Investigation Of A Ring Fragmentation Reaction For The Synthesis Of Tethered Aldehyde Ynones And Medium Sized Cyclic Ynones And Ynolides

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INVESTIGATION OF A RING FRAGMENTATION REACTION FOR THE SYNTHESIS OF TETHERED ALDEHYDE YNONES AND MEDIUM Sized CYCLIC YNONES AND YNOLIDES

A Dissertation Presented

by

Ali Bayir

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The Faculty of the Graduate College

of

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ABSTRACT

The fragmentation of $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazoesters to provide tethered aldehyde ynoates was discovered and developed in Prof. Brewer’s laboratory. This reaction is a Lewis acid mediated heterolytic cleavage of the $\text{C}\beta$-$\text{C}\gamma$ bond of a $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazocarbonyl functional group array contained in a ring compound.

This dissertation describes a further study of this ring fragmentation reaction and application of this fragmentation to the preparation of synthetically useful organic molecules. The purpose of this dissertation work was three fold. The first objective was to extend this ring fragmentation reaction to the synthesis of tethered aldehyde ynoles by fragmenting various $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazo ketone compounds. The second objective was to develop a new way to make medium size rings by fragmenting fused bicyclic $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazo ketones. The final goal was to use this reaction to make medium size ynoles by fragmentation of fused bicyclic $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazo esters to provide core structures for medium-size lactones which are synthetically challenging to make using other available methods.
CITATIONS

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CHAPTER 1 : A GENERAL BACKGROUND ON ALPHA-DIAZOCARBONYL COMPOUNDS, FRAGMENTATION REACTIONS AND MEDIUM SIZE RING SYSTEMS

Many organic chemists are primarily concerned with making bioactive molecules which are present in nature. In order to make these complex molecules in higher yields and lower cost, new transformations that facilitate the making and breaking of bonds are necessary. This dissertation is an account of just such a new method that results in the fragmentation of ring systems. Specifically, the fragmentation of γ-silyloxy-β-hydroxy-α-diazocarbonyl compounds is a Lewis acid mediated process that results in the heterolytic cleavage of the Cβ-Cγ bond that was discovered and developed in Prof. Brewer’s laboratory. This dissertation describes a further study of this ring fragmentation reaction and the application of this fragmentation to the preparation of synthetically useful organic molecules.

The purpose of this dissertation work was three fold: The first was to apply this ring fragmentation reaction to various γ-silyloxy-β-hydroxy-α-diazo ketone compounds to make tethered aldehyde yrones. The second goal was to develop a new way to make medium size rings by fragmentation of fused bicyclic γ-silyloxy-β-hydroxy-α-diazo ketones. The final goal was to use this reaction to make medium size ynolides by fragmentation of fused bicyclic γ-silyloxy-β-hydroxy-α-diazo esters to provide core structures for medium-size lactones which are synthetically challenging to make using other available methods.
1.1 α-diazo carbonyl compounds

The majority of my work in the Brewer group has involved using α-diazo carbonyl compounds for ring fragmentation reactions. In this section I will provide a brief background on the properties, structures and reactivity of α-diazo carbonyl compounds to put my research in context.

Diazo chemistry dates back to 1858 when Peter Griess discovered the first aromatic diazo-compounds while treating aromatic amino acids with nitrous acid.¹ In 1883, Theodor Curtius made the first aliphatic diazo compound via diazotization of glycine ethyl ester (Figure 1).

![Figure 1.1 The structure of ethyl diazoacetate](image)

In 1894 von Pechmann made the notable discovery that when $N\text{-methy-N-nitroso carbamate was reacted with methanol and potassium carbonate diazomethane (CH}_2\text{N}_2$ was formed.² Later alkanediazonium (R-N$_2^+$), alkenediazonium (R-CH=CH-N$_2^+$) and alkynediazonium (R-C≡C-N$_2^+$) species were discovered and characterized.³⁴ Although these types of aliphatic diazo compounds are structurally interesting, they are not highly stable and are less synthetically useful.

In 1902, Wolff discovered that diazo ketones rearrange into carboxylic acids when reacted with water and silver oxide. Aliphatic diazo compounds started to gain
importance synthetically in 1935, when Arndt and Eistert showed that diazoketones could be made from acid chlorides using diazomethane, and subsequent Wolff rearrangement in the presence of various nucleophiles provided homologs of the initial carboxylic acid (Scheme 1.1).²

![Scheme 1.1. Arnd-Eister synthesis of α-diazo carbonyl compounds and subsequent Wolff rearrangement.](image)

These findings were followed by the discovery of metal complexes of diazo carbonyl compounds in the 1960s. Diazo compounds attracted even more interest from synthetic chemists after Huisgen showed that diazo carbonyl compounds react very well as 1,3-dipoles in 1,3-dipolar cycloaddition reactions. Finally, the discovery that aliphatic diazo compounds readily form a variety of metal carbenes added yet more interest into the chemistry of aliphatic diazo compounds. These important reactivities of diazo carbonyl compounds have made them a very well-studied functional group as shown in the next section.

### 1.1.1 Properties of α-diazo carbonyl compounds

When aliphatic diazo compounds were discovered, two structures were proposed: cyclic structure **1.1** and linear structure **1.2** (Figure 1.2).
Figure 1.2 Initially proposed structures of α-diazo carbonyl compounds

An electron diffraction experiment done by Boersch in 1935, and a subsequent labelling experiment done by Clusius in 1957, proved that the correct structure for aliphatic diazo compounds is the linear structure (1.2). The bonding structure of α-diazo carbonyls is described by the resonance structures shown in Figure 1.3, and the diazo carbonyl functional group was found to be strictly planar.

Figure 1.3 Resonance contributing structures of α-diazo carbonyls

Most aliphatic diazo compounds are yellow to red in color and all diazo compounds show a strong absorption in the IR region from 1950 to 2300 cm\(^{-1}\) which is assigned to the N-N stretching mode. In \(^{13}\)C NMR spectra, the signal for the diazo carbon of diazomethane appears at \(\delta = 23.1\) ppm relative to TMS, whereas for α-diazo carbonyl compounds the diazo carbon signal is shifted downfield. In \(^1\)H-NMR spectra of α-diazo carbonyl compounds, the chemical shift of the proton attached to the diazo
carbon atom depends on the solvent, but in my experience it is typically in the 4.70 ppm region in CDCl₃.

Diazo compounds in general are known to be thermo-labile but α-diazo carbonyl compounds are more thermally stable than diazo alkanes. The thermal stability of diazo compounds varies very much with substituents attached to the diazo group. Substituents with electron acceptor ability make α-diazo carbonyl compounds less thermally stable via stabilizing the resonance contributing structure (1.4) (Figure 1.3) through delocalization of the charge and hence favoring the nitrogen elimination.

α-Diazo carbonyl compounds decompose thermally to give a carbene intermediate that can undergo the Wolff rearrangement (Scheme 1.2), but carbene insertion products are also formed in thermal decomposition reactions. Wolff rearrangement products can be favored by the use of acids and catalysts such as metals and metal oxides (e.g. Ag₂O).

![Scheme 1.2. Thermal decomposition of α-diazo carbonyl compounds](image)

**1.1.2 Synthesis of α-diazo carbonyl compounds**

There are many methods available to make α-diazo carbonyl compounds; herein I will summarize some of the most widely used methods.
Acylation of diazo alkanes is one of the most important methods to make α-diazo carbonyl compounds, and as will be discussed in chapter 2 of this thesis I have used this method to make α-diazoketone compounds. The Arndt-Eistert synthesis of diazo ketones through the reaction of acid chlorides with diazomethane is the most well-known example of this reactivity (Scheme 1.3). Acylation reactions of diazo compounds can also be achieved using anhydrides, phosgene and benzoyl bromide.

![Scheme 1.3. Acylation reaction of diazomethane](image)

Another common way to prepare diazo carbonyls is through diazo transfer reactions. All reactions where the intact N₂ group is transferred from a donor to an acceptor molecule by either exchange or addition are called diazo transfer reactions.

![Scheme 1.4. Diazotransfer reaction](image)

In a diazo transfer reaction, the α-methylene position of a carbonyl compound has to be deprotonated under mild conditions. This typically requires that the methylene be flanked by two activating groups one of which has to be removed after the diazo transfer process. For example β-keto ester (1.6) reacts with tosyl azide to provide diazo ester acetoacetate (1.7) which is then reacted with a base to cleave off the acetoacetate group to yield diazoester 1.8 (Scheme 1.4).
A third common and useful method is *diazotization of amines*, which was the original method developed by Curtius to make ethyl diazoacetate. This is a very useful method to introduce the diazo group into compounds that already contain an amine, especially amino acids (Scheme 1.5).\(^8\)

![Scheme 1.5. Diazotization of α-amino carbonyl compounds](image)

Finally, *the Bamford-Stevens reaction* is one of the most efficient methods to make α-diazo carbonyl compounds. As will be described in Chapter 4, I used various modifications of this reaction to make key diazoester compounds.

![Scheme 1.6. Bamford-Stevens synthesis of α-diazo carbonyl compounds](image)

In this method, an α-tosylhydrazone carbonyl compound is treated with a base or heat, which results in the loss of the tosyl group and formation of the diazo functional group (Scheme 1.6). α-Tosylhydrazone carbonyl compounds can be made from diketones and α-ketoesters. In the House method, α-tosylhydrazone esters were made by the reaction of an alcohol with p-toluenesulfonylhydrazone glyoxylic acid chloride and the tosyl group was then cleaved with triethylamine to deliver the diazoester compounds.\(^9\)
Scheme 1.7 House method of making α-diazo esters

In addition to these methods of making α-diazo carbonyl compounds, there are various less frequently used methods such as: the Forster reaction in which an α-oxime ketone reacts with chloroamine to provide diazoketones, and dehydrogenation of hydrazones.5

1.1.3 Reactivity of α-diazo carbonyl compounds

α-Diazo carbonyl compounds can go through a multitude of reactions through the loss of nitrogen by thermal, photochemical and chemical pathways to give several different types of reactive intermediates. For example, they can form free carbenes (1.9) upon treatment with light and heat, metal carbenoids (1.10) on treatment with transition metals, carbonyl ylides (1.11) via reaction of transiently formed carbenes with heteroatoms (e.g. oxygen, sulfur), and diazonium ions (1.12) upon treatment with Brönsted acids and electrophiles.

Figure 1.4 Reactive intermediates of α-diazo carbonyls
These reactive intermediates lead to a wide variety of reactions, which can be organized into the following categories: 1,3-dipolar cycloaddition reactions of the diazo group, [3+2] cycloaddition reactions of carbonyl ylides from carbene intermediates, cyclopropanations, aromatic cycloadditions, insertion into X-H (X = C, O, S, N) bonds, Wolff rearrangements (Scheme 1.1), ylide formation and its subsequent reactions, α,α-substitution reactions and oxidation of the α-diazo group. Reactions of α-diazocarbonyl compounds with Brönsted acids, Lewis acids and aldehyde and ketones will be explained in detail since they relate to the chemistry to be discussed in this dissertation.

1.1.3.1 Reactions of α-diazo carbonyl compounds with Brönsted acids

Diazo compounds are known to be sensitive to Brönsted acids, however α-diazo carbonyl compounds are less sensitive towards acids than diazo alkanes due to stabilization attributed to resonance contributing enolate 1.15 (Scheme 1.8).

![Scheme 1.8. Acid reactivity of α-diazocarbonyls](image-url)
Protonation at the oxygen of enol diazonium 1.17 was observed with super acids at -60 to -80 °C temperatures. However, in aqueous acids protonation occurs primarily at α-diazo carbon to give diazonium ion 1.16 (Scheme 1.8). Protonation of α-diazo carbonyl compounds is followed by decomposition of diazonium ion 1.16 (Scheme 1.9).

Scheme 1.9. Acid decomposition of α-diazocarbonyls

The decomposition step can happen either via S\textsubscript{N}2 displacement of molecular nitrogen by a nucleophile, or by an S\textsubscript{N}1 process in which molecular nitrogen departs first to form a carbenium ion (1.18), which then reacts with a nucleophile (Scheme 1.9). The operative decomposition pathway depends on the solvent and the substituents at the α-carbon atom.\textsuperscript{5} Acid decomposition of α-diazo carbonyl compounds gives α,α-substitution type products (Scheme 1.10).\textsuperscript{11,12} However, these types of reactions are prone to rearrangements due to possible involvement of carbenium ion formation.

Scheme 1.10. α,α-substitution reaction of α-diazo carbonyls via acid decomposition
Acid decomposition of $\alpha$-diazo carbonyl compounds and subsequent reaction with intramolecular nucleophiles provides rather useful carbocycles and heterocycles. The intramolecular nucleophiles range from alkene, alkyne and aromatic functional groups to oxygen, nitrogen and sulfur heteroatoms. Mander used this method in the synthesis of Gibberillic acid (I, Scheme 1.11), while Fadel made a butyrolactone intermediate (II, Scheme 1.11) to synthesize sesquiterpene core structures using acid catalyzed cyclization of diazoketones.

![Scheme 1.11](image)

1.1.3.2 Reactions of $\alpha$-diazo carbonyl compounds with Lewis acids

Similar to Brönsted acids, Lewis acids also promote loss of molecular nitrogen in $\alpha$-diazo carbonyl compounds. Hence they can also enable $\alpha,\alpha$-substitution reactions (Scheme 1.12) in $\alpha$-diazo carbonyl compounds.

![Scheme 1.12](image)
Intramolecular cyclization of α-diazo carbonyl compounds by Lewis acids is a much more common method to make carbocycles than Brönsted acid mediated processes (Scheme 1.13).\textsuperscript{16} For the mechanism of Lewis acid mediated intramolecular cyclization reactions two reaction pathways were proposed. Lewis acid could complex to the α-carbon of 1.19 (Scheme 1.13) followed by nucleophilic attack through an S\textsubscript{N}2 type reaction with the loss of nitrogen. Alternatively, the carbonyl oxygen could complex the Lewis acid to give enol diazonium species 1.20 (Scheme 1.12) which, could then go through an S\textsubscript{N}1 type reaction via loss of molecular nitrogen forming a vinyl cation intermediate 1.21.\textsuperscript{17}

Scheme 1.13

Upon treatment with trialkylborane Lewis acids, α-diazo carbonyl compounds form stable vinyloxyboranes which after hydrolysis provide α-alkylated carbonyl compounds. In this process, complexation of trialkylborane at the α-carbon is followed by 1,2-alkyl shift from boron to the α-carbon with loss of nitrogen. Next, boron migrates to oxygen to form a stable vinyloxyborane intermediate (Scheme 1.14).\textsuperscript{18}
Reactions of Lewis acids with α-diazocarbonyl compounds in the presence of nitriles follow a different reaction course. In the presence of an excess of Lewis acid, such as aluminum chloride, the carbonyl oxygen complexes with the Lewis acid to form an enol diazonium species. Displacement of molecular nitrogen by nucleophilic attack of the nitrile at the α-carbon provides a vinyl nitrilium intermediate that results in the formation of an oxazole (Scheme 1.15).¹⁹

A different reactivity mode is apparent in the Lewis acid mediated homologation of ketones and aldehydes by α-diazo carbonyl compounds. In these types of reactions, Lewis acids activate the carbonyl group of an aldehyde or ketone, but not the carbonyl of the diazoester. In this case nucleophilic attack of the α-diazo carbonyl compound onto the activated ketone, followed by 1,2-alkyl migration with nitrogen loss yields homologated carbonyl compounds (Scheme 1.16).²⁰
Homologated β-dicarbonyl compounds were also observed to form via reaction of α-diazo carbonyl compounds with aldehydes in the presence of Lewis acids (Scheme 1.17).\textsuperscript{21,22} In this reaction a β-hydroxy-α-diazo carbonyl intermediate forms in situ and a subsequent 1,2-hydrogen shift with loss of molecular nitrogen provides the β-dicarbonyl compound.

In a similar way, α,β-unsaturated ketones undergo cyclopropanation by α-diazocarbonyl compounds in the presence of Lewis acids. Here, Lewis acid activation of the carbonyl group of an α, β-unsaturated ketone is followed by 1,4-addition of the α-diazo carbonyl group. Nucleophilic attack of the intermediate enolate on the α-carbon of the diazonium species provides the cyclopropane ring (Scheme 1.18).\textsuperscript{23}
To sum up, Lewis acids can react with α-diazo carbonyl compounds via complexation with the α-carbon or with the carbonyl oxygen atom to form enol diazonium species (Scheme 1.8). However, Lewis acids seem to preferentially complex with other carbonyl compounds (aldehydes and ketones) when they are present in the reaction mixture.

1.1.3.3 Aldol-type addition of metalated α-diazo carbonyl compounds with aldehydes and ketones

A very important reactivity of α-diazocarbonyl compounds is their base promoted aldol type addition to aldehydes and ketones to provide β-hydroxy-α-diazo carbonyl compounds (Scheme 1.9). These reactions are especially important to the work presented here.

In order to facilitate an Aldol type addition of a α-diazo carbonyl compound, the diazo carbon must first be deprotonated. This is most commonly achieved by treating the diazocarbonyl compound with $n$-butyllithium, sodium hydride,$^{24}$ potassium...
hydroxide in methanol,\textsuperscript{25} lithium diisopropyl amide (LDA) \textsuperscript{26} or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).\textsuperscript{27} Among these LDA is the most common base used for aldol addition of α-diazo carbonyl compounds. Zinc derivatives of α-diazo carbonyl compounds have been developed for addition reactions to base sensitive carbonyl compounds that require milder conditions.\textsuperscript{28}

The aldol addition adducts (i.e. β-hydroxy-α-diazo carbonyl compounds) have been shown to yield synthetically useful β-dicarbonyl products by reacting with a catalytic amount of rhodium(II) acetate (Scheme 1.20).\textsuperscript{29}

![Scheme 1.20](image)

Importantly, when Wenkert and McPhearson\textsuperscript{30} treated β-hydroxy-α-diazo carbonyl compounds with BF\textsubscript{3}.OEt\textsubscript{2}, they observed acetylene formation (Scheme 1.21).

![Scheme 1.21](image)

They proposed that elimination of the β-hydroxyl group is promoted by complexation with BF\textsubscript{3} which provides a vinyl diazonium intermediate (1.22) which in turn forms the acetylene product via elimination of nitrogen (Scheme 1.21).
Padwa and Pellicciari\textsuperscript{31,32} studied this interesting reactivity of β-hydroxy-α-diazo carbonyl compounds with BF\textsubscript{3}.OEt\textsubscript{2} in various solvents and they observed an array of products resulting from a very reactive vinyl cation intermediate 1.25, which could originate from vinyl diazonium precursor 1.24 (Scheme 1.22). They proposed that the reactive vinyl cation 1.25 undergoes a series of ring expansion and ring contraction rearrangements to attain the thermodynamically most stable carbenium ion. The stable carbenium ion 1.27 reacts with the solvent or other functional groups present in the molecule to provide the majority of the products. Some of the minor products could result from the reaction of vinyl cation 1.25 and ring expansion intermediate 1.26.

Scheme 1.22

Pellicciari also observed that upon reaction with BF\textsubscript{3}.OEt\textsubscript{2} biaryl substituted β-hydroxy-α-diazoesters form N-acyl β-enamino ester derivatives in which vinyl cation...
goes through a 1,2-aryl shift to reach to a more stable carbenium ion followed by reaction with acetonitrile to yield the N-acyl β-enamino ester (I, Scheme 1.23).  

![Scheme 1.23](attachment:image)

In yet another study, Pellicciari observed a similar reactivity of indole derivatives of β-hydroxy-α-diazoesters with Lewis acids in which the vinyl cation undergoes a ring expansion followed by entrapment with solvents to provide quinolinone derivatives (II, Scheme 1.23).

The key vinyl cation intermediate shown in the above reaction pathways in Scheme 1.21 and 1.22 has been observed before in electrophilic addition to alkynes and allenes, in participation of alkynes and allenes in solvolysis reactions and in the ionization of vinylic compounds. Less commonly they were observed in deamination of vinyl triazenes and in photolysis, oxidative decarboxylation and electro-oxidation reactions. The reactivity of vinyl cations can be explained through their sp-hybridized carbon with an empty π-orbital. They are known to react with lone pair electrons, π-bonds and σ-bond electrons very rapidly. As we have seen from the examples in the
above reactions, vinyl cations in general rearrange into allylic cations (I, Scheme 1.24) and when possible they isomerize into more stable vinyl cations (II, Scheme 1.24).

\[
\begin{align*}
\text{(I)} & \quad \text{R} & \quad \text{R}^+ \\
\text{(II)} & \quad \text{R}^+ & \quad \text{R}^+ \\
\end{align*}
\]

\text{Scheme 1.24}

One noteworthy example of vinyl cation formation was observed by Grob\textsuperscript{36} in the heterolytic fragmentation of α,β-unsaturated ketoxime compounds (Scheme 1.25). The vinyl cation formed from the fragmentation reaction is trapped by the solvent (ethanol) to form E and Z isomers of the enol ether.

\text{Scheme 1.25}

1.1.4 Conclusion

In summary, in this section I have described the discovery, physical properties, preparation, and relevant synthetic reactivities and applications of α-diazo carbonyl compounds. I have tried to impress upon you the importance of this class of organic compounds.
In the next section I will describe an important class of organic reactions, heterolytic carbon-carbon bond fragmentation reactions, which are the basis of this dissertation.

1.2 Heterolytic Carbon-Carbon Bond Fragmentation Reactions

Organic synthesis is mainly concerned with the formation of new bonds such as carbon-carbon, carbon-heteroatom and heteroatom-heteroatom to construct a target molecule. Fragmentation reactions, which involve carbon-carbon bond cleavages, are less often used in organic synthesis. However, heterolytic carbon-carbon fragmentation reactions are powerful in that they can provide latent functional groups and difficult to prepare synthetic intermediates such as alkene, alkyne, nitrile, carbonyls and various functionalized carbocycles and heterocycles. They may be viewed as an indirect method for constructive synthetic chemistry.

1.2.1 Description of heterolytic carbon-carbon bond fragmentation reaction and its development

Grob defines heterolytic bond fragmentation reactions as a breakage of a molecule into three fragments which are an electrophuge (+a=b), an unsaturated fragment (c=d) and a nucleofuge (LG:\(\text{^-}\)) (Figure 1.5).\(^37\)

\[ \overset{\rightarrow}{a} \overset{\rightarrow}{b} \overset{\rightarrow}{c} \overset{\rightarrow}{d} \overset{\leftarrow}{\text{LG}} \rightarrow \Theta a=b + c=d + LG^{\ominus} \]

Figure 1.5 Heterolytic bond fragmentations
Fragmentation substrates are in general 1, 3-diheterofunctionalized compounds consisting of a nucleophilic atom with a negative charge or a lone pair of electrons (,:) and a leaving group (LG). A fragmentation reaction is only possible if the molecule is polarized through the presence of an electrofuge at one end acting as a source of electron flow and a nucleofuge at the other end to which the electrons flow. Overall, two σ-bonds are broken to form two new π-bonds.

The first reported fragmentation reaction was the Beckmann fragmentation which was considered to be a side product of Beckmann rearrangement. It’s a cleavage of oximes to nitriles which was developed by Wallach as a method to make nitriles in 1911 (Scheme 1.26). \(^{38}\) It was not recognized as a fragmentation reaction until Grob’s work in the 1960s.

![Scheme 1.26](image)

The first heterolytic carbon-carbon bond fragmentation reaction was reported and mechanistically explained by Eschenmoser in 1952. \(^{39}\) He showed that an alkene could be made under basic conditions via cleavage of a carbon-carbon bond (Scheme 1.27).
Later, Slawjanow\textsuperscript{40} and Kalishev\textsuperscript{41} reported the acid catalyzed cationic fragmentations of 1,3-diols (Scheme 1.28), which was later studied by English, who showed the importance of cationic intermediates in this process.

\begin{equation}
\text{HO} \quad \text{OH} \quad - \text{H}_2\text{O} \quad \text{H}^+ \\
\begin{array}{c}
\text{R}_1 \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_2 \\
\end{array}
\end{equation}

\text{Scheme 1.28}

In 1953, Henbest observed the importance of the stereochemical arrangement of the reaction centers while investigating steroid substrates.

\begin{equation}
\begin{array}{c}
\text{Me} \quad \text{H} \quad \text{Cl} \\
\end{array}
\end{equation}

\text{Scheme 1.29}

Henbest realized that the fragmentation of a C-C bond is possible only if the bonds to be broken are in an antiperiplanar arrangement (Scheme 1.29).\textsuperscript{42}

A few years later Stork reported the first ring expansion by a fragmentation reaction (Scheme 1.30).\textsuperscript{43}
In the 1960s, Grob and coworkers reported the fragmentation of acyclic, monocyclic and bicyclic γ-substituted amines. Like Henbest, Grob observed that these reactions followed a concerted mechanism and required an antiperiplanar arrangement of bonds to be broken (Scheme 1.31).

Grob also undertook mechanistic studies of the Beckmann fragmentation and formulated it as a fragmentation reaction. Later, the Beckmann fragmentation was used by Stork in the total synthesis of byssochlamic acid and by Colvin in the total synthesis of trichodermine. Grob generalized fragmentation reactions and extensively studied the mechanism of fragmentation reactions. It was through his efforts that organic chemists distinguished fragmentation reaction from other reactions such as 1, 2-elimination reactions. Not surprisingly these types of reactions are known as Grob type reactions.
The efficacy of fragmentation reactions was later shown by Corey in his now classic total synthesis of caryophyllene (Scheme 1.32).47

**Scheme 1.32**

### 1.2.2 Mechanism of heterolytic C-C bond fragmentation reactions

As I have explained before, most of the early mechanistic work on fragmentation reactions was carried out by Grob. Based on his work and subsequent work in this area, we now know that heterolytic C-C bond fragmentation substrates can potentially react in several alternative ways. In addition to fragmentation, they can go through substitution, elimination and ring closure reactions as well (Scheme 1.33). The course of the reaction depends on the structure, configuration and conformation of the substrate.37

**Scheme 1.33**
If the substrates do undergo a fragmentation reaction, it can occur through either a one-step (concerted) or two-step mechanism (Scheme 1.34).

Scheme 1.34

In the two-step mechanism, there are two possibilities. The more common two-step pathway occurs through carbonium ion (1.28) formation. The carbonium ion intermediate can react via fragmentation, substitution, elimination or ring closure depending on the substrate and reaction conditions. The other, less likely, two-step pathway involves elimination of the electrofugal group followed by formation of an anion 1.29. The anion 1.29 can eliminate the leaving group and form a double bond or it can be stabilized via protonation.

The concerted one-step fragmentation has strict structural and stereoelectronic requirements that require coplanarity of breaking bonds. Therefore lone-pair electrons on the electrofuge and all sigma bonds must be in anti-periplanar arrangement for maximum overlap of orbitals in the transition state leading to the newly formed π-bonds (Scheme 1.34).
The all anti-periplanar arrangement of five centers in a fragmentation substrate is satisfied in staggered as well as in skew and eclipsed conformations (Scheme 1.35). All other conformations obtained via rotation around Cα-Cβ bond will not go through the concerted mechanism, instead they will most likely go through the carbonium intermediate 1.28 which may fragment or undergo other reactions shown in scheme 1.36.

\[ \text{one-step (concerted)} \]

\[ \text{staggered} \]

\[ \text{skew} \]

\[ \text{eclipsed} \]

Scheme 1.35

Strict stereoelectronic requirements of the concerted fragmentation reaction can be exemplified in the Wharton’s studies of 1,10-decalindol monotosylates shown in scheme 1.36. Both all-anti-periplanar arranged substrates on the left provide fragmented product, whereas the substrate on the right, which violates the antiperiplanar arrangement of bonds to be broken, gives only elimination products.\textsuperscript{48}
1.2.3. Types of fragmentation reactions and synthetic applications

Heterolytic C-C bond fragmentation reactions can be categorized as alkyne, alkene and allene forming reactions. Alkene generating C-C bond fragmentation reactions are more common, and most of the early examples of fragmentations belong to this class of reactions. A notable example of an alkene forming fragmentation reaction was reported by Wharton and is shown in Scheme 1.36. Allene forming fragmentation reactions are relatively new. For example, Williams reported that allenes can be made by concerted addition and fragmentation of vinyl triflates (Scheme 1.37).49

Alkyne generating fragmentation reactions are the focus of this dissertation; therefore they will be explained in detail. Alkyne generating fragmentation precursors in general contain an olefinic group (c-d, in figure 1.5) to which the nucleofuge and electrofuge is attached. As described by Dudley and Williams50, this structural feature
provides an all anti-periplanar arrangement for these fragmentation precursors. This in turn lowers the entropic barrier to fragmentation due to near perfect orbital overlap of atoms involved in the fragmentation. However, the bonds between the sp\(^2\) hybridized olefinic group and the nucleofuge and electrofuge are stronger than bonds in sp\(^3\) hybridized alkene generating fragmentation precursors. Hence, the enthalpic barrier is increased in the fragmentation of alkyne generating species. However this enthalpic barrier is partially lowered by the formation of stronger alkyne bonds. Also, use of powerful nucleofuges such as molecular nitrogen and triflate and powerful electrofuges further lower enthalpic barrier and favors fragmentation reaction in the alkyne generating reactions.

The first known alkyne forming fragmentation reaction was reported by Bodendorf. He observed that β-chloroacroleins provided acetylenes upon reaction with sodium hydroxide (Scheme 1.38).\(^{51}\) This reaction was proposed to occur by a decarboxylative fragmentation mechanism to give the observed alkyne.

![Scheme 1.38](image)

Grob also observed similar reactivity in the reaction of the Z isomer of β-bromocinnamic acid with a base and reported that the β-bromocinnamic acid precursor underwent a decarboxylative fragmentation to give the phenylacetylene (Scheme 1.39).\(^{52}\)
The most well-known alkyne forming fragmentation reaction is the Eschenmoser-Tanabe reaction (I, Scheme 1.40).\textsuperscript{53,54} This reaction provides acyclic alkynyl ketones via a concerted fragmentation of cyclic epoxy sulfonyl hydrazones. The necessary epoxy sulfonyl hydrazones can easily be made from enones via epoxidation and hydrazone formation reactions. Tanabe later used this method in the synthesis of secosteroids (II, Scheme 1.40).

Coke et al. developed the method in which an alkyllithium reagent is added to β-halo-α,β-unsaturated ketones which results in ring fragmentation leading to alkynyl ketones.\textsuperscript{55} They have used this method in the synthesis of \textit{exo}-brevicomin 1.30 (Scheme 1.41).
Much more recently this nucleophile addition approach such as alkyls was further developed by Dudley to make alkynes (I, Scheme 1.42). He showed that addition of methyl Grignard to vinylogous acyl triflates provided alkynes via heterolytic C-C bond fragmentation.\(^{56}\)

Dudley later used this method to make the eastern hemisphere of the macrolide palmerolide A (II, Scheme 1.42).

### 1.2.4 Conclusions

Despite the strict stereoelectronic requirements heterolytic C-C bond fragmentation reactions are useful because they unmask latent functional groups and provide easy access to interesting molecular building blocks. They can be thought of as very useful indirect methods for organic synthesis as was exemplified in Corey’s
classical total synthesis of caryophyllene. The examples shown above indicate that heterolytic C-C bond fragmentations are powerful methods of ring opening and ring expansion providing very useful synthetic intermediates. Ring expansion reactions that lead to medium sized rings via fragmentation will be shown in the following section.

1.3 Medium size rings and lactones

The formation of medium size rings via ring fragmentation is the major focus of this dissertation. Medium size rings are defined as rings composed of 8 to 11 atoms, small rings are 3 and 4 membered, common rings are 5,6 and 7 membered and finally large rings are classified as 12 membered and above. Medium size carbocycles and heterocyclic compounds such as lactones, ethers, amines and amides are important classes of compounds in organic chemistry, because they are found in many natural products.57-61

1.3.1. Significance of medium and large (macrocyclic) rings

Medium and large (macrocyclic) rings are biologically more potent than their equivalent acyclic structures, because they are conformationally more rigid and have well defined conformations. However, they are flexible enough to fit biologically relevant binding sites (e.g. receptors, enzymes) without an excessive cost in entropic energy.62,63 For example, James et al. compared macrocyclic peptides to their acyclic analogs and found that macrocyclic peptides have a 420-fold higher affinity for enzymes due to their conformational constraints which makes them preorganized for the binding site and lowers the entropic barrier to binding. However, the linear analogs do not have this ability.64 Imming et al. also showed that various medium size rings
could inhibit cyclooxygenase (COX) and lipoxygenase (LOX) enzymes effectively.\textsuperscript{65} These cyclic compounds were more potent because their conformational flexibility allowed them to adapt to the binding sites of these enzymes. They also concluded that these medium size rings are bioisosteric to alkylphenyl moieties which were known to inhibit such enzymes. So, medium rings and large rings are preorganized through conformational constraints but flexible enough to achieve optimal binding properties for a specific receptor, which is why they are potent agonists and antagonists. In medium rings, conformations are governed by transannular interactions and conformational strains which are not present in larger rings, this make them less advantageous than large rings.\textsuperscript{66} In comparison to medium and large rings, small and common rings have less flexibility, which means they have to be just right for a receptor, otherwise they won’t be able to fit into the binding site.

Among medium size rings, medium size lactones hold a significant position due to occurrence of bioactive lactone natural products. Medium sized lactone natural products have been reported to have biological activities including phytotoxicity, antifungal activity, antibacterial activity, antimalarial activity and enzyme inhibition. Some of the most noted examples to bioactive medium size lactones are as follows. Diplodialide A, B, C and D are metabolites found in phytopathogenic fungus \textit{Diplodia pinea}, and diplodialide A was reported to be a steroid hydroxylase inhibitor (Scheme 1.43).\textsuperscript{67}
Several members of the ten membered Decarestrictine lactone families were isolated from *Penicillium* strains (Scheme 1.44). They have been shown to inhibit the biosynthesis of cholesterol and they have been attractive medicinal targets to make cholesterol-lowering drugs.\(^{68}\)

Several ten membered lactones have shown antibacterial activity (Scheme 1.45). For example, Modiolide A and B were shown to be active against *Micrococcus luteus*. Additionally, modiolide A showed antibacterial activity against the human pathogens *Bacillus cereus*, *Listeria monocytogenes*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.\(^{69}\) Another medium size lactone, stagonolide F, was reported to be active against the following strains of bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, and *Pseudomonas aeruginosa*.\(^{70}\) A final example of antibacterial medium size lactones are phomolide A and B, which showed antibacterial activity against *Escherichia coli* CMCC44103, *Candida albicans* AS2538, and *Saccharomyces cerevisiae* ATCC9763.\(^{71}\)
Pyrenolide metabolites isolated from the fungus *Pyrenophora teres* were reported to have antifungal activities (Scheme 1.46), and Multiplolide A and B were shown to have antifungal activity against *Candida albicans*.  

Stagonolide F was also reported to show cytotoxic activity against THP-1 and U-937 human cancer lines (Scheme 1.45). Ten membered microcarpalide was reported to be a strong microfilament disrupting agent and to be weakly cytotoxic to mammalian cells, whereas the medium size sonnerlactones were reported to inhibit the growth of multi-drug resistant human oral floor carcinoma cells (Scheme 1.47).
Ten membered lactones herbarumin I and II were isolated from the fungus *Phoma herbarum* (Scheme 1.48). These lactones were found to have phytotoxic effects. For example herbarumin I showed significant phytotoxic effects in assay where germination and growth of *Amaranthus hypochondriacus* seedlings were monitored.\(^{75}\)

\[
\text{Herbarumin I} \quad \text{Herbarumin II}
\]

**Scheme 1.48**

Ten membered lactone structures have also been found in alkaloids such as aspidochibine (Scheme 1.49). Aspidochibine is an alkaloid isolated from the bark of the tree *Aspidosperma quebracho blanco* Schlecht. In South America, aspidochibine is used to treat bronchial asthma and dyspnoe.\(^{76}\)

**Scheme 1.49**

Eleven membered lactones are less common in natural products, but examples include the insect pheromones ferrulactone I and suspensolide (Scheme 1.50).\(^{77}\) Another eleven membered lactone structurally similar to suspensolide was also isolated from the fungus *Botrytis cynerea* (Scheme 1.50).\(^{78}\)
The eleven membered biphenylether-lactones, aspercyclides A-C, are fungal metabolites isolated from *Aspergillus sp* (Scheme 1.51). Aspercyclide A was reported to inhibit the IgE receptor and hence it prevents IgE binding and release of inflammatory compounds. This compound may be effective in the treatment of allergic diseases such as asthma, rhinitis and atopy. 

Eleven membered lactones were also found to be part of alkaloids (Scheme 1.52). (+)-Macropodumine A is an example of this type of compound. It was isolated from the stem of the plant *Daphniphyllum macropodum*, and this plant is used in Chinese traditional medicine for the treatments of inflammations.
In addition to medium size lactones there are also bioactive medium sized carbocycles present in nature. Caryophyllene or (−)-β-caryophyllene is a sesquiterpenoid present in essential oils such as clove oil, it contains a nine membered carbocyclic ring and shows anti-inflammatory activity. As we have mentioned in section 1.2.2, caryophyllene was synthesized by Corey via a fragmentation reaction (Scheme 1.32). 6-Hydroxypunctaporin E is another caryophyllene type sesquiterpene alcohol that was found in cultures of the fungicidal fungus Pestalotiopsis disseminate (Scheme 1.53). This medium size carbocyclic molecule showed activity against Gram-positive bacteria.

Ten membered carbocyclic sesquiterpenoids are common in plant material, especially in Compositae. In addition to being pheromones, they have various biological activities including antibacterial, cytotoxicity and antitumor activities. They are made up of isoprene units according to the Wallach-Ruzicka rule for sesquiterpenoids. Some of the most noted examples of this class of natural products are shown in scheme 1.54. For example, Periplanone B is a potent sex hormone isolated from females of the Periplanata Americana cockroaches. This cockroach pheromone

Scheme 1.52

Scheme 1.53
acts over short distances as opposed to long-range sex pheromones.\textsuperscript{85} Dihydrocostunolide was shown to have moderate cytotoxic activity,\textsuperscript{86} and furanodiene exhibited inhibitory effects on the growth of uterine cervical and sarcoma tumors in mice models.\textsuperscript{87}

\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {isobicyclogermacrenal};
\node[above] at (2,0) {acoragermacrone};
\node[above] at (4,0) {(+)-helminthogermacrene};
\node[above] at (0,-2) {Furanodiene};
\node[above] at (2,-2) {dihydrocostunolide};
\node[above] at (4,-2) {periplanone B};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.54}

Clavilactones A-D, containing a ten member carbocyclic ring, were isolated from a culture of the fungus \textit{Clitocybe clavipes} and they showed antifungal and antibacterial activities (Scheme 1.55). Clavilactones A, B and D are also potent kinase inhibitors against Ret/ptc1 and epidermal growth factor receptor (EGF-R) tyrosine kinases.\textsuperscript{88}
Eleven and twelve membered carbocycles have also been observed in natural products. For example, the eleven membered diterpenoids euphoperfolianes and the twelve membered jatrophanes were isolated from *Euphorbia semiperfoliata* which is a spurge endemic to mountain areas of Sardinia and Corsica (Scheme 1.56). Spurges have used in the treatment of cancerous conditions in traditional medicine.\(^{89}\)

**Scheme 1.55**

In summary, due to their structural advantages medium size rings are more efficient at binding to receptors and, as can be seen from the listed examples above, are prevalent in nature as metabolites in various types of plants and microorganism. Many of these compounds have potent biological activities.

**1.3.2 Synthesis of Medium Size Rings**

With the biological significance of medium size lactones and carbocycles in mind, it is no surprise that there is an increasing demand to find effective preparative approaches to these compounds. However, the synthesis of medium-sized ring compounds is difficult.\(^{90}\) This fact can be demonstrated by considering the rate of lactonization reactions of \(\omega\)-hydroxy acids of varying chain lengths (Figure 1.6). As
shown, the rate of cyclization drops to a minimum for medium-sized rings (8 to 11 membered), whereas the cyclization rate is very high for common rings and it almost becomes constant for large rings.

Figure 1.6 Reactivity profile for lactone formation (Reprinted from Illuminati, G.; Mandolini, L. Accounts. Chem. Res. 1981, 14, 95.)

The difficulty in making medium size rings via cyclization reactions can be explained by enthalpic and entropic reasons.\textsuperscript{9} The enthalpic barrier for cyclization to form medium size rings is caused by steric interactions. These steric interactions are: i) torsional effects in single bonds (Pitzer strain), ii) deformation of bond angles from their optimal values (Baeyer strain) and iii) transannular strain which is due to repulsive
interactions between atoms across the ring when they are in close proximity.\textsuperscript{57} Transannular strain is particularly important in medium rings. The activation energy of cyclization also reflects the strain of the transition state of the ring to be made; hence medium size rings with the most strain are formed in the lowest yields. On the other hand, the entropic cost of cyclization is related to the probability of the chain terminals coming close enough to each other for the cyclization reaction to occur. This probability decreases with increasing chain length in the acyclic molecule. Hence, as the chain length becomes longer, the entropic cost to bring the acyclic molecule to a ring shaped transition state increases. This in turn makes the $\Delta S^f$ term more negative due to a decrease in the freedom of internal rotation around single bonds.

For the reasons listed above, the formation of medium size rings is the most difficult case among all the ring sizes. The slow rate of cyclization of the bifunctional acyclic precursors often leads to the formation of dimers and polymers via competitive intermolecular reactions. These intermolecular polymerization reactions are kinetically second order, whereas intramolecular cyclization reactions are first order reactions. Therefore as first proposed by Ruggli, high substrate concentrations favor second order intermolecular reactions, whereas low concentrations disfavor these competitive reactions.\textsuperscript{92} Zeigler was the first to use this high dilution technique to make various sizes of rings.\textsuperscript{93} In this so called high dilution technique either the compound to be cyclized is added in one portion at the beginning of the reaction into a large volume of solvent or the compound is added slowly in a small volume of solvent to maintain its concentration at very low levels during the reaction. However, even under high dilution
conditions cyclization reactions to form medium-sized rings are the most difficult to effect, due to the reasons explained above and performing large scale reactions under high dilution conditions requires a huge quantity of solvent which is operationally impractical.

The cyclization of medium size rings can also be facilitated via introduction of heteroatoms, aromatic groups and cis-alkene groups on the acyclic precursor compounds (Scheme 1.57). These functional groups in the medium-size ring reduce the strain caused by torsional effects, bond angle deformations and transannular interactions and hence lower the enthalpic cost for the cyclization reaction.

![Scheme 1.57](image)

In addition to these methods, various other methods to make medium-sized rings have been developed. These alternative methods will be highlighted in the following section.

### 1.3.3 Methods to make medium size rings

The methods of constructing medium-sized rings can be broadly categorized as cyclization reactions, ring expansion strategies and fragmentation reactions.
1.3.3.1 Medium rings formed via cyclization reactions

We can classify cyclization strategies as lactonization reactions, metal mediated carbon-carbon bond forming reactions, and other carbon-carbon bond forming reactions. As explained before, these cyclization reactions are almost always carried out under high dilution conditions to prevent side reactions and to improve yields.

*Lactonization of seco-acids* is a very common method of forming medium-sized lactones as well as other ring size lactones. It is achieved by the direct cyclization of seco-acids (long chain hydroxy acids) via activation of either the alcohol or carboxylic acid terminal (Scheme 1.58).96,97

![Scheme 1.58](image-url)

In the acid activation approach, the acid functional group is typically converted to a more reactive functional group which then reacts intramolecularly with the alcohol to form the lactone (Scheme 1.58). There are numerous acid activation approaches, the most noteworthy ones used in the synthesis of medium-sized lactone rings are as follows.

The Yamaguchi lactonization98 is by far the most common method used in effecting lactonization reactions.68,99 It has been used in the synthesis of many ten
membered lactones. For example, this approach was used to form the ten-membered lactone intermediate in the synthesis of ascidiatrienolide A (Scheme 1.59).^100

![Scheme 1.59](image)

Activation by Mukiyama’s salt is another lactonization method used for the synthesis of medium sized lactones. For example, Mukiyama’s salt was used in the synthesis of the ten membered lactone prostaglandin F₂α 1,9-lactone (Scheme 1.60).^101

![Scheme 1.60](image)

In the Boeckman method, the acid functional group is replaced by dioxolenone which under mild conditions generates β-acetylketene derivatives. The alcohol present in the molecule then traps the ketene intermediate via nucleophilic attack providing lactones. This method was used to make the ten membered lactone (+)-diploalide A (Scheme 1.61).^102
Activation of the acid by thioester formation using Corey’s method is another common strategy to make lactones. This approach was used in the synthesis of the eleven membered ferrulactone I as shown in scheme 1.62.

The second approach used in lactonization reactions is to activate the alcohol and then displace it with the free acid to provide the lactone ring (Scheme 1.58).

There are various methods of activating the alcohol, but among these the most common approach is the Mitsunobu reaction. For example, Danishefsky et al. used the Mitsunobu to make a ten membered lactone which was converted into the natural product xestodecalactone A (Scheme 1.63).
The Mitsunobu reaction was also used in the lactonization step in the synthesis of an eleven membered natural product $E,E$-suspensolide (Scheme 1.64).\textsuperscript{108}

\begin{center}
\begin{equation}
\begin{array}{c}
\text{OH} \\
\text{COOH}
\end{array}
\xrightarrow{\text{PPh}_3, \text{DEAD} \text{ benzene} 25\%} \begin{array}{c}
\text{O} \\
\text{E,E-suspensolide}
\end{array}
\end{equation}
\end{center}

\textbf{Scheme 1.64}

\textit{Metal mediated cyclization reactions} have also been exploited to make medium size rings.\textsuperscript{109} Among these, ring closing metathesis (RCM) appears to be the most commonly used method to make medium sized carbocycles and lactones, especially ten-membered lactones.\textsuperscript{75,99,110-112} RCM is an efficient and powerful tool for the formation of carbon-carbon bonds in organic synthesis, but its success depends on many factors, such as the structure of the substrates, the nature of the catalyst, and the steric crowding around the forming cyclic olefin.\textsuperscript{113} Several examples of successful RCM reactions are as follows.

A ten membered lactone intermediate was made via RCM using the first generation Grubbs’ catalyst en route to (+)-diplodialide A (Scheme 1.65).\textsuperscript{114}

\begin{center}
\begin{equation}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\xrightarrow{1. \text{Grubbs 1} \ 2. \text{H}_2, \text{Pd/C} 88\%} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\end{equation}
\end{center}

\textbf{Scheme 1.65}
Similarly, in the synthesis of aspercyclide C, an eleven membered lactone was made via RCM using the second generation Grubbs’ catalyst (Scheme 1.66).\textsuperscript{115}

\[ 	ext{Scheme 1.66} \]

As a final example, the ten membered carbocyclic ring in (+)-Clavilactone B was synthesized by RCM, again using second generation Grubbs’ catalyst (Scheme 1.67).\textsuperscript{88}

\[ 	ext{Scheme 1.67} \]

The Nozaki-Hiyama-Kishi (NHK) coupling reaction\textsuperscript{116} is another widely used metal mediated cyclization strategy to make medium-sized rings. In this reaction vinyl halide is induced to react with an aldehyde in the presence of a Cr/Ni catalyst. There are many examples of this reaction applied to the synthesis of medium-sized lactones.\textsuperscript{99}

For example, (-)-decaerestrictine D a ten membered lactone natural product was made via an intramolecular NHK reaction under high dilution conditions (Scheme 1.68).\textsuperscript{117}
Scheme 1.68

Another example of the NHK cyclization strategy was shown in the synthesis of marine metabolite (-)-7-deacetoxyalcyonin acetate. The key ten membered carbocyclic ring of this diterpene was made using chromium/nickel catalysts by Overman and McMillan (Scheme 1.69).\textsuperscript{118}

Scheme 1.69

Palladium mediated carbon-carbon bond forming reactions\textsuperscript{119} were also applied to create difficult-to-make medium sized rings. Trost was a pioneer in developing intramolecular palladium catalyzed allylic alkylation reactions to make medium-sized lactones. He showed that a sulfonyl anion reacted with an allyl acetate in the presence of a palladium catalyst to provide the ten membered lactone precursor for the natural lactone phoracantholid I (Scheme 1.70).\textsuperscript{120}
Kukovinets et al. used the palladium catalyzed allylic alkylation reaction to make the eleven membered lactone intermediate for the synthesis of ferrulactone I (Scheme 1.71).121

As a final example, Negishi et al. showed that ω-haloallenes can be cyclized to give medium-sized carbocycles through the carbopalladation reaction using a palladium catalyst (Scheme 1.72).122

In addition to the methods shown above, various Intramolecular Carbon-Carbon Bond Making Reactions such as Alkylations, Friedel-Crafts acylation, Horner-
Wadsworth-Emmons (HWE), Julia-Kocienski, Wittig, Diels-Alder, and Reformatsky reactions have also been applied to make medium-sized rings.\textsuperscript{57,99,123}

For example, a ten membered carbocycle was made via an intramolecular alkylation reaction in presence of a strong base as a precursor to a sesquiterpene (Scheme 1.73).\textsuperscript{124,125}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\includegraphics[width=0.5\textwidth]{scheme1.73.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.73}

The synthesis of the ten membered aromatic lactone sporostatin was realized utilizing an intramolecular Friedel-Crafts acylation reaction as the ring closing step (Scheme 1.74).\textsuperscript{126}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\includegraphics[width=0.5\textwidth]{scheme1.74.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.74}

Harwood \textit{et al.} used an intramolecular Diels-Alder approach to make the ten membered lactone core structure of colletocfragarones type lactone natural products (Scheme 1.75).\textsuperscript{127}
In addition, an intramolecular modified Reformatsky reaction,\textsuperscript{128} in which a cross aldol condensation of $\alpha$-haloketones with tethered aldehydes was promoted by \(\text{Et}_2\text{AlCl}\) and zinc, provided medium sized rings. This approach was used in the synthesis of a large number of ten membered lactones and carbocycles. For example, Tsuji \textit{et al.} synthesized the ten membered lactone diplodialide A using this effective reaction (Scheme 1.76),\textsuperscript{129}

\begin{equation}
\begin{array}{c}
\text{Br} & \text{O} \\
\text{C} & \text{H} \\
\text{CHO} & \text{O} \\
\text{Et}_2\text{AlCl}, \text{Zn} & \text{THF} \rightarrow 45\% \\
\end{array}
\end{equation}

Scheme 1.76

and Moriya \textit{et al.} synthesized ferrulactone I via an intramolecular Reformatsky reaction which provided the eleven membered lactone intermediate (Scheme 1.77).\textsuperscript{130}

\begin{equation}
\begin{array}{c}
\text{CHO} & \text{Br} \\
\text{O} & \text{O} \\
& \text{i)Sml}_2\text{-THF, ii)BzCl(O)Cl, DMAP, rt, 47\%} \\
\end{array}
\end{equation}

Scheme 1.77
In conclusion, though some of the cyclization strategies such as lactonization and RCM reactions are very powerful and robust, they always suffer from the need for high dilution techniques. To circumvent the difficulties arising from the cyclization step, organic chemists have come up with other solutions such as ring expansion and fragmentation reactions. In the following subsections these methods for medium-sized ring formations will be exemplified.

**1.3.3.2 Ring Expansion reactions to make medium size rings**

The ring expansion of cyclic compounds to larger rings has long been an effective strategy for the synthesis of specific ring sizes. Ring expansion strategies take advantage of starting with easier to make smaller rings and enlarging them into medium size rings, thereby avoiding cyclization reactions. Some of the noteworthy examples of ring expansion methods developed to make medium-sized rings via various organic reactions are shown below.

The Baeyer-Villager oxidation of cyclic ketones provides medium-sized lactones as a ring expansion method. Ban et al. used this strategy to synthesize the ten membered lactone phoracantholide I from a nine membered cyclic ketone intermediate (Scheme 1.78).  

![Scheme 1.78](image-url)
Rousseau et al. prepared ten membered lactones such as (S)-(+)‐phoracantholide I by iterative one‐carbon ring expansion approaches starting from commercially available lactones. In this method, addition of chlorocarbene to a silylenol ether intermediate provided a highly reactive three membered ring which upon ring expansion yielded a larger ring (Scheme 1.79).\textsuperscript{133,134}

![Scheme 1.79](image)

The strategy of enlargement of smaller rings to medium size rings was followed by Mahajan et al. to make eleven membered lactones. They exploited an intramolecular reverse Dieckmann reaction on a six‐membered cyclohexane‐1,3‐diones to obtain eleven membered lactones (Scheme 1.80).\textsuperscript{135}

![Scheme 1.80](image)

Pericyclic ring expansion reactions are the next useful strategy exploited in making medium size rings. One of the most noteworthy pericyclic ring expansion
reaction generating medium size lactones is an ester Claisen rearrangement developed by Petrzilka. He synthesized a ten membered lactone (±)-phoracantholide J using this strategy (Scheme 1.81).\textsuperscript{136,137}

![Scheme 1.81](image)

Bellus \textit{et al.} developed a different version of the Claisen rearrangement to make medium size lactones. In this strategy, the reaction of dichloroketene with a cyclic allylic ether provided the Claisen intermediate which after pericyclic rearrangement yielded the desired medium sized lactones (Scheme 1.82).\textsuperscript{138} They were able to synthesize the ten membered lactones (±)-phoracantholide I and (±)-phoracantholide J using this method.

![Scheme 1.82](image)

The Evans modification of the oxy-Cope rearrangement provided a ten membered carbocyclic intermediate which was applied in the synthesis of acoragermacrone and preisocalamendiol natural products (Scheme 1.83).\textsuperscript{84}
Lange et al. expanded a cycloadduct obtained from a cycloaddition of four membered and six membered rings to make various ten membered medium-sized carbocyclic sesquiterpenoids. Thermolysis of the cycloadduct provided cis, trans-germacranolide (Scheme 1.84). They also made various derivatives of this cycloadduct to make other germacranolides.\(^{139}\)

In another ring expansion strategy, a tandem Cope-Claisen rearrangement provided a ten membered carbocyclic intermediate which was carried over for the synthesis of (+)-dihydrocostunolide by Raucher et al. (Scheme 1.85).\(^{140}\)
1.3.3.3 Medium rings formed via fragmentation reactions

Medium sized ring formation via fragmentation reactions are similar to ring expansion strategies in that they rely on the reaction of pre-existing rings. In this case, the fragmentation of ring-fusion bonds of bicyclic precursors provides medium-sized rings which are challenging to make via cyclization methods.

Herein follows examples from the literature that highlight the use of fragmentation reactions forming alkene, allene and alkyne containing medium size rings.

The most well-known cyclic alkene forming reaction to date via fragmentation was developed by Wharton (Scheme 1.36). Wharton’s method of fragmentation was used in various syntheses of medium ring containing system with some modifications. One of the classical examples of this method was that used in the synthesis of the nine membered ring containing caryophyllene which was shown earlier in scheme 1.32.

This anionic fragmentation has been used in numerous other total syntheses. For example Saicic et al. used fragmentation reaction to make a ten membered exo-olefin as the key intermediate used in the synthesis of (±)-periplanones (Scheme 1.86).
Mehta and Kumaran synthesized medium sized sesquiterpenoids $Z,Z$-germacratrienones and $E,Z$-germacratrienones via fragmentation of bicyclic carbocycles precursors which were made from carvone (Scheme 1.87).\textsuperscript{142}

Honan \textit{et al.} showed another eloquent example of fragmentation reaction at the late stage of their synthesis of furanogermacrane sesquiterpene sericenine. They fragmented a furan fused bicyclic ring system via Wharton’s method to yield sericenine in moderate yield (Scheme 1.88).\textsuperscript{143}
Mander et al. prepared ten membered carbocyclic 9-Methyl-1-decalones via fragmentation reaction to be used for the synthesis of germacranes and related sesquiterpenes such as tulipinolide (Scheme 1.89).\(^{144}\)

A clever modification of Wharton’s approach to make medium sized rings was developed by Molander et al. In their method they used a Barbier type cyclization followed by fragmentation to form medium sized rings containing Z alkenes (Scheme 1.90).\(^{145}\)

Preparation of \textit{allenes via fragmentation of carbon-carbon bonds} is a relatively new area and there are very few studies done towards application of this strategy for the
synthesis of cyclic allenes. However, Kuwajima et al. showed that fragmentation of vinyl triflates under thermal conditions provided medium sized cyclic allenes stereospecifically (Scheme 1.91).\textsuperscript{146}

![Scheme 1.91](image1.jpg)

Williams et al. also fragmented vinyl triflates to make cyclic allenes. In their approach, treatment of the bicyclic vinyl triflates with a fluoride source afforded a ten membered cyclic allene in good yield (Scheme 1.92).\textsuperscript{147}

![Scheme 1.92](image2.jpg)

The Eschenmoser-Tanabe fragmentation is one of the most well-known cyclic alkyne forming reactions. Eschenmoser and Tanabe independently reported the preparation of medium sized cyclic alkynes from the fragmentation of fused bicyclic α,β-epoxyketones (Scheme 1.93).\textsuperscript{53,54}
In alternative approach, Kuwajima et al. made a vinyl triflate adjacent to the fused bond of a bicyclic system and under thermal conditions it fragmented to give a medium sized cyclic alkyne (Scheme 1.94).  

Lastly, Dudley and Tummatorn used a reductive cyclization followed by ring expansion via fragmentation approach to make medium sized cyclic alkynes (Scheme 1.95).
1.3.4 Conclusions

Thus, fragmentation and ring expansion strategies have some advantages over cyclization methods to make medium sized rings. However, they require rigorous preparation of the precursor. In other words, the precursors to be fragmented have to have specific stereochemistry due to the strict stereoelectronic requirements of the fragmentation strategies. In the ring expansion strategies via sigmatropic rearrangements proper orbital alignments are necessary, and the synthesis of precursors requires careful planning. Despite these drawbacks, fragmentation reactions stand out as a powerful alternative to cyclization methods for the formation of medium sized rings.

Although there are not many fragmentation reactions available in the literature, those that are known are very useful reactions. In the following chapters I will introduce a new fragmentation reaction that we have developed, and I will describe my work to develop this reaction as a way to prepare tethered aldehyde ynones and medium sized rings; specifically cyclic ynones and ynolides.
CHAPTER 2: TETHERED ALDEHYDE YNONES

2.1 Ring fragmentation chemistry

In their work with diazo compounds, Brewer and Draghici discovered a new ring fragmentation. Specifically, when they treated γ-silyloxy-β-hydroxy-α-diazoesters with Lewis acids, they observed that the β-hydroxyl group was removed, the Cβ-Cγ bond was cleaved, and the α-diazo group was eliminated to yield a tethered aldehyde ynoate (alkynyl ester) product (Table 2.1). After optimizing this reaction they were able show that the Cβ-Cγ bonds of various γ-silyloxy-β-hydroxy-α-diazoesters fragment in the presence of SnCl₄ at 0 °C in dichloromethane to provide tethered aldehyde ynoates in good to excellent yield.¹⁴⁹

Table 2.1 Fragmentation of γ-silyloxy-β-hydroxy-α-diazoesters

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂Et</td>
<td>94 %</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>95 %</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>71 %</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>97 %</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>91 %</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>27 %</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>76 %</td>
</tr>
</tbody>
</table>
As discussed in section 1.2.3, these types of tethered aldehyde ynoate compounds had not been made via fragmentation prior to this report. This is a very powerful reaction because in just one step two latent functional groups are unmasked and these newly formed functional groups could be used in various other reactions to make useful and more complicated molecules.

Brewer et al. later capitalized on these results by using these tethered aldehyde ynoates as synthetic intermediates in the total synthesis of natural products. To that end, after fragmenting γ-silyloxy-β-hydroxy-α-diazoesters, the resulting aldehyde tethered ynoates were treated with an amino acid silyl ester. The reaction of the unmasked aldehyde functional group with the amino acid silyl ester resulted in the formation of an azomethine ylide which underwent an intramolecular 1,3-dipolar cycloaddition reaction with the tethered alkyne group to provide a 2,5-dihydropyrrole (Scheme 2.1).\(^{150}\)

![Scheme 2.1](image)

This ring fragmentation 1,3-dipolar cycloaddition sequence has been used by the Brewer group to prepare demisidine\(^ {151}\) and cycloclavine\(^ {152}\) (Scheme 2.2).
2.2 Tethered aldehyde ynones via ring fragmentation chemistry

At the early discovery stages of this ring fragmentation chemistry, I became interested in exploring the scope of this reaction. We were curious to know whether this useful reaction would work if the diazoester group was replaced by various diazoketones (i.e.: γ-silyloxy-β-hydroxy-α-diazoketones). We thought this modification would allow us to obtain functionally diverse tethered aldehyde ynones (alkynyl ketones) as a result of fragmentation (Scheme 2.3). This plan is summarized graphically in scheme 2.3.
As highlighted by the work done in the Brewer group, tethered aldehyde ynoates and ynones are useful synthetic intermediates. These functional groups are in fact extremely rich in reactivity and in the next subsection the reactivity of these functional groups will be shown through examples taken from the literature.

2.3 Significance of tethered aldehyde ynones and synthetic utility of ynones

The significance of the aldehyde functional group in organic synthesis is very well known and a comprehensive review of this functional group is outside the scope of this document. The applications of ynones in organic synthesis are more limited, but still substantial. For example, because of the electrophilic properties of conjugated alkyne and carbonyl groups, they can undergo 1,2-addition, 3,4-addition, and 1,4-addition reactions (Figure 2.1).

\[
\begin{align*}
R &= \text{Alkyl, Aryl and a-amino}
\end{align*}
\]

**Figure 2.1 Tethered aldehyde ynones**

In addition to our group’s work, others have exploited tethered aldehyde ynones to make synthetically useful intermediates. For example, Krische et al. developed an enantioselective reductive cyclization of tethered aldehyde ynones using transition metal catalysts to make five membered heterocyclic alcohols (Scheme 2.4).
Burke *et al.* made a diol intermediate starting from a tethered aldehyde ynone in multiple steps for their synthesis of (+)-compactin and (+)-dihydrocompactin (Scheme 2.5).\(^{159}\)

Cho *et al.* used tethered aldehyde ynones as substrates for the synthesis of tetrahydropyran derivatives via a Prins-type cyclization reaction (Scheme 2.6).\(^{160}\)

Ynones and aldehydes have also been used in intermolecular processes. For example, Shibasaki *et al.* prepared dihydropyranones through a sequential copper (I)
catalyzed aldol addition of yrones to aldehydes followed by a silver (I) catalyzed oxy-
Michael reaction (Scheme 2.7).  

![Scheme 2.7](image)

Yrones themselves are quite useful. For example, Gouault and coworkers used
gold catalysis to cyclize protected amino acid derivatives of yrones to make pyrrolin-4-
one. These products are useful intermediates for the synthesis of pyrrolidines and
nitrogen containing natural products (Schemes 2.8).

![Scheme 2.8](image)

Larock et al. further showed the utility of the ynone functional group by using
them in the synthesis of pyrazole derivatives which are important functional groups
present in natural products (Scheme 2.9).

![Scheme 2.9](image)
Another very common mode of reactivity of ynones is their use as dienophiles in Diels-Alder reactions. For example, Arndt et al. used ynones to make 3-hydroxypyridines via a Diels-Alder reaction to provide a key intermediate for the synthesis of the natural product nosiheptide (Scheme 2.10).^{164}

![Scheme 2.10](image)

Overall, aldehyde and ynone functional groups or tethered aldehyde ynones are very useful synthetic intermediates because of their abundant and variable modes of reactivity. New methods are needed to make such useful organic structures. Therefore, we sought to make various tethered aldehyde ynones via fragmentation of γ-silyloxy-β-hydroxy-α-diazoketones.

**2.4 Results and discussion - Tethered aldehyde ynones via a ring fragmentation reaction**

Our investigation into tethered aldehyde ynone synthesis via a ring fragmentation reaction started with the preparation of alky, aryl and N-Cbz protected α-amino acid derivatives of γ-silyloxy-β-hydroxy-α-diazoketones, which is described in the following sections.
2.4.1 Synthesis of $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazoketones as fragmentation precursors

The fragmentation precursors needed to make tethered aldehyde ynones (i.e. $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazoketones 2.1) were synthesized by following the general synthetic route shown in Scheme 2.11.

\[ \text{Scheme 2.11} \]

First, $\beta$-t-butyldimethylsilyloxy cyclohexanone 2.4 was made via treatment of the 2-hydroxy cyclohexanone dimer with TBSCI in the presence of a base. Alkyl and aryl $\alpha$-diazoketones (2.6) were made by the reaction of commercially available acid chlorides with diazomethane (the Arndt-Eistert reaction).\(^{165}\) In cases where acid chlorides were not commercially available, they were made from the corresponding carboxylic acids. In the next step, LDA was added into a mixture of $\alpha$-diazoketone 2.6 and $\beta$-t-butyldimethylsilyloxy cyclohexanone 2.4, to facilitate the aldol addition that provided the fragmentation precursors (2.1) as a mixture of cis and trans diastereomers which were separated via chromatography (Scheme 2.11). Once the necessary $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazoketones 2.1 were made, they were fragmented with one
equivalent of SnCl₄ at 0 °C. Upon treatment with the Lewis acid, the yellow color of the diazoketone solution disappeared together with vigorous gas evolution to provide the tethered aldehyde ynones.

### 2.4.2 Tethered aldehyde alkyl ynones

We were delighted to observe that the major diastereomer of alkyl γ-silyloxy-β-hydroxy-α-diazoketones fragmented to give the corresponding tethered aldehyde alkyl-ynones in almost pure form in the crude reaction mixtures. The crude products could be further purified via silica gel column chromatography to provide the desired tethered aldehyde alkyl-ynones in good yield (Table 2.2). The tethered aldehyde n-butyl (2.8), cyclohexyl (2.10) and tert-butyl (2.12) substituted ynones were obtained in 82%, 83% and 80% yield, respectively. It appears that the steric bulk of the alkyl group did not play any role in the outcome of this fragmentation reaction. However, the benzyl ether substituted tethered aldehyde ynone 2.14 was obtained in only 50% yield. In contrast to other substrates, this benzyl ether γ-silyloxy-β-hydroxy-α-diazoketone required 2 equivalent of SnCl₄ to fragment, most likely due to competitive complexation of the Lewis acid with the oxygen atom of benzyl group. It is also possible that the benzyl oxygen and the β-hydroxy groups may form a seven membered bidentate complex with SnCl₄, such complexes are known and this phenomenon was also observed in the fragmentation of bicyclic diazolactone 4.5 in chapter 4.¹⁶⁶,¹⁶⁷ This complexation could slow down elimination of the β-hydroxyl group, ultimately resulting in undesired reaction paths that lower the yield of the fragmentation process.
Table 2.2 Fragmentations yielding tethered aldehyde alkyl ynone

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-diazo ketone</th>
<th>Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ynone</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structure 1" /></td>
<td>66 (4:1)</td>
<td><img src="image" alt="Structure 2" /></td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 3" /></td>
<td>85 (9:1)</td>
<td><img src="image" alt="Structure 4" /></td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 5" /></td>
<td>50 (4:1)</td>
<td><img src="image" alt="Structure 6" /></td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 7" /></td>
<td>46 (4:1)</td>
<td><img src="image" alt="Structure 8" /></td>
<td>50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 9" /></td>
<td>50 (4:1)</td>
<td><img src="image" alt="Structure 10" /></td>
<td>70</td>
</tr>
</tbody>
</table>

<sup>a</sup> Combined yield of cis and trans diastereomers. <sup>b</sup> Yield of product from reaction of major diastereomer. <sup>c</sup> 2 equiv of SnCl4 was used.

The minor diastereomers of alkyl derivatives of γ-silyloxy-β-hydroxy-α-diazo ketones were also fragmented; they also provided the desired tethered aldehyde ynones in comparable albeit slightly lower yields. For example, in entry 5 (Table 2.2) the trans diastereomer of tert-butyl diazoketone derivative 2.15 was fragmented to give the corresponding tethered aldehyde ynone 2.16 in 70% yield.
2.4.3 Tethered aldehyde aryl yrones

The fragmentation of the major diastereomers of aryl substituted γ-silyloxy-β-hydroxy-α-diazoketones provided the corresponding tethered aldehyde aryl-ynones in constantly lower yields than the tethered aldehyde alkyl-ynones (Table 2.3).

Table 2.3 Fragmentations yielding tethered aldehyde aryl yrones

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-diazoketone</th>
<th>Yield(%)* Cis:Trans</th>
<th>Ynone</th>
<th>Yield (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 2.17" /></td>
<td>83 (9:1)</td>
<td><img src="image2" alt="Ynone 2.18" /></td>
<td>60°</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Structure 2.19" /></td>
<td>88 (1:0)</td>
<td><img src="image4" alt="Ynone 2.20" /></td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Structure 2.21" /></td>
<td>70 (2:1)</td>
<td><img src="image6" alt="Ynone 2.22" /></td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Structure 2.23" /></td>
<td>77 (7:1)</td>
<td><img src="image8" alt="Ynone 2.24" /></td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Structure 2.25" /></td>
<td>83 (9:1)</td>
<td><img src="image10" alt="Ynone 2.26" /></td>
<td>70</td>
</tr>
</tbody>
</table>

* Combined yield of cis and trans diastereomers. ** Yield of product from reaction of major diastereomer. ‡ Product was lost during purification.

The electron rich p-methoxybenzene 2.19 and o-iodobenzene 2.21 derivatives and the neutral phenyl derivative 2.17 gave yrones in higher yield than the electron
poor $p$-trifluoromethyl substituted fragmentation precursor 2.23. Thus, we concluded that the efficiency of the formation of the tethered aldehyde aryl ynones depends on the electronics of the aryl substituent. We also observed that the crude reaction mixtures of the aryl ynones were less clean than the alkyl ynones by NMR spectroscopy. The other reason for the relatively lower yield for aryl ynones was due to their decomposition during column chromatography. It appears that because of the reactive nature of the aryl ynones, they tend to decompose under purification conditions. In addition, we also observed the auto-oxidation of the aldehyde functional group to give carboxylic acids which further contributed to a reduction in yield.

The trans diastereomers of aryl derivatives of γ-silyloxy-β-hydroxy-α-diazoketones were also fragmented, and they also provided the desired tethered aldehyde ynones in comparable yields. For example, in entry 5 in table 2.3 trans diastereomer of phenyl diazoketone 2.25 fragmented to give the tethered aldehyde ynone 2.26 in 70% yield.

2.4.5 Tethered aldehyde α-amino ynones

Tethered aldehyde α-amino ynones were made by fragmentation of the corresponding N-Cbz protected α-amino acid substituted γ-silyloxy-β-hydroxy-α-diazoketones (2.30-2.38, Table 2.4). These fragmentation precursors (e.g. 2.29, Scheme 2.12) were prepared by the same method used to make alkyl and aryl substituted diazoketones. However, in this case the N-Cbz-protected α-amino α-diazoketones 2.28 were made using McKervey’s method,168 in which N-Cbz protected α-amino acids
(2.27) were converted into anhydrides in situ by reaction with a chloroformate, and then treated with diazomethane to provide the requisite α-diazoketones (2.28).

\[
\text{R'ROH} \xrightarrow{\text{TEA, OCOCl, CH}_2\text{N}_2} \text{R'RO}_{\text{N}_2} \xrightarrow{\text{THF, EtN} \text{er (1:1), -20 °C to rt}} \text{R'RO}_{\text{N}_2}\text{R''} \xrightarrow{\text{LDA, THF, -78 °C}} \text{R''CO}_\text{OH} \text{OTBS}
\]

**Scheme 2.12**

It was interesting to note that in the aldol addition of lithiated N-Cbz-protected α-amino α-diazoketone 2.28 to the β-\(\text{-}t\)-butyldimethylsilyloxy cyclohexanone 2.4, only one equivalent of LDA was needed. This observation shows us that the pKa of the proton on the diazocarbon is more acidic than the N-H proton of the carbamate. The aldol addition provided the N-Cbz protected α-amino acid substituted γ-silyloxy-β-hydroxy-α-diazoketones 2.29 as a cis and trans diastereomeric mixture and this mixture was used without separation in the fragmentation reactions. Our initial plan was to use N-Boc protected α-amino acids instead of N-Cbz protected amino acids. To that end, I first made the N-Boc protected α-amino acid substituted γ-silyloxy-β-hydroxy-α-diazoketones 2.38 (entry 5, Table 2.4), however upon fragmentation with the Lewis acid, we observed that the yield of the tethered aldehyde N-Boc protected α-amino ynone 2.39 was only in 36% (Table 2.4). We also observed greater than normal gas evolution during the reaction which we attributed to the instability of the Boc protecting group to Lewis acids. With this in mind, we switched to N-Cbz protected α-amino acids.
Table 2.4 Fragmentations yielding tethered aldehyde α-amino ynone

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ynone</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>[α]&lt;sup&gt;c&lt;/sup&gt;°</th>
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</thead>
<tbody>
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<td></td>
<td>69</td>
<td>+21.9</td>
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<td></td>
<td>62</td>
<td>-46.9</td>
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<td></td>
<td>76 (3:2)</td>
<td></td>
<td>74</td>
<td>+17.6</td>
</tr>
<tr>
<td>4</td>
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<td>74 (3:2)</td>
<td></td>
<td>74</td>
<td>-15.8</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>69 (3:2)</td>
<td></td>
<td>36</td>
<td>+35.7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Combined yield of diastereomers. <sup>b</sup>Yield of product from reaction of diastereomer mixture. <sup>c</sup>Optical rotation values.

With this modification, we were pleased to observe that the fragmentation proceeded smoothly and provided the corresponding tethered aldehyde α-amino ynone in good yield (Table 2.4). We were curious whether the stereochemistry of the chiral natural α-amino acids was conserved during the fragmentation reaction under Lewis acidic conditions. To that end, the optical rotation of the tethered aldehyde α-amino
ynones was measured and we observed that the chiral center was conserved under the fragmentation reaction conditions (Table 2.4). As a control experiment, I made both enantiomers of the phenyl alanine derivative of the fragmentation precursor (entries 3 and 4, table 2.4). These fragmented to give α-amino acid ynones that had almost equal but opposite optical rotation. This result further indicated that the chiral centers of the α-amino acids were kept intact under the fragmentation conditions.

2.4.6 Mechanism of the ring fragmentation reaction

In order to rationalize why the trans diastereomers consistently fragmented in slightly lower yields, we must consider the mechanism of this fragmentation reaction. Previous work done by several researchers helped us to propose a mechanism for the fragmentation of γ-silyloxy-β-hydroxy-α-diazo ketones. As I mentioned earlier in section 1.1.3.3, in scheme 1.21, Wenkert and McPhearson\(^{30}\) reported the formation of ynoates from the reaction of β-hydroxy-α-diazo esters with Lewis acids. They proposed that elimination of the β-hydroxyl group is promoted by complexation with BF\(_3\) which provides a vinyl diazonium intermediate (1.22) which in turn forms the acetylene product via elimination of nitrogen. In scheme 1.22 of that same section, I also showed the worked done by Padwa and Pelliccian\(^{32}\) on the reaction of β-hydroxy-α-diazo esters with Lewis acids. They observed formation of various products resulting from a vinyl cation intermediate, which was proposed to originate from a vinyl diazonium precursor via elimination of the β-hydroxy group. Based on these two works, we proposed that in the first step of the fragmentation mechanism, the β-hydroxyl group is eliminated via
complexation with the Lewis acid to provide a vinyl diazonium intermediate 2.41 (Scheme 2.13).

![Scheme 2.13]

The vinyl diazonium intermediate (2.41) then undergoes a Grob type fragmentation reaction. Here, while the Cβ-Cγ bond is broken, the silyloxy group acts as an electrofuge and molecular nitrogen acts as a nucleofuge. The silyl protecting group would then be lost from 2.42 to provide the tethered aldehyde ynone product 2.22.

As I explained in the discussion of heterolytic carbon-carbon bond fragmentation reactions, Grob type fragmentation reactions can occur either by concerted or two-step mechanisms (Chapter 1, Scheme 1.36). Therefore, in the fragmentation of γ-silyloxy-β-hydroxy-α-diazo carbonyl compounds, the vinyl diazonium intermediate can either fragment in one-step through a concerted mechanism or it can fragment in two-steps (Scheme 2.14). In the two-step mechanism, first the molecular nitrogen would be eliminated to form a vinyl cation (2.43). Subsequently, the vinyl cation could either fragment to provide the ynone product (2.22) or it may go...
through other reactions such as substitution, elimination, or rearrangements depending on the substrate or functional groups present.

Scheme 2.14

Efficient elimination of β-hydroxyl group is essential to the successful fragmentation of γ-silyloxy-β-hydroxy-α-diazocarbonyl compounds. For example, Draghici and Brewer observed that the cis (2.44) and trans (2.45) diastereomers of a steroid derived fragmentation precursor gave vastly different product yields (Scheme 2.15).\textsuperscript{149}

Scheme 2.15
Brewer and Jabre later showed that the difference in the reactivity of these diastereomers is due to the stereoelectronic requirements of the β-hydroxyl group elimination step.\textsuperscript{169} In order for the elimination of the β-hydroxyl to occur, the diazo and ester groups must lie in a plane that is perpendicular to the leaving β-hydroxyl group. As shown in Figure 2.2, on the cis-diazoester \textbf{2.46}, steric interactions do not prevent the leaving hydroxyl group to be aligned with the perpendicular p-orbital of the diazo ester group. However, for the trans-diazoester \textbf{2.47}, steric interactions between the diazo ester and the γ-silyloxy group prevent the diazo ester from adopting the proper orbital alignment with the leaving β-hydroxyl group and hence fragmentation cannot be effected.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.2.png}
\caption{Stereoelectronic requirements of the β-hydroxyl group elimination}
\end{figure}

With this in mind, we concluded that the difference observed in the yield of tethered aldehyde ynone results from fragmentation of cis and trans diastereomers of aryl and alkyl γ-silyloxy-β-hydroxy-α-diazoketones is most likely due to difference in the elimination of the β-hydroxyl group, in other words stereoelectronic requirements of fragmentation reaction.
2.6 Conclusions

In conclusion, the fragmentation of γ-silyloxy-β-hydroxy-α-diazoketones was explored. This process provided good yields of tethered aldehyde ynones which are known to be useful synthetic intermediates. The diazoketone fragmentation precursors were easily made in few steps either from commercially available carboxylic acids or acid chlorides. The successful fragmentation of a variety of different γ-silyloxy-β-hydroxy-α-diazoketones proves that this is a general reaction. Alkyl, aryl and N-Cbz protected α-amino acid diazoketones reacted to provide the corresponding ynones in good to excellent yield. It is also notable that proton NMR showed the crude reaction mixtures to be exceptionally clean. However, in some cases the desired products were susceptible to decomposition during purification. In addition auto-oxidation upon standing converted the fragmentation products into the corresponding tethered ynone carboxylic acids.

2.7 Future perspectives

The significance of ynones and tethered aldehyde ynones/ynoates was shown through the work done by Brewer et al. and the few select examples summarized in the previous sections. For future work, tethered aldehyde ynones obtained from fragmentation of γ-silyloxy-β-hydroxy-α-diazoketones could be used to make more complex and useful intermediates for small molecule and natural product synthesis. For example, the tethered aldehyde α-amino ynones shown in table 2.4 could be used to make pyrrolin-4-ones as precedented by Gouault and coworkers (Scheme 2.16). These could be used in making pyrrolidines and alkaloid natural products.
In addition, steroid based γ-silyloxy-β-hydroxy-α-diazoketones could be made and fragmented to provide the corresponding tethered aldehyde ynones. These ynones could be carried through the steps followed in the synthesis of demisidine to make demisidine derivatives that have various alkyl and aryl ketone groups as side chains (Scheme 2.17).

Furthermore, the ketone could be reduced to an alcohol or it could be removed to give a methylene group. This example should be taken as an indication of the versatile nature these compounds have.
CHAPTER 3 : SYNTHESIS OF MEDIUM SIZE CYCLIC YNONES VIA RING FRAGMENTATION METHOD

3.1 Introduction

Medium sized carbocyclic rings form the core of many bioactive natural products; some examples of this class of compound were illustrated in chapter 1.3. In view of their significance it is unfortunate that there are difficulties with the synthesis of medium sized carbocyclic rings as was explained in detail in that earlier chapter. Having this synthetic problem in perspective, we thought we could use the ring fragmentation reaction described in chapter 2 to make medium sized carbocyclic rings. We hypothesized that if we could prepare a γ-silyloxy-β-hydroxy-α-diazo ketone as a fused bicyclic system such that the γ-silyloxy and β-hydroxy groups flanked the ring fusion bond (e.g. 3.1, Scheme 3.1), then fragmentation with SnCl₄ should provide a medium sized cyclic ynone (e.g. 3.3).

Scheme 3.1

This process is beneficial because it not only provides medium sized rings, but also gives synthetically useful ynones contained in the ring system. We could exploit the rich chemistry of ynones to functionalize and manipulate these rings to make more complex systems.
3.2 Methods to make cyclic ynones and limitations of those methods

Despite the abundant modes of reactivity of ynones, and the potential usefulness of medium sized cyclic ynones, there are surprisingly few methods available to make these species. This could be due to the rigid linear geometry of alkyne functional group, which may hinder cyclization reactions. The examples that follow highlight known approaches to these species.

A steroid based ten membered cyclic ynone was synthesized by Covey et al. as an irreversible inhibitor of both bacterial and mammalian Δ⁵-3-keto steroid isomerasers. In their synthetic route, they used the Eschenmoser-Tanabe fragmentation reaction in a very clever way to make the ten membered cyclic alkynyl acetate alcohol steroid intermediate. This material was carried over to the desired 5,10-secoestr-4-yn-3,10,17-trione in several additional steps (Scheme 3.2).\textsuperscript{170}

![Scheme 3.2](image)

Nicolaou et al. made a ten membered cyclic ynone which was used for the synthesis of the antitumor agent eleutherobin. They first carried out an intramolecular aldol addition of a terminal alkyne to a ketone in the presence of LiHMDS to provide a ten membered ring alcohol, which was subsequently oxidized via the Dess-Martin reagent to afford the ten membered cyclic ynone (Scheme 3.3).\textsuperscript{171}
Larger ring size cyclic ynones have also been prepared before. For example, Marshall et al. used a twelve membered cyclic ynone to make bridged allenes (Scheme 3.4). They made the twelve membered cyclic ynone intermediate via Friedel-Crafts cyclization of \( \omega \)-TMS alkynyl acid chloride in the presence of a Lewis acid under high dilution conditions according to the method developed by Utimoto (Scheme 3.4).\(^{172,173}\)

Marshall et al. also made twelve membered cyclic ynones through Lewis acid promoted ene cyclization. These were used in the synthesis of diterpenoid natural products (Scheme 3.5).\(^{174}\)
Lastly, Bakstad et al. made a nine membered cyclic ynone via ring enlargement of an eight membered ring through the ring opening of a tribromocyclopropane ring to form an alkynyl ketal. Upon hydrolysis this ketal provided the nine membered cyclic ynone (Scheme 3.6).

![Scheme 3.6](image)

None of these routes was ideal. The cyclization methods had to be carried out under high dilution conditions usually resulting in low yields, and the fragmentation and ring expansion methods required further synthetic manipulations in order to reach to the requisite ynone functional group.

### 3.3 Cyclic ynone formation via fragmentation reaction

#### 3.3.1 Synthesis of the fragmentation precursor: a fused bicyclic γ-silyloxy-β-hydroxy-α-diazoketone

To synthesize the fragmentation precursor (bicyclic γ-silyloxy-β-hydroxy-α-diazoketones 3.1a and 3.1b), we followed the synthetic route shown in scheme 3.7. We started the synthesis by condensation of (R)-phenylethylamine and the α-silyloxy cyclohexanone 3.4 to provide imine 3.5. Next, according to the method developed by D’Angelo, imine 3.5 and methyl acrylate were reacted to give Michael adduct 3.6.
which upon hydrolysis with aqueous acetic acid yielded ester 3.7 in 60% yield over three steps.

![Scheme 3.7](image)

Hydrolysis of ester 3.7 with LiOH provided carboxylic acid 3.8 in 75% yield. Following McKervey’s method, acid 3.8 was converted in situ to an anhydride through reaction with ethyl chloroformate, which upon treatment with ethereal diazomethane provided the uncyclized diazoketone 3.9 in 31% yield. The acyclic diazoketone 3.9 cyclized upon treatment with LDA to provide a diastereomeric mixture of cis and trans bicyclic diazoketones 3.1a and 3.1b. The mixture of diastereomers was separated by silica gel chromatography to give the cis-diastereomer (3.1a) in 32% yield and the trans-diastereomer (3.1b) in 23% yield.
3.3.2 Fragmentation of fused bicyclic \( \gamma \)-silyloxy-\( \beta \)-hydroxy-\( \alpha \)-diazo ketones to make cyclic ynones

With bicyclic diazo species 3.1a and 3.1b in hand, we set our sights on assessing their ability to fragment. We were pleased to observe that treating cis-diastereomer 3.1a and trans-diastereomer 3.1b with one equivalent of SnCl\(_4\) at 0 °C provided ten membered cyclic ynones 3.3 in 80 % and 71% yield respectively (Scheme 3.8). This result was important because it demonstrated that our hypothesis was valid. That is, it was possible to make medium-sized cyclic 2-alkynone in good yield, by this fragmentation route.

![Scheme 3.8](image)

This result was an important turning point shaping the direction of my thesis research. After proving that it was possible to make ten membered cyclic ynones in good yield, I sought to apply this methodology to make medium sized ynlides (lactones adjacent to alkyne group, chapter 4). I planned to use the ynlides made via fragmentation for the synthesis of several medium sized lactone natural products.

Because I choose to focus my attention on making ynlides, my collaborator Dr. Nikolay Tsvetkov took over the ynone project and optimized the synthetic route to
make bicyclic γ-silyloxy-β-hydroxy-α-diazoketone precursors in better yields. He also made homologs of fragmentation precursors enlarged on the cycloalkane portion of the fused bicyclic system (Scheme 3.9). Upon fragmentation of these different size precursors he was able make 11 and 12 membered cyclic ynones in very good yields.

![Scheme 3.9](image)

### 3.4 Conclusion and future work

In conclusion we were able make unprecedented 10, 11 and 12 membered cyclic ynones in very good yields without facing the difficulties of cyclization strategies. This work showed that our ring fragmentation strategy is a useful way to make medium and large size rings which are synthetically challenging to make by other means. After obtaining these fascinating results, we were encouraged to apply this method to make medium size lactones and lactone natural products as will be discussed in the next chapter.

The cyclic ynone products are very promising synthetic intermediates. As I have shown in chapter 2, due to the wide spectrum of reactivity of ynones, cyclic ynones can
be a very lucrative synthetic platform that could be used to make more complex natural products such as carbocyclic sesquiterpenoids shown in section 1.3.1 in scheme 1.54. In addition to the ynone functional group, other functional groups such as alkenes, indoles, or aromatics could likely also be incorporated into the cyclic ynone ring system by including these functional groups in the fragmentation precursor as shown in scheme 3.10. This way, it may be easier to make more complex natural products.

Scheme 3.10

Finally, the bioactivity of the cyclic ynones needs to be investigated. As was shown in Scheme 3.2, a steroid based ten membered cyclic ynone was reported to be an inhibitor of both bacterial and mammalian \( \Delta^5 \)-3-keto steroid isomerases. It’s possible that cyclic ynones 3.3, 3.11, and 3.13 and their derivatives, such as the ones in scheme 3.10, might have biological activity as well.
CHAPTER 4 : YNOLIDES

4.1 Introduction

As shown in chapter 1.4, medium size lactones are present in a wide variety of natural products with various biological properties. However, their synthesis via cyclization strategies and other methods is challenging due to the reasons explained in chapter 1, section 3.2.

After showing that the ring fragmentation reaction could be used to make medium-size cyclic ynone, I was motivated to apply this reaction to make medium-size ynolides (cyclic ynoates). We hypothesized that a fused diazolactone and carbocyclic ring system (e.g. 4.1) containing the necessary functional groups on the bicyclic ring could fragment through its fused Cγ-Cβ bond to provide medium sized ynolides (e.g. 4.3).

Scheme 4.1

The resulting medium sized ynolides could be used as core structures to make medium size lactone natural products such as diplodialide C (Scheme 1.43) and phorocantholide I (Scheme 1.70).123
4.2 Background

Lactones with an alkyne group adjacent to the ester group are either called ynolides or cyclic ynoates interchangeably in the literature. We preferred to use the term ynolide introduced by Samuel J. Danishefsky. Medium size and large size ynolides are very unique structures, very few ynolides had been made before and most of them were large sized rings.

Smith and Malamas reported the first ynolide which they made using Mukaiyama’s macrolactonization strategy under high dilution conditions (Scheme 4.2). The ynolide intermediate was later transformed into natural product jatraphone analogs cis- and trans-normethyljatropholactone.

![Scheme 4.2]

Later, Ogasawara et al. made large sized ynolides using palladium mediated carboxymacrolactonization of terminal hydroxyacetylenes. They used the sixteen membered ynolide intermediate to synthesize macrrocyclic lactone exaltolide (Scheme 4.3). They also made 15- to 20 membered ynolides using the same method.
Evans and Fitch also used large sized ynolides in their synthesis of the C1-C19 subunit of phorboxazole B, which is among the most cytostatic natural products known, inhibiting the growth of tumor cells at nanomolar concentrations and it has antifungal activity as well. In their synthetic route, they made a 21-membered ynolide intermediate via Yamaguchi macrolactonization reaction and they carried this ynolide intermediate to the final product phorboxazole B (Scheme 4.4)\textsuperscript{180,181}.

\begin{center}
\textbf{Scheme 4.3}
\end{center}

Danishefsky and Yang also used ynolides for the synthesis of benzofused macrolactone cycloproparadicicol which was found to be a potential antitumor agent (Scheme 4.5). Their initial attempts to make the ynolide via cyclization failed due to the rigid linear geometry of the alkyne group. Instead, they had to make a dicobalt carbonyl complex of the alkyne to affect the cyclization via ring closing metathesis reaction to provide a fourteen membered ring. After removal of the cobalt complex, they obtained the fourteen membered ynolide intermediate which was carried over to the desired cycloproparadicicol in several additional steps\textsuperscript{177}.
Danishefsky et al. later used this same approach for the synthesis of benzo fused macrolide aigialomycin D, which was found to be a potent antimalarial and antitumor agent (Scheme 4.6).  

In summary, ynolides and especially medium sized ynolides are difficult to make via cyclization strategies due to the rigid linear geometry of the alkyne group. Almost all the ynolides made prior to my work were either very large sized rings, or had to be modified via formation of cobalt complexes of the alkyne group in order for cyclization to occur. With this in mind, we thought that our route to medium sized
ynolides was worth investigating and we saw opportunities to use the fragmentation in the synthesis of medium sized lactone natural products. With this goal in mind, we started work to make the fragmentation precursors.

4.3 Synthesis and fragmentation of a γ,β-dihydroxy-α-diazo bicyclo[4.4.0]lactone precursor as a first route to provide medium size lactones

Initially, we focused all our efforts on to making the ten membered ynolide 4.31 (Scheme 4.7). Our first approach to make the fragmentation precursor for the synthesis of this compound was to make bicyclic diazolactone diol 4.5 from 1,2-keto diol 4.4 shown in scheme 4.7. This strategy differed from previous fragmentation precursors in that we chose to leave the γ-hydroxy unprotected with a silyl group which would allow us to prepare the requisite fragmentation precursor in fewer steps.

![Scheme 4.7](image_url)

4.3.1 Synthesis of 1,2-ketodiol

Our synthesis started with the preparation of 1,2-ketodiol 4.4 (Scheme 4.8). Our first attempt to make this keto diol was via one step addition of an enol formed from α-hydroxy cyclohexanone 4.7 to formaldehyde under basic conditions. However, despite the literature precedence for this reaction, our many attempts failed reproduce this procedure. Next, we made vinyl chloride 4.9 in 75% yield via formylation of
cyclohexanone (4.8) with Vilsmeier reagent\textsuperscript{184} followed by reduction with sodium borohydride.\textsuperscript{185} The vinyl chloride was then epoxidized to give a mixture of chloro epoxide 4.10 and keto epoxide 4.11. This epoxide mixture was converted into the desired 1,2-ketodiol 4.4 through a Payne rearrangement, however the yield was only 7\%.\textsuperscript{186}

\begin{center}
\textbf{Scheme 4.8}
\end{center}

We next attempted to convert vinyl chloride 4.9 into 1,2-ketodiol via a Sharpless’ asymmetric dihydroxylation reaction,\textsuperscript{187} which did not yield any of the desired product. I also followed a multistep route to make the 1,2 ketodiol 4.4 starting from cyclohexanone. Here, cyclohexanone was converted into α-hydroxy acetal 4.12 in 71\% yield. Oxidation of α-hydroxy acetal 4.12 under Swern conditions gave ketone 4.13 in 100\% yield. Next ketone 4.13 was converted into alkene 4.14 via a Wittig reaction in 73\% yield, and this alkene was treated with \textit{m}-CPBA to provide epoxide
4.15 in 56% yield. Finally, the acetal group of epoxide 4.15 was hydrolyzed with acid to yield 1,2-ketodiol 4.4 in only 50% as a crude mixture. Deciding that this multistep route was long and not efficient, as a last attempt we dihydroxylated vinyl chloride 4.9 with OsO₄ in the presence of NMO,¹⁸⁸ and this gave the desired 1,2-ketodiol 4.4 in 34% yield in just one step. Despite extensive efforts to optimize this reaction, the yield could not be enhanced. It is known that electron withdrawing groups connected to alkene retard oxidation reaction by osmium tetroxide.¹⁸⁹ Therefore, it is most likely that electron withdrawing chloride and allylic alcohol functional groups diminish the efficiency of the dihydroxylation reaction.

4.3.2 Synthesis of bicyclic diazo lactone (4.5) and its fragmentation

With reasonable quantities of 1,2-ketodiol 4.4 in hand, we set our sights on preparing diazolactone 4.5. To achieve this, 1,2-ketodiol 4.4 was reacted with p-toluenesulfonylhydrazone glyoxylic acid chloride to form the toluenesulfonylhydrazone ester which was decomposed in situ by triethylamine to give diazoester 4.16 in 68% yield according to the House variation of the Bamford-Stevens reaction (Scheme 4.9).⁹ Diazoester 4.16 cyclized in the presence of DBU to provide bicyclic diazolactone 4.5 in 58% yield as a single diastereomer through an intramolecular aldol addition reaction.
To our disappointment, treatment of bicyclic diazolactone 4.5 with SnCl$_4$ did not give the desired ynlolide; instead it formed an insoluble precipitate instantly.

Bidentate complexes of SnCl$_4$ are known in the literature,\textsuperscript{166,167} we presume that SnCl$_4$ formed an insoluble complex with the diol group that is present in bicyclic diazolactone 4.5, and that this prevented fragmentation from occurring.

**4.4 Initial, failed route for the synthesis of the γ-silyloxy-β-dihydroxy-α-diazo bicyclo [4.4.0] lactone fragmentation precursor**

After observing that bicyclic diazolactone 4.5 bearing an unprotected γ-hydroxy group did not fragment, and in view of the fact that in all of the previous fragmentation precursors the γ-hydroxy group was protected with a silyl ether group, we decided to protect that γ-hydroxy group with a silyl ether group to make γ-silyloxy-β-dihydroxy-α-diazo bicyclo [4.4.0] lactone 4.20. Unfortunately, attempts to directly protect the alcohol in 4.16 failed. So, we designed the synthetic route shown in scheme 4.10, which takes advantage of the previously made 1,2-keto diol 4.4.
Originally we planned to protect only the diol groups in 1,2-keto diol 4.4 as silyl ethers to give a bis(tert-butyldimethylsilyl)ether. To our surprise the ketone group also reacted and these conditions ultimately gave the tris-silyl ether 4.17. We tried to selectively deprotect the silyl enol ether and the primary silyl alcohol in the presence of the tertiary silyl alcohol. Despite our extensive attempts under varying conditions, we could only make the desired keto alcohol 4.18 in 40% yield after treatment with HF.Pyridine. Due to the low yielding keto alcohol step, we deserted this route. However, the tris-silyl ether protection step wherein the ketone was incidentally converted into a silyl enol ether inspired a different route to reach to the desired keto alcohol 4.18, which is explained in the next section.

4.5 Second and successful route for the synthesis of the γ-silyloxy-β-dihydroxy-α-diazo bicyclo[4.4.0] diazolactone fragmentation precursor

In this second route, our synthesis started with a palladium mediated α-oxygenation of commercially available ethyl 2-oxocyclohexane carboxylate 4.21 to make the α-hydroxy-β-keto ester 4.22 in 69% yield (Scheme 4.11).190 Inspired by the previous route shown in scheme 4.10, we protected the α-hydroxy-β-keto ester 4.22 as
the bis(silyl ether) to give ester 4.23 in 99% yield. This protecting group strategy would allow us to reduce the ester group to an alcohol without interfering with the ketone which was unconventionally protected as the silyl enol ether.

Scheme 4.11

Reduction of the ester group in 4.23 to make the alcohol 4.24 required some optimization (Table 4.1). Reduction of ester 4.23 with varying equivalents of DIBAL-H in various different solvents provided alcohol 4.24 in moderate yields, whereas reduction with either LiAlH₄ or LiEt₃BH did not give any of the desired alcohol. Use of six equivalent of LiBH₄/MeOH provided a better yield than DIBAL-H, but purification via silica gel chromatography was very difficult due to the presence of a side product that had a similar Rf value to the desired alcohol. Finally, it was found that slow addition of 2.2 equivalent of DIBAL-H in toluene provided alcohol 4.24 in 69% yield.
Table 4.1 Optimization of reduction of ester group

<table>
<thead>
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<th>Reducing agent</th>
<th>Amount of reducing agent</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Other reagents</th>
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</tr>
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<tr>
<td>DIBAL-H</td>
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<td>55%</td>
</tr>
<tr>
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<td>THF</td>
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<td></td>
<td>-</td>
</tr>
<tr>
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<td>THF</td>
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<tr>
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<td>0 °C to RT</td>
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<td>-</td>
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<tr>
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<td>Toluene</td>
<td>-78 °C</td>
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</table>

Selective deprotection of the silyl enol ether in the presence of the silyl protected tertiary alcohol was achieved with CsF in acetic acid to give the desired keto alcohol 4.18 in 86% yield.

We tried several different methods to make the fragmentation precursor 4.20 from keto alcohol 4.18. First, we followed the method used in the synthesis of diazolactone 4.5. We made the tosyl hydrazone ester by reacting keto alcohol 4.18 with p-toluenesulfonylhydrazone glyoxylic acid chloride and then treated it with triethyl amine in situ to deliver the diazoester 4.19 according to the House method (Scheme 4.12).⁹ Diazoester 4.19 was cyclized with DBU via an intramolecular aldol addition reaction to provide bicyclic diazolactone 4.20 as trans and cis diastereomers in 28% and 14% yields over two steps. Although the yields were reasonable for an initial route, the purification of diastereomeric products was painstaking.
In a modified method to make diazoester 4.19\textsuperscript{191} two equivalents of dimethylaniline was added in addition to the triethylamine into the mixture of keto alcohol 4.18 and \textit{p}-toluenesulfonylhydrazone glyoxylic acid chloride, which caused the diazo intermediate spontaneously cyclize to provide a diastereomeric mixture of bicyclic diazolactone 4.20. However, purification and separation was cumbersome. To circumvent the purification issues, we took a different approach and tried to couple \textit{p}-toluenesulfonylhydrazone glyoxylic acid with the keto alcohol 4.18 using DCC and DMAP to make diazoester 4.19\textsuperscript{192}. Unfortunately this method gave a complex mixture.

Alternatively, keto alcohol 4.18 was converted into chloroformate 4.25 by treatment with triphosgene and pyridine (Scheme 4.13).\textsuperscript{193} Unfortunately, acylation of freshly prepared diazomethane with crude chloroformate 4.25 provided the desired diazoester 4.19 in only 12\% yield over the two steps.
Eventually, we acylated alcohol 4.18 with bromoacetylbromide to make bromoacetate 4.26 in 90% yield (Scheme 4.14). In the next step, the diazo group was transferred to the boromoacetate upon treatment with \(N,N'\)-ditosylhydrazine and DBU to provide the diazo ester in situ.\(^{194}\) The diazoester cyclized spontaneously under the reaction conditions to provide the bicyclic diazolactones 4.20-trans and 4.20-cis as separable diastereomers in very good yields.

![Scheme 4.14](image)

The cis- and trans-fused bicyclic diazolactones were easily distinguishable by NMR spectroscopy. The conformational flexibility of the cis-fused bicyclic systems led to broad signals in the \(^1\)H and \(^{13}\)C NMR spectra, which sharpened upon warming. The trans-fused diastereomers showed sharp signals in the \(^1\)H and \(^{13}\)C NMR spectra at room temperature. Also, the hydroxyl proton of the cis-fused bicyclic diazolactones appeared further down field, possibly due to intramolecular hydrogen bonding with the adjacent silyl ether.

**4.6 Fragmentation of bicyclo [4.4.0] diazolactone: results and discussion**

Before the route for the synthesis of bicyclic diazolactones 4.20 was optimized, we had access to only small amounts of the fragmentation precursor which were obtained from the unoptimized routes. With this small amount of material we started
our investigation of the key fragmenting step. In contrast to the fragmentation reactions carried out previously to make tethered aldehyde ynone and cyclic ynone, when we fragmented both of the diastereomers of \textbf{4.20} using SnCl$_4$ at 0 °C, we obtained a very complex mixture. Initially, we were concerned that we might have mischaracterized the structures of bicyclic diazolactones \textbf{4.20} which would explain why we did not observe any of the desired fragmented products. Our concern stemmed from the fact that during the synthesis of keto alcohol \textbf{4.18} (Scheme 4.15), we obtained a side product with a similar Rf value as that of the keto alcohol. We had initially characterized this compound as the silyl transferred tertiary alcohol \textbf{4.27} (Scheme 4.15). What caught our attention was that the $^1$H and $^{13}$C NMR data of tertiary alcohol \textbf{4.27} was very similar to the keto alcohol, and it was not possible to unequivocally distinguish these two compounds via NMR spectroscopy. If the compound we had thought was \textbf{4.18} was actually \textbf{4.27}, then we would have ended up making bicyclic diazolactone \textbf{4.29} as the final product (II, Scheme 4.15), which would naturally not fragment upon reaction with SnCl$_4$. We also observed that when keto alcohol \textbf{4.18} was treated with base, it was converted into the tertiary alcohol \textbf{4.27} (III, Scheme 4.15). To solve this puzzle, we came up with a chemical means to distinguish structures \textbf{4.18} and \textbf{4.27}. Specifically, we subjected what appeared to be the keto alcohol \textbf{4.18} to Swern oxidation condition and indeed we found that it did provide the corresponding aldehyde \textbf{4.30} (IV, Scheme 4.15). Therefore, keto alcohol \textbf{4.18} had in fact been characterized correctly, because tertiary alcohol \textbf{4.27} would not be oxidized to an aldehyde. This quick experiment proved to us that the structure assigned for keto alcohol \textbf{4.18} was correct.
Ultimately I was able to obtain an X-ray quality crystal of compound \textbf{4.20-cis} by crystallization from an ethyl acetate and hexanes mixture. Single crystal X-ray diffraction confirmed our structural assignment of the fragmentation precursors \textbf{4.20-cis} (Figure 4.1).
After clearing out the questions related to the assignment of the structures for bicyclic diazolactone 4.20-cis and trans, our efforts focused on determining why the fragmentation of bicyclic lactones did not yield the desired ynolide. By that time we had optimized the route for the synthesis of bicyclic diazolactone 4.20-cis and trans as explained in the previous sections, and we were able to make them on gram scale. When bicyclic diazolactone 4.20-cis was fragmented on a larger scale under standard conditions (0 °C with one equivalent of SnCl$_4$), we could isolate the desired ten membered ynolide 4.31 in 12% yield (entry 1, Table 4.2). The major product was the chloro-bicyclic lactone 4.32 which was isolated in 54% yield. We also observed three minor products, chloride 4.34, (a diastereomer of 4.32) in 4% yield, bicyclic lactone alcohol 4.33 in 9% yield and bicyclic lactone diene 4.35 in 5% yield.

Fragmentation of the bicyclic diazolactone 4.20-trans also provided the ynolide 4.31 but in only 10% isolated yield (entry 2, Table 4.2). This reaction gave similar side products as the fragmentation of 4.20-cis, though in relatively lower yields, together with other unidentified minor products. Additionally, we observed desilylated bicyclic lactone diene 4.37 in 7% yield.
We were able to crystallize ymolide 4.31 from cold methanol, and the structure of 4.31 was further confirmed by single-crystal X-ray diffraction, which showed that the alkyne was distorted from linearity by approximately 10° (Figure 4.2). This distortion is consistent with values computed for cyclodecyne.195

![Figure 4.2 X-ray of ymolide 4.31](image)
### Table 4.2: Fragmentation of bicyclic diazolactone 4.20-cis & 4.20-trans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isomer</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>cis 4.31</th>
<th>cis 4.32</th>
<th>cis 4.33</th>
<th>cis 4.34</th>
<th>cis 4.35</th>
<th>cis 4.36</th>
<th>cis 4.37</th>
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<tr>
<td>1</td>
<td>cis</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>12%</td>
<td>54%</td>
<td>9%</td>
<td>4%</td>
<td>5%</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>trans</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
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<td>10%</td>
<td>7%</td>
<td>N/A</td>
<td>13%</td>
<td>N/A</td>
<td>7%</td>
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</tr>
<tr>
<td>3</td>
<td>trans</td>
<td>SnCl₄ /</td>
<td>CDCl₃</td>
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<tr>
<td></td>
<td></td>
<td>Mol. siev</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>4</td>
<td>trans</td>
<td>ZnCl₂</td>
<td>CDCl₃ / ET₂O</td>
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<td></td>
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<td></td>
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<tr>
<td>5</td>
<td>cis</td>
<td>In(OEt)₃</td>
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<tr>
<td>6</td>
<td>cis</td>
<td>BF₃ OEt₂</td>
<td>CH₂CN</td>
<td>0</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>cis</td>
<td>BF₃ OEt₂ / proton sponge</td>
<td>CH₂CN</td>
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<td>✓</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>trans</td>
<td>BF₃ OEt₂</td>
<td>CH₂Cl₂</td>
<td>-78 to RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>9</td>
<td>trans</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
<td>-78 to 0</td>
<td>✓</td>
<td>✓ (w/o TBS)</td>
<td>✓ (w/o TBS)</td>
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</tr>
<tr>
<td>10</td>
<td>cis</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
<td>RT</td>
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<tr>
<td>11</td>
<td>cis</td>
<td>SnCl₄ (2 eq)</td>
<td>CH₂Cl₂</td>
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<tr>
<td>12</td>
<td>cis</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>20%</td>
<td></td>
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<td></td>
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</tbody>
</table>
We rationalized formation of other products via the proposed mechanism of the fragmentation reaction disclosed earlier in chapter 2, section 2.4.6. After hydroxyl group cleavage upon complexation with tin tetrachloride, the vinyl diazonium species 4.39 should form and its Grob type fragmentation would give the ymolide 4.31 (I, Scheme 4.16). However, if the fragmentation reaction is not a facile process, then the vinyl cation 4.41 may form upon loss of molecular nitrogen, and this in turn might form the more stable allylic cation (4.42) via a hydride shift from the nearby methylene group (4.41). All the side products could be formed from this common allylic cation intermediate 4.42.
A nucleophilic attack of chlorine atoms from the tin complex to the carbocation center of 4.42 would provide chloro-bicyclic lactones diastereomers 4.32 and 4.34 (II, Scheme 4.16). The bicyclic lactone alcohol 4.33 might be formed via a nucleophilic attack of the hydroxyl group from the tin complex present in the medium (III, Scheme 4.16), and the bicyclic lactone diene 4.35 could be formed by loss of a proton adjacent to the cationic center (IV, Scheme 4.16).

Although we were puzzled by the outcome of this reaction, we are certain of the results because all the products were very well characterized with all the available instrumentation techniques including exhaustive 2D-NMR experiments. We were also able to obtain a crystal structure for chloro-bicyclic lactone 4.32.

4.6.1 Optimization of fragmentation of bicyclo [4.4.0] diazolactone

After confirming that we could indeed form the desired ynolide 4.31, we set our sights on optimizing the conditions to increase the yields. As a first step, we performed the fragmentation reaction in the presence of molecular sieves to prevent potential hydrolysis of the strained ynolide. However, this did not improve the yield (entry 2, Table 4.2). Next, we tried to fragment the bicyclic diazolactones 4.20-cis and trans with other Lewis acids. Treatment with ZnCl₂ did not provide any of the ynolide (entry 4), whereas In(OTF)₃ gave the bicyclic lactone diene 4.35 in 31% yield and an epoxide (4.36) in 5% yield (entry 5). The formation of epoxide 4.36 can be rationalized via the proposed mechanism shown in scheme 4.17. Indium salts were determined to be azaphilic through the work done by Kobayashi et al. Therefore, preferential
complexation of indium triflate with the diazo group might provide intermediate 4.43. The free hydroxyl group could then attack the α-diazo carbon to form intermediate 4.44, which could lose molecular nitrogen. A final proton transfer would provide epoxide 4.36 (Scheme 4.17).

Scheme 4.17

We also tried fragmenting bicyclic diazolactone 4.20-cis with BF₃OEt₂ in acetonitrile at 0 °C and we obtained ynolide 4.31 in only 6% isolated yield together with diene 4.35 in 5% yield (entry 6, Table 4.2). To buffer against acid that may be formed during the fragmentation reaction and hydrolyze the ynolide, we carried out the reaction in the presence of proton sponge. However, this did not change the yield of the desired ynolide (entry 7). When we performed the fragmentation reaction with BF₃OEt₂ in dichloromethane at -78 °C, none of the ynolide was observed. Instead we isolated desilylated diene 4.37 as the major product (entry 8). We carried out the fragmentation with SnCl₄ at -78 °C too. However, this did not improve the yield of the ynolide and the side products observed in entry 2 were also present (entry 9). When we treated fragmentation precursor 4.20-cis with one equivalent of SnCl₄ at room temperature, we were surprised to see the yield of the desired ynolide increase to 21% (entry 10). We thought that increasing the amount of tin tetrachloride might have an effect on the
outcome of the reaction and we tried to fragment with 2 equivalent of SnCl$_4$ at room temperature, but that did not improve the yield, but instead lowered it down a little bit to 17% (entry 11). Lastly, seeing that increasing the temperature improved the yield for the ten membered ynonole, one equivalent of SnCl$_4$ was added into a refluxing solution of bicyclic diazolactone 4.20-cis at 40 °C, unfortunately we did not observe any change in the outcome of the reaction (entry 12). At this point, we were able to make the desired ten membered ynonole in only 21% yield.

We considered the possibility that the first step of the mechanism (hydroxyl group removal) was not a facile process, which would prevent fragmentation. To ensure the hydroxyl group removal, we wanted to make a carbonate form of the diazolactone from bicyclic diazolactone 4.5 and planned to fragment it with SnCl$_4$. However, the carbonate diazolactone could not be isolated; upon warming to room temperature it yielded products similar to the ones observed in the fragmentation of bicyclic diazolactone 4.20-cis in entry 1, table 4.2 (Scheme 4.18).

![Scheme 4.18](image_url)

**4.7 Synthesis and fragmentation of diazoacetate (4.48)**

As was shown in chapter 3, bicyclic diazoketones fragmented to provide the cyclic ynonoles in very good yield. However, we could not attain the same success with
the bicyclic diazolactones. Puzzling as it was, we reasoned that the culprit for the low yield of the ynolide could be the ester functional group of the bicyclic diazolactone. We hypothesized that the electron withdrawing ester group being in close proximity to the $\gamma$-carbon might slow down the bond breaking step during the fragmentation step. To test this hypothesis we prepared diazoacetate fragmentation precursor (4.47) (Scheme 4.19), which has an ester at the same position as 4.20.

![Scheme 4.19](image)

To prepare the diazoacetate fragmentation precursor 4.47, keto alcohol 4.18 was acylated using acetic anhydride in the presence of a base to yield keto ester 4.46 in 86% yield. The aldol addition of lithiated diazo ethyl acetate to keto ester 4.46 in THF provided a diastereomeric mixture of diazoacetate which were separated to give a major diastereomer in 41% yield and a minor diastereomer in 8% yield. The relative configuration of diazoacetate diastereomers 4.47 could not be determined. When both of these diazoacetate fragmentation precursors were treated with one equivalent of SnCl$_4$ at 0 °C, the ynoate 4.48 were made in 70% and 67% yield from major and minor diastereomers respectively. This experiment proved that the low yields observed in the fragmentation of bicyclic lactone 4.20-cis and trans were most likely not caused by the position of the electron withdrawing ester group.
4.8 Synthesis and fragmentation of bicyclo [5.4.0] diazolactone (4.59)

We also considered that it might be difficult to make a ten membered ymolide in good yields because of its small size, whereas increasing the ring size of ymolides might also increase their yield. Hence, to assess the effect of ring size on the formation of ymolides we increased the ring size of the lactone portion of the fragmentation precursor by one methylene group to make bicyclo [5.4.0] diazolactone 4.59 (Scheme 4.22).

To synthesize bicyclo [5.4.0] diazolactone 4.59, we first needed to make a keto alcohol. In our first attempt to make the keto alcohol, we tried a hydroboration and oxidation sequence on the alkene 4.50 in presence of Wilkinson’s catalyst (Scheme 4.20). We observed that upon formation the primary alcohol cyclized spontaneously to provide hemiacetal 4.51 in a disappointingly low yield of 17% yield. Unfortunately the yield for hemiacetal formation was not only low but it was also not reproducible. I was able make it just once with newly bought catechol borane, but could not reproduce it later. Other hydroboration agents as well as various other conditions were tried, but they were not successful either.

![Scheme 4.20](image-url)

Scheme 4.20
In an alternative route, we first made lithiated benzyloxyacetylene via treatment of benzyl (1,2-dichlorovinyl) 4.53 with n-butyllithium198 which was added into 2-silyloxy cyclohexene-2-ene to provide the tertiary alcohol 4.54 (Scheme 4.21). A subsequent silyl transfer followed by a hydrogenation reaction was expected to provide the hemiacetal. However, the addition reaction consistently gave a complex mixture. Also, the preparation of benzyl (1,2-dichlorovinyl) 4.53 was very cumbersome, and because of these drawbacks we decided to desert this route.

Scheme 4.21

In our successful route to bicyclic diazolactone 4.59, we started our synthesis with addition of allylmagnesiumbromide to known 2-silyloxy cyclohexene-2-ene (4.49) followed by a base catalyzed silyl group transfer, which provided alkene 4.55 in 83% yield over two steps (Scheme 4.22).199

Scheme 4.22
As the next step, alkene 4.55 was cleaved via ozonolysis to provide the aldehyde (4.56) and selective reduction of the aldehyde using Raney nickel\(^{200}\) provided the desired hemiacetal 4.51 in good yield. Hemiacetal 4.51 was converted into the bromoacetyl ester (4.57), which was subjected to the diazo group transfer reaction\(^{194}\) used in the preparation of bicyclic diazolactone 4.20 to provide the uncyclized diazo ester 4.58. Interestingly, diazoester 4.58 did not cyclize spontaneously to provide bicyclic diazolactone, and the cyclization reaction to form the seven membered ring turned out to be challenging. After various attempts, we found out that addition of LDA into a very dilute solution of diazoester 4.58 in THF at very low temperatures provided the bicyclic diazolactone in 10-20% yields as a single diastereomer. Other bases such as KOH and DBU did not effect the cyclization at all. Attempts to cyclize the diazoester 4.58 to the bicyclic diazolactone with SnCl\(_4\) was also unsuccessful. Eventually, we found that slow addition of a solution of diazoester 4.58 in THF into a dilute solution of LiHMDS in THF at -78 °C provided the bicyclic diazolactone 4.59 as a single diastereomer in 69% yield (Scheme 4.22). The configuration of diazolactone 4.59 was tentatively assigned as trans.

When we fragmented bicyclic diazolactone 4.59 with one equivalent SnCl\(_4\) at 0 °C, we isolated the eleven membered ynlode in 50% yield, together with an epoxide (4.61) in 15% and an acetal (4.62) in 15% yields (Scheme 4.23). The increase in yield going from a ten membered ynlode to an eleven membered ynlode showed us that ring size does play a role in the outcome of the fragmentation reaction.
The side products (epoxide 4.61 and acetal 4.62) were very well characterized and their structures were assigned using 2D-NMR experiments. To account for these side products, the following mechanistic pathway might be possible (Scheme 4.24).

The efficient hydroxyl group removal followed by fragmentation reaction should give the desired ymolide as shown in equation I, scheme 4.24. However, if hydroxyl group removal is not a facile process, then as shown in equation II, scheme 4.24, hydroxyl group attack on the carbon atom of a tin complexed diazo group should provide epoxide 4.66, and after proton transfer and nitrogen group removal epoxide 4.61 could be created. Acetal 4.62 could be formed via the mechanism in equation III (Scheme 4.24). A hydride delivery to the carbon atom of a tin complexed diazo group would form oxacarbenium intermediate 4.67, and a subsequent intramolecular nucleophilic attack by the hydroxyl group would give acetal 4.68. Next, a proton transfer and nitrogen removal would create acetal 4.62.
Although the mechanism shown for the formation of epoxide 4.61 and acetal 4.62 may seem contradictory to the proposed mechanism for the fragmentation product such as in equation I, it is possible that fragmentation precursors might follow a similar mechanistic pathway to provide the desired ynolides (IV, Scheme 4.24). The tin complexed diazo 4.69 could go through a Grob type fragmentation reaction to form the intermediate 4.70, which upon removal of hydroxyl group and nitrogen could provide ynolide 4.60.
4.9 Synthesis and fragmentation of bicyclo [4.5.0] diazolactone and bicyclo [4.6.0] diazolactone

To assess the effect of ring size on the fragmentation reaction, we also enlarged the carbocyclic ring of the bicyclic diazolactone 4.20 by one or two methylene units. To that end, we planned to synthesize bicyclo [4.5.0] diazolactone and bicyclo [4.6.0] diazolactone by the route used for the preparation of the bicyclo [4.4.0] diazolactone (4.20) (Scheme 4.25).

Scheme 4.25

Starting from the seven and eight membered cyclic β-keto esters (4.71a and 4.71b), we were able to make the corresponding bromoacetyl esters 4.76a and 4.76b in very good yields (Scheme 4.25). The diazo transfer reaction on bromoacetyl ester 4.76a was followed by a spontaneous cyclization to provide a diastereomeric mixture of bicyclic diazolactones **4.78-trans** and **4.78-cis** in 33% and 25% yields respectively.
However, when the diazo transfer reaction was applied to bromoacetyl ester 4.76b, an uncyclized diazoester 4.77b was isolated in 68% yield. Cyclization of this material to the requisite bicyclic structure will be described in section 4.9.2.

### 4.9.1 Fragmentation of bicyclo [4.5.0] diazolactone precursor

The fragmentation of bicyclic diazolactones 4.78-cis and trans with one equivalent of SnCl₄ at 0 °C provided the eleven membered ynonide 4.79 in 64% and 57% yield respectively (Scheme 4.26).

![Scheme 4.26](image)

Thus, once again we concluded that the ring size of the ynonide to be formed determines the outcome of the fragmentation reaction. As the ring size increased, so is the yield. It seems it is easier to form larger sized ynonides as opposed to smaller sized ones under the standard fragmentation reaction conditions.

### 4.9.2 Cyclization attempts of diazo ester 4.77b and its unexpected rearrangement to a bicyclo [3.6.0] diazolactone

To prepare the desired bicyclo [4.6.0] diazolactone, we tried to cyclize the diazo ester 4.77b using various bases such as DBU and LDA, however all our attempts failed. Finally, we found out that slow addition of a THF solution of diazo ester 4.77 into a
THF solution of LiHMDS at -78 °C provided what appeared to be the bicyclic diazolactone 4.80 in 64% yield (Scheme 4.27). When we fragmented the supposed bicyclic diazolactone 4.80 under standard fragmentation conditions, we only observed an epoxide 4.82 in 80% yield, and we did not obtain any of the expected twelve membered ynolide 4.81.

Scheme 4.27

This result was confounding because all the experiments done so far predicted that we would have a higher yield for the twelve membered ynolide, whereas we had none! The supposed bicyclic diazolactone 4.80 and epoxide 4.82 were characterized by $^1$H and $^{13}$C NMR and the bicyclic diazolactone was determined to have the cis configuration based on the chemical shift of the alcohol and tert-butyldimethylsilyl group protons. The structure for epoxide 4.82 was assigned based on 2D-NMR experiments. However, when we did a 1D-NOE experiment on epoxide 4.82 to certify the stereochemistry, we were not able to obtain the expected NOE signals. This led us to question our data for this compound as well as its precursor bicyclic diazolactone 4.80. Surprisingly, when we more closely analyzed 1D-NMR data for bicyclic diazolactone 4.80, we found peaks which did not correlate with the assigned structure. Next, 2D-NMR experiments done on bicyclic diazolactone 4.80 indicated that the
correct structure was a rearranged bicyclic diazolactone 4.85 (Scheme 4.28). Furthermore, the structure for the rearranged bicyclic diazolactone 4.85 was confirmed unequivocally by single-crystal X-ray diffraction.

![Scheme 4.28](image)

We think that the desired cyclization occurs to provide alkoxide 4.83, but due to the conformational strain of eight membered rings, a silyl group migration is favored to provide alkoxide 4.84 which goes through a trans-lactonization process in the next step to provide bicyclic diazolactone 4.85 as the final product. We did not observe silyl group transfer in any of the cyclization reactions before, however we observed a silyl group transfer in the synthesis of keto alcohol 4.18 which was explained in detail in section 4.6 in scheme 4.15.

We also had difficulty in the preparation of bicyclic diazoketones 3.12a and 3.12b of the same ring size (chapter 3, Scheme 3.9). They could only be made in low yields and the uncyclized diazoketone was recovered as the major product. We noted that at equilibrium these systems exist predominantly in the ring-opened form.
Therefore, we think that the ring closing step might also be difficult in bicyclic diazolactone formation. However, in this case the system favors the formation of bicyclic diazolactone 4.85 through a silyl migration and trans-lactonization processes.

When bicyclic diazolactone 4.85 was treated with SnCl₄ at 0 °C it actually forms cyclic ether 4.86, not epoxide 4.82. All the characterization data, 2D-NMR experiments and more importantly 1D-NOE experiments indicates that the product from the fragmentation of bicyclic diazolactone 4.85 is indeed cyclic ether 4.86.

Thus we were able to resolve this puzzling result in our investigation of the fragmentation of bicyclic diazolactones. Since we did not have access to the fragmentation precursor bicyclic diazolactone 4.80, we could not make a twelve membered ymolide. However, it should be possible to make this compound from a bicyclo [5.5.0] diazolactone precursor which has a two fused seven membered rings by following the route in scheme 4.29.

![Scheme 4.29](image-url)
4.10 Optimized conditions for the fragmentation of bicyclic diazolactones

At this point in our investigation, we could make a ten membered ynolide in only 12 % yield at 0 °C. When we increased the ring size of fragmentation precursors on the carbocyclic and diazolactone rings, we observed an increase in the yield of eleven membered ynolides under the same conditions. This showed us that ring size affects the outcome of fragmentation of bicyclic diazolactones. Although we tried fragmenting bicyclic diazolactone 4.20 at room temperature and 40 °C, the yield went up to only about 20% (entries 11 and 12, Table 4.3). Later, we suspected that in the fragmentation reaction done at 40 °C, the diazolactone 4.20 might decompose while exposed to heat for longer times, and thus the yield might be lowered than optimal. To prevent decomposition of bicyclic diazolactones at refluxing temperatures, we decided to add the solution of bicyclic diazolactone 4.20-cis into a refluxing SnCl₄ solution at 40 °C (i.e. inverse addition). Upon carrying out this experiment, we successfully isolated the desired ten membered ynolide 4.31 in 33% yield (entry 13, Table 4.3). Fragmentation of bicyclic diazolactone 4.20-trans at refluxing SnCl₄ solution also provided the ynolide 4.31 in a higher yield of 17% (entry 14). We were excited to try the fragmentation reaction at higher temperatures, upon seeing the increase on the yield of ynolide 4.31 with increasing temperatures. However, when a solution bicyclic diazolactone 4.20-cis in dichloromethane was added into refluxing solution of SnCl₄ in CDCl₃ at 61 °C, we did not observe an increase in the yield (entry15,). We think that at this elevated temperatures, most of the diazolactone was decomposed before it fragmented and the physical appearance of the reaction mixture supported this view.
We also noted that when bicyclic diazolactones were fragmented using this reverse addition method, as the yield of the ynolide increased the yields of side products decreased (entry13, Table 4.3). For example, chloro-bicyclic lactones diastereomer 4.32 and 4.34, were isolated in only 14 % total yield, as opposed to 58% total yield when they were isolated from a reaction conducted at 0 °C.
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<th>4.32</th>
<th>4.33</th>
<th>4.34</th>
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<th>4.36</th>
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<td>(w/o TBS)</td>
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*Table 4.3 Fragmentation of bicyclic diazolactone 4.2b-cis & 4.2b-trans*
Thus we were able to discover the optimum conditions for the fragmentation of bicyclic diazolactone 4.20, which is the addition of a solution of bicyclic diazolactone into a refluxing SnCl$_4$ solution at 40 °C. We fragmented other bicyclic diazolactones under the same conditions and observed an increase in their yield for the corresponding ynolides as well (Scheme 4.30).

![Scheme 4.30](image)

For example, bicyclic diazolactone 4.59 fragmented to give the eleven membered ynolide 4.60 in 63% yield, whereas at standard conditions it was 50%. Fragmentation of bicyclic lactones 4.78-cis and 4.78-trans provided eleven membered ynolide 4.79 in 83% and 67% yields respectively as opposed to 64% and 57% yields obtained under standard conditions. In summary, we were able to make ynolides from fragmentation of bicyclic diazolactones in higher yields at elevated temperatures with the reverse addition method.

### 4.11 Discussion and Conclusion

When we compare the yields obtained from the fragmentation of bicyclic diazolactones 4.20 at 0 °C to those obtained for the fragmentation of bicyclic...
diazoketones 3.1 under the same conditions, we observe a drastic difference (Scheme 4.31).

Scheme 4.31

The difference in yield has to be caused by the presence of the ester functional group in the diazolactones or the ynolide products. How could the ester functional group create such a difference in the fragmentation reaction? Esters prefer to be in a syn conformation, for example, the anti conformation of methyl acetate was found to be 8.5 kcal/mol higher in energy than the syn conformation (I, Figure 4.3). The difference in energy is due to the lack of dipole-dipole stabilization that is present in the syn conformation and both methyl-methyl and lone pair-lone pair steric repulsion in the anti conformation. The ester group is one of the sources of strain in lactone molecules, since in a lactone it is forced to exist in the least stable anti conformation (II, Figure 4.3).
In addition to the other aforementioned major strain elements (see section 1.3.2, chapter 1), the strain caused by the conformation of the ester group affects formations of lactones via cyclization reactions. Huisgen and Otto\textsuperscript{203} showed that lactones with ring sizes of seven and less have the ester group in the less stable anti conformation, and lactones with ring size of ten or larger have the ester in the more stable syn conformation. For 8 and 9 membered lactones the two conformations are in equilibrium the anti conformation is predominant in 8 membered rings and the syn conformation is predominant in 9 membered rings. For this reason, 8 and 9 membered rings are the most difficult to make among other medium sized rings, since the ester group is forced into the less stable anti conformation (Figure 1.6, Chapter 1).\textsuperscript{204} Overall, anti and syn conformational effects are important contributing factors in determining the observed reactivity in lactone formation. Wiberg and Waldron also calculated strain energies of lactones from enthalpies of reduction, and they found that 5 to 9 membered rings have the highest strain energy among other ring sizes, since they are forced to take the less stable anti conformation for the ester group.\textsuperscript{205}

Thus, in addition to Pitzer strain, Baeyer strain and transannular strain present in medium sized rings, the conformational strain of the ester group and also the strain introduced by the rigid linear ynone group is likely to make it more difficult to form the
ynolides than cyclic ynone. As can be seen in the hypothetical energy diagram for the fragmentation of the bicyclic diazoketone and the bicyclic diazolactone (Scheme 4.32), the energy difference between the starting materials and the transition state complexes and intermediate vinyl diazonium species formed during the fragmentation reaction of bicyclic diazoketones might be smaller than the corresponding energy difference for the fragmentation of the bicyclic diazolactones.

![Energy Diagram](image)

**Scheme 4.32**

The reason for the high energy transition complexes and intermediates in the case of the bicyclic diazolactones as opposed to bicyclic diazoketones could be explained by the differing dipole-dipole interactions in the initial diazolactone, its transition state complexes and the vinyl diazonium intermediate as shown in scheme 4.33. On paper the bicyclic diazolactone seems to have a smaller net dipole due to the
opposing dipoles of the functional groups. However, loss of the hydroxyl group would result in an increased dipole which should result in a higher energy transition state complex and vinyl diazonium intermediate. This effect should be smaller in the bicyclic diazoketone system.

This could explain the reason for the difference in the yield for ynolides in comparison to cyclic ynones as well as the need for higher temperatures for the formation of ynolides. The reason for the energy difference could also be due to some strain we have not yet clearly identified in the transition state complexes, intermediates or the product ynolide itself. In general, strain has been found to be the major factor in determining the structure, energies and reactivities of organic compounds. Therefore, it may once again be the cause for the lower yields observed for the formation of ynolides from the fragmentation of bicyclic diazolactones.

Additionally, the fact that yields increase as the size of the ynolide formed increases supports this view too. With increasing ring size, the strain in the transition state complexes, vinyl diazonium intermediate and ynolide product would be reduced,
hence the energy barrier for the formation of larger rings ynolides would be reduced and as a result the yield would increase.

Analysis of some of the side products generated from the fragmentation reactions (e.g. epoxide 4.61 and acetal 4.62 in scheme 4.23 and trace amounts of epoxide 4.36 in entry 15, table 4.2), indicate that hydroxyl group removal may not be facile in the case of bicyclic diazolactones. As I explained it in section 2.4.6, chapter 2, hydroxyl group cleavage is a necessary step in the ring fragmentation mechanism and it has stereoelectronic requirements. Because of these aforementioned dipole-dipole interactions, hydroxyl group removal may not be facile in the fragmentation of bicyclic diazolactones.

As can be seen in scheme 4.35, after hydroxyl group removal, ynolide 4.31 is formed (eq. I). If hydroxyl group removal does not occur, then a carbocation intermediate could be formed through a hydride shift which could lead to all the side products observed in the fragmentation of bicyclic diazolactone 4.20-cis. Once the carbocation 4.87 is formed, either free chloride ions or chlorine atoms at the nearby tin complex could add to the carbocationic center to provide the chloro-bicyclic lactone diastereomers 4.32 and 4.34 (eq. II). Nucleophilic attack by the alcohol group complexed to tin on the carbocation would yield epoxide 4.90, which could open up after the nitrogen group is eliminated to provide bicyclic lactone alcohol 4.33 (eq. III). Last of all, deprotonation at the α-position of the carbocation together with elimination of nitrogen and tin complexed alcohol would provide the bicyclic lactone diene 4.35 (eq. IV).
Alternatively, a mechanism for the formation of these side products that involves a common epoxide intermediate (4.93) could also be envisioned (Scheme 4.36). This epoxide might form because of inefficient hydroxyl group removal. Once epoxide 4.93 is formed, deprotonation at the α-position would provide alkene 4.94. Nucleophilic addition of hydroxide and chloride ions to alkene 4.94, followed by elimination of tin complexed alkoxide would provide bicyclic lactone alcohol 4.33 and
chloro-bicyclic lactone diastereomers 4.32 and 4.34. The bicyclic lactone diene 4.35 could be created via a 1,4-type elimination of hydrogen and tin complexed alkoxide.

However, the experiment shown in scheme 4.18 refutes this possibility. In that experiment, which was designed to ensure the hydroxyl group removal, we made a carbonate diazolactone which upon warming yielded products similar to the ones observed in the fragmentation of bicyclic diazolactone 4.20-cis in entry 1, table 4.2 and none of the desired ynolide was observed (Scheme 4.18). If this approach was good enough to remove the hydroxyl group, we should have obtained the ten membered ynolide in very good yield, unfortunately this was not the case.

Overall, it is more likely that strain present in the transition state complexes and vinyl diazonium intermediate and any other possible intermediates which were formed...
during the fragmentation of bicyclic lactones disfavor the formation of the ynonolide products. Hence, they were made in lower yields.

In summary, we found that bicyclic diazolactones did not fragment efficiently under standard conditions. We observed that it is less productive to make ynonolides from the fragmentation of bicyclic diazolactones than the corresponding cyclic ynones from bicyclic diazoketones. We discovered the optimum conditions for the fragmentation of bicyclic diazolactones and we were able to make the smallest ynonolides, e.g. ten and eleven membered ynonolides, reported to date. We also noted that it is easier to make larger sized ynonolides than smaller sized ones.

4.12 Future work and perspectives

One of the initial goals of this project was to synthesize lactone natural products (−)-phoracantholide I and (−)-diplodialide C using a ten membered ynonolide as the intermediate (Scheme 4.37). However, low yielding fragmentation of bicyclic lactones and work necessary to optimize the fragmentation reaction did not allow me to focus on this goal. Now that the method for fragmentation of bicyclic diazolactones is optimized, one of my group members took over this project and the application of this method to those natural products syntheses is ongoing.
In addition to (-)-phoracantholide I and (-)-dipodialide C, other ten membered and eleven membered lactone natural products could also be synthesized using the fragmentation of bicyclic diazolactones and these were exemplified in chapter 1, section 1.3.1.

Unfortunately, we were not able to make the twelve membered ynolide because the diazo ester rearranged under the cyclization conditions. However, as shown in scheme 4.29, it should be possible to make twelve membered rings through fragmentation of bicyclos [5.5.0] diazolactone.

For reasons not clear to us, fragmentation of bicyclic diazolactones is not as efficient as their counterpart bicyclic diazoketones. Computational studies might give insight into understanding the fragmentation of this unique system.

Finally, it would be worthwhile to determine if the fragmentation reaction could also be used to make cyclic ynamides such as shown in scheme 4.38. Starting from known alkene 4.55, the secondary tosyl amine could be made in several steps. After p-toluenesulfonylhydrazone glyoxylic acid is coupled to the amine, based on the
procedure developed by Corey and Felix, the diazo group would be created upon treatment with NaH. This would hopefully cyclize spontaneously to provide the bicyclic diazo amide fragmentation precursor. Treatment of the bicyclic diazo amide with SnCl₄ may provide the cyclic ynamide. Cyclic ynamide structures could be used to synthesize cyclic amide natural products.

Scheme 4.38
5.1 General Experimental Information

All reactions were carried out under an atmosphere of nitrogen using flame-dried glassware. A Büchi rotary evaporator equipped with a water condenser and attached to a KNF Neuberger Laboport vacuum system was used to concentrate in vacuo. Samples were further dried under reduced pressure on a high vacuum line.

Tetrahydrofuran (THF), dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}), acetonitrile (CH\textsubscript{3}CN) and diethyl ether (Et\textsubscript{2}O) were dried via a Glass Contour solvent dispensing system.\textsuperscript{208} Triethyl amine and diisopropyl amine were distilled from CaH\textsubscript{2} before use and subsequently distilled under nitrogen and stored in a septum sealed bottle over solid KOH. Commercially available SnCl\textsubscript{4} was distilled twice from P\textsubscript{2}O\textsubscript{5} under inert atmosphere conditions and stored in sealed tubes under an atmosphere of nitrogen as a 1 M solution in CH\textsubscript{2}Cl\textsubscript{2}. All other commercial reagents were purchased from Acros Organics, VWR International, Fluka, Aldrich, Chem-impex.

Flash column chromatography was performed using Merck grade 60 silica gel (230-400 mesh) and TLC analysis was carried out using Merck 60F - 254 silica on glass plates. Visualization of TLC plates was achieved using ultraviolet light, polyphosphomolybdic acid and cerium sulfate in EtOH with H\textsubscript{2}SO\textsubscript{4}, ceric ammonium molybdate, or iodine.
Reactions were cooled to –78 °C via dry ice-acetone baths. 1H and 13C NMR spectra were recorded on a Bruker ARX 500 or a Varian Unity Inova 500 spectrometer in CDCl$_3$. 1H chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane. Solvent peaks were used as internal references for all 13C NMR. Mass spectra were recorded on a LCT Premier (Waters) operated in positive ion electrospray mode by John Greaves at the University of California-Irvine. IR spectrum were recorded on Thermo Nicolet IR 200 Spectrometer with EZ OMNIC Software. Optical rotation of aminoacid derivatives of tethered ynone aldehydes were recorded on AUTOPOL IV Automatic Polarimeter using a path length of 10cm. X-Ray diffraction data were collected on a Bruker APEX 2 CCD platform (MoKα, λ = 0.71073 Å) at set temperature of 135 K. A suitable crystal was mounted in a nylon loop under Paratone-N cryoprotectant oil. Direct methods and standard difference map techniques were used for solution structure followed by refinement using full-matrix least squares procedures on F2 via SHELXTL (version 6.14; Sheldrick, G. M., Acta Cryst. 2008, A64, 112-122).

All α-diazoketones used are known compounds prepared by standard literature procedures by the reaction of diazomethane with the corresponding acid chlorides or mixed carboxylic-carbonic anhydrides: [phenyl],$^{194}$ [benzyloxy],$^{209}$ [2-iodophenyl],$^{210}$ [p-methoxyphenyl],$^{211}$ [ trifluorophenyl],$^{212}$ [ aminoacids],$^{213}$ [n-butyl],$^{214}$ [cyclohexyl],$^{215}$ [t-butyl]$^{216}$. 

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5.2 Experimental Procedures for Chapter 2

2-(tert-butyldimethylsilyloxy)cyclohexanone (2.4): tert-Butyldimethylsilyl chloride (26.31 mmol, 3 equiv) was added to a r.t. mixture of 2-hydroxy cyclohexanone dimer 2.3 (8.77 mmol, 1 equiv), imidazole (35.08 mmole, 4 equiv) and DMAP (1.75 mmol, 0.2 equiv) in dichloromethane (90 ml) and the solution was allowed to stand overnight under an N\textsubscript{2} atmosphere. Aqueous NH\textsubscript{4}Cl solution (80 mL) was added, the layers were separated, and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layers were combined, washed with brine (200 mL), dried over anhydrous MgSO\textsubscript{4}, and the volatiles were removed \textit{in vacuo} to provide an oily residue that was purified by silica gel flash chromatography (Hexane:Ethylacetate 10:1) to afford the known 2-(tert-butyldimethylsilyloxy) cyclohexanone as a colorless oil in 93\% yield. Characterization data matched previously reported values.\textsuperscript{217}

General experimental procedure for the preparation of cyclic γ-silyloxy-β-hydroxy-α-diazoketones (2.1):

A cold (-78 °C) solution of lithium diisopropylamide [prepared by the addition of n-butyllithium in hexanes (0.46 mL, 0.66 mmol) to a solution of diisopropylamine (0.11 mL, 0.75 mmol) in THF (2 mL)] was added via cannula over a period of 30 min to a stirred -78 °C solution of 2-(tert-butyldimethylsilyloxy)cyclohexanone (2.4)\textsuperscript{218} (0.1 g, 0.44 mmol) and an α-diazoketone (0.17 g, 0.70 mmol) in THF (2 mL). The mixture was maintained at -78 °C until complete conversion was achieved as monitored by TLC (ca. 1 h). Saturated aqueous NH\textsubscript{4}Cl solution (10 mL) was added to the cold reaction
mixture and upon reaching room temperature the mixture was diluted further with saturated aqueous NH₄Cl. The aqueous layer was extracted three times with EtOAc (15 mL), the combined organic layers were washed with brine (50 mL), dried over anhydrous CaCl₂, and concentrated under reduced pressure to provide the desired product as a separable mixture of diastereomers. The residue was subjected to flash silica gel chromatography to afford the γ-silyloxy-β-hydroxy-α-diazoketone products.

**Characterization data for cyclic γ-silyloxy-β-hydroxy-α-diazoketones:**

The cyclic γ-silyloxy-β-hydroxy-α-diazoketone fragmentation precursors were formed as separable mixtures of diastereomers. Most of the fragmentation reactions were performed on the isolated major diastereomer, and the characterization data is reported for these diastereomers only. The fragmentation precursors derived from Cbz protected valine and proline were obtained as a 1:1 mixture of diastereomers that were carried onto the fragmentation as a mixture. In these cases, characterization data is provided for both of the diastereomers.

**1-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-1-diazohexan-2-one**

(2.7): Obtained as a 4:1 ratio of diastereomers in 66% yield. Purification by silica gel flash column chromatography (5:1 Hexane:Ethylacetate) afforded the major diastereomer in 51% yield. ¹H NMR (500 MHz, CDCl₃) δ 4.17 (dd, J = 10.8, 5.3 Hz, 1H), 3.20 (d, J = 2.1 Hz, 1H), 2.47 (ddd, J = 15.2, 8.1, 7.1 Hz, 1H ), 2.38 (ddd, J = 15.1, 8.1, 6.8 Hz, 1H), 2.11 (tt, J = 13.5, 2.3 Hz, 1H), 1.83-1.26 (m, 11H), 0.91(t, J = 7.3 Hz, 3H), 0.87(s, 9H), 0.05 (s,3H), -0.02(s,3H);
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 193.5, 75.0, 72.2, 71.6, 39.1, 33.5, 31.4, 26.7, 25.9, 23.8, 22.6, 21.0, 17.9, 14.0, -4.3, -5.1; MS (ESI): Calculated for [C$_{18}$H$_{34}$O$_3$N$_2$SiNa]$^+$: 377.2236, Found: 377.2230.

2-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-1-cyclohexyl-2-diazoethanone (2.9): Obtained as a 9:1 ratio of diastereomers in 85% yield. Purification by silica gel flash column chromatography (5:1 Hexane:Et$_2$O) afforded the major diastereomer in 78% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.20 (dd, $J = 10.6, 5.7$ Hz, 1H), 3.23 (d, $J = 2.1$ Hz, 1H), 2.47 (tt, $J = 11.5, 3.3$ Hz, 1H), 2.10 (tt, $J = 13.6, 2.2$ Hz, 1H), 1.81 – 1.18 (m, 17H), 0.9 (s, 9H), 0.04 (s, 3H), -0.03 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 197.0, 73.8, 72.1, 71.6, 47.2, 33.5, 31.5, 29.7, 28.4, 26.0, 25.9, 25.7, 23.7, 21.0, 18.0, -4.0, -4.7; MS (ESI): Calculated for [C$_{20}$H$_{36}$N$_2$O$_3$SiNa]$^+$: 403.2393, Found: 403.2379.

1-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-1-diazo-3,3-dimethylbutan-2-one (2.11): Formed in 50% yield as a 4:1 ratio of diastereomers. Purification by silica gel flash column chromatography (12:1 Hexane:Ethylacetate) afforded the major diastereomer in 30% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.29 (dd, $J = 10.9, 5.4$ Hz, 1H), 3.24 (d, $J = 2.2$ Hz, 1H), 2.09 (tt, $J = 13.8, 2.4$ Hz, 1H), 1.77 (d, $J = 12.3$ Hz, 2H), 1.66-1.46 (m, 5H), 1.24(s, 9H), 0.90(s, 9H), 0.05 (s,3H), -0.09(s,3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 199.3, 72.7, 71.4, 70.8, 44.7, 33.3, 31.7, 27.0, 26.0, 23.8, 21.2, 17.9, -3.7, -4.6; MS (ESI): Calculated for [C$_{18}$H$_{34}$O$_3$N$_2$SiNa]$^+$: 377.2236, Found: 377.2230.
3-(benzyloxy)-1-(2-(tert-butyldimethyldimethylsilyloxy)-1-hydroxycyclohexyl)-1-diazo propan-2-one (2.13): Obtained as a 4:1 ratio of diastereomers in 46% yield. Purification by silica gel flash column chromatography (8:1 Hexane:EtO) afforded the major diastereomer in 35% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37-7.30 (m, 5H), 5.10 (s, 1H), 4.58 (d, $J = 20.4$ Hz, 1H), 4.54 (d, $J = 20.0$ Hz, 1H), 4.21 (d, $J = 31.2$ Hz, 1H), 4.14 (d, $J = 31.6$ Hz, 1H), 3.98 (s, 1H), 1.93 (t, $J = 12.2$ Hz, 1H), 1.81-1.68 (m, 2H), 1.60-1.49 (m, 4H), 1.39 (d, $J = 13.0$ Hz, 1H), 0.88 (s, 9H), 0.03 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 193.5, 136.6, 128.5, 128.1, 128.0, 74.5, 74.3, 73.8, 72.4, 72.0, 29.3, 28.9, 25.9, 20.4, 19.1, 18.0, -4.5, -5.0; MS (ESI): Calculated for [C$_{22}$H$_{34}$O$_4$N$_2$SiNa]$^+$: 441.2186, Found: 441.2186.

2-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-2-diazo-1-phenylethanone (2.17): Obtained as a 9:1 ratio of diastereomers in 83% yield. The major diastereomer was isolated via column chromatography (16:1 Hexane:Ethylacetate) and subsequent recrystallization from MeOH at 0°C in 49% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.56-7.54 (m, 2H), 7.48 (tt, $J = 7.2$, 2.2 Hz, 1H), 7.42 (t, $J = 7.2$ Hz, 2H), 4.41 (dd, $J = 10.6$, 5.3 Hz, 1H), 3.20 (d, $J = 2.3$ Hz, 1H), 2.26 (tq, $J = 11.8$, 2.4 Hz, 1H), 1.95 (d, $J = 11.0$ Hz, 1H), 1.82-1.36 (m, 6H), 0.87 (s, 9H), 0.08 (s, 3H), -0.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.8, 138.8, 131.6, 128.8, 127.4, 75.3, 72.9, 71.6, 33.5, 31.6, 25.9, 23.8, 21.1, 18.0, -4.0, -4.6; MS (ESI): Calculated for [C$_{20}$H$_{30}$O$_3$N$_2$SiNa]$^+$: 397.1924, Found: 397.1931.
2-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-2-diazo-1-(4-methoxy phenyl) ethanone (2.19): Purification by silica gel flash column chromatography (12:1 Hexane:Ethylacetate) afforded the major diastereomer in 88% yield. \( ^1 \text{H NMR} \) (500 MHz, \( \text{CDCl}_3 \)) \( \delta \) 7.55 (d, \( J = 9.0 \) Hz, 2H), 6.91 (d, \( J = 8.5 \) Hz, 2H), 4.41 (dd, \( J = 10.6, 5.1 \) Hz, 1H), 3.85 (s, 3H), 3.31 (d, \( J = 2.1 \) Hz, 1H), 2.24 (t, \( J = 12.5 \) Hz, 1H), 1.95 (d, \( J = 11.8 \) Hz, 1H), 1.82-1.38 (m, 6H), 0.86 (s, 9H), 0.07 (s, 3H), -0.03 (s, 3H); \( ^{13} \text{C NMR} \) (125 MHz, \( \text{CDCl}_3 \)) \( \delta \) 187.9, 162.3, 131.4, 129.4, 113.9, 74.4, 72.9, 71.6, 55.6, 33.5, 31.5, 25.9, 23.8, 21.1, 17.9, -4.1, -4.7; MS (ESI): Calculated for \([\text{C}_{21}\text{H}_{32}\text{O}_4\text{N}_2\text{SiNa}]^+\): 427.2029, Found: 427.2023.

2-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-2-diazo-1-(2-iodophenyl) ethanone (2.21): Obtained as a 10:4.7 ratio of diastereomers in 70% yield. Purification by silica gel flash column chromatography (20:1 Hexane:Ethylacetate) followed by trituration in MeOH afforded the major diastereomer in 49% yield. \( ^1 \text{H NMR} \) (500 MHz, \( \text{CDCl}_3 \)) \( \delta \) 7.84 (d, \( J = 8.7 \) Hz, 1H), 7.39 (t, \( J = 7.4 \) Hz, 1H), 7.26 (dd, \( J = 7.4, 1.4 \) Hz, 1H), 7.09 (td, \( J = 7.6, 1.6 \) Hz, 1H), 4.39 (dd, \( J = 10.8, 4.9 \) Hz, 1H), 3.29 (d, \( J = 1.8 \) Hz, 1H), 2.31 (t, \( J = 12.5 \) Hz, 1H), 2.09 (dd, \( J = 13.9, 2.3 \) Hz, 1H), 1.82 (d, \( J = 12.9 \) Hz, 1H), 1.71-1.55 (m, 4H), 1.42 (qt, \( J = 12.9, 3.2 \) Hz, 1H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); \( ^{13} \text{C NMR} \) (125 MHz, \( \text{CDCl}_3 \)) \( \delta \) 189.3, 143.9, 140.1, 131.3, 128.6, 127.5, 92.2, 72.9, 71.9, 33.3, 31.6, 25.9, 23.7, 20.9, 18.1, -3.8, -4.4; MS (ESI): Calculated for \([\text{C}_{20}\text{H}_{29}\text{O}_3\text{N}_2\text{SiNa}]^+\): 523.0890, Found: 523.0902.
2-(2-\((\text{tert-butyldimethylsilyloxy})\)-1-hydroxycyclohexyl)-2-diazo-1-(4-(trifluoromethyl) phenyl)ethanone (2.23): Obtained as a 10:1.5 ratio of diastereomers in 77% yield. Purification by silica gel flash column chromatography (12:1 Hexane:Ethylacetate) afforded the major diastereomer in 66% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.71-7.56 (m, 4H), 4.39 (dd, $J = 10.9$, 5.7 Hz, 1H), 3.30 (d, $J = 2.2$ Hz, 1H), 2.25 (tq, $J = 13.4$, 2.3 Hz, 1H), 1.96 (d, $J = 14.2$ Hz, 1H), 1.81 (d, $J = 13.2$ Hz, 1H), 1.71 (d, $J = 13.4$ Hz, 1H), 1.66-1.52 (m, 3H), 1.44-1.35 (m, 1H), 0.87 (s, 9H), 0.09 (s, 3H), -0.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 187.2, 141.7, 133.2 (q, $J = 32.7$ Hz, F$_3$C-C), 127.7, 125.9 (q, $J = 3.7$ Hz, F$_3$C-C-CH), 123.8 (q, $J = 273.2$ Hz, F$_3$C), 76.1, 73.1, 71.6, 33.5, 31.5, 25.9, 23.8, 21.1, 18.0, -4.0, -4.7; MS (ESI): Calculated for [C$_{21}$H$_{29}$F$_3$O$_3$N$_2$SiNa]$^+$: 465.1797, Found: 465.1797.

Benzyl(S)-1-(2-(\(\text{tert-butyldimethylsilyloxy}\))-1-hydroxycyclohexyl)-1-diazo-4-methyl-2-oxopentan-3-ylcarbamate (2.30): Obtained as a 5:4 ratio of diastereomers. Purification by silica gel flash column chromatography (gradient elution 100% Hexanes to 10:1 Hexane:Ethylacetate) afforded the mixture of two diastereomers in 80% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38-7.28 (m, 5H), 5.54 (d, $J = 9.1$ Hz, 1H), 5.11 (d, $J = 12.4$ Hz, 1H), 5.05 (d, $J = 12.7$ Hz, 1H), 4.43 (dd, $J = 9.1$, 5.7 Hz, 1H), 4.17 (dd, $J = 10.9$, 5.4 Hz, 1H), 3.20 (d, $J = 1.9$ Hz, 1H), 2.08 (t, $J = 13.6$ Hz, 1H), 2.00-1.94 (m, 1H), 1.81 (d, $J = 13.6$ Hz, 1H), 1.75-1.27 (m, 6H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H), 0.83 (s, 9H), -0.01 (s, 3H), -0.14 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$
191.7, 156.4, 136.5, 128.7, 128.4, 128.4, 128.4, 128.4, 72.6, 72.4, 67.2, 60.7, 33.7, 31.7, 31.3, 25.9, 23.6, 20.9, 20.1, 18.0, 16.9, -3.3, -4.8; MS (ESI): Calculated for [C_{26}H_{41}O_{5}N_{3}SiNa]^+: 526.2713, Found: 526.2720. Observed Resonances from the Minor Diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33-7.28 (m, 5H), 5.42 (d, $J = 8.9$ Hz, 1H), 5.24 (s, 2H), 4.42 (d, $J = 4.5$ Hz, 1H), 4.08 (dd, $J = 10.7$, 5.1 Hz, 1H), 3.44 (s, 1H), 1.99-1.23 (m, 9H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.84 (s, 11H), 0.81(s, 1H), 0.05 (s, 3H), -0.02 (s, 3H).

(S)-benzyl2-(2-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-2-diazoacetyl) pyrrolidine-1-carboxylate (2.32): Formed as a 1:1 mixture of two diastereomers in 70 % yield. Separation by silica gel flash column chromatography (gradient elution 10:1 to 8:1 Hexane:Ethylacetate) provided pure diastereomers. $^1$H and $^{13}$C NMR spectrums show each diastereomer as a mixture of two carbamate rotamers. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.26 (m, 5H), 5.27 (d, $J = 12.7$ Hz, 0.5H), 5.13 (d, $J = 12.3$ Hz, 0.5H), 5.12 (d, $J = 12.6$ Hz, 0.5H), 4.97 (d, $J = 12.7$ Hz, 0.5H), 4.64 (dd, $J = 8.1$, 2.2 Hz, 0.5H), 4.55 (dd, $J = 8.1$, 3.4 Hz, 0.5H), 4.19 (dd, $J = 10.7$, 5.1 Hz, 0.5H), 4.13 (dd, $J = 10.9$, 5.4 Hz, 0.5H), 3.62-3.46 (m, 2H), 3.33 (s, 0.5H), 3.26 (s, 0.5H), 2.28-1.26 (m, 12H), 0.89 (s, 5H), 0.83 (s, 4H), 0.09 (s, 2H), 0.06 (s, 2H), 0.01 (s, 1H), -0.07 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.8, 192.5, 154.8, 154.6, 136.9, 136.8, 128.6, 128.1, 128.1, 128.0, 127.9, 72.5, 72.4, 71.9, 71.8, 71.4, 67.1, 67.1, 63.5, 62.6, 47.1, 46.6, 33.4, 33.2, 31.6, 31.5, 31.3, 30.0, 25.9, 25.8, 24.4, 23.7, 23.5, 21.0, 17.9, 17.8, -4.16, -4.29, -4.82, -4.87; MS (ESI): Calculated for [C_{26}H_{39}O_{5}N_{3}SiNa]^+: 524.2557, Found: 524.2555.
Observed Resonances from the Minor Diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.26 (m, 5H), 5.20-5.03 (m, 2H), 4.62 (dd, $J = 7.6$, 2.7 Hz, 0.5H), 4.53 (dd, $J = 8.2$, 3.5 Hz, 0.5H), 4.25 (dd, $J = 10.5$, 4.9 Hz, 0.5H), 4.18-4.14 (m, 0.5H), 3.63-3.49 (m, 2H), 3.19 (d, $J = 1.8$ Hz, 0.5H), 3.10 (d, $J = 1.0$ Hz, 0.5H), 2.17-1.43 (m, 12H), 0.88 (s, 4H), 0.86 (s, 5H), 0.07 (s, 2H), 0.05 (s, 2H), 0.01 (s, 1H), -0.02 (s, 1H).

**Benzyl (S)-4-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-4-diazo-3-oxo-1-phenylbutan-2-ylcarbamate (2.34):** Obtained as a 3:2 ratio of diastereomers in 76% yield. Purification by silica gel flash column chromatography (gradient elution 100% Hexane to 10:1 Hexane:Ethylacetate) afforded the major diastereomer in 42% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37-7.23 (m, 8H), 7.15 (d, $J = 7.1$ Hz, 2H), 5.59 (d, $J = 8.5$ Hz, 1H), 5.10 (d, $J = 12.4$ Hz, 1H), 5.09 (d, $J = 12.2$ Hz, 1H), 4.75 (td, $J = 8.4$, 5.6 Hz, 1H), 4.12 (dd, $J = 10.9$, 5.4 Hz, 1H), 3.07 (d, $J = 2.2$ Hz, 1H), 3.02 (dd, $J = 13.2$, 5.2 Hz, 1H), 2.93 (dd, $J = 13.2$, 8.5 Hz, 1H), 1.94 (t, $J = 13.7$ Hz, 1H), 1.70 (d, $J = 10.3$ Hz, 1H), 1.61 (t, $J = 9.3$ Hz, 2H), 1.52-1.42 (m, 3H), 1.32-1.24 (m, 1H), 0.80 (s, 9H), -0.02 (s, 3H), -0.14 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 190.1, 155.4, 136.6, 135.6, 129.7, 128.6, 128.5, 128.2, 128.1, 127.3, 76.2, 72.1, 71.1, 66.9, 56.5, 40.5, 32.9, 31.2, 25.7, 23.6, 20.8, 17.8; MS (ESI): Calculated for [C$_{30}$H$_{41}$O$_5$N$_3$SiN$_3$Na]$^+$: 574.2713, Found: 574.2718. Observed Resonances from the Minor Diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34-7.27 (m, 8H), 7.17 (d, $J = 6.9$ Hz, 2H), 5.30 (d, $J = 8.7$ Hz, 1H), 5.01 (d, $J = 11.7$ Hz, 1H), 5.00 (d, $J = 12.4$ Hz, 1H), 4.74 (broad s, 1H), 4.14-4.08(m, 1H), 3.47 (s, 1H), 3.04 (dd, $J = 13.7$, 5.2 Hz, 1H), 2.79 (dd, $J = 13.9$, 8.7 Hz,
1H), 1.95-1.24 (m, 8H), 0.85 (s, 9H), 0.05 (s, 3H), -0.04 (s, 3H); 13C NMR (125 MHz, CDCl$_3$) $\delta$ 191.0, 155.7, 136.4, 129.5, 128.7, 128.6, 128.2, 128.1, 127.1, 74.6, 72.7, 71.9, 66.9, 57.2, 38.8, 33.6, 31.2, 25.8, 23.6, 20.8, 17.9, -3.7, -4.8.

tert-butyl(S)-1-(2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-1-diazo-4-methyl-2-oxopentan-3-ylcarbamate (2.38): Obtained as a 3:2 ratio of diastereomers in 69% yield. Purification by silica gel flash column chromatography (gradient elution 100% Hexane to 10:1 Hexane:Ethylacetate) afforded the major diastereomer in 39% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.24 (d, $J = 8.8$ Hz, 1H), 4.39 (dd, $J = 9.2$, 5.4 Hz, 1H), 4.18 (dd, $J = 11.0$, 5.2 Hz, 1H), 3.19 (d, $J = 2.1$ Hz, 1H), 2.10 (tq, $J = 13.6$, 2.2 Hz, 1H), 1.94 (sextet, $J = 6.4$ Hz, 1H), 1.81 (d, $J = 13.9$ Hz, 1H), 1.73 (d, $J = 12.4$ Hz, 1H), 1.66 (dq, $J = 12.5$, 2.7 Hz, 1H), 1.62-1.45 (m, 4H), 1.42 (s, 9H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 7.1$ Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), -0.05 (s, 3H); 13C NMR (125 MHz, CDCl$_3$) $\delta$ 191.9, 155.4, 79.4, 75.2, 72.2, 71.3, 59.7, 33.1, 32.3, 31.2, 28.5, 25.9, 23.7, 20.9, 19.3, 17.9, 17.4, -4.2, -5.0; MS (ESI): Calculated for [C$_{23}$H$_{43}$O$_5$N$_3$SiNa]$^+$: 492.2870, Found: 492.2868.

**General procedure for the preparation of tethered aldehyde ynone:**

SnCl$_4$ (0.21 mL of a 1M solution in CH$_2$Cl$_2$, 0.21 mmol) was added in a steady stream to a 0 °C solution of the cyclic $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazo ketone (2) (0.21 mmole, 1 equiv) in anhydrous CH$_2$Cl$_2$ (2 mL) under a nitrogen atmosphere. The yellow solution turned colorless and gas evolution was observed. After 10 minutes (some
compounds require 30 minutes), saturated aqueous NaHCO$_3$ (10 mL) was added and the mixture was transferred with the aid of CH$_2$Cl$_2$ (10 mL) into a separatory funnel containing additional saturated aqueous NaHCO$_3$ (10 mL). The layers were separated and the aqueous layer was extracted three times with CH$_2$Cl$_2$ (20 mL). The organic layers were combined, washed with water (80 mL), brine (80 mL) and dried over anhydrous CaCl$_2$. The solvents were removed in vacuo and the residue was subjected to flash silica gel chromatography to afford the pure tethered ynone aldehyde.

For the fragmentation of the amino acid derived cyclic $\gamma$-silyloxy-$\beta$-hydroxy-$\alpha$-diazoketones, the following modification was made: the reaction was worked up with water (10 ml) instead of aqueous NaHCO$_3$. The tethered aldehyde yrones of these substrates were isolated in lower yield under basic workup conditions. Davisil® Silica Gel 200-425 Mesh was used to purify these compounds.

**Characterization data for tethered-aldehyde-yrones:**

**8-oxododec-6-ynal (2.8):** The flash silica gel chromatography (5:1 Hexane:Ethylacetate) afforded the title ynone aldehyde in 82% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.78 (t, $J = 1.4$ Hz, 1H), 2.53 (td, $J = 7.3$, 1.1 Hz, 2H), 2.49 (t, $J = 7.1$ Hz, 2H), 2.41 (td, $J = 7.1$, 1.0 Hz, 2H), 1.76 (quintet, $J = 7.5$ Hz, 2H), 1.67-1.60 ( m, 4H), 1.35 (sextet, $J = 6.3$, 1.0 Hz, 2H), 0.92 (td, $J = 7.5$, 1.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.9, 188.6, 93.1, 81.5, 45.4, 43.4, 29.9, 27.3, 26.4, 21.4, 18.9, 13.9; IR (film): 2932.6, 2212.9, 1707.5, 1669.8 cm$^{-1}$; MS (ESI): Calculated for [C$_{12}$H$_{18}$O$_2$Na]$^+$: 217.1205, Found: 217.1204. *Observed peaks for n-*
**butyl-ynone-Carboxylic acid:** $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 178.5, 93.2, 81.4, 27.2, 24.1, 18.9.

**8-cyclohexyl-8-oxooct-6-ynal (2.10):** The flash silica gel chromatography (4:1 Hexane:Ethylacetate) afforded the title ynone aldehyde in 83% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.78 (s, 1H), 2.50 (t, $J = 7.2$, 2H), 2.41 (t, $J = 7.2$, 2H), 2.36 (tt, $J = 10.6$, 3.7 Hz, 1H), 1.96 (d, $J = 10.4$ Hz, 1H), 1.80- 1.74 (m, 3H), 1.65-1.61 (m, 4H), 1.40 (qd, $J = 11.7$, 2.6 Hz, 2H), 1.45-1.19 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.7, 191.5, 93.6, 80.5, 52.2, 43.2, 28.2, 27.1, 25.8, 25.3, 21.2, 18.8; IR (film): 2929, 2854, 2209, 1706, 1664 cm$^{-1}$; MS (ESI): Calculated for [C$_{14}$H$_{20}$O$_2$Na]$^+$: 243.1361, Found: 243.1362.

**9,9-dimethyl-8-oxodec-6-ynal (2.12):** The flash silica gel chromatography (4:1 Hexane:Ethylacetate) afforded the title ynone aldehyde in 80% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.78 (app. s, $J = 1.3$ Hz, 1H), 2.50 (t, $J = 7.2$, 2H), 2.43 (t, $J = 7.0$, 2H), 1.79–1.76 (m, 2H), 1.67–1.63 (m, 2H), 1.19 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.6, 194.2, 94.4, 79.1, 44.5, 43.1, 27.4, 26.2, 21.4, 19.0; IR (film): 2930, 2209, 1722, 1665 cm$^{-1}$; MS (ESI): Calculated for [C$_{12}$H$_{18}$O$_2$Na]$^+$: 217.1205, Found: 217.1206.

**9-(benzyloxy)-8-oxonon-6-ynal (2.14):** The flash silica gel chromatography (5:1 Hexane:Ethylacetate) afforded the title ynone aldehyde in 50% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.76 (s, 1H), 7.37- 7.26 (m, 5H), 4.64 (s, 2H), 4.19 (s, 2H), 2.46 (td, $J = 7.1$, 1.25 Hz, 2H), 2.41 (t, $J = 7.0$ Hz, 2H), 1.77-
1.71 (m, 2H), 1.64-1.58 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.8, 185.2, 137.3, 128.7, 128.2, 128.1, 96.5, 79.2, 75.9, 73.5, 43.3, 27.1, 21.3, 19.1; IR (film): 2924.9, 2208.8, 2093.3, 1719.4, 1687.9 cm$^{-1}$; MS (ESI): Calculated for [C$_{16}$H$_{18}$O$_3$Na]$^+$: 281.1154, Found: 281.1156.

8-oxo-8-phenyloct-6-ynal (2.18): The flash silica gel chromatography (2.5:1 Hexane:Ethylacetate) afforded the title ynone aldehyde in 60 % yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.80 (d, $J = 1.1$ Hz, 1H), 8.13 (d, $J = 8.1$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 2H), 2.54 (q, $J = 7.1$ Hz, 4H), 1.87-1.81 (m, 2H), 1.76-1.70 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.8, 178.2, 137.0, 134.2, 129.7, 128.7, 95.8, 80.2, 43.4, 27.4, 21.5, 19.3; IR (film): 2933.8, 2234.4, 2201.1, 1720.5, 1639.8, 1596.3 cm$^{-1}$; MS (ESI): Calculated for [C$_{14}$H$_{14}$O$_3$NH$_4$]$^+$: 232.1338, Found: 232.1331.

8-(4-methoxyphenyl)-8-oxooct-6-ynal (2.20): The flash silica gel chromatography (3:1 Hexane:Ethylacetate) afforded the title ynone aldehyde in 70 % yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.80 (s, 1H), 8.10 (d, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 8.6$ Hz, 2H), 3.89 (s, 3H), 2.53 (t, $J = 7.1$ Hz, 4H), 1.86-1.80 (m, 2H), 1.76-1.69 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 202.1, 176.9, 164.5, 132.1, 130.3, 113.9, 94.9, 80.1, 55.7, 43.4, 27.4, 21.4, 19.1; IR (film): 2925.9, 2844.9, 2360.6, 2341.2, 2236.6, 2199.8, 1718.9, 1634.9, 1594.5 cm$^{-1}$; MS (ESI): Calculated for [C$_{15}$H$_{16}$O$_3$Na]$^+$: 267.099, Found: 267.100. Observed peaks for p-
methoxy -aryl-ynone-Carboxylic acid: $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.1, 95.0, 80.1, 33.4, 31.7, 31.1, 24.1, 22.8, 19.1, 14.3.

8-(2-iodophenyl)-8-oxoct-6-ynal (2.22): The flash silica gel chromatography (8:1:0.1 Hexane:Ethylacetate:Acetic acid) afforded the title ynone aldehyde in 69 % yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.79 (t, $J = 1.3$ Hz, 1H), 8.04 (qd, $J = 7.9, 1.7$ Hz, 2H), 7.47 (td, $J = 7.6, 1.0$ Hz, 1H), 7.18 (td, $J = 8.0, 1.5$ Hz, 1H), 2.52 (tq, $J = 6.9, 1.7$ Hz, 4H), 1.84- 1.78 (m, 2H), 1.73-1.67 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.9, 178.2, 142.3, 139.4, 133.5, 133.3, 128.2, 97.2, 92.8, 80.5, 43.4, 27.2, 21.5, 19.4; IR (film); 2924.2, 2856.1, 2202.2, 1719.5, 1647.3; MS (ESI): Calculated for [C$_{14}$H$_{13}$I$_2$O$_2$Na]$^+$: 362.9858, Found: 362.9854.

8-oxo-8-(4-(trifluoromethyl)phenyl)oct-6-ynal (2.24): The flash silica gel chromatography (4:1 Hexane:Ethylacetate) afforded the title ynone aldehyde in 41 % yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.81 (t, $J = 1.4$ Hz, 1H), 8.24 (d, $J = 8.3$ Hz, 2H), 7.75 (d, $J = 7.8$ Hz, 2H), 2.57 (t, $J = 7.1$ Hz, 2H), 2.55 (td, $J = 7.1, 1.03$ Hz, 2H), 1.87- 1.81 (m, 2H), 1.77- 1.71 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.8, 177.0, 139.5, 135.0 (q, $J = 32.7$ Hz, F$_3$C-C-), 130.0, 125.8 (q, $J = 3.7$ Hz, F$_3$C-C=CH), 123.7 (q, $J = 274.4$ Hz, F$_3$C-), 97.3, 79.9, 43.4, 29.7, 27.4, 21.5, 19.4; IR (film); 2923.9, 2238.2, 2201.1, 1722.1, 1650.2; MS (ESI): Calculated for [C$_{15}$H$_{13}$F$_3$O$_2$Na]$^+$: 305.0765, Found: 305.0762.
(S)-benzyl 2-methyl-4,11-dioxoundec-5-yn-3-ylcarbamate (2.31): The flash chromatography (5:1 to 4:1 Hexane:Ethylacetate) on a Davisil® solid support provided the title ynone aldehyde in 69% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.77 (t, J = 1.4 Hz, 1H), 7.42-7.30 (m, 5H), 5.35 (d, J = 8.4 Hz, 1H), 5.12 (d, J = 12.3 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 4.44 (dd, J = 8.9, 3.8 Hz, 1H), 2.48 (td, J = 7.1, 1.2 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H), 1.77-1.71 (m, 2H), 1.67-1.59 (m, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.8, 186.6, 156.6, 136.5, 128.7, 128.4, 128.3, 97.3, 80.0, 67.2, 66.5, 43.3, 30.6, 27.1, 21.3, 19.9, 19.2, 16.7; IR (film); 3340.0, 2961.2, 2932.6, 2360.9, 2209.5, 1705.8, 1673.8; MS (ESI): Calculated for [C$_{20}$H$_{25}$O$_4$NNa]$^+$: 366.1681, Found: 366.1681.

(S)-benzyl 2-(8-oxooct-2-ynoyl)pyrrolidine-1-carboxylate (2.33): The flash chromatography (3:1 to 1:1 Hexane:Ethylacetate) on a Davisil® solid support provided the title ynone aldehyde in 62% yield. Both the $^1$H and $^{13}$C NMR show the presence of two carbamate rotamers in solution at room temperature. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.76 (s, 1H), 7.39-7.26 (m, 5H), 5.16 (s, 1H), 5.11 (dd, J = 16.7, 12.6 Hz, 1H), 4.49 (dd, J = 8.7, 4.1 Hz, 0.5H), 4.36 (dd, J = 8.7, 4.8 Hz, 0.5H), 3.60 (t, J = 6.8 Hz, 1.5H), 3.57-3.49 (m, 0.5H), 2.45 (t, J = 7.2 Hz, 2H), 2.37 (t, J = 6.9 Hz, 1H), 2.32 (t, J = 7.0 Hz, 1H), 2.29-2.16 (m, 1H), 2.10-2.05 (m, 1H), 1.97-1.85 (m, 2H), 1.75-1.65 (m, 2H), 1.61-1.50 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 201.9, 187.6, 186.9, 155.1, 154.5, 136.8, 136.5, 128.5, 128.4, 128.05, 128.0, 96.9, 96.8, 79.4, 79.36, 67.26, 67.2, 67.1, 66.6, 47.4, 46.8, 43.2, 30.5, 29.2, 27.1, 24.2,
23.6, 21.3, 19.0; IR (film); 2949.1, 2360.6, 2209.6, 1701.2, 1411.9; MS (ESI): Calculated for [C_{20}H_{23}O_{4}NNa]^+: 364.1525, Found: 364.1534. Observed peaks for Cbz-N-Proline-ynone-Carboxylic acid: $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.6, 177.5, 155.1, 154.6, 136.4, 96.5, 96.3, 78.98, 78.9, 67.3, 53.6, 33.4, 33.3, 27.1, 23.9, 18.9.

(S)-benzyl 3,10-dioxo-1-phenyldec-4-yn-2-ylcarbamate (2.35): The flash chromatography (4:1 to 3:1 Hexane:Ethylacetate) on a Davisil® solid support provided the title ynone aldehyde in 74 % yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.77 (s, 1H), 7.36-7.21 (m, 8H), 7.13 (d, $J$ = 7.5 Hz, 2H), 5.30 (d, $J$ = 7.8 Hz, 1H), 5.09 (s, 2H), 4.71 (dd, $J$ = 13.5, 6.1 Hz, 1H), 3.25 (dd, $J$ = 14.2, 5.7 Hz, 1H), 3.19 (dd, $J$ = 14.1, 5.9 Hz, 1H), 2.47 (t, $J$ = 7.1 Hz, 2H), 2.40 (t, $J$ = 6.9 Hz, 2H), 1.76-1.70 (m, 2H), 1.63-1.57 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.8, 185.5, 155.7, 136.4, 135.6, 129.6, 128.7, 128.6, 128.3, 128.2, 98.1, 79.6, 67.1, 62.4, 43.2, 37.3, 33.1, 27.1, 23.9, 21.3, 19.1; IR (film); 3323.1, 2933.5, 2210.7, 1701.6, 1674.3; MS (ESI): Calculated for [C$_{24}$H$_{25}$O$_4$NNa]$^+$: 414.1681, Found: 414.1687.

(S)-tert-butyl 2-methyl-4,11-dioxoundec-5-yn-3-ylcarbamate (2.39): The flash chromatography (4:1 Hexane:Ethylacetate) on a Davisil® solid support provided the title ynone aldehyde in 36 % yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.79 (s, 1H), 5.10 (d, $J$ = 8.1 Hz, 1H), 4.36 (dd, $J$ = 8.7, 3.4 Hz, 1H), 2.50 (td, $J$ = 6.9, 1.1 Hz, 2H), 2.44 (t, $J$ = 6.9 Hz, 2H), 1.76 (quintet, $J$ = 7.4 Hz, 2H), 1.67-1.61 (m, 3H), 1.44 (s, 9H), 1.03 (d, $J$ = 6.9 Hz, 3H), 0.83 (d, $J$ = 6.5 Hz, 3H); $^{13}$C...
NMR (125 MHz, CDCl$_3$) $\delta$ 201.8, 187.2, 155.9, 96.9, 80.2, 80.0, 66.1, 43.3, 30.5, 28.5, 27.2, 21.4, 19.9, 19.2, 16.8; IR (film); 3342.6, 2964.2, 2931.3, 2210.1, 1706.5, 1673.2; MS (ESI): Calculated for [C$_{17}$H$_{27}$O$_4$NNa]$^+$: 332.1838, Found: 332.1837.

5.3 Experimental Procedures for Chapter 3

**Methyl 3-(1-(tert-butyldimethylsilyloxy)-2-oxocyclohexyl)propanoate (3.7)**

A mixture of 4 A° molecular sieves (1.0575 g), basic aluminum oxide (0.2327 g) and silica gel (0.1142 g) was flame dried under vacuum for 10 minutes, cooled to room temperature and suspended in 3 mL cyclohexane. 2-(tert-butyldimethylsilyloxy)cyclohexanone 2.4 (0.9641 g, 4.23 mmol) in 2 mL cyclohexane was added followed by addition of (R)-(+) -phenylethylamine (0.5637 g, 4.65 mmol) into suspension. The mixture was stirred for 24 h (reaction was monitored by 1H NMR in CDCl$_3$). The mixture was filtered off and the solvent was removed under reduced pressure to give crude imine. The crude imine (1.4291 g, 4.32 mmol) was mixed with methyl acrylate (6 mL, 0.066 mmol) and stirred at room temperature for 48 hours. The excess methyl acrylate was removed under vacuum to yield crude imine. The crude oily imine was dissolved in 3 mL THF and mixed with 20% aqueous acetic acid (3 mL) at 0 °C. The mixture was stirred for 5 hours at room temperature at which point the solvent was removed under reduced pressure to give an oily residue. The oily residue was dissolved in 20 mL Et$_2$O and mixed with 1M aqueous HCl (5 mL) solution. The resultant layers were separated and aqueous layer was washed with Et$_2$O (3 x 20 mL). Combined organic layers were washed with saturated NaHCO$_3$ (3 x 50 mL), brine (2 x 30 mL) and dried over anhydrous MgSO$_4$, 154
filtered and solvent was reduced under reduced pressure to give title compound as oily residue. The crude compound was isolated using flash silica gel column chromatography (hexanes:EtOAc 30:1, 10:1; Rf = 0.50 in hexanes:EtOAc 2:1) (0.90 g) 60% yield. 1H NMR (500 MHz, CDCl$_3$) δ 3.66 (s, 3H), 2.53–2.39 (m, 3H), 2.24–2.16 (m, 2H), 1.98–1.92 (m, 3H), 1.85–1.63 (m, 4H), 0.88 (s, 9H), 0.18 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 211.4, 174.2, 174.1, 81.4, 51.8, 41.5, 39.6, 33.3, 28.3, 27.5, 26.1, 22.7, 18.7, -2.4, -2.7.

3-(1-(tert-butyldimethylsilyloxy)-2-oxocyclohexyl) propanoic acid (3.8):

Ketone 3.7 (8.6545 g, 27.6 mmol) was dissolved in 140 mL MeOH and cooled down to 0 °C in ice bath. LiOH (1.3198 g, 55.1 mmol) in 40 mL distilled water was mixed and it was stirred at room temperature for 3 hour at which point methanol was removed under reduced pressure. The remaining aqueous mixture was cooled down to 0 °C and 1M HCl (6 mL) was mixed until pH became acidic which is determined via change in the color of Litmus paper. The aqueous mixture was extracted with Et$_2$O (4 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous MgSO$_4$, filtered and solvent was removed under reduced pressure to give crude compound in (6.2046 g) 75% yield (Rf = 0.47 in hexanes:EtOAc 3:1). 1H NMR (500 MHz, CDCl$_3$) δ 2.55–2.40 (m, 3H), 2.29–2.15 (m, 2H), 1.96–1.92 (m, 3H), 1.83–1.79 (m, 2H), 1.74–1.65 (m, 2H), 0.88 (s, 9H), 0.19 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 211.5, 179.8, 81.3, 41.4, 39.6, 33.1, 28.4, 27.5, 26.2, 22.6, 18.7, -2.4, -2.7.
2-(tert-butyldimethylsilyloxy)-2-(4-diazo-3-oxobutyl)cyclohexanone (3.9):

Carboxylic acid 3.8 (1.7794 g, 5.95 mmol) was dissolved in 1:1 THF: Et₂O (50 mL) and cooled down to -20 °C at which point first Et₃N (0.83 mL, 5.95 mmol), then ethyl chloroformate (0.57 mL, 5.95 mmol) were added. After stirring about half hour at -20 °C, 50 mL hexane was added and the mixture was filtered off via a fritted funnel. The filtrate was evaporated to an oily mixed anhydride residue under reduced pressure, and then it was re-dissolved in 1:1 THF: Et₂O (20 mL). The solution was cooled down to -10 °C, and then premade CH₂N₂ (0.5 g, 11.9 mmol)²²⁰ was cannulated drop wise into the solution of mixed anhydride. It was slowly warmed up to room temperature and stirred overnight. The solvent was removed under reduced pressure, diazoketone was isolated via flash column chromatography on Davisil (hexanes:EtOAc 6:1, 5:1; Rf = 0.47 in hexanes:EtOAc 3:1) in (0.59 g) 31% yield. 1H NMR (500 MHz, CDCl₃) δ 5.22 (bs, 1H), 2.51–2.40 (m, 3H), 2.26–2.17 (m, 2H), 1.95–1.89 (m, 3H), 1.85 –1.64 (m, 4H), 0.88 (s, 9H), 0.19 (s, 3H), 0.01 (s, 3H); 13C NMR (126 MHz, CDCl₃) δ 211.4, 194.4, 81.4, 54.4, 41.5, 39.6, 34.7, 33.0, 27.3, 26.0, 22.6, 18.6, -2.3, -2.79; IR (film): 2928.8, 2855.4, 2101.1, 1720.1, 1641.9, 1471.1, 1461.7, 1374.9, 1339.8, 1252.7, 1170.5, 1123.9, 1075.3, 835.1, 776.9; MS (ESI): Calculated for [C₁₆H₂₈N₂O₃SiNa]⁺: 347.1767, Found: 347.1762.

**Bicyclic diazoketones:** A cold (-78 ºC) solution of lithium diisopropylamide [prepared by the addition of n-butyllithium in hexanes (0.15 mL, 0.20 mmol) to a solution of diisopropylamine (0.03 mL, 0.21 mmol) in THF (1 mL)] was added via cannula over a period of 10 min to a stirred -78 ºC solution of diazoketone 3.9 (0.0446
g, 0.14 mmol) THF (1 mL). The mixture was stirred at -78 ºC for 1 h, at which point saturated aqueous NH₄Cl solution (3 mL) was added to the cold reaction mixture and upon reaching room temperature the mixture was diluted further with saturated aqueous NH₄Cl (2 mL). The aqueous layer was extracted three times with EtOAc (20mL), the combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous CaCl₂, and concentrated under reduced pressure to provide the desired product as a separable mixture of diastereomers. The residue was subjected to flash chromatography on Davisil to afford diastereomeric bicyclic diazoketones with the following characterization data:

(4aR,8aS)-4a-(tert-butyldimethylsilyloxy)-1-diazo-8a-hydroxyoctahydro napththalen-2(1H)-one (3.1a): (0.0145 g, 32% yield; Rf = 0.27 in hexanes:EtOAc 3:1): 1H NMR (500 MHz, CDCl₃) δ 2.97 (s, 1H), 2.54 (dt, J = 18.5, 7.4 Hz, 1H), 2.34 (dt, J = 18.3, 6.3 Hz, 1H), 2.03–1.90 (m, 4H), 1.74–1.62 (m, 4H), 1.46–1.39 (m, 2H), 0.90 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); 13C NMR (126 MHz, CDCl₃) δ 191.8, 75.6, 74.1 (b), 73.4, 35.1 (b), 33.3 (b), 29.4 (b), 27.4, 26.0, 21.9 (b), 18.5, -1.8, -2.3; IR (film): 3534, 2932, 2855, 2091, 1635, 1466, 1303, 1258, 1080, 833, 779. MS (ESI): Calculated for [C₁₆H₂₈N₂O₃SiNa]⁺: 347.1767, Found: 347.1757.
(4aR,8aR)-4a-(tert-butyldimethylsilyloxy)-1-diazo-8a-hydroxyoctahydro naphthalen-2(1H)-one (3.1b): (0.0105 g, 23% yield; Rf = 0.36 in hexanes:EtOAc 3:1): 1H NMR (500 MHz, CDCl₃) δ 2.58 (d, J = 2.4 Hz, 1H), 2.48–2.43 (m, 2H), 2.28–2.21 (m, 1H), 2.05–2.00 (m, 1H), 1.78–1.59 (m, 8H), 0.90 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); 13C NMR (126 MHz, CDCl₃) δ 192.8, 76.8, 77.0, 71.7, 34.7, 33.5, 31.3, 31.0, 26.0, 23.1, 20.0, 18.2, -2.5, -3.1; IR (film): 3557, 2932, 2862, 2091, 1636, 1466, 1288, 1257, 1203, 1049, 1003, 918, 833, 779; MS (ESI): Calculated for [C₁₆H₂₈N₂O₃SiNa]⁺: 347.1767, Found: 347.1765.

Cycloundec-5-yne-1,4-dione (3.3a and 3.3b): A 1 M solution of SnCl₄ in CH₂Cl₂ (0.33 mL, 0.33 mmol) was added in a steady stream to a solution of the cis-bicyclic diazoketone 3.1a (0.1061 g, 0.33 mmol) in dry CH₂Cl₂ (6 mL) at 0 °C. The yellow solution initially turned colorless at which point 5% aqueous NaHCO₃ (10 mL) was added and the mixture was transferred with the aid of CH₂Cl₂ (10 mL) into a separatory funnel. The layers were separated, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the organic layers were combined and dried over anhydrous NaSO₄. The solvents were removed in vacuo and the residue was subjected to flash column chromatography on Davisil (hexanes:EtOAc 3:1; Rf = 0.22 in hexanes:EtOAc 2:1) to afford pure cyclic ynone 3.3a in (0.0433 g) 80% yield. Following the same procedure at 0 °C, trans-diazoketone 3.1b provided the title compound 3.3b in 71% yield after purification via flash column chromatography on Davisil (hexanes:EtOAc; Rf = 0.27 in hexanes:EtOAc). 1H NMR (500 MHz, CDCl₃) δ 2.93–2.91 (m, 2H), 2.75–2.70 (m, 4H), 2.38–2.35 (m, 2H), 1.99–1.94 (m, 2H), 1.82 –
1.78 (m, 2H); 13C NMR (126 MHz, CDCl$_3$) δ 209.7, 187.1, 101.5, 82.6, 43.7, 41.7, 37.5, 24.7, 22.5, 18.8; IR (film): 2922.9, 2852.4, 2207.8, 1705.9, 1671.4, 1455.3, 253.7, 1056.6, 836.4, 669.1, 577.6; MS (ESI): Calculated for [C$_{10}$H$_{12}$O$_2$Na]$^+$: 187.0735, Found: 187.0730.

5.4 Experimental Procedures for Chapter 4

5.4.1 Preparation of bicyclic diazolactone (4.5)

(2-Chloro-1-cyclohexen-1-yl)methanol (4.9): POCl$_3$ (9.32 mL, 0.1 mmol) was added slowly into a 0 °C solution of DMF (10.84 mL, 0.14 mmol) in trichloroethylene (20 mL) at such a rate as to maintain the reaction temperature below 10 °C. The mixture was allowed to warm to room temperature and cyclohexanone 4.8 (11.4 mL, 0.11 mmol) in trichloroethylene (25 mL) was added at such a rate as to maintain the reaction temperature below 60 °C and the reaction was then maintained at 55-60 °C for 3 hours. The mixture was cooled in an ice bath and a solution of NaOAc (40 g) in water (94 mL) was added slowly over 1 hour keeping the reaction temperature below 35 °C. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The organic layers were combined, washed with brine (2 x 200 mL), water (200 mL) and dried over anhydrous Na$_2$SO$_4$. Anhydrous NaOAc (1 g) was added into the dried organic layer and the solvent was reduced in vacuo. The residue was dissolved in 50 mL MeOH and the pH was adjusted to 8 by adding a 10% NaOH (aq) solution at ice-bath temperature. NaBH$_4$ (3.78 g, 0.1 mmol) powder was added in small portions and the mixture was stirred overnight at room temperature. The mixture was treated with 90 mL water and extracted with EtOAc (3 x
90 mL). The organic layers were combined, washed with brine and dried over anhydrous MgSO₄. The solvent was evaporated and the crude product was purified via flash silica gel chromatography (hexanes:EtOAc 20:1 to 5:1; Rf = 0.62 in hexanes:EtOAc 2:1) to afford the title compound in (10.99 g) 75% yield. The ¹H and ¹³C NMR data for this material matched previously reported values.¹⁸⁴,¹⁸⁵

2-Hydroxy-2-(hydroxymethyl) cyclohexanone (4.4): OsO₄ (2.78 g, 0.27 mmol) was added to a room temperature solution of (2-chloro-1-cyclohexen-1-yl) methanol (4.9) (2 g, 13.67 mmol) and NMO (3.20 g, 27.33 mmol) in a mixture of THF (46 mL) and water (23 mL). The mixture was stirred for 48 h and then Na₂SO₃ (10 g) was added and the mixture was stirred for an additional hour. The mixture was filtered through a pad of silica gel which was then washed with EtOAc (150 mL). The solvents were removed in vacuo to provide an oily residue that was purified by silica gel flash chromatography (hexanes:EtOAc 2:1; Rf = 0.23 in hexanes:EtOAc 1:1) to afford the known 2-hydroxy-2-(hydroxymethyl)cyclohexanone as a colorless oil (0.66 g, 34%). The ¹H and ¹³C NMR data for this material matched previously reported values.¹⁸³,²²¹

(1-hydroxy-2-oxocyclohexyl) methyl 2-diazoacetate (4.16): 2-hydroxy-2-(hydroxymethyl)cyclohexanone (4.4) (0.15 g, 1.03 mmol) in CH₂Cl₂ (1 mL) was added to a 0 °C solution of p-toluenesulfonylhydrazone glyoxylic acid chloride⁹,²²² (0.29 g, 1.14 mmol) in CH₂Cl₂ (10 mL) to provide a light-yellow solution. Et₃N (0.35 mL, 2.30 mmol) in CH₂Cl₂ (0.7 mL) was added dropwise causing the color of the reaction to become deep yellow. The reaction was allowed to
warm in the ice bath to room temperature over a period of 4 hours at which point the solvent was removed in vacuo. The solid residue was suspended in toluene (10 mL), mixed with florisil (1 g) and the solids were removed by filtration and rinsed with toluene (75 mL). The filtrate was concentrated under reduced pressure and the crude product was used in the next step for the formation of 4.5 without further purification (Rf = 0.50 in hexanes:EtOAc 1:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.76 (bs, 1H), 4.72 (d, \(J = 11.65\) Hz, 1H), 4.21 (d, \(J = 11.72\) Hz, 1H), 4.12 (s, 1H), 2.60–2.58 (m, 2H), 2.26–2.22 (m, 1H), 2.16–2.12 (m, 1H), 1.85–1.84 (m, 1H), 1.71–1.65 (m, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 210.8, 166.6, 78.2, 67.9, 46.5, 38.4, 38.1, 27.7, 22.7; IR (film): 3500 (br), 2940.1, 2866.2, 2111.7, 1692.9, 1453.2, 1389.7, 1337.9, 1246.2, 1175.2, 1128.1, 1050.7, 1008.1, 851.2, 738.6.

**rel-(4aS,8aR)-4-Diazo-4a,8a-dihydroxyhexahydro-1H-isochromen-3(4H)-one** (4.5): DBU (0.15 mL, 0.97 mmol) was added dropwise to a solution of diazoester 4.16 (0.14 g, 0.65 mmol) in CH\(_2\)Cl\(_2\) (13 mL) at room temperature and the mixture was stirred for 12 h at which point saturated aq NH\(_4\)Cl (15 mL) was added. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 X 15 mL). The organic layers were combined, dried over anhydrous MgSO\(_4\) and filtered. The filtrate was evaporated under reduced pressure to give an orange/red oily residue. Flash column chromatography (hexanes:EtOAc 3:1; Rf = 0.21 in hexanes:EtOAc 1:1) on a Davisil solid support provided the title bicyclic diazolactone as a yellow solid in (0.081 g) 37% yield over two steps starting from 1,2-ketodiol 4.4. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.29 (d, \(J = 11.4\) Hz, 1H), 4.17 (bs, 1H),
3.90 (d, J = 10.3 Hz, 1H), 3.15 (s, 1H), 1.96 (t, J = 11.6 Hz, 1H), 1.82–165 (m, 5H),
1.30 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 166.3, 71.5, 70.9, 68.2, 63.0, 32.6, 30.8,
22.4, 20.5; IR (film): 3371.6, 2935.9, 2106.1, 1659.4, 1392.3, 1298.60 cm−1; MS (ESI):

5.4.2 Preparation of bicyclic diazolactone fragmentation precursors 4.20-
cis/trans, 4.78-cis/trans and 4.77b

Representative experimental procedure for the preparation of α-hydroxy β-
ketoesters:

Ethyl 1-hydroxy-2-oxocyclohexanecarboxylate (4.22): A mixture of
commercially available ethyl 2-oxocyclohexane carboxylate 4.21 (4.69
mL, 29.4 mmol), 10% Pd/carbon (1.5 g) and Et3N (4.5 mL, 32.3 mmol) in
EtOH (150 mL) was attached to a balloon of O2 via a three-way stopcock. The air in the
reaction flask was evacuated via an aspirator and replaced with oxygen three times and
the reaction was stirred under O2 overnight. The mixture was filtered through celite, the
solids were rinsed with EtOH (100 mL) and the filtrate was concentrated in vacuo. The
oily residue was purified by silica gel flash column chromatography (hexanes:EtOAc
6:1; Rf = 0.35 in hexanes:EtOAc 5:1) to give the α-oxygenated product as a colorless
oil in (3.77 g) 69% yield. 1H and 13C NMR spectral data matched previously reported
values.
Ethyl 1,2-bis(tert-butyldimethylsilyloxy)cyclohex-2-enecarboxylate (4.23):

2,5-Lutidine (0.35 g, 3.25 mmol) and TBSOTf (0.86 g, 3.25 mmol) were added sequentially into a 0 °C solution of α-hydroxy β-ketoester (4.22) (0.20 g, 1.08 mmol) in CH₂Cl₂ (5 mL). The mixture was allowed to warm to room temperature overnight and was then cooled to 0 °C before the addition of saturated aqueous NaHCO₃ (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The organic layers were combined, dried over anhydrous MgSO₄ and filtered. Upon removal of solvent, the filtrate gave an oily residue that was purified by silica gel flash column chromatography (hexanes:Et₂O 40:1; Rf = 0.78 in hexanes:EtOAc 5:1) to give the bis-silyl ether as a colorless oil in (0.44 g) 99% yield. ¹H NMR (500 MHz, CDCl₃) δ 4.89 (dd, J = 4.9, 3.2 Hz, 1H), 4.19 (qd, J = 10.8, 7.1 Hz, 1H), 4.09 (qd, J = 10.8, 7.2 Hz, 1H), 2.09 (m, 2H), 1.95 (dt, J = 13.2, 3.2 Hz, 1H), 1.85 (dt, J = 13.2, 3.4 Hz, 1H), 1.77–1.68 (m, 1H), 1.62–1.56 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.5, 149.6, 105.9, 78.0, 61.0, 37.0, 26.1, 25.9, 24.1, 18.8, 18.3, 17.8, 14.3, -2.9, -3.0, -4.4, -4.5; MS (ESI): Calculated for [C₂₁H₄₂O₄Si₂Na]⁺: 437.25138, Found: 437.25164.

(1,2-Bis(tert-butyldimethylsilyloxy)cyclohex-2-enyl)methanol (4.24):

DIBAL-H (44.4 mL, 52.97 mmol) was added dropwise into a -78 °C solution of 4.23 (9.98 g, 24.08 mmol) in toluene (240 mL) and the resulting mixture was stirred for 1 h at -78 °C, transferred to a 0 °C bath and quenched with 150 mL of saturated potassium sodium tartrate tetrahydrate. The mixture was
allowed to warm to room temperature overnight with efficient stirring. The reaction mixture was extracted with EtOAc (3 x 150 mL) and the organic layers were combined, washed with water, brine and dried over anhydrous MgSO₄. The mixture was filtered and concentrated in vacuo to give an oily residue which was purified via silica gel flash column chromatography (hexanes:Et₂O 20:1; Rf = 0.68 in hexanes:EtOAc 5:1) to afford the title compound as a colorless oil in (6.19 g) 69% yield. 

\[ ^1H \text{NMR (500 MHz, CDCl}_3 \] \delta 4.91 (t, \( J = 3.7 \text{ Hz, 1H} \)), 3.59 (dd, \( J = 10.4, 4.5 \text{ Hz, 1H} \)), 3.51 (dd, \( J = 10.5, 8.6 \text{ Hz, 1H} \)), 2.10–1.96 (m, 2H), 1.85–1.65 (m, 4H), 1.58–1.51 (m, 1H), 0.94 (s, 9H), 0.87 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); 

\[ ^13C \text{NMR (125 MHz, CDCl}_3 \] \delta 150.9, 107.5, 75.5, 68.1, 34.6, 26.13, 26.1, 24.5, 18.9, 18.6, 18.4, -2.78, -2.8, -4.2, -4.4; MS (ESI): Calculated for \([C_{19}H_{40}O_3Si_2Na]^+\): 395.24082, Found: 395.24092.

**2-(tert-Butyldimethylsilyloxy)-2-(hydroxymethyl) cyclohexanone (4.18)**:

Acetic acid (0.45 g, 0.53 mL, 7.42 mmol) and CsF (0.56 g, 3.7 mmol) were added sequentially to a 0 °C solution of 4.24 (0.55 g, 1.48 mmol) in a mixture of CH₃CN (21.4 mL) and MeOH (8.6 mL). The mixture was allowed to warm to room temperature overnight and was then re-cooled to 0 °C, diluted with 20 mL EtOAc and saturated NaHCO₃ solution was added. The resulting white precipitate was separated via vacuum filtration and the layers in the filtrate were separated. The aqueous layer was extracted with Et₂O (3 x 30 mL), the organic layers were combined, washed with saturated NaHCO₃ and brine, and dried over anhydrous MgSO₄. The solvents were evaporated and the oily residue was purified by silica gel flash column chromatography (hexanes:EtOAc 8:1; Rf = 0.41 in hexanes:EtOAc 5:1) to give the title compound.
compound as an oil in (0.33 g) 86% yield. 

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.67 (d, $J = 7$ Hz, 2H), 2.73 (ddd, $J = 13.6, 8.8, 5.5$ Hz, 1H), 2.36 (t, $J = 7.4$ Hz, 1H), 2.30 (dt, $J = 7.2, 7.0$ Hz, 1H), 1.98–1.87 (m, 3H), 1.85–1.73 (m, 2H), 1.66–1.59 (m, 1H) 0.90 (s, 9H), 0.18 (s, 3H), 0.04 (s, 3H); 

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.7, 81.4, 67.4, 39.3, 37.8, 27.7, 26.1, 21.4, 18.7, -2.4, -3.1; MS (ESI): Calculated for [C$_{13}$H$_{26}$O$_3$SiNa]$^+$: 281.15434, Found: 281.15428.

**(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)methyl 2-bromoacetate (4.26):** Bromoacetyl bromide (0.57 mL, 6.51 mmol) was added dropwise to a 0 °C solution of alcohol (4.18) (0.56 g, 2.17 mmol) and pyridine (0.44 mL, 5.43 mmol) in dry CH$_2$Cl$_2$ (21 mL), and the resulting white suspension was stirred at room temperature for five hours. The mixture was cooled to 0 °C, and MeOH (0.7 mL) was added, at which point the white suspension became a clear solution. Saturated aq. NH$_4$Cl (20 mL) was added, the layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic layers were combined, dried over anhydrous MgSO$_4$, the solvents were removed *in vacuo* and the resulting oily residue was purified by flash silica gel column chromatography (hexanes:EtOAc 8:1; Rf = 0.47 in hexanes:EtOAc 5:1) to provide the desired bromoacetate as an oil in (0.74 g) 90% yield. 

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.34 (d, $J = 11.6$ Hz, 1H), 4.31 (d, $J = 11.7$ Hz, 1H), 3.81 (s, 2H), 2.72 (ddd, $J = 15.4, 9.9, 5.6$ Hz, 1H), 2.32 (td, $J = 13.5, 5.6$ Hz, 1H), 1.98–1.86 (m, 3H), 1.80–1.74 (m, 2H), 1.68–1.62 (m, 1H), 0.88 (s, 9H), 0.13 (s, 3H), 0.03 (s, 3H); 

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.1,
166.9, 79.5, 68.9, 38.9, 38.1, 27.6, 25.9, 25.6, 21.2, 18.6, -2.4, -3.1; MS (ESI): Calculated for [C\textsubscript{15}H\textsubscript{27}BrO\textsubscript{4}SiH]\textsuperscript{+}: 379.09347, Found: 379.09340.

8a-\textit{(tert-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1H iso}

\textbf{chromen-3(4H)-one (4.20-cis and 4.20-trans):\textsuperscript{194}} N,N\textsuperscript{-}ditosylhydrazine (3.81 g, 11.19 mmol) was added to a 0 \degree C solution of bromoacetate 4.26 (2.12 g, 5.59 mmol) in THF (56 mL) at which point DBU (5.19 mL, 34.6 mmol) was added dropwise. The mixture was stirred at room temperature for 8 hours, was cooled to 0 \degree C, and saturated aq. NaHCO\textsubscript{3} (60 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 60 mL). The organic layers were combined, dried over anhydrous CaCl\textsubscript{2} and the solvents were removed by evaporation to give a crude solid product. The crude product was purified via flash column chromatography (hexanes:EtOAc 8:1, 6:1, 4:1, 2:1, 1:1) on a Davisil solid support to provide the bicyclic diazo lactone as two separated diastereomers which had the following spectral data:

\textbf{rel-(4aS,8aR)-8a-\textit{(tert-Butyldimethylsilyloxy)-4-diazo-4a-}

\textbf{hydroxyhexahydro-1H iso chromen-3(4H)-one (4.20-cis) (0.62 g, 34% yield; Rf = 0.31 in hexanes:EtOAc 5:1): \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \textit{δ}} 4.23 (d, \textit{J} = 10.2 Hz, 1H), 4.12 (bs, 1H), 2.95 (bs, 1H), 1.98 (bs, 1H), 1.91–1.86 (m, 1H), 1.83–1.73 (m, 2H), 1.71–1.65 (m, 2H), 1.42 (bs, 2H), 0.92 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \textit{δ} 164.7, 72.4, 72.1, 69.7, 63.1, 34.5 (b), 32.0, 25.9, 21.8 (b), 18.4, -2.2, -2.5 (b); IR (film): 2928.1, 2857.7, 2102.5, 1690.7,
167.1, 1391.7 cm\(^{-1}\); MS (ESI): Calculated for \([C_{15}H_{26}N_2O_4SiH]^+\): 327.17346, Found: 327.17385.

**rel-(4aR,8aR)-8a-(tert-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1H-iso chromen-3(4H)-one (4.20-trans):** (0.90 g, 49% yield; R\(_f\) = 0.45 in hexanes:EtOAc 5:1): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.23 (d, \(J = 10.9\) Hz, 1H), 3.76 (d, \(J = 10.9\) Hz, 1H), 2.64 (d, \(J = 1.7\) Hz, 1H), 1.94 (dt, \(J = 14.7, 4.4\) Hz, 1H), 1.80–1.67 (m, 5H), 1.61–1.55 (m, 1H), 1.22–1.12 (m, 1H), 0.90 (s, 9H), 0.16 (s, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 163.9, 75.2, 70.9, 68.4, 61.6, 32.4, 30.0, 25.9, 22.7, 19.5, 18.1, -2.7, -3.2; IR (film): 3538.6, 2952.2, 2859.6, 2103.5, 1699.4, 1465.0, 1388.8, 1302.9 cm\(^{-1}\); MS (ESI): Calculated for \([C_{15}H_{26}N_2O_4SiH]^+\): 327.17346, Found: 327.17401.

**4-Oxacyclodecyne-3,6-dione (4.31):** *Representative experimental procedure 1:*

*Fragmentation reactions conducted at 0 °C and at room temperature:*

A 1 M solution of SnCl\(_4\) in CH\(_2\)Cl\(_2\) (0.25 mL, 0.25 mmol) was added in a steady stream to a solution of the bicyclic diazolactone **4.20-cis** (0.0826 g, 0.25 mmol) in dry CH\(_2\)Cl\(_2\) (6.3 mL) at 0 °C. The yellow solution initially turned colorless and then became deep yellow in color. After 30 minutes 5% aqueous NaHCO\(_3\) (12 mL) was added and the mixture was transferred with the aid of CH\(_2\)Cl\(_2\) (10 mL) into a separatory funnel. The layers were separated, the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL) and the organic layers were combined and dried over anhydrous NaSO\(_4\). The solvents were removed in vacuo and the residue was subjected to flash column chromatography on Davisil (hexanes:EtOAc 10:1, 6:1, 1:1; R\(_f\) = 0.13 in hexanes:EtOAc 1:1).
1:1) to afford pure cyclic ynoate 4.31 in (0.005 g) 12% yield. The yield increased to (0.0089 g) 21% when the same procedure was followed at room temperature. Following the same procedure at 0 °C, diazolactone 4.20-trans provided the title compound in 10% yield as determined via NMR using mesitylene as an internal standard. Crystallization from cold methanol provided crystals suitable for X-ray crystallography (M.P.: 95 °C); 1H NMR (500 MHz, CDCl₃) δ 4.85 (s, 2H), 2.53–2.50 (m, 2H), 2.39 (t, J = 6.0 Hz, 2H), 2.04–1.99 (m, 2H), 1.86–1.82 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 204.5, 153.5, 99.9, 74.7, 72.2, 41.0, 25.5, 24.6, 19.7; IR (film): 2923.3, 2854.8, 2229.8, 1734.1, 1558.6, 1454.4, 1376.3, 1280.8, 1194.9, 1124.6, 1078.3, 1037.7, 985.7, 922.0, 738.8; MS (ESI): Calculated for [C₉H₁₀O₃H]⁺: 167.07027, Found: 167.07016.

**Representative experimental procedure 2: fragmentation reactions conducted at 40 °C:** A 1 M solution of SnCl₄ in CH₂Cl₂ (0.25 mL, 0.25 mmol) was added into refluxing CH₂Cl₂ (4 mL) and the bicyclic diazolactone 4.20-cis (0.0818 g, 0.25 mmol) in dry CH₂Cl₂ (1 mL) was then added in one portion. The vial containing the bicyclic diazolactone was rinsed with 1.3 mL CH₂Cl₂ and this too was added to the refluxing reaction mixture. The mixture was held at reflux for 10 minutes and was then cooled in an ice bath at which point 5% aqueous NaHCO₃ (8 mL) was added and the mixture was transferred with the aid of CH₂Cl₂ (10 mL) into a separatory funnel. The layers were separated, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the organic layers were combined and dried over anhydrous Na₂SO₄. The solvents were removed *in vacuo* and the residue was subjected to flash column chromatography on Davisil
(hexanes:EtOAc 10:1, 6:1, 1:1; Rf = 0.13 in hexanes:EtOAc 1:1) to afford pure cyclic ynoate 4.31 in (0.0134 g) 33% yield. Following the same procedure, diazolactone 4.20-trans provided the title compound in 17% yield as determined by NMR using mesitylene as an internal standard.

8a-(tert-butyldimethylsilyloxy)-5-chloro-6,7,8,8a-tetrahydro-1H-isochromen-3(5H)-one (4.32): This compound was isolated as a major side product from fragmentation of bicyclic diazolactone 4.20-cis (0.0826 g, 0.25 mmol) at 0 °C in (0.0043 g) 54% yield. At 40 °C, it was observed only in (0.0061 g) 8% yield. It was isolated using flash chromatography on Davisil (hexanes:EtOAc 12:1, 10:1, 6:1, 5:1, 1:1, Rf = 0.54 in hexanes:EtOAc 3:1 ). Bicyclic diazolactone 4.20-trans also provided desilylated form of this side product in a complex mixture. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.34 (d, $J = 2.2$ Hz, 1H), 4.70 (ddd, $J = 12.2$, 5.4, 2.2 Hz, 1H), 4.32 (d, $J = 12.5$ Hz, 1H), 4.21 (d, $J = 12.5$ Hz, 1H), 2.47-2.44 (m, 1H), 1.97-1.90 (m, 2H), 1.79-1.71 (m, 2H), 1.39 (ddd, $J = 13.9$, 13.8, 3.4 Hz, 1H), 0.88 (s, 9H), 0.16 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.9, 157.4, 116.5, 75.2, 69.7, 56.9, 37.5, 36.6, 25.7, 20.3, 18.4, -3.3, -4.0; IR (film): 2957.0, 2927.1, 1724.4, 1706.1, 1639.6, 1558.6, 1456.3, 1399.4, 1290.4, 1256.7, 1228.7, 1210.4, 1173.7, 1154.5, 1132.3, 1070.5, 1051.3, 1033.9, 1000.1, 976.9, 904.7, 896.9, 775.4, 765.8, 682.8; MS (ESI): Calculated for [C$_{15}$H$_{25}$O$_3$SiClH]$^+$: 313.13343, Found: 317.13358.
8a-(tert-butyldimethylsilyloxy)-5-hydroxy-6,7,8a-tetrahydro-1H-
isochoromen-3(5H)-one (4.33): This alcohol was observed as a side product from fragmentation of bicyclic diazolactone 4.20-cis (0.0826 g, 0.25 mmol) at 0 °C in (0.0071 g) 9% yield and in (0.0052 g) 7% yield at refluxing dichloromethane at 40 °C. Interestingly, it was not observed in the fragmentation of bicyclic diazolactone 4.20-trans. It was isolated using flash chromatography on Davisil (hexanes:EtOAc 12:1, 10:1, 6:1, 5:1, 1:1, Rf = 0.21 in hexanes:EtOAc 2:1 ). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.18 (d, $J = 2.2$ Hz, 1H), 4.47 (ddd, $J = 11.9$, 5.8, 2.2 Hz, 1H), 4.32 (d, $J = 12.5$ Hz, 1H), 4.20 (d, $J = 12.5$ Hz, 1H), 3.35 (bs, 1H), 2.26–2.22 (m, 1H), 1.89–1.84 (m, 2H), 1.74–1.70 (m, 1H), 1.42 (ddd, $J = 25.2$, 12.2, 3.9 Hz, 1H), 1.34–1.30 (m, 1H), 0.85 (s, 9H), 0.15 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.5, 161.9, 112.9, 75.4, 69.2, 68.2, 36.9, 35.8, 25.7, 18.6, 18.4, -3.3, -3.9; IR (film): 3435.4 (b), 2950.3, 2939.9, 2884.7, 2857.7, 1720.6, 1472.7, 1462.1, 1293.3, 1255.7, 1230.6, 1174.7, 1159.3, 1127.4, 1076.3, 1049.3, 1022.3, 997.2, 960.6, 912.4, 897.9, 884.4, 837.1, 825.6, 812.1, 777.4, 737.8, 686.7, 660.7; MS (ESI): Calculated for [C$_{15}$H$_{26}$O$_4$SiH]: 299.16731, Found: 299.16755.

8a-(tert-butyldimethylsilyloxy)-5-chloro-6,7,8a-tetrahydro-1H-
isochoromen-3(5H)-one (4.34): This compound was isolated as a minor side product from fragmentation of bicyclic diazolactone 4.20-cis (0.0826 g, 0.25 mmol) at 0 °C in (0.003 g) 4% yield and at 40 °C in (0.0046 g) 6% yield. Desilylated form of this compound was also observed in the fragmentation of bicyclic diazolactone 4.20-trans in a complex mixture. It was isolated using flash
chromatography on Davisil (hexanes:EtOAc 12:1, 10:1, 6:1, 5:1, 1:1, Rf = 0.21 in hexanes:EtOAc 2:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.00 (s, 1H), 4.74 (bs, 1H), 4.29 (d, \(J = 12.3\) Hz, 1H), 4.11 (d, \(J = 12.5\) Hz, 1H), 2.32 (qt, \(J = 13.5, 3.0\) Hz, 1H), 2.26–2.21 (m, 1H), 1.94 (ddd, \(J = 14.3, 5.3, 2.3\) Hz, 1H), 1.86 (dddt, \(J = 14.7, 13.1, 3.8\) Hz, 1H), 1.66–1.60 (m, 1H), 1.28 (td, \(J = 13.4, 3.7\) Hz, 1H), 0.90 (s, 9H), 0.19 (s, 3H), 0.10 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 163.6, 155.3, 120.1, 76.1, 67.2, 55.8, 35.6, 34.2, 25.8, 18.4, 14.8, -2.9, -3.8; IR (film): 2952.2, 2931.9, 2858.6, 1736.9, 1554.7, 1472.7, 1463.1, 1390.7, 1302.0, 1262.5, 1226.8, 1185.3, 1125.5, 1104.3, 1068.6, 1057.0, 1030.0, 999.2, 958.7, 911.4, 837.2, 827.5, 777.4, 733.4, 680.9; GC-MS (m/z): 317.2 (100) [M+H]+, 319.1 (38.5) [(M+2)+H]+.

**Reaction of diazolactone 4.20-cis with indium triflate providing 4.35 and 4.36:**

A solution of diazolactone 4.20-cis (0.100 g, 0.31 mmol) in CH\(_2\)Cl\(_2\) (4 mL) was added to a -78 °C suspension of In(OTf)\(_3\) (0.173 g, 0.31 mmol, dried in a vacuum oven at 180 °C for 16 hours before use) in CH\(_2\)Cl\(_2\) (4 mL). The mixture was allowed to warm to room temperature over 2 h at which point water (8 mL) was added. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The organic layers were combined, dried over anhydrous MgSO\(_4\), filtered and the solvent was evaporated to give an oily residue which was purified by flash column chromatography on Davisil (hexanes:EtOAc 8:1, 5:1, 3:1) to provide epoxide 4.36 in (0.005 g) 5% yield (Rf = 0.46 in hexanes:EtOAc 5:1) and diene 4.35 in (0.027 g) 31% yield (Rf = 0.21 in hexanes:EtOAc 5:1) with the following spectral data:
8a-(tert-Butyldimethylsilyloxy)-8,8a-dihydro-1H-isochromen-3(7H)-one

(4.35): The diene 4.35 was also observed as a side product from fragmentation of bicyclic diazolactone 4.20-cis (0.0826 g, 0.25 mmol) with SnCl$_4$ at 0 °C in (0.0035 g) 5% yield and in (0.0066 g) 9% yield at refluxing dichloromethane at 40 °C. However, it was not observed in the fragmentation of bicyclic diazolactone 4.20-trans. It was isolated using flash chromatography on Davisil (hexanes:EtOAc 12:1, 10:1, 6:1, 5:1, 1:1, Rf = 0.21 in hexanes:EtOAc 5:1 ). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.38 (ddd, $J = 9.7, 6.0, 1.9$ Hz, 1H), 6.20 (dd, $J = 9.9, 2.8$ Hz, 1H), 5.69 (s, 1H), 4.31 (d, $J = 12.1$ Hz, 1H), 4.18 (d, $J = 12.1$ Hz, 1H), 2.59–2.51 (m, 1H), 2.27(dt, $J = 18.9, 5.4$ Hz, 1H), 1.87 (dd, $J = 13.2, 4.6$ Hz, 1H), 1.47 (ddd, $J = 12.9, 11.6, 5.1$ Hz, 1H), 0.84 (s, 9H), 0.11 (s, 3H), -0.02 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.9, 151.2, 140.0, 124.6, 113.9, 76.0, 66.4, 32.0, 25.6, 22.2, 18.5, -3.4, -3.9; IR (film): 2956.0, 2929.0, 2856.7, 1725.4, 1631.9, 1472.7, 1462.1, 1290.4, 1250.9, 1250.9, 1222.9, 1201.7, 1161.2, 1114.9, 1060.9, 1028.1, 892.1, 828.5, 777.4; MS (ESI): Calculated for [C$_{15}$H$_{24}$O$_3$SiH]$^+$: 281.15675, Found: 281.15654.

rel-(11S,5aR,8aR)-5a-(tert-Butyl dimethyl silyloxy)hexahydrooxireno[2,3-d]isochromen-8(8aH)-one (4.36): $^1$H NMR (500 MHz, CDCl$_3$) δ 4.30 (d, $J = 12.3$ Hz, 1H), 3.93 (d, $J = 11.9$ Hz, 1H), 3.43 (s, 1H), 2.38 (dt, $J = 13.7, 4.2$ Hz, 1H), 1.84–1.69 (m, 5H), 1.50–1.43 (m, 2H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 167.3, 72.6, 71.9, 64.6, 55.9, 32.5, 27.3, 25.9, 23.0, 20.1, 18.5, -2.5, -3.0; IR (film): 2950.3, 2933.9, 2848.9, 1753.4, 1635.7,
1462.1, 1295.3, 1263.4, 1179.5, 1074.4, 957.7, 909.5, 838.1, 778.3, 735.9; MS (ESI): Calculated for \([\text{C}_{15}\text{H}_{26}\text{O}_4\text{SiH}]^+\): 299.16731, Found: 299.16731.

**8a-hydroxy-8,8a-dihydro-1H-isochromen-3(7H)-one (4.37):** BF$_3$·OEt$_2$ (0.045 mL, 0.36 mmol) was added in a steady stream to a solution of the bicyclic diazolactone 4.20-**trans** (0.12 g, 0.36 mmol) in dry CH$_2$Cl$_2$ (7 mL) at -78 °C. After 1.5 hours, distilled water (7 mL) was added at 0 °C and the mixture was transferred with the aid of CH$_2$Cl$_2$ (10 mL) into a separatory funnel. The layers were separated, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL) and the organic layers were combined and dried over anhydrous MgSO$_4$. The solvents were removed *in vacuo* and the residue was subjected to flash column chromatography on Davisil (hexanes:EtOAc 2:1, 1:1; Rf = 0.45 in CH$_2$Cl$_2$:EtOAc 1:1) to afford 4.37 in (0.0153 g) 26% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.44 (ddd, $J$ = 11.3, 6.3, 2.2 Hz, 1H), 6.24 (dd, $J$ = 10.3, 2.9Hz, 1H), 5.71 (s, 1H), 4.34 (d, $J$ = 11.9 Hz, 1H), 4.25 (d, $J$ = 11.8 Hz, 1H), 2.65–2.57 (m, 1H), 2.53 (bs, 1H), 2.33 (dtt, $J$ = 18.8, 5.8, 1.3 Hz, 1H), 1.93 (ddt, $J$ = 13.4, 5.1, 0.8 Hz, 1H), 1.51 (dddt, $J$ = 13.4, 11.6, 5.4 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.2, 151.8, 140.7, 124.1, 113.3, 76.3, 64.5, 29.5, 21.9; IR (film): 3394.9 (b), 2920.4, 2854.8, 1720.6, 1694.5, 1681.0, 1624.1, 1455.4, 1288.5, 1248.9, 1229.7, 1101.4, 1057.1, 877.7, 734.9, 710.8; MS (ESI): Calculated for \([\text{C}_{9}\text{H}_{10}\text{O}_3\text{H}]^+\): 167.07027, Found: 167.06980.
Acetic anhydride (0.43 mL, 4.58 mmol), DMAP (0.0023 g, 0.02 mmol), and Et₃N (0.71 mL, 5.08 mmol) were added sequentially into a 0 °C solution of alcohol 4.18 (0.26 g, 1 mmol) in CH₂Cl₂ (5 mL). The mixture was stirred for 2 h at 0 °C, and then water (5 mL) was added. The organic layer was separated, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), the organics were combined, dried (Na₂SO₄), and concentrated. The product was purified by silica gel flash column chromatography (hexanes:EtOAc 10:1; Rf = 0.42 in hexanes:EtOAc 5:1) to give the keto acetate in (0.26 g) 86% yield. 1H NMR (500 MHz, CDCl₃) δ 4.26 (d, J = 11.7 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 2.72 (ddd, J = 13.7, 9.5, 5.4 Hz, 1H), 2.33 (ddd, J = 12.7, 6.8, 5.7 Hz, 1H), 2.06 (s, 3H), 1.96–1.85 (m, 3H), 1.82–1.74 (m, 2H), 1.68–1.61 (m, 1H), 0.89 (s, 9H), 0.14 (s, 3H), 0.05 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ 209.3, 170.6, 79.7, 67.4, 38.9, 38.4, 27.6, 25.9, 21.3, 20.9, 18.6, -2.6, -3.2; MS (ESI): Calculated for [C₁₅H₂₈O₄SiH]⁺: 301.18296, Found: 301.18300.

Ethyl 2-(2-(acetoxyethyl)-2-(tert-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-2-diazoacetate (4.47): Lithium bis(trimethylsilyl)amide (1 M in THF/ethyl benzene, 0.75 mL, 0.75 mmol) was added dropwise over 1.5 h into a -78 °C solution of ketone 4.46 (0.20 g, 0.65 mmol) and ethyl diazoacetate (0.08 g, 0.72 mmol) in THF (12 mL). After the mixture was stirred for 30 min at -78 °C, saturated aqueous NH₄Cl (12 mL) was added and the mixture was allowed to warm to room temperature and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL), the organic layers
were combined, washed with brine and dried over anhydrous CaCl$_2$. The solvents were evaporated and the crude yellow oily residue was purified via silica gel flash column chromatography (hexanes:Et$_2$O 7:1, 5:1, 3:1) on Davisil support to provide the acetate diazoester as two separate diastereomers. Both diastereomers were isolated together with an inseparable unknown impurity. The major-diastereomer was obtained in (0.14 g) 41% yield (determined by NMR using mesitylene as an internal standard; R$_f$ = 0.42 in hexanes:EtOAc 5:1) and the minor-diastereomer was obtained in (0.030 g) 8% yield (determined by NMR using mesitylene as an internal standard; R$_f$ = 0.26 in hexanes:EtOAc 5:1). **Observed Resonances for Major Diastereomer:** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 4.46 (d, $J$ = 12.2 Hz, 1H), 4.19 (q, $J$ = 7.2 Hz, 2H overlapped with peaks from impurity), 3.97 (d, $J$ = 12.2 Hz, 1H), 2.24–2.17 (m, 1H), 2.09 (s, 3H), 1.93–1.89 (m, 2H), 1.71 (apparent tt, $J$ = 13.3, 3.9 Hz, 3H), 1.62 (m, 2H), 1.54–1.51 (m, 1H), 1.26 (t, $J$ = 7.1 Hz, 3H), 0.87 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 170.5, 166.6, 81.9, 73.3, 66.7, 62.2, 60.7, 32.8, 32.7, 26.2, 22.8, 21.1, 20.3, 18.6, 14.6, 1.9, 2.2; IR (film): 3505.8, 2930.9, 2893.4, 2094.8, 1747.6, 1693.6, 1471.7, 1464.0, 1388.8, 1367.6, 1297.2, 1251.9, 1234.5; MS (ESI): Calculated for [C$_{19}$H$_{34}$N$_2$O$_6$SiNa]$^+$: 437.20783, Found: 437.20797. **Observed Resonances for Minor Diastereomer:** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 4.28 (d, $J$ = 11.8 Hz, 1H), 4.21 (q, $J$ = 7.0 Hz, 2H overlapped with peaks from impurity), 4.08 (d, $J$ = 11.8 Hz, 1H), 2.09 (s,3H), 1.94–1.85 (m, 2H), 1.72–1.52 (m, 7H overlapped with peaks from impurity), 1.27 (t, $J$ = 7.1 Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 171.2, 169.7, 79.1, 75.7, 68.9, 64.1, 61.2, 33.7, 30.4, 26.5, 26.2, 22.7, 21.0, 18.8, 14.6,
1.8, -1.9; IR (film): 3481.7, 2954.1, 2860.6, 2096.7, 1746.6, 1471.7, 1389.8, 1367.6, 1293.3, 1253.8, 1111.1, 1033.9; MS (ESI): Calculated for [C_{19}H_{34}N_{2}O_{6}SiNa]^+: 437.20783, Found: 437.20810.

**Ethyl 9-acetoxy-8-oxonon-2-ynoate (4.48):** Following representative experimental procedure 1 that was used to prepare 4.31, the major diastereomer of diazoester 4.47 (0.060 g, 0.14 mmol) reacted at 0 °C to give tethered ketone ynoate 4.48 in (0.024 g) 70% yield after purification via flash chromatography on Davisil (hexanes:EtOAc 10:1, 8:1, 6:1, 4:1, 3:1, 2:1, 1:1; Rf = 0.11 in hexanes:EtOAc 5:1); the yield was determined to be 83% via NMR using mesitylene as an internal standard. Under the same experimental conditions, the minor diastereomer of diazoester 4.47 (0.049 g, 0.12 mmol) provided the title compound in (0.012 g) 54% isolated yield; the yield was determined to be 61% via NMR using mesitylene as an internal standard. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.63 (s, 2H), 4.20 (q, \(J = 7.1\) Hz, 2H), 2.45 (t, \(J = 7.1\) Hz, 2H), 2.34 (t, \(J = 7.1\) Hz, 2H), 2.16 (s, 3H), 1.73 (tt, \(J = 7.9, 7.0\) Hz, 2H), 1.60 (tt, \(J = 7.6, 7.1\) Hz, 2H), 1.29 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 203.4, 170.4, 153.8, 88.5, 73.7, 68.1, 61.9, 38.1, 26.9, 22.4, 20.6, 18.6, 14.2; IR (film): 2900.1, 2233.7, 1751.4, 1730.2, 1705.2, 1419.7, 1367.6, 1251.9, 1234.5, 1076.3, 1026.2, 910.4, 858.4, 753.2, 735.9; MS (ESI): Calculated for [C_{13}H_{18}O_{5}Na]^+: 277.10464, Found: 277.10486.
**2- Allyl-2-(tert-butylidimethylsilyloxy)cyclohexanone (4.49):** Freshly prepared allyl magnesium bromide (2.40 g, 19.88 mmol) in Et₂O (20 mL) was added dropwise into a 0 °C solution of 2-silyloxy cyclohex-2-enone (23) (3.0 g, 13.25 mmol) in Et₂O (24 mL). 2-silyloxy cyclohex-2-enone was made following the literature procedure. During the addition the colorless solution became yellow in color. After stirring three hours at 0 °C, the reaction mixture was quenched with 50 mL NH₄Cl (aq) solution and warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with Et₂O (3 x 50 mL). The organic layers were combined, washed with brine, dried over anhydrous MgSO₄ and concentrated to an oily residue. This residue, containing the crude tertiary alcohol, (2.72 g, 10.13 mmol) was dissolved in 50 mL dry MeOH, cooled to 0 °C, K₂CO₃ (0.07 g, 0.5 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated to an oily residue, dissolved in 50 mL Et₂O and washed with brine. The organic layer was dried over anhydrous MgSO₄ and concentrated down to an oily residue. Purification via flash silica gel chromatography (hexanes:Et₂O 50:1; Rf = 0.45 in hexanes:EtOAc 40:1) provided the title compound in (2.95 g) 83% yield. H and C NMR spectral data was identical to reported values.

**2-(1-(tert-Butyldimethylsilyloxy)-2-oxocyclohexyl)acetaldehyde (4.55):** A solution of allylketone (4.49) (1.27 g, 4.73 mmol) in CH₂Cl₂ (50 mL) was cooled to -78 °C and ozonized oxygen gas was passed at a rate of 1 L/min through the solution until it became blue in color, at which point the solution was purged with nitrogen until the blue color disappeared and then triphenylphosphine (2.48
g, 9.46 mmol) was added. After 30 min the mixture was allowed to warm to room temperature over a period of two hours. The solvent was removed and the crude product was purified via flash column chromatography on Davisil support (hexanes:EtOAc 10:1, 2:1; Rf = 0.23 in hexanes:EtOAc 8:1) to afford the title aldehyde in (1.19 g) 93% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.73 (t, $J = 2.4$ Hz, 1H), 2.76 (dd, $J = 15.4$, 2.5 Hz, 1H), 2.78–2.73 (m, 1H overlapping with dd at 2.76), 2.61 (dd, $J = 15.4$, 2.4 Hz, 1H), 2.36 (ddd, $J = 13.6$, 6.2, 5.7 Hz, 1H), 2.02–1.87 (m, 4H), 1.82–1.73 (m, 1H), 1.68–1.61 (m, 1H), 0.90 (s, 9H), 0.17 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.8, 200.6, 80.1, 50.5, 41.1, 38.7, 27.5, 25.9, 21.5, 18.6, -2.1, -2.7; MS (ESI): Calculated for [C$_{14}$H$_{26}$O$_3$SiNa]$^+$: 293.15434, Found: 293.15429.

An aqueous suspension of Raney-nickel (5.67 g of the suspension) was transferred with THF (20 mL) into a solution of aldehyde 4.56 (0.87 g, 3.21 mmol) in THF (10 mL). The suspension was stirred at room temperature for 30 min, diluted with Et$_2$O (50 mL), filtered through Celite and the solvent was evaporated to yield an oily residue. The crude product was purified via silica gel flash column chromatography (hexanes:EtOAc 20:1, 10:1; 15:1; 5:1; Rf = 0.40 in hexanes:EtOAc 4:1) to afford the hemiacetal in (0.60 g) 69% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.10 (ddd, $J = 8.9$, 8.5, 4.6 Hz, 1H), 3.84 (dt, $J = 8.4$, 6.9 Hz, 1H), 3.29 (s, 1H), 2.14 (ddd, $J = 11.2$, 10.0, 6.9 Hz, 1H), 1.91 (ddd, $J = 12.4$, 8.3, 4.1 Hz, 1H), 1.86 (dt, $J = 14.3$, 4.4 Hz, 1H), 1.79–1.74 (m, 1H), 1.67–1.60 (m, 2H), 1.54–1.47 (m, 2H), 1.44–1.37 (m, 2H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 102.7, 80.3,
2-(1-(tert-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 2-bromoacetate (4.57): Pyridine (0.47 mL, 5.81 mmol) and bromoacetylbromide (0.61 mL, 6.98 mmol) were added sequentially into a 0 °C solution of hemiacetal 4.51 (0.63 g, 2.33 mmol) in CH₂Cl₂ (23 mL) and the resulting heterogeneous mixture was stirred overnight at room temperature. The mixture was cooled to 0 °C and MeOH (0.25 mL) was added at which point the white suspension became a clear solution. Saturated aq. NH₄Cl (25 mL) was added, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The organic layers were combined, dried over anhydrous MgSO₄ and filtered. The solvents were removed in vacuo and the resulting oily residue was purified by flash silica gel column chromatography (hexanes:EtOAc 20:1; Rf = 0.48 in hexanes:EtOAc 4:1) to provide the desired bromoacetate as an oil in (0.52 g) 57% yield. ¹H NMR (500 MHz, CDCl₃) δ 4.26–4.23 (m, 2H), 3.77 (s, 2H), 2.56–2.45 (m, 2H), 2.30 (dt, J = 21.5, 7.2 Hz, 1H), 1.98–1.93 (m, 3H), 1.86–1.79 (m, 2H), 1.74–1.65 (m, 2H), 0.87 (s, 9H), 0.18 (s, 3H), 0.02 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 210.9, 167.1, 80.7, 62.3, 42.1, 39.6, 37.1, 27.7, 26.1, 25.8, 22.7, 18.7, -2.4, -2.7; MS (ESI): Calculated for [C₁₆H₂₉BrO₄SiH]⁺: 393.10913, Found: 393.10952.
2-(1-(tert-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 2-diazoacetate

(4.58): Diazoeater 4.58 was prepared from the bromoacetate 4.57 by the same procedure used to make 4.20-cis/trans. The product was purified via filtration through a pad of Davisil using 8:1 hexanes:EtOAc mixture as eluent to provide the title compound in (0.51 g) 85% yield (Rf = 0.28 in hexanes:EtOAc 4:1); ^1H NMR (500 MHz, CDCl3) δ 4.57 (bs, 1H), 4.29–4.19 (m, 2H), 2.53–2.44 (m, 2H), 2.31 (dd, J = 14.4, 7.3, 7.0 Hz, 1H), 1.99–1.93 (m, 2H), 1.91 (dd, J = 6.1, 5.3 Hz, 1H), 1.87–1.77 (m, 2H), 1.74–1.63 (m, 2H), 0.88 (s, 9H), 0.19 (s, 3H), 0.02 (s, 3H); ^13C NMR (125 MHz, CDCl3) δ 210.7, 166.3 (b), 80.6, 60.6, 45.9 (b), 42.2, 39.4, 37.5, 27.6, 25.9, 22.6, 18.5, -2.6, -2.9; IR (film): 2928.1, 2855.73, 2112.14, 1724.4, 1697.4, 1472.7, 1394.6, 1394.6, 1359.8, 1248.0; MS (ESI): Calculated for [C_{16}H_{28}N_{2}O_{4}SiNa]^+: 363.17106, Found: 363.17147.

rel-(5aR,9aS)-5a-(tert-Butyldimethylsilyloxy)-1-diazo-9a-hydroxy octahydro benzo [d] oxepin-2(1H)-one (4.59): A solution of diazoeaster 4.58 (0.05 g, 0.15 mmol) in THF (3 mL) was added dropwise over 16 hours by a syringe pump into a stirred -78 °C solution of lithium bis(trimethylsilyl)amide (1 M in THF/ethyl benzene, 0.20 mL, 0.18 mmol) in THF (30 mL). After 1 h saturated aqueous NH_4Cl solution (24 mL) was added into the reaction mixture at -78 °C and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 70 mL), the organic layers were combined, washed with brine, dried over anhydrous CaCl_2, filtered and concentrated to a solid residue. Flash column chromatography of the crude product over Davisil
(hexanes:EtOAc 4:1, 2:1, 1:1; Rf = 0.21 in hexanes:EtOAc 3:1) afforded a single diastereomer of the title product in (0.035 g) 69% yield. 

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.37 (dd, $J = 12.8, 9.8, 1.8$ Hz, 1H), 4.26 (dd, $J = 12.8, 6.1, 2.8$ Hz, 1H), 2.34 (dd, $J = 15.8, 9.8, 2.8$ Hz, 1H), 1.97 (s, 1H), 1.93 (dt, $J = 12.6, 4.9$ Hz, 1H), 1.80 (dt, $J = 13.9, 4.3$ Hz, 1H), 1.72–1.55 (m, 6H), 1.52–1.48 (m, 1H), 0.92 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.6, 75.6, 74.0, 67.9, 65.4, 38.6, 35.3, 32.8, 26.1, 20.4, 20.2, 18.8, -1.7, -1.9; IR (film): 3358.2 (b), 2927.1, 2855.7, 2106.4, 1727.3, 1635.7, 1471.7, 1398.5, 1305.9, 1259.6; MS (ESI): Calculated for [C$_{16}$H$_{28}$N$_2$O$_4$SiH]$: 341.18911$, Found: 341.18924.

**4-Oxacycloundecyne-3,7-dione (4.60):** Following representative experimental procedure 1 or 2 that were used to prepare 4.31, diazolactone 4.59 provided 11-membered ynnolide 4.60 in (0.022 g) 50% yield at 0 °C and (0.0063 g) 63% yield at 40 °C. The title compound was isolated via flash column chromatography on Davisil (hexanes:EtOAc 4:1, 3:1, 2:1, 1:1; Rf = 0.16 in hexanes:EtOAc 2:1). 

$^1$H NMR (500 MHz, CDCl$_3$) δ 4.65–4.63 (m, 2H), 2.79–2.77 (m, 2H), 2.76–2.73 (m, 2H), 2.42–2.39 (m, 2H), 1.92 (tt, $J = 5.9, 4.0$ Hz, 2H), 1.76–1.72 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.8, 154.4, 97.9, 73.1, 65.5, 44.4, 41.7, 25.0, 20.9, 18.2; IR (film): 2922.3, 2851.9, 2229.8, 1714.8 (b), 1463.1, 1387.8, 1382.7, 1228.7, 1079.2, 740.7; MS (ESI): Calculated for [C$_{10}$H$_{12}$O$_3$H]$^+$: 181.08592, Found: 181.08584.
5a-(tert-butyldimethylsilyloxy)hexahydro-2H-benzo[d]oxireno[2,3-c]oxepin-9(9aH)-one (4.61): Epoxide 4.61 was observed from fragmentation of bicyclic diazolactone 4.59 (0.25 mmol, 0.086 g) at 0 °C in (0.0139 g) 15% yield. It was isolated via flash column chromatography on Davisil (hexanes:EtOAc 4:1, 3:1, 2:1, 1:1; Rf = 0.60 in hexanes:EtOAc 2:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.60 (ddd, \(J = 12.3, 7.9, 2.4\) Hz, 1H), 4.12 (ddd, \(J = 12.30, 6.76, 2.48\) Hz, 1H), 3.47 (s, 1H), 2.46 (td, \(J = 13.4, 4.7\) Hz, 1H), 2.10–2.00 (m, 2H), 1.82–1.69 (m, 4H), 1.62–1.54 (m, 2H), 1.03–0.99 (m,1H), 0.92 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.4, 75.2, 68.8, 63.5, 63.3, 41.2, 39.5, 31.0, 26.2, 22.9, 20.5, 18.7, -1.7, -1.8; IR (film): 2949.3, 2932.8, 2859.5, 1731.2, 1472.7, 1463.0, 1435.1, 1401.3, 1361.8, 1303.9, 1288.5, 1278.8, 1260.5, 1225.8, 1166.0, 1140.9, 1119.7, 1082.1, 1047.4, 1007.8, 925.8, 906.5, 876.6, 837.1, 803.4, 775.4, 732.9, 667.4; MS (ESI): Calculated for [C\(_{16}\)H\(_{28}\)O\(_4\)]\(^+\): 313.18296, Found: 313.18316.

Bicyclic lactone acetal (4.62): Acetal 4.62 was observed from the fragmentation of bicyclic diazolactone 4.59 (0.25 mmol, 0.086 g) at 0 °C in (0.0121 g) 15% yield. It was isolated via flash column chromatography on Davisil (hexanes:EtOAc 4:1, 3:1, 2:1, 1:1; Rf = 0.52 in hexanes:EtOAc 2:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.75 (dd, \(J = 5.85, 0.7\) Hz, 1H), 3.17 (d, \(J = 18.8\) Hz, 1H), 2.39 (d, \(J = 18.6\) Hz, 1H), 2.37–2.33 (m, 1H), 2.15 (app. d, \(J = 14.3\) Hz, 1H), 1.92–1.85 (m, 2H), 1.59–1.40 (m, 6H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); \(^{13}\)C NMR (125 MHz, (CD\(_3\))\(_2\)CO) \(\delta\) 168.2, 101.3, 82.6, 79.2, 49.8, 39.7, 38.8, 31.8, 26.2, 21.5, 21.4, 18.7, -2.7, -2.9; MS (ESI): Calculated for [C\(_{16}\)H\(_{28}\)O\(_4\)]\(^+\): 313.18296, Found: 313.18304.
Methyl 1-hydroxy-2-oxocycloheptanecarboxylate (4.72a): The title compound was prepared from commercially available methyl 2-oxocycloheptanecarboxylate (4.71a) (2.01 g, 11.8 mmol) by the method described for the preparation of 4.22. Purification of the crude product via flash silica gel chromatography (hexanes:EtOAc 8:1; Rf = 0.25 in hexanes:EtOAc 5:1) afforded the title compound in (1.44 g) 66% yield. $^1$H and $^{13}$C NMR spectral data matched previously reported values.\(^{229}\)

Ethyl 1-hydroxy-2-oxocyclooctanecarboxylate (4.72b): The title compound was prepared from commercially available ethyl 2-oxocyclooctanecarboxylate (4.71b) (4.88 g, 24.8 mmol) by the method described for the preparation of 4.22. Purification of the crude product via flash silica gel chromatography (hexanes:EtOAc 6:1; Rf = 0.27 in hexanes:EtOAc 5:1) afforded the title compound in (5.26 g) 99% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.35 (d, $J$ = 1.6 Hz, 1H), 4.19 (q, $J$ = 7.1 Hz, 2H), 3.05 (dd, $J$ = 12.4, 3.9 Hz, 1H), 2.74–2.68 (m, 1H), 2.40–2.36 (m, 1H), 2.15 (dt, $J$ = 15.3, 3.9 Hz, 1H), 1.98–1.93 (m, 1H), 1.82–1.63 (m, 4H), 1.47–1.32 (m, 2H), 1.26 (t, $J$ = 7.1 Hz, 3H), 0.90–0.86 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 213.1, 170.4, 83.0, 62.0, 36.8, 30.4, 30.1, 25.4, 24.1, 22.2, 13.9; MS (ESI): Calculated for [C$_{21}$H$_{42}$O$_4$Si$_2$Na]$^+$: 237.1103, Found: 237.1105.

Methyl-1,2-bis(tert-butyldimethylsilyloxy)cyclohept-2-ene-carboxylate (4.73a): Compound 4.73a was prepared from 4.72a (0.15 g, 0.79 mmol) by the method described for the preparation of 4.23. Purification by silica gel flash column chromatography (hexanes:Et$_2$O 50:1; Rf = 0.75 in...
hexanes:EtOAc 5:1) provided the title compound as a colorless oil in (0.30 g) 93% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.02 (dd, $J = 6.9$, 5.6 Hz, 1H), 3.68 (s, 3H), 2.14 (ddd, $J = 14.5$, 11.6, 4.7 Hz, 1H), 2.10–2.02 (m, 2H), 1.94–1.86 (m, 1H), 1.76 (td, $J = 14.6$, 3.9 Hz, 2H), 1.67–1.52 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.16 (s, 6H), 0.15 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.6, 152.9, 110.5, 83.0, 51.9, 35.7, 26.7, 26.3, 26.1, 23.3, 22.4, 19.2, 18.4, -2.7, -2.8, -4.3, -4.6; MS (ESI): Calculated for [C$_{21}$H$_{42}$O$_4$Si$_2$H]$^+$: 415.26944, Found: 415.26939.

**(E)-Ethyl 1,2-bis(tert-butyldimethylsilyloxy)cyclooct-2-enecarboxylate**

(4.73b): Compound 4.73b was prepared from 4.72b (0.20 g, 0.91 mmol) by the method described for the preparation of 4.23. Purification by silica gel flash column chromatography (hexanes:Et$_2$O 30:1; Rf = 0.72 in hexanes:EtOAc 5:1) provided the title compound as a colorless oil in (0.38 g) 94% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.74 (dd, $J = 9.8$, 8.5 Hz, 1H), 4.19 (qd, $J = 10.8$, 7.2 Hz, 1H), 4.05 (qd, $J = 10.8$, 7.1 Hz, 1H), 2.42 (tdd, $J = 14.2$, 9.7, 7.0 Hz, 1H), 2.21 (dt, $J = 14.5$, 7.3 Hz, 1H), 2.16–2.03 (m, 2H), 1.76–1.64 (m, 3H), 1.58–1.48 (m, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 0.89 (two singlet, 18H), 0.17 (s, 3H), 0.14 (s, 3H), 0.137 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.9, 152.7, 105.6, 82.7, 60.9, 37.0, 27.4, 26.3, 26.1, 23.7, 23.3, 22.6, 19.2, 18.5, 14.2, -2.5, -2.6, -4.3, -4.4; MS (ESI): Calculated for [C$_{23}$H$_{46}$O$_4$Si$_2$H]$^+$: 443.30074, Found: 443.30074.
(1,2-Bis(tert-butyldimethylsilyloxy)cyclohept-2-enyl)methanol (4.74a): The title compound was prepared from 4.73a (2.84 g, 6.85 mmol) following the same procedure used to prepare 4.24. Purification by silica gel flash column chromatography (hexanes:EtOAc 5:1; Rf = 0.80 in hexanes:EtOAc 5:1) provided compound 4.74a as a colorless oil in (2.13 g) 80% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.06 (dd, $J$ = 7.9, 5.6 Hz, 1H), 3.58 (s, 1H), 3.56 (d, $J$ = 1.6 Hz, 1H), 2.20 (dqd, $J$ = 16.2, 5.3, 2.5 Hz, 1H), 2.00 (dd, $J$ = 7.4, 6.2 Hz, 1H), 1.94 (dq, $J$ = 7.8, 2.3 Hz, 1H), 1.88–1.83 (m, 3H), 1.74–1.68 (m, 1H), 1.65–1.61 (m, 1H), 1.48–1.40 (m, 1H), 0.94 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.9, 111.1, 80.0, 68.8, 34.4, 26.9, 26.2, 26.19, 23.6, 23.1, 18.8, 18.5, -2.6, -2.7, -4.1, -4.4; MS (ESI): Calculated for [C$_{20}$H$_{42}$O$_3$Si$_2$Na]$^+$: 409.25647, Found: 409.25635.

(E)-(1,2-Bis(tert-butyldimethylsilyloxy)cyclooct-2-enyl)methanol (4.74b): The title compound was prepared from 4.73b (0.27 g, 0.61 mmol) following the same procedure used to prepare 4.24. Purification by silica gel flash column chromatography (hexanes:EtOAc 5:1; Rf = 0.79 in hexanes:EtOAc 5:1) provided compound 4.74b as a colorless oil in (0.16 g) 64% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.79 (dd, $J$ = 9.9, 8.6 Hz, 1H), 3.76 (dd, $J$ = 11.0, 3.9 Hz, 1H), 3.47 (dd, $J$ = 10.9, 10.0 Hz, 1H), 2.84 (dddd, $J$ = 14.0, 12.2, 9.9, 5.6 Hz, 1H), 2.18 (dd, $J$ = 9.9, 3.8 Hz, 1H), 1.99–1.88 (m, 2H), 1.80–1.74 (m, 1H), 1.63–1.57 (m, 4H), 1.49–1.37 (m, 2H), 0.94 (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.1, 107.5, 80.6, 68.8, 37.0, 28.1, 26.3, 26.1, 24.1,
2.8, 22.4, 18.8, 18.4, -2.6, -3.7, -4.6; MS (ESI): Calculated for \([\text{C}_{21}\text{H}_{44}\text{O}_3\text{Si}_2\text{H}]^+\): 401.29017, Found: 401.29030.

**2-(tert-Butyldimethylsilyloxy)-2-(hydroxymethyl) cycloheptanone (4.75a):**

Compound 4.75a was prepared from 4.74a (0.15 g, 0.40 mmol) by the method described for the preparation of 4.18. The title compound was obtained in (0.09 g) 87% yield after purification by silica gel flash column chromatography (hexanes:EtOAc 8:1; Rf = 0.36 in hexanes:EtOAc 5:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.70 (dd, \(J = 11.4, 7.2\) Hz, 1H), 3.60 (dd, \(J = 11.4, 6.4\) Hz, 1H), 2.77-2.72 (m, 1H), 2.44 (ddd, \(J = 13.7, 12.5, 4.8\) Hz, 1H), 2.29 (dd, \(J = 7.1, 6.5\) Hz, 1H), 1.78–1.71 (m, 5H), 1.63–1.56 (m, 2H), 1.47–1.38 (m, 1H), 0.90 (s, 9H), 0.21 (s, 3H), 0.09 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 214.5, 84.5, 68.5, 40.1, 36.0, 29.3, 26.1, 25.3, 23.9, 18.8, -2.3, -2.8; MS (ESI): Calculated for [\(\text{C}_{14}\text{H}_{28}\text{O}_3\text{SiNa}\)]\(^+\): 295.16999, Found: 295.17004.

**2-(tert-Butyldimethylsilyloxy)-2-(hydroxymethyl) cyclooctanone (4.75b):**

Compound 4.75b was prepared from 4.74b (0.16 g, 0.39 mmol) by the method described for the preparation of 4.18. The title compound was obtained in (0.10 g) 85% yield after purification by silica gel flash column chromatography (hexanes:EtOAc 8:1; Rf = 0.31 in hexanes:EtOAc 5:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.75 (dd, \(J = 11.4, 7.2\) Hz, 1H), 3.57 (dd, \(J = 11.4, 6.4\) Hz, 1H), 2.69 (ddd, \(J = 12.1, 7.9, 4.0\) Hz, 1H), 2.39 (ddd, \(J = 12.3, 9.3, 4.2\) Hz, 1H), 2.15 (dd, \(J = 6.5, 7.1\) Hz, 1H), 2.04 (dd, \(J = 14.6, 3.4\) Hz, 1H), 1.94–1.80 (m, 3H), 1.74–1.66 (m, 1H), 1.63–1.44 (m, 3H), 1.39–1.34 (m, 2H), 0.91 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H); \(^{13}\)C
NMR (125 MHz, CDCl$_3$) $\delta$ 217.9, 84.4, 68.6, 37.8, 34.1, 28.9, 26.3, 26.2, 25.3, 22.3, 18.9, -2.3, -2.7; MS (ESI): Calculated for [C$_{15}$H$_{30}$O$_3$SiH]$^+$: 287.20370, Found: 287.20376.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocycloheptyl)methyl 2-bromoacetate (4.76a): The title compound was prepared from 4.75a (1.38 g, 5.08 mmol) following the same procedure used to prepare 4.26. The crude product was purified via flash silica gel column chromatography (hexanes:EtOAc 10:1; Rf = 0.56 in hexanes:EtOAc 5:1) to provide compound 4.76a in (1.91 g) 95% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.34 (d, $J = 11.2$ Hz, 1H), 4.15 (d, $J = 11.3$ Hz, 1H), 3.82 (s, 2H), 2.70 (ddd, $J = 11.7$, 7.1, 4.7 Hz, 1H), 2.52 (ddd, $J = 12.8$, 10.6, 4.1 Hz, 1H), 1.86–1.75 (m, 4H), 1.68–1.61 (m, 2H), 1.59–1.50 (m, 1H), 1.47–1.38 (m, 1H), 0.88 (s, 9H), 0.19 (s, 3H), 0.08 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 211.4, 166.8, 82.6, 69.9, 40.3, 35.7, 29.3, 25.9, 25.6, 25.5, 23.6, 18.6, -2.4, -2.9; MS (ESI): Calculated for [C$_{16}$H$_{29}$BrO$_4$SiH]$^+$: 393.10913, Found: 393.10927.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclooctyl)methyl 2-bromoacetate (4.76b): The title compound was prepared from 4.75b (0.11 g, 0.38 mmol) following the same procedure used to prepare 4.26. The crude product was purified via flash silica gel column chromatography (hexanes:EtOAc 8:1; Rf = 0.68 in hexanes:EtOAc 5:1) to provide compound 4.76b in (0.15 g) 98% yield. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.41 (d, $J = 11.6$ Hz, 1H), 4.15 (d, $J = 11.6$ Hz, 1H), 3.80 (s, 2H), 2.63 (ddd, $J = 12.3$, 7.6, 3.6 Hz, 1H), 2.45 (ddd, $J = 12.3$, 10.2, 4.0 Hz, 1H), 2.09 (ddd, $J = 14.5$, 11.2, 3.5 Hz, 1H), 1.95–1.80 (m, 3H), 1.74–1.66 (m, 1H), 1.64–187
1.57 (m, 1H), 1.52–1.44 (m, 2H), 1.40–1.29 (m, 2H), 0.89 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 214.8, 166.8, 82.5, 70.2, 37.6, 33.7, 29.1, 26.3, 26.0, 25.4, 24.8, 22.2, 18.8, -2.4, -2.8; MS (ESI): Calculated for [C$_{17}$H$_{31}$BrO$_4$SiNa]$^+$: 429.10672, Found: 429.10707.

9a-(tert-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyoctahydrocyclohepta[c]pyran-3(1H)-one (4.78-cis and 4.78-trans): Diazo lactones 4.78-cis and 4.78-trans were prepared from bromoester 4.76a (0.16 g, 0.40 mmol) by the same method used to make 4.20-cis/trans. Purification of the crude product by flash chromatography on Davisil support (hexanes:EtOAc 12:1, 10:1, 5:1, 3:1) provided the bicyclic diazo lactones as two separated diastereomers with the following spectral data:

4.78-cis: (0.034 g, 25% yield; Rf = 0.19 in hexanes:EtOAc 5:1): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.01 (d, $J$ = 12.3 Hz, 1H), 3.96 (d, $J$ = 12.3 Hz, 1H), 3.60 (d, $J$ = 1.7 Hz, 1H), 2.02–1.90 (m, 3H), 1.87–1.73 (m, 3H), 1.59–1.46 (m, 3H), 1.37–1.28 (m, 1H), 0.92 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.5, 75.5, 75.2, 70.1, 65.9, 35.9, 34.7, 28.9, 25.9, 21.6, 20.2, 18.6, -2.6, -2.9; IR (film): 3503.8, 2929.0, 2857.7, 2102.5, 1693.57, 1464.0, 1392.7, 1287.5, 1128.4 cm$^{-1}$; MS (ESI): Calculated for [C$_{16}$H$_{28}$N$_2$O$_4$SiH]$^+$: 341.18911, Found: 341.18928.
4.78-trans: (0.045 g, 33% yield; Rf = 0.36 in hexanes:EtOAc 5:1): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.18 (d, \(J = 10.8\) Hz, 1H), 3.73 (d, \(J = 10.7\) Hz, 1H), 2.99 (d, \(J = 2.2\) Hz, 1H), 2.14–2.04 (m, 2H), 1.84 (tt, \(J = 13.9, 1.7\) Hz, 1H), 1.78–1.69 (m, 3H), 1.68–1.52 (m, 3H), 1.39–1.31 (m, 1H), 0.90 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 164.6, 79.8, 73.3, 70.8, 62.8, 33.9, 29.9, 25.9, 25.3, 19.9, 18.2, 17.4, -2.6, -3.1; IR (film): 3515.4 (b), 2952.2, 2932.9, 2859.6, 2102.5, 1699.4, 1465.9, 1383, 1302.9, 1264.4 cm\(^{-1}\); MS (ESI): Calculated for \([C_{16}H_{28}N_2O_4SiH]^+\): 341.18911, Found: 341.18915.

(1-(tert-Butyldimethylsilyloxy)-2-oxocyclooctyl)methyl 2-diazoacetate (4.77b): Diazooester 4.77b was prepared from the corresponding bromoester 4.76b (2.64 g, 6.48 mmol) by the method used to make 4.20-cis/trans. Purification of the crude product by flash chromatography on Davisil support (hexanes:EtOAc 10:1, 8:1, 6:1, 4:1, 2:1, 1:1; Rf = 0.46 in hexanes:EtOAc 5:1) provided diazoester 4.77b in (1.57 g) 68% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.72 (bs, 1H), 4.38 (d, \(J = 11.5\) Hz, 1H), 4.16 (d, \(J = 11.5\) Hz, 1H), 2.57 (ddd, \(J = 12.3, 6.8, 3.9\) Hz, 1H), 2.46 (dt, \(J = 11.2, 4.3\) Hz, 1H), 2.08 (ddd, \(J = 14.3, 11.6, 3.3\) Hz, 1H), 1.92–1.78 (m, 3H), 1.75–1.67 (m, 1H), 1.65–1.58 (m, 1H), 1.51–1.35 (m, 3H), 1.32–1.24 (m, 1H), 0.88 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 215.0, 166.2 (b), 82.8, 69.1, 46.3 (b), 37.7, 33.6, 29.2, 26.3, 25.9, 24.8, 22.2, 18.8, -2.5, -2.8; IR (film): 3125.8, 2946.4, 2857.7, 2114.1, 1701.3, 1471.8, 1388.8, 1351.2, 1249.9, 1156.4; MS (ESI): Calculated for \([C_{17}H_{30}N_2O_4SiNa]^+\): 377.18671, Found: 377.18683.
4-Oxacycloundecyne-3,6-dione (4.79): Following representative experimental procedure 1 or 2 that were used to prepare 4.31, diazolactone 4.78a-cis provided 11-membered cyclic ynoate 4.79 in 64% yield (0.056 g) at 0 °C and 84% yield (0.089 g) at 40 °C. Diazolactone 4.78a-trans provided 4.79 in 57% yield (0.0093 g) at 0 °C and in 67% yield (0.074 g) at 40 °C. The product was purified via flash chromatography on Davisil (hexanes:EtOAc 8:1, 6:1, 4:1, 2:1, and 1:1; Rf = 0.22 in hexanes:EtOAc 1:1). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.90 (s, 2H), 2.54–2.51 (m, 2H), 2.45 (t, \(J = 6.3\) Hz, 2H), 1.84 (dtd, \(J = 12.6, 7.0, 3.5\) Hz, 2H), 1.67–1.62 (m, 2H), 1.59 (ddt, \(J = 19.5, 7.1, 1.7\) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 204.2, 153.5, 97.2, 72.8, 71.7, 37.7, 24.1, 23.0, 22.9, 18.3; IR (film): 2946.4, 2876.9, 2224.0, 1726.4, 1554.7, 1464.0, 1430.3, 1371.5, 1280.8, 1209.4, 1192.1, 1162.2, 1128.4, 1092.7, 1028.1, 1011.7, 954.8, 738.8; MS (ESI): Calculated for [C\(_{10}\)H\(_{12}\)O\(_3\)H]\(^+\): 181.08592, Found: 181.08585.

rel-(3aS,9aR)-3a-((tert-butyldimethylsilyl)oxy)-3-diazo9a (hydroxymethyl) octa hydro cyclo octa[b] furan-2(3H)-one (4.85): Lithium bis(trimethylsilyl)amide (1 M in THF/ethyl benzene, 1.90 mL, 1.89 mmol) was added to -78 °C THF (142 mL). A solution of diazoester 4.77b (0.50 g, 1.42 mmol) in THF (10 mL) was added dropwise via a syringe pump over 24 hours while maintaining the reaction at -78 °C. The reaction was then quenched with saturated aq. NH\(_4\)Cl (70 mL) at which point it was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 70 mL). The organic layers were combined, washed with brine, dried over anhydrous
CaCl$_2$ and concentrated to a solid residue. Flash column chromatography (hexanes:EtOAc 6:1, 4:1, 2:1, 1:1) afforded 0.32 g (64% yield) of the title compound as an oil (Rf = 0.16 in hexanes:EtOAc 5:1): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.99–3.94 (m, 1H), 3.88–3.84 (m, 1H), 2.33 (dt, $J = 13.3$, 2.5 Hz, 1H), 2.04–1.74 (m, 9H), 1.46–1.35 (m, 2H), 1.13–1.05 (m, 1H), 0.98 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 167.9, 96.4, 81.4, 65.1, 62.6, 33.7, 29.5, 28.6, 28.4, 26.5, 26.3, 25.3, 18.8, -2.9, -3.1; IR (film): 3490.9 (b), 2930.9, 2857.7, 2095.75, 1743.7, 1471.8, 1464.0, 1371.5, 1255.7; MS (ESI): Calculated for [C$_{17}$H$_{30}$N$_2$O$_4$SiH]$^+$: 355.20476, Found: 355.20539.

$rel$-(3aS,9aR)-3a-((tert-butyldimethylsilyl)oxy)octahydro-2H-3,9a-
(epoxymethano) cyclo octa[b]furan-2-one (4.86): Following representative experimental procedure 1 that was used to prepare 4.31, diazolactone 4.85 (0.027 g, 0.075 mmol) reacted at 0 °C to give 0.020 g (80% yield) of ether 4.86 after purification via flash column chromatography on Davisil (hexanes:EtOAc 10:1; Rf = 0.57 in hexanes:EtOAc 2:1). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.31 (d, $J = 8.9$ Hz, 1H), 3.91 (s, 1H), 3.74 (d, $J = 9.0$ Hz, 1H), 2.16–2.10 (m, 1H), 2.06–1.93 (m, 5H), 1.86–1.81 (m, 1H), 1.78–1.71 (m, 1H), 1.63–1.55 (m, 1H), 1.31–1.22 (m, 2H), 1.13–1.06 (m, 1H), 0.91 (m, 9H), 0.14 (s, 3H), 0.12 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.3, 95.6, 84.9, 83.4, 70.9, 33.1, 31.1, 29.2, 25.8, 25.7, 23.8, 22.5, 18.4, -2.3, -2.4; IR (film): 2929.0, 2857.7, 1791.9, 1472.7, 1454.4, 1362.8, 1255.7, 1199.8, 1174.7, 1133.2, 1087.9, 1067.7, 1007.9, 907.6, 837.1, 809.2, 778.3, 675.1; MS (ESI): Calculated for [C$_{17}$H$_{30}$O$_4$SiH]$^+$: 327.19861, Found: 327.19871.
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APPENDIX

Spectroscopic Data
2.22
4.78 - cis