The chain extension of beta-keto phosphonates and the synthesis of polycyclopropanes

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THE CHAIN EXTENSION OF β-KETO PHOSPHONATES

and

THE SYNTHESIS OF POLYCYCLOPROPANES

by

Christopher A. Verbicky

B.S., The State University of New York at Albany, 1994

DISSERTATION

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in

Chemistry

December, 1999
This dissertation has been examined and approved.

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September 24, 1999
Date
DEDICATION

I would like to dedicate this work to the memory of all those who have lived and died with unrealized potential and to those who have helped me realize my own. Over the course of my education and life, several people have touched me; of whom, some are no longer with us. From those who live, I have learned to never give up working toward happiness. Those who have died have shown me how precious and short life is. I have always dreamed of earning a doctorate in chemistry and without the instruction I have received, both in and out of the classroom, I would certainly not be writing this now.
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LIST OF ABBREVIATIONS

AIBN.................................................................azodiisobutyrylnitrile
Bn.................................................................................benzyl
\( t\)-Boc.................................................................\textit{tertiary}-butyloxycarbonyl
BSA..............................................................................N,O-bis-(trimethylsilyl)acetamide
Bz..................................................................................benzoyl
Cbz.................................................................................carboxybenzyl
CDI...........................................................................carbonyldiimidazole
DCC.............................................................................dicyclohexylcarbodiimide
DDQ..........................................................................2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H...............................................................diisobutylaluminum hydride
DME...........................................................................1,2-dimethoxyethane
DMSO........................................................................dimethylsulfoxide
EDA..............................................................................ethyl diazoacetate
LAH...........................................................................lithium aluminumhydride
KHMDS..............................................................potassium hexamethyldisilylamide
LDA............................................................................lithium diisopropylamide
LiHMDS.............................................................lithium hexamethyldisilylamide
MDA...........................................................................methyl diazoacetate
NaHMDS......................................................................sodium hexamethyldisilylamide
NMO......................................................................N-methylmorpholine-N-oxide
PCC........................................................................pyridiniumchlorochromate
PDC..........................................................................pyridiniumdichromate
PMB...........................................................................\textit{p}-methoxybenzyl
TBAF.......................................................................tetrabutylammonium fluoride
TBDMS......................................................................\textit{tertiary}-butyldimethylsilyl
TBDPS......................................................................\textit{tertiary}-butyldiphenylsilyl
TBS.............................................................................\textit{tertiary}-butyldimethylsilyl
TEA...........................................................................triethylamine
TIPS.................................................................triisopropylsilyl
TMS.................................................................trimethylsilyl
TPAP...............................................................tetrapropylammonium perruthenate
Trit.................................................................triphenylmethyl
ABSTRACT

CHAIN EXTENSION OF β-KETO PHOSPHONATES

and

THE SYNTHESIS OF POLYCYCLOPROPANES

by

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University of New Hampshire, December, 1999

A series of β-keto phosphonates was prepared and their reactivity with the Furukawa-modified Simmons-Smith zinc carbenoid was studied. Various functionality was incorporated into these molecules in efforts to broaden the scope of the zinc-mediated chain extension reaction. The mechanism of the chain extension of dimethyl (2-oxopropyl)phosphonate was probed by nuclear magnetic resonance in efforts to observe key intermediates of these reactions.

The stereochemistry of bis-, tris-, and tetrakis-cyclopropanes was confirmed by a one directional asymmetric independent synthesis. Application of an olefin cross-metathesis reaction allowed vinyl tetrakis-cyclopropane to be elaborated into an advanced intermediate toward the preparation of FR-900848, a polycyclopropanated natural product displaying desirable biological activity. The application of olefin metathesis chemistry represents both a novel and efficient means of incorporating both the intervening E-olefin and sequestered cyclopropane contained within these compounds.

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CHAPTER I

CHAIN EXTENSION OF \( \beta \)-KETO PHOSPHONATES

A. Introduction to Chain Extension Reactions:

The conversion of 1,3-dicarbonyl compounds to 1,4-dicarbonyl compounds is the most frequently used synthetic route to \( \gamma \)-keto esters.\(^1\) Four different methodologies have been employed to effect this conversion and all are believed to proceed through a cyclopropyl alkoxy intermediate. The first method developed by Bieraugel\(^2\) and later improved upon by Saigo\(^3\) involves the cyclopropanation of \( \beta \)-keto ester derivatives, by treatment with a zinc-carbenoid. Reissig and coworkers reported a similar method,\(^4\) which involves the carbenoid-mediated cyclopropanation of an enol ether and proceeds through intermediates similar to those reported by Saigo. Dowd reported a similar radical-based method for the conversion of 1,3-dicarbonyl compounds to 1,4-dicarbonyl compounds.\(^5\) The final and most recent method, described by Zercher,\(^6\) involves the exposure of a \( \beta \)-keto ester, to Furukawa-modified Simmons-Smith cyclopropanation
conditions. Each of these methods provides a unique route to 1,4-dicarbonyl compounds and upon examination of each, the advantages of the final method become apparent.

1. **Saigo's Carbenoid Chain Extension:**

   ![Chemical Structure](image)

   **Scheme 1.** Preparation of Saigo's TMS-Cyclopropyl Ether Intermediate

Saigo's initial report described the treatment of preformed trimethylsilyl (TMS) enol ether 2 with a copper-carbenoid prepared by exposing ethyl diazoacetate to copper(II) sulfate (Scheme 1). The cyclopropyl ring of trimethylsilyl ether 3 was opened by treatment with aqueous acid (Scheme 2). Tautomerization of the enol provided the chain extended product 6. A fluoride-mediated cleavage of the TMS-cyclopropyl ether was reported to proceed with similar efficiency. Although unreported, saponification and decarboxylation of 6 could be envisioned to provide the access to the simple unsubstituted γ-keto ester.
Scheme 2. Fragmentation of Saigo's Intermediate TMS-Cyclopropyl Ether

In efforts to prepare the unsubstituted γ-keto esters, Saigo and coworkers reported a similar strategy in which Simmons-Smith conditions were utilized to effect cyclopropane formation (Scheme 3). Exposure of the TMS-enol ether to a zinc-carbenoid was anticipated to provide the unsubstituted γ-keto ester. Surprisingly, saponification revealed that the reaction produced a mixture of carboxylic acids 7 and 8.

Scheme 3. Attempted Chain Extension Through the Utilization of Zinc-Carbenoids

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The mechanism proposed by Saigo to explain the formation of these unexpected products is outlined in Scheme 4. A zinc-mediated silatropic rearrangement was postulated to result in the ketene acetal 9, which can be cyclopropanated. Another silatropic rearrangement resulted in the chain-extended TMS enol ether 11. Following a second cyclopropanation event to provide 12, the cyclopropyl ether can ring open through cleavage of one of the two cyclopropane bonds, and generate the corresponding products 13 and 14. While this mechanism can be used to rationalize the products formed in the reaction, no evidence supporting these intermediates or the mechanism has been reported.

Scheme 4. Saigo’s Proposed Mechanism Resulting in Unexpected Products
2. Reissig's Chain Extension Method:

Reissig et al. reported the application of an effective chain extension reaction for the preparation of γ-butyrolactones (Scheme 5). This method, similar to that of Saigo, involved the cyclopropanation of a preformed TMS-enol ether. Typically, cyclopropane formation was effected by treatment with an α-diazoester and catalyst.

\[
\begin{align*}
\text{OTMS} & \xrightarrow{\text{MDA, Rh(II)}} \text{TMSO} & \xrightarrow{\text{K}_2\text{CO}_3, \text{MeOH}} \text{CO}_2\text{CH}_3 \\
\text{15} & \xrightarrow{\text{p-TsOH, toluene, 110 °C}} \text{OH} & \xrightarrow{\text{KBH}_4, \text{MeOH}} \text{OCH}_3 \\
\text{19 cis:trans 1:1.5} & \xrightarrow{\text{cis:trans 1:1.5}} \text{18}
\end{align*}
\]

Scheme 5. Reissig's Approach Toward γ-Butyrolactones

The methodology described by Reissig differed from Saigo's in that the ester moiety of the resulting γ-keto ester was added as part of the carbenoid utilized in the cyclopropanation event. Treatment of the trimethylsilyl cyclohexyl enol ether 15 with methyl diazoacetate (MDA) and rhodium (II) acetate resulted in the formation of the TMS cyclopropyl ether 16. Exposure of this cyclopropyl ether to potassium carbonate in methanol resulted in the cleavage of the TMS-ether and a ring-opening event, resulting in γ-keto ester 17. The ketone moiety was reduced with potassium borohydride, providing the γ-hydroxy ester 18. This four-step conversion of a ketone to a γ-hydroxy ester was

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improved through the cleavage of the TMS-ether with methanolic potassium borohydride; the resulting \( \gamma \)-keto ester is then reduced with residual borohydride and provides the identical compound. The resulting \( \gamma \)-hydroxy ester 18 was cyclized by treatment with \( p \)-toluenesulfonic acid in toluene at 110 °C to provide \( \gamma \)-butyrolactone 19.

3. Dowd’s Radical Mediated Chain Extension:

Dowd and coworkers reported a radical-mediated process (Scheme 6), whereby an \( \alpha \)-substituted-\( \beta \)-keto ester was converted to an \( \alpha \)-substituted-\( \gamma \)-keto ester. Through the alkylation of the substituted \( \beta \)-keto ester with a 1,1-dibromoalkane, the chain-extension substrate 20 was formed. This process resulted in the insertion of a methylene unit between two carbonyls and has been proposed to proceed through a cyclopropoxy radical 22, which is believed to result from the addition of the primary radical 21 into the neighboring ketone carbonyl. Fragmentation of 22 would provide an ester-stabilized radical, which abstracts a hydrogen atom to form 24.

\[
\begin{align*}
\text{Scheme 6. Proposed Mechanism of Dowd’s Radical Mediated Chain Extension}
\end{align*}
\]
In practice, this method involves a two-step reaction sequence. Alkylation of methyl 2-oxocyclopentane carboxylate 25 with sodium hydride and methylene bromide afforded the bromomethyl substituted β-keto ester 26 (Scheme 7). Radical initiation by exposing 26 to azodiisobutylnitrile (AIBN) in the presence of tri-butyltin hydride resulted in the preparation of methyl 3-oxocyclohexyl carboxylate 27.

Scheme 7. Application of Dowd’s Radical-Mediated Ring Expansion

Application of this methodology has provided a variety of α,β-substituted-γ-keto esters; however, there has been no report of the application of this strategy to unsubstituted β-keto esters, presumably due to secondary chemistry arising from elimination of the necessary halide. Additional complications may also be incurred when functionality incompatible with radical character is present in the substrate. Investigation of the compatibility of olefinic functionality with this methodology has yet to be reported.
4. **Zercher's Zinc-Carbenoid Chain Extension:**

![Scheme 8. Zercher's Zinc-Mediated Chain Extension Reaction](image)

A report from the Zercher laboratory describing the reaction of β-keto esters under Furukawa-modified Simmons-Smith cyclopropanation conditions identifies the first one-pot conversion of β-keto esters to γ-keto esters (Scheme 8). Treatment of a β-keto ester with a preformed zinc-carbenoid cleanly resulted in a chain extension reaction, whereby a methylene group was inserted between the ketone and ester carbonyls. This reaction is in essence a one-pot reaction that is equivalent to the reaction described by Saigo. This efficient one-step conversion of β-keto esters 28 to γ-keto esters 29 has been optimized through the use of a fivefold excess of the zinc-carbenoid, generated from a 1:1 mixture of diethylzinc and methylene iodide. Under these conditions, consumption of starting material requires only a few minutes.
Scheme 9. Possible Mechanisms for Zercher's One-Pot Chain Extension

At the time of its initial report, relatively little was known about the mechanism by which this process occurred. Based on the aforementioned chain extension methodologies, three different mechanisms were proposed for the transformation of a β-keto ester to a γ-keto ester under these conditions. Since the basicity of the carbenoid...
was unknown, the first proposed mechanism (Scheme 9A) involved the concerted
cyclopropanation of the enol tautomer 30 of the β-keto ester 28, resulting in the
cyclopropanol 31. Acid-induced fragmentation of 31 was proposed to occur in the
aqueous work-up, resulting in the chain extended material 29. A second mechanism
(Scheme 9B) proposed initial deprotonation of the β-keto ester and the concerted
cyclopropanation of the zinc-enolate 33 to provide the zinc cyclopropyl alkoxide 34.
Fragmentation of 34 and protonation of ester enolate 35 was envisioned to result in the
chain-extended material. Analogous to the method of Dowd, a third mechanism (Scheme 9C)
was proposed to proceed initially by the alkylation of the zinc-enolate 33 with
ethyl(iodomethyl)zinc. Addition of the zinc anion of 36 into the neighboring ketone
carbonyl would provide cyclopropyl alkoxide 34. The fragmentation of 34 was proposed
to occur in a fashion similar to the previous mechanism (Scheme 9B).

Interestingly, the results of some preliminary studies with β-keto sulfones
(Scheme 10) lend support to the mechanism illustrated in Scheme 9C.7 When deuterated
(2-oxo-2-phenylethyl)phenyl sulfone 37 was exposed to chain extension conditions, the
chain extended product anticipated to result from intermediate 39 was not observed.
Instead, phenyl vinyl ketone 40 was produced with deuterium exclusively located on the
carbon adjacent to the carbonyl. This product is proposed to result from elimination of
the phenylsulfinate anion from the intermediate corresponding to 38. The fact that no
deuterium was incorporated at the β-position of the product clearly indicates that the α-
carbon from the starting material translates to the α-carbon in the product.
Scheme 10. Reaction of β-Keto Sulfones Exposed to Chain Extension Conditions.

B. Introduction to γ-keto phosphonates:

In order to explore the generality of the one-pot zinc carbenoid-mediated chain extension reaction, we have subjected a series of β-keto phosphonates to these same carbenoid conditions. The anticipated products of such reactions are γ-keto phosphonates, compounds which have received attention in the recent literature.8, 9, 10, 11, 12 Functionalized phosphonates are important intermediates in the synthesis of many biologically active compounds.13 Compounds containing the phosphonate moiety have been found to exhibit desirable biological activity as anti-viral,14 herbicidal, insecticidal,15 and anti-acidosis agents,16 as well as antibiotics.17

Figure 1. Imidazole Glycerol Phosphonate (IGP) Dehydratase Inhibitors.

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γ-Keto phosphonates are also useful precursors for the preparation of γ-hydroxy phosphonates and phosphonic acids. Both γ-hydroxy phosphonate 42 and γ-hydroxy phosphonic acid 43 were designed as inhibitors of imidazole glycerol phosphate (IGP) dehydratase.9b,10,18 γ-Keto phosphonates 44 have both been reported to be precursors to yet another IGP dehydratase inhibitor.19 This enzyme is responsible for the conversion of D-erythro-(2R,3S)-imidazole glycerol phosphate (IGP) to imidazole acetol phosphate (IAP) in the histidine biosynthesis pathway. Phosphonate analogs of phosphate natural products have also been reported to be useful in the study of enzyme active sites in the glycolytic pathway, as well as in lipid and glycerol related processes.8,20

![Diagram of γ-Keto Phosphonates with Enzyme Inhibitory Activity](image)

**Figure 2.** γ-Keto Phosphonates with Enzyme Inhibitory Activity

The use of γ-keto phosphonates as analogues of peptido-phosphates has become more prevalent in the recent literature and has resulted in the discovery of several
biologically active γ-keto phosphonates. Four γ-keto phosphonates that have been found to inhibit enzymes are illustrated in Figure 2. Recently, the investigation of protease inhibitors has resulted in several active pharmaceutical agents. The α-substituted-γ-keto phosphonate 45 exhibits activity as a matrix metalloprotease inhibitor,\textsuperscript{21} most active against MMP-2 (IC\textsubscript{50}: 35 nM). Similarly, the L-phenylalanine-derived α-substituted-γ-keto phosphonate 46 inhibits kininogenase,\textsuperscript{22} which is the protease that initiates the blood-coagulation cascade.

γ-Keto phosphonic acids are in some cases more active than their phosphonate derivatives. γ-Keto phosphonic acid 47 has been found to be an inhibitor of 5-alanine levulinic acid (ALA) dehydratase (porphobilinogen synthase),\textsuperscript{23} which is an early enzyme in the tetrapyrrole biosynthetic pathway. Along with its 3-thia analog, 47 is a potent mechanism-based inhibitor that inactivates by acylation of an active-site lysine residue.

Another amino acid derived δ-amino-γ-keto phosphonic acid 48 was identified as a tight binding inhibitor of D-alanine:D-alanine ligase (ADP-forming).\textsuperscript{12b,24} Along with alanine racemase, D-alanine:D-alanine ligase is an important enzyme for the synthesis of bacterial cell walls.

The application of γ-keto phosphonates for a particular biological activity ranges from protease inhibitors to agrochemicals. α-Butyl-γ-keto phosphonate 49 is useful as an anti-hypertensive and an analgesic.\textsuperscript{25} The four variants of the γ-keto diphosphonate 50 display a variety of pharmacologically desirable activities, through their action as: non-specific anti-inflammatory, anti-pyretic, analgesic, and anti-arthritic agents. Their use has also been proposed for the treatment of osteoporosis.\textsuperscript{26}
Alternatively, the γ-keto phosphonates 51 and 52a and b are herbicides and fungicides. The γ-hydroxy phosphonate 51, derived from the γ-carbonyl phosphonate, displays pronounced activity against Setaria (at 2000 g/ha). Phosphonates 52a and 52b have been found to be modestly active as herbicides and fungicides.

![Chemical structures](image)

**Figure 3.** Other Biologically Active γ-Keto Phosphonates.

1. Synthetic Routes to γ-Keto Phosphonates:
   a) Conjugate Addition of Silyl Phosphites:

   Birum and Richardson initially reported the addition of silyl phosphites into α,β-unsaturated carbonyl systems in 1963. However, the lack of specific reaction conditions and unreported reported product ratios led Evans and coworkers to study these reactions in greater detail. As well as extending the scope of the reaction, Evans' study reinvestigated the original work describing this methodology and addressed some
“misconceptions.” Despite the efforts of Evans and coworkers, the reaction parameters resulting in 1,2- vs. 1,4-addition could be neither predicted nor controlled. This methodology was utilized by Liotta and coworkers\textsuperscript{29} to prepare diethyl (3-oxocyclohexyl)phosphonate; however, the reaction conditions required to achieve 1,4-addition were harsh and produced inconsistent results.

BSA = N,N-bis(trimethylsilyl)acetamide

Scheme 11. Evans' Approach to \( \gamma \)-Keto Phosphonates as Modified by Mori

Mori \textit{et al.} reported that addition of a Lewis acid catalyst induced 1,4-addition with reaction temperatures as low as 0 °C.\textsuperscript{10a} These conditions (Scheme 11) utilized trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst and N,O-bis(trimethylsilyl)acetamide (BSA) to prepare the silyl phosphite \textit{in situ} from the corresponding phosphinic acid. Therefore, addition of a phosphinic acid to BSA in the presence of an \( \alpha,\beta \)-unsaturated ketone and catalytic TMSOTf provides access to \( \gamma \)-keto phosphonates 55. The typical yields reported for these reactions range from moderate to good (30-80%). When the unsaturated system contained \( \beta,\beta \)-disubstitution, 1,2-addition predominated. Nonetheless, if stoichiometric Lewis acid was added, the 1,4-addition product could be prepared with modest efficiency.
b) Savignac’s Methodology of Preparing γ-Keto Phosphonates:

\[
\begin{align*}
(RO)_{2}P & \xrightarrow{1. \ nBuLi} (RO)_{2}P \xrightarrow{2. \ CuI} (Cl)BrYZ \\
& \xrightarrow{(RO)_{2}P \xrightarrow{Cu} \xrightarrow{conc. \ H_{2}SO_{4}} (RO)_{2}P \xrightarrow{Y=H, \ Z=Br \ or \ Cl} \xrightarrow{(RO)_{2}P \xrightarrow{Y=Br \ or \ Cl, \ Z=H}} \xrightarrow{(RO)_{2}P \xrightarrow{Y=H, \ Z=Br \ or \ Cl} \xrightarrow{(RO)_{2}P \xrightarrow{Y=Br \ or \ Cl, \ Z=H}}}
\end{align*}
\]

Scheme 12. Savignac’s Synthetic Approach to γ-Keto Phosphonates

In 1979, Savignac and coworkers reported a new strategy for the preparation of β- and γ-keto phosphonates, which utilized a Wichterle30 type reaction (Scheme 12). Through the intermediacy of a vinyl halide, β- or γ-keto phosphonates were accessible in good overall yields. Deprotonation of an alkyl phosphonate with n-butyl lithium, followed by the addition of stoichiometric copper(I) iodide provided the copper phosphonate anion 57. When an appropriate dihaloalkene was added to this anion, the vinyl halide 58 was generated. Treatment with concentrated sulfuric acid resulted in hydrolysis to the corresponding keto phosphonate 59. Although this procedure provides γ-keto phosphonates in good yields, its application is limited by the harsh conditions of the hydrolysis step.
c) Conjugate Addition of Trialkyl Phosphites:

A route similar to that developed by Mori and Evans, initially reported by Gorenstein$^{31}$ and further developed by McClure and coworkers$^8$ (Scheme 13), utilizes the carbon analogue of the Ramirez condensation.$^{32}$ This process involves the conjugate addition of a trialkyl phosphite into an $\alpha,\beta$-unsaturated ketone. When the intermediate oxaphosphorane 61 is quenched with water, the simple unsubstituted $\beta$-keto phosphonate 55 results. In contrast, the addition of an electrophile provides a route to $\beta$-substituted $\gamma$-keto phosphonates 62. The application of this method provides reasonable yields of $\gamma$-keto phosphonates; however, this procedure requires access to the readily polymerizable vinyl ketones and has not successfully been performed on $\beta$-substituted vinyl ketones.

\[
\begin{align*}
\text{H}_2\text{O} & \quad \text{(R'OR)_{2\text{P}}C\text{O}_2\text{R}} \\
\text{RCHO} & \quad \text{(R'OR)_{2\text{P}}\text{OC\text{O}R}}
\end{align*}
\]

Scheme 13. McClure's Synthetic Approach to $\gamma$-Keto Phosphonates

\[
\begin{align*}
\text{Scheme 13. McClure's Synthetic Approach to $\gamma$-Keto Phosphonates}
\end{align*}
\]

d) Preparation of $\gamma$-Keto Phosphonates from Vinyl Phosphonates:

Another strategy recently reported by Kabalka and coworkers utilizes the antithetical approach to prepare $\gamma$-keto phosphonates (Scheme 14).$^{33}$ An acyl anion equivalent is prepared by exposing a cuprate to carbon monoxide. When a vinyl
phosphonate 64 is added to this acyl anion, 1,4-addition provides a γ-keto phosphonate anion 65. Addition of an electrophile to the reaction mixture, subsequent to formation on intermediate 65, provides access to α-substituted-γ-keto phosphonates. This method is sensitive to the size of the ketone substituent and the degree of substitution on the vinylphosphonate. The electrophiles utilized in this study were all allylic bromides and increased steric size about the C3-position of the allylic bromide resulted in decreased yields. Most cuprate additions into allylic systems proceed by an $S_N2'$ mechanism; therefore, the use of non-allylic electrophiles may complicate the application of this strategy.

Scheme 14. Kabalka’s Synthetic Route to γ-Keto Phosphonates
C. Results and Discussion:

1. Initial Studies of β-Keto Phosphonates:

As with the β-keto esters, the reaction of unsubstituted β-keto phosphonates with the Furukawa-modified Simmons-Smith reagent was remarkably efficient and a single product was observed by chromatographic analysis. Although the reaction proceeds with as few as 3 equivalents of the presumed ethyl(iodomethyl)zinc species and at temperatures as low as 0 °C, the conversion was optimized when a six-fold excess of both diethylzinc and methylene iodide were used at room temperature. The typical reaction conditions for chain extension of β-keto phosphonates involve addition of the phosphonate to a methylene chloride solution that contained 6 equivalents of diethylzinc and methylene iodide at room temperature.

The proposed mechanism for the zinc-carbenoid mediated conversion of β-keto phosphonates to γ-keto phosphonates is depicted in Figure 4. The reaction is believed to proceed through an anionic intermediate 68, which is formed by the reaction of a β-keto phosphonate with some base in solution; presumably diethylzinc or ethyl(iodomethyl)zinc. The use of ethyl(iodomethyl)zinc as an electrophile was reported by Knochel and coworkers, and is proposed to provide 69. It is unknown to what extent the deprotonation is assisted by the Lewis acidic zinc(II).
This mechanism predicts a decreased reactivity for systems with less acidic α-protons. Therefore, we might expect a decrease in the rate of chain extension of β-keto phosphonates ($pK_a = \sim 17$ in DMSO) as compared with β-keto esters ($pK_a = \sim 14$ in DMSO), which is in fact, observed. The correlation between reactivity and α-proton acidity is further supported by the fact that triethyl phosphonoacetate $72a$ ($pK_a = \sim 18.5$ in DMSO) remained unreacted when exposed to carbenoid conditions. Attempts to increase the reactivity of the phosphonoacetate by utilizing the more acidic bis(2,2,2-trifluoroethoxy)phosphonate $72b$ were also unsuccessful. These results appear to indicate that the ketone functionality is an important entity in the chain extension mechanism and also suggest that acidity alone does not govern reactivity.
In contrast to the unreactive phosphonoacetates 72a and 72b, the chain extension of simple β-keto phosphonates is both facile and efficient. Analysis of the crude reaction mixtures by \textsuperscript{1}H NMR indicated that the consumption of the starting material was accompanied only by product formation, illustrating the efficacy of these reactions. The isolated yields appear to reflect the efficiency of the extraction in the work-up, rather than the efficiency of the chain extension chemistry. The type of phosphonate ester has little or no affect on the reaction, as observed when the commercially available dimethyl and diethyl phosphonates, 73 and 75 respectively, were exposed to carbenoid conditions. The decreased water solubility may explain the high yield obtained of 78. Interestingly,
Mikolajcyk and coworkers have reported the conversion of γ-keto phosphonate 76, resulting from the chain extension of β-keto phosphonate 75, to Methylenomycin B 79 in an overall yield of 34%.37

![Chemical structure diagram]

**Figure 5.** Use of γ-Keto Phosphonates Toward the Synthesis of Methylenomycin B 79.

### 2. Scope of Study:

In spite of the fact that β-keto phosphonates are fairly common in organic synthesis, few are commercially available. Although these few were suitable for initial studies, a complete study required access to β-keto phosphonates that were not commercially available. Several methods have been reported for the preparation of β-keto phosphonates and provided access to substrates containing a wide range of available functionality. We desired to study β-keto phosphonates that were analogous to the β-keto esters studied earlier. By studying similar systems we hoped to identify both general limitations and substrate specificity of this chain extension methodology. Therefore, β-keto phosphonate substrates were chosen to include α-substitution and olefinic functionality. In addition, the effects of remote Lewis basic functionality were examined in a study of amino acid derived β-keto phosphonates.
3. **Chain Extension of α-Substituted β-Keto Phosphonates:**

Based upon the results of the chain extension reaction of β-keto esters, a prediction regarding the location of the new methylene unit in the product could be made. As in the case of the β-keto esters, it was expected that the newly inserted methylene would be located adjacent to the ketone carbonyl. This hypothesis was tested through the reaction of β-keto phosphonates with α-substitution. The α-substituent served as a label to indicate which carbon was originally in the molecule and which was inserted. In the case of the phosphonates, the assignment of connectivity was simplified by the NMR spin-spin coupling to phosphorus.

**a) Diethyl (1-methyl-2-oxopropyl)phosphonate:**

Deprotonation of the commercially available diethyl (2-oxopropyl)phosphonate 75 with sodium hydride and alkylation with methyl iodide provided easy access to diethyl (1-methyl-2-oxopropyl)phosphonate 80.

![Chemical Reaction](attachment:image.png)

**Scheme 15. Alkylation of Diethyl (2-Oxopropyl)phosphonate 75**

The standard chain extension reaction conditions, as optimized for the substrates shown in Table 1, involve the exposure of substrate to 6 equivalents of an equimolar mixture of diethylzinc and methylene iodide. Application of the “standard” conditions to diethyl (1-methyl-2-oxopropyl)phosphonate 80 (Scheme 16) resulted in poor yields of...
the product 81, although significant amounts of starting material were recovered. As the reaction times were increased, higher yields were observed. The reaction time was eventually optimized at 6 hours with a 70% yield. Compared to the β-keto ester study, where α-substitution negatively impacted the chain extension chemistry,

\[
\text{Scheme 16. Chain Extension of } \alpha\text{-Substituted Phosphonate 80}
\]

Analysis of the product 81 confirmed that the new methylene unit was inserted adjacent to the carbonyl and that the product contained a methyl substituent on the carbon adjacent to the phosphorus. This assignment was confirmed by \( ^1\text{H} \), \( ^{13}\text{C} \), and DEPT NMR experiments, which indicated the presence of a methyl group with \( ^2J_{PC} = 5.2 \text{ Hz} \), \( ^3J_{PH} = 18.3 \text{ Hz} \) and a methine carbon with \( ^1J_{PC} = 143.7 \text{ Hz} \). These coupling constants confirm the location of the methyl substituent to be on the carbon adjacent to the phosphorus, which indicates that the methylene group was incorporated adjacent to the ketone in a fashion similar to the β-keto esters and the previously reported methodologies.

b. Diethyl (2-oxocyclopentyl)phosphonate:
Acyclic β-keto phosphonates rearrange irreversibly to provide enol phosphates.\textsuperscript{39} Interestingly, the preparation of cyclic alkyl β-keto phosphonates has been reported to proceed through an enol phosphate. When a cyclic enol phosphate is treated with lithium diisopropylamide (LDA) at low temperatures, a 1,3-phosphorus shift resulting in the β-keto phosphonate ensues. This procedure was utilized to prepare diethyl (2-oxocyclopentyl)phosphonate 84 (Scheme 17). Treatment of cyclopentanone with LDA at low temperature followed by addition of diethyl chlorophosphate results in the generation of cyclic enol phosphate 83. Subsequent treatment with more LDA promotes the 1,3-phosphorus shift, providing diethyl (2-oxocyclopentyl)phosphonate 84. Alternatively, isolation and purification of the enol phosphate 83, followed by treatment with LDA at low temperature provides a higher yielding two-step procedure.

\begin{equation}
\begin{array}{c}
\text{82} \\
\xrightarrow{1) \text{LDA}} \\
\xrightarrow{2) \left(\text{CH}_3\text{CH}_2\text{O}\right)_2\text{P(O)Cl}} \\
\text{83} \\
\xrightarrow{\text{LDA}} \\
\text{84}
\end{array}
\end{equation}

\textbf{Scheme 17. Synthesis of Diethyl (2-Oxocyclopentyl)phosphonate 84}

Once again, application of the zinc carbenoid-mediated chain extension reaction conditions to an α-substituted-β-keto phosphonate 84 resulted in poor yields when the reaction times were limited. However, with increased reaction times, the ring expansion/chain extension reaction of 84 provided a high-yielding route to diethyl (3-oxocyclohexyl)phosphonate 85. Analysis of the product by \textsuperscript{1}H, \textsuperscript{13}C and DEPT NMR confirmed that the methylene was inserted adjacent to the carbonyl and provided spectra.
consistent with the literature.\textsuperscript{10b} The observation of the phosphorus coupling to the methine carbon ($J_{PC} = 145.7$ Hz) provided compelling evidence for the assigned connectivity of product 85.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\ce{\(\text{P(OCH}_2\text{CH}_3\)}\text{\_2} \rightarrow \text{Et}_2\text{Zn} \text{CH}_2\text{I}_2}};
\node at (2.5,0) {\ce{\(\text{P(OCH}_2\text{CH}_3\)}\text{\_2}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 18.} Chain Extension-Ring Expansion Reaction.

Interestingly, compound 85 is a precursor to several biologically active compounds. Conversions of 85 to the imidazole glycerol phosphate dehydratase inhibitors 42 and 43, a structurally similar herbicide 86, active against \textit{Stellaria} and \textit{Setaria},\textsuperscript{40} and a modestly active neurotransmitter antagonist of excitatory synapses in the lateral perforant path of the rat hippocampus 87\textsuperscript{10b} have all been reported.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\ce{\text{N} - \text{N} - \text{C(C}_6\text{H}_3\text{)}_3 \text{\_O \text{P(OCH}_2\text{CH}_3\)}\text{\_2}}};
\node at (3,0) {\ce{\text{H} - \text{N} - \text{N} - \text{H} \text{\_O \text{P(OH}_2\text{)}}}};
\node at (0,-1) {\ce{\text{H}_2\text{N} - \text{N} - \text{H} \text{\_O \text{P(OCH}_2\text{CH}_3\)}\text{\_2}}};
\node at (3,-1) {\ce{\text{H}_2\text{N} - \text{H} \text{\_O \text{P(OH}_2\text{)}_2}}};
\end{tikzpicture}
\end{center}

\textbf{Figure 6.} Biologically Active Compounds Derived from $\gamma$-Keto Phosphonate 85

4. \textbf{Chain extension of olefin-containing phosphonates:}

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This chain extension chemistry utilizes the same zinc-carbenoid that is used for the cyclopropanation of electron rich olefins. For the chain extension reaction to be a synthetically useful tool, the chemoselectivity needs to be understood. When β-keto esters that contain olefinic functionality were examined, the chain extension event occurred more rapidly than the cyclopropanation of olefins. Therefore, when reaction times were reduced, chain extension was observed in the absence of cyclopropane formation. The β-keto phosphonate functionality undergoes chain extension more slowly than the β-keto esters. This fact suggests that the chemoselectivity between cyclopropanation and chain extension may be less efficient than that observed for the β-keto esters. For this reason we felt it may be interesting to investigate the chain extension both-electron rich and electron-deficient olefin containing substrates. Electron deficient olefins undergo cyclopropanation very slowly under Furukawa-modified Simmons-Smith conditions; therefore, the chain extension of substrates that contained electron-deficient olefins were expected to the exclusion of cyclopropane formation.

a. Dimethyl (2-oxo-5-hexenyl)phosphonate:
Scheme 19. Alkylation of a β-Keto Phosphonate Dianion.

By applying a procedure used for the alkylation of similar systems, a β-keto phosphonate that contained an electron-rich olefin was prepared. Alkylation of the dianion of commercially available dimethyl (2-oxopropyl)phosphonate 73, prepared by treatment with excess sodium hydride followed by stoichiometric n-butyl lithium, with allyl bromide provided a β-keto phosphonate 88 which contained the desired electron-rich olefin. Attempts to chain extend dimethyl (2-oxo-5-hexenyl)phosphonate 88 to the exclusion of cyclopropane formation were unsuccessful. Variables such as reaction time and temperature, as well as equivalents of diethylzinc and methylene iodide, were adjusted in efforts to effect exclusive chain extension (Table 2). Although the chain extension reaction appears to occur faster than cyclopropane formation, no reaction conditions were identified which resulted exclusively in chain extension. All of the NMR spectra contained resonances for at least two of the following: starting material 88, chain extended product 89, and cyclopropanated chain extended product 90. The chain extended products were inseparable by simple chromatographic techniques. Although this result was not entirely unexpected, it does describe a limitation of the zinc-carbenoid mediated chain extension reaction.

Table 2. Attempts to optimize the chain extension of Dimethyl (2-oxo-5-hexenyl)phosphonate 88.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method*</th>
<th>Et₂Zn:CH₂I₂</th>
<th>Equivalents</th>
<th>Time</th>
<th>Temperature</th>
<th>89:90:88 (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>1:1</td>
<td>6</td>
<td>180 min</td>
<td>25 °C</td>
<td>1:1:0 (80%)</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>1:1</td>
<td>6</td>
<td>40 min</td>
<td>25 °C</td>
<td>2:1:0 (75%)</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>1:1</td>
<td>6</td>
<td>30 min</td>
<td>25 °C</td>
<td>43:1:0 (37%)</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>1:1</td>
<td>6</td>
<td>25 min</td>
<td>25 °C</td>
<td>3:1:0</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>1:1</td>
<td>6</td>
<td>25 min</td>
<td>0 °C</td>
<td>6:1:trace</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>1:1</td>
<td>3</td>
<td>20 min</td>
<td>25 °C</td>
<td>4:1:4</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>1:1 c</td>
<td>6</td>
<td>30 min</td>
<td>25 °C</td>
<td>8:2:1</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>1:1 d</td>
<td>6</td>
<td>30 min</td>
<td>25 °C</td>
<td>10:2:1</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>1:1</td>
<td>6</td>
<td>20 min</td>
<td>25 °C</td>
<td>3:1:0</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>1:1</td>
<td>6</td>
<td>10 min</td>
<td>25 °C</td>
<td>7.1:1:6.5</td>
</tr>
<tr>
<td>11</td>
<td>C</td>
<td>1:1</td>
<td>6</td>
<td>5 min</td>
<td>25 °C</td>
<td>7.8:1.3:1</td>
</tr>
<tr>
<td>12</td>
<td>C</td>
<td>1:1</td>
<td>6</td>
<td>5 min</td>
<td>25 °C</td>
<td>6.7:1:2.9</td>
</tr>
<tr>
<td>13</td>
<td>C</td>
<td>2:1</td>
<td>3</td>
<td>30 min</td>
<td>25 °C</td>
<td>6.6:1:1.4</td>
</tr>
<tr>
<td>14</td>
<td>C</td>
<td>3:2</td>
<td>2</td>
<td>30 min</td>
<td>25 °C</td>
<td>7.6:1:2</td>
</tr>
<tr>
<td>15</td>
<td>C</td>
<td>6:5</td>
<td>1</td>
<td>30 min</td>
<td>25 °C</td>
<td>20:4:1.1</td>
</tr>
<tr>
<td>16</td>
<td>C</td>
<td>1:1</td>
<td>6</td>
<td>30 min</td>
<td>0 °C</td>
<td>8:1:3.1</td>
</tr>
</tbody>
</table>

a) see text. b) Results of an NMR experiment, no yield was obtained. c) The carbenoid solution was allowed to stir for precisely 10 minutes prior to phosphonate addition. d) The carbenoid solution was allowed to stir for precisely 15 minutes prior to phosphonate addition.

Three general methods were used to study the chemoselectivity of the chain extension reaction. Method A utilized the preformed carbenoid solution, generated by the addition of equimolar amounts of methylene iodide to diethylzinc before addition of the phosphonate. Method B utilized diethylzinc to preform the zinc-enolate of the phosphonate prior to addition to the preformed carbenoid solution. Method C also...
utilized diethylzinc to preform the enolate; however, at this point methylene iodide was added directly to this solution. This method appeared to afford similar results to that of method B, and was used exclusively due to its experimental simplicity.

Regardless of the temperature, reaction time, ratio of diethylzinc to methylene iodide, number of equivalents, or the order of addition of reagents, the product mixture contained some cyclopropanated material. The ratio of uncyclopropanated to cyclopropanated product for these reactions approached an optimized ratio of ~7:1 with one non-reproducible exception (entry 3). The best overall yield was obtained (80%) with a mixture containing approximately 50% of the cyclopropanated material (entry 1). When reaction times were decreased, the percent of cyclopropanated material was decreased; however, the reaction yield was sacrificed. The scattered nature of these data indicated the first hint of irregularity in the performance of the zinc-carbenoid. The working assumption had been that the reaction of diethylzinc and methylene iodide was instantaneous and complete. These results seem to indicate that the chemistry that produced the carbenoid “soup” was much more complicated than originally believed. The generation of the zinc carbenoid will be the topic of a later discussion.

b. Dimethyl (trans-2-oxo-4-phenyl-3-butenyl)phosphonate:

A β-keto phosphonate that contained an electron-deficient olefin was desired to compare with dimethyl (2-oxo-5-hexenyl)phosphonate 88. Through the application of a procedure similar to that utilized by Koskinen et. al., \(^{42}\) dimethyl (E-2-oxo-4-phenyl-3-butenyl)phosphonate 92 was prepared. Treatment of dimethyl methylphosphonate by the slow addition of n-butyl lithium at low temperature followed by the slow addition of
methyl cinnamate, also at low temperature, resulted in dimethyl (E-2-oxo-4-phenyl-3-butenyl)phosphonate 92 in good yield.

