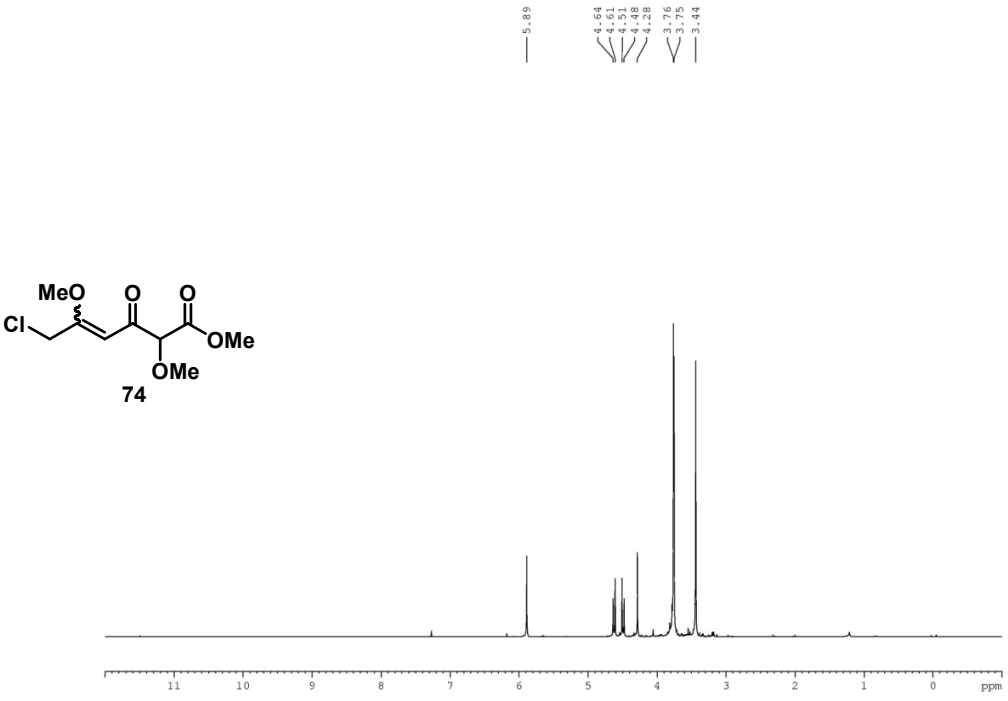
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OMe
OMe
74
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10
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8
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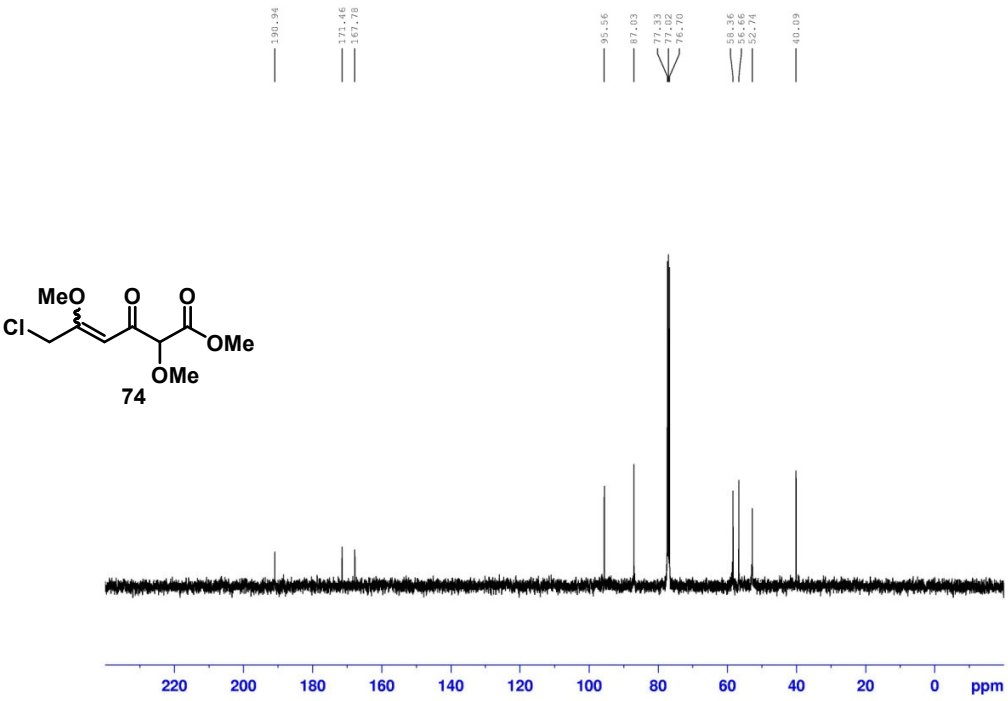
6
5
4
3
2
1
0
ppm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OMe
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20
0
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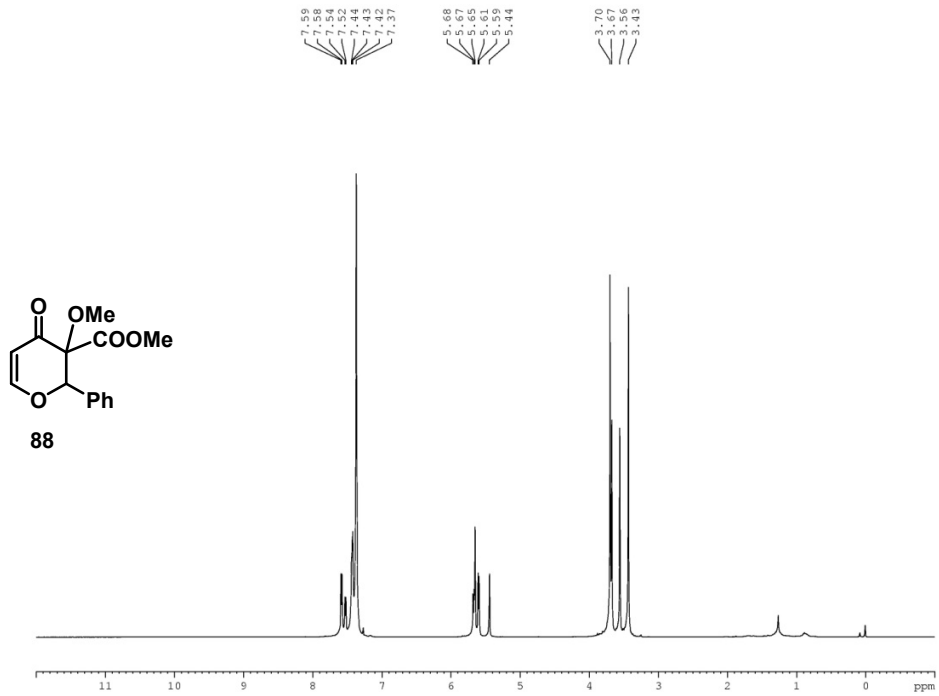
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3.67
3.56
3.43
