Tandem Metathesis-Based Natural Product Synthesis &
Synthesis of Cyclopropenes and Their Rearrangements

BY

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THESIS

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This thesis is dedicated to my parents Jiming Li and Haixian Fang, and my wife Chunrui Sun, without whom it would have never been accomplished.
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<td>Acetyl</td>
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<tr>
<td>Ar</td>
<td>Aryl</td>
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<td>Azobis(isobutynitrile)</td>
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<td>9-Borabicyclo[3.3.1]nonane</td>
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<td>bda</td>
<td>Benzyldene acetone</td>
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<td>Butylated hydroxy toluene (2,6-di-t-butyl-4-methylphenol)</td>
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<td>2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl</td>
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<td>Butyl</td>
</tr>
<tr>
<td>tBu</td>
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<td>Ceric ammonium nitrate</td>
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<td>cat.</td>
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<td>Carbon-13 Nuclear Magnetic Resonance</td>
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<td>Pentamethylene cyclopentadienyl</td>
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<td>δ</td>
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<td>de</td>
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<td>DIAD</td>
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<td>DIBAL</td>
<td>(DIBAH) Diisobutylaluminum hydride</td>
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<td>DMF</td>
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<td>DMPU</td>
<td>N,N'-Dimethyl-N,N'-propylene urea</td>
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<td>dr</td>
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<td>ee</td>
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<td>LHMDS</td>
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<td>rt</td>
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<td>Tetra-(n)-butylammonium difluorotriphenylsilicate</td>
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<td>Tetramethylsilane, also Trimethylsilyl</td>
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<td>Z</td>
<td>Zusammen (together, (cis))</td>
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TANDEM METATHESIS-BASED NATURAL PRODUCT SYNTHESIS & SYNTHESIS OF CYCLOPROPENES AND THEIR REARRANGEMENTS

SUMMARY

This thesis contains two parts. Part I is about the development and application of tandem metathesis reactions to the synthesis of natural products, which is comprised of first four chapters. Part II is about the synthesis of silylated cyclopropenes and their rearrangement to allenes, which are described in last three chapters, respectively.

In the four chapters of Part I, the chapter 1 surveys briefly the recent development in the application of tandem metathesis to natural product synthesis. The chapter 2 depicts total syntheses of four epoxyquinoid natural products by employing enyne metathesis-based tandem reactions as key steps, in which concise total syntheses of (+)-Asperpentyn, (-)-Harveynone, and (-)-Tricholomenyn A were achieved by using a relay metathesis-induced enyne ring-closing metathesis (RCM) and metallocyclic [1,3]-shift tandem sequence, and the total synthesis of (+)-Panepophenanthrin was accomplished by using a tandem reaction involving relay metathesis-induced enyne RCM followed by cross-metathesis (CM). The chapter 3 demonstrates a highly diastereoselective ring-rearrangement metathesis (dRRM) of symmetric cyclopentene derivatives to construct the cyclohexene skeletons containing an all-carbon quaternary stereogenic center. And a total synthesis of (±)-nitramine and the synthetic efforts towards galanthamine and caribenol A using this dRRM methodology, are also presented in this chapter. The chapter 4 describes details of the experiments in Part I.

In Part II, chapter 5 discloses an unprecedented cyclopropenation reaction involving Cα-Si bond insertion wherein alkylidene carbenes derived from α-silyl ketones selectively insert into more electron-rich Cα–Si bond. Chapter 6 mainly discusses transition metal-catalyzed ring opening of cyclopropenes, including the development of a novel PtCl₂-catalyzed rearrangement of silylated cyclopropenes to the corresponding allenes and the preliminary results regarding PtCl₂-catalyzed dimerization of 1-alkylcyclopropene 3-carboxylates to trienes. The experiments about Part II are detailed in the chapter 7.
PART I
TANDEM METATHESIS-BASED NATURAL PRODUCT SYNTHESIS
Chapter 1. Tandem metathesis in total synthesis of natural products

Olefin metathesis is a synthetic transformation in which carbon-carbon double bonds are cleaved and then reassembled to generate products containing new carbon-carbon double bonds.\(^1\) Since its discovery in 1950’s,\(^2\) olefin metathesis has evolved into one of the most versatile, powerful, and reliable reactions in organic synthesis.\(^1\)