![Chemical structure](image)

**Scheme 21.** Preparation of Cinnamyl Derived \( \beta \)-Keto Phosphonate 92

Exposure of dimethyl (E-2-oxo-4-phenyl-3-butenyl)phosphonate 92 to chain extension conditions were expected to provide access to \( \gamma \)-keto phosphonate 93, a compound which has been found to have anti-herpes (type 1) activity in mice.\(^{43}\) However, the chain extension of 92 provided unexpected results. The consumption of starting material occurred more rapidly than any other \( \beta \)-keto phosphonate that has been studied, perhaps a result of the increased acidity of the \( \alpha \)-protons. Once again, application of “standard” reaction parameters (6 equivalents of diethylzinc and 6 equivalents of methylene iodide) resulted in some cyclopropane formation as determined by \(^1\)H and \(^{13}\)C NMR. Attempts to eliminate the cyclopropane formation by manipulation of the reaction conditions were unsuccessful. The cyclopropanation of the electron deficient olefin in 92 was unexpected. However, it is important to recognize that deprotonation and generation of the zinc-enolate results in a change in the electronics of the \( \pi \)-system. This change results in an increased electron density in the olefin, thus increasing its susceptibility to cyclopropane formation.
Scheme 22. Attempted Chain Extension of 92

Table 3. Attempts to optimize the reaction of Dimethyl (E-2-oxo-4-phenyl-3-butenyl)phosphonate 92

<table>
<thead>
<tr>
<th>Entry</th>
<th>Et₂Zn:CH₂I₂</th>
<th>Equivalents</th>
<th>Time</th>
<th>Temperature</th>
<th>93:94:92 (%yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>6</td>
<td>120 min</td>
<td>25 °C</td>
<td>6:1:0*</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>6</td>
<td>45 min</td>
<td>25 °C</td>
<td>4:1:0 (76%)</td>
</tr>
<tr>
<td>3</td>
<td>1:1</td>
<td>6</td>
<td>15 min</td>
<td>25 °C</td>
<td>24:7:1</td>
</tr>
<tr>
<td>4</td>
<td>1:1</td>
<td>6</td>
<td>10 min</td>
<td>25 °C</td>
<td>1.3:1:trace*</td>
</tr>
<tr>
<td>5</td>
<td>1:1</td>
<td>6</td>
<td>5 min</td>
<td>25 °C</td>
<td>5.3:1:2.3*</td>
</tr>
<tr>
<td>6</td>
<td>1:1</td>
<td>6</td>
<td>5 sec</td>
<td>25 °C</td>
<td>0:0:1*</td>
</tr>
<tr>
<td>7</td>
<td>1:1</td>
<td>6</td>
<td>30 min</td>
<td>0 °C</td>
<td>1.3:1:2.2*</td>
</tr>
<tr>
<td>8</td>
<td>1:1</td>
<td>6</td>
<td>30 min</td>
<td>-78 °C</td>
<td>0:0:1*</td>
</tr>
<tr>
<td>9</td>
<td>1:1</td>
<td>3</td>
<td>30 min</td>
<td>25 °C</td>
<td>4:0:1*</td>
</tr>
<tr>
<td>10</td>
<td>1:1</td>
<td>3.5</td>
<td>30 min</td>
<td>25 °C</td>
<td>11:1:1*</td>
</tr>
<tr>
<td>11</td>
<td>1:1</td>
<td>4</td>
<td>30 min</td>
<td>25 °C</td>
<td>23:4:1*</td>
</tr>
<tr>
<td>12</td>
<td>1:1</td>
<td>3</td>
<td>40 min</td>
<td>25 °C</td>
<td>4:trace:1*</td>
</tr>
<tr>
<td>13</td>
<td>1:1</td>
<td>3.25</td>
<td>30 min</td>
<td>25 °C</td>
<td>8:1:0 (69%)</td>
</tr>
</tbody>
</table>

a) Results of an NMR experiment, no yield was obtained. b) Other olefin-containing product was also found in significant concentration.

Characterization of the second component of the product mixture, presumed to be the cyclopropanated chain extended compound 94, was impossible, as the mixture was inseparable by normal chromatographic techniques. However, exposure of the product mixture to anhydrous ethereal diazomethane in the presence of palladium (II) acetate (Scheme 23), a method described by Denmark for the cyclopropanation of electron deficient olefins, resulted in a single compound confirmed to be the cyclopropanated γ-keto phosphonate 94.
5. Effects of Lewis Basic Functionality on the Chain Extension Reaction:

The studies of β-keto esters and β-keto phosphonates had revealed few limitations of this chain extension reaction; however, the effects of Lewis basic functionality had yet to be investigated. The proposed mechanism (Scheme 9c) for formation of the intermediate cyclopropoxide involves an alkylation of a zinc-enolate, followed by nucleophilic addition of the zinc-anion into the carbonyl. None of the substrates in either the β-keto ester or the β-keto phosphonate studies have challenged the chain extension chemistry through the provision of alternative sites of alkylation. Furthermore, the presence of an additional electrophilic moiety that is susceptible to nucleophilic attack may complicate this reaction. We chose to address these issues through the preparation of a series of β-keto phosphonates derived from amino acids. These β-keto phosphonate compounds possess both nucleophilic and electrophilic components that will probe the scope of the zinc-carbenoid mediated chain extension reaction.
The anticipated products of these chain extension reactions are γ-keto δ-amino phosphonates 96. Compounds of this type incorporate the use of the phosphonate replacement for the phosphate moiety and resemble analogs of amino acid phosphates 97. Compounds similar to 97 have been utilized to probe the structure and mechanism for enzymatic systems. McClure and coworkers reported the preparation of substituted γ-keto phosphonates for use as analogs of sphingomyelin and ceramide-1-phosphate. A phosphonate group as in 96 is predicted to have enhanced hydrolytic stability due to the removal of the labile P-O-C bond and replacement with a more robust P-C bond.

Since the methodology utilized earlier to prepare β-keto phosphonate 92 was developed for amino acid substrates, its application for the preparation of these β-keto phosphonate substrates had ample precedent. The starting materials for the generation of β-keto phosphonates are usually methyl esters, therefore it was necessary to protect the amine of the amino acids. Two protecting group options were available. Urethane derivatives of amines are very commonly utilized in peptide chemistry to prevent their reaction with ester intermediates. In addition, the primary structure of peptides includes repeating amide linkages. For these reasons, both urethane and amide protecting groups...
were targeted in this study in an effort to assess the potential application of this chain extension reaction on peptidomimetics.

a. 1-Carboxybenzyl-2-(2-(dimethylphosphono)-1-oxoethyl)pyrrolidine:

The proposed mechanism for the chain extension reaction was believed to proceed through an initial deprotonation event. Our initial studies of amino acid derived β-keto phosphonates focused on proline in order to minimize the number of acidic protons in our substrates. Protection of L-proline 98 with benzyl chloroformate followed by esterification with diazomethane afforded the precursory methyl ester 99. Slow addition of a tetrahydrofuran solution of ester 99 to dimethyl lithiomethylphosphonate at reduced temperature provided the desired β-keto phosphonate 100 in reasonable yield (86%).

\[
\begin{align*}
\text{Scheme 25. Preparation of Cbz-Proline Derived β-Keto Phosphonate 100}
\end{align*}
\]

Exposure of β-keto phosphonate 100 to zinc-carbenoid conditions for the standard 2-hour reaction time provided an inseparable mixture of products. The mixture appeared to contain both the chain-extended material 101 and some other structurally similar compound that could not be identified. When reaction times were decreased, the product
mixture was found to favor the desired material. However, in order to prevent formation of the unidentified product, it was necessary to reduce the reaction time to the point where unreacted starting material was recovered. The reaction was optimized at 45 minutes, providing 46% of the starting β-keto phosphonate and a 33% yield of product (62% based on recovered starting material). The unidentified impurity is believed to result from consumption of 101 and may be a result of the urethane moiety being precariously perched in close proximity to the reaction’s anionic center. However, no direct evidence is available to support this assertion.

![Scheme 26. Chain Extension of Cbz-Proline Derived β-Keto Phosphonate 100](image)

b. 1-Benzoyl-2-(2-dimethylphosphono-1-oxoethyl pyrrolidine:

In efforts to determine whether the unidentified product observed in the reaction of 1-carboxybenzyl-2-(2-dimethylphosphono-1-oxoethyl)pyrrolidine 100 was a consequence of the urethane moiety or simply from the presence of Lewis basic functionality, a second substrate was proposed. Replacement of the urethane moiety with the more robust amide functionality allowed us to probe the protecting group’s role in the secondary chemistry.
Scheme 27. Preparation of Benzoyl Proline derived β-Keto Phosphonate 103

Protection of L-proline with benzoyl chloride, followed by esterification with anhydrous HCl/methanol, provided the methyl ester 102. Slow addition of 102 to a low temperature solution of dimethyl lithiomethyl phosphonate provided 1-benzoyl-2-(2-dimethylphosphono-1-oxoethyl) pyrrolidine 103 in modest yield (52%).

Scheme 28. Chain Extension of Benzoyl Proline Derived β-Keto Phosphonate

Exposure of β-keto phosphonate 103 to the zinc-carbenoid conditions for two hours confirmed that the presence of Lewis basic functionality does not hinder the reaction. The chain extension of 103 proceeded cleanly and provided 1-benzoyl-2-(3-dimethylphosphono-1-oxopropyl)pyrrolidine 104 in high yield (90%). This result confirmed that the Lewis basic functionality was not the source of the secondary chemistry observed in the case of the Cbz-protected β-keto phosphonate 100.
Furthermore, the compatibility of amide functionality with the chain extension reaction supports its potential utility in the field of polypeptide chemistry.

c. **Dimethyl (3-aminocarboxy-\(t\)-butyl-2-oxobutyl)phosphonate:**

The reaction of \(\beta\)-keto phosphonate 103 indicated that Lewis basic functionality does not interfere with the chain extension reaction, yet the question about the stability of the urethane moiety needed to be addressed. Since urethane-protecting groups are prevalent in amino acid and protein chemistry, it is necessary to understand the relationship between urethane functionality and the carbenoid-mediated chain extension reaction. The observed secondary chemistry in the chain extension of \(\beta\)-keto phosphonate 100 has been hypothesized to originate from either the urethane's inherent reactivity or simply from its position near the reactive center. Exposure of an acyclic Boc-protected \(\gamma\)-amino-\(\beta\)-keto phosphonate to the zinc-carbenoid was proposed to address the compatibility of the urethane moiety with the chain extension reaction conditions. The targeted \(\beta\)-keto phosphonate 106 was prepared through the addition of commercially available Boc-D-alanine methyl ester 105 to dimethyl lithiomethylphosphonate at low temperature.

![Chemical reaction](image)

**Scheme 29. Preparation of Boc-Alanine Derived \(\beta\)-Keto Phosphonate 106**
Addition of phosphonate 106 to the zinc-carbenoid afforded the chain extended material 107 in good yield (77%), thereby indicating that the urethane moiety is stable to these reaction conditions; however, care should be taken not to overanalyze this data. Since both the urethane substituent and the amino acid were different in 106 and 100, this study did not address the question as to whether the Cbz-group is stable under these reaction conditions, nor did it address the question about a urethane protected proline. Nonetheless, a Lewis basic urethane survived the reaction. Additional work on the chain extension of amino acid-derived β-keto esters has conclusively shown that the urethane moiety is compatible with the zinc carbenoid, as both Cbz-alanine and Cbz-glycine derived β-keto esters experience chain extension efficiently.\textsuperscript{47} It is important to note that the presence of a modestly acidic N-H in substrate 106 did not interfere with the reaction. Further investigation will be necessary to completely understand the limitations the chain extension reaction places on the protecting group.

Scheme 30. Chain Extension of Boc-Alanine Derived β-Keto Phosphonate 106

6. Application of Chain Extension Chemistry to the Preparation of Isosteric Analogs of Peptido Phosphates:

Successful application of the chain extension chemistry to the amino acid-derived β-keto phosphonates indicated that the Lewis basic functionality does not have a
detrimental effect on the reaction. The inefficient reaction of the Cbz-proline derived \( \beta \)-keto phosphonate 100 suggested that the Cbz protecting group might not be stable to the chain extension reaction conditions. The questionable stability of the Cbz-group was addressed while examining the potential chain extension of dipeptide derived \( \beta \)-keto phosphonates. By utilizing a protected dipeptide we planned to probe the stability of the Cbz-group, which was located in a more remote location.

The anticipated products of these reactions contain the keto-methylene isosteric replacement for the hydrolyzable amide bonds. Use of the keto-methylene isostere generates a hydrolytically stable substrate, which has the potential of acting as an inhibitor of the enzymes responsible for the hydrolytic cleavage of peptides.\(^{48}\) In addition, the predicted products of these reactions also contain the methylene-phosphonate replacement of the phosphate group in peptido-phosphates, which also increases hydrolytic stability.

a. **Dimethyl (3-(2-(carboxybenzylamino)acetamido)-2-oxopropyl)phosphonate:**

A simple dipeptide without stereogenic centers was targeted as our initial substrate. This compound was envisioned to allow assessment of the Cbz-group’s stability to chain extension reaction conditions, while avoiding the potential for increased complexity due to the epimerization of stereocenters.
Scheme 31. Synthesis of Cbz-Glycyl-Glycine Derived β-Keto Phosphonate 110

Treatment of glycyl-glycine 108 with benzyl chloroformate and aqueous sodium carbonate followed by acidification and esterification with anhydrous methanolic hydrogen chloride resulted in the carboxybenzyl dipeptide methyl ester 109. In an analogous fashion to the individual protected amino acids, slow addition of the ester 109 to dimethyl lithiomethylphosphonate at low temperature provided β-keto phosphonate 110. As a result of the high polarity, the purification of 110 by column chromatography was inefficient and resulted in poor yields.

Scheme 32. Attempted Chain Extension of β-Keto Phosphonate 110

Upon exposure to chain extension conditions, phosphonate 110 appears to provide the anticipated product 111 by crude $^1$H NMR; however, the polarity of the γ-keto
phosphonate resulted in significant loss in the aqueous work-up and hindered its purification by normal phase chromatography. Analysis of the crude reaction mixture by $^1$H NMR indicated that the chain extension proceeded as indicated by the disappearance of resonances for the $\alpha$-protons of the starting material and the appearance of the characteristic multiplets of the $\alpha$- and $\beta$-methylene protons. However, the inability to isolate and purify this product limits our ability to make conclusions regarding the stability of the Cbz-group to these reaction conditions.

b. Dimethyl (3-(2-benzamidoacetamido)-2-oxopropyl)phosphonate:

In the case of the amino acid derived $\beta$-keto phosphonate 103, the benzoyl-protecting group provided much better results than did the Cbz-protecting group. Therefore, the benzoyl-protected dipeptide 113 was studied and contrasted with the Cbz-protected substrate 110 in order to assess the feasibility of the chain extension chemistry.

\[ \text{H}_2\text{N} \text{C}(\text{O})\text{CH}_2\text{Li} \text{-78 °C, THF} \]

\[ \text{Bz-Glycyl-Glycine Derived P-Keto Phosphonate 113} \]

Scheme 33. Preparation of Bz-Glycyl-Glycine Derived $\beta$-Keto Phosphonate 113
Treatment of glycyl-glycine with benzoyl chloride in saturated aqueous sodium carbonate followed by acidification and esterification with anhydrous methanolic hydrogen chloride provided the benzoyl-protected glycyl-glycine methyl ester 112. Slow addition of this ester to a cold solution of dimethyl lithiomethylphosphonate provided the benzoyl-glycyl-glycine-derived β-keto phosphonate 113. Being similar to the Cbz-derived substrate 110 with respect to polarity, compound 113 was difficult to purify by chromatographic methods and resulted in poor yields. Nevertheless, analysis of the crude reaction mixture by $^1$H NMR again suggested that the chain extension reaction had occurred. This result indicated that the difficulties encountered with the Cbz-protected substrate 110 were, at least in part, inherent to the glycyl-glycine system.

Scheme 34. Attempted Chain Extension of Bz-Glycyl-Glycine Derived β-Keto Phosphonate 113

c. Dimethyl (3-isobutyryl-3-(2-carboxybenzylamino)acetamido)-2-oxopropylophosphonate:

The glycyl-glycine family was chosen in order to simplify analysis by NMR, however, its selection may have made experimental handling more difficult. The absence of the lipophilic sidechains significantly influenced the solubility properties of these starting materials and their products. Substitution of a more lipophilic amino acid for one
of the glycine residues in the dipeptide was anticipated to provide compounds that would be more easily handled.

Scheme 35. Synthesis of Cbz-Glycyl-Leucine Derived β-Keto Phosphonate 117

Esterification of Cbz-glycyl-leucine 115 by treatment with anhydrous methanolic hydrogen chloride provided the ester precursor 116 to the β-keto phosphonate formation. Addition of the methyl ester to a cold stirring solution of dimethyl lithiomethylphosphonate afforded the β-keto phosphonate 117 in reasonable yield. As anticipated, the β-keto phosphonate was more easily purified.

Scheme 36. Attempted Chain Extension of β-Keto Phosphonate 117
Exposure of the glycyl-leucine dipeptide derived β-keto phosphonate 117 to chain extension reaction conditions resulted in the consumption of starting material within 2 hours. Analysis of the product mixture resulted in the initial assignment of a successful chain extension reaction; the product was observed as a single material by chromatographic analysis and the increased complexity of the NMR spectra were rationalized to result from amide rotamers. Analysis of the product by $^{31}$P NMR provided multiple resonances; also thought to result from amide rotamers. Variable temperature $^1$H NMR studies, ranging from 226-353K, and $^{13}$C NMR studies, ranging from 221-298K, were performed, in order to either “freeze” out the rotamers or speed up their interconversion. Ambient temperature $^{13}$C NMR at reduced field strength (22.5 MHz) was also performed in an attempt to simplify the spectrum by effectively slowing down the NMR time scale. The results of these studies indicated that the slow exchange and fast exchange limits were beyond the temperature ranges allowed by the solvents. Detailed analysis of the product by extensive DEPT, COSY, and HETCOR NMR experiments led to the determination that secondary chemistry had occurred. This was most noticeable by the presence of a methyl singlet in the $^1$H NMR at 3.1 ppm, assigned to be the result of N-methylation. Analysis of the product by electrospray mass spectrometry (Figure 7) unambiguously indicated that multiple compounds were formed. The product with the lowest molecular weight (465 amu) corresponded to the anticipated chain extended product 118. Five additional compounds were formed, each separated by an increase in mass of 14 amu, which corresponds to the addition of extra methylene groups. Alkylation of the amide or urethane nitrogens could account for two of the additional products; however, the remaining three compounds cannot be explained
as resulting from simple alkylation. Potential sources for the methyl groups will be discussed shortly.

Figure 7. Electrospray Mass Spectrum of the Product Resulting from the Chain Extension of Cbz-Gly-Leu-Derived β-Keto Phosphonate 117

d. 1-Carboxybenzyl-2-(3-dimethylphosphono-2-oxopropyl)carboxamido pyrrolidine:

In parallel with the preparation of the Cbz-glycyl-leucine derived β-keto phosphonate 117, an additional substrate that possessed a Cbz-group 121 was prepared. Through attachment of a glycine residue to the Cbz-proline we envisioned moving the reactive β-keto phosphonate to a location more remote with respect to the Cbz-group. In doing so, an increased stability of the Cbz-group to these reaction conditions was anticipated.
Treatment of Cbz-proline 119 with carbonyl diimidazole was sufficient to activate the carboxylate and the addition of glycine methyl ester hydrochloride salt in the presence of imidazole resulted in efficient preparation of the Cbz-dipeptide methyl ester 120. The slow addition of the methyl ester to a cold stirring solution of dimethyl lithiomethylphosphonate afforded β-keto phosphonate 121. Once again, the solubility properties of 121 facilitated purification as compared to the original glycyl-glycine substrates 110 and 113.

Scheme 37. Synthesis of Cbz-Prolyl-Glycine Derived β-Keto Phosphonate 121

Scheme 38. Attempted Chain Extension of β-Keto Phosphonate 121
Upon exposure to chain extension conditions, β-keto phosphonate 121 was quickly consumed and a single product was indicated by chromatographic analysis. Purification by chromatography again provided what appeared to be a single compound whose complex NMR spectra were again interpreted to result from rotamers. Extensive analysis of the product by DEPT, COSY, and HETCOR NMR experiments were not instrumental in deciphering the complex spectra and identifying the product. However, electrospray mass spectrometry (Figure 8) again provided unambiguous evidence that the product was a mixture. In this case, the product mixture appeared to contain two compounds with molecular weights 463 and 477 amu, which do not correspond to the anticipated product, but are 14 and 28 amu higher than the mass of the expected product, respectively.

There appear to be two potential sources for the additional methylene groups. The presence of excess ethyl(iodomethyl)zinc in the reaction mixture is one potential source. Certainly, products arising from additional chain extension could account for an increase in molecular weight by a multiple of 14. Furthermore, the zinc-carbenoid has been demonstrated to methylate amide nitrogens, and could very well be the source of additional methyl groups. A second potential source for additional methylene units resulting from methylation with the dimethyl phosphonate cannot be ruled out. Further studies of dipeptide derived β-keto esters should clarify the source of the additional methylene groups.
7. **Mechanistic Investigations:**

At the time of its discovery by Brogan and Zercher, little was known about the mechanism of the zinc-mediated chain extension reaction. Based upon the previously reported methodologies, three mechanisms were postulated (Scheme 9). Although it is possible that the β-keto esters and the β-keto phosphonates do not proceed through the same mechanism, an investigation of the β-keto phosphonate system may shed light on a generalized mechanism. Toward that end, NMR studies were initiated with the β-keto phosphonates.
a. Observation of the Reaction of Dimethyl (2-Oxopropyl)phosphonate by NMR:

The proposed mechanism for this chain extension process involves a number of intermediates, some of which may persist long enough to be observed by NMR. For clarity, Scheme 39 illustrates the proposed mechanism for the conversion of dimethyl (2-oxopropyl)phosphonate 73 to dimethyl (3-oxobutyl)phosphonate 74. Studies in the chain extension of β-keto phosphonate 92 indicated that when the zinc-enolate was preformed with excess diethylzinc, followed by addition of methylene iodide, the chain extended products 93 and 94 were formed. The reaction was presumed to proceed through the same general mechanism as when the β-keto phosphonate was added directly to the preformed carbenoid, although we needed to be aware that a change in the order of addition of reagents might affect the mechanism of the chain extension reaction. The advantage of this modest change in reaction conditions (incorporated into Scheme 39) lies in that it provides an alternative to attempting to transfer the carbenoid "soup", while minimizing the amount of solvent to that which fits in a standard NMR tube. The precipitate inherent to carbenoid formation precludes the ability to quantitatively transfer a carbenoid solution into an NMR tube. Since gas evolution was observed when diethylzinc was added to the substrate, the zinc-enolate 123 was anticipated to be observable by NMR.
Scheme 39. The Proposed Mechanism of the Chain Extension of Dimethyl (2-Oxopropyl)phosphonate 73

Initial studies were performed by treating dimethyl (2-oxopropyl)phosphonate 73 with diethylzinc in deuterated methylene chloride. Comparison of the $^1$H NMR spectra for the β-keto phosphonate before (Figure 9a) and after the addition of diethylzinc (Figure 9b) served to illustrate enolate formation. Upon treatment with diethylzinc, the doublet that results from proton attached to the α-carbon ($^2J_{PH} = 15.8$ Hz) is found at 4.02 ppm. This downfield shift and decreased integration are consistent with enolate formation. The increased olefin character results in the downfield shift, which is modulated by the increased anionic character that typically results in an upfield shift. In addition, the singlet observed for the terminal methyl group adjacent to the carbonyl is observed to shift upfield (from 2.3 to 2.0 ppm). These spectra indicate that a stable intermediate, which is observable by $^1$H NMR, is present in solution after the addition of diethylzinc. It is worth noting that the singlet at 0.85 ppm in the spectrum (and...
subsequent spectra) corresponds to solubilized ethane gas and may be utilized as an internal standard.

![Figure 9](image)

**Figure 9.** $^1$H NMR Study of the Chain Extension of 73
a) Dimethyl (2-oxopropyl)phosphonate. b) Reaction of Dimethyl (2-oxopropyl)phosphonate and Diethylzinc. c) Result of the Addition of a Slight Excess of CH$_2$I$_2$ to the Reaction of Dimethyl (2-oxopropyl)phosphonate and Diethylzinc.

Addition of excess methylene iodide is marked by a drastic increase in complexity (Figure 9c.). A quartet (3.2 ppm) and a triplet (1.7 ppm) mark the generation of ethyl iodide, a byproduct of the carbenoid formation. Consumption of diethylzinc can be observed by the disappearance of the quartet at 0.2 ppm. The formation of propylzinc
iodide, indicated by the multiplet (1.58 ppm), triplet (0.96 ppm) and triplet (0.58 ppm), is consistent with the report by Charette and is believed to result from the decomposition of ethyl(iodomethyl)zinc.\footnote{51} The formation of ethyl iodide indicates that the methylene iodide is reacting with diethylzinc in a manner expected in the absence of a substrate and suggests that carbenoid formation is unaffected by the substrate.

More important are those changes observed in the resonances for the substrate. The singlet from the methyl group has shifted back downfield. The disappearance of the doublet (4.05 ppm) assigned to the α-proton of 123 is expected. This methine would be expected to shift significantly upfield if it was part of a cyclopropane ring 125 or β- to an anion center as in the ring opened intermediate 126. Unfortunately, with the increased complexity of the upfield region of the spectrum, the presence of cyclopropane resonances cannot be ruled out by these spectra. Perhaps the most informative change observed upon addition of methylene iodide is seen in the signals for the phosphonate methyl esters. In the starting material and enolate intermediate, these methyl groups are chemically and magnetically equivalent, thereby giving rise to a doublet ($^3J_{PH} = 12 \text{ Hz}$). With the addition of methylene iodide, the appearance of two doublets ($^3J_{PH} = 11 \text{ Hz}$) is consistent with diastereotopic methyl groups, which result from the formation of a stereogenic center. This series of NMR experiments indicate that this reaction produces intermediates that are persistent enough to be observed by NMR and that the changes observed between these intermediate spectra are consistent with the proposed mechanism.
The $^1$H-NMR-study of the chain extension reaction of dimethyl (2-oxopropyl)phosphonate was repeated and followed by $^{13}$C, DEPT-135, and $^{31}$P NMR studies. The DEPT-135 and $^{13}$C NMR spectra obtained for the intermediate resulting from the reaction of diethylzinc and dimethyl (2-oxopropyl)phosphonate (Figure 10a and b respectively) appear in complete agreement with the formation of the zinc-enolate. As
seen in the $^1$H-NMR, a signal for solubilized ethane gas is observed in Figure 10b at ~7 ppm. Adjacent to this signal, both upfield and downfield, are the two resonances expected for diethylzinc (CH$_3$ at ~11 ppm and CH$_2$ at ~4.5 ppm). The remainder of the resonances can be interpreted as resulting from the enolate, with one exception. The singlet at ~63 ppm is not coupled to phosphorus, nor is it believed to originate from some species associated with zinc, as broadening is commonly seen in organo-zinc compounds. The zinc enolate is believed to be responsible for the remainder of the resonances observed in Figure 10a and b. A single resonance at 53 ppm can be seen for the methyl phosphonates, indicating that some element of symmetry makes the two methyl groups isochronous. The terminal methyl is seen as a doublet at 28.5 ppm ($^2$J$_{PC}$= 20 Hz) and most significantly, the $\alpha$-carbon identified as the doublet at 74.5 ppm (shifted ~30 ppm downfield compared to the substrate) is marked by the large phosphorus coupling ($^1$J$_{PC}$= 190 Hz). The final resonance anticipated for the intermediate is seen at 185 ppm and has been assigned to the enolate oxygen-bound carbon.

Addition of methylene iodide (Figure 10c and d) results in a significant increase in complexity. As observed in the $^1$H NMR spectra, this addition results in the consumption of diethylzinc, the formation of ethyl(iodomethyl)zinc and propylzinc iodide. When all of the possible species in solution are considered, we would expect to see seven signals for methylene groups in the DEPT-135 spectrum (Figure 10c): one from methylene iodide, two from ethyl(iodomethyl)zinc, one from ethyl iodide, two from propylzinc iodide, and one from the reaction intermediate. The methylene iodide can be assigned as the fold-over peak in the $^{13}$C NMR (~27 ppm), which doesn’t appear in the DEPT spectrum. The signals resulting from ethyl iodide can be assigned as the
resonances at 20.3 and -1.2 ppm. The anticipated methylene signals from ethyl(iodomethyl)zinc are not observed (~5 ppm and ~ -13 ppm). The remaining signals, those at 42, 31, and 22 ppm may be interpreted as resulting from propylzinc iodide and the reactive intermediate. Other notable spectral changes upon addition of methylene iodide are observed for the signals corresponding to the phosphonate esters and the carbonyl carbon. Upon addition of methylene iodide, the singlet assigned to the phosphonate methyl esters (easiest seen in the DEPT spectra Figure 10a and c) becomes a pair of singlets. This change can be explained by the incorporation of a new stereocenter in the molecule, resulting in a diastereotopic relationship between the methyl groups. This change is also in agreement with that observed in the $^1$H NMR. The carbonyl carbon, assigned to the resonances at 185 ppm (Figure 10b) and 219.5 ppm (Figure 10d) may serve to indicate the nature of the intermediate formed in this reaction. If the cyclopropyl alkoxide 125 remains closed, a carbonyl carbon would not be anticipated. However, if the cyclopropyl alkoxide intermediate ring opens, resulting in the phosphonate homo-enolate 126, a ketone carbonyl carbon would be anticipated. The final spectral observation is the lack of a methylene signal in the DEPT spectrum of the second intermediate that would arise from a cyclopropane (5-20 ppm) (Figure 10c). Additional support for the ring opened intermediate 126 is the appearance of an apparent methine doublet with a large phosphorus coupling (11.5 ppm; $^{1}J_{PC} = 136$ Hz).

Utilizing $^{31}$P NMR as a probe, the reaction intermediates were examined to determine the number of species in solution that contain phosphorus. Treatment of dimethyl (2-oxopropyl)phosphonate with diethylzinc resulted in a single resonance (32.1 ppm), indicating one species that contained phosphorus was present in solution. The
addition of methylene iodide results in multiple phosphorus-containing species: one major new species (48.9 ppm), a minor new species (49.9 ppm), and some unreacted enolate. These NMR spectra indicate that there is one major species in solution that contains phosphorus, thereby supporting the presence of a stable intermediate. Analysis of these samples by coupled $^{31}$P NMR resulted in complex spectra that provided no new information.

Figure 11. Result on Chain Extension of Utilizing Excess Diethylzinc
Spectrum obtained from adding CH$_2$I$_2$ (1 eq.) to a solution of dimethyl (2-oxopropyl)phosphonate 73 (1 eq.) and diethylzinc (3 eq.): a) –CH$_3$ of intermediate formed from the addition of a slight excess of CH$_2$I$_2$ to a solution of diethylzinc and dimethyl (2-oxopropyl)phosphonate 73. b) –CH$_3$ of intermediate resulting from the addition of diethylzinc to dimethyl (2-oxopropyl)phosphonate 73. c) propylzinc iodide resulting from the decomposition of ethyl(iodomethyl)zinc.

These NMR studies appeared to be very informative and indicate that intermediates were persistent enough to be observed by NMR. While the proposed cyclopropyl alkoxide intermediate 125 cannot be ruled out by these studies, the observation of a carbonyl carbon in the second intermediate provides much stronger...
support for 126 as the second intermediate. In order to simplify the aliphatic region of the $^1$H NMR spectrum, we sought to limit the number of compounds in solution that give rise to resonances in this region. Specifically, we hoped to reduce the amount of propylzinc iodide, known to result from the decomposition of ethyl(iodomethyl)zinc, by limiting the amount of methylene iodide. Treatment of dimethyl (2-oxopropyl)phosphonate with three equivalents of diethylzinc resulted in a spectrum consistent with the zinc-enolate intermediate. Subsequent addition of one equivalent of methylene iodide was anticipated to result in chain extension and consumption of the carbenoid. However, when one equivalent of methylene iodide was added, significant amounts of propylzinc iodide were observed (Figure 11) and very little of the intermediate believed to be the homo-enolate 126 was formed (~10 : 1 enolate : homo-enolate). Although disappointing, this result confirmed earlier observations that more than one equivalent of the zinc-carbenoid is necessary to promote efficient chain extension.\(^6\)

b. Carbenoid Decomposition Studies:

To this point, the reaction of diethylzinc and methylene iodide was presumed to be complete and instantaneous. A study by Charette indicated that ethyl(iodomethyl)zinc, formed in the absence of a complexing agent, underwent rapid decomposition.\(^5\)\(^1\) Charette, et al reported that when a complexing agent was added to solubilize the carbenoid, decomposition of ethyl(iodomethyl)zinc and formation of propylzinc iodide began to occur within 40 minutes (Figure 12) and the ethyl(iodomethyl)zinc was completely consumed within 80 minutes. Based upon this
study, the immediate use of a freshly prepared carbenoid solution was deemed necessary to avoid decomposition of the carbenoid.

\[
\text{Et}_2\text{Zn} + \text{CH}_2\text{I}_2 \rightarrow \text{EtI} + \text{EtZnCH}_2\text{I}_{(\text{sol})} \xrightarrow{\text{EtZnCH}_2\text{I}_{(\text{pp})}} \text{EtZnCH}_2\text{I}
\]

\[t_{1/2} \approx 40 \text{ min}\]

**Figure 12.** Zn-Carbenoid Decomposition Reported by Charette\(^{51}\)

The previous experiment (*Figure 11*) had indicated that when 1 equivalent of methylene iodide was added to a mixture of 1 equivalent of dimethyl (2-oxopropyl)phosphonate and 3 equivalents of diethylzinc, most of the ethyl(iodomethyl)zinc decomposed with the concomitant generation of propylzinc iodide. In every study in which diethylzinc and methylene iodide were used to effect cyclopropanation, methylene iodide was either used in excess or stoichiometrically. No studies addressing the effect of excess diethylzinc on these reactions have been reported.

We sought to investigate how diethylzinc affected the carbenoid in the absence of excess methylene iodide. Furthermore, we hoped to probe the efficiency of the chain extension reaction in the presence of excess diethylzinc. By preparing a series of different mixtures of diethylzinc and methylene iodide and monitoring the \(^1\text{H}\) NMR spectra as a function of time (*Figure 13*), we hoped to determine the stability of the carbenoid in the absence of complexing agents and the effects of excess diethylzinc. A
series of NMR tubes were purged with nitrogen and charged with deuterated methylene chloride. Into each of these tubes, diethylzinc was added by syringe. White smoke was generated during the transfer, which indicated that some of the diethylzinc had reacted with something in the tube, most likely ambient oxygen or water. Therefore, some degree of uncertainty in the delivery of diethylzinc must be factored into any discussion and it is likely that less diethylzinc was present in the solution than reported in the following study. Methylene iodide was added to each tube immediately before the tube was inserted in the NMR. A series of solutions were generated that range from 1:2 to 1:0.9 (diethylzinc : methylene iodide). Each of these solutions were monitored by $^1$H NMR over 60 minutes for changes in the amounts of diethylzinc and carbenoid (the presence of ethyl(iodomethyl)zinc is observed by a singlet at 1.5 ppm) and for the appearance of propylzinc iodide. The disappearance of diethylzinc was slower in the cases where the ratio neared 1:1; however, after 60 minutes diethylzinc was consumed in every case. The results of each of these studies are illustrated by the series of spectra generated for a 1:2 mixture of diethylzinc : methylene iodide in Figure 13a-c. When additional diethylzinc (~1.5 eq.) was added to the solution of diethylzinc : methylene iodide (1 : 2) that had been stirring for 60 minutes, the consumption of carbenoid was complete within seconds (Figure 13d).
**Figure 13.** $^1$H NMR Study of Zinc Carbenoid Decomposition

a) Reaction of Diethylzinc and $\text{CH}_2\text{I}_2$ (1:2) immediately after addition of $\text{CH}_2\text{I}_2$.

b) Reaction of Diethylzinc and $\text{CH}_2\text{I}_2$ (1:2) after 30 minutes at room temperature.

c) Reaction of Diethylzinc and $\text{CH}_2\text{I}_2$ (1:2) after 60 minutes at room temperature.

d) Result of the additional Diethylzinc (1.5 eq.) added to the room temperature solution of Diethylzinc and $\text{CH}_2\text{I}_2$ (1:2) immediately after addition.

An analogous study was performed whereby diethylzinc and methylene iodide were combined in a 1:1 ratio and solubilized with 1 equivalent of dimethoxyethane in
deuterated chloroform. When additional diethylzinc was added (solution was observed by \(^1\text{H NMR}\) the carbenoid decomposed at an increased rate. The carbenoid (distinguishable by a singlet at 1.6 ppm in deuterated chloroform) was observed to decrease in concentration as propylzinc iodide increased. The consumption of carbenoid was complete within 13 minutes in the presence of excess diethylzinc.

In the process of studying the decomposition of ethyl iodomethylzinc, it was also found that the decomposition was greatly accelerated by the presence of an excess of solvating agents such as dimethoxyethane and tetrahydrofuran. The addition of these ether solvents increases the solubility of the zinc species, which is believed to enhance the availability of this zinc-carbenoid. However, when more than 2 coordinating moieties were added (1 eq. of DME or 2eq. of THF), carbenoid decomposition was greatly accelerated. When a solution of diethylzinc and methylene iodide (1:1) was treated with an excess of either DME (greater than 2 equivalents) or THF (greater than 4 equivalents), the carbenoid decomposition was found to be complete within 10 minutes.

In conclusion, these studies have shown that the ethyl(iodomethyl)zinc is much more stable than originally proposed by Charette in the absence of solvating agents. Even after 60 minutes no significant decomposition is observed. This contrasts with the 40-minute half-life for the decomposition in the presence of DME found by Charette and coworkers. The decomposition of this carbenoid species appears to be greatly accelerated by the presence of excess diethylzinc and coordinatin compounds such as ether solvents. In the absence of solvating agents and when prepared with excess methylene iodide, the carbenoid appears to be stable for an indefinite amount of time (up to ~4 hours).
c. **Deprotonation Studies:**

The studies of carbenoid stability indicated that the excess diethylzinc promotes decomposition of ethyl(iodomethyl)zinc. For this reason, the stoichiometry of the deprotonation reaction between diethylzinc and the $\beta$-keto phosphonate is crucial and required investigation. Since there are two alkyl ligands in diethylzinc, there are two possible stoichiometries for the reaction of diethylzinc and a chelating $\beta$-keto ester substrate. It may be argued that the first deprotonation and coordination makes the second alkyl ligand less reactive and less likely to deprotonate another substrate resulting in a $1:1$ stoichiometry 127. Alternatively, diethylzinc appears capable of reacting with two substrates to form a Zn(acac)$_2$ type species 128.
may play a role in the product stoichiometry; however, this was not a parameter varied in this study.

Figure 14. $^1$H NMR Study of the Reaction Between Diethylzinc and 73
Expected ratio of Diethylzinc and Dimethyl (2-oxopropyl)phosphonate 73:

- a) 0.4 : 1
- b) 0.75 : 1
- c) reaction of Dimethyl (2-oxopropyl)phosphonate 73 with excess diethylzinc (Figure 9b).

A series of deprotonation reactions were carried out and followed by $^1$H NMR, wherein the ratio of diethylzinc and dimethyl (2-oxopropyl)phosphonate 73 were varied.
from 0.4:1 to 0.75:1. Again, it must be emphasized that the targeted ratio of reagents may not be the actual ratio due to difficulty in delivering the diethylzinc. The amount of diethylzinc in the reaction is probably less than the target amount. With this in mind, the spectra observed for these reactions strongly support the notion that diethylzinc deprotonates two molecules of substrate to make the Zn(acac)$_2$ type species 128 (Figure 14). If the deprotonation stoichiometry is 1:1, resonances in the NMR spectrum for the remaining ethyl ligand (a triplet ~1.15 ppm and a quartet ~0.5 ppm) would be expected, not only in this study (Figure 14), but in previous spectral studies (Figure 9b) as well. Although these spectra don’t identify the exact point at which the substrate is consumed, nearly all of the substrate is deprotonated when a 0.75:1 (Et$_2$Zn : 73) ratio is used, as marked by the disappearance of the doublet at 3.1 ppm and the singlet at 2.3 ppm, as well as by the appearance of the singlet at 2.0 ppm. The spectrum obtained when 0.75 equivalents of diethylzinc are added to substrate 73 is remarkable identical to that observed when excess diethylzinc was added (Figure 14c), with the exception of the presence of excess diethylzinc and the doublet observed for the $\alpha$-methine (~4.15 ppm). The absence of this resonance in Figure 14a and b may simply be a result of the change of solvent, or the result of deuterium exchange with the chloroform-d (Figure 14a and b) that was not seen when methylene chloride-d$_2$ was used as the solvent (Figure 14c). We can predict with some confidence that the deprotonation stoichiometry is 2:1.

D. Conclusion:

We have described a new synthetic method for the preparation of $\gamma$-keto phosphonates, resulting in a high yielding three-step route from a methyl ester. The
direct comparison between β-keto esters and phosphonates has been addressed and, with two exceptions, they are similar with respect to the chain extension reaction. Olefinic functionality limits the application of this methodology due to competitive cyclopropane formation. This evidence indirectly suggests that the β-keto phosphonates react more slowly than their β-keto ester counterparts. The application of this methodology on α-substituted-β-keto phosphonates proceeds more cleanly than their ester counterparts.

In addition, application of this chain extension methodology towards the preparation of peptidomimetics appears successful with individual amino acids; however, its application to dipeptides is restricted by the tendency of the dipeptide-derived β-keto phosphonates to incorporate additional methylene units. The precise location and source of the additional methylene groups has not been established.

While the mechanism of this reaction is not completely understood, these data appear to support the intermediacy of both a zinc-enolate and the homo-enolate. While the precise zinc species responsible for the chain extension reaction has not been proven to be ethyl(iodomethyl)zinc, these results indicate that it is generated and consumed during the chain extension reaction. The mode by which the zinc-species reacts has yet to be determined; however, the data generated by this study are consistent with a preliminary alkylation of the α-carbon followed by addition into the carbonyl.

In addition, we have described the diethylzinc-enhanced decomposition of the ethyl(iodomethyl)zinc. This study has impact, not only on the application of these reagents in chain extension reactions, but in cyclopropanation reactions as well. We have determined that performing these reactions in the presence of a slight excess of methylene iodide greatly enhances the longevity of the carbenoid, thereby increasing
product yields. The addition of solvating agents has been suggested to enhance the reactivity of zinc-carbenoids and that generation of zinc-carbenoids in the absence of such solvating agents results in rapid decomposition. The results of our studies show that the carbenoid is reactive when formed in the absence of solvating agents and is much longer lived when diethylzinc is not present in excess. The addition of solvating agents such as THF or DME assists in solvating the zinc salts inherent to this chemistry; however, addition of an excess of ligating moieties also enhances its decomposition. Additional mechanistic studies will be essential to optimizing this zinc-mediated chain extension reaction. Future work in this area is necessary to determine the complete scope of the chain extension chemistry.
CHAPTER II

STUDIES TOWARD THE STEREOSELECTIVE PREPARATION OF POLYCYCLOPROPANES

A. Introduction:

Most synthetic methodologies were developed for the preparation of racemic materials. With the recognition of enantiospecific biological activities, the preparation of stereochemically pure compounds have been pursued vigorously. This interest has caused researchers to "update" the previously reported methodologies with the goal of developing methods that will facilitate the stereoselective synthesis of organic compounds.

Several general strategies for the synthesis of 3-membered carbocycles or cyclopropanes have been described in the literature. Similar to most synthetic methodologies, initial procedures described for the preparation of cyclopropanes involved little or no effort to control or determine the absolute stereochemistry of the products.
The increasing number of biologically active cyclopropane-containing molecules has prompted further study into the stereoselective preparation of cyclopropanes.\textsuperscript{55}

1. Discovery of FR-900848:

Interest in the stereocontrolled preparation of cyclopropanes was enhanced by the discovery and report of the polycyclopropanated natural product FR-900848 (129) (Figure 15).\textsuperscript{56} Discovered in the fermentation broths of \textit{Streptoverticillium fervens}, FR-900848 has received a great deal of attention from the scientific community since its 1990 debut; not only for its unprecedented structure, but for its specific biological activity as well. While exhibiting little activity against gram-positive or gram-negative bacteria or non-filamentous fungi (yeasts), FR-900848 displays a remarkably selective potency toward filamentous fungi (molds). Combined with this selective activity, its low mammalian toxicity has stimulated interest in FR-900848 as a potential lead compound for the development of new anti-fungal agents.

![Figure 15. Polycyclopropanated Natural Product FR-900848.](image)

In addition to a 5,6-dihydrouridine moiety and a 5'-deoxy-5'-amino ribose unit, FR-900848 contains a remarkable five cyclopropanes; four of which are contiguous, while one is separated from the others by a single alkene. Although in its initial report

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the relative and absolute stereochemistries were not determined, spectral data confirmed that the natural product was a single diastereomer. The report of this unusually complex structure has prompted a number of studies into the stereoselective preparation of polycyclopropanes. Efforts to this end have resulted in the identification and confirmation of a repeating trans-syn-trans scaffold within the contiguous polycyclopropane fragment and a syn-relationship between the isolated and contiguous cyclopropanes (vida infra).^{57,58}

2. Discovery of U-106305:

In 1995 the report of a second polycyclopropanated natural product once again brought attention to the area of polycyclopropane research. Isolated from *Streptomyces* sp. UC 11136, the Upjohn Company reported the isolation, structure, and biosynthesis of U-106305 (130) (Figure 16).^{59} Differing only by an additional cyclopropane and a less complex amide substituent, U-106305 displayed dramatically different biological activity as compared with FR-900848. U-106305 is an inhibitor of cholesteryl ester transfer protein (CETP), an enzyme responsible for the distribution cholesteryl esters. Decreased activity of this enzyme has been linked to high levels of high-density lipoproteins (HDL’s), which have in turn been associated with a decreased incidence of coronary heart disease. Investigations into the antifungal activity of U-106305 have yet to be reported.
At the time U-106305 first appeared in the literature, the stereochemical characterization was limited. The stereochemistry of each cyclopropane had been determined to be trans- by a series of NMR studies; however, the assignment of absolute and relative stereochemistries had not been made. Considering the structural similarities to FR-900848, a trans-syn-trans scaffolding for U-106305 seemed likely. The carbon-backbone of U-106305 was determined to originate from acetate units by an $^{13}$C-enriched acetate feeding experiment. An additional feeding experiment utilizing [methyl-$^{13}$C]-L-methionine, demonstrated that the methylene groups that make up the six cyclopropanes originated from methionine.

**B. Synthetic Strategies Toward the Formation of Disubstituted Cyclopropanes:**

Of the numerous methods reported to result in cyclopropane formation, the most synthetically diverse and useful methods utilize Simmons-Smith type zinc-carbenoids, diazo-derived metal carbenoids, or ylides to effect a 2+1-type reaction. Other somewhat less common methods for cyclopropane formation utilize free carbenes, anionic-, cationic- or radical-mediated ring closures, or the extrusion of small molecules.
1. **Zinc-Carbenoid Mediated Cyclopropane Formation:**

The Simmons-Smith cyclopropanation, initially reported in 1959, makes use of an organozinc species that adds a methylene unit across a double bond. The mechanism of this reaction (Scheme 41) is not completely understood; however, an iodomethyl-metal species is generally regarded as the reactive species. The addition of a methylene across an olefin is believed to occur by a concerted mechanism, with the olefin stereochemistry maintained in the cyclopropane. The organozinc species is formed by the reaction of an activated zinc-copper couple with a 1,1-diiodoalkane. Although the reaction proceeds with reasonable yields, there are several disadvantages to this procedure. The expense of diiodomethane, which is the commonly used diiodoalkane, is most obvious. Efforts to extend this methodology to substituted alkylidenes have been limited; the transfers of benzylidene and ethylidene have been the most extensively studied. Somewhat futile efforts to utilize less expensive reagents have resulted in a method whereby dibromomethane is sonicated with the zinc-copper couple.

```
W Y
X Z
```

```
CH2I2
Zn-Cu
```

```
W Y
X Z
[...]
```

```
W Y
X Z
```

Scheme 41. Simmons-Smith Cyclopropanation of Olefins

Generation of the activated species has been the greatest source of difficulty in the application of the Simmons-Smith protocol. The preparation of this zinc-copper couple, most often generated *in situ* by heating zinc dust with copper(I) chloride in refluxing...
ether under nitrogen, is somewhat messy and often provides inconsistent results.

Difficulty in the formation of the active species and the erratic results obtained from its use combine to make the zinc-copper couple method impractical.

An alternative method for cyclopropane formation was reported by Furukawa et al. in 1968, which is often referred to as a “modified Simmons-Smith reaction.” Diethylzinc is used as the source of the activated zinc, thereby avoiding the use of the erratic zinc-copper couple. The more reactive diethylzinc, albeit spontaneously combustible, provides more reproducible results. In addition, the Furukawa-modified Simmons-Smith protocol utilizes reagents that are easier to manipulate, thereby simplifying experimental conditions. Until recently, the active species utilized in the Furukawa-modified Simmons-Smith cyclopropanation, bis(iodomethyl)zinc, was thought to be in equilibrium with the less reactive iodomethylzinc iodide. Spectroscopic work reported by Charette has not only characterized the active species (ethyl(iodomethyl)zinc and bis(iodomethyl)zinc), but has conclusively disproved the existence of this equilibrium. In Charette’s study, the ethyl(iodomethyl)zinc species was reported to decompose into propylzinc iodide, with a half-life of approximately 40 minutes in the presence of a stoichiometric solvating agent such as 1,2-dimethoxyethane (DME). As discussed in Chapter 1, we have shown (Figure 13) that ethyl(iodomethyl)zinc remains in solution for longer periods of time in the absence of these solvating agents.
2. Diazo-Derived Metal Carbenoid Cyclopropanations:

Metallocarbenoids have also been found to be extremely effective reagents for the formation of cyclopropanes. Although a host of metals have been studied (Table 4), the most commonly used catalysts are typically based on rhodium, copper, and palladium. Other catalysts used for the cyclopropanation of olefins with diazo compounds include ruthenium, cobalt, tungsten, and iron. Although these catalysts are rarely used, they have shown promise and deserve some consideration.

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{EDA}} \text{CO}_2\text{CH}_2\text{CH}_3 + \text{Ph} \\
134 & 135 & 136
\end{align*}
\]

Scheme 42. Catalyst Selectivity in the Cyclopropanation of Styrene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>135 : 136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl(_2)(PhCN)(_2)</td>
<td>52</td>
<td>62 : 38</td>
</tr>
<tr>
<td>2</td>
<td>Rh(_2)(acam)(_4)</td>
<td>86</td>
<td>68 : 32</td>
</tr>
<tr>
<td>3</td>
<td>Rh(_2)(OAc)(_4)</td>
<td>93</td>
<td>62 : 38</td>
</tr>
<tr>
<td>4</td>
<td>Cu(acac)(_2)</td>
<td>71</td>
<td>72 : 28</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)(_2)</td>
<td>97</td>
<td>65 : 35</td>
</tr>
<tr>
<td>6</td>
<td>OsCl(_2)(p-cymene)(_2)</td>
<td>78</td>
<td>62 : 38</td>
</tr>
<tr>
<td>7</td>
<td>OsTPP</td>
<td>79</td>
<td>91 : 9</td>
</tr>
<tr>
<td>8</td>
<td>Co(α-cpd)(_2)H(_2)O</td>
<td>92</td>
<td>46 : 54</td>
</tr>
<tr>
<td>9</td>
<td>Co(salen)I</td>
<td>76</td>
<td>98 : 2</td>
</tr>
<tr>
<td>10</td>
<td>&quot;(CO)(_2)W&quot;</td>
<td>41</td>
<td>62 : 38</td>
</tr>
<tr>
<td>11</td>
<td>[Cp(CO)(_2)Fe(THF)](^+)</td>
<td>40</td>
<td>16 : 84</td>
</tr>
<tr>
<td>12</td>
<td>RuCl(_2)(Pybox-ip)</td>
<td>73</td>
<td>91 : 9</td>
</tr>
<tr>
<td>13</td>
<td>RuCl(_2)(PPh(_3))</td>
<td>93</td>
<td>56 : 44</td>
</tr>
</tbody>
</table>

Table 4. Catalyst Influence of Diastereoselectivity in the Cyclopropanation of Styrene by Ethyl Diazoacetate (EDA).
a. **Cyclopropanation Reactions Utilizing Diazooalkanes:**

The most common diazoalkane used for the cyclopropanation of olefins is diazomethane. Of the catalysts used for cyclopropanation reactions with diazomethane, palladium catalysts often provide the best results. Perhaps the greatest utility of palladium carbenoids lies in their ability to cyclopropanate electron deficient, conjugated olefins. Electron poor olefins are traditionally less reactive than electron rich olefins, yet methyl methacrylate and styrene possess comparable reactivity in terms of the rate of cyclopropanation and are ~200 times more reactive than cyclohexene when exposed to a palladium carbenoid.

![Scheme 43. Illustration of the Selectivity of Palladium (II) Catalysts](image)

The reactivity of palladium (II) catalysts is greatly enhanced by ring strain. High product yields and short reaction times are characteristic of reactions with medium-sized rings, norbornenes, and related strained bicyclic or polycyclic alkenes and allenes. Conversely, low yields are characteristic of the reaction of cyclohexenes, cyclopropenes, and linear alkenes. The enhanced selectivity of palladium (II) catalysts as compared with copper (I) or rhodium (II) is best illustrated by the cyclopropanation reaction of...
norbornene with diazomethane (Scheme 43).\textsuperscript{70} The \textit{exo}-selectivity observed with Pd(II) catalysts (>98%) is remarkable when contrasted to copper and rhodium catalysts, which give mixtures of \textit{exo}– and \textit{endo}– products.

\begin{align*}
\text{Pd(II)} & \quad \xrightarrow{\text{CH}_2\text{N}_2} \\
\text{Rh(II)} & \quad \xrightarrow{\text{CH}_2\text{N}_2}
\end{align*}

**Scheme 44.** Comparison of the Reactivity of Palladium(II) and Rhodium(II) Catalysts

In cases where heteroatoms are present, such as in allylic amines, alcohols and ethers, the difference in reactivity between Pd(II) and Rh(II) is obvious. When such allylic systems are cyclopropanated with diazomethane, palladium (II) has been found to result exclusively in the cyclopropanated product, while rhodium (II) provides competitive or exclusive ylide formation, which results in the formation of a 2,3-sigmatropic rearrangement product (Scheme 44). The increased yields and reaction rates of allylic systems have been proposed to result from an enhanced interaction and activation of the olefins by the palladium (Figure 17).\textsuperscript{66} Efforts to effect the stereoselective cyclopropanation of olefins with diazomethane have provided encouraging results. However, these methods utilize covalently bound chiral auxiliaries, making their application somewhat less attractive.\textsuperscript{71}
b. Cyclopropanation Reactions with Diazocarbonyl Compounds:

Diazocarbonyl compounds are the preferred substrates for diazo decomposition reactions, primarily due to their ease of preparation and increased stability as compared with the diazoalkanes. Prior to 1961, when Stork reported the first intramolecular application of diazo cyclopropanation reactions, these reactions received little attention. Major advances in this field resulted from the introduction of homogeneous catalysis. The use of catalysts that were soluble in organic solvents provided the opportunity to exchange ligands in efforts to control the reaction selectivity.

The rate limiting step for these cyclopropanation reactions is the diazo decomposition, which is influenced by both the catalyst and diazo substituents. The rate of diazo decomposition is decreased with an increase in carbonyl substitution. The reactivity is also dependent upon the type of carbonyl as well; the reactivity increases as the carbonyl is changed from an amide to an ester to a ketone.
A limitation of metal carbenoids derived from diazo carbonyl compounds lies in the electrophilic nature of the carbenoid. Thus, only electron-rich olefins are susceptible to cyclopropanation under these reaction conditions. An additional limitation arises from the promiscuous reactivity of these carbenoids, which results in undesired side reactions. Fortunately, this reactivity can be modulated by choice of catalyst and rate of addition of the diazo compound to the reaction mixture.

Intermolecular cyclopropanation reactions with diazo-derived metal carbenoids are not greatly influenced by the steric interactions of either the carbenoid or the olefin substituents. This insensitivity to steric environment has been attributed to the reactivity of the carbenoid and the distance between substituents in the initial bond-forming step. A model, proposed by Doyle, can serve to explain and predict the selectivity of these reactions (Figure 18).
Figure 18. Doyle's Model of Carbonyl Carbenoid Reactivity

The initial interaction between the olefin and carbenoid has been proposed to be a reversible $\pi$-type interaction. The stereochemistry of this $\pi$-complex results from the steric interactions between the metal-ligand field and the olefin substituent. Bond formation occurs in a Markovnikov fashion, allowing the olefin substituents ($R'$) to
stabilize the resulting electropositive center. Further stabilization of this cationic charge character is believed to result from a favorable interaction between the carbonyl oxygen and the cationic center as illustrated in 148 or 151. The formation of the π-complex is thought to be reversible and the favorable interaction depicted in 148 and 151 serves to influence the cis/trans stereochemistry. By assisting in the stabilization of the cationic intermediate, the reorganization that allows for the ring closure occurs more rapidly for the path proceeding through 151 and to the trans-product 155. In the cyclopropanation of styrene with the benzylidene carbenoid, the cis-product is formed in excess (~3:1) indicating that in the absence of this favorable interaction, other factors determine the stereochemical outcome of the product.

3. Ylide-Mediated Cyclopropane Formation:

While the carbenoid cyclopropanation reactions have been described to convert both electron-rich and electron-deficient olefins to cyclopropanes, the vast majority of carbenoid reagents are more efficient for the cyclopropanation of electron-rich olefins. In contrast to the carbenoids, ylidic species predominantly convert electron-deficient olefins to cyclopropanes, although there have been reports of copper-catalyzed reactions of sulfur ylides and simple alkenes.78

Ylides are compounds that bear both positive and negative charges on adjacent atoms that possess a full complement (octet) of electrons. Sulfur ylides, in which the positive charge is localized on sulfur, are predominantly used for cyclopropane formation.79 Other ylides based on phosphorus, selenium and arsenic have been utilized.
to a lesser extent. The general mechanism of these reactions is illustrated in Scheme 43 and can be described as a tandem carbanionic addition/intramolecular alkylation reaction.

\[
\begin{align*}
\text{R} & \quad \text{G}^+ \\
\text{R'} & \quad \text{H} \\
\text{X} & \quad \text{base} \\
\text{---} \\
\text{154} & \quad \text{155} \\
\text{---} \\
\text{EWG} & \quad \text{EWG} \\
\text{---} \\
\text{157} & \quad \text{156}
\end{align*}
\]

Scheme 45. Mechanism of Ylide-Mediated Cyclopropane Formation

Formation of the ylide 155 is accomplished by treating an onium salt 154 with a non-nucleophilic base. Subsequent addition of an electron-deficient olefin results in a zwitterionic intermediate 156 referred to as a "betaine". Intramolecular displacement of the onium group results in ring formation. As a consequence of the stepwise mechanism of ylide-mediated cyclopropanations, the double bond stereochemistry may be lost. The stereospecificity of these reactions depends upon the lifetime of the betaine intermediate, compared to carbon-carbon single bond rotations.\textsuperscript{80}
Three general types of sulfur ylides have been reported. The first two, dimethyloxysulfonium methylide 158 and dimethylsulfonium methylide 159 were investigated simultaneously. While dimethyloxysulfonium methylide 158 is an efficient reagent for the formation of cyclopropanes, dimethylsulfonium methylide 159 is applied predominantly in the epoxidation of ketones. The final type of sulfur ylide described in the literature includes methyl(dimethylamino)oxysulfonium methylide 160. Johnson and coworkers have extensively investigated the use of these ylides for effecting asymmetric cyclopropanations; however, they were unable to achieve selectivities greater than 50% ee.

4. **Intramolecular Ring Closures and Small Molecule Extrusions:**

While there are several methods for the formation of cyclopropanes, the aforementioned methodologies most closely reflect the specific chemistry related to the synthesis of 1,2-disubstituted cyclopropanes and this project. Additional procedures for the formation of cyclopropanes include ring closures that involve the intermediacy of carbanions, carbocations, and radicals. Since cyclopropane rings can fragment when adjacent cationic or radical character is present, these methods can complicate attempts to form systems that contain adjacent cyclopropanes.
The extrusion of small molecules and use of free carbenes provide neutral routes to cyclopropanes. The photolysis\textsuperscript{83} and thermolysis\textsuperscript{84} of pyrazolines to extrude nitrogen gas results in a ring contraction to form cyclopropanes. Complications such as thermal decomposition of the products result in decreased yields for these reactions. In addition, the potential radical intermediates of these reactions are incompatible with polycyclopropane formation. Another neutral method of forming cyclopropanes employs “free” carbenes, which are generally prepared from di- or tri-halo alkanes or the thermolysis of diazo compounds. The unselective reactivity of free carbenes limits their application and often results in poor yields.

C. Nomenclature of polycyclopropanes:

The development of any field requires that a “language” be described to allow for efficient and constructive communication. Several naming systems have been used to describe polycyclopropanes, most of which are confusing and non-specific. For purposes of clarity, the nomenclature system utilized herein to describe both structure and stereochemistry of polycyclopropanes needs to be identified. We have defined polycyclopropanes as compounds that contain two or more 1,2-disubstituted-cyclopropanes connected by a sigma bond, which are not part of a larger cyclic system. This definition most accurately and distinctly limits polycyclopropanes to contain members that resemble the fatty amide side-chains of the two aforementioned natural products.

The atoms that connect to form a cyclopropane ring define a plane. The substituents attached to the ring then lie on one side or the other of that plane (Figure

83

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20). If two substituents lie on the same side of the plane, those substituents are described as *cis*- to one another and if they lie on opposite sides of the plane, they are described as *trans*- to one another.

![Cis and Trans Cyclopropane Stereochemistry](image)

**Figure 20.** Illustration of *cis* and *trans* cyclopropane stereochemistry

The *cis/trans* nomenclature is sufficient to describe the relationship between two substituents on the same ring. However, when more than one cyclopropane is present within the same molecule an additional element of stereochemistry arises and the *cis/trans* nomenclature is no longer adequate. When two or more cyclopropanes are connected, either by a sigma bond or by a chain, there arises relative stereochemistry of the cyclopropanes with respect to one another. Although use of the R/S nomenclature system circumvents this issue, its application can be tedious and confusing for polycyclopropanes. To avoid using the confusing R/S nomenclature system and to allow an accurate description of relative stereochemistry in a racemic system, the use of the *syn/anti* naming system can be applied (Figure 21).
When a carbon chain is substituted, either at adjacent or non-adjacent carbons, the relative stereochemistry of the substituents is described by their position as it relates to the chain relative to one another. When the carbon chain is drawn in its most extended (staggered) form, so that the atoms comprising the chain are coplanar, the substituents lie on either the same side of the plane or on opposite sides (Figure 21A). The relationship of substituents is described as \textit{syn} or \textit{anti} when the substituents are on the same side or opposite side of the plane, respectively. Applying the same principles to the polycyclopropane, when the chain containing the cyclopropane units is drawn in its most extended form, the apex (methylene unit) of the cyclopropanes are either on the same side of the plane (\textit{syn}) or on opposite sides (\textit{anti}) (Figure 21B).

When multiple cyclopropanes are connected, the \textit{cis/trans} and \textit{syn/anti} nomenclatures are sufficient to describe the relative stereochemistries. Although the \textit{syn/anti} nomenclature can be used to describe non-adjacent cyclopropanes, its use is limited in polycyclopropanes to describe the relationship between adjacent cyclopropanes. Thus, when naming a polycyclopropane, first the \textit{cis/trans}
stereochemistry of the terminal ring is described, then the syn/anti stereochemistry relative to the adjacent cyclopropane followed by the cis/trans stereochemistry of the adjacent cyclopropane. Repeating this sequence of stereochemical assignments, any size polycyclopropane can be described (Figure 22).

The final parameter required to describe polycyclopropanes describes the quantity of sequential cyclopropanes. Several terminologies are found in the literature; however, the term bis- will be used to describe two sequential cyclopropanes and tris- three, etc.

Figure 22. Use of both cis/trans and syn/anti nomenclatures to describe the stereochemistry of tris-cyclopropanes.
D. **History of Polycyclopropane Formation:**

![Diagram of reactions]

**Scheme 46. First Syntheses of bis-Cyclopropanes**

The synthesis of polycyclopropanes has been investigated for nearly half a century. The simplest polycyclopropanes, *bis*-cyclopropanes, were initially prepared in the 1950's. The first *bis*-cyclopropane to be introduced by Smith and Rogier in 1951, 2-phenyl-*bis*-cyclopropane 162 was formed by the decomposition of pyrazoline 161 (Scheme 46A). The unsubstituted *bis*-cyclopropane was reported one year later by Slabey and was prepared by reaction of chlorocyclopropane with lithium metal (Scheme 46B). Since these initial reports, several syntheses of *bis*-cyclopropanes have appeared in the literature. Methods used to prepare *bis*-cyclopropanes have predominately employed free carbenes, but others utilized diazomethane-derived metal-carbenoids, Simmons-Smith chemistry, reductive coupling of halocyclopropanes, small molecule extrusion, and anionic ring closures. It is important to recognize that mono-substituted *bis*-cyclopropanes require only the *cis/trans* stereochemical assignment. Not until the 2,2′-disubstituted-*bis*-cyclopropane are considered does the *syn/anti* stereochemistry become an issue.
The first 2,2'-disubstituted-bis-cyclopropane, 2-carboxanilide-2'-methyl-bis-cyclopropane, was reported in a patent by BASF in 1962.93 No efforts to determine the stereochemistry of bis-cyclopropanes were made until 1969 when Schrumpf reported the synthesis of syn- and anti-2,2'-dibromo-bis-cyclopropane.94 Efforts to control the relative stereochemistry were first made in 1975, when Skatteboel reported the stereoselective cyclopropanation of bulky symmetric dienes by dibromocarbene (Scheme 47).95 Several reported syntheses of 2,2'-disubstituted-bis-cyclopropanes have peppered the literature, employing a variety of reagents including, free carbenes,87m,96 electrolysis,97 cationic ring closures,98 small molecule extrusion,99 sulfur ylides,100 Simmons-Smith chemistry,87m,101 diazo-derived metal-carbenoids,87m,102 and oxidative coupling.103

![Scheme 47](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>166 (meso) (%)</th>
<th>167 (racemic) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>165a CH₃</td>
<td>92</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>165b C(CH₃)₃</td>
<td>27</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>165c Ph</td>
<td>44</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
tris-Cyclopropane has been successfully formed by two different methods. The first synthesis was introduced in 1963 by Doering and Roth who formed tris-cyclopropane 169 by the copper(II) catalyzed reaction of diazomethane with hexatriene 168 (Scheme 48A). The second preparation of tris-cyclopropane was reported twenty years later and utilized a Ramburg-Backlund reaction in the formation of a mixture of cis and trans-1,2-dicyclopropylcyclopropane 174 (Scheme 48B). Once again, these polycyclopropanes, 169 and 174, did not require the control of syn/anti stereochemistry. The only synthetic efforts toward a tris-cyclopropane in which syn/anti stereochemistry was an issue were made by Yanovskaya and coworkers, which employed a cationic chain extension reaction in an iterative process (Scheme 49). Unfortunately, rearrangement of the terminal cyclopropane complicated the elaboration of the bis-cyclopropane 181 into the tris-cyclopropane.
Prior to the introduction of FR-900848 (129), no polycyclopropanes larger than disubstituted-

bis-cyclopropanes had been prepared in which syn/anti stereochemistry was assigned or controlled. None of the methods used to generate polycyclopropanes prior to the isolation of FR-900848 were capable of facilitating efficient syn/anti stereocontrol. Approaches to the total synthesis of both FR-900848 and U-106305 required that not only the cis/trans stereochemistry be controlled, but the syn/anti stereochemistry as well. This challenge resulted in the initiation of our studies into polycyclopropanes.
E. Methodological Development Toward Polycyclopropane Preparation:

Since the discovery of the polycyclopropanated natural products 129 and 130 the stereocontrolled synthesis of polycyclopropanes has been the focus of multiple research efforts. Cationic-, ylide-, and carbenoid-mediated cyclopropanation methodologies have all been investigated in the stereoselective synthesis of polycyclopropanes. The applicability of each of these methods to the stereoselective formation of polycyclopropanes is described below.

1. Carbocation-Mediated Cyclopropane Formation:

The equilibrium between cyclopropyl carbinyl and homo-allylic cations is well documented. Closure of a homo-allylic cation to a cyclopropyl carbinyl cation has been used in the preparation of bis-cyclopropanes (Scheme 50). Taylor and coworkers were able to prepare both trans-1-phenoxyethyl-2-vinylcyclopropane 187a and trans-1-benzyloxymethyl-2-vinylcyclopropane 187b in high enantiomeric purity from the corresponding optically active glycidyl ethers. Epoxide opening of the glycidyl ethers 184a and b with 1-lithio-3-trimethylsilyl-1-propyne provided the mono-protected 1,2-diol 185a and b, which was hydrogenated with Lindlar's catalyst to provide the enantiomerically enriched cis-homoallylic alcohols 186a and 186b. Solvolysis, initiated by triflate formation, resulted in cyclopropane formation and loss of the strategically placed trimethylsilyl group to generate vinyl cyclopropane 187a and b. Stereorandom epoxidation of 187a and b completed the first iteration of this strategy.
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proposed as illustrated in Scheme 50 (syn-bis-cyclopropane arising from the syn-alcohol). However, no evidence has been reported to unambiguously determine whether the syn/anti stereochemistry of the alcohols 190 and 191 translates into the bis-cyclopropanes as proposed. The reaction was found to be stereospecific, as a single bis-cyclopropane was produced from each diastereomeric alcohol. Work in this area is focused on the application of this methodology to forming more than one cyclopropane concurrently.

2. Ylide-Mediated Cyclopropane Formation:

Sulfur ylides are useful reagents for transforming electron-deficient olefins into 1,2-disubstituted cyclopropanes. The two-step mechanism involves reversible nucleophilic attack of the ylide at the β-carbon of an α,β-unsaturated ester followed by intramolecular displacement of the sulfoxide by the resultant enolate. As a consequence of minimized steric interactions in the second step, the newly formed cyclopropanes possess exclusive trans-stereochemistry, while the absolute stereochemistry is determined by facial selectivity in the conjugate addition.

\[
\begin{align*}
\text{HO-CO}_2\text{Et} \quad & \xrightarrow{1. \text{TPAP, NMO Sieves}} \quad \text{r-BuO}_2\text{C-CO}_2\text{r-Bu} \\
\text{194} \quad & \xrightarrow{2. \text{NaH (EtO)}_2\text{P(O)CH}_2\text{CO}_2\text{Et}} \quad \text{(CH}_3\text{)}_2\text{S(O)CH}_2^- \quad \text{DMSO} \\
\text{HO-CO}_2\text{Et} \quad & \xrightarrow{\text{DIBAL-H}} \quad \text{r-BuO}_2\text{C-CO}_2\text{r-Bu} \\
\text{197} \quad & \xrightarrow{\text{196}} \quad \text{195}
\end{align*}
\]

Scheme 51. Two Directional Application of Sulfur Ylide Cyclopropanations

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The two-directional application of sulfur ylides has resulted in the preparation of a diastereomeric mixture of \textit{tris}-cyclopropane diols 197 (Scheme 51).\textsuperscript{109} The starting divinyl cyclopropane was made from \textit{trans}-1,2-\textit{bis}-hydroxymethylcyclopropane 194 via oxidation and exposure of the dialdehyde to Horner-Emmons reaction conditions. Treatment of the divinyl cyclopropane 195 with excess dimethyloxsulfonium methylide, followed by DIBAL-H reduction produced a mixture of three diastereomeric \textit{bis}-hydroxymethyl-\textit{tris}-cyclopropanes 197. The results of this study suggest that sulfur ylides may not be suitable reagents for the stereoselective preparation of polycyclopropanes, as an equimolar mixture of the \textit{syn}-\textit{syn}-, \textit{syn}-\textit{anti}-, and \textit{anti}-\textit{anti}-\textit{tris}-cyclopropanes were formed.

3. \textbf{Zinc Carbenoids:}

By far, the most widely used reagents for formation of cyclopropanes are zinc-carbenoids. Application of the Furukawa-modified Simmons-Smith reagents with either chiral auxiliaries or on chiral molecules has comprised the greatest effort to effect the asymmetric preparation of polycyclopropanes.

\textbf{a. Furukawa-Modified Simmons-Smith Reaction:}

Attempts to prepare \textit{bis}-cyclopropanes from dienols using the Furukawa-modified Simmons-Smith protocol has been reported by Barrett.\textsuperscript{110} As expected, the use of one equivalent of the zinc carbenoid resulted exclusively in cyclopropanation of the olefin with allylic alcohol functionality 199. Application of excess zinc carbenoid generated the \textit{anti-bis}-cyclopropane 202 with modest to good substrate-based selectivity. However,
when a hydroxymethylcyclopropane was chain extended to provide an equivalent
cyclopropyl allylic alcohol 200 and cyclopropanated, the anti-bis-cyclopropane 202 was
formed with poor diastereocontrol. Barrett proposed the anti-preference to be a result of
orbital and steric effects and suggested that these effects could be easily overwhelmed by
a neighboring heteroatom providing modest cyclopropane-induced stereocontrol.

Although this iterative strategy of chain extension and cyclopropanation is very attractive
for trans-polycyclopropane preparation, the lack of substrate-based stereocontrol
diminishes its utility for stereoselective synthesis.

\[
\begin{align*}
\text{A.} & \quad \text{Ph} \overset{\text{Et}_2\text{Zn (1 eq)}}{\text{CH}_2\text{I}_2 (2eq)} \quad \text{Ph} \overset{\text{OH}}{\text{\longrightarrow}} \\
& \quad 198 \quad 199 \\
\text{B.} & \quad \text{Ph} \overset{\text{Et}_2\text{Zn}}{\text{CH}_2\text{I}_2} \quad \text{Ph} \overset{\text{OH}}{\text{\longrightarrow}} \\
& \quad 200 \quad 201 \quad 202 \\
& \quad 1 : 5 \quad 1 : 1
\end{align*}
\]

Scheme 52. Barrett's Investigation into Substrate-Based Stereocontrol of the
Furukawa-Modified Simmons-Smith Cyclopropanation Reaction

Previous work reported from the Zercher research laboratory, which will be
discussed in later sections, describes the investigation of substrate-based stereocontrol for
the formation of bis- and tris-cyclopropanes using the Furukawa protocol. The results of
found in these studies are in concert with those reported by Barrett and coworkers.
b. Yamamoto Asymmetric Cyclopropanation:

The Yamamoto asymmetric cyclopropanation reaction utilizes a zinc-carbenoid to cyclopropanate chiral allylic acetals. The zinc-carbenoid is believed to be directed by Lewis acid-base pairing between the carbenoid and the acetal to deliver the methylene to one face of the olefin in preference to the other. In 1995, Barrett reported a two-directional application of the Yamamoto asymmetric cyclopropanation (Scheme 53). Formation of the diacetal of muconaldehyde 203 with diisopropyl L-tartrate via the Noyori method followed by Yamamoto cyclopropanation gave rise to the C2-symmetric bis-cyclopropyl-bis-acetal 206. Similarly, work by Theberge and Zercher described the application of the Yamamoto asymmetric cyclopropanation; however, efforts to remove the chiral acetal moiety proved troublesome.

\[
\text{OHC} = \text{CHCHO} \xrightarrow{\text{TMSOTf, CH}_3(\text{OTMS}) = \text{NTMS}} \begin{array}{c}
\text{OTMS} \\
\text{PrO}_2 \text{C} \\
\text{CO}_2 \text{Pr} \\
\text{OTMS}
\end{array} \\
\begin{array}{c}
\text{PrO}_2 \text{C} \\
\text{CO}_2 \text{Pr}
\end{array}
\]

\[
\xrightarrow{\text{Et}_2 \text{Zn, CH}_2 \text{J}_2} \begin{array}{c}
\text{H} \\
\text{PrO}_2 \text{C}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{CO}_2 \text{Pr}
\end{array} \\
\begin{array}{c}
\text{H} \\
\text{PrO}_2 \text{C}
\end{array}
\]

Scheme 53. Barrett’s Application of the Yamamoto Asymmetric Cyclopropanation

An approach to bis-cyclopropanes, reported by Armstrong in 1995, made use of a modified Yamamoto protocol (Scheme 54), in which a hydrobenzoin acetal was used.
instead of the tartrate acetal. Upon cyclopropanation of 208 with standard Furukawa conditions, it was found that the \textit{syn-bis-cyclopropane} formed with $<50\% \ de$, which was clearly inferior to the tartrate method. Interestingly, the stereochemical influence of the hydrobenzoin group was opposite to that predicted for the tartrate analog. Efforts to make the tartrate analog of phosphonium salt 207 proved difficult and considering the results of the hydrobenzoin acetal, Armstrong and coworkers sought an alternative route.

Application of the Yamamoto asymmetric cyclopropanation methodology to iterative polycyclopropane preparation is hampered by several required protection-deprotection steps. Armstrong and coworkers developed a creative method for iterative cyclopropane formation (Scheme 55), which avoided the troublesome acid-mediated deprotection of the acetal.\textsuperscript{114} Yamamoto cyclopropanation of crotonaldehyde provided a cyclopropyl acetal 211, which was treated with allyl trimethylsilane and titanium tetrachloride. The resulting homoallylic alcohol 212 was subjected to ozonolysis and treated with triethylamine to eliminate the tartrate and provided aldehyde 214.
unsaturated aldehyde 214 was subjected to acetal formation conditions and the resulting vinyl cyclopropane was exposed once again to the cyclopropanation conditions. This creative approach to iterative cyclopropane formation was not only shorter than the traditional strategies, but avoided the harsh acidic conditions required for acetal cleavage.

Scheme 55. Armstrong’s Iterative Application of the Yamamoto Asymmetric Cyclopropanation

The Yamamoto asymmetric cyclopropanation protocol has been applied successfully to diastereoselective polycyclopropane formation in one and two directions,
yet the major shortcoming of this method is that the chiral auxiliary is covalently bound to the substrate. The additional steps required for the incorporation and removal of the auxiliary hinder overall yields.

c. **Fujisawa Asymmetric Cyclopropanation:**

The Fujisawa asymmetric cyclopropanation methodology utilizes stoichiometric diethyl tartrate as a non-covalently bound chiral additive, thereby creating an undefined, chiral environment about the zinc-carbenoid. The diethyl tartrate can be washed away in the work-up, which conveniently eliminates the need for protection-deprotection steps.

![Scheme 56. Barrett's Application of the Fujisawa Asymmetric Cyclopropanation Toward bis-Cyclopropanes](image)

In 1994, Barrett utilized this method to generate diastereomERICally enriched bis-cyclopropanes 218 and 219.\textsuperscript{11a} The enantiomerically enriched vinyl cyclopropane 217 was prepared via the Yamamoto protocol (above) and was exposed to the Fujisawa conditions to form the phenyl substituted bis-cyclopropyl alcohols 218 and 219. The yield of bis-cyclopropane formation was higher than that found for the Yamamoto cyclopropanation; however, the stereoselectivity observed when attempting to form either the syn or anti isomer was modest (6:1).
d. **Charette Asymmetric Cyclopropanation:**

![Chemical Structures]

**Figure 23.** Charrette’s Chiral Dioxaboralane Chiral Auxiliaries

Charette and coworkers reported that allylic alcohols can be cyclopropanated with high enantioselectivity by using a zinc-carbenoid in conjunction with chiral dioxaboralanes 220 and 221, which were prepared from butylboronic acid and chiral N,N,N',N'-tetramethyl tartaramides. By employing Charette’s model for simple allylic alcohol cyclopropanation (Figure 24) the stereochemistry of the carbenoid delivery can be predicted. The Lewis-acidic carbenoid is believed to interact with the Lewis-basic carbonyl and boronic ester oxygens of the auxiliary, which is coordinated through boron to the oxygen of the allylic alcohol. This Lewis acid-base pairing is believed to result in the preferential delivery of the carbenoid to one face of the olefin. The stereochemistry of the products resulting from the application of this strategy were determined by x-ray crystallography and found to be in concert with that predicted by the application of this model.\(^{115}\)
Barrett reported the use of Charette’s methodology in the cyclopropanation of the
divinyl-bis-cyclopropane 223 (Scheme 55). The C$_2$-symmetric tetrakis-trans-
cyclopropyl-diols, syn-syn-syn- 224 and anti-syn-anti- 225, were made with very high
efficiency. The stereochemistry of the products was assigned by analogy with
Charette’s model for the cyclopropanation of simple allylic alcohols. Earlier work by
the Zercher group has described the application of Charette’s protocol in two directions
successfully forming two enantiomerically enriched C$_2$-symmetric tris-cyclopropanes and
two C$_2$-symmetric quinque-cyclopropanes, which will be the topic of a later section.
Scheme 57. Application of Charrette’s Asymmetric Cyclopropanation Protocol

The most rapid and efficient method for forming $C_2$-symmetric polycyclopropanes has proven to be the two-directional application of Charette’s asymmetric cyclopropanation. The obvious limitation of this two-directional strategy is that non-symmetric polycyclopropanes cannot be prepared. One-directional approaches increase the total number of steps and minimize material throughput. Nevertheless, access to stereochemically-defined non-symmetric bis-cyclopropanes would be highly desirable.
Theberge and Zercher pioneered the one-directional application of the Charette methodology, as illustrated in the formation of a series of eight bis-cyclopropanes 226-233 (Figure 25) (ása infra). Since the results from Theberge’s work are central to this thesis, a more complete discussion of the bis-cyclopropane formation will be the topic of a later section.

4. Cyclopropane Coupling Strategies:

In most of the polycyclopropane preparations described to this point, chain extension reactions and cyclopropanation reactions have been utilized in an iterative fashion. Two alternative approaches to polycyclopropane synthesis that have been reported are the copper-mediated dimerization and the Suzuki-type cross-coupling of cyclopropanes. In these attractive methodologies, pre-formed monocyclopropanes of known enantiopurity can be directly coupled, thereby avoiding the problems associated with conflicting reagent-mediated and substrate-mediated stereocontrol.
a. **Copper-Mediated Oxidative Dimerizations:**

Falck reported the application of Hiyama’s copper-mediated oxidative dimerization of cyclopropanes\(^{103}\) toward the formation of diastereomerically enriched bis-cyclopropane 236 and *tetrakis*-cyclopropane 239 (Scheme 58).\(^{58}\) By exposing the vinyl stannane 234 to Charrette’s asymmetric cyclopropanation protocol and copper mediated oxidative coupling, *bis*-cyclopropane 236 was prepared. The protected *bis*-hydroxymethyl-*bis*-cyclopropane was mono-deprotected. The free hydroxymethyl group was oxidized to the carboxylic acid, which was subsequently converted to a bromine substituent by the radical-mediated Barton decarboxylation method.\(^{118}\) A second oxidative coupling reaction of 2,2’-dibromo-*bis*-cyclopropane resulted in dimerization and formation of a diastereomerically enriched *tetrakis*-cyclopropane 239.

![Scheme 58. Iterative Application of the Copper-Mediated Oxidative Coupling](image)

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This method eliminates the problem of substrate-mediated stereocontrol by coupling enantiomerically enriched components, yet there are limitations. Since preparation of the cyclopropyl bromide proceeds through the intermediacy of a cyclopropyl radical, this method appears to be restricted to trans-cyclopropanes. Furthermore, the methodology has been developed for the coupling of two identical cyclopropane units, thereby limiting its applicability to C$_2$-symmetric targets.

b. **Suzuki Cross-Coupling Reactions:**

Some of the difficulties described in the previous coupling strategy are avoided in the application of a Suzuki-type cross-coupling reaction as reported by Charette. Non-symmetric polycyclopropanes are accessible through the palladium-catalyzed coupling of iodocyclopropanes and cyclopropyl boronate esters (Scheme 59). Yields ranging from 10% to 70% were reported, along with the observation that basicity of the substituents on boron appears to play an important role in these reactions.

![Scheme 59. Charrette's Application of the Suzuki Cross-Coupling Strategy](image)

This study was carried out with racemic materials and, therefore, \textit{syn/anti} stereocontrol was not addressed. However, since optically active cyclopropylboronate

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esters are available\cite{120} and the enantioselective cyclopropanation of 3-iodoallylic alcohols should be possible, the stereoselective synthesis of polycyclopropanes by Suzuki coupling appears likely.

F. Previous Work Resulting in the Formation of Diastereomeric bis-Cyclopropanes:

Previous work described by Theberge and Zercher pioneered the iterative approach to polycyclopropanes that made use of the Charette protocol.\cite{121} Through the stereoselective preparation of each diastereomeric variant of 2-hydroxymethyl-2'-phenyl-bis-cyclopropanes (Figure 25), the application of Charette's asymmetric cyclopropanation method was described for polycyclopropane synthesis.\cite{113}

Retrosynthetic analysis of the desired bis-cyclopropanes 226-233 identified E- and Z-cinnamyl alcohols as the desired starting materials. Cyclopropanation of commercially available E-cinnamyl alcohol with diethylzinc, methylene iodide, and L-tartrate derived dioxaboralane 220 was reported by Charette in his initial study (>85% yield, 88-93 %ee) and provided cyclopropane 244 (Scheme 60). Oxidation of 244 with catalytic tetrapropylammonium perruthenate (TPAP) and stoichiometric 4-methylmorpholine-N-oxide (NMO) provided nearly quantitative yields of trans-2-phenylcyclopropylcarboxaldehyde 245. Extension of the carbon backbone was effected by Horner-Emmons chemistry to provide ethyl E-3-(trans-(1R,2S)-2-phenylcyclopropyl)propenoate 246. Reduction of ester 246 with excess diisobutylaluminum hydride (DIBAL-H) provided the precursory allylic alcohol 247 in excellent yield. Application of Charette's asymmetric cyclopropanation protocol
utilizing L-tartrate-derived dioxaboralane 220 afforded syn-bis-cyclopropane 226 (10:1, syn:anti) in good yield. Cyclopropanation of 247 by the same procedure utilizing the D-tartrate-derived dioxaboralane 221 provided equally impressive results for the synthesis of the anti-bis-cyclopropane 227 (1:10, syn:anti).

Scheme 60. Theberge's Iterative Preparation of bis-Cyclopropanes 226 and 227

The synthesis of bis-cyclopropanes 228 and 229 required that a Z-olefin be incorporated into the precursor allylic alcohol 249 (Scheme 60). Exposing cyclopropyl carboxaldehyde 245 to the Z-selective Horner-Emmons conditions developed by Still\textsuperscript{122} efficiently resulted in methyl Z-3-(trans-(1R,2S)-2-phenylcyclopropyl)propenoate 248 (10:1, Z:E). Reduction of ester 248 with excess DIBAL-H provided the precursor allylic alcohol 249. Exposing 249 to Charette's cyclopropanation protocol with L-tartrate-derived dioxaboralane unfortunately resulted in modest selectivity of the trans-anti-cis-bis-cyclopropane 229 (1:6, syn:anti). When allylic alcohol 249 was exposed to the D-tartrate-
derived dioxaboralane 221 directed cyclopropanation protocol, the formation of trans-syn-
cis-bis-cyclopropane 228 showed improved selectivity (10:1, syn:anti).

\[ \text{PhCHO} \xrightarrow{(\text{CF}_3\text{CH}_2\text{O})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{CH}_3} \text{PhCO}_2\text{CH}_3 \xrightarrow{\text{DIBAL-H}} \]

Scheme 61. Formation of trans-cis-bis-Cycloproanes

The remaining bis-cyclopropanes required the preparation of Z-cinnamyl alcohol 252, which was prepared as described in Scheme 62. Treatment of phenylacetylene with
\[ n\text{-butyl lithium} \] followed by the addition of gaseous formaldehyde resulted in 3-
phenylpropargyl alcohol 251. Hydrogenation of 251 with Lindlar's catalyst (Pd-CaCO3
PbO) cleanly resulted in the Z-cinnamyl alcohol 252.

\[ \text{Ph} \xrightarrow{n\text{BuLi}} \text{Ph} \xrightarrow{\text{H}} \text{Ph} \xrightarrow{\text{H}_2} \]

Scheme 62. Synthesis of cis-Cinnamyl Alcohol 252

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Cyclopropanation of cinnamyl alcohol 252 with the L-tartrate-derived dioxaboralane (220)-directed Charette protocol resulted in hydroxymethyl cyclopropane 253 (Scheme 63), which was determined to be 83 % ee by chiral GLC. Extension of the carbon backbone, analogous to the trans-cyclopropane 245 (above) afforded ethyl E-3-(cis-(1R,2R)-2-phenylcyclopropyl)propenoate (6:1, E:Z). Following reduction of ester 255, exposing the cis-cyclopropyl-E-allylic alcohol to Charette’s asymmetric cyclopropanation conditions provided the desired bis-cyclopropanes; L-tartrate-derived dioxaboralane provided the cis-syn-trans-bis-cyclopropane 230 (2.5:1, syn:anti) and D-tartrate-derived dioxaboralane resulted in the cis-anti-trans-bis-cyclopropane 231 (1:>10, syn:anti).

Scheme 63. Synthetic Approach to cis-trans-bis-Cyclopropanes
In a similar fashion, cyclopropyl carboxaldehyde 254 was chain extended with the Z-selective Horner-Emmons conditions to provide ester 257, which was reduced with DIBAL-H to provide the precursory allylic alcohol 258. Exposing the cis-cyclopropyl-Z-allylic alcohol 258 to the Charette cyclopropanation conditions provided the anticipated bis-cyclopropanes; L-tartrate-derived dioxaboralane resulted in cis-anti-cis-bis-cyclopropane 233 (1:5, syn:anti) and D-tartrate-derived dioxaboralane provided the cis-syn-cis-bis-cyclopropane 232 (5:1, syn:anti).

While the predicted products were predominantly formed, the selectivities observed in the formation of the second cyclopropane were not consistent. In efforts to understand the potential substrate-based stereocontrol, each of the four cyclopropyl allylic alcohols were subjected to Furukawa-modified Simmons-Smith cyclopropanation conditions in the absence of chiral auxiliaries. The results of this study are summarized in Table 5 along with those obtained from studies performed in the presence of chiral dioxaboralanes.

Scheme 64. Synthetic Approach to cis-cis-bis-Cyclopropanes

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The results obtained from the trans-cyclopropyl allylic alcohols 245 and 249 reveal virtually no substrate-based stereocontrol. The cis isomers 256 and 258 reveal varying degrees of substrate-based stereocontrol assist in governing the diastereoselectivity of the directed cyclopropanations. The most remarkable of these resulted when the cis-cyclopropyl-E-allylic alcohol 256 was exposed to undirected cyclopropanation conditions excellent substrate-based stereocontrol was observed (1:9, syn:anti). When the dioxaboralane directing agents were utilized for the cyclopropanation of allylic alcohol 256 the results were dramatically different. The substrate-based stereocontrol effectively negates much of the directing ability of the L-tartrate-derived dioxaboralane (2.5:1, syn:anti) and significantly enhances the directing ability of the D-tartrate-derived dioxaboralane (1:>10, syn:anti).
G. Results and Discussion:

Upon entering the area of polycyclopropane synthesis, our group’s initial goal was to develop a strategy that provided a route to every diastereomeric variant of a polycyclopropane. While formulating an iterative methodology for the synthesis of polycyclopropanes, the aforementioned work by Theberge and Zercher revealed one limitation of Charette’s asymmetric cyclopropanation protocol. The use of chiral auxiliaries to effect an asymmetric reaction on chiral substrates can either be enhanced or diminished by substrate-based stereocontrol. In the cyclopropanation of cis-cyclopropyl-E-allylic alcohol 256, the substrate-based stereocontrol clearly modulates the efficiency of the dioxaboralane directing agents. As a result of the substrate-based stereocontrol of 256, the 2-hydroxymethyl-2’-phenyl-cis-syn-trans-bis-cyclopropane 230 cannot be prepared efficiently through the application of the Charette protocol. In order to further investigate the substrate-based stereocontrol of vinyl-cyclopropane systems we directed our efforts to study rhodium carbenoid and sulfur ylide cyclopropanations. The substrates for our studies were chosen specifically to provide the same bis-cyclopropanes as formed in the study of Theberge.

1. Rhodium Carbenoid Study:

The remarkable substrate-based stereocontrol displayed when 256 was exposed to zinc-carbenoids prompted our studies into the rhodium-carbenoid cyclopropanation of analogous systems. In analysis of the zinc carbenoid study, Theberge and Zercher explained the increased substrate-based stereocontrol with cis-cyclopropanes like 256 to result from a steric biasing of the conformational equilibrium (Figure 26). Virtually the

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only bond that requires consideration in the analysis of these systems is the
cyclopropane-olefin bond. Specifically in the case of the cis-cyclopropane-E-allylic
alcohol 256, the conformational bias would be expected to be enhanced by the steric
interactions with the phenyl substituent.

![Diagram of conformational biasing of cyclopropanation](image)

**Figure 26.** Theberge’s Model for Conformational Biasing of the
Cyclopropanation of Vinyl cis-Cyclopropane 256

In the bisected conformation 256b, cyclopropanation with a zinc-carbenoid could
occur equally well from either face. When the olefin is rotated towards the phenyl group
as in gauche conformer 256a, the face leading to the *syn-bis*-cyclopropane appears to be
the only face accessible to the carbenoid. As the olefin rotates in this direction towards
the substituent, not only does one face of the olefin become “blocked” but also steric
interactions between the olefin and phenyl ring cause an increase in energy, which would
be anticipated to result in the decreased occupancy of this conformation. Rotation of the
vinyl group away from phenyl substituent as in conformer 256c, does not appear to
encounter serious steric interactions and was argued to result in an increased availability of the olefinic face leading to the experimentally observed anti-bis-cyclopropane formation. Through application of the same conformational model to vinylcyclopropane 259, it appears that the most accessible face of the double bond, as shown in 259c, will facilitate formation of the cis-syn-trans-bis-cyclopropane 230 through reaction with the rhodium carbenoid.

Scheme 65. Rhodium-Carbenoid Study

The substrates for this study were prepared according to Scheme 65. Cyclopropanation of cinnamyl alcohols 243 and 252 provided the racemic cis- and trans-2-phenylhydroxymethyl cyclopropanes 260 and 262, respectively. Oxidation of alcohols

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260 and 262 with TPAP/NMO, followed immediately by Wittig olefination with triphenylphosphonium methylide, provided vinyl cyclopropane substrates 259 and 263. The substrates were exposed to cyclopropanation conditions and the resulting product mixtures were reduced with excess DIBAL-H. Through analysis of the resulting product mixture by $^{13}$C NMR and comparison with the respective $^{13}$C NMR spectra of the aforementioned eight diastereomERICally-enriched $bis$-cyclopropanes, the product mixture was deciphered (Table 6).

![Chemical Structure](image)

**Table 6. Product Ratios in Rhodium Carbenoid Cyclopropanations**

<table>
<thead>
<tr>
<th>Cyclopropane</th>
<th>syn-trans</th>
<th>anti-trans</th>
<th>syn-cis</th>
<th>anti-cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans</td>
<td>25</td>
<td>35</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>cis</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a. $[\text{Rh(OAc)}_2]_2$, EDA; b. DIBAL-H

When the $trans$-vinyl cyclopropane 263 was exposed to ethyl diazoacetate in the presence of the rhodium acetate dimer and the products were reduced with DIBAL-H, the $trans$-$syn$-$trans$- and $trans$-$anti$-$trans$-$bis$-cyclopropanes 226 and 227 respectively, comprised the majority of the product mixture (60%) in a 1:1.4 ratio. The remainder of the products (40%) was an equimolar mixture of the $trans$-$syn$-$cis$- and $trans$-$anti$-$cis$-$bis$-cyclopropanes 228 and 229. Although a single diastereomer was not formed, the results obtained from the $trans$-vinyl cyclopropane 263 are in agreement with Doyle's model (Figure 18), which predicted a preference for $trans$-selectivity. In addition to their agreement with Doyle's model, these results also are in concert with those obtained by...
Theberge in the identification of little olefin facial selectivity in the zinc-carbenoid cyclopropanations of \textit{trans}-vinyl cyclopropanes.

When the \textit{cis}-vinyl cyclopropane 259 was exposed to the identical reaction sequence, however, the product mixture contained only the \textit{cis-syn-trans} and \textit{cis-anti-trans-bis}-cyclopropanes 230 and 231. Although Doyle’s model predicts a strong \textit{trans}-preference when the steric environment about terminal mono-substituted olefins is increased,\textsuperscript{77b,123} the generation of newly formed cyclopropanes that possessed exclusive \textit{trans}-stereochemistry was intriguing. Considering the absence of selectivity found in the analogous \textit{trans}-vinyl cyclopropane 263, the \textit{cis}-stereochemistry of 259 is inarguably a predominant factor in effecting substrate-based stereocontrol. The exact reason for this lack of facial selectivity is unclear and indicates that the proposed conformational model (Figure 27) is simplified and inadequate. Additional work in this area may illuminate the factors governing the stereoselectivity, however; it is clear that the application of this methodology is insufficient for the stereocontrolled synthesis of polycyclopropanes.

2. Studies in Sulfur Ylide Cyclopropanations:

The lack of substrate-based stereocontrol in the rhodium-carbenoid cyclopropanation of vinyl cyclopropanes 259 and 263 and the limitations of the zinc-carbenoid methodology suggested that other cyclopropanation methods be investigated. Given the inability of both rhodium- and zinc-carbenoids to prepare the \textit{cis-syn-trans-bis}-cyclopropane 230, a selective means for the construction of the \textit{cis-syn-trans} diastereomeric relationship of polycyclopropanes was deserved. Since sulfur ylide
cyclopropanation reactions are known to predominantly form trans-cyclopropanes, their application toward the preparation of 230 was possible.

Since sulfur ylides predominantly react with electron deficient olefins, 3-cyclopropylpropenoate esters were targeted as the subjects of this study. Previous work in this area has identified α,β-unsaturated i-butyl esters as the substrates which provide the highest yield,\textsuperscript{124} presumed to result from a decreased rate of hydrolysis by residual hydroxide as compared with methyl and ethyl analogues. The i-butyl cyclopropylpropenoate esters 265-268 (Figure 28) were chosen as substrates for the study of substrate-based stereocontrol in the sulfur ylide cyclopropanation reaction primarily because the resulting bis-cyclopropyl esters can be reduced with DIBAL-H to provide a mixture of bis-cyclopropanes. The reaction mixture can be deciphered as in the previous study by comparison with the eight bis-cyclopropanes 226-233 prepared by Theberge (Figure 25).

\[ \text{Figure 28. Substrates for Sulfur Ylide Study} \]

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Figure 29. Mechanistic Analysis of Sulfur Ylide Cyclopropanation

Since nucleophilic addition of the sulfur ylide is reversible, (Figure 29) the overall product distribution will be determined by the competitive rate of intramolecular displacement of DMSO. Since product distribution will not be determined by facial selectivity as with the zinc and rhodium carbenoid methods, the sulfur ylide-mediated method provides a fundamentally different approach to stereocontrol.
Preparation of both cis- and trans-3-cyclopropyl-Z-propenoate esters required the synthesis of Z-selective Horner-Emmons reagent t-butyl bis-(2,2,2-trifluoroethyl)phosphonoacetate 277 (Scheme 66). Exposing methane phosphonic dichloride 274 to 2,2,2-trifluoroethanol cleanly provided bis-(2,2,2-trifluoroethyl)methylphosphonate 275, which upon deprotonation with methyl lithium and quench with di-t-butyl-pyrocarbonate 276 provided the desired Z-selective reagent 277.

The substrates containing a Z-olefin were prepared from the cis- and trans-cyclopropyl carboxaldehydes as outlined in Scheme 65. Exposure of cyclopropyl carboxaldehydes 278 and 279 to the potassium salt of phosphonate 277 in the presence of 18-crown-6 efficiently resulted in the corresponding Z-propenoates 268 and 266. Similarly, exposing aldehydes 278 and 279 to the sodium salt of commercially available t-butyl diethylphosphonoacetate cleanly provided the E-propenoate esters 267 and 265.
Scheme 67. Synthesis of Substrates for the Sulfur Ylide Study

Each substrate was subjected to excess dimethyloxysulfonium methylide and the crude reaction mixture was reduced with DIBAL-H to provide diastereomeric mixtures of bis-cyclopropanes. Analysis of the product mixtures by $^{13}$C NMR and comparison to the spectra of Theberge allowed the mixture to be deciphered easily (Table 7).

Table 7. Selectivity Observed in Sulfur Ylide Cyclopropanation Studies

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Cyclopropane</th>
<th>Olefin</th>
<th>syn-trans</th>
<th>anti-trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>265</td>
<td>trans</td>
<td>E</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>266</td>
<td>trans</td>
<td>Z</td>
<td>44</td>
<td>56</td>
</tr>
<tr>
<td>267</td>
<td>cis</td>
<td>E</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>268</td>
<td>cis</td>
<td>Z</td>
<td>67</td>
<td>33</td>
</tr>
</tbody>
</table>

a. NaH, (CH$_3$)$_2$S$^-$OCH$_3$, DMSO; b. DIBAL-H

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In the rhodium- and zinc-carbenoid studies, little or no substrate-based stereocontrol was observed when the substrate contained a \textit{trans}-cyclopropane. Therefore, it was not surprising that \( t \)-butyl \( E \)-3-(\textit{trans}-2-phenylcyclopropyl)propenoate 265 and \( t \)-butyl \( Z \)-3-(\textit{trans}-2-phenylcyclopropyl)propenoate 266 provided little substrate-based stereocontrol when exposed to dimethyloxysulfonium methyliide. The small amounts of stereocontrol appeared to favor the \textit{anti-bis}-cyclopropane, which is identical to that observed in each of the carbenoid studies.

Also in agreement with the zinc- and rhodium-carbenoid studies was the fact that increased substrate-based stereocontrol was observed when the substrate contained a \textit{cis}-cyclopropane. When each of the two substrates that contained a \textit{cis}-cyclopropane 267 and 268 was exposed to sulfur-ylide cyclopropanation conditions, the \textit{cis-syn-trans-bis-cum}cyclopropane 230 was predominantly formed. The substrate-based stereocontrol in each of these two systems is remarkable. Efforts to employ the Charette protocol in the formation of 230 required stoichiometric amounts of an expensive additive and provided a 2.5:1 selectivity. While the diastereoselectivity (3:1) of the sulfur ylide reactions are not significantly better than the aforementioned studies, the application of sulfur ylides is based solely on the influence of substrate stereocenters. Interestingly, the substrate-based stereocontrol observed in the zinc-carbenoid study is opposite to the results obtained with the sulfur ylides. For this reason, it appears that when the \textit{cis-syn-trans} relative stereochemistry is desired, the reagent of choice is a sulfur ylide.
H. Conclusions:

The efforts of Theberge, among others, have resulted in an iterative process that utilizes the Charette protocol for the asymmetric preparation of polycyclopropanes. The application of this iterative process has become the most commonly used route to polycyclopropanes; however, in the preparation of certain stereoisomeric relationships it appears to be deficient. As described by Theberge, the application of Charette's protocol on systems with existing stereocenters can result in matched or mis-matched stereochemical influences. Modest substrate-based stereocontrol can be overwhelmed by directing reagents. However, when pronounced substrate-based stereocontrol is displayed, it has the potential to effectively "negate" the effects of the directing agents. This was the case when the Charette protocol was applied to the synthesis of the cis-syn-trans-bis-cyclopropane 230. Our efforts to identify a more efficient route for the preparation of this stereochemical combination of cyclopropanes have resulted in the investigation of both rhodium-carbenoids and sulfur ylides. The results of our rhodium-carbenoid study identified a deficiency of substrate-based stereocontrol and the inapplicability of these carbenoids to the stereoselective preparation of polycyclopropanes. The application of sulfur ylides that utilize substrate-based stereocontrol in the synthesis of polycyclopropanes is promising and appears to provide access to diastereomers that are inefficiently prepared by the application of the Charette protocol. Further work in this area is required to completely develop the sulfur ylide-mediated synthesis of polycyclopropanes.
CHAPTER III

EFFORTS TOWARD THE TOTAL SYNTHESSES OF
POLYCYCLOPROPA NATED NATURAL PRODUCTS FR-900848 AND U-106305

A. Synthetic Routes to Polycyclopropanated Natural Products:

The total synthesis of polycyclopropanated natural products 131 and 132 pose two synthetic challenges. The first and most obvious challenge lies in the stereocontrolled synthesis of the polycyclopropanated portion central to each compound. The recent advances in polycyclopropane synthesis has indicated that this challenge, although formidable, can be addressed in a number of ways. The second synthetic challenge inherent in these natural products is the incorporation of the olefin that interrupts the polycyclopropane framework. Two total syntheses have been reported for each of these natural products. A review of these syntheses, with an emphasis on the efforts to incorporate the intervening olefin, will serve to illustrate the need for an alternative methodology that incorporates complete diastereoselective flexibility.
1. Total Syntheses of FR-900848:

a. Barrett's Approach Toward FR-900848:\textsuperscript{125}

In their original retrosynthetic analysis (Figure 30), incorporation of the intervening olefin of FR-900848 was anticipated to result from a Whitham elimination of benzylidene acetal 281. Access to 281 was proposed to result from the E-selective Wittig coupling reaction, reported by Schlosser,\textsuperscript{126} of aldehyde 282 and phosphonium salt 283. After all efforts to convert mono-protected bis-hydroxymethyl-tris-cyclopropane 284 to

\[ 129 \xrightarrow{\text{H}_3\text{C}} \xrightarrow{\text{H}_3\text{C}} \]

\[ \xrightarrow{\text{OP}} \]

\[ 280 \]

\[ \xrightarrow{\text{OP}} \]

\[ 281 \]

\[ \xrightarrow{\text{CHO}} + \xrightarrow{\text{X}^+\text{Ph}_3\text{P}^-} \]

\[ 282 \] \[ 283 \]

\[ \xrightarrow{\text{OP}} \]

\[ 284 \]

Figure 30. Barrett's Original Retrosynthetic Analysis of FR-900848 (129)

the alkyl halide precursory to 283 had failed, another strategy was devised (Figure 31). In this new strategy, Barrett anticipated utilizing his studies in the selective mono-
cyclopropanation of dienols (Scheme 50) to incorporate the cyclopropane secluded by an E-olefin.

By applying Charette's asymmetric cyclopropanation protocol in an iterative strategy similar to that of Theberge and McDonald, Barrett was able to elaborate hexadiendiol 289 into bis-hydroxymethy-tetrakis-cyclopropane 224 in five steps (overall yield, 52%). Mono-protection of diol 224 via the McDougal protocol, followed by oxidation of the free alcohol and Horner-Emmons homologation afforded α,β,γ,δ-bis-unsaturated ester as a mixture of 292a E,E- and 292b E,Z- isomers (5:1). After chromatographic separation, the Hunter isomerization method was used in order to convert the E,Z-isomer 292b to the E,E-isomer 292a. Reduction of 292a with excess

Figure 31. Barrett's Revised Retrosynthetic Analysis of FR-900848 (129)
DIBAL-H followed by mono-cyclopropanation provided the functionalized polycyclopropane precursor 293 to FR-900848.

Scheme 68. Barrett's Synthetic Assembly of Polycyclopropane Precursor to FR-900848

The removal of the undesired hydroxyl functionality proved to be difficult. Conversion of the hydroxyl-group to a phenyl sulfide was accomplished by treatment with N-(phenylthio)succinimide and tributylphosphine. Efforts to remove the sulfide moiety by oxidizing to the sulfone and cleaving with various dissolving metal reduction
systems were unsuccessful. However, Raney nickel hydrogenolysis of the phenylsulfide successfully afforded the desulfurized terminal-methyl compound 295. Deprotection of

\[
\begin{align*}
\text{293} & \xrightarrow{\text{Bu}_3\text{P (89\%)}} \text{N-(phenylthio)succinimide} \\
\text{PhS} & \xrightarrow{\text{OTBS}} \text{294} \\
1. \text{Raney nickel, } \text{H}_2 & \\
2. \text{TBAF (49\% two steps)} \\
\text{295} & \xrightarrow{\text{1. PCC}} \\
2. (\text{E})-\text{MeO}_2\text{CCH=CHCH}_2\text{P(0)(OMe)}_2 & \xrightarrow{\text{NaH (63\% two steps)}} \\
\text{NaH} & \\
\text{296} & \xrightarrow{\text{1. KOTMS (85\%)}} \\
2. \text{BOP-Cl, TEA} & \xrightarrow{\text{297 (69\%)}} \\
\text{297} & \\
\text{129}
\end{align*}
\]

Scheme 69. Conclusion of Barrett's Total Synthesis

the silyl ether, followed by oxidation and Horner-Emmons chemistry afforded the fatty acid side-chain of FR-900848 296. Plagued by the mono-protection of 224 (44\%) and the desulfurization of 294 (49\%), Barrett's synthesis of FR-900848 (17 steps, 2.0\% overall yield) is clearly an inefficient process.
b. Falck's Oxidative Dimerization Approach to FR-900848: \(^{58}\)

![Chemical Structure](image)

**Figure 32.** Falck's Retrosynthetic Analysis of FR-900848 (129)

Similar to that of Barrett (above), Falck's retrosynthetic analysis of FR-900848 (Figure 32) broke the natural product into four parts with plans to utilize both olefination and amide chemistry to assemble the pieces. The novelty of Falck's synthetic strategy lies in the synthesis of the \textit{tetraakis}-cyclopropane 239 (Scheme 58). By utilizing an oxidative copper mediated-coupling strategy, Falck made use of one cyclopropanation reaction in his assembly of the \textit{tetraakis}-cyclopropane 239 (8 Steps, 17.2% overall yield). While this is an attractive route for the preparation of polycyclopropanes, it must be noted that its application is limited to the preparation of \(C_2\)-symmetric polycyclopropanes.
Mono-deprotection of bis-siloxy methyl-tetrakis-cyclopropane 239 with a single equivalent of tetrabutylammonium fluoride (TBAF) followed by tetrapropylammonium perruthenate oxidation provided the corresponding aldehyde 301. Efforts to utilize the Julia olefination to elaborate aldehyde 301 into the polycyclopropanated portion of FR-900848 under a variety of conditions resulted in “structural collapse.” However, the Peterson-olefination\textsuperscript{129} afforded vinyl sulfone 302 in moderate yield. Dissolving metal desulfurization was accomplished with lithium naphthalenide providing the polycyclopropanated portion of the side chain. Following removal of the protecting group with TBAF, the fatty acid side-chain 303 of FR-900848 was prepared by oxidation.
and Horner-Emmons chemistry. While Falck’s convergent total synthesis of FR-900848 is longer than Barrett’s linear synthesis, the overall yield is slightly higher (>20 steps, <3.0% overall yield). Similar to Barrett’s synthesis, the removal of unwanted functionality is the lowest yielding step in Falck’s synthesis of 129.

2. Total Syntheses of U-106305:

a. Barrett’s Total Synthesis of U-106305: 130

In a strategy very similar to that used to prepare FR-900848 (120), Barrett built the polycyclopropanated central portion of the U-106305 (130) backbone by the Charette protocol. Starting from E-2-buten-1,4-diol 304, Barrett was able to assemble the bis-hydroxymethyl-quinque-cyclopropane 309 quickly (7 steps, 29.6% overall yield) through iterative application of the Charette cyclopropanation, oxidation, Horner-Emmons chain-extension, and reduction sequence of transformations.
Scheme 71. Barrett’s Approach to the quinque-Cyclopropane Fragment of U-106305 (130)

Mono-protection of diol 309 allowed for the one-directional chain extension via oxidation, Horner-Emmons chemistry to provide $\alpha,\beta,\gamma,\delta$-unsaturated ester 311. Following DIBAL-H reduction, mono-cyclopropanation provided the functionalized polycyclopropanated portion 312 of U-106305. Once again, the removal of undesired functionality resulted in poor overall yields. Conversion of alcohol 312 to the phenyl sulfide 313, followed by Raney nickel hydrogenolysis afforded the terminal methyl compound 314 (44%). Removal of the protecting group, oxidation, and Horner-Emmons-type chemistry concluded the total synthesis of U-106305 (130) (19 conversions, 4.9% overall yield).
b. Charette’s Approach to U-106305: ¹³¹

In a method similar to that of Falck, Charette’s retrosynthetic analysis of U-106305 (130) centered upon the synthesis of the polycyclopropane fragment. Also choosing to employ a convergent synthesis, Charette proposed incorporation of the sequestered cyclopropane portion via an olefination approach utilizing aldehyde 317 and a suitable precursor of the type 316.
Figure 33. Charette’s Retrosynthetic Analysis of U-106305 (130)

Starting with the known *trans-bis*-hydroxymethylcyclopropane 319, the *bis*-hydroxymethyl-*quinque*-cyclopropane 318 (8 steps, 12.7% overall yield) was assembled in a two-directional method analogous to that of Barrett (above). Mono-protection of diol 318 with triisopropylsilyl triflate and 2,6-lutidine in methylene chloride afforded 323 in modest yield following two recycles. Oxidation of the alcohol 323 followed by Julia-olefination\(^{132}\) with benzothiazoyl sulfone 324 provided the polycyclopropanated side chain 315 of U-106305. Unfortunately, the Julia olefination with 324 was found to
provide modest selectivity for E-olefins in polar solvents, resulting in 315 (4:1, E:Z with NaHMDS in a THF/DME mixture). In fact, by utilizing less polar solvents the selectivity was reversed and dramatically improved to selectivity form the Z-olefin (1:10, E:Z with NaHMDS in CH$_2$Cl$_2$). Deprotection, followed by oxidation and Horner-Emmons-type chemistry completed Charette’s synthesis of (+)-U-106305 (ent-130) (>14 steps, <4.5% overall yield).
B. Previous Work Toward the Synthesis of Polycyclopropanated Natural Products:

Concurrent with the efforts of Barrett and Charette, work by McDonald and Zercher\textsuperscript{133} identified that the iterative strategy for polycyclopropane preparation, as described by Theberge and Zercher, was applicable in two-directions. The bi-directional application of this four-step iterative strategy was used to prepare two $C_2$-symmetric tris-cyclopropanes, while a third non-symmetric tris-cyclopropane was prepared in one direction. In addition, elaboration of the tris-cyclopropane, believed to possess the syn-syn-stereochemistry resulted in two $C_2$-symmetric quinque-cyclopropanes.

Cyclopropanation of allylic alcohol 325 with the L-tartrate-derived dioxaboralane-directed Charette asymmetric cyclopropanation protocol provided cyclopropyl methanol 326, which was deprotected to provide $\text{trans-1,2-bis-(hydroxymethyl)cyclopropane}$ 319. Bi-directional oxidation of 319 with TPAP/NMO, immediately followed by Horner-Emmons chemistry afforded diester 320. Reduction of 320 with excess DIBAL-H provided the divinylcyclopropane 327 precursor to the tris-cyclopropanes. When exposed to D-tartrate-derived dioxaboralane 221 directed cyclopropanation conditions, 327 cleanly afforded a $C_2$-symmetric bis-hydroxymethyl-tris-cyclopropane. Provided the Charette model was accurate in these two-directional systems, the anticipated anti-anti-stereochemistry is illustrated by 328. Similarly, when the divinylcyclopropane 327 was cyclopropanated with direction from L-tartrate-derived dioxaboralane 220, a $C_2$-symmetric bis-hydroxymethyl-tris-cyclopropane resulted and according to Charette’s model, should contain syn-syn-stereochemistry 321. While there is ample precedence supporting the predictions in one-directional application of Charette’s model (Figure 24), the question
arose concerning the two-directional application of this model and the resulting stereochemistry of the products. This issue will be discussed as the topic of a later section.

Scheme 74. McDonald and Zercher’s Route to C$_2$-Symmetric tris-Cyclopropanes

Further elaboration of tris-cyclopropane 321 by a second iteration of the two-directional preparation of polycyclopropanes provided bis-allylic alcohol 329. Two-directional cyclopropanation of 329 directed by D-tartrate-derived dioxaboralane, provided a C$_2$-symmetric bis-hydroxymethyl-quinque-cyclopropane, predicted to possess anti-syn-syn-anti-relative stereochemistry 330. Analogously, cyclopropanation of 329 directed by L-tartrate-derived dioxaboralane provided a different C$_2$-symmetric bis-hydroxymethyl-quinque-cyclopropane 320 that is predicted to have syn-syn-syn-syn-relative stereochemistry by application of Charette’s model.
Scheme 75. McDonald and Zercher’s Approach to the quinque-Cyclopropane Segment of U-106305

The preparation of quinque-cyclopropanes 318 and 330 serve to illustrate the difficulties of an iterative approach to these complex natural products. The inability to separate diastereomers of the polycyclopropanes generated by these reactions propagates the stereochemical impurity with each iteration. Thus, in the absence of stereospecific reactions, the longer the synthesis the greater the stereochemical impurity of the products.

A second difficulty in the two-directional iterative approach to polycyclopropanes lies in its restriction to C\textsubscript{2}-symmetric polycyclopropanes. While a one-directional linear synthetic approach allows any variant of a polycyclopropane to be prepared, it requires multiple steps and therefore is less efficient.
C. Results and Discussion:

1. Confirmation of the Relative Stereochemistries of the C<sub>2</sub>-Symmetric tris-Cyclopropanes:

The relative stereochemistry predicted by Charette’s model for each of the C<sub>2</sub>-symmetric tris-cyclopropanes prepared by McDonald was brought into question, since the two-directional application of this model had not yet been reported. Independent confirmation of the stereochemistry of previously reported tris-cyclopropanes 321 and 338 was required. After efforts to grow a X-ray quality crystal of a derivative of the quinque-cyclopropane 318 failed, we determined the best way to address this issue was to prepare the syn-syn-tris-cyclopropane 321 via a one-directional route. Stereochemistry of the intermediate syn- or anti- bis-cyclopropane could be assigned through its ability to rotate plane-polarized light. Conversion of the syn-bis-cyclopropane 335 (C<sub>2</sub>-symmetric) to a C<sub>2</sub>-symmetric tris-cyclopropane would allow assignment of the syn-syn-stereochemistry. The conversion of an anti-bis-cyclopropane 336 (meso) to a C<sub>2</sub>-symmetric tris-cyclopropane would lead to assignment of anti-anti-stereochemistry.
Scheme 76. Synthesis and Stereochemical Confirmation of *trans*-syn-*trans*-bis-cyclopropane 335

Preparation of the *trans*-1-*t*-butyldimethylsilyloxymethyl-2-hydroxymethylcyclopropane was accomplished through the procedure of McDonald. However, rather than removing the protecting group, alcohol 331 was oxidized by application of the catalytic TPAP methodology. Immediately following the oxidation, the reaction mixture was flushed through a plug of silica and the resulting concentrated oil was exposed to Horner-Emmons conditions to afford vinylcyclopropane 332. Following reduction of 332 with excess DIBAL-H, the L-tartrate-derived dioxaboralane-directed cyclopropanation of 333 proceeded efficiently. The stereochemistry of bis-cyclopropane 334 was confirmed to be *syn*- by independent synthesis through the two-directional cyclopropanation of hexadienediol 289 and mono-trityl protection of the C$_2$-symmetric *bis*-cyclopropane 335. Compound 335 rotated plane polarized light ([α]$_D$= -55.38...
+55.38; c. 0.0065, CH₂Cl₂) and could be assigned as the syn-isomer. The anti-bis-
cyclopropane 336 is a meso-compound and would not rotate plane-polarized light.

With the stereochemistry of bis-cyclopropane 334 unambiguously determined to
be syn, further elaboration of 334 to provide vinyl-bis-cyclopropane 338 proceeded
efficiently. Cyclopropanation of 338 directed by L-tartrate-derived dioxaboralane 220
provided mono-protected bis-hydroxymethyl-tris-cyclopropane 339, which provided
spectra consistent with the product of the mono-protection of bis-hydroxymethyl-tris-
cyclopropane 321.¹³⁵

2. Efforts Resulting in the Formal Synthesis of FR-900848:

The initial goal of our research-group was to develop a versatile methodology
capable of preparing every diastereomeric variation of these polycyclopropanated natural
products 129 and 130. The work of Theberge described an iterative methodology for the
preparation of polycyclopropanes and McDonald described its application in two directions. With the ability to prepare diastereomERICALLY-enriched polycyclopropanes, we turned our attention toward the incorporation of the sequestered cyclopropane and intervening E-olefin.

a. Efforts Toward the Whitham Elimination Route:

As described by Barrett, the Whitham elimination of a 4,5-dicyclopentyldienbenzylidene acetal is capable of stereospecifically incorporating both E- and Z-olefins between two cyclopropanes.\textsuperscript{57a, 136} Our original retrosynthetic analysis (Figure 34) proposed to utilize the Whitham elimination of 341 to incorporate the internal olefin of these natural products. Access to the Whitham elimination precursor 341a and 341b was proposed through the addition of a vinyl Grignard reagent derived from 345 into an enantiomerically enriched protected α-hydroxy aldehyde 344. The addition of various nucleophiles into protected α-hydroxy aldehydes have been
Figure 34. Our Original Retrosynthetic Analysis of Polycyclopropanated Natural Products FR-900848 129 and U-106305 130

extensively studied.\textsuperscript{137} The desired $\text{syn}$-stereochemistry is illustrated by 343, is best achieved by the addition of Grignard reagents into benzyl protected $\alpha$-hydroxy aldehydes. Cram’s model\textsuperscript{138} of chelate-derived stereochemical induction (Figure 35) has been proposed to both explain and predict the product stereochemistry of these reactions. The benzyl protected $\alpha$-hydroxy aldehyde 344, which was to be prepared by another

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graduate student, was proposed to be accessed by the Sharpless asymmetric
dihydroxylation of a protected divinyl carbinol followed by treatment with sodium
periodate.

![Diagram](image)

**Figure 35.** Cram-chelate Model Illustrating the Selectivity Observed in the
Addition of Grignard Reagents into α-Hydroxy Aldehydes

Access to the vinyl Grignard was proposed from the corresponding vinyl iodide
345, which could be accessed via a chromium(II)-mediated coupling of the corresponding
aldehyde with iodoform. Our initial efforts to test this chemistry were performed on
benzaldehyde. When benzaldehyde was exposed to excess chromium(II) chloride in the
presence of iodoform, β-iodostyrene 347a was obtained in good yield (67%). Rapid
decomposition of iodostyrene 347a was unavoidable and was marked by a purple
discoloration.
Scheme 78. Chromium Mediated Conversion of Aldehydes to Vinyl Iodides

Attempts to stabilize the iodostyrene with copper were unsuccessful. When trans-1,2-cyclopropane-dicarboxaldehyde 348 was converted to the bis-iodovinyl cyclopropane 349, no product was observed prior to decomposition. The production of 349 could only be inferred by the rapid onset of purple color. Similarly, purification of the reaction mixture resulting from the conversion of cyclopropyl carboxaldehyde 350 to iodovinyl cyclopropane 351 was not achieved prior to complete decomposition of product.
Due to the required use of excess chromium, messy reaction conditions, the instability of the product vinyl iodides and the difficulty of consistently preparing the Grignard reagent from the vinyl iodides, we sought an alternative nucleophilic precursor. Exposure of 344 to the magnesium salt of a terminal alkynyl cyclopropane, also prepared from the corresponding aldehyde 344, followed by reduction of the propargyl alcohol 352...
with lithium aluminum hydride, was proposed to result in the identical allylic alcohol 343.

![Scheme 79](image)

**Scheme 79.** Synthetic Route to Alkynylcyclopropanes

Exposure of aldehyde 335 to α-diazo-β-keto phosphonate 358 in anhydrous methanolic potassium carbonate cleanly afforded alkynyl cyclopropane 356 in nearly quantitative yield. The preparation of α-diazo-β-keto phosphonate 358 was accomplished by treating β-keto phosphonate 73 with LDA and p-carboxybenzenesulfonyl azide 357.\(^{139}\)

With a suitable nucleophile in hand and an efficient means of producing alkynyl cyclopropanes, we turned our attention to the preparation of a model system that would identify the feasibility of the proposed nucleophilic coupling. We anticipated that addition of a nucleophile into an α-benzyloxyaldehyde should afford a mono-protected...
1,2-diol (Figure 36). This approach would require the removal of the benzyl protecting group and subsequent incorporation of the benzylidene acetal for the Whitham elimination. Two systems were considered for the purpose of shortening this synthesis. Mono-p-methoxybenzyl-protected glycols can be converted to acetals through oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).\textsuperscript{140} Provided the p-methoxybenzylidene acetal resulting from such a reaction would undergo Whitham elimination similar to benzylidene acetals, the additional protection/deprotection steps could be avoided. Alternatively, if a simple mono-benzyl protected glycol is capable of oxidative conversion to the benzylidene acetal in a similar fashion to the p-methoxy-derivative, the protection/deprotection steps again could be avoided. For these reasons, we directed our attention to the potential reaction of mono-benzyl protected glycols with DDQ and the possible Whitham-type elimination of p-methoxybenzylidene acetals. If either the DDQ reaction or Whitham-elimination was successful, the protection/deprotection steps could be removed from the synthesis of these polycyclopropanated natural products.

In order to rapidly determine the ability of mono-benzyl protected glycols to react with DDQ, 1,2-butanediol 359 was protected with benzyl chloride. The resulting mixture of primary and secondary benzyl ethers was separated by distillation. Upon treatment with DDQ, benzyl ether 360 failed to react and only starting material was recovered. Efforts to enhance the reaction by adjusting the reaction conditions were unsuccessful and the potential use of the benzyl-protecting group was discounted.
Scheme 80. Efforts to Test the DDQ-Oxidation of 2-Benzylxybutanol

Two approaches to determine the success of the Whitham-type elimination of p-methoxybenzylidene acetals were attempted. The first involved the preparation of the p-methoxybenzylidene acetals 361a-c by standard acid-catalyzed conditions and treatment with n-butyl lithium. The reaction mixture was analyzed for benzylic alcohols, phenyl ketones, and benzoic acids, the predicted by-products of the elimination reaction; however, no compounds containing aromatic functionality were recovered from the reaction mixture. Since the alkene which was to be generated was not isolable, we redirected our efforts to prepare acetals that should give rise to an isolable olefin.

The cis-cyclohexane-derived acetal 362 was prepared by standard acid catalyzed dehydration conditions, while 364 was prepared by the method of Noyori\textsuperscript{112} (Scheme 81). Treatment of 1,2;5,6-diisopropyldiene mannitol with excess trimethylsilyl chloride (TMS-Cl) and triethylamine (TEA) afforded the bis-TMS ether 363. Exposing 363 to anisaldehyde and catalytic trimethylsilyl trifluoromethanesulfonate (TMSOTf) resulted in
the p-methoxybenzylidene acetal 364. No olefin-containing products were observed by $^1$H NMR when acetals 362 and 364 were treated with n-butyl lithium. We believe these results indicate that the Whitham-type elimination of p-methoxybenzylidene acetals was not possible.

Scheme 81. Attempted Whitham-type Elimination of p-Methoxybenzylidene Acetals
With the inability of benzyl ethers to react with DDQ and the absence of Whitham-type elimination from p-methoxybenzylidene acetics, we recognized that the manipulation of protecting groups was necessary to effect efficient conversion of the α-benzyloxyaldehyde to the olefin. We focused our efforts on the utilization of the p-methoxybenzyl (PMB) protecting group due to its facile cleavage with mild acid. The treatment of 1,2-butanediol 359 with triphenylmethyl chloride (TritylCl) in the presence of pyridine, conditions reported to selectively protect primary alcohols in the presence of secondary alcohols, resulted in the formation of trityl ether 365. The remaining hydroxyl-group of 365 was protected by exposure to sodium hydride and p-methoxybenzyl chloride or benzyl chloride. Subsequent removal of the trityl protecting group afforded the secondary benzyl ether 367a and p-methoxybenzyl ether 367b in modest overall yields. When mono-protected diols 367a and b were oxidized with TPAP/NMO, poor to moderate yields of 368a and 368b were obtained. The corresponding aryl aldehydes 369a and b were observed in the respective reaction mixtures and may reflect a decomposition pathway that competes with the formation of 368. This decomposition pathway might not occur with the substrates designed for the preparation of the natural products; however, careful study will be necessary to ensure the efficient preparation of the desired α-benzyloxy aldehyde 344.
Scheme 82. Preparation of Test α-Alkoxy Aldehyde Substrates

Initial studies in the addition of vinyl and alkynyl Grignard reagents into α-hydroxy aldehydes 368a and b provided ambiguous results. The syn/anti-stereochemistry could not be assigned at the α-hydroxy ether stage, and the elimination step was not performed due to a change in the strategy. Nevertheless, the tools appear to be available for the completion of this approach to the natural products FR-900848 and U-106305. The preparation of 344 has not been completed and presents the major obstacle to the further investigation of this approach.
b. **Use of Olefin Metathesis in the Preparation of Polycyclopropanated Natural Products:**

![Scheme 83. Cross Olefin Metathesis Reported by Grubbs](image)

Olefin metathesis has been extensively studied for the preparation of symmetric E-olefins.\(^\text{142}\) A recent report from Grubbs and coworkers describes the extension of this method to the preparation of non-symmetric E-olefins, as well (Scheme 83).\(^\text{143}\) These high-yielding E-selective reactions are particularly attractive for the incorporation of the sequestered cyclopropane of polycyclopropanated natural products 129 and 130, because of the concerted 2+2 mechanism (Figure 37) by which the carbenoid substituents are interconverted. The absence of radical- or charge-character developed in metathesis reactions reduced the likelihood of decomposition through cyclopropane rearrangements.
A new retrosynthetic analysis of the polycyclopropanated fatty amide side-chain of 129 and 130 is shown in Figure 38. This newly proposed strategy would utilize olefin metathesis in a three-step transformation of a hydroxymethyl polycyclopropane 386 to the non-polar polycyclopropane 382. The application of this strategy requires the access to the symmetric olefin 383. Barrett reported a 10-step synthesis of this compound starting from the expensive 3,4-isopropyldine-D-mannitol. However, an olefin metathesis reaction could be envisioned for the conversion of vinylcyclopropane 385 to
the cross-metathesis homo-dimer 383. Vinylcyclopropane 385 would be available from inexpensive crotyl alcohol via a four-step route.

![Figure 38. Retrosynthetic Analysis Incorporating Olefin Metathesis](image)

When crotyl alcohol 387 was exposed to cyclopropanation conditions, poor yields resulted from the water solubility of 388. Efforts to increase the yields by extensive extraction were unsuccessful. Furthermore, efforts to convert racemic 389 into 390 resulted in significant loss of mass due to the volatility of aldehyde 390.
In order to test the olefin cross-metathesis strategy on a less volatile system, cinnamyl alcohol was converted to the optically active cyclopropane 391 through the influence of D-tartrate-derived dioxaboralane 221. Cyclopropylmethanol 391 was oxidized with TPAP/NMO and the resulting aldehyde was olefinated with triphenylphosphonium methyldie to provide vinyl cyclopropane 392. The exposure of 392 to 5 mol% of Grubbs' catalyst in refluxing methylene chloride, followed by an additional 5 mol% of catalyst and further reflux provided the homo-dimer 393 (62%).144
The cross-metathesis reaction was tested on a racemic mixture of diastereomers of vinyl-tris-cyclopropane 394. A mixture of vinyl-tris-cyclopropanes 395 and homo-dimer 393 (1:2) was exposed to Grubbs' catalyst in refluxing methylene chloride. Analysis of the product mixture by $^1$H NMR clearly indicated that the terminal olefin had been consumed, new olefin resonances were present, and the polycyclopropanes were intact. While this result was encouraging, the product mixture was complex and contained an inseparable mixture of diastereomers.

\[
\begin{align*}
\text{TBSO}_3 & \text{OH} \\
394 & \text{1. TPAP, NMO} \\
& \text{2. Ph}_3\text{P}=\text{CH}_2 \\
\text{TBSO}_3 & \text{CH}_2 \\
395 \\
\text{TBSO}_3 & \text{Ph} \\
396 & \text{(Ph}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh} \\
393 \\
\end{align*}
\]

Scheme 86. Application of Olefin-metathesis Adjacent to a Polycyclopropane.

The polycyclopropanated portion of the fatty amide side-chain was prepared similar to the method of McDonald (Scheme 87). However, improved selectivity in the enantioselective cyclopropanation was found when the allylic alcohol was combined in solution with the dioxaboralane prior to addition to the carbenoid. Reduction of butyne-1,4-diol 397 with lithium aluminum hydride (LAH) followed by mono-protection with $t$-butyldimethylsilyl chloride (TBS-Cl) and triethylamine (TEA) afforded allylic alcohol 156.

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The exposure of 325 to D-tartrate-derived dioxaboralane-directed cyclopropanation conditions followed by removal of the silyl group resulted in trans-(1R,2R)-bis-hydroxymethylcyclopropane 305. In a two-directional fashion, the alcohol functionalities were oxidized and chain extended via Horner-Emmons chemistry to provide divinylcyclopropane 306. Following reduction with excess DIBAL-H, the bis-allylic alcohol 398 was exposed to D-tartrate-derived dioxaboralane-directed cyclopropanation conditions to provide bis-hydroxymethyl-tris-cyclopropane 307. Mono-protection of 307 with TBS-Cl and TEA afforded 399 in reasonable yields. Oxidation and chain extension of 399 provided α,β-unsaturated ester 400, which was reduced with excess DIBAL-H. Cyclopropanation of vinyl-tris-cyclopropane 401 was once again directed by D-tartrate-derived dioxaboralane 221. The removal of the silyl protecting group of 291 with TBAF confirmed the anticipated C2-symmetry of bis-hydroxymethyl-tetrakis-cyclopropane 224. Oxidation of 291 followed by olefination with triphenylphosphonium methylide provided vinyl-tetrakis-cyclopropane 402 in high yield. The vinyl-tetrakis-cyclopropane 402 and homo-dimer 391 were combined and exposed to Grubbs’ catalyst in refluxing methylene chloride for 20 hours. Following chromatographic purification, the phenyl analog 403 of the polycyclopropanated side chain was formed in excellent yield (94%) as a mixture of E- and Z-olefins (3.5:1).
Scheme 87. Synthesis of a Phenyl Analog of the Polycyclopropanated Side-Chain of FR-900848
Although the preparation of FR-900848 through the olefin metathesis route was impaired by the inability to prepare the homo-dimer 383, a second olefin metathesis route to FR-900848 was envisioned. Interception of Barrett’s intermediate 408 through a cross-metathesis route was proposed and would constitute a formal synthesis of FR-900848 (Scheme 86). Mono-protection of *cis*-hydroxymethylcyclopropane 305 with benzoyl chloride (BzCl) followed by oxidation and olefination provided vinyl cyclopropane 405. The exposure of 405 to Grubbs’ catalyst in a procedure similar to that used for 392 (above) provided homo-dimer 406. When compound 406 was combined with vinyl-*tetrakis*-cyclopropane 402 and exposed to Grubbs’ catalyst, the cross-coupled product 407 was formed in good yield (82%). Selective removal of the benzoyl protecting group with potassium hydroxide provided polycyclopropane 408, which is identical to the targeted advanced intermediate in Barrett’s total synthesis of FR-900848. The preparation of 408 completed an enantioselective formal synthesis of FR-900848 and further demonstrated the power of olefin metathesis as a tool in organic synthesis.
D. Conclusion:

We have applied a strategy for the differentiation between $C_2$-symmetric polycyclopropanes toward the unambiguous identification of the syn-bis-, the syn-syn-tris-, and the syn-syn-syn-tetrakis-cyclopropanes. The rotation of plane-polarized light by the syn-bis-cyclopropane allowed the assignment of syn-stereochemistry. Both the tris- and tetrakis-cyclopropanes were prepared by one-directional cyclopropanation of protected bis- and tris-cyclopropanes, respectively. Deprotection of the tris- and tetrakis-cyclopropanes allowed the confirmation of $C_2$-symmetry by their $^{13}$C-NMR spectra, thereby confirming their relative stereochemistries.

While the syntheses of each of the two polycyclopropanated natural products have been reported in the literature, either poor yielding transformations or a deficiency of stereochemical flexibility has provided ample reason for further development of efficient synthetic approaches to these natural products. We have described a strategy for the preparation of the natural products that utilizes olefin metathesis to incorporate the internal E-olefin and the sequestered cyclopropane. While rapid access to each of the
side-chains of these natural products would be greatly enhanced by utilizing the known homo-dimer 383, efforts to prepare 383 by a short route from inexpensive starting materials were unsuccessful. Nevertheless, the olefin metathesis methodology has been applied to the preparation of two polycyclopropane analogues, one of which constituted a formal synthesis of FR-900848 (129).

We have not been able to determine the feasibility of our original approach in which a Whitham elimination was proposed for the stereoselective incorporation of the troublesome E-olefin. The major hindrance to this approach is the absence of an efficient route to the required α-hydroxy aldehyde 344. Nevertheless, the attractive feature of this route is that variation of every element of stereochemistry would be possible, including the E- or Z-stereochemistry of the internal olefin. Further work in this area is required in order to completely explore the application of the Whitham elimination route toward the total synthesis of FR-900848 (129) and U-106305 (130).
CHAPTER IV

EXPERIMENTAL SECTION

A. General Experimental:

Unless otherwise noted, all reactions were run in oven-dried glassware under nitrogen atmosphere and stirred with teflon-coated magnetic stir-bars. The terms concentrated in vacuo or under reduced pressure refer to the use of a rotary-evaporator.

Solvents

Tetrahydrofuran (THF) and diethyl ether were distilled from purple benzophenone ketyl prior to use. Benzene was distilled from calcium hydride prior to use. Methylene chloride (CH$_2$Cl$_2$) was distilled from P$_2$O$_5$ prior to use. Acetonitrile (CH$_3$CN) was distilled from calcium hydride prior to use. Ethyl acetate (EtOAc) was purchased from VWR and used without purification. Hexanes were purchased from various commercial sources and distilled prior to use. Pyridine was distilled from calcium hydride and stored over potassium hydroxide. Triethyl amine (Et$_3$N) was distilled from and stored over
potassium hydroxide. Methanol (\(\text{CH}_3\text{OH}\)) was distilled from sodium methoxide and stored over 4 Å sieves. Toluene was purchased from various commercial sources and distilled prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride and stored over 4 Å sieves.

**Reagents:**

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. N,N,N',N'-Tetramethyl-D-tartaramide is commercially available, however was prepared from commercially available diethyl D-tartrate by a literature procedure.\(^{145}\) Diethylzinc was purchased both as a solution (1.0 M in hexanes) and neat. Methylene iodide (\(\text{CH}_2\text{I}_2\)) was purchased both from Sigma-Aldrich and Lancaster chemical companies; when purchased from Lancaster, non-oxidized copper wire was added as a stabilizer.

**Chromatography:**

Column chromatography was performed on EM Science flash silica gel (35-75μm). Mobile phases were used as noted.

Thin Layer Chromatography (TLC) was carried out on EM Science F254 glass plates and visualized by UV and anisaldehyde or phosphomolybdic acid stains. The term \(R_f\) refers to the use of the specified solvent system in TLC analysis.

Gas Chromatography was performed on a Hewlett-Packard model 5890A series GC with a 25-meter methyl silicone (OV-1) capillary column connected to a flame ionization detector.
Spectroscopy:

Nuclear Magnetic Resonance (NMR) spectroscopy was performed on a Bruker EM-360A instrument operating at 360.130 MHz for $^1$H nuclei and 90.55 MHz for $^{13}$C nuclei. All $^{13}$C spectra are $^1$H-decoupled, therefore, coupling is due to nuclei other than $^1$H. $^{31}$P-NMR spectra were obtained on a JEOL FX90Q instrument operating at 36.2 MHz. Unless otherwise noted, all NMR experiments were carried out in deuterochloroform (CDCl$_3$) solvent purchased from Cambridge Isotope Laboratory and stored over 4 Å sieves. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (TMS) internal standard. A DEPT-135 spectrum was used to assign the number of attached hydrogen atoms, which was indicated by C, CH, CH$_2$, CH$_3$, respectively.

Infrared spectroscopy was performed on a Nicolet 205 Fourier Transform spectrometer.

Combustion analysis (CHN) was performed by the University of New Hampshire Instrumentation Center on a Perkin-Elmer 2400 Analyzer.

Electrospray Mass Spectroscopy was performed by the University of New Hampshire Mass Spectrometry Labs on a Finnigan MAT model LCQ IT-MS spectrometer equipped with a Paul Ion Trap.

Low Resolution Mass Spectroscopy was performed by the University of New Hampshire Instrumentation Center on a Hewlett-Packard model 5988A GC/MS quadropolar spectrometer equipped with a 25-meter methyl silicone (OV-1) capillary column.

High Resolution Mass Spectroscopy was performed at the University of California Riverside Mass Spectrometry Facility.
Experimentation:

Optical rotations were conducted using a Rudolf Research Autopol III automatic polarimeter in specified solution and concentrations are given in g/mL.

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected.

B. Preparation and Study of Chain Extension Substrates:

Dimethyl (3-oxobutyl)phosphonate (74)

Into a flask containing 5 mL of methylene chloride, 1.8 mL (1.8 mmol) of a 1.0 M solution of diethylzinc in hexane was added under an inert atmosphere. This solution was cooled to 0 °C and a solution of 0.48 g (0.15 mL, 1.8 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was added slowly. The reaction was allowed to warm to room temperature over 5 minutes, during which time a white precipitate formed. A solution containing 50 mg (0.13 mmol) of dimethyl (2-oxopropyl)phosphonate 73 dissolved in 1 mL of methylene chloride was added and the reaction was allowed to stir at room temperature. The starting material appeared by TLC to be consumed within 1 hour. The reaction was quenched with a saturated aqueous solution of ammonium chloride and the aqueous layer was extracted with three 5 mL portions of diethyl ether. The combined extracts were dried over anhydrous MgSO$_4$ and concentrated in vacuo. The residue was chromatographed on silica (ethyl acetate; $R_f = 0.1$) to yield 46 mg (85%) of γ-keto phosphonate 74 as a clear colorless oil.$^{146}$ $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 3.75 (d, 6H, $J = 10.8$ Hz), 2.75 (ddd, 2H, $J = 15.3, 11.8, 7.6$ Hz), 2.19 (s, 3H), 2.04 (ddd, 2H, $J = 18, 15.3, 7.6$ Hz); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 205.8 (d, $J_{PC} = 14.5$ Hz), 52.7 (d, $J_{PC} =$ ~165

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6.5 Hz), 36.3 (d, $J_{PC} = 3.9$ Hz), 29.9, 18.5 (d, $J_{PC} = 143.8$ Hz); IR (film) 3650-3400, 2950, 2850, 1710, 1410, 1380, 1250, 1175, 1050, 810; Anal. Calcd. for $C_6H_{13}O_4P$: C, 40.00; H, 7.27. Found: C, 40.27; H, 7.47.

**Diethyl (3-oxobutyI)phosphonate (76)**

Into a flask containing 40 mL of methylene chloride, 3.1 mL (3.1 mmol) of a 1.0 M solution of diethylzinc in hexane was diluted under an inert atmosphere. The solution was cooled to 0 °C and a solution of 830 mg (0.25 mL, 3.1 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was slowly added. The reaction was allowed to warm to room temperature, during which time a white precipitate formed. A solution containing 101 mg (0.10 mL, 0.52 mmol) of diethyl (2-oxopropyl)phosphonate 75 dissolved in 1 mL of methylene chloride was added and the reaction was stirred at room temperature for 2 hr. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted thrice with 10 mL of diethyl ether. The combined extracts were dried over MgSO$_4$ and concentrated in vacuo. The residue was chromatographed on silica (ethyl acetate; $R_f = 0.2$) to give 74 mg (69%) of γ-keto phosphonate 76 as a clear yellow liquid that provided spectra which were in agreement with those reported in the literature.$^{8a}$ $^1$H NMR (360 MHz, CDCl$_3$) δ 4.09 (m, 4H), 2.75 (ddd, 2H, $J = 15.4, 11.5, 7.7$ Hz), 2.19 (s, 3H), 2.02 (ddd, 2H, $J = 18, 15.4, 7.7$ Hz), 1.32 (t, 6H, $J = 7.0$ Hz); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 205.7 (d, $J_{PC} = 15.1$ Hz), 61.7 (d, $J_{PC} = 6.6$ Hz), 36.3 (d, $J_{PC} = 3.6$ Hz), 29.7, 19.4 (d, $J_{PC} = 143.7$ Hz), 16.4 (d, $J_{PC} = 6.1$ Hz).

**Diethyl (3-oxo-3-phenylpropyl)phosphonate (78)**
Into a flask containing 40 mL of methylene chloride, 2.3 mL (2.3 mmol) of a 1.0 M solution of diethylzinc in hexane was added under an inert atmosphere. A solution containing 616 mg (0.19 mL, 2.3 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was added slowly at room temperature, at which time a white precipitate formed. The reaction was stirred for 5 minutes and a solution containing 100 mg (0.39 mmol) of diethyl (2-oxo-2-phenylethyl)phosphonate 77 dissolved in 1 mL of methylene chloride was added. Upon addition of the β-ketophosphonate some precipitate disappeared. The reaction was stirred for 2 hours at room temperature and was quenched with saturated ammonium chloride. The aqueous phase was extracted three times with 10 mL of diethyl ether. The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The resulting residue was chromatographed on silica (ethyl acetate; R_f = 0.23) to give 103 mg (98%) of γ-keto phosphonate 78 as a clear yellow liquid that provided spectra which were in agreement with those reported in the literature.¹⁴⁷ ¹H NMR (360 MHz, CDCl₃) δ 7.97 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 4.12 (m, 4H), 3.30 (ddd, 2H, J = 15.6, 10.7, 7.9 Hz), 2.19 (ddd, 2H, J = 17.7, 15.6, 7.9 Hz), 1.33 (t, 6H, J = 7 Hz); ¹³C (90 MHz, CDCl₃) δ 197.4 (d, J_PC = 15.8 Hz), 136.3, 133.4, 128.7, 128.1, 61.8 (d, J_PC = 6.6 Hz), 31.7 (d, J_PC = 3.0 Hz), 19.7 (d, J_PC = 143.8 Hz), 16.5 (d, J_PC = 5.9 Hz); IR (film) 3044, 2987, 2924, 1687, 1440, 1265, 1026, 963.

**Diethyl (1-methyl-2-oxopropyl)phosphonate (80)**

A solution containing 101 mg (0.10 mL, 0.53 mmol) of diethyl (2-oxopropyl)phosphonate 75 and 227 mg (0.10 mL, 1.6 mmol) of methyl iodide dissolved in 1 mL of diethyl ether was added slowly to 21 mg (0.52 mmol) of a 60% dispersion of
sodium hydride in mineral oil, which was suspended in 10 mL of diethyl ether. The solution was refluxed for 6 hours under an atmosphere of nitrogen and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with 10 mL portions of diethyl ether. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The resulting oil was chromatographed on silica (ethyl acetate; Rf = 0.34) to give 57 mg (53%) of β-keto phosphonate 80 as a clear colorless oil that provided spectra which were in agreement with those reported in the literature.¹⁴

¹H NMR (360 MHz, CDCl₃) δ 4.15 (m, 4H), 3.22 (dq, 1H, J = 25.6, 7.1 Hz), 2.34 (s, 3H), 1.40-1.28 (m, 9H); ¹³C (90 MHz, CDCl₃) δ 203.8 (d, JPC = 4.0 Hz), 62.6 (d, JPC = 7.0 Hz), 62.5 (d, JPC = 7.3 Hz), 47.6 (d, JPC = 125.9 Hz), 30.4, 16.4 (d, JPC = 5.8 Hz), 10.9 (d, JPC = 6.5 Hz).

Diethyl (1-methyl-3-oxobutyl)phosphonate (81)

Into 10 mL of methylene chloride was diluted 1.6 mL (1.6 mmol) of a 1.0 M solution of diethylzinc in hexane under an inert atmosphere. The solution was cooled to 0 °C. A 1 mL methylene chloride solution containing 429 mg (0.13 mL, 1.6 mmol) of methylene iodide was added slowly to the stirring diethylzinc solution. The reaction mixture was allowed to warm to room temperature and 50 mg (0.24 mmol) of diethyl (1-methyl-2-oxopropyl)phosphonate 80 was added as a solution in 1 mL of methylene chloride. The reaction mixture was allowed to stir for 6 hours. (A decrease in reaction time results in the recovery of unreacted starting material.) The reaction was quenched with saturated aqueous ammonium chloride and the aqueous phase was extracted with three 10 mL portions of diethyl ether. The combined organic extracts were dried over MgSO₄ and...
concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (ethyl acetate; R*/* = 0.2) to provide 37 mg (70%) of γ-keto phosphonate 81 as a clear yellow oil that provided spectra which were consistent with those reported in the literature.*9a* 1H NMR (360 MHz, CDCl₃) δ 4.10 (m, 4H), 2.88 (m, 1H), 2.48 (m, 2H), 2.17 (s, 3H), 1.32 (td, 6H, J = 7.1, 1.6 Hz), 1.16 (dd, 3H, J = 18.3, 7.0 Hz); 13C NMR (90 MHz, CDCl₃) δ 205.9 (d, J*PC* = 15.1 Hz), 61.9 (d, J*PC* = 7.0 Hz), 61.8 (d, J*PC* = 7.2 Hz), 44.1 (d, J*PC* = 2.1 Hz), 30.5, 26.2 (d, J*PC* = 143.7 Hz), 16.6 (d, J*PC* = 5.7 Hz), 13.9 (d, J*PC* = 5.2 Hz); IR (film) 3515, 2994, 1708, 1426, 1370, 1223.

**Diethyl (2-oxo-cyclopentyl)phosphonate (84)**

Into 20 mL of THF was dissolved 1.32 g (1.85 mL, 13.0 mmol) of diisopropyl amine. The solution was cooled to −78 °C under an inert atmosphere. To this stirring solution, 5.4 mL (11.9 mmol) of a 2.2 M solution of n-butyl lithium in pentane was added slowly. Following the addition, the reaction was stirred for an additional 10 minutes and allowed to warm to room temperature. The solution was cooled to −78 °C and a 10 mL THF solution containing 1.0 g (11.9 mmol) of cyclopentanone 82 was added. The reaction was warmed to −42 °C [CH₃CN / CO₂ bath] and stirred for 2 hours. To this stirring solution, 2.05 g (1.72 mL, 11.9 mmol) of diethyl chlorophosphate was added dropwise and the reaction was allowed to stir for an additional 6 hours at −42 °C. The reaction mixture was transferred via cannula to a 35 mL solution of 22.7 mmol of LDA in THF (preparation described below) at −78 °C. The reaction was allowed to warm to −61 °C [chloroform / CO₂ bath] and stirred for 19 hours, at which time it was quenched through the sequential addition of 5 mL of glacial acetic acid and 5 mL of H₂O. The aqueous
phase was extracted twice with 20 mL of diethyl ether. The combined organic extracts were sequentially washed with 1 mL of 1 M HCl and 20 mL of saturated aqueous NaHCO₃. The organic solution was dried over MgSO₄ and concentrated under reduced pressure. The residue was chromatographed on silica (ethyl acetate; Rf = 0.22) to give 163 mg (7%) of β-keto phosphonate 84 as a clear colorless oil that provided spectra which were in agreement with those reported in the literature.³⁹b ¹H NMR (360 MHz, CDCl₃) δ 4.17 (m, 4H), 2.73 (ddd, 1H, J = 25.9, 8.5, 8.2 Hz), 2.42-2.12 (m, 5H), 1.89 (m, 1H), 1.35 (td, 6H, J = 7.0, 2.7 Hz); ¹³C (90 MHz, CDCl₃) δ 221.2 (d, JPC = 4.6 Hz), 62.5 (d, JPC = 34.1 Hz), 62.4 (d, JPC = 34.1 Hz), 47.0 (d, JPC = 136.7 Hz), 38.9 (d, JPC = 3.7), 25.6 (d, JPC = 3.2), 21.7 (d, JPC = 8.7), 16.4 (d, JPC = 6.2).

Preparation of LDA solution:
In a separate flask, 2.9 g (4.0 mL, 28.6 mmol) of diisopropyl amine was dissolved in 20 mL of THF and cooled to −78 °C. To this stirring solution, 12.45 mL (27.4 mmol) of a 2.2 M solution of n-butyl lithium in pentane was added slowly. The reaction mixture was allowed to warm to room temperature briefly and cooled back down to −78 °C prior to use.

**Diethyl (3-oxo-cyclohexyl)phosphonate (85)**
Into 20 mL of methylene chloride was diluted 3.1 mL (3.1 mmol) of a 1.0 M solution of diethylzinc in hexane. The solution was cooled to 0 °C under an inert atmosphere. A solution containing 429 mg (0.25 mL, 3.12 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was added slowly to the diethylzinc solution. The reaction mixture
was allowed to warm to room temperature and a white precipitate formed. A solution of 100 mg (0.52 mmol) of diethyl (2-oxo-pentyl)phosphonate 84 dissolved in 1.5 mL of methylene chloride was added to the zinc-carbenoid solution. The reaction was allowed to stir for 4 hours at room temperature and quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted twice with 10 mL of methylene chloride. The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica (ethyl acetate; Rf = 0.2) to provide 94 mg (83%) of γ-keto phosphonate 85 as a clear yellow oil that provided spectra which were consistent with those reported in the literature.¹⁰b ¹H NMR (360 MHz, CDCl₃) δ 4.12 (m, 4H), 2.45 (m, 4H), 2.16 (m, 3H), 1.78 (m, 2H), 1.34 (t, 6H, J = 7.1 Hz); ¹³C (90 MHz, CDCl₃) δ 208.8 (d, JPC = 16.5 Hz), 61.9 (d, JPC = 4.0 Hz), 61.8 (d, JPC = 4.0 Hz), 41.0 (d, JPC = 2.0 Hz), 40.5 (d, JPC = 5.3 Hz), 35.8 (JPC = 145.7 Hz), 25.9 (d, JPC = 19.1 Hz), 24.3 (d, JPC = 4.6 Hz), 16.4 (d, JPC = 5.3 Hz).

**Dimethyl (2-oxo-5-hexenyl)phosphonate (88)**

A slurry of 116 mg (2.9 mmol) of a 60% dispersion of sodium hydride in mineral oil and 20 mL of THF was cooled to 0 °C under an inert atmosphere. To this solution was added 241 mg (0.2 mL, 1.45 mmol) of dimethyl (2-oxopropyl)phosphonate 73. The reaction was allowed to warm to room temperature and a white precipitate developed. The mixture was cooled to −78 °C and 0.64 mL (1.45 mmol) of a 2.25 M solution of n-butyl lithium in pentane was added slowly. During the addition the white precipitate appeared to dissolve slightly and a light yellow color developed. The stirring solution was allowed to warm slowly to room temperature at which time 175 mg (0.13 mL, 1.45 mmol) of 3-
bromopropene was added drop-wise. The reaction was allowed to stir for 1 hr and quenched with saturated aqueous ammonium chloride, which was accompanied by violent gas evolution. The aqueous layer was extracted thrice with 10 mL portions of diethyl ether and the combined organic extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica (ethyl acetate; Rf = 0.23) to give 127 mg (42%) of β-keto phosphonate 88 as a clear viscous oil with a slight yellow tint.¹¹ \(^1\)H NMR (360 MHz, CDCl₃) δ 5.79 (ddt, 1H, J = 16.8, 10.3, 6.5 Hz), 5.08 (dd, 1H, J = 17.1, 1.5 Hz), 4.98 (dd, 1H, J = 10.1 Hz, 1.5 Hz) 3.79 (d, 6H, J = 11.2), 3.10 (d, 2H, J = 22.7), 2.73 (t, 2H, J = 7.2), 2.33 (td, 2H, J = 7.2, 6.5 Hz); \(^1\)³C NMR (90 MHz, CDCl₃) δ 202.3 (d, J_P= 6.6 Hz), 137.4, 115.5, 53.0 (d, J_F= 6.5 Hz), 43.1, 41.3 (d, J_F= 127.5 Hz), 27.3; IR (film) 2952, 2910, 1715, 1245, 1194, 1039; HRMS (EI) M⁺ Calcd for C₈H₁₅O₄P: 206.0708 found: 206.0699.

**Attempted Chain Extension of Dimethyl (2-oxo-5-hexenyl)phosphonate (88)**

Method A: (for equivalents and time refer to Table 2 on page 29)

To a solution of \(x\) equivalents of diethylzinc dissolved in 10 mL of methylene chloride under an inert atmosphere was added \(x\) equivalents of methylene iodide as a solution in 1 mL of methylene chloride. The reaction was allowed to stir for approximately 15 minutes (except in entries 7 and 8, which the time was as specified) at the designated temperature, during which time a white precipitate formed. To this solution was added 1 equivalent of β-keto phosphonate 88 as a solution in 1.5 mL of methylene chloride. The reaction was allowed to stir for \(y\) minutes at the designated temperature and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with three
10 mL portions of ethyl acetate and the combined organic extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica gel (entries 1, 2 and 3 only) (ethyl acetate) to give a clear yellow oil which was found to contain a mixture of chain extended product 89 along with the cyclopropanated product 90.

Method B:

Into 5 mL of methylene chloride was added 0.6 mL (0.6 mmol) of a 1.0 M solution of diethylzinc in hexane. To this solution was added 48 µL (0.6 mmol) of methylene iodide as a solution in 0.5 mL of methylene chloride. The reaction was allowed to stir for approximately 5 minutes. In a separate flask were combined 0.2 mL (0.2 mmol) of a 1.0 M solution of diethylzinc in hexane and a 1.0 mL methylene chloride solution of 20 mg (0.1 mmol) of β-keto phosphonate 88. After gas evolution subsided (~ 5 min), the phosphonate solution was transferred by syringe to the stirring solution of diethylzinc and methylene iodide. The reaction was allowed to stir for approximately 25 minutes and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with three 10 mL portions of ethyl acetate and the combined organic extracts were dried over MgSO₄. The concentrated residue was analyzed by ¹H NMR.

Method C: (for equivalents and time refer to Table 2 on page 29)

To a solution of 6 molar equivalents of diethylzinc diluted to ~0.1 M into methylene chloride was added 1 molar equivalent of β-keto phosphonate 88 as a solution in 1.5 mL of methylene chloride. Upon the addition of β-keto phosphonate 88, gas evolution was observed. The reaction was allowed to stir for approximately 5 minutes and x molar equivalents of methylene iodide were added as a solution in 1 mL of methylene chloride.
The reaction was allowed to stir for the specified time. No precipitate was observed in contrast to the other methods. The reaction was quenched with saturated ammonium chloride and the aqueous layer was extracted with three 10 mL portions of ethyl acetate. The organic extracts were combined and dried over MgSO₄. The concentrated residue was analyzed by ¹H NMR.

**Dimethyl (E-2-Oxo-4-phenyl-3-butenyl)phosphonate (92)**

A solution consisting of 1.54 g (1.35 mL, 12.4 mmol) of dimethyl methylphosphonate was dissolved in 25 mL of THF and was cooled to −78 °C. A 2.25 M solution of n-butyl lithium in hexane (6.0 mL, 13.6 mmol) was added to the phosphonate solution via syringe pump [0.15 mL/min]. The reaction mixture was allowed to stir at −78 °C for 90 minutes, after which time a 5 mL solution of 1.0 g (6.2 mmol) of methyl E-cinnamate 91 was added by syringe pump[0.15 mL/min]. The reaction mixture was allowed to warm to room temperature over a period of 20 hours, during which time a brown curdy precipitate formed. The reaction was quenched with 10 mL of 1 M aqueous HCl. The aqueous layer was separated and extracted twice with 20 mL of methylene chloride. The combined organic layers were dried over MgSO₄, concentrated under reduced pressure and chromatographed (ethyl acetate; Rf = 0.31) to give 1.33 g (84%) of β-keto phosphonate 92 as a clear, slightly yellow oil.¹⁴⁹ ¹H NMR (360 MHz, CDCl₃) δ 7.66 (d, 1 H, J = 16.1 Hz), 7.59 (m 2 H), 7.38 (m, 3 H), 6.88 (d, 1 H, J = 16.1 Hz), 3.81 (d, 6 H, Jₖₚ = 11.3 Hz), 3.34 (d, 2 H, Jₖₚ = 22.7 Hz); ¹³C NMR (90 MHz, CDCl₃) δ 192.1 (d, Jₖₚ = 6.6 Hz), 145.1, 134.1, 131.0, 129.0, 128.7, 125.6, 51.2 (d, Jₖₚ = 6.3 Hz), 39.9 (d, Jₖₚ = 128.3); IR
Attemped Chain Extension of Dimethyl \((E-2\text{-oxo-4-phenyl-3-butenyl})\)phosphonate \((92)\)

General Procedure: (for equivalents and times refer to Table 3 on page 32)

A 1.0 M solution of diethylzinc in hexane \((x\text{ equiv})\) was diluted to \(-0.1\text{ M}\) diethylzinc methylene chloride under an inert atmosphere. To this stirring solution was added \(y\) molar equivalents of methylene iodide as a solution in 1 mL of methylene chloride. The reaction was allowed to stir for approximately 15 minutes at ambient temperature, after which time the temperature was adjusted to that indicated and 1 equivalent of \(\beta\)-keto phosphonate \(92\) was added as a solution in 2 mL of methylene chloride. The reaction was allowed to stir for the specified time and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with 10 mL methylene chloride and the combined organic extracts were dried over MgSO\(_4\). The concentrated residue was analyzed by \(^1\text{H}\) NMR, except for entries 2 and 13 when the residue was chromatographed on silica (ethyl acetate; \(R_f = 0.16\)) to give a clear colorless oil as a mixture of \(\gamma\)-keto phosphonates \(93\) and \(94\).\(^{43}\)

Cyclopropanation of the Chain Extension Product Mixture Resulting from \((\text{trans-2-Oxo-4-phenyl-3-butenyl})\)phosphonate \((93\text{ and }94)\)

A mini-diazald kit was charged with 3 mL of 2-(2-ethoxyethoxy)ethanol, 1 mL of a 50% aqueous solution of potassium hydroxide and 5 mL of diethyl ether. Into the receiving
flask were placed the product mixture from the chain extension of phosphonate 92 and approximately 5 mg of palladium(II) acetate dissolved in 5 mL of diethyl ether. The receiving flask was cooled to 0 °C with stirring and the diazald kit mounted securely behind a blast shield. The cold finger was charged with acetone/CO₂ and the still pot was heated to 70 °C in an oil bath as a solution of 172 mg (0.8 mmol) of diazald [N-methyl-N-nitroso-p-toluenesulfonamide] dissolved in 5 mL of diethyl ether was added through an addition funnel at a rate equal to the rate of distillation. Additional diethyl ether was added through the addition funnel to the still pot until the distillate was colorless. The solution in the receiving flask was filtered through silica and the silica was rinsed with excess (~100 mL) acetone. The concentrated residue was found to contain one compound, which was identified as cyclopropanated phosphonate 94. ¹H NMR (360 MHz, CDCl₃) δ 7.38-7.16 (m, 3H), 7.1-6.97 (m, 2H), 3.74 (d, 3H, J = 10.7 Hz), 3.73 (d, 3H, J = 10.9 Hz), 2.93-2.85 (m, 2H), 2.53-2.47 (m, 1H), 2.19-2.14 (m, 1H), 2.09-1.99 (m, 2H), 1.68-1.63 (m, 1H), 1.41-1.35 (m, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 205.8 (d, JₚC = 14.4 Hz), 139.9, 128.5, 126.6, 126.0, 52.4 (d, JₚC = 5.5 Hz), 36.3, 32.0, 29.2, 19.1, 18.3 (d, JₚC = 140.4 Hz); HRMS (El) M⁺ calcd for C₁₄H₁₉O₄P: 282.1021, found: 282.1029.

(S)-1-Carboxybenzyl-2-carboxymethylpyrrolidine (99)

Into a scratch-free 125 mL Erlenmeyer flask equipped with a stir bar, 1.65 g (16 mmol) of N-methyl-N-nitroso-urea was dissolved into 50 mL of diethyl ether. The flask was secured behind a blast shield and cooled to 0 °C. The solution was treated with 8 mL of 50% aqueous KOH. The mixture was stirred for 30 min during which time a bright canary yellow color developed. A solution of 2.0 g (8 mmol) of Cbz-L-proline dissolved
in 10 mL of THF was added via pipette, which resulted in gas evolution. The reaction was allowed to stir for 4 hours at 0 °C and glacial acetic acid was added drop-wise until the yellow color disappeared. The layers were separated and the aqueous layer was extracted twice with 10 mL portions of diethyl ether. The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The resulting 2.04 g (97%) of a colorless oil was identified as 99 whose NMR spectra were complicated by the appearance of rotamers (~3.3:1 at 25 °C). The compound was used without further purification. Major rotamer: \( ^1H \) NMR (360 MHz, CDCl₃) \( \delta 7.29 \) (m, 5H), \( 5.17 \) (t, \( J = 12.4 \) Hz, 2H), \( 4.39 \) (dd, \( J = 8.6, 3.7 \) Hz, 1H), \( 3.58 \) (s, 3H), \( 3.66-3.44 \) (m, 2H), \( 2.05-1.84 \) (m, 4H); \( ^{13}C \) (90 MHz, CDCl₃) \( \delta 173.3, 154.3, 136.6, 128.4, 128.0, 127.9, 66.9, 58.8, 52.2, 46.9, 30.9, 23.5 \). Minor rotamer: \( ^1H \) NMR (360 MHz, CDCl₃) \( \delta 7.34 \) (m, 5H), \( 5.06 \) (t, \( J = 12.4 \) Hz, 2H), \( 4.34 \) (dd, \( J = 8.6, 3.7 \) Hz, 1H), \( 3.74 \) (s, 3H), \( 3.66-3.44 \) (m, 2H), \( 2.26-2.17 \) (m, 4H); \( ^{13}C \) (90 MHz, CDCl₃) \( \delta 173.1, 154.9, 136.7, 128.4, 128.0, 127.8, 67.0, 59.2, 52.0, 46.4, 29.9, 24.3 \); IR (film) 2959, 2889, 1743, 1708, 1405, 1370, 1215, 1166, 1124, 998, 779, 702.

(S)-1-Carboxybenzyl-2-(2-(dimethylphosphono)-1-oxo)ethyl pyrrolidine (100)

Into 20 mL of THF was dissolved 1.89 g (1.65 mL, 15.2 mmol) of dimethyl methylphosphonate and the solution was cooled to -78 °C under an inert atmosphere. To this solution was added 7.0 mL (16 mmol) of a 2.25 M solution of n-butyl lithium in pentane via syringe pump [0.15 mL/min]. Following the addition of n-butyl lithium, the reaction mixture was allowed to stir at -78 °C for an additional 90 minutes and then a solution containing 2.0 g (7.6 mmol) of (S)-1-carboxybenzyl-2-carboxymethylpyrrolidine
99 dissolved in 8 mL of THF was added via syringe pump [0.3 mL/min]. The reaction mixture was allowed to stir for 12 hours, during which time the temperature slowly increased to -50 °C. The reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with 10 mL portions of diethyl ether, followed by two 10 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate; Rᵣ = 0.13) to give 2.33 g (86%) of β-keto phosphonate 100 as a clear slightly yellow oil that appeared by NMR to be a mixture of rotamers (~1:1 at 25 °C). ¹H NMR (360 MHz, CDCl₃) δ 7.32 (m, 5H), 5.2-5.0 (m, 2H), 4.55-4.40 (m, 1H), 3.82-3.73 (m, 6H), 3.73-3.62 (m, 1H), 3.60-3.46 (m, 1H), 3.33-3.14 (m, 1H), 3.13-2.84 (m, 1H), 2.26-1.98 (m, 2H), 1.97-1.79 (m, 2H); ¹³C (90 MHz, CDCl₃) δ 201.0 (d, Jₑₑ = 6.6 Hz), 155.1, 154.2, 136.5, 136.3, 128.2, 128.1, 128.0, 127.8, 67.2, 67.1, 65.9, 65.6, 53.0, 47.3, 46.8, 38.3 (d, Jₑₑ = 132.0 Hz), 37.3 (d, Jₑₑ = 132.7 Hz), 29.5, 28.4, 24.4, 23.5; IR (film) 3473, 2966, 2875, 1701, 1412, 1349, 1258, 1117, 1040, 801; Calcd. for C₁₆H₂₂NO₃P: C, 54.08; H, 6.24; N, 3.94. Found: C, 53.95; H, 6.26; N, 3.95.

1-Carboxybenzyl-2-(3-(dimethylphosphono)-1-oxo)propyl pyrrolidine (101)
Into 10 mL of methylene chloride was diluted 1.2 mL (1.2 mmol) of a 1.0 M solution of diethylzinc in hexane. To this stirring solution of diethylzinc was slowly added a solution of 330 mg (0.1 mL, 1.2 mmol) of methylene iodide dissolved in 1.0 mL of methylene chloride. The reaction mixture was allowed to stir at ambient temperature for 15 minutes and a solution containing 70 mg (0.2 mmol) of β-keto phosphonate 100 in 1.0 mL of methylene chloride was added. After stirring for an additional 45 minutes, the
reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with two 10 mL portions of methylene chloride and the combined organic extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica (1:1, ethyl acetate: acetone; Rf = 0.34 for 101) to give 24 mg (33%) of γ-keto phosphonate 101 as a clear yellow liquid and 32 mg (46%) of the starting β-keto phosphonate. [An increase in reaction time was found to result in the consumption of starting material, but at the expense of subsequent chemistry that appeared to consume the product.] Two rotameric forms were observable by NMR. ¹H NMR (360 MHz, CDCl₃) δ 7.41-7.2 (m, 10H), 5.18-5.00 (m, 4H), 4.42 (dd, 1H, J = 8.5, 4.0 Hz), 4.34 (dd, 1H, J = 8.5, 4.2 Hz), 3.8-3.5 (m, 16H), 2.86-2.65 (m, 4H), 2.22-1.85 (m, 12H); ¹³C (90 MHz, CDCl₃) δ 207.1, 207.0, 155.1, 154.2, 136.6, 136.3, 128.5, 128.1, 128.0, 127.8, 67.1, 64.9, 64.7, 52.4, 47.3, 46.8, 32.4, 31.8, 29.9, 28.9, 24.4, 23.6, 18.0 (d, JPC = 144.4 Hz), 18.8 (d, JPC = 144.6 Hz); IR (film) 3459, 2945, 1695, 1412, 1363, 1216, 1068; HRMS (EI) M⁺ calcd for C₁₇H₂₄NO₆P: 369.1341, found: 369.1342.

1-Benzoyl-2-carboxymethylpyrrolidine (102)

Into 75 mL of saturated aqueous sodium bicarbonate was dissolved 3.0 g (26 mmol) of L-proline and 3.8 mL (32.6 mmol) of benzoyl chloride was added. The reaction mixture was stirred vigorously for 2 hours and acidified with saturated aqueous citric acid to pH = 3. The solution was extracted with five 50 mL portions of ethyl acetate and the combined extracts were dried over MgSO₄. The concentrated residue was placed on a high vacuum line for ~12 hours. The residue was dissolved in 100 mL of anhydrous methanol and 10 mL of a 0.15 M anhydrous solution of HCl in methanol was added. The solution was
allowed to stir for 1 hour and concentrated under reduced pressure. The residue was
dissolved once again in 100 mL of anhydrous methanol and 10 mL of a 0.15 M
anhydrous solution of HCl in methanol was added. The solution was stirred for 1 hour
and concentrated. The residue was dissolved in a mixture of 100 mL of saturated
aqueous sodium bicarbonate and 100 mL of diethyl ether. The aqueous layer was
extracted thrice with 50 mL portions of diethyl ether. The combined organic extracts
were dried over MgSO₄ and concentrated. The resulting 5.47 g (90%) of ester 102 was a
colorless solid (mp = 90-91 °C), which provided spectra that agree with those reported in
the literature.¹¹¹ H NMR (360 MHz, CDCl₃) δ 7.58-7.55 (m, 2H), 7.45-7.36 (m, 3H),
4.67 (dd, 1H, J = 8.3, 5.2 Hz), 3.77 (s, 3H), 3.66-3.62 (m, 1H), 3.56-3.46 (m, 1H), 2.37-
2.21 (m, 1H), 2.07-1.99 (m, 2H), 1.93-1.83 (m, 1H); Major rotamer: ¹³C NMR (90 MHz,
CDCl₃) δ 172.7, 169.5, 136.0, 130.2, 128.2, 127.3, 59.1, 52.3, 49.9, 29.4, 25.4; Minor
rotamer: ¹³C (90 MHz, CDCl₃) δ 137.1, 129.8, 128.3, 126.5, 61.9, 52.3, 46.8, 31.9, 22.8;
IR (film) 3058, 2994, 1743, 1623, 1412, 1258.

1-Benzoyl-2-(1-oxo-2-(dimethylphosphono)ethyl)pyrrolidine (103)
Into 30 mL of THF was dissolved 1.86 mL (17.2 mmol) of dimethyl methylphosphonate
and the solution was cooled under an inert atmosphere to -78 °C. To this stirring solution
was added 8.4 mL (18.9 mmol) of a 2.25 M solution of n-butyl lithium in pentane by
syringe pump [0.15 mL/min]. Following the n-butyl lithium addition, the reaction was
allowed to stir for 90 minutes at -78 °C and 2.0 g (8.6 mmol) of 1-benzoyl-2-
carboxymethylpyrrolidine 102 was added as a solution in 15 mL of THF by syringe pump
[0.15 mL/min]. The reaction was allowed to stir at -78 °C for 2 hours and then allowed
to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with three 20 mL portions of methylene chloride and the combined organic extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica (1:1, ethyl acetate: acetone; Rf = 0.4) to give 1.53 g (52%) of β-keto phosphonate 103 as a viscous, clear, colorless oil. ¹H NMR (360 MHz, CDCl₃) δ 7.6-7.56 (m, 2H), 7.45-7.32 (m, 3H), 4.82 (dd, 1H, J = 7.9, 6.4 Hz), 3.83 (d, 3H, J = 6.1 Hz), 3.80 (d, 3H, J = 6.1 Hz), 3.75-3.60 (m, 1H), 3.59-3.2 (m, 3H), 2.32-2.20 (m, 1H), 2.19-2.0 (m, 2H), 1.95-1.83 (m, 1H); ¹³C (90 MHz, CDCl₃) δ 200.9, 169.8, 135.6, 130.4, 128.3, 127.3, 65.7, 53.0, 50.4, 39.3 (d, JPC = 130.3 Hz), 28.3, 25.6; IR (film) 3473, 2959, 1728, 1616, 1427, 1265, 1033; HRMS (Cl, DCl/CH₄) [M+H]+ calcd for C₁₅H₂₁NO₅P: 326.1157, found: 326.1164.

1-Benzoyl-2-(1-oxo-3-(dimethylphosphono)propyl)pyrroli dine (104)

Into 20 mL of methylene chloride was added 1.8 mL (1.8 mmol) of a 1.0 M solution of diethylzinc in hexane and a solution of 500 mg (0.15 mL, 1.84 mmol) of methylene iodide in 1 mL of methylene chloride. The reaction was allowed to stir for 10 minutes, during which time a white precipitate formed. A solution of 100 mg (0.31 mmol) of β-keto phosphonate 103 dissolved in 1.0 mL of methylene chloride was added. The reaction was allowed to stir at room temperature for 3 hours and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with 10 mL portions of methylene chloride. The combined extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (1:1, ethyl acetate: acetone) to give 94 mg (90%) of γ-keto phosphonate 104 as a clear yellow oil. ¹H NMR (360 MHz,
CDCl$_3$ δ 7.57-7.54 (m, 2H), 7.46-7.3 (m, 3H), 4.73 (dd, 1H, $J = 8.3, 5.8$ Hz), 3.9-3.4 (m, 10H), 3.02-2.85 (m, 2H), 2.28-1.8 (m, 4H); $^{13}$C (90 MHz, CDCl$_3$) δ 206.3 (d, $J_{PC} = 13.9$), 169.7, 135.8, 130.4, 128.3, 127.3, 64.8, 52.5 (d, $J_{PC} = 5.3$ Hz), 52.4 (d, $J_{PC} = 5.3$ Hz), 50.3, 32.9, 28.4, 25.5, 18.0 (d, $J_{PC} = 144.6$ Hz); IR (film) 3459, 2952, 1722, 1623, 1427, 1230, 1033; HRMS (Cl, DCl/CH$_4$) [M+H]$^+$ calcd for C$_{16}$H$_{23}$NO$_5$P: 340.1314, found: 340.1302.

(R)-Dimethyl (2-oxo-3-N-(carboxy-t-butyI)aminobutyl)phosphonate (106)

Into 20 mL of THF was dissolved 1.19 g (1.0 mL, 9.6 mmol) of dimethyl methylphosphonate and the solution was cooled to $-78{^\circ}C$. To this stirring THF solution was added 4.7 mL (10.6 mmol) of a 2.25 M of n-butyl lithium in hexane via syringe pump [0.15 mL/min]. The reaction was stirred at $-78{^\circ}C$ for 90 minutes, after which a solution containing 1.03 g (1.0 mL, 4.8 mmol) of methyl ester 105 dissolved into 10 mL of THF was added via syringe pump [0.15 mL/min]. The reaction was stirred for an additional 8 hours at $-78{^\circ}C$. The reaction mixture was allowed to warm to ambient temperature and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with 10 mL portions of methylene chloride. The combined organic extracts were dried over MgSO$_4$ and the concentrated residue was chromatographed on silica (1:4, acetone : ethyl acetate; $R_f = 0.54$) to give 715 mg (50%) of β-keto phosphonate 106 as a clear yellow tinted oil that provided spectra which were consistent with those reported in the literature.$^{12a}$ $^1$H NMR (360 MHz, CDCl$_3$) δ 5.45-5.35 (NH), 4.4-4.3 (m, 1H), 3.80 (d, 3H, $J = 11.3$ Hz), 3.79 (d, 3H, $J = 11.2$ Hz), 3.31 (dd, 1H, $J = 22.5, 14.2$ Hz), 3.12 (dd, 1H, $J = 22.2, 14.2$ Hz), 1.45 (s, 9H), 1.36 (d, 3H, $J = 1.45$ Hz).
(R)-Dimethyl (3-oxo-4-N-(carboxy-t-butyl)aminopentyl)phosphonate (107)

Into 20 mL of methylene chloride was diluted 2.0 mL (2 mmol) of a 1.0 M solution of diethylzinc in hexane under an inert atmosphere and a solution of 532 mg (0.16 mL, 2.04 mmol) of methylene iodide dissolved in 1.0 mL of methylene chloride was added slowly. The solution was stirred for 15 minutes and a solution of 100 mg (0.34 mmol) of β-keto phosphonate 106 dissolved in 2.0 mL of methylene chloride was added. The reaction was allowed to stir for 45 minutes at which time TLC analysis indicated consumption of the starting material. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with three 10 mL portions of methylene chloride, followed by five 10 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (1:1, acetone : ethyl acetate; Rₜ = 0.3) to give 81 mg (77%) of γ-keto phosphonate 107 as a clear yellow oil, which provided spectra that agree with those found in the literature. \(^{12b}\)

\(^1\)H NMR (360 MHz, CDCl₃) δ 5.17 (bs, 1H), 4.31 (m, 1H), 3.73 (dd, 6H, \(J = 10.9\) Hz), 2.89-2.68 (m, 2H), 2.17-2.02 (m, 2H), 1.44 (s, 9H), 1.33 (d, 3H, \(J = 7.2\) Hz);

\(^13\)C (90 MHz, CDCl₃) δ 207.4 (d, \(J_{PC} = 13.3\) Hz), 155.2, 80.0, 55.1, 52.5 (d, \(J_{PC} = 5.3\) Hz), 31.9, 28.3, 18.3 (d, \(J_{PC} = 144.6\) Hz), 17.6; IR (film) 3437, 2973, 1708, 1511, 1377, 1265, 1180, 1061.

Cbz-glycyl-glycine methyl ester (109)
Into 50 mL of anhydrous methanol was dissolved 2.0 g (7.5 mmol) of Cbz-glycyl-glycine and methanolic anhydrous HCl was added. The reaction was allowed to stir at ambient temperature for 2 hours. The reaction mixture was concentrated and the residue was dissolved into 50 mL of saturated aqueous NaHCO₃ and extracted once with 20 mL of methylene chloride and then with three 10 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and concentrated. The resulting solid was recrystallized from diethyl ether/hexanes to give 1.95 g (93%) of 109 as a colorless solid (mp = 66.9 - 68.0 °C).¹⁵² ¹H NMR (360 MHz, CDCl₃) δ 7.37-7.32 (m, 5H), 6.52 (bs, 1H), 5.42 (NH), 5.15 (s, 2H), 4.07 (d, 2H, J= 5.1 Hz), 3.94 (d, 2H, J=5.8 Hz), 3.77 (s, 3H); ¹³C (90 MHz, CDCl₃ ) δ 170.2, 169.4, 156.7, 156.1, 128.6, 128.3, 128.1, 67.3, 52.4, 44.4, 41.1; IR (film) 3367, 3255, 3058, 2980, 1736, 1673, 1567, 1448, 1258, 1216.

**Dimethyl (3-N-(2-N-carboxybenzylaminoacetyl)amino-2-oxopropyl)phosphonate (110)**

Into 10 mL of THF was dissolved 447 mg (0.39 mL, 3.6 mmol) of dimethyl methylphosphonate and the solution was cooled to −78 °C under an inert atmosphere. To this stirring solution was added 1.8 mL (4.0 mmol) of a 2.25 M solution of n-butyl lithium in hexane by syringe pump [0.15 mL/min]. Following addition of n-butyl lithium, the reaction was allowed to stir at −78 °C for an additional 90 minutes, at which time 500 mg (1.8 mmol) of methyl ester 109 was added as a solution in 10 mL of THF by syringe pump [0.15 mL/min]. The reaction was allowed to warm slowly to room temperature over a period of 10 hours and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with five 10 mL portions of ethyl acetate.
acetate and the combined extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica (9:1, acetone : hexanes; Rₜ = 0.3) to give 480 mg (72%) of β-keto phosphonate 110 as a colorless, viscous semi-solid that was difficult to visualize by TLC. The product was observed as a mixture of rotamers. ¹H NMR (360 MHz, CDCl₃) δ 7.38-7.30 (m, 5H), 6.93 (bs, 1H), 5.54 (bs, 1H), 5.15 (s, 2H), 4.27 (d, 2H, J = 5.2 Hz), 3.94 (d, 2H, J = 5.8 Hz), 3.79 (d, 6H, JₚH = 11.3 Hz), 3.14 (d, 2H, J = 22.8 Hz); ¹³C (90 MHz, CDCl₃) δ 197.3 (d, JₚC = 6.0 Hz), 170.2, 169.5, 169.4, 156.7, 136.2, 136.1, 128.6, 128.2, 128.1, 67.2, 53.4, 53.3, 52.4, 49.9, 44.4, 41.1, 38.8 (d, JₚC = 128.7 Hz).

Attempted Chain Extension of Dimethyl (N-(N-carboxybenzyl-2-aminoacetyl)-4-amino-3-oxobutyl)phosphonate (110)

Into 20 mL of methylene chloride was diluted 2.4 mL (2.4 mmol) of a 1.0 M solution of diethylzinc in hexane. A solution of 632 mg (0.19 mL, 2.4 mmol) of methylene iodide dissolved in 1 mL of methylene chloride was added to the stirring diethylzinc solution. The reaction was allowed to stir for approximately 5 minutes at ambient temperature and 150 mg (0.4 mmol) of β-keto phosphonate 110 was added as a solution dissolved in 1.5 mL of methylene chloride. The reaction was allowed to stir for 90 minutes and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with five 20 mL portions of ethyl acetate and the combined organic extracts were dried over MgSO₄. Purification of the small amount of residue was attempted by chromatography on silica (acetone; Rₜ = 0.2). The product was difficult to visualize by TLC and was not recovered.
Bz-glycyl-glycine methyl ester (112)

Into 75 mL of anhydrous methanol was dissolved 3.5 g (14.8 mmol) of Bz-glycyl-glycine and 10 mL of a 0.15 M anhydrous methanolic HCl solution was added. The reaction was allowed to stir for 90 minutes. The solution was concentrated and the resulting residue was dissolved in 100 mL of anhydrous methanol and 10 mL of a 0.15 M anhydrous methanolic HCl solution was again added. The reaction was allowed to stir for 1 hour and concentrated. The residue was dissolved in 50 mL of saturated aqueous NaHCO₃ and extracted twice with 20 mL portions of methylene chloride and then twice with 40 mL portions of ethyl acetate. The combined extracts were dried over MgSO₄ and concentrated to provide 2.32 g (63%) of ester 112 as a colorless powder (mp = 117.8 - 118.9 °C).¹⁵³ ¹H NMR (360 MHz, CDCl₃) δ 7.85-7.82 (m, 2H), 7.56-7.40 (m, 3H), 7.05 (NH), 6.76 (bs, 1H), 4.2 (d, 2H, J = 5.2 Hz), 4.1 (d, 2H, J = 5.4 Hz), 3.76 (s, 3H); ¹³C (90 MHz, CDCl₃) δ 170.0, 169.3, 167.8, 133.4, 131.9, 128.6, 127.1, 52.5, 43.6, 41.2; IR (film) 3297, 3058, 2980, 1750, 1673, 1637, 1271, 1223.

Dimethyl (N-(N-benzoyl-2-aminoacetyl)-3-amino-2-oxopropyl)phosphonate (113)

Into a flask containing 20 mL of THF was diluted 996 mg (0.87 mL, 8 mmol) of dimethyl methylphosphonate and the solution was cooled to −78 °C under an inert atmosphere. To this stirring solution was added 3.9 mL (8.8 mmol) of a 2.25 M solution of n-butyl lithium in hexanes by syringe pump [0.15 ml/min]. The reaction was allowed to stir at −78 °C for 90 minutes, after which a solution containing 1.0 g (4 mmol) of ester 112 dissolved in 13 mL of THF and 3 mL of DME was added by syringe pump [0.15 mL/min]. The reaction was allowed to slowly warm to 0 °C over 12 hours and was
quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with 20 mL portions of ethyl acetate. When the aqueous layer was checked for product, TLC analysis indicated that the extractions had not removed all the organic materials. The aqueous phase was concentrated and the resulting solid was extracted with 20 mL of acetone. The combined organic extracts were dried over MgSO$_4$ and concentrated. The resulting viscous oil was chromatographed on silica (ethyl acetate; $R_f$ = 0.04) to provide 310 mg (23%) of β-keto phosphonate 113 as a slightly yellow viscous semi-solid. $^1$H NMR (360 MHz, CDCl$_3$) δ 7.86-7.83 (m, 2H), 7.54-7.40 (m, 3H), 7.35-7.31 (m, 2H), 4.27 (d, 2H, $J$ = 5.3 Hz), 4.19 (d, 2H, $J$ = 5.3 Hz), 3.78 (d, 6H, $J$ = 11.3 Hz), 3.17 (d, 2H, $J$ = 22.6); (360 MHz, acetone-d$_6$) δ 8.17 (bs, 1H), 7.95-7.93 (m, 2H), 7.72 (bs, 1H), 7.55-7.44 (m, 3H), 4.19 (d, 2H, $J$ = 5.5), 4.09 (d, 2H, $J$ = 5.8 Hz), 3.71 (d, 6H, $J$ = 11.2 Hz), 3.26 (d, 2H, $J$ = 22.4 Hz); $^{13}$C (90 MHz, CDCl$_3$) δ 198.3 (d, $J_{PC}$ = 6.0 Hz), 169.8, 167.3, 134.7, 131.7, 128.7, 127.7, 52.7 (d, $J_{PC}$ = 6.1 Hz), 49.9, 43.4, 38.2 (d, $J_{PC}$ = 127.1 Hz); IR (film) 3423, 3318, 3043, 2994, 1729, 1673, 1525, 1419, 1258, 1019.

**Attempted Chain Extension of Dimethyl (N-(N-benzoyl-2-aminoacetyl)-4-amino-2-oxopropyl)phosphonate (113)**

Into a flask containing 20 mL of methylene chloride was diluted 1.8 mL (1.8 mmol) of a 1.0 M solution of diethylzinc in hexanes and a solution containing 499 mg (0.15 mL, 1.8 mmol) of methylene iodide was added slowly. The reaction was allowed to stir at ambient temperature for 15 minutes, when 100 mg (0.3 mmol) of β-keto phosphonate 113 was added as a solution in 2.0 mL of methylene chloride. The reaction was allowed to stir for 90 minutes at room temperature, after which it was quenched with 5 mL of...
saturated aqueous citric acid. The aqueous layer was extracted with five 20 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and concentrated. Attempts to purify the resulting residue by chromatography resulted in loss of material. Further efforts to effect the chain extension of this substrate were unsuccessful.

**Cbz-glycyl-leucine methyl ester (116)**

Hydrogen chloride gas, generated by the drop-wise addition of 10 mL of concentrated sulfuric acid onto 20 g of sodium chloride, was bubbled through a solution containing 1.0 g (3.1 mmol) of Cbz-glycyl-leucine in 60 mL of anhydrous methanol. The solution was allowed to stir for 14 hours and was then concentrated under reduced pressure. The residue was dissolved in 20 mL ethyl acetate and washed with 20 mL saturated aqueous NaHCO₃. The aqueous layer was extracted twice with 10 mL portions of ethyl acetate. The combined extracts were dried over MgSO₄ and concentrated under reduced pressure. The resulting 538 mg (52%) of 116 as a clear oil that appeared to be pure by H NMR and was taken on without further purification. H NMR (360 MHz, CDCl₃) δ 7.42-7.30 (m, 5H), 6.35 (bs, 1H), 5.41 (bs, 1H), 5.15 (s, 2H), 4.65 (m, 1H), 3.92 (m, 2H), 3.74 (s, 3H), 1.64-1.52 (m, 3H), 0.93 (d, 6H, J = 4.4 Hz); 13C (90 MHz, CDCl₃) δ 173.4, 169.0, 156.7, 136.2, 128.6, 128.3, 128.1, 67.2, 53.4, 50.7, 44.4, 41.5, 24.8, 22.8, 21.9.

**Dimethyl (N-(N-carboxybenzyl-2-aminoacetyl)3-amino-2-oxo-isohexyl)phosphonate (117)**

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Into 25 mL of THF was dissolved 389 mg (0.34 mL, 3.1 mmol) of dimethyl methylphosphonate and the solution was cooled to -78 °C. To this THF solution was added 1.53 mL (3.4 mmol) of a 2.25 M solution of n-butyl lithium in hexanes by syringe pump [0.15 mL/min]. Following the n-butyl lithium addition, the reaction was allowed to stir for 90 minutes, at which time the 500 mg (1.5 mmol) of ester 116 was added as a solution in 1.5 mL of THF. The reaction was allowed to warm slowly to 0 °C over 10 hours and quenched with ammonium chloride. The aqueous layer was extracted thrice with 15 mL of ethyl acetate. The combined organic extracts were dried over MgSO4 and concentrated under reduced pressure. The residue was chromatographed on silica (ethyl acetate; $R_f = 0.17$) to give 227 mg (35%) of β-keto phosphonate 117 as a slightly yellowed semi-solid. $^1$H NMR (360 MHz, CDCl3) δ 7.42-7.29 (m, 5H), 7.01 (bs, 1H), 5.62 (bs, 1H), 5.14 (s, 2H), 4.71 (ddd, 1H, $J = 12.8, 10.1, 3.8$ Hz), 4.04-3.84 (m, 2H), 3.77 (d, 6H, $J = 11.3$ Hz), 3.57-3.35 (m, 1H), 3.08-2.97 (m, 1H), 1.75-1.44 (m, 3H), 0.92 (d, 6H, $J = 6.3$ Hz); $^{13}$C (90 MHz, CDCl3) δ 201.4 (d, $J_{PC} = 6.6$ Hz), 169.3, 156.6, 136.2, 128.6, 128.2, 128.1, 67.2, 57.4, 53.3, 44.6 39.5, 38.4 (d, $J_{PC} = 128.3$ Hz), 24.8, 23.2, 21.4; IR (film) 3325, 2959, 1722, 1525, 1356, 1237, 1019.

**Attempted Chain Extension of Dimethyl (N-(N-carboxybenzyl-2-aminoacetyl)3-amino-2-oxo-iso-heptyl)phosphonate (117)**

Into a flask containing 20 mL of methylene chloride was diluted 0.7 mL (0.7 mmol) of a 1.0 M solution of diethylzinc in hexanes and 56 µL (0.7 mmol) of methylene iodide was added. The reaction was allowed to stir for approximately 10 minutes, during which a white precipitate was formed. A solution containing 50 mg (0.12 mmol) of β-keto
phosphonate 117 dissolved in 1.5 mL of methylene chloride was added. The reaction was allowed to stir at ambient temperature for 2 hours and was then quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with four 15 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (ethyl acetate; Rf = 0.07) to give 51 mg (96%) of a yellow viscous oil. Extensive analysis of the product by NMR suggested that additional methylene group(s) were incorporated, which was confirmed by electrospray mass spectral analysis.

N-Carboxybenzyl-2-N-(2-(carboxymethyl)ethyl)carboxamide pyrrolidine (120)
Into 20 mL of THF was dissolved 1.0 g (4 mmol) of Cbz-L-proline and 850 mg (5.2 mmol) of carbonyl diimidazole was added as a solution in 16 mL of THF. The reaction was allowed to stir at ambient temperature and monitored by TLC. After approximately 2 hours the reaction was complete and 500 mg (4 mmol) of the hydrochloride salt of glycine methyl ester was added as a solution in 10 mL of methanol. The reaction mixture was stirred for 1 hour and became cloudy, after which the solvent was removed under reduced pressure. The resulting residue was dissolved into 50 mL of ethyl acetate and was washed with saturated aqueous NaHCO₃. The aqueous phase was extracted thrice with 10 mL portions of ethyl acetate. The combined organic phases were dried over MgSO₄ and the concentrated residue was chromatographed on silica (ethyl acetate; Rf = 0.4) to give 1.07 g (84%) of methyl ester 120 as a colorless solid whose ¹H-NMR spectrum was complicated by a mixture of rotamers (mp = 178.3 - 179 °C). ¹H NMR (360 MHz, CDCl₃) δ 7.45-7.29 (m, 5H), 7.14 (bs, ~½H), 6.37 (bs, ~¼H), 5.24-5.06 (m,
N-carboxybenzyl-2-N-(2-oxo-3-(dimethylphosphono)propyl)carboxamide

pyrrolidine (121)

A flask which contained 25 mL of THF and 389 mg (0.34 mL, 3.1 mmol) of dimethyl methylphosphonate was cooled under an inert atmosphere to -78 °C. To this stirring solution was added 1.53 mL (3.4 mmol) of a 2.25 M solution of n-butyl lithium in hexanes via syringe pump [0.15 mL/min] and the reaction was allowed to stir for 90 minutes. Into 2 mL of THF was dissolved 500 mg (1.6 mmol) of ester 120 and the solution was added to the stirring reaction mixture by syringe pump [0.15 mL/min]. The reaction was allowed to slowly warm to 0 °C over a 10 hour period and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with three 10 mL portions of ethyl acetate and the combined extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica (ethyl acetate; Rf = 0.05) to provide 263 mg (40%) of β-keto phosphonate 121 as a yellow viscous oil. ¹H NMR (360 MHz, CDCl₃) δ 7.4-7.3 (m, 5H), 5.16 (m, 2H), 4.45-4.15 (m, 3H), 3.79 (d, 6H, J = 11.3 Hz), 3.67-3.45 (m, 2H), 3.3-3.0 (m, 2H), 2.37-1.85 (m, 4H); ¹³C (90 MHz, CDCl₃) δ 208.3, 176.8, 172.2, 136.4, 128.5, 128.1, 127.9, 67.3, 60.7, 53.3 (d, JPC = 6.6 Hz), 50.0, 47.1, 39.0 (d, JPC = 126.0 Hz), 29.0, 24.6.
Attempted Chain Extension of N-carboxybenzyl-2-(N-2-oxo-3-(dimethylphosphono)propyl)carboxamide pyrrolidine (121)

Into a flask containing 5 mL of methylene chloride was diluted 0.73 mL (0.73 mmol) of a 1.0 M solution of diethylzinc in hexanes under an inert atmosphere and 59 μL (0.73 mmol) of methylene iodide was added. The reaction was allowed to stir for approximately 10 minutes. A solution containing 50 mg (0.12 mmol) of β-keto phosphonate 121 dissolved in 1 mL of methylene chloride was added and the reaction was allowed to stir for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with five 10 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (1:1, ethyl acetate : acetone; \( R_f = 0.17 \)) to provide 40 mg (78%) of a yellow viscous oil. Extensive analysis of the product by NMR did not serve to conclusively indicate either purity or the identity of the product; however, analysis of the product by electrospray mass spectrometry indicated the product was a mixture of compounds that correspond to multiple additions of methylene units.

C. Preparation of Substrates for the Study of Cyclopropane Formation:

trans-2-Phenyl-1-(hydroxymethyl)cyclopropane (262)

A round-bottomed flask containing 200 mL of methylene chloride was cooled to 0 °C and 2.75 mL (26.8 mmol) of neat diethylzinc was added. To this solution was added 5 mL (62.3 mmol) of methylene iodide as a solution in 25 mL of methylene chloride by syringe pump [0.2 ml/min]. Following the addition, the reaction mixture was stirred for 10 minutes and then 20 mL of methylene chloride containing 1.2 g (8.9 mmol) of cinnamyl
alcohol 243 was added slowly. The reaction mixture was allowed to warm to room
temperature and stirred for 4 hours, when it was quenched with 50 mL of saturated
aqueous ammonium chloride. The aqueous phase was extracted twice with 10 mL of
diethyl ether. The ether extracts were combined with the methylene chloride solution and
dried over MgSO₄. The solvent was removed under reduced pressure and the resulting
oil was distilled at 0.8 mm Hg and 90-93 ℃ to result in cyclopropane 262 (1.1 g, 87%) as
a clear yellow oil.¹⁵⁴¹H NMR (360 MHz, CDCl₃) δ 7.27-7.02 (m, 5H), 3.6 (m, 2H), 1.80
(ddd, 1H, J = 8.7, 5.2, 4.5 Hz), 1.44 (ddddd, 1H, J = 8.3, 5.5, 5.3, 4.5 Hz), 1.41 (s, 1H),
0.95 (ddd, 1H, J = 8.3, 5.2, 5.1 Hz) 0.91 (ddd, 1H, J = 5.1, 5.5, 8.7 Hz); ¹³C NMR (90
MHz, CDCl₃) δ 142.2, 128.3, 125.7, 125.6, 66.5, 25.2, 21.2, 13.8; IR (film) 3353, 3022,
2860, 1609, 1503, 1461, 1412, 1096, 1026.

* cis-2-Phenyl-1-(hydroxymethyl)cyclopropane (260) *

Into a round-bottomed flask charged with 100 mL of methylene chloride, 2.75 mL (26.8
mmol) of diethylzinc was added. The solution was cooled to 0 ℃ and 10 mL of
methylene chloride containing 5.0 mL (62.3 mmol) of methylene iodide was added by
syringe pump [0.2 ml/min]. After the addition was complete the reaction mixture was
allowed to stir for 10 min at room temperature and a 10 mL methylene chloride solution
containing 1.2 g (8.9 mmol) of *cis*-3-phenyl-2-propenol 260¹⁵⁵ was added. The reaction
mixture was stirred for 5 hours at room temperature and was quenched with 50 mL of
saturated aqueous ammonium chloride. The organic phase was dried over MgSO₄ and
was concentrated under reduced pressure. The resulting oil was distilled at 0.6 mm Hg
and 83-87 ℃ to give 1.2 g (92%) of 260 as a clear yellow oil.¹⁵⁶¹H NMR (360 MHz,
CDCl₃ δ 7.32-7.17 (m, 5H), 3.48 (dd, 1H, J = 11.4, 6.0 Hz), 3.27 (dd, 1H, J = 11.4, 8.6 Hz), 2.30 (ddd, 1H, J = 8.5, 8.5, 5.8 Hz), 1.51 (dddd, 1H, J = 8.6, 8.5, 8.5, 6.0, 5.8 Hz), 1.07 (s, 1H), 1.05 (ddd, 1H, J = 8.5, 8.5, 5.4 Hz), 0.89 (ddd, 1H, J = 5.8, 5.8, 5.4 Hz); ¹³C NMR (90 MHz, CDCl₃) δ 138.2, 128.8, 128.3, 126.2, 62.9, 20.9, 20.7, 7.6.

cis-2-Phenylcyclopropylcarboxaldehyde (278)

Into a round-bottomed flask were combined 300 mg (2 mmol) cis-2-phenyl-1-hydroxymethylcyclopropane 260, 700 mg (6 mmol) NMO and 1.0 g of crushed 4Å molecular sieves. To this flask were added 10 mL of methylene chloride and a catalytic amount of tetrapropylammonium perruthenate (~10 mg). The resulting solution was allowed to stir overnight at ambient temperature under an inert atmosphere. The reaction mixture was loaded onto a column of silica and purified by chromatography (CH₂Cl₂; Rf = 0.54) to give 206 mg (70%) of 278 as a clear, pungent oil. ¹H NMR (360 MHz, CDCl₃) δ 8.67 (d, 1H, J = 6.8 Hz), 7.35-7.2 (m, 5H), 2.83 (ddd, 1H, J = 8.6, 8.0, 7.3 Hz), 2.14 (ddd, 1H, J = 8.6, 8.0, 5.4 Hz), 1.88 (ddd, 1H, J = 7.3, 5.4, 5.2 Hz), 1.59 (ddd, 1H, J = 8.0, 8.0, 5.4 Hz); ¹³C NMR (90 MHz, CDCl₃) δ 201.3, 135.7, 129.2, 128.5, 127.1, 29.7, 26.4, 11.5.

trans-2-Phenylcyclopropylcarboxaldehyde (279)

Into a flask were weighed 300 mg (2.0 mmol) of trans-2-phenyl-1-(hydroxymethyl)cyclopropane 262, 700 mg (6 mmol) of N-methyl morpholine-N-oxide (NMO), and 1.0 g of oven-dried 4Å molecular sieves. Into this flask were added 10 mL of methylene chloride and a catalytic amount (~10 mg) of tetrapropylammonium
perruthenate. The reaction mixture was stirred for 6 hours at room temperature, at which
time the mixture was filtered through silica. The filtrate was concentrated under reduced
pressure and purified by flash chromatography through silica with methylene chloride to
give 186 mg (63%) of 279 as a clear oil. 113 1H NMR (360 MHz, CDCl3) δ 9.3 (d, 1H, J =
4.7 Hz), 7.32-7.08 (m, 5H), 2.61 (ddd, 1H, J = 9.3, 6.7, 4.0 Hz), 2.15 (dddd, 1H, J = 8.3,
5.1, 4.7, 4.0 Hz), 1.71 (ddd, 1H, J = 9.3, 5.1, 5.1 Hz), 1.51 (ddd, 1H, J = 8.3, 6.7, 5.1 Hz);
13C NMR (90 MHz, CDCl3) δ 199.6, 138.9, 128.5, 126.7, 126.2, 33.7, 26.4, 16.3.

**Bis-(2,2,2-trifluoroethoxy)-methylphosphonate (275)**

A three-necked round-bottomed flask equipped with an addition funnel and thermometer
was charged with 40 mL of tetrahydrofuran (THF), 3.95 g (39.5 mmol) of 2,2,2-
trifluoroethanol and 4.0 g (39.5 mmol) of triethylamine. The mixture was cooled to −10
°C with an ice/saltwater bath, and 10 mL of THF solution containing 2.5 g (18.8 mmol)
of methylphosphonic dichloride was added through the addition funnel over a 30 minute
period. Following the addition, the reaction was stirred for 3 hours at room temperature.
A white precipitate, triethylammonium hydrochloride, was removed by filtration. The
precipitate was rinsed with 10 mL of THF and the filtrate was concentrated under
reduced pressure. The resulting oil was taken up in 50 mL of diethyl ether and cooled in
the freezer for 1.5 hours, during which time white, pin-like crystals formed. The crystals
were removed by filtration, and the solution was concentrated. The resulting oil was
distilled at 14 mm Hg and 68-70 °C to give 3.5 g (71%) of 275 as a clear liquid. 157 1H
NMR (360 MHz, CDCl3) δ 4.5-4.28 (m, 4H), 1.68 (d, 3H, JPH = 18.3 Hz); 13C NMR (90
MHz, CDCl$_3$) $\delta$ 121.2 (qd, $J_{FC} = 277.6$ Hz, $J_{PC} = 7.3$ Hz), 61.8 (qd, $J_{FC} = 38.0$ Hz, $J_{PC} = 6.0$ Hz), 11.2 (d, $J_{PC} = 147.0$ Hz).

$t$-Butyl bis-(2,2,2-Trifluoroethyl)phosphonoacetate (277)

To a flask equipped with an addition funnel and charged with 50 mL THF was added 46.2 mL (23.1 mmol) of a 0.5 M potassium hexamethyldisilylamide (KHMDS) solution in toluene. The solution was cooled to $-78 \, ^\circ$C and a 20 mL THF solution containing 3.0 g (11.5 mmol) of bis-(2,2,2-trifluoroethoxy)-methylphosphonate and 2.77 g (12.7 mmol) of di-$t$-butylpyrocarbonate was added over a period of 15 minutes through the addition funnel. Following the addition, the reaction mixture was stirred for 1 hour at $-78 \, ^\circ$C and then placed in freezer at $-20 \, ^\circ$C overnight, where the solution became slush-like and red. The mixture was poured directly into a mixture of 100 mL methylene chloride, ~50 mL crushed ice, and 100 mL of 2N HCl. The mixture was stirred until the ice melted, and the organic layer was separated. The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. The resulting oil was distilled at 0.6 mm Hg and 86-91°C to give 2.6 g (62%) of 277 as a clear oil.$^{157}$ $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 4.45 (m, 4H), 3.08 (d, 2H, $J_{PH} = 21.0$), 1.48 (s, 9H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 163.8 (d, $J_{PC} = 4.6$ Hz), 122.3 (qd, $J_{FC} = 277.3$ Hz, $J_{PC} = 8.6$ Hz) 83.6, 62.7 (qd, $J_{FC} = 37.6$ Hz, $J_{PC} = 5.3$ Hz), 35.5 (d, $J_{PC} = 141.7$ Hz), 28.0.

$t$-Butyl (E)-3-(trans-2-phenylcyclopropyl)propenoate (265)

A flask containing 50 mL of THF and 400 mg (1.8 mmol) of $t$-butyl dimethyl phosphonoacetate was cooled to $-78 \, ^\circ$C, and 1.2 mL (1.7 mmol) of a 1.4 M solution of
methyl lithium in ether was added. The reaction mixture was allowed to warm to room
temperature and a 5 mL THF solution containing 200 mg (1.4 mmol) of trans-2-
phenylcyclopropylcarboxaldehyde was added. The reaction mixture was stirred
overnight and quenched with 20 mL of saturated aqueous ammonium chloride. The
aqueous phase was extracted with 10 mL of diethyl ether and the combined organic
phases were dried over magnesium sulfate. The resulting solution was concentrated
under reduced pressure and purified by chromatography (16:1, hexanes : diethyl ether) to
yield 175 mg (52%) of 265 as a clear yellow oil. $^1$H NMR (360 MHz, CDCl$_3$) δ 7.32-7.01
(m, 5H), 6.49 (dd, 1H, $J = 15.4$, 9.8 Hz), 5.81 (d, 1H, $J = 15.4$ Hz), 2.13 (ddd, 1H, $J =
9.0$, 6.0, 4.2 Hz), 1.76 (dddd, 1H, $J = 9.8$, 8.4, 5.3, 4.2 Hz), 1.47 (s, 9H), 1.39 (ddd, 1H, $J$
= 8.4, 6.0, 5.3 Hz), 1.25 (ddd, 1H, $J = 9.0$, 5.3, 5.3 Hz); $^{13}$C NMR (90 MHz, CDCl$_3$) δ
165.9, 150.2, 140.8, 128.4, 126.0, 125.8, 120.5, 79.9, 28.1, 26.6, 26.4, 17.5.

r-Butyl (Z)-3-(trans-2-phenylcyclopropyl)propenoate (266)

A flask containing 670 mg (1.8 mmol) of bis-(2,2,2-trifluoroethoxy)-(carbo-tert-
butoxymethyl)phosphonate 276 and 1.5 g (5.5 mmol) of 18-crown-6 was charged with 50
mL THF and cooled to −78 °C. To this solution 3.7 mL (1.85 mmol) of a 0.5 M KHMDS
solution in toluene was added and the reaction was stirred for 30 minutes at −78 °C. To
this stirring solution was added 5 mL of THF containing 135 mg (0.92 mmol) of trans-2-
phenylcyclopropylcarboxaldehyde 279, and the reaction was stirred for 6 hours at −78
°C. The reaction was quenched at −78 °C with 10 mL of saturated aqueous ammonium
chloride and warmed to room temperature. The mixture was separated and the organic
phase was dried over MgSO$_4$. The solution was concentrated under reduced pressure and
purified by flash chromatography (8:1, hexanes:diethyl ether) to give 190 mg (84.5%) of 
266 as a clear yellow oil.\textsuperscript{113} \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.31-7.05 (m, 5H), 5.65 (d, 
1H, \(J = 11.4\) Hz), 5.53 (dd, 1H, \(J = 11.4, 10.5\) Hz), 3.21 (dddd, 1H, \(J = 10.5, 8.9, 8.6, 4.0\) Hz), 2.06 (ddd, 1H, \(J = 10.0, 8.9, 4.4\) Hz), 1.46 (s, 9H), 1.43 (ddd, 1H, \(J = 13.9, 8.6, 4.4\) Hz), 1.17 (ddd, 1H, \(J = 13.9, 10.0, 4.0\) Hz); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 166.5, 151.5, 
141.3, 128.6 (2), 126.2, 119.7, 80.2, 28.4, 27.3, 24.1, 18.8.

\textbf{t-Butyl (E)-3-(cis-2-Phenylcyclopropyl)propenoate (267)}

A flask containing 230 mg (1.0 mmol) of triethyl phosphonoacetate was charged with 60 
ml of THF and 0.73 mL (1 mmol) of a 1.4 M methyl lithium solution in diethyl ether 
was added slowly. The reaction mixture was stirred for 5 minutes before a 10 mL THF 
solution containing 100 mg of cis-2-phenylcyclopropylcarboxaldehyde 278 was added. 
The reaction was stirred for 20 minutes and was quenched with 10 mL of saturated 
aqueous ammonium chloride. The THF solution was separated, dried over magnesium 
sulfate and concentrated under reduced pressure. The resulting oil was purified by 
chromatography (16:1, hexanes : ether) to give 134 mg (81%) of 267 as a clear colorless 
oil.\textsuperscript{155} \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.31-7.17 (m, 5H), 6.17 (dd, 1H, \(J = 15.4, 10.5\) Hz), 5.85 (d, 1H, \(J = 15.4\) Hz), 2.55 (ddd, 1H, \(J = 8.4, 8.4, 6.9\) Hz), 1.97 (dddd, 1H, \(J = 
10.5, 8.4, 8.4, 5.4\) Hz), 1.43 (ddd, 1H, \(J = 8.4, 8.4, 5.3\) Hz), 1.39 (s, 9H), 1.25 (ddd, 1H, \(J = 
6.9, 5.4, 5.3\) Hz); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 165.7, 148.5, 137.5, 128.9, 128.3, 

\textbf{t-Butyl (Z)-3-(cis-2-phenylcyclopropyl)propenoate (268)}
To a flask charged with 60 mL of THF were added 500 mg (1.4 mmol) of bis-(2,2,2-trifluoroethoxy)-(carbo-tert-butoxymethyl)phosphonate 276 and 1.1 g (4.1 mmol) of 18-crown-6. The solution was cooled to -78 °C and 2.7 mL (1.4 mmol) of a 0.5 M solution of KHMDS in toluene was added. The reaction solution was stirred for 5 minutes and a 10 mL THF solution containing 100 mg (0.7 mmol) of cis-2-phenylcyclopropylcarboxadehyde 278 was added. The reaction mixture was allowed to stir at -78 °C for 8 hours when it was quenched with 10 mL of saturated aqueous ammonium chloride. The quenched reaction mixture was allowed to warm to room temperature. The organic phase was separated, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (16:1, hexanes:ether) to afford 130 mg (78%) of 268 as a clear colorless oil.\[^{113}\] \(^{1}\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.16 (m, 5H), 5.54 (d, 1H, \(J = 11.3\) Hz), 5.28 (dd, 1H, \(J = 11.3, 11.3\) Hz), 3.26 (dddd, 1H, \(J = 8.6, 8.6, 5.2\) Hz), 2.61 (dd, 1H, \(J = 8.6, 8.6, 6.7\) Hz), 1.5 (s, 9H), 1.5 (dd, 1H, \(J = 8.6, 8.6, 5.2\) Hz), 1.18 (ddd, 1H, \(J = 6.7, 5.2, 5.2\) Hz); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 166.6, 149.7, 137.9, 129.3, 128.2, 126.3, 120.2, 79.8, 28.3, 25.5, 19.2, 14.0.

**General Procedure for the Sulfur Ylide Cyclopropanation and DIBAL-H Reduction of (265-268)**

Sodium hydride (2.5 equiv.) was weighed into a round-bottomed flask, and to this flask 2.5 equiv of trimethylsulfoxonium iodide was added as a solution in dimethylsulfoxide (0.25 M). The reaction was stirred for 20 minutes at room temperature, and 1 equiv of the corresponding \(\alpha,\beta\)-unsaturated ester 265-268 was added as a solution in
dimethylsulfoxide (0.1 M). The reaction solution was stirred for 3 days before it was quenched with a 1:5 mixture of DI H2O : ether and stirred for 8 hours. The quenched reaction mixture was diluted with 10 mL of DI H2O and extracted with diethyl ether (9 x 5 mL). The ether extracts were combined, dried over magnesium sulfate, and concentrated to give a mixture of bis-cyclopropyl esters as a colorless oil. This oil was dissolved in THF and cooled to 0 °C. To this solution 8 equivalents of a 1.2 M solution of DIBAL-H in toluene was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with sequential addition of 2N NaOH and DI H2O (0.56 mL / mmol DIBAL-H), and stirred overnight. The reaction was washed with DI H2O (2 x 5 mL). The organic phase was dried over magnesium sulfate, filtered through silica, and concentrated to give a mixture of bis-cyclopropyl alcohols 226-233 that were identified by 13C NMR through comparison to literature data.155

**Reaction of t-Butyl (E)-3-(trans-2-Phenylcyclopropyl)propenoate (265)**

Yield of bis-cyclopropyl esters: 87%. Yield of DIBAL-H reduction: 95%.

**Reaction of t-Butyl (Z)-3-(trans-2-Phenylcyclopropyl)propenoate (266)**

Yield of bis-cyclopropyl esters: 90%. Yield of DIBAL-H reduction: 92%.

**Reaction of t-Butyl (E)-3-(trans-2-Phenylcyclopropyl)propenoate (267)**

Yield of bis-cyclopropyl esters: 52%. Yield of DIBAL-H reduction: 57%.

**Reaction of t-Butyl (Z)-3-(trans-2-Phenylcyclopropyl)propenoate (268)**
Yield of bis-cyclopropyl esters: 78%. Yield of DIBAL-H reduction: 86%.

_trans-2-Phenyl-1-vinylcyclopropane (263)_

A flask containing 350 mg (0.9 mmol) of methyltriphenylphosphonium bromide was charged with 20 mL of THF and cooled to −78 °C. To this solution 0.58 mL (0.8 mmol) of a 1.4 M solution of methyl lithium in ether was added one portion, and stirred for 5 minutes. A solution of 100 mg (0.7 mmol) of _trans_-2-phenylcyclopropylcarboxaldehyde 279 in 10 mL of THF was added, and the solution was allowed to warm to room temperature. The reaction solution was stirred for 8 hours and quenched with 10 mL of saturated aqueous ammonium chloride. The organic phase was separated, dried over magnesium sulfate and filtered through silica. The filtrate was concentrated under reduced pressure and purified by flash chromatography (hexanes) to provide 40 mg (41%) of 263 as a clear, volatile, odiferous oil.\[^{155}\] \[^{1}H\text{ NMR}\ (360 \text{ MHz, } \text{CDCl}_3)\ \delta\ 7.29-7.05\ \text{(m, 5H)},\ 5.53\ \text{(ddd, 1H, } J = 17.1, 10.2, 8.5\ \text{Hz)},\ 5.10\ \text{(dd, 1H, } J = 17.1, 1.5\ \text{Hz)},\ 4.93\ \text{(dd, 1H, } J = 10.2, 1.5\ \text{Hz)},\ 1.92\ \text{(ddd, 1H, } J = 8.5, 5.4, 5.4\ \text{Hz)},\ 1.69\ \text{(dddd, 1H, } J = 8.5, 8.5, 5.4, 4.4\ \text{Hz)},\ 1.20\ \text{(dddd, 1H, } J = 8.5, 5.4, 5.4\ \text{Hz)},\ 1.10\ \text{(dddd, 1H, } J = 8.8, 5.4, 5.4\ \text{Hz)};\ \[^{13}C\text{ NMR}\ (90 \text{ MHz, } \text{CDCl}_3)\ \delta\ 142.3,\ 140.6,\ 128.3,\ 125.7,\ 125.6,\ 112.5,\ 27.4,\ 25.2,\ 16.7.

_cis-2-Phenyl-1-vinylcyclopropane (259)_

To a flask charged with 50 mL of THF was added 1.57 g (4.4 mmol) of methyltriphenylphosphonium bromide and the solution was cooled to −78 °C. To this solution 2.8 mL (4 mmol) of a 1.4 M solution of methyl lithium in ether was added. The reaction was stirred at −78 °C for 5 minutes and 500 mg (3.4 mmol) of _cis_-2-
phenylcyclopropylcarboxaldehyde 278 was added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with 50 mL of saturated aqueous ammonium chloride. The organic phase was dried over MgSO₄, concentrated under reduced pressure and purified by chromatography (hexanes) to give 420 mg (85%) of 259 as a clear, volatile, odiferous oil.¹¹³ H NMR (360 MHz, CDCl₃) δ 7.30-7.15 (m, 5H), 5.13-5.08 (m, 2H), 4.88-4.82 (m, 1H), 2.35 (m, 1H), 1.86 (m, 1H), 1.26 (ddd, 1H, J = 8.4, 8.4, 5.2 Hz), 1.04 (dd, 1H, J = 5.4, 5.4, 5.2 Hz). ¹³C NMR (90 MHz, CDCl₃) δ 138.7, 138.1, 129.1, 128.0, 125.9, 114.0, 23.3, 22.9, 11.7.

**General Procedure for the Rhodium Carbenoid-Mediated Cyclopropanation and Subsequent DIBAL-H Reduction of 259 and 263**

Into a round-bottomed flask was weighed 1.00 equiv of vinylcyclopropane 259 or 263. Sufficient benzene was added to bring the concentration to 0.1 M. A catalytic amount of Rh₂(OAc)₄ was added and the solution was stirred while a 0.2 M solution of ethyl diazoacetate in benzene was added via syringe pump [0.2 mL/min]. The reaction was stirred for 6 hours at room temperature, the mixture was filtered through celite, and the solution was concentrated under reduced pressure. The reaction mixture was separated by flash chromatography (16:1, hexanes : diethyl ether) to give a mixture of bis-cyclopropyl esters, starting material, and ethyl cycloheptatrienoate. The mixture of bis-cyclopropyl esters was added to a round-bottomed flask which was then charged with 10 mL of THF. The solution was cooled to 0 °C and excess DIBAL-H was added. The reaction mixture was stirred at room temperature for 6 hours, and quenched with sequential addition of 2N NaOH and DI H₂O (0.056 mL / mmol DIBAL-H), and stirred.
overnight. The quenched reaction mixture was filtered through celite and dried over magnesium sulfate. The solution was concentrated under reduced pressure to give a mixture of bis-cyclopropyl alcohols 226-233 which were identified by $^{13}$C NMR through comparison to literature data.\textsuperscript{155}

**Reaction of trans-2-Phenyl-1-vinylcyclopropane (263)**
Yield of bis-cyclopropyl esters: 38%. Yield of ethyl cycloheptatrienoate: 25%.
Recovered starting material 263: 10%. Yield of DIBAL-H reduction: 85%.

**Reaction of cis-2-Phenyl-1-vinylcyclopropane (259)**
Yield of bis-cyclopropyl esters: 14%. Yield of ethyl cycloheptatrienoate: 32%.
Recovered starting material 264: 25%. Yield of DIBAL-H reduction: 96%.

D. Preparation of Substrates Directed Toward the Synthesis of Polycyclopropanated Natural Products:

**Ethyl E-3-(trans-(1S,2R)-2-triphenylmethoxymethylcyclopropyl)propenoate (332)**
A flask containing 500 mg (1.45 mmol) of trans-(1S,2S)-1-triphenylmethoxymethyl-2-hydroxymethylcyclopropane 331, 510 mg (4.35 mmol) of NMO and 725 mg of crushed 4Å molecular sieves was charged with 50 mL of CH$_2$Cl$_2$. A catalytic amount of TPAP (~10 mg) was added and the reaction was allowed to stir at ambient temperature for 2 hours. The reaction mixture was filtered through a plug of silica and the silica was rinsed with excess methylene chloride (~300 mL). The resulting clear solution was
concentrated and the residue was dissolved into 30 mL of THF and set aside (Solution 1).

In a separate flask, a solution of 583 mg (2.6 mmol) triethyl phosphonoacetate in 20 mL of THF was added to 116 mg (2.9 mmol) of a 60% dispersion of NaH in mineral oil. After gas evolution subsided, solution 1 was added and the reaction was allowed to stir at ambient temperature for 15 minutes. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with two portions of diethyl ether. The combined extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (10:1, hexanes : ether) to give 494 mg (83%) of 232 as a clear colorless viscous oil.¹³³¹H NMR (360 MHz, CDCl₃) δ 7.44 (m, 6H), 7.27 (m, 9H), 6.5 (dd, 1H, J = 15.4, 9.9 Hz), 5.85 (d, 1H, J = 15.4 Hz), 4.17 (q, 2H, J = 7.1 Hz), 3.03 (m, 2H), 1.44 (m, 1H), 1.39 (m, 1H), 1.29 (t, 3H, J = 7.1 Hz), 0.86 (m, 2H); ¹³C NMR (90 MHz, CDCl₃) δ 166.7, 152.5, 144.1, 128.6, 127.7, 126.9, 118.4, 86.4, 65.9, 60.0, 22.5, 20.0, 14.3, 13.5.

E-3-(trans-(1S,2R)-2-Triphenylmethoxymethylcyclopropyl)-2-propen-1-ol (333)

Into a solution of 490 mg (1.2 mmol) of 332 dissolved in 50 mL of THF was added 3.5 mL (4.2 mmol) of a 1.2 M solution of DIBAL-H in toluene. The reaction was allowed to stir for approximately 12 hours and was quenched by the sequential addition of 1.0 mL of DI H₂O and 3 mL of a 2 N aqueous solution of NaOH. The quenched reaction was allowed to stir for 4 hours and the aqueous layer was extracted twice with 20 mL of diethyl ether. The combined extracts were washed with 20 mL of DI H₂O and dried over MgSO₄. The concentrated residue was chromatographed on silica (2:1, hexanes : ether) to provide 349 mg (78%) of 333 as a clear, colorless oil. [α]D=+1.86 (c=0.0698, CDCl₃)¹⁵⁸

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\textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \( \delta 7.44 \) (m, 6H), 7.27 (m, 9H), 5.67 (dt, 1H, \( J = 15.3, 6.1 \) Hz), 5.31 (dd, 1H, \( J = 15.3, 8.7 \) Hz), 4.10 (dd, 2H, \( J = 6.0, 1.2 \) Hz), 3.02 (dd, 1H, \( J = 9.6, 6.2 \) Hz), 2.97 (dd, 1H, \( J = 9.6, 6.2 \) Hz), 1.55 (s, 1H), 1.24 (m, 1H), 1.15 (m, 1H), 0.65 (m, 2H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \( \delta 153.2, 144.3, 135.9, 128.6, 127.7, 126.9, 86.2, 66.6, 63.6, 20.6, 19.1, 11.9 \).

1-Triphenylmethoxymethyl-6-hydroxymethyl-(1S,3R,4R,6S)-bis-cyclopropane (334)

Method A: Into a flask containing 20 mL of methylene chloride were added 600 mg (1.6 mmol) of 333 and 870 mg (3.2 mmol) of L-tartrate-derived dioxaboralane 220. The solution was allowed to stir at ambient temperature. In a separate flask, 3.2 mL (3.2 mmol) of a 1.0 M solution of diethylzinc in hexanes was diluted into 50 mL of methylene chloride. A solution containing 0.52 mL (6.4 mmol) of methylene iodide dissolved in 5 mL of methylene chloride was added slowly to the diethylzinc solution. Following the addition of methylene iodide, the carbenoid solution was allowed to stir for 5 minutes and the solution of 333 and dioxaboralane 220 was added via cannula. The reaction was allowed to stir for 12 hours and was quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted thrice with 10 mL of methylene chloride and twice with 10 mL of diethyl ether. The combined extracts were concentrated under reduced pressure. The resulting residue was dissolved in a combination of 10 mL of 5N KOH and 50 mL of diethyl ether and stirred vigorously for 12 hours. The aqueous phase was extracted with six 10 mL portions of diethyl ether and the combined extracts were dried over MgSO\textsubscript{4}. The concentrated residue was chromatographed on silica (2:1, hexanes : diethyl ether, \( R_f = 0.1 \)) to give 600 mg (98%) of bis-cyclopropane 334 as a clear
colorless oil. \[^{109}\] [\(\alpha\)]\(_D\) = +41.45 (c. 0.027, CH\(_2\)Cl\(_2\)); \(^{1}\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.50-7.35 (m, 6H), 7.30-7.15 (m, 9H), 3.55-3.35 (m, 2H), 2.93 (dd, 1H, \(J = 9.6, 6.3\) Hz), 2.87 (dd, 1H, \(J = 9.6, 6.9\) Hz), 1.62 (s, 1H), 0.95-0.65 (m, 4H), 0.5-0.2 (m, 4H); \(^{13}\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 144.4, 128.7, 127.7, 126.8, 86.0, 67.3, 66.9, 19.7, 18.2, 17.9, 17.1, 8.33, 8.27.

**Method B:** A round-bottomed flask was charged with 1 mL of dry pyridine, 17 mg (0.12 mmol) of bis-cyclopropane 335 and 40 mg (0.14 mmol) of triphenylmethylchloride were added and the solution was heated in an oil bath to 80 °C. The reaction was allowed to stir for approximately 12 hours, when TLC analysis indicated its completion. The reaction was allowed to cool to room temperature and the reaction was diluted with saturated aqueous ammonium chloride. The aqueous solution was extracted with four 5 mL portions of diethyl ether and the combined extracts were dried over MgSO\(_4\). The concentrated residue was chromatographed on silica (1:1, hexanes : ether) to provide 19 mg (41%) of a colorless, viscous oil whose spectra are consistent with those obtained from method A. [\(\alpha\)]\(_D\) = +29.3 (c. 0.0041, CH\(_2\)Cl\(_2\)).

**1,6-bis-Hydroxymethyl-(1S,3R,4R,6S)-bis-cyclopropane (335)**

Into a solution containing 945 mg (3.5 mmol) of L-tartrate-derived dioxaboralane 220 dissolved in 20 mL of methylene chloride, was added 100 mg (0.88 mmol) of 2,4-hexadien-1,6-diol 289. The solution was heated on a steam bath to dissolve the diol and set aside (solution 1). In a separate flask, 3.5 mL (3.5 mmol) of a 1.0 M solution of diethylzinc in hexane was diluted into 5 mL of methylene chloride and a solution
containing 0.6 mL (7 mmol) of methylene iodide dissolved in 10 mL of methylene chloride was added via syringe pump [0.4 mL/min]. Following methylene iodide addition, the reaction was allowed to stir for 10 minutes and solution 1 was added via cannula. The reaction was allowed to stir for 4 hours at which time it was quenched with 1 mL of saturated aqueous ammonium chloride and the organic phase was separated and combined with 20 mL of 5N KOH. The biphasic solution was stirred vigorously for approximately 16 hours and the aqueous layer was extracted thrice with 10 mL of ethyl acetate. The combined extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (ethyl acetate) to give 50 mg (40%) of bis-cyclopropane 335 as a yellow oil found to be 78% ee.125b [α]D=+55.38 (c. 0.0065, CH₂Cl₂); ¹H NMR (360 MHz, CDCl₃) δ 3.48 (dd, 2H, J = 12.8, 7.9 Hz), 3.38 (dd, 2H, J = 12.8, 7.2 Hz), 2.50 (bs, 2H), 0.94-0.84 (m, 2H), 0.81-0.69 (m, 2H), 0.37 (m, 4H); ¹³C NMR (90 MHz, CDCl₃) δ 66.8, 19.9, 18.3, 8.3.

1-(E-2-Ethoxycarbonyl-ethenyl-6-triphenylmethoxymethyl-(1S,3S,4R,6S)-bis-cyclopropane (337)

Into a 100 mL round-bottomed flask were combined 600 mg (1.56 mmol) of bis-cyclopropane 334, 550 mg (4.68 mmol) of NMO, and 750 mg of oven dried 4Å molecular sieves. The mixture was stirred in 20 mL of methylene chloride and a catalytic amount (~10 mg) of TPAP was added. The reaction was allowed to stir at ambient temperature for 2 hours at which time the reaction mixture was filtered through a plug of silica, which was rinsed with an excess of methylene chloride. The concentrated residue was dissolved in 20 mL of THF and set aside (solution 1). In a separate flask, 138 mg

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(3.43 mmol) of a 60% dispersion of sodium hydride in mineral oil was suspended in 10 mL of THF. Into this flask was added 0.62 mL (3.12 mmol) of triethyl phosphonoacetate drop-wise. After gas evolution subsided, solution 1 was added and the reaction was allowed to stir at ambient temperature for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with two 10 mL portions of diethyl ether. The combined extracts were dried over MgSO4 and the concentrated residue was chromatographed on silica (10:1, hexanes : diethyl ether) to give 463 mg (66%) of 337 as a yellow oil. 1H NMR (360 MHz, CDCl3) δ 7.45-7.40 (m, 6H), 7.33-7.17 (m, 9H), 6.46 (dd, 1H, J = 15.4, 10.0 Hz), 5.83 (d, 1H, J = 15.4 Hz), 4.16 (q, 2H, J = 7.2 Hz), 2.98 (dd, 1H, J = 9.6, 6.3 Hz), 2.83 (dd, 1H, J = 9.6, 6.9 Hz), 1.45-1.30 (m, 1H), 1.27 (t, 3H, J = 7.2), 1.22-1.10 (m, 1H), 0.95-0.80 (m, 2H), 0.80-0.65 (m, 2H), 0.35-0.20 (m, 2H); 13C NMR (90 MHz, CDCl3) δ 166.9, 153.2, 144.3, 128.7, 127.7, 126.9, 117.8, 86.1, 67.0, 60.0, 24.4, 21.1, 17.9, 17.5, 14.3, 14.0, 8.0.

1-Triphenylmethoxymethyl-6-(E-1-propen-3-ol)-(1S,3R,4S,6S)-bis-cyclopropane (338)

A flask was charged with 20 mL of THF and 450 mg (0.99 mmol) of bis-cyclopropane 337 was dissolved. The solution was cooled to 0 °C and 3.2 mL (3.2 mmol) of a 1.0 M solution of DIBAL-H in toluene was added. The reaction was allowed to warm slowly to room temperature and monitored by TLC. After 5 hours, TLC analysis indicated the reaction was complete and it was quenched with the sequential addition of 3.2 mL of DI H2O followed by 3.2 mL of 2N NaOH. Celite was added and the quenched reaction was allowed to stir for approximately 12 hours, during which a white precipitate formed. The
reaction mixture was filtered through celite and the filtrate dried over MgSO₄. The concentrated residue was chromatographed on silica (1:1, hexanes : diethyl ether; Rf = 0.23) to yield 342 mg (84%) of 338 as a yellow tinged oil. ¹H NMR (360 MHz, CDCl₃) δ 7.57-7.13 (m, 15H), 5.68 (dt, 1H, J = 15.3, 6.4 Hz), 5.26 (dd, 1H, J = 15.3, 8.9 Hz), 4.08 (d, 2H, J = 5.6 Hz), 2.96 (dd, 1H, J = 9.5, 6.4 Hz), 2.86 (dd, 1H, J = 9.5, 6.7 Hz), 1.35-1.12 (m, 1H), 1.03-0.80 (m, 2H), 0.78-0.67 (m, 1H), 0.62-0.47 (m, 2H), 0.37-0.23 (m, 2H); ¹³C NMR (90 MHz, CDCl₃) δ 144.4, 136.8, 128.7, 127.7, 126.8, 86.1, 67.2, 63.8, 22.1, 22.0, 18.0, 17.2, 12.0, 7.8.

1-Triphenylmethoxymethyl-9-hydroxymethyl-(1S,3R,4S,6S,7R,9S)-tris-cyclopropane (339)

Method A: A solution containing 340 mg (0.83 mmol) of bis-cyclopropyl allylic alcohol 338 and 450 mg (1.66 mmol) of L-tartrate-derived dioxaboralane 220 dissolved in 10 mL of methylene chloride was prepared and set aside. Into a separate flask, 1.7 mL (1.7 mmol) of a 1.0 M solution of diethylzinc in hexanes was diluted into 10 mL of methylene chloride and a 5 mL solution containing 0.27 mL (3.31 mmol) of methylene iodide was added via syringe pump [0.2 mL/min]. The solution of dioxaboralane and allylic alcohol was added and the reaction was allowed to stir for two hours at ambient temperature. The reaction was quenched with saturated aqueous ammonium chloride. The organic solution was combined with 5N KOH and stirred vigorously for 6 hours. The aqueous layer was extracted twice with 20 mL of diethyl ether and the combined extracts were concentrated. A small portion of the residue was set aside for analysis and the remainder was dissolved in 20 mL of diethyl ether. To this stirring solution was added 2 mL of
concentrated HCl and the reaction was monitored by TLC. After 30 minutes the reaction mixture was washed sequentially with 10 mL of DI H$_2$O, twice with 10 mL of saturated aqueous NaHCO$_3$, and once with 10 mL of brine. The resulting organic solution was dried over MgSO$_4$ and concentrated. NMR analysis of the resulting residue indicated the complete decomposition of the tris-cyclopropane 339, as no cyclopropane resonances were observed. The small portion saved earlier was chromatographed on silica (1:1, hexanes : ether) to provide enough material for an NMR sample. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.50-7.40 (m, 6H), 7.38-7.18 (m, 9H), 3.52-3.35 (m, 2H), 2.93 (dd, 1H, $J = 9.5, 6.3$ Hz), 2.83 (dd, 1H, $J = 9.4, 6.8$ Hz), 0.90-0.55 (m, 7H), 0.50-0.35 (m, 5H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 144.4, 128.7, 127.7, 126.8, 86.0, 67.4, 67.0, 19.8, 18.42, 18.39, 18.3, 18.0, 17.0, 8.4, 8.32, 8.26.

**Method B:** Into a flask charged with 5 mL of dry pyridine was added 8 mg (0.04 mmol) of tris-cyclopropane 321 remaining from the work of McDonald$^{160}$ and the solution was heated to 80 °C in an oil bath. To this stirring solution, 120 mg (0.43 mmol) of triphenylmethyl chloride was added in small portions over 24 hours, at which time the reaction had proceeded nearly to completion. The reaction was diluted with 20 mL of diethyl ether and then washed with five 10 mL portions of saturated aqueous NaHCO$_3$. The remaining organic solution was dried over MgSO$_4$ and the concentrated residue was chromatographed on silica (1:1, hexanes : ether; $R_f = 0.35$) to give 8 mg (48%) of 329 as a viscous oil whose spectra are identical with those obtained in method A.

**$\beta$-Iodostyrene (347a)**
A flask, wrapped with aluminum foil, containing 3.5 g (28.3 mmol) of CrCl₂ was charged with 20 mL of THF and cooled to 0 °C. To this flask was slowly added a 10 mL THF solution containing 500 mg (4.7 mmol) of benzaldehyde and 3.7 g (9.4 mmol) of iodoform. The reaction was allowed warm to ambient temperature and stir for approximately 12 hours. The reaction mixture was filtered through silica and the silica was washed with diethyl ether. The concentrated organic filtrate was distilled at aspirator pressure in a Kugelrohr to provide 718 g (67%) of a clear liquid that quickly discolored (purple) upon standing. ¹H NMR (360 MHz, CDCl₃) δ 7.44 (d, 1H, J = 14.9 Hz), 7.40-7.30 (m, 5H), 6.84 (d, 1H, J = 14.9); ¹³C NMR (90 MHz, CDCl₃) δ 145.0, 137.7, 128.7, 128.4, 126.0, 76.7; IR (film) 3050, 3022, 1595, 1567, 1504, 1448, 1216, 1166, 1075, 955, 737, 695; LRMS (El) M⁺ 230.05, 127.9, 103.1, 77.1, 51.1.

Attempted Preparation of trans-1,2-bis-(E-2-Iodoethyl)cyclopropane (349)

Into a flask containing 5 mL of THF was placed 455 mg (3.7 mmol) of CrCl₂ and the resulting suspension was cooled to 0 °C. To this stirring mixture was slowly added a 3 mL THF solution containing 480 mg (1.22 mmol) of iodoform and 30 mg (0.31 mmol) of trans-1,2-bis-(carboxaldehyde)cyclopropane 348. The reaction was allowed to stir for approximately 12 hours at ambient temperature. The reaction mixture was filtered through silica and the silica was rinsed with hexanes. The clear solution discolored rapidly to a translucent purple. The concentrated residue was analyzed by NMR, which indicated that neither starting dialdehyde nor product was present.
Attempted Preparation of \textit{trans-1-(\textit{t}-Butyldimethylsiloxymethyl)-2-(\textit{E}-2-iodoethenyl)cyclopropane (351)}

A 250 mL round-bottomed flask containing 895 mg (7.3 mmol) of \( \text{CrCl}_2 \) was charged with 20 mL of THF. The suspension was cooled to 0 °C and a solution comprised of 945 mg (2.4 mmol) of iodoform and 260 mg (1.2 mmol) of \textit{trans-2-(\textit{t}-butyldimethylsiloxymethyl)cyclopropane carboxaldehyde 350} dissolved in 10 ml of THF was added slowly. The reaction was allowed to warm to room temperature and stir for 24 hours, at which time the mixture was filtered through silica with hexanes. Analysis of the concentrated residue by NMR indicated the absence of both starting material and product. The rapid discoloration of the clear solution, resulting in the appearance of a purple color was the only indication that the reaction had proceeded.

\textbf{Dimethyl (1-diazo-2-oxopropyl)phosphonate (358)}

A 25 mL round-bottomed flask was charged with 5 mL of THF and 283 mg (2.8 mL) of freshly distilled diisopropyl amine was added. The solution was cooled to 0 °C and 1.53 mL (2.6 mmol) of a 1.7 M solution of n-butyl lithium in pentane was added. The reaction was allowed to warm to room temperature over 15 minutes and a 10 mL THF solution containing 200 mg (1.2 mmol) of dimethyl (2-oxopropyl)phosphonate 73 and 555 mg (2.4 mmol) of \( p \)-carboxybenzenesulfonylazide 357 was added slowly. The stirring reaction mixture was monitored by TLC and was complete after 1 hour. The reaction was quenched with saturated ammonium chloride and the aqueous layer was extracted twice with 10 mL of ethyl acetate. The combined extracts were chromatographed on silica (ethyl acetate) to provide 220 mg (96%) of 358 as a clear yellow oil.\textsuperscript{161} \textsuperscript{1}H NMR
(360 MHz, CDCl₃) δ 3.85 (d, 6H, J_PH = 11.9 Hz), 2.27 (s, 3H); ¹³C NMR (90 MHz, CDCl₃) δ 197.1 (d, J_PC = 15.3 Hz), 53.5 (d, J_PC = 5.5 Hz), 27.1.

1-Triphenylmethoxymethyl-2-ethynylcyclopropane (356)

Into 100 mL of methylene chloride, 450 mg (1.35 mmol) of trans-2-triphenylmethoxymethyl-1-hydroxymethylcyclopropane, 457 mg (3.9 mmol) of NMO and 650 mg of oven dried 4 Å molecular sieves were combined. Into the resulting solution a catalytic amount (~10 mg) of TPAP was added and the reaction was monitored by TLC. After approximately 4 hours, TLC analysis indicated that the reaction was complete and the solution was filtered through a plug of silica. The silica was rinsed with an excess of methylene chloride and the resulting solution was concentrated under reduced pressure. The resulting residue was combined with 269 mg (1.4 mmol) of dimethyl (1-diazo-2-oxopropyl)phosphonate 358 and dissolved in 10 mL of anhydrous methanol. The solution was cooled to 0 °C and 360 mg (2.6 mmol) of anhydrous potassium carbonate was added. The reaction was allowed to warm to ambient temperature and stir for approximately 10 hours.¹⁶¹ The reaction mixture was concentrated under reduced pressure and the residue was dissolved into 10 mL of diethyl ether and 5 mL of DI H₂O. The aqueous layer was extracted twice with 10 mL of diethyl ether and the combined extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica (9:1, hexanes : CH₂Cl₂) to give 436 mg (99%) of a colorless powder (mp = 81.4 - 82.7 °C). ¹H NMR (360 MHz, CDCl₃) δ 7.47-7.44 (m, 6H), 7.35-7.10 (m, 9H), 3.02 (d, 2H, J = 9.4 Hz), 1.83 (d, 1H, J = 5.1 Hz), 1.55-1.40 (m, 1H), 1.23-1.13 (m, 1H), 0.97-0.85 (m, 1H), 0.82-0.70 (m, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 144.1,
128.6, 127.8, 127.0, 86.8, 86.4, 65.3, 64.1, 21.8, 12.9, 4.5; IR (film) 3297, 3058, 2854, 2116, 1483, 1440, 1265, 1208, 1054, 906.

**Attempted DDQ Oxidation of 1-Benzylxoy-2-butanol (360)**

Into 30 mL of methylene chloride was dissolved 100 mg (0.55 mmol) of 1-benzylxoy-2-butanol 360. To ensure dryness, 415 mg of powdered 4Å molecular sieves, recently flame-dried under high vacuum, were added. The solution was allowed to stir for 30 minutes and 189 mg (0.83 mmol) of DDQ was added. After approximately 14 hours, TLC analysis indicated that a product might have been formed; however, a large amount of starting material remained. After 2 days, the reaction mixture still contained starting material. Furthermore, TLC analysis indicated that the small product spot appeared to be fading and a new spot corresponding to the over-oxidized ester product had formed. Efforts to speed up the reaction by heating to reflux and decreasing the reaction time, as well as ensuring the reaction mixture was rigorously dry, were unsuccessful.

**Attempted Whitham Elimination of 2-p-Methoxyphenyl-1,3-dioxolane (361b)**

A flask containing 500 mg (2.77 mmol) of 361b was charged with 20 mL of THF and 1.98 mL (2.77 mmol) of a 1.4 M solution of n-butyl lithium in hexane was added. The reaction was monitored by TLC and the consumption of starting material was observed within 2 hours. The reaction was quenched with DI H$_2$O and the aqueous layer was separated and acidified with concentrated HCl. The acidified aqueous layer was extracted with diethyl ether and the combined extracts were concentrated. Analysis of the concentrated organic layers was inconclusive, as were efforts to purify the residues.
produced by evaporation of the solvent. In effort to effect the reaction, several bases were employed including NaH, KHMDS, and t-butyl lithium. Efforts also included the variation of the number of equivalents of base, increasing the reaction time, and heating the reaction mixtures. In all cases, efforts to effect the reaction were unsuccessful in producing the p-methoxybenzoic acid or its derivatives.

**Attempted Whitham Elimination of 4,5-Divinyl-2-p-methoxyphenyl-1,3-dioxolane (361c)**

Into 5 mL of THF was dissolved 44 mg (0.19 mmol) of p-methoxybenzylidene acetal 361c and the solution was cooled to 0 °C. To this stirring solution was slowly added 0.18 mL (0.28 mmol) of a 1.6 M solution of n-butyl lithium in hexane. The reaction was monitored by TLC. After 12 hours no reaction was apparent and the reaction was abandoned.

**Attempted Whitham Elimination of cis-Cyclohexyl-fused 1,3-Dioxolane (362)**

A solution containing 100 mg (0.43 mmol) of 362 dissolved in 10 mL of diethyl ether and 105 mg (0.74 mmol) of decane, to serve as an internal standard, was cooled to 0 °C. To this stirring solution, 0.36 mL (0.9 mmol) of a 2.5 M solution of n-butyl lithium in hexane was slowly added. The reaction was monitored for cyclohexene by GLC for 13 hours, during which time none was observed and the reaction was quenched. Efforts to effect the reaction, such as increasing the amount of base and varying the base were unsuccessful.
Attempted Whitham Elimination of 1,2,5,6-Diisopropylidene-3,4-\textit{p}-methoxybenzylidene-L-mannitol (364)

Into 5 mL of THF was dissolved 36 mg (0.1 mmol) of \textit{p}-methoxybenzylidene acetal 364 and the solution was cooled to 0 °C. To this stirring solution, 0.6 mL (0.11 mmol) of a 1.7 M solution of \textit{i}-butyl lithium\textsuperscript{162} in hexane was added and the reaction was monitored by TLC. The starting material was consumed within 3 hours and the reaction was quenched with saturated aqueous ammonium chloride. The organic layer was dried over MgSO\textsubscript{4}, filtered and evaporated. The complex reaction mixture was chromatographed on silica (4:1, hexanes : diethyl ether). The isolated materials did not contain any olefinic functionality.

\textbf{1-Triphenylmethoxy-2-butanol (365)}

A 250 mL round-bottomed flask was charged with 50 mL of anhydrous pyridine, 5.0 g (55.5 mmol) of 1,2-butanediol and 15.5 g (55.5 mmol) of triphenylmethylchloride were added. The resulting solution was heated to 90 °C in an oil bath and monitored by TLC. After 24 hours the reaction appeared complete and the pyridine was removed under vacuum (~5.5 torr). The resulting oil was dissolved in 50 mL of diethyl ether and the salts were removed by filtration. The filtrate was concentrated and the residue was chromatographed on silica (20:1, hexanes : diethyl ether; \(R_f = 0.07\)) to give 13.7 g (75%) of 365 as a slightly yellow viscous oil (darkens upon sitting to resemble amber).\textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.48-7.44 (m, 6H), 7.35-7.14 (m, 9H), 3.75-3.65 (m, 1H), 3.20 (dd, 1H, \(J = 9.3, 3.4\) Hz), 3.05 (dd, 1H, \(J = 9.3, 7.4\) Hz), 2.30 (s, 1H), 1.46 (qd, 2H, \(J = 7.4, 6.8\) Hz), 0.89 (t, 3H, \(J = 7.4\) Hz); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 144.1, 128.9, 128.1, 128.9, 128.1, 1
2-Benzylxoybutanol (367a)

A solution comprising of 100 mg (0.3 mmol) of 365 dissolved in 5 mL of THF was added to a 25 mL round-bottomed flask containing 48 mg (1.2 mmol) of a 60% dispersion of NaH in mineral oil and 114 mg (0.9 mmol) of benzyl chloride. After gas evolution subsided, the reaction was brought to reflux and monitored by TLC. After approximately 9 hours the reaction appeared to be complete and was quenched with saturated aqueous ammonium chloride. The aqueous solution was extracted twice with 10 mL of diethyl ether and the combined extracts were dried over MgSO₄. The concentrated residue was crudely chromatographed through a short plug of silica (3:1, hexanes : diethyl ether) to remove residual butanol starting material. After the evaporation of the eluent, the residue which consisted of benzyl chloride and bis-protected butane-diol was dissolved in 50 mL of a 40:1 mixture of methanol : THF. To this stirring solution 2.0 mL of concentrated HCl was added drop-wise and the reaction was monitored by TLC. After 6 hours the reaction was complete and 5 mL of 2N NaOH was added. The reaction mixture was concentrated in vacuo and the resulting solution was extracted thrice with 10 mL of diethyl ether. The combined organic extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (6:1, hexanes : diethyl ether, Rf = 0.08) to afford 29 mg (54%) of butanol 367a. ¹H NMR (360 MHz, CDCl₃) δ 7.40-7.21 (m, 5H), 4.63 (d, 1H, J = 11.6 Hz), 4.56 (d, 1H, J = 11.6 Hz), 3.67 (dd, 1H, J = 11.5, 3.6 Hz), 3.56 (dd, 1H, J = 11.5, 6.1 Hz), 3.49-3.38 (m, 1H), 2.66 (s, 1H), 1.58 (m, 2H), 0.96
2-(p-Methoxybenzyloxy)butanol (367b)

Into a 100 mL round-bottomed flask containing 35 mg (0.88 mmol) of a 60% dispersion of NaH in mineral oil was added a 1.5 mL THF solution containing 145 mg (0.44 mmol) of 1-triphenylmethoxy-2-butanol 365. Following gas evolution, a 1.0 mL THF solution containing 96 mg (0.62 mmol) of p-methoxybenzyl chloride was added and the reaction was brought to reflux for 12 hours. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with 10 mL of diethyl ether. The combined organic solutions were dried over MgSO$_4$ and the concentrated residue was dissolved in 5 mL of methanol with the aid of a few drops of THF. To this stirring solution was added 1.0 mL of glacial acetic acid. After 3 hours, TLC analysis indicated the reaction was complete and it was quenched with saturated aqueous NaHCO$_3$. The aqueous layer was extracted with 20 mL of diethyl ether and the combined organic solutions were dried over MgSO$_4$. The concentrated residue was chromatographed on silica (2:1, hexanes : diethyl ether, $R_f = 0.1$) to afford 45 mg (49%) of 367b as a yellow liquid. $^1$H NMR (360 MHz, CDCl$_3$) δ 7.28 (d, 2H, $J = 8.6$ Hz), 6.90 (d, 2H, $J = 8.6$), 4.57 (d, 1H, $J = 11.1$ Hz), 4.47 (d, 1H, $J = 11.1$ Hz), 3.82 (s, 3H), 3.68 (m, 1H), 3.54 (m, 1H), 3.45 (m, 1H), 1.90 (s, 1H), 1.64 (m, 2H), 0.94 (t, 3H, $J = 7.5$ Hz); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 159.3, 130.6, 129.4, 113.9, 80.7, 71.2, 63.9, 55.3, 23.5, 9.7; IR (film) 3465, 3064, 2959, 1609, 1504, 1265, 723.
E-2-Buten-1,4-diol (304)

Into a 5L 3-necked round-bottomed flask were placed 82.5 g (2.17 mol) of lithium aluminum hydride. The flask was equipped with a mechanical stirrer in the center neck and a condenser on one of the other necks. A Claisen adapter with an addition funnel and a condenser was placed in the final neck and each opening was affixed with a ground glass gas adapter. The system was purged with nitrogen and an ice bath was placed under the flask. Through the addition funnel 2.0 L of THF was slowly added to the LiAlH₄ powder (As a result of the high heat of solution, the solvent began to boil). A sturdy blast shield was placed in front of the apparatus and the ice bath refilled. The suspension was stirred as a solution of 93.6 g (1.09 mol) of butyne-1,4-diol 397 dissolved in 1.5 L of THF was added slowly. (Careful attention was paid to the vigorous gas evolution that accompanied the addition. Great care should be taken to ensure that the salt formed by the reaction of LiAlH₄ with the diol does not build up and form a crust or a pocket that allows the diol solution to accumulate, since an explosive reaction results when large amounts of diol are added in a short period.) Following the addition of the diol, the reaction was brought to reflux for 16 hours. (The prudent researcher should not leave the reaction unattended.) The reaction was allowed to cool to ambient temperature and then placed in an ice bath. While maintaining the ice bath, the reaction was quenched by the slow sequential addition of 82.5 mL of DI H₂O, 247.5 mL of 2N NaOH, and 82.5 mL of DI H₂O. The quenched reaction mixture was allowed to stir for 15 hours at ambient temperature. The reaction mixture was filtered in several portions through celite and the salt cakes rinsed with excess ethyl acetate. The resulting concentrated oil was distilled at 35 torr and 145-150 °C to afford 76.2 g (80%) of 304 as a clear
slightly yellow tinged oil.\textsuperscript{109} \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 5.89 (m, 2H), 4.17 (m, 4H), 2.01 (s, 2H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 130.5, 62.9; IR (film) 3655-2615, 2917, 2868, 1695, 1426, 1187, 1096, 980.

\textbf{E-1-\textit{t}-Butyldimethylsiloxy-4-hydroxy-2-butene (325)}

A 1000 mL round-bottomed flask was charged with 300 mL of methylene chloride. Into this solution were dissolved 10 g (113.5 mmol) of E-2-butendiol 304 and 24 mL (170.3 mmol) of triethyl amine. To this stirring solution was slowly added 100 mL of a methylene chloride solution containing 18.8 g (124.8 mmol) of \textit{t}-butyldimethylsilyl chloride. The reaction was allowed to stir at ambient temperature for 24 hours, during which time a white precipitate formed. The solvent was removed under reduced pressure and the residue was extracted with 300 mL of diethyl ether. The crystalline precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was distilled at 1.1 torr and 90-95 °C to afford 19.6 g (86%) of 325 as a clear colorless oil.\textsuperscript{133} \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 5.83 (m, 2H), 4.16 (m, 4H), 1.44 (s, 1H), 0.91 (s, 9H), 0.08 (s, 6H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 131.2, 129.2, 129.2, 63.7, 63.5, 26.2, 18.6, -5.0; IR (film) 3353, 2959, 2925, 2868, 1469, 1356, 1264, 1103, 997, 836.

\textit{trans-}(1R,2R)-\textit{bis}-Hydroxymethylcyclopropane (305)

Into an Erlenmyer flask were combined 3.09 g (15.3 mmol) of 325 and 4.95 (18.3 mmol) of D-tartrate-derived dioxaboralane 221 and the mixture was dissolved into 20 mL of
methylene chloride. A 500 mL round-bottomed flask was charged with 300 mL of methylene chloride and 4.7 mL (45.9 mmol) of neat diethylzinc was added. The diethylzinc solution was cooled to 0 °C and a 15 mL methylene chloride solution containing 3.7 mL (45.9 mmol) of methylene iodide was added by syringe pump [0.2 mL/min]. Following the addition, the reaction mixture was allowed to stir for 5 minutes and the solution containing 325 and 221 was added. The reaction was allowed to warm to room temperature and stir for 4 hours. The reaction was quenched with saturated aqueous ammonium chloride and the organic solvent was removed under reduced pressure. The resulting biphasic mixture was combined with 200 mL of 5N KOH and stirred vigorously for 14 hours. The mixture was extracted twice with 75 mL of methylene chloride, followed by three 100 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The concentrated residue was dissolved in 180 mL of a 1/1/1 mixture of acetic acid/THF/DI H₂O. The solution was allowed to stir for 20 hours and was concentrated under reduced pressure. The residue was chromatographed on silica (1:1, hexanes:acetone) to afford 1.34 g (86%) of 305 as a clear slightly yellow oil \([\alpha]_D= \approx 26.5\) (c. 0.0282, CH₂Cl₂).\(^{164}\) \(^1\)H NMR (360 MHz, CDCl₃) \(\delta\) 3.8 (dd, 2H, \(J = 11.3, 4.8\) Hz), 3.10 (dd, 2H, \(J = 11.2, 8.5\) Hz) 2.56 (s, 2H), 1.07-0.98 (m, 2H), 0.45 (dd, 2H, \(J = 7.0, 6.6\)). \(^{13}\)C NMR (90 MHz, CDCl₃) \(\delta\) 66.1, 20.0, 7.1; IR (film) 3648-2720, 2868, 1427, 1251, 1068, 1026.

**trans-(1R,2R)-bis-Ethyl (E-3-Prop-2-enoyl)cyclopropane (306)**

In a 1000 mL round-bottomed flask 932 mg (9.1 mmol) of bis-hydroxymethylcyclopropane 305, 6.35 g (54.7 mmol) of NMO and 13.65 g of crushed...
4Å molecular sieves were combined. The flask was charged with 600 mL of methylene chloride and a catalytic amount (~20 mg) of TPAP was added. The reaction was allowed to stir at ambient temperature for two days. After the reaction was complete the mixture was filtered through a plug of silica and the silica washed with an excess of diethyl ether (~200 mL). The solvent was removed under reduced pressure and the residue was dissolved in 10 mL of THF (solution 1). In a separate flask, 9 mL (45.5 mmol) of triethyl phosphonoacetate was added to a slurry of 1.93 g (48.2 mmol) of a 60% suspension of NaNH in mineral oil mixed with 20 mL of THF. After gas evolution ceased, solution 1 was added and the reaction was allowed to stir for 1 hour, at which time it was quenched by the addition of saturated aqueous ammonium chloride. The aqueous layer was extracted twice with 20 mL of diethyl ether and the combined extracts were dried over MgSO4. The concentrated residue was chromatographed on silica (4:1, hexanes : diethyl ether) to afford 1.69 g (78%) of 306 as a colorless oil. 1H NMR (360 MHz, CDCl3) δ 6.45 (dd, 2H, J = 15.4, 6.3 Hz) 5.90 (d, 2H, J = 15.4 Hz), 4.15 (q, 4H, J = 7.1), 1.85 (dd, 2H, J = 15.3, 8.2), 1.25 (m, 8H); 13C NMR (90 MHz, CDCl3) δ 166.3, 149.5, 119.9, 60.2, 25.1, 19.0, 14.3; IR (film) 3050, 2980, 2938, 1714, 1644, 1265, 1145, 1046.

trans-(1R,2R)-bis-(E-1-Proen-3-ol)cyclopropane (398)

A 1000 mL round-bottomed flask that contained 2.9 g (12.2 mmol) of diester 306 was charged with 500 mL of THF and 73 mL (73 mmol) of a 1.0 M solution of DIBAL-H in toluene was added. The reaction was allowed to stir at room temperature for 13 hours and was cooled to 0 °C, at which time it was quenched by the slow sequential addition of 4 mL of DI H2O, 4 mL of 2N NaOH, 4 mL of DI H2O, and 4 mL of 2N NaOH. The
The quenched reaction was allowed to warm to room temperature as it stirred for an additional 10 hours. The salts were filtered and rinsed with ethyl acetate. The concentrated residue was chromatographed on silica (1:1, hexanes : ethyl acetate) to afford 1.37 g (73%) of 398 as a slightly yellow viscous oil. $^1$H NMR (360 MHz, CDCl$_3$) δ 5.71 (dt, 2H, $J = 15.3, 6.1$), 5.28 (dd, 2H, $J = 15.3, 8.4$), 4.08 (d, 4H, $J = 6.1$ Hz), 1.45 (m, 2H), 1.29 (s, 2H), 0.87 (dd, 2H, $J = 6.8, 6.7$); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 135.1, 127.6, 63.8, 23.5, 15.3; IR (film) 3669-3093, 3002, 2945, 1658, 1440, 1265, 1065.

1,9-bis-Hydroxymethyl-(1R,3S,4R,6R,7S,9R)-tris-cyclopropane (307)

In an Erlenmeyer flask 1.0 g (6.5 mmol) of 398 was combined with 4.21 g (15.6 mmol) of D-tartrate-derived dioxaboralane 221 and the mixture was dissolved into 10 mL of methylene chloride. In a separate flask, 38.9 mL (38.9 mmol) of a 1.0 M solution of diethylzinc in hexanes was added to a solution of 3.66 mL (45.4 mmol) of methylene iodide dissolved in 250 mL of methylene chloride. The reaction was allowed to stir for 15 minutes and the solution containing 398 and dioxaboralane was added to the zinc carbenoid. The reaction was allowed to stir for 12 hours and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with four 100 mL portions of ethyl acetate and the combined extracts were concentrated. The resulting residue was mixed with 90 mL of 2N NaOH and 15 mL of 35% H$_2$O$_2$ and stirred vigorously for 45 minutes. The mixture was extracted with four 100 mL portions of ethyl acetate and the combined extracts were dried over MgSO$_4$. The resulting solution was concentrated under reduced pressure and the resulting residue was chromatographed on silica (diethyl ether; $R_f = 0.1$) to provide 713 mg (60%) of 307 as a clear, slightly
yellow oil that solidified upon standing \([\alpha]_D = -117.66\) (c. 0.07076, CHCl₃).\(^{167}\)

\(^1\)H NMR (360 MHz, CDCl₃) \(\delta\) 3.41 (m, 4H), 1.34 (m, 2H), 0.90-0.78 (m, 2H), 0.77-0.67 (m, 2H), 0.65-0.53 (m, 2H), 0.32-0.25 (m, 4H), 0.18-0.13 (m, 2H); \(^{13}\)C NMR (90 MHz, CDCl₃) \(\delta\) 66.9, 19.7, 18.3, 18.2, 8.3, 8.1; IR (film) 3346, 3058, 3002, 2938, 2875, 1419, 1026.

1-\(t\)-Butyldimethylsiloxyethyl-9-hydroxymethyl-(1R,3S,4R,6R,7S,9R)-tris-cyclopropane (399)

A solution comprised of 700 mg (3.84 mmol) of bis-hydroxymethyl-tris-cyclopropane 307 dissolved in 400 mL of diethyl ether and 2.7 mL of triethylamine was placed in a flask. To this stirring solution was added 3.0 mL of diethyl ether containing 579 mg (3.84 mmol) of \(t\)-butyldimethylsilyl chloride. The reaction was allowed to stir at ambient temperature and was monitored by TLC. After 14 hours the reaction progress appeared to be complete and was filtered through celite. The concentrated residue was chromatographed on silica, first eluted with hexanes, then with ether and finally with ethyl acetate. The first eluent successfully removed residual silyl chloride and silanol, the second provided 239 mg (21%, 98% BORSM) of 399 and the final afforded 550 mg (79%) of the starting diol 307. The recovered starting material was recycled three times, affording 772 mg (68%) total yield of 399. \(^1\)H NMR (360 MHz, CDCl₃) \(\delta\) 3.50-3.36 (m, 4H), 0.89 (s, 9H), 0.88-0.80 (m, 3H), 0.78-0.66 (m, 3H), 0.62-0.57 (m, 2H), 0.36-0.10 (m, 5H), 0.05 (s, 6H); \(^{13}\)C NMR (90 MHz, CDCl₃) \(\delta\) 67.0, 66.6, 26.0, 19.8, 19.5, 18.4 (2), 18.1 (2), 8.3, 8.2, 8.0, 0.01, -5.1.

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1-\textit{t-}Butyldimethylsiloxymethyl-9-ethyl-(3-\textit{E-}prop-2-enoyl)-(1R,3S,4R,6S,7S,9R)-tris-cyclopropane (400)

In a 500 mL round-bottomed flask 770 mg (2.6 mmol) of 399, 914 mg (7.8 mmol) of NMO and 1.3 g of 4Å molecular sieves were combined. The mixture was dissolved in 250 mL of methylene chloride and a catalytic amount (~20 mg) of TPAP was added. The reaction was allowed to stir at ambient temperature and monitored by TLC. After 4 hours the reaction was complete and the mixture was filtered through a plug of silica, which was rinsed with excess diethyl ether. The filtrate was concentrated and the residue was dissolved in 5 mL of THF, (solution 1). In a separate flask, 281 mg (7.0 mmol) of a 60% suspension of NaH in mineral oil was combined with 50 mL of THF and cooled to 0 °C. To this slurry was added 1.29 mL (6.5 mmol) of triethyl phosphonoacetate and after the gas evolution subsided, solution 1 was added. The reaction was allowed to stir for 30 minutes and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with 50 mL of diethyl ether and the combined organic extracts were dried over MgSO$_4$. The resulting solution was concentrated under reduced pressure and the residue was chromatographed on silica (2:1, hexanes : diethyl ether) to give 869 mg (92%) of 400 as a colorless viscous oil. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 6.44 (dd, 1H, $J = 15.4, 10.0$ Hz), 5.81 (d, 1H, $J = 15.4$ Hz) 4.16 (q, 2H, $J = 7.1$ Hz) 3.50 (dd, 1H, $J = 10.8, 6.0$ Hz) 3.40 (dd, 1H, $J = 10.8, 6.4$ Hz), 1.38-1.21 (m, 1H), 1.28 (t, 3H, $J = 7.1$), 0.89 (s, 9H), 0.88 (m, 1H), 0.80-0.58 (m, 6H), 0.33-0.14 (m, 4H), 0.05 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 166.9, 153.3, 117.6, 66.5, 60.0, 29.7, 26.0, 24.7, 21.1, 19.6, 18.8, 18.1, 18.0, 14.3, 13.9, 8.0, 7.8, 0.01, -5.1.
1-t-Butyldimethylsiloxymethyl-9-(E-1-propen-3-ol)-(1R,3S,4R,6S,7S,9S)-tris-cyclopropane (401)

Into 100 mL of THF which contained 850 mg (2.3 mmol) of 400 was added 7.0 mL (7.0 mmol) of a 1.0 M solution of DIBAL-H in toluene. The reaction was allowed to stir for 8 hours at ambient temperature, at which time it was quenched by the slow sequential addition of 0.4 mL of DI H₂O, 0.4 mL of 2N NaOH, 0.4 mL of DI H₂O and 0.4 mL of 2N NaOH. The quenched reaction mixture was allowed to stir for 12 hours and the resulting salts were filtered. The resulting solution was concentrated in vacuo and the residue was chromatographed on silica (3:1, hexanes : diethyl ether) to afford 395 mg (53%) of 401 as a slightly yellow oil. ¹H NMR (360 MHz, CDCl₃) δ 5.65 (dt, 1H, J = 15.2, 6.1 Hz), 5.23 (dd, 1H, J = 15.2, 8.8 Hz), 4.06 (m, 2H), 3.48 (dd, 1H, J = 10.8, 6.1 Hz), 3.41, (dd, 1H, J = 10.8, 6.4 Hz), 1.26 (m, 1H), 1.20-1.10 (m, 1H), 0.89 (s, 9H), 0.88-0.80 (m, 1H), 0.80-0.53 (m, 5H), 0.53-0.40 (m, 2H), 0.30-0.01 (m, 3H), 0.05 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 136.8, 126.0, 66.6, 63.8, 26.0, 22.4, 19.9, 19.5, 18.5, 18.2, 18.1, 11.9, 8.0, 7.8, 0.01, -5.1.

1-t-Butyldimethylsiloxymethyl-12-hydroxymethyl-(1R,3S,4R,6S,7S,9R,10S,12R)-tetrakis-cyclopropane (291)

Into an Erlenmeyer flask were weighed 370 mg (1.15 mmol) of tris-cyclopropyl allylic alcohol 401 and 373 mg (1.4 mmol) of D-tartrate-derived dioxaboralane 221. The mixture was dissolved into 5 mL of methylene chloride and set aside. In a separate flask 3.45 mL (3.45 mmol) of a 1.0 M solution of diethylzinc in hexane was added to a stirring solution of 0.32 mL (4.0 mmol) of methylene iodide dissolved in 100 mL of methylene chloride.
chloride. The reaction was allowed to stir for 15 minutes and the solution containing 401 and dioxaboralane 221 was added. The reaction was allowed to stir for 8 hours and was quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted with three 50 mL portions of ethyl acetate and the combined organic extracts were concentrated. The resulting residue was dissolved in 5 mL of diethyl ether and combined with 8 mL of 2N NaOH and 2 mL of 35% H₂O₂. The mixture was stirred vigorously for 1 hour and was extracted with three 50 mL portions of ethyl acetate. The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The concentrated residue was chromatographed on silica (1:2, hexanes : diethyl ether; RF = 0.2) to afford 368 mg (95%) of 291 as a clear oil. [α]D = -107.0 (c. 0.0242, CH₂Cl₂); ¹H NMR (360 MHz, CDCl₃) δ 3.49-3.35 (m, 4H), 0.90 (s, 9H), 0.90 (m, 1H), 0.89-0.78 (m, 1H), 0.77-0.63 (m, 3H), 0.62-0.48 (m, 4H), 0.31-0.17 (m, 4H), 0.15-0.03 (m, 4H), 0.05 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 67.0, 66.7, 26.0, 19.7, 19.5, 18.6, 18.4 (2), 18.1 (2), 18.0, 8.3 (3), 8.25, 0.01, -5.1.

1,12-bis-Hydroxymethyl-(1R,3S,4R,6S,7S,9R,10S,12R)-tetrakis-cyclopropane (224)

To a solution containing 50 mg (0.15 mmol) of silyl ether 291 dissolved in 5 mL of THF was added 165 µL (0.165 mmol) of a 1.0 N solution of tetrabutylammonium fluoride (TBAF) in THF. The reaction was allowed to stir at ambient temperature and was monitored by TLC. After 90 minutes the reaction was complete and 2 mL of DI H₂O was added. The mixture was extracted thrice with 20 mL of ethyl acetate and the combined organic extracts were dried over MgSO₄. The concentrated residue was chromatographed on silica (ether; RF = 0.4) to provide 22 mg (67%) of 224 as a slightly yellow oil found to
be 87% ee.\textsuperscript{57c} [\(\alpha\)]\textsubscript{D} = -158.3 (c. 0.0048, CH\textsubscript{2}Cl\textsubscript{2}); \(^1\)H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 3.46-3.32 (m, 4H), 1.64 (s, 2H), 0.88-0.75 (m, 2H), 0.74-0.62 (m, 2H), 0.60-0.45 (m, 4H), 0.32-0.20 (m, 4H), 0.18-0.03 (m, 4H); \(^{13}\)C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 66.9, 19.7, 18.5, 18.3, 18.0, 8.2 (2); IR (film) 3395, 3065, 3001, 2938, 2882, 1258, 1018.

1-\(t\)-Butyldimethylsiloxyethyl-12-ethenyl-(1R,3S,4R,6S,7R,9S,10R,12S)-tetrakis-cyclopropane (402)

A 250 mL round-bottomed flask was charged with 300 mg (0.89 mmol) of tetrakis-cyclopropyl methanol 291, 313 mg (2.67 mmol) of NMO and 445 mg of powdered 4Å molecular sieves. The mixture was dissolved in 50 mL of methylene chloride and a catalytic amount (~20 mg) of TPAP was added. The reaction was allowed to stir at ambient temperature and monitored by TLC. The reaction appeared to be complete after 8 hours and was filtered through a plug of silica, which was rinsed with an excess of diethyl ether. The resulting solution was concentrated and the residue was taken up in 5 mL of THF (solution 1). In a separate flask, 479 mg (1.34 mmol) of methyltriphenylphosphonium bromide was dissolved into 40 mL of THF and cooled to 0 °C. To this cooled solution was added 1.84 mL (1.34 mmol) of a 0.73 M solution of methyl lithium in hexane, which afforded an opaque canary yellow solution. The reaction was allowed to warm to ambient temperature over 30 minutes and solution 1 was added, which caused the yellow color to diminish. The reaction was allowed to stir for an additional 12 hours and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with five 10 mL portions of diethyl ether and the combined extracts were dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure and
the residue was chromatographed on silica (hexanes; Rf = 0.1) to afford 223 mg (75%) of 402 as a clear colorless oil. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 5.36 (ddd, 1H, $J = 17.1, 10.3, 9.7$ Hz), 4.99 (d, 1H, $J = 17.1$ Hz), 4.80 (d, 1H, $J = 10.3$ Hz), 3.49-3.38 (m, 2H), 1.21-1.10 (m, 1H), 0.90 (s, 9H), 0.89-0.80 (m, 1H), 0.79-0.62 (m, 3H), 0.61-0.50 (m, 5H), 0.49-0.40 (m, 2H), 0.28-0.18 (m, 2H), 0.15-0.02 (m, 2H), 0.05 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 141.9, 111.1, 66.7, 26.0, 22.3, 21.2, 19.5, 18.6, 18.4, 18.2 (2), 18.1, 11.8, 8.2, 8.1, 7.8, 0.01, -5.1.

1-Hydroxymethyl-2-phenyl-(1R,2R)-cyclopropane (391)

Into an Erlenmeyer flask were combined 2.5 g (18.6 mmol) of cinnamyl alcohol 243 and 6.03 g (22.3 mmol) of D-tartrate-derived dioxaboralane 221 and the mixture was dissolved in 20 mL of methylene chloride. In a separate flask, 55.9 mL (55.9 mmol) of a 1.0 M solution of diethylzinc in hexane was added via syringe pump [0.3 mL/min] to a stirring 0 °C solution of 200 mL methylene chloride which contained 5.25 mL (65.1 mmol) of methylene iodide. Following the addition of diethylzinc, the reaction was allowed to stir for 30 minutes and the solution containing 243 and dioxaboralane 221 was added. The resulting reaction mixture was allowed to slowly warm to ambient temperature while stirring for 8 hours. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted thrice with 50 mL of ethyl acetate. The combined extracts were concentrated under reduced pressure and 120 mL of 2N NaOH and 20 mL of 35% H$_2$O$_2$ were added. The resulting solution was stirred vigorously for 1 hour and was extracted with four 50 mL portions of ethyl acetate. The combined extracts were dried over MgSO$_4$ and the concentrated residue was
chromatographed on silica (2:1, hexanes : diethyl ether) to afford 2.71 g (98%) of 391 as a clear, slightly yellow oil, which was determined to be 89% ee.\textsuperscript{154} [\alpha]_{D}^{20} = -74.84 (c. 0.0339, CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.29-7.25 (m, 2H), 7.19-7.14 (m, 1H), 7.10-7.07 (m, 2H), 3.63 (m, 2H), 1.87 (m, 1H), 1.80 (s, 1H), 1.50 (m, 1H), 1.05-0.90 (m, 2H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 142.4, 128.3, 125.7, 125.6, 66.5, 25.2, 21.2, 13.8.

1-Phenyl-2-ethenyl-(1R,2S)-cyclopropane (392)

Into a 1000 mL round-bottomed flask were combined 2.0 g (13.5 mmol) of cyclopropylmethanol 391, 4.74 g (40.5 mmol) of NMO and powdered 4Å molecular sieves. The flask was charged with 700 mL of methylene chloride and a catalytic amount (~30 mg) of TPAP was added. The reaction was allowed to stir at ambient temperature for 6 hours, at which time TLC analysis indicated its completion. The mixture was filtered through a plug of silica and the silica was washed with excess diethyl ether (~200 mL). The solvent was removed under reduced pressure and the residue was dissolved in 10 mL of THF (solution 1). In a separate flask 9.65 g (27 mmol) of methyltriphenylphosphonium bromide was dissolved in 200 mL of THF and 37 mL (27 mmol) of a 0.73 M solution of methyl lithium in hexane was added slowly. The reaction was allowed to stir for 30 minutes and solution 1 was added. The reaction was allowed to stir for an additional 2 hours and was quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted with three 50 mL portions of diethyl ether and the combined extracts were dried over MgSO\textsubscript{4}. The solvent was carefully removed under reduced pressure and the resulting residue was chromatographed on silica (hexanes) to provide 1.61 g (83%) of 392 as a odiferous, clear, colorless oil. \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.36-7.27 (m, 2H), 7.22-7.17 (m, 1H), 7.15-7.08 (m, 2H), 5.58 (ddd,
E-1,2-bis-(2-Phenyl-(1S,2R)-cyclopropyl)ethylene (393)

A 250 mL round-bottomed flask was charged with 100 mL of a methylene chloride solution containing 400 mg (2.8 mmol) of vinylcyclopropane 392 and 114 mg (5 mol%) of Grubbs' catalyst [(Cy$_3$P)$_2$Cl$_2$Ru=CHPh] was quickly added. The reaction was refluxed for 8 hours, at which time an additional 114 mg (5 mol%) of Grubbs' catalyst was added. The reaction was allowed to reflux for an additional 12 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica (hexanes) to provide 224 mg (62%) of 393 as a clear, colorless oil. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.42-7.0 (m, 10H), 5.28 (m, 2H), 1.98-1.80 (m, 2H), 1.74-1.60 (m, 2H), 1.30-1.17 (m, 2H), 1.16-1.10 (m, 2H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 147.5, 131.0, 128.3, 125.7, 125.6, 26.6, 25.1, 16.7.

1-t-Butyldimethylsiloxymethyl-12-(E-2-phenyl-(1S,2R)-cyclopropyl)ethenyl)-(1R,3S,4R,6S,7R,9S,10S,12R)-tetrakis-cyclopropane (403)

Into a 50 mL round-bottomed flask 92 mg (0.28 mmol) of vinyl-tetrakis-cyclopropane 402 and 144 mg (0.55 mmol) of dicyclopentylethylene 393 were combined and dissolved into 20 mL of methylene chloride. To this stirring solution 12 mg (5 mol%) of Grubbs' catalyst [(Cy$_3$P)$_2$Cl$_2$Ru=CHPh] was added and the reaction mixture was brought to
reflux. After 20 hours the reaction appeared (TLC analysis) to be complete and was concentrated under reduced pressure. The resulting residue was chromatographed on silica (hexanes) to afford 118 mg (94%) of 403 as a clear, colorless oil. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.40-7.03 (m, 5H), 5.17 (dd, 1H, $J = 15.2, 7.8$ Hz), 5.08 (dd, $J = 15.2, 8.0$ Hz), 3.55-3.35 (m, 2H), 1.98-1.68 (m, 1H), 1.66-1.54 (m, 1H), 1.21-1.00 (m, 2H), 0.90 (s, 9H), 0.95-0.31 (m, 11H), 0.30-0.18 (m, 1H), 0.18-0.02 (m, 4H), 0.05 (s, 6H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 132.5, 129.5, 128.3, 125.7, 125.5, 125.4, 66.7, 26.6, 26.0, 25.0, 22.0, 20.1, 19.5, 18.6, 18.4, 18.1 (2), 16.7, 11.6, 8.4, 8.2, 8.1, 7.8, -5.1.

1-Benzoyloxy-2-hydroxymethyl-(1R,2R)-cyclopropane (404)

Into 200 mL of diethyl ether was dissolved 1.1 g (10.7 mmol) of $\text{bis}$-hydroxymethylcyclopropane 305 and 15 mL (107.6 mmol) of triethylamine was added. To this stirring solution was added in a drop-wise fashion 1.25 mL (10.7 mmol) of benzoyl chloride. The reaction was allowed to stir for 2 hours, the solvent was removed under reduced pressure and the residue was chromatographed on silica (2:1, hexanes : diethyl ether) to afford 770 mg (35%) of 404 as a clear, colorless oil. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 8.1-7.9 (m, 2H), 7.61-7.51 (m, 1H), 7.50-7.40 (m, 2H), 4.29-4.15 (m, 2H), 3.61-3.45 (m, 2H), 1.70 (s, 1H), 1.29-1.15 (m, 2H), 0.75-0.55 (m, 2H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 166.7, 133.0, 130.3, 129.6, 128.4, 68.2, 66.0, 19.9, 15.7, 8.6.

1-Benzoyl-2-ethenyl-(1R,2S)-cyclopropane (405)

Into a 1000 mL round-bottomed flask were combined 765 mg (3.7 mmol) of cyclopropylmethanol 404, 1.3 g (11.1 mmol) of NMO, and 1.85 g of powdered 4Å
molecular sieves. The flask was charged with 500 mL of methylene chloride and a catalytic amount (~30 mg) of TPAP was added. The reaction was allowed to stir at ambient temperature for 4 hours and was monitored by TLC. The mixture was filtered through silica and the silica was rinsed with excess diethyl ether. The resulting solution was concentrated and the residue was dissolved in 10 mL of THF (solution 1). In a separate flask, 2.64 g (7.4 mmol) of methyltriphenylphosphonium bromide was dissolved in 100 mL of THF and 10.1 mL (7.4 mmol) of a 0.73 M solution of methyl lithium in hexane was added slowly. The reaction mixture was allowed to stir for 30 minutes during which time a canary yellow color developed. Solution 1 was added and the reaction mixture was allowed to stir for an additional 30 minutes, at which time TLC analysis indicated the reaction was complete. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous phase was extracted thrice with 20 mL of diethyl ether. The combined extracts were dried over MgSO₄ and the concentrated residue was chromatographed on silica (hexanes) to provide 530 mg (71%) of 405 as a clear, colorless oil. ¹H NMR (360 MHz, CDCl₃) δ 8.15-8.00 (m, 2H), 7.61-7.52 (m, 1H), 7.50-7.41 (m, 2H), 5.45 (ddd, 1H, J = 17.1, 10.1, 8.4 Hz), 5.09 (d, 1H, J = 17.1 Hz), 4.91 (d, 1H, J = 10.1 Hz), 4.26 (dd, 1H, J = 11.5, 7.0 Hz), 4.19 (dd, 1H, J = 11.5, 7.1 Hz), 1.57-1.47 (m, 1H), 1.45-1.30 (m, 1H), 0.95-0.74 (m, 2H); ¹³C NMR (90 MHz, CDCl₃) δ 166.7, 140.1, 132.9, 130.4, 129.6, 128.3, 112.8, 68.1, 20.9, 19.3, 12.0.

**E-1,2-bis-(2-Benzoyloxymethyl-(1S,2R)-cyclopropane)ethylene (406)**

Into a 250 mL round-bottomed was quickly weighed 91 mg (5 mol%) of Grubbs’ catalyst [(Cy₃P)₂Cl₂Ru=CHPh], which was immediately placed under an inert atmosphere. To
this flask was added a 100 mL methylene chloride solution containing 450 mg (2.2 mmol) of vinyl cyclopropane 405. The flask was swiftly equipped with a condenser, and the reaction was brought to reflux. Another 91 mg (5 mol%) portion of Grubbs’ catalyst was added after 8 hours. The reaction was allowed to reflux for an additional 8 hours, at which time TLC analysis indicated only a small amount of starting material remained. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica\textsuperscript{168} (6:1, hexanes: diethyl ether) to provide 262 mg (64%; 11.3:1, E:Z) of 406 as a clear colorless oil. \([\alpha]_D = -13.77\) (c. .0094, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta 8.13-8.00\) (m, 4H), 7.62-7.51 (m, 2H), 7.50-7.40 (m, 4H), 5.18 (m, 2H), 4.29-4.20 (m, 2H), 4.18-4.12 (m, 2H), 1.46-1.38 (m, 2H), 1.33-1.23 (m, 2H), 0.85-0.63 (m, 4H); \(^13\)C NMR (90 MHz, CDCl\(_3\)) \(\delta 166.7, 132.9, 131.2, 130.5, 129.6, 128.3, 68.3, 19.8, 19.1, 11.9.\)

\(1\text{-t-Butyldimethylsiloxy}3\text{methyl-12-(E-2-(methy}lbenzoyl-(1S,2R)-cyclopropyl)ethenyl)-(1R,3S,4R,6S,7R,9S,10S,12R)-tetrakis-cyclopropane (407)\)

Into a 50 mL round-bottomed flask were combined 97 mg (0.29 mmol) of vinyl-tetrakis-cyclopropane 402 and 220 mg (0.58 mmol) of dicyclopentylethylene 406. The mixture was dissolved into 20 mL of methylene chloride. To this stirring solution was added 12 mg (5 mol%) of Grubbs’ catalyst [(Cy\(_3\)P)\(_2\)Cl\(_2\)Ru=CHPh]. The reaction was refluxed under an inert atmosphere for 24 hours, at which time TLC analysis indicated the reaction was complete. The reaction mixture was concentrated under reduced pressure and the resulting residue was chromatographed on silica (25:1, hexanes: diethyl ether) to afford 121 mg (82%) of 407 as a clear colorless oil. \([\alpha]_D = -109.38\) (c. 0.00256, CDCl\(_3\)); \(^1\)H
NMR (360 MHz, CDCl₃) δ 8.12-8.01 (m, 2H), 7.60-7.51 (m, 1H), 7.50-7.41 (m, 2H), 5.1 (m, 2H), 4.34-4.21 (m, 1H), 4.19-4.08 (m, 1H), 3.52-3.38 (m, 2H), 1.67-1.53 (m, 1H), 3.52-3.38 (m, 1H), 1.35-1.20 (m, 3H), 1.10-1.01 (m, 1H), 0.98-0.66 (m, 5H), 0.89 (s, 9H), 0.65-0.48 (m, 3H), 0.43-0.32 (m, 2H), 0.30-0.05 (m, 4H), 0.04 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 166.7, 132.8, 132.3, 130.5, 129.6, 128.9, 128.3, 68.4, 66.7, 26.0, 21.9, 20.9, 20.0, 19.8, 19.5, 19.0, 18.6, 18.4, 18.1 (2), 11.8, 11.5, 8.2, 8.1, 7.7, 0.01, -5.1.

1-β-Butyldimethylsiloxymethyl-12-(E-2-hydroxymethyl-(1S,2R)-cyclopropyl)ethenyl)-(1R,3S,4R,6S,7R,9S,10S,12R)-tetrakis-cyclopropane (408)

Into 5 mL of methanol was dissolved 57 mg (0.11 mmol) of benzoate ester 407. To this solution was added 1 mL of 1M KOH in methanol. The reaction was stirred vigorously for 1 hour and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 2 mL of DI H₂O and extracted with ten 5 mL portions of diethyl ether. The combined organic extracts were dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was chromatographed on silica (2:1, hexanes : diethyl ether; Rₜ = 0.15) to provide 39 mg (89%) of 408 as a colorless oil found to be 86% ee.¹²⁵b [α]D = -148.0 (c. 0.010, CH₂Cl₂); ¹H NMR (360 MHz, CDCl₃) δ 5.04 (m, 2H), 3.65-3.35 (m, 4H), 1.48-1.18 (m, 3H), 1.17-0.96 (m, 2H), 0.89 (s, 9H), 0.82-0.45 (m, 8H), 0.42-0.33 (m, 2H), 0.29-0.17 (m, 2H), 0.16-0.03 (m, 4H), 0.04 (s, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 132.0, 129.3, 66.7, 66.6, 26.0, 22.8, 21.9, 20.0, 19.5 (2), 18.6, 18.4, 18.1 (3), 11.5, 11.4, 8.4, 8.2, 7.8, 0.01, -5.1.
APPENDIX A

REFERENCES


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38 For Reference: the coupling constants found in the spectra for diethyl (1-methyl-2-oxopropyl)phosphonate for the methyl carbon $^{2}J_{PC} = 6.5$ Hz and methine carbon $^{1}J_{PC} = 125.9$ Hz.


Note: The actual amount of diethylzinc that is added is less than the expected amount due to an unavoidable reaction with either atmospheric oxygen or water. Therefore the ratio of diethylzinc to substrate is actually smaller than expected.


a) Simmons, H. E.; Smith, R. D., J. Am. Chem. Soc. 1958, 80, 5323.

b) Simmons, H. E.; Simth, R. D., J. Am. Chem. Soc. 1959, 81, 4256.


87 Reported routes to bis-cyclopropane:


Procedures for the preparation of mon-substituted bis-cyclopropanes:


88 Reported procedures to bis-cyclopropane:


Reported routes to mono-substituted bis-cyclopropanes:


Reported procedures to bis-cyclopropane:


Reported routes to mono-substituted bis-cyclopropanes:


BASF, patent # DE 640782, 1962; *Chem. Abstr.* 1965, 63, 1769f.


134 It is worthy of note that if care is not taken to keep the alcohol concentration below 0.022 N, a dimer similar to that observed by McDonald competes with the desired aldehyde formation. McDonald, W. S., M. S. Thesis, University of New Hampshire, 1995.


Homodimerizations are typically low yielding, thought to result from decomposition of the methylidene ruthenium species (L₄Ru=CH₂). This adapted procedure for homo-dimerization was reported by Schreiber. Diver, S. T.; Schreiber, S. L., *J. Am. Chem. Soc.* 1997, *119*, 5106.


This optical rotation correlates with a 3.95% ee as compared with the values found in McDonald, W. S., M. S. Thesis, University of New Hampshire, 1995.

Hexadiendiol is marginally soluble in hot methylene chloride and immediately prior to addition, solution 1 was heated on a steam bath. Concurrent with the addition of solution 1 to the reaction, a crystalline precipitate formed.

The sample was purified by chromatography and provided NMR spectra in concert with those reported by McDonald: McDonald, W. S., M. S. Thesis, University of New Hampshire, 1995.

162 When n-butyl lithium was employed, the reaction produced a complex mixture of products that appeared to result predominantly from $S_N2$ type chemistry at the peripheral isopropylidene acetals.

163 Personal Communication with Doug Taber, Univ. of Delaware: The ethyl acetate solution resulting from rinsing the salt-cake should be distilled immediately to prevent low yields due to *trans*-esterification.

164 According to values obtained by reported by McDonald this value correlates to a 160 %ee.

165 In light of the results of the NMR studies described in chapter 1, the reversal of normal reagent addition seemed to be warranted and was found to yield excellent results.


167 This rotation correlates with a 61.4% ee according to McDonald. McDonald, W. S., M. S. Thesis, University of New Hampshire, 1995.

168 The catalyst was found to co-elute on silica with the product, and several sequential columns were required in order to remove the catalyst, observable by a purple hue. The catalyst slowly decomposes on silica, which enables its removal from the product.
\[(\text{H}_3\text{CH}_2\text{CO})_2\text{P} \]
$\text{(H}_3\text{CH}_2\text{CO})_2\text{P}$
1. Sulfur Ylide
2. DIBAL-H
1. Sulfur Ylide
2. DIBAL-H