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OMe
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O
Ph
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6
5
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2
1
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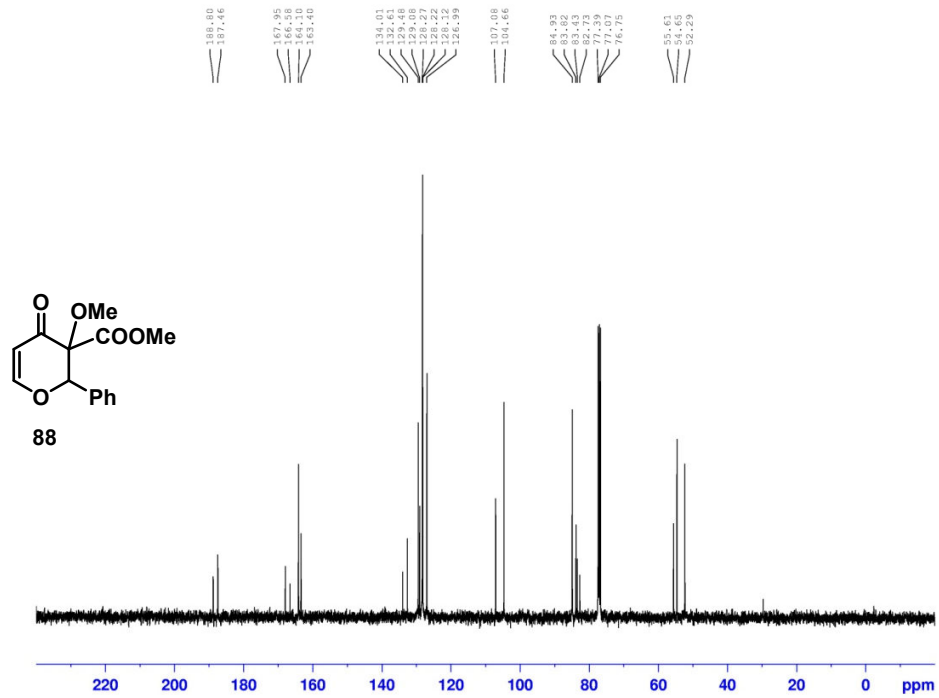
ppm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126.99
107.08
104.66
84.93
83.02
83.43
82.73
77.39
77.07
76.75
55.61
54.65
52.29
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OMe
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O
Ph
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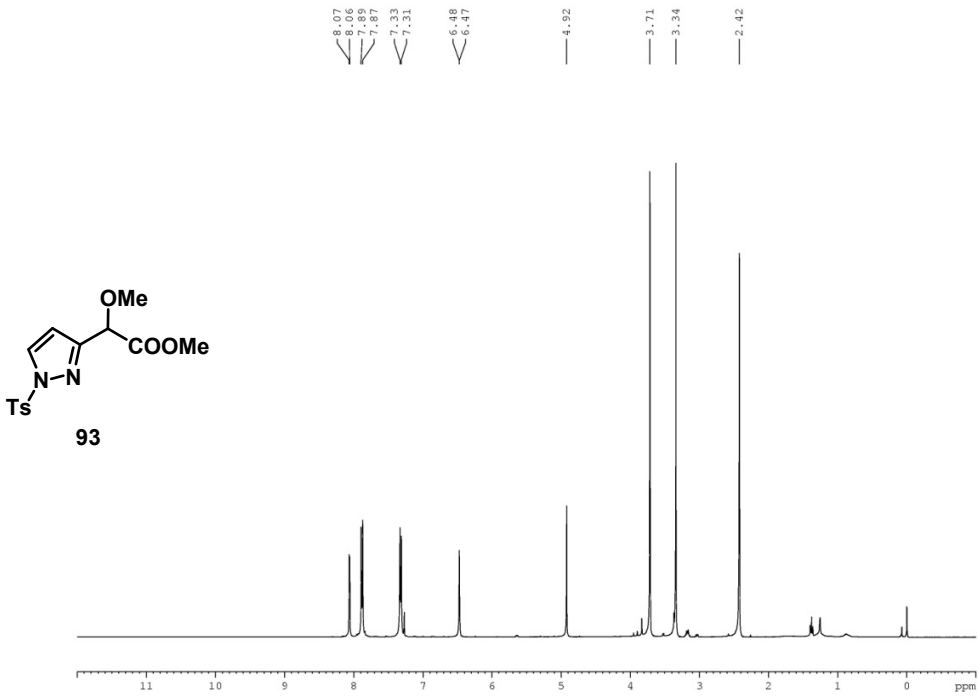
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COOMe
N–N
Ts
93
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10
9
8
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6
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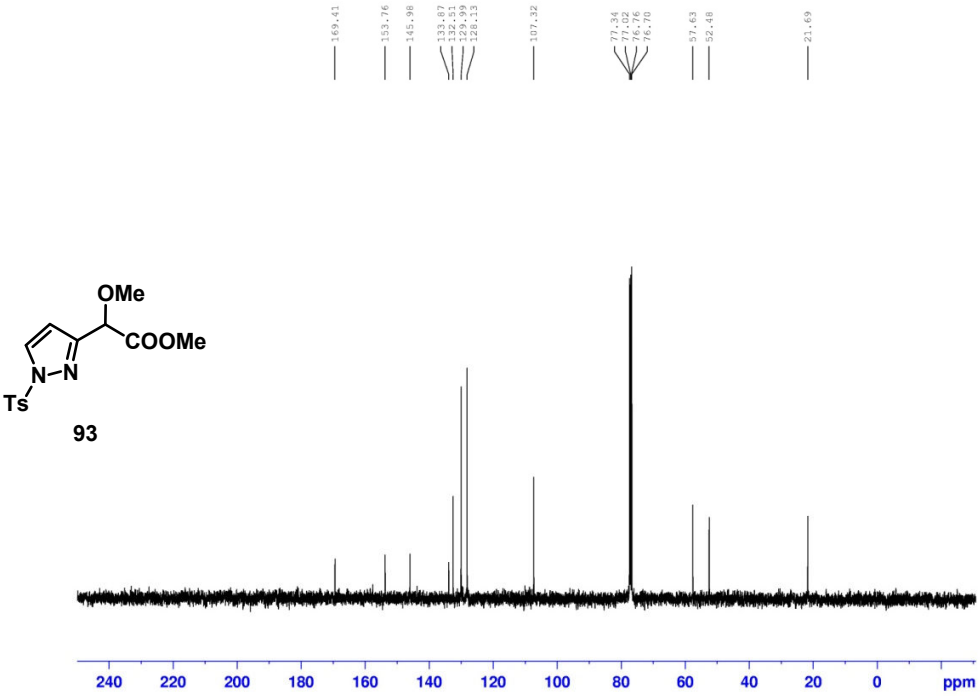
3
2
1
0
ppm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21.69
OMe
COOMe
N–N
Ts
93
240
220
200
180
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140
120
100
80
60
40
20
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ppm

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