Olefin metathesis was initially conducted with heterogeneous catalysts, such as WCl\(_6\)/SnMe\(_4\) or \(n\)-BuLi,\(^3\) and Re\(_2\)O\(_7\)/Al\(_2\)O\(_3\).\(^4\) While they are highly active, these catalysts have exceedingly low functional group tolerance due to their Lewis acidic nature. Also, very little is known about the nature of the actual catalytic species in these systems. Early olefin metathesis mechanistic study greatly promotes the development of new catalytic systems.\(^5\) In 1971, Chauvin and coworkers proposed a generally accepted mechanism for the transition metal-catalyzed olefin metathesis, which invokes metal carbene (metal alkylidene) intermediates as key propagating species in the catalytic cycle.\(^6\) In this mechanism, a metal alkylidene first reacts with an olefin substrate, forming a metalloyclobutane intermediate via \([2+2]\) cycloaddition. The metalloyclobutane then cleaves to yield a new metal alkylidene derived from the starting olefin substrate via a retro \([2+2]\) cycloaddition. This new metal alkylidene reacts with a new olefin substrate to form another metalloyclobutane intermediate, which undergoes \([2+2]\) cycloreversion to produce an internal alkene product and regenerate the metal alkylidene as catalyst to reenter the catalytic cycle. On the basis of the Chauvin’s mechanism, Katz and coworkers found the first single-component and well-defined catalyst.\(^7\) Since then, various well-defined homogenous catalysts have emerged. Among them, the most representative catalysts are ruthenium-based Grubbs catalysts\(^8\) and molybdenum or tungsten-based Schrock catalysts\(^9\) (Figure 1.1). Their widespread use in organic chemistry is due to their tolerance of various functional groups combined with their efficiency. Usually Grubbs catalysts are preferred over Schrock catalysts from a synthetic standpoint because of easy handling in air. However, Schrock catalysts are more reactive and have been utilized for asymmetric metathesis.\(^10\) In 2005, the Nobel Prize in Chemistry was awarded to Yves Chauvin, Robert H. Grubbs,
and Richard R. Schrock in recognition of their contribution to elucidation of the reaction mechanism and
discovery of a variety of highly efficient and selective catalysts for olefin metathesis.\textsuperscript{11}

Based on the features of the structural change induced by the metathesis reaction, olefin
metathesis can be classified into five categories: cross metathesis (CM), ring-closing metathesis (RCM),
ingo-opening metathesis (ROM), ROM polymerization (ROMP), and acyclic diene metathesis
polymerization (ADME) (\textbf{Scheme 1.1}). All of these olefin metatheses have been utilized both
academically and industrially in many research fields.\textsuperscript{1}

\textbf{Figure 1.1}

\textbf{Scheme 1.1}
In addition to olefin metathesis, enyne metathesis\textsuperscript{12} (metathesis between an olefin and an alkyne) and alkyne metathesis\textsuperscript{13} (metathesis between two alkynes) are also known, which gained increased interests lately (Scheme 1.2).

\begin{align*}
\text{Diene metathesis} \\
\begin{array}{c}
\text{M} \\
\text{A} \\
\text{B} \\
\text{C}
\end{array} + \begin{array}{c}
\text{M} \\
\text{A} \\
\text{C} \\
\text{B}
\end{array} \xrightarrow{\text{cyclo-addition}} \begin{array}{c}
\text{M} \text{C} \\
\text{A} \\
\text{B}
\end{array} \xrightarrow{\text{cyclo-reversion}} \begin{array}{c}
\text{M} = \text{C} \\
\text{A} \\
\text{B}
\end{array}
\end{align*}

\begin{align*}
\text{Enyne metathesis} \\
\begin{array}{c}
\text{M} \\
\text{A} \\
\text{C} \\
\text{B}
\end{array} + \begin{array}{c}
\text{M} \\
\text{A} \\
\text{B}
\end{array} \xrightarrow{\text{cyclo-reversion}} \begin{array}{c}
\text{M} \text{C} \\
\text{A} \\
\text{B}
\end{array} \xrightarrow{\text{cyclo-reversion}} \begin{array}{c}
\text{M} = \text{C} \\
\text{A} \\
\text{B}
\end{array}
\end{align*}

\begin{align*}
\text{Diyne metathesis} \\
\begin{array}{c}
\text{M} \\
\text{A} \\
\text{C} \\
\text{B}
\end{array} + \begin{array}{c}
\text{M} \\
\text{A} \\
\text{B} \\
\text{C}
\end{array} \xrightarrow{\text{cyclo-reversion}} \begin{array}{c}
\text{M} \text{C} \\
\text{A} \\
\text{B}
\end{array} \xrightarrow{\text{cyclo-reversion}} \begin{array}{c}
\text{M} = \text{C} \\
\text{A} \\
\text{B}
\end{array}
\end{align*}

Scheme 1.2

Tandem reactions are the processes that involve a consecutive sequence of reactions by which many bond-forming and breaking events are achieved in one single synthetic operation.\textsuperscript{14} They are atom- and step-economical\textsuperscript{15} and are environmentally more benign than the corresponding step-by-step operations because they require fewer steps of isolation and purification and thus generate reduced amounts of chemical waste. Furthermore, tandem reactions often allow an efficient access to complex product structures that are not easily obtained via conventional operations. Therefore, the development of tandem reactions should have a significant ramification in efficient synthetic strategy development and green chemistry and remains a highly pursued goal in organic chemistry.\textsuperscript{16}

Because the elementary steps of the widely-accepted mechanism of metal carbene-catalyzed metathesis are common to all metathesis processes (except diyne metathesis, see Scheme 1.2), it is possible to concatenate them, through which structurally intricate compounds may be constructed rapidly from relatively simple starting materials in one pot. In the past decades, much effort has been made in
developing such tandem metathesis and applying them to the synthesis of complicated organic molecules including biologically active natural products.\textsuperscript{2k,12k}

1.1. Diene metathesis-based tandem reaction in total synthesis of natural products

1.1.1. ROM–RCM (Ring-rearrangement metathesis)

Among the possible combinations of three basic olefin metathesis reactions, the combination of ring-opening metathesis (ROM) and ring-closing metathesis (RCM), in particular, has proved to be a powerful and efficient method to construct carbo- and heterocycles. In 1996, Grubbs group published the first example of ROM-RCM tandem reaction.\textsuperscript{17} In 1999, Blechert put forward a term “ring-rearrangement metathesis (RRM)” to describe this type of tandem metathesis.\textsuperscript{18} In this tandem metathesis reaction, usually a strained cycloalkene is transformed into a new cycloalkene by a combination of ROM and RCM with an tethered alkene. These reversible processes are driven by thermodynamic factors including loss of ring strain, substitution pattern, or release of a volatile olefin, and kinetic factors, such as the formation of a less reactive carbene complex. During RRM, the stereochemistry is transferred completely from the starting material to the product, which makes RRM a rapid and flexible access to complex molecular framework.

In 2000, Blechert and coworkers applied this strategy to the synthesis of alkaloid tetraponerines T4, T6, T7 and T8.\textsuperscript{19} As a representative example shown in Scheme 1.3, treatment of 1-1 with Grubbs first- generation catalyst (5 mol%) in dichloromethane resulted in almost quantitative yield of the corresponding tetrahydropyridine product 1-2 with complete transfer of chirality, which was then elaborated to tetraponerine T4.

Scheme 1.3
In 2004, Mariano and coworkers utilized a regioselective RRM reaction of unsymmetrically protected aminocyclopentenediols 1-3 and 1-5 to finish the syntheses of (+)-castanospermine and (−)-swainsonine, respectively (Scheme 1.4). Under the same reaction condition, two diastereomers 1-3 and 1-5 delivered two different regioisomers, which could be ascribed to the energy difference between two possible tricyclic ruthenacyclobutane intermediates.20

Scheme 1.4

Synthesis of tetrahydropyridine derivatives could be achieved not only from RRM of cyclopentenes but also cyclohexenes since the resulting heterocycle is thermodynamically more favorable than the corresponding cyclohexene. In 2005, Blechert and coworkers synthesized a frog alkaloid, (+)-trans-195A, featuring a RRM of six-membered cycloolefin (Scheme 1.5).21 Exposure of 1-7 to 5 mol% Grubbs first-generation catalyst in dichloromethane smoothly delivered the disubstituted tetrahydropyridine 1-8 in almost quantitative yield, which was further elaborated to the natural product.

Scheme 1.5
Norbornenes are suitable substrates for RRM due to their strained nature, which makes them more reactive and allows for the synthesis of fused bicyclic compounds with well-defined relative stereochemistry. In 2004, Aubé and coworkers applied RRM of norbornene derivative as key step to accomplish the total synthesis of alkaloid 251F. Treatment of 1-9 with Grubbs first-generation catalyst (5 mol%) in dichloromethane under ethylene atmosphere afforded diquinane 1-10 after an overall [2.2.1] to [3.3.0] skeletal rearrangement (Scheme 1.6). In 2005, Phillips and Chandler used RRM of 7-oxa-norbornene derivative to complete the synthesis of trans-kumausyne. Likewise, Hoveyda and Schrock utilized RRM of norbornene skeleton in the synthesis of (+)-africanol. In their approach, an enantioselective RRM of 1-11 was demonstrated by a chiral molybdenum complex 1-13 (Scheme 1.7).

Scheme 1.6

Scheme 1.7

A very recent example of RRM of a norbornene derivative in total synthesis of natural product is reported by Fukuyama and coworkers (Scheme 1.8). In their synthesis of (−)-isoschizogamine, they
treated 1-14 with the highly reactive Stewart-Grubbs catalyst 1-16 in the presence of 1,6-heptadiene in benzene at 60 °C to afford 1-15 in 73% yield.

Scheme 1.8

1.1.2. RCM–ROM–RCM

Normally, the ROM–RCM sequences in RRM end up with the alkylidene exchange between newly formed metal alkylidene complex and substrate or ethylene to form the final product and regenerate the active catalyst. If other double bonds are available in the substrate, the extension of the tandem sequences could be made. Blechert and coworkers employed this strategy as a key step for the total syntheses of a variety of structurally diverse alkaloids including (+)-dumetorine,26 (+)-astrophylline37 and (+)-dihydrocuscohygrine28 (Scheme 1.9). Although the migration of the double bond in 1-18 into α,β-unsaturated ester is required for the completion of (+)-dumetorine, cyclopentene derivatives 1-17 was chosen as metathesis substrate. In the presence of titanium isopropoxide (30 mol%), the tandem metathesis of triene 1-17 generated the desired bicycle 1-18 in 80% yield. Similarly, substrates 1-19 and 1-21 were converted to the corresponding metathesis products 1-20 and 1-22, respectively, which were further elaborated to the target natural products.
Similarly, Phillips and Pfeiffer applied this RCM–ROM–RCM cascade sequence to their synthesis of (+)-cyanthiwigin U. In this case, a [2.2.2] bicyclic metathesis precursor 1-23 was treated with the Grubbs-II catalyst, leading to the formation of a fused tricyclic compound 1-24 having two all-carbon quaternary stereogenic centers (Scheme 1.10).

Scheme 1.10

1.1.3. ROM–RCM–CM

Cross metathesis can also be combined with ROM–RCM sequences. Often CM has some limitation and problems, such as Z/E selectivity and chemoselectivity, so the choice of suitable substrates and catalysts becomes important. In the synthesis of quinolizidine alkaloid (-)-lasubine II, treatment of cyclic enone 1-25 with 5 mol% Grubbs second-generation catalyst and 3 equivalents of styrene 1-26
resulted in the formation of $E$-isomeric product 1-27 in decent yield (Scheme 1.11).\(^{30}\) The major byproduct came from cross metathesis between 1-25 and 1-26. Worthy to note is that they did not choose cyclopentene 1-28 as substrate since the bulky TBDMS group may have an adverse steric hindrance on cross metathesis.

\[
\begin{align*}
\text{1-25} & \quad + \quad \text{1-26} & \quad \text{GnI (5 mol\%)} & \quad \text{DCM, reflux} & \quad \text{1-27} \\
\text{1-28} & \quad \quad & \quad & \quad & \quad \text{(-)-Lasubine II}
\end{align*}
\]

Scheme 1.11

In 2006, Phillips and coworkers also adopted this ROM–RCM–CM strategy for the syntheses of (+)-cylindramide A and the core of (+)-geodin A (Scheme 1.12).\(^{31}\) They obtained bicyclic product 1-31 with a desired side chain after exposure of the norbornene derivative 1-29 and terminal olefin 1-30 to metathesis condition.

\[
\begin{align*}
\text{1-29} & \quad + \quad \text{1-30} & \quad \text{GnI (4 mol\%)} & \quad \text{DCM, reflux} & \quad \text{1-31} \\
\text{1-31} & \quad \quad & \quad & \quad & \quad \text{(+)Geodin A} & \quad \text{(+)-Cylindramide A}
\end{align*}
\]

Scheme 1.12
1.1.4. RCM–CM

Relay metathesis is one of the best starting points for tandem metathesis process, by which the
metathesis can be initiated indirectly at sterically hindered olefins or other unreactive olefins with the
extrusion of a kinetically favorable five-membered ring. The concept of relay metathesis was developed
by Hoye\textsuperscript{32} and Lee,\textsuperscript{33} respectively, in 2004. Several years later, this relay RCM–CM sequence was nicely
implemented by Kim \textit{et al.} in their synthesis of (Z)-laureatin, where the Z-1,3-enyne moiety of \textit{1-34} was
effectively constructed from the CM of \textit{1-32} and \textit{1-33} using bispyridine substituted ruthenium catalyst,
so called Grubbs third-generation catalyst (\textit{Scheme 1.13}).\textsuperscript{34}

\begin{center}
\textbf{Scheme 1.13}
\end{center}

1.1.5. ROM–CM

ROM–CM sequence usually needs a small-sized endocyclic olefin as substrate. The driving force
of this tandem process is release of ring strain and formation of a thermodynamically stable product.
Snapper and Limanto constructed the characteristic tricyclic core structure of (+)-asteriscanolide using a
ROM–CM followed by a Cope rearrangement (\textit{Scheme 1.14}).\textsuperscript{35} They treated the highly strained
cyclobutene \textit{1-35} with Grubbs second-generation catalyst (5 mol\%) in refluxing benzene under ethylene
atmosphere, initially affording a ROM–CM intermediate \textit{1-36}, which then underwent a [3,3]-sigmatropic
rearrangement under the metathesis condition to yield tricyclic compound \textit{1-38}. 
Scheme 1.14. Reagents and conditions: (a) G-II (5 mol%), H₂C=CH₂ (1 atm), benzene, 50-80 °C, 74%; (b) PCC, 4Å M.S., DCM, rt, 79%.

Following the same principle, a substituted olefin could be employed as a cross metathesis partner instead of ethylene gas. In 2004, Kozmin and coworkers employed a ROM–CM sequence of cyclopropenone acetal 1-39 with olefin 1-40 in their synthesis of bistramide A (Scheme 1.15). Treatment of a mixture of terminal olefin 1-38 and cyclopropene acetal 1-39 (1.5 equiv) with G-II catalyst (10 mol%) in benzene at 70 °C followed by acidic hydrolysis of the crude metathesis product led to divinyl ketone 1-41 in 63% yield.

Scheme 1.15. Reagents and conditions: (a) G-II (10 mol%), benzene, 70 °C; (b) aq. H₂SO₄, MeCN, 0 °C, 63% overall yield, E/Z = 3:2; (c) 1-42, G-II (10 mol%), DCM, 36 °C, 68%.
1.1.6. Olefin metathesis–nonmetathesis sequence

Along with the development of metathesis chemistry, non-metathetic catalytic reactivities of ruthenium alkylidene-oriented complexes have attracted chemists’ considerable attention. Thus, a variety of metathesis-nonmetathesis tandem processes were developed. In 2001, Grubbs group demonstrated a “one-pot” synthesis of \((R)-(\text{–})\)-muscone, a principal classical source of musk odors (Scheme 1.16).\(^{37}\) In this synthesis, RCM of the readily available diene 1-44 afforded macrocyclic alcohol 1-45, which was then treated with 3-pentanone and NaOH to initiate a Ru-catalyzed transfer hydrogenation, affording the ketone 1-46. Unsaturated ketone 1-46 was subsequently exposed to \(\text{H}_2\) atmosphere to deliver \((R)-(\text{–})\)-muscone in 56% overall yield.

![Scheme 1.16](image.png)

**Scheme 1.16. Reagents and conditions:** (a) G-II (7 mol%), mesitylene (0.4 equiv.), DCE, 50 °C, 74%; (b) NaOH, 3-pentanone, DCE, reflux, 76%; (c) \(\text{H}_2\) (800 psi), 80 °C, 100%.

1.2. Enyne metathesis-based tandem reaction in total synthesis of natural products

Unlike diene and diyne metatheses that regenerate the same functionality present in the starting material, enyne metathesis creates a new functionality, 1,3-diene from the union of an alkene and an alkyne. In enyne metathesis, two distinctive propagating species are involved, alkylidene and vinyl alkylidene, to form 1,3-diene product. Once formed, the 1,3-diene becomes a versatile intermediate to undergo further reactions in a non-metathetic manner\(^{12k}\) such as Diels-Alder cycloaddition\(^{38}\), cyclopropanation\(^{39}\) and hydrovinylation\(^{40}\). On the other hand, the vinyl alkylidene can be engaged in subsequent steps to allow additional metathesis depending on the nature of substrates. These characteristics provide an outstanding opportunity for the development of tandem enyne metathesis reactions to form multiple bonds and polycyclic systems from simpler precursors.
1.2.1. Multiple enyne RCM

In 1998, Grubbs and co-workers demonstrated one of the earliest examples of tandem enyne RCM reactions with carefully designed substrate 1-47 to generate tetracarbocyclic polyene 1-48 in a highly regiocontrolled mode (Scheme 1.17).\(^{41}\) The reaction was assumed to initiate from the terminal alkene to form ruthenium alkylidene that reacts with an appropriate internal alkyne to close the first ring and generate a vinyl alkylidene. The preformed vinyl alkylidene was allowed to react with another alkyne and repeat the similar RCM events until the termination with olefin RCM. In this reaction, each alkyne functional group serves as a metathesis relay unit.

![Scheme 1.17](image1.png)

1.2.2. Enyne RCM–diene RCM

If the preformed vinyl alkylidene in enyne RCM is intercepted intramolecularly by another appropriately located olefin, in most of the cases, a fused bicyclic ring system could be obtained through a tandem enyne RCM–Diene RCM sequence. Obviously, this type of tandem metathesis requires a dienyne substrate, so it is also called dienyne metathesis. In dienyne metathesis, a group selectivity issue may arise because two discrete alkylidenes could be generated in the initiation step (when \(X \neq Y\)), which then undergo tandem ring closure to form respective products A and B (Scheme 1.18).\(^{42}\)

![Scheme 1.18](image2.png)
In 1994, Grubbs and coworkers first reported a highly selective dienyne metathesis by replacing one of two terminal alkenes with a 1,2-disubstituted alkene. This result is consistent with the earlier study in diene metathesis, in which the reactivity of any alkene in a metathesis decreases when alkyl substituents are introduced on or near the alkene. By applying this strategy to their synthetic approach to thapsigargin, Kaliappan and co-workers observed that the RCM of dienyne 1-49 containing a methyl substituted olefin and terminal olefin afforded only the tandem RCM product 1-50 in high yield (Scheme 1.19).

![Scheme 1.19](image)

Honda and co-workers utilized a similar dienyne RCM of 1-51 in the synthesis of (−)-securinine. A selective initiation of the RCM from the less hindered alkene yielded 1-52 in 74% yield in the presence of catalyst 1-53, a more active version of GH-II (Scheme 1.20).

![Scheme 1.20](image)

Another example of selective dienyne metathesis using steric differentiation has been reported by Hanna and coworkers in their synthesis of guanacastepene A. They constructed the tricyclic skeleton 1-55, a pivotal intermediate toward guanacastepene A, by treating dienyne 1-54 with the G-II catalyst in refluxing CH$_2$Cl$_2$ (Scheme 1.21).
Scheme 1.21

For the total syntheses of (–)-acylfulvene and (–)-irofulven, Movassaghi et al. employed a dienyne RCM of trienyne 1-56 with G-II catalyst to generate dihydrooxasilepine 1-57, which was further converted to an advanced intermediate triol 1-58 by deprotection in high yield (Scheme 1.22).47

Scheme 1.22

Most recently, Metz and Schubert utilized a tandem dienyne RCM reaction by which substrate 1-59 was effectively cyclized to the tetracyclic core 1-60 of kempene-1, kempene-2 and 3-epi-kempene-1 (Scheme 1.23).48

Scheme 1.23
The initiation of enyne metathesis can be controlled by the substituent not only on the alkene but also near the alkene. Mori and Hatakeyama, respectively, implemented this group-differentiation strategy as the key step in the total syntheses of (±)-erythrocarine and (±)-erythravine (Scheme 1.24). The initiation of metathesis occurs at the kinetically favoured N-allyl group of 1-61, which then undergoes two RCMs to form the cyclic diene 1-62 from which erythrocarine and its hydroxy epimer 1-63 are generated by acetate removal.

Scheme 1.24

A coordinating group such as unprotected hydroxyl nearby the olefin could also facilitate the group selectivity. In the synthesis of ent-lepadin G, Blechert and coworkers subjected 1-64 to catalyst G-I in dichloroethane at 60 °C and isolated 1-65 in 90% without significant formation of byproducts (Scheme 1.25).

Scheme 1.25
In 2005, Lee group described a tandem dienyn RCM of alkynyl silaketals containing two tethered olefins to provide bicyclic siloxanes, which further gave stereochemically defined (1E,3Z)-dienes by removal of the silicon tether with fluoride. The RCM of 1-66 afforded siloxane 1-67, which was further treated with TBAF to provide a direct precursor of the E/Z-1,3-diene moiety of tartrolool B (Scheme 1.26).\(^5\) Similarly, the tandem enyne RCM of dienynyl silaketal 1-69 provided bicyclic siloxane 1-70, which was elaborated to E,Z-1,3-diene 1-71, the Roush’s intermediate for the total synthesis of (−)-cochleamycin A (Scheme 1.27).\(^5\)
Very recently, Parker and Lee reported a formal asymmetric total synthesis of englerin A using relay RCM induced–enyne RCM–diene RCM tandem sequence (Scheme 1.28).54 Linear substrate 1-72 was converted to Δ4,6-guaiadiene-9,10-diol derivative 1-73, which is disubstituted on both ends and contains a tetrasubstituted olefin and was further elaborated to an advance intermediate 1-74.

Scheme 1.28

1.2.3. Enyne RCM–diene CM sequence

If the preformed vinyl alkylidene in enyne RCM is intercepted by another olefin intermolecularly, a substituted 1,3-diene could be formed through a enyne RCM–diene CM sequence. Martin and coworkers applied this tandem strategy involving RCM–CM of 1-75 to the total synthesis of (+)-8-epi-xanthatin (Scheme 1.29).55 Recently, Kim and coworkers also achieved efficient synthesis of piperidine-containing sphingoid base analogues via the RCM–CM sequence.56

Scheme 1.29

1.2.4. Enyne CM–diene RCM sequence

Based on the study on the RCM of tartrate-derived enyne 1-76, our group summarized a general trend of mode selectivity: the formation of small to medium sized (5 to 11) rings generally follows the exo-mode closure to generate 1-77, whereas formation of larger membered (12 to 15) rings adopts the endo-mode closure to provide 1-79 (Scheme 1.30).57 Importantly, we found, under ethylene atmosphere,
the enyne metathesis switched from RCM to CM, thereby the 1,3-diene CM product 1-78 formed first, which then underwent a diene RCM to afford exclusively the endo-mode product 1-79 with complete E-selectivity.

Scheme 1.30

Shair and co-workers\(^5\) had utilized this strategy successfully to generate a macrocycle 1-82 in the synthesis of (−)-longithorone A. This ring closure was conducted under ethylene, therefore, an enyne cross metathesis of the alkyne 1-80 with ethylene followed by RCM between the two sterically least hindered terminal double bonds in the intermediate 1-81 afforded 1-82 (Scheme 1.31). A more detailed investigation reported subsequently by the same group supports this conclusion.\(^5\)

Scheme 1.31

1.2.5. Enyne RCM–metallotropic shift

In addition to the tandem enyne metatheses that only involve basic metathesis reactions, enyne RCM–metallotropic [1,3]-shift sequence has evolved as a new tandem process. From a mechanistic standpoint, enyne RCM and metallotropic [1,3]-shift of ruthenium alkylidenes are considered to be the
same class of transformation. As shown in Scheme 1.32, metallotropic [1,3]-shift can be considered a special case of enyne RCM when the tether size between the carbene carbon and the alkyne becomes zero.

Scheme 1.32

In the early examples of enyne RCM of substrates 1-83 and 1-84, Lee and coworkers observed formation of two regioisomeric products 1-87 and 1-88. It was hypothesized that through the reversible metallotropic [1,3]-migration of alkylidenes 1-85 and 1-86, formation of a more conjugated system 1-88 is favored but sterically hindered substituents such as triethylsilyl group, retarded or prohibited the [1,3]-shift, generating a cross-conjugated product 1-87 (Scheme 1.33). This hypothesis was confirmed by the formation of fully conjugated products 1-89–1-91 from substrates that contain hydrogen or alkyl substituents at the terminal position of the 1,3-diynes.

Scheme 1.33
This enyne metathesis and metallotropic [1,3]-shift sequence was effectively utilized in the total synthesis of \((3R,9R,10R)\)-panaxytriol. In the presence of the excess amount of an external alkene \(1-92\) and G-II catalyst, a tandem relay metathesis–metallotropic [1,3]-shift–cross metathesis sequence with \(1-93\) delivered 1,3-diyne-5-ene product \(1-94\) with Z-stereoselectivity, which was readily transformed to \((3R,9R,10R)\)-panaxytriol with following standard manipulations (Scheme 1.34). Later, this enyne RCM–metallotropic [1,3]-shift was also applied to the synthesis of various epoxyquinoids by us (chapter 2).

Scheme 1.34

1.2.6. Tandem enyne metathesis–nonmetathesis

Due to the chemical property of 1,3-diene functionality and ruthenium catalysts, 1,3-diene is often juxtaposed with other nonmetathesis reactions. For example, in a key step of a recent total synthesis of (+)-lycoflexine by Ramharter and Mulzer, the authors cascaded a group-selective dienyne tandem metathesis and hydrogenation (Scheme 1.35). They treated dienyne \(1-95\) with G-II catalyst to yield a moderately stable tricyclic diene \(1-96\). Without isolation, a selective hydrogenation of the cis-disubstituted double bond was executed by applying a high pressure of hydrogen gas to the reaction mixture to form \(1-97\), a pivotal intermediate for lycoflexine.
Scheme 1.35

With appropriate substituents on enyne substrates, the metathesis-derived 1,3-dienes can be further elaborated to other functional groups of interests. Kozmin and coworkers developed an RCM of silyl-protected ynoyl ethers such as 1-98, which upon removal of the silyl protecting group provided α,β-unsaturated enone 1-99. This tandem sequence was nicely implemented as the key step in the total synthesis of β-eremophilane (Scheme 1.36).65

Scheme 1.36

1.3. Summary

This brief survey reveals that a number of tandem metathesis reactions have been developed successfully and applied to the synthesis of natural products. This could be attributed to their advantages in terms of atom and step-economy, as well as gaining molecular complexity with high regio- and stereoselectivity. However, the availability of more reactive catalysts coupled with better understanding of their performance is still required to further improve the efficiency and selectivity of tandem reactions, especially for enyne metathesis-based tandem processes. Thus, with thorough study of the behaviour of propagating ruthenium-alkylidene species in various environments and elaborate design of substrates, the
logical extension of these tandem processes to the next sophisticated level of complexity will be achieved soon.
Chapter 2. Application of enyne metathesis-based tandem reaction to total synthesis of epoxyquinoids

2.1. Introduction and background

Naturally occurring epoxycyclohexanes were isolated from various organisms including fungi, bacteria, worms, and mushrooms.\textsuperscript{66} Most of these compounds display interesting pharmacological and biological properties, such as antibiotic, antibacterial and antitumor activities. Epoxyquinoid family is very important and the largest class in epoxycyclohexanes. Figure 2.1 shows some representative members in this family.

Among them, (+)-asperpentyn, (–)-harveynone and their prenylated homolog (–)-tricholomenyn A all have a 1,5-dien-3-yne moiety. (+)-Asperpentyn (2-4) was isolated from the antimicrobial extracts of \textit{Aspergillus duricaulis}.\textsuperscript{67} (–)-Harveynone (2-5) was first isolated from the mold \textit{Curvularia harveyi} and found to possess anticancer activity (inhibitor spindle formation in sea urchin eggs).\textsuperscript{68} Its enantiomer, (+)-harveynone, which was isolated from the tea gray blight fungus \textit{Psetalotiopsis theae}, shows phytotoxic activity.\textsuperscript{69} (–)-Tricholomenyn A (2-6) was isolated from the fruiting bodies of the mushroom \textit{Tricholoma acerbum} and reported to display antimiotic activity by Garlaschelli et al.\textsuperscript{70}

Panepophenanthrin (2-7) belongs to a class of structurally more complex members\textsuperscript{71} of epoxyquinoid natural products, which are generally derived from Diels-Alder dimerization of structurally simpler monomeric epoxyquinols.\textsuperscript{72} Panepophenanthrin was first isolated and fully characterized by Sekizawa and coworkers in 2002 from a mushroom strain \textit{Panus rudis} Fr. IFO8994.\textsuperscript{72a} This natural product was proven to be the first naturally occurring inhibitor of ubiquitin activating enzyme (E1). The inhibition of E1 may block the ubiquitin-proteasome pathway (UPP) and ubiquitin functions that are linked to serious diseases.\textsuperscript{73} By analysis of inhibition of E1 binding to ubiquitin, the IC\textsubscript{50} value of panepophenanthrin was determined to be 17.0 μg/mL.
The densely functionalized intricate structural characteristics and their important biological activities have made them of considerable interest to synthetic chemists.

2.2. Syntheses of (+)-asperpentyn, (−)-harveynone and (−)-tricholomenyn A by other groups

2.2.1. Approaches based on Pd-catalyzed coupling reactions

Although there have been a number of syntheses reported for epoxyquinoids bearing an acetylenic side chain at the C2 position, most synthetic approaches utilized Pd-catalyzed Sonagashira, Stille or Negishi cross coupling reactions of the preformed 2-iodo epoxycyclohexene derivatives and appropriate 1,3-enzyme partners to form 1,5-dien-3-yne moiety (Scheme 2.1). After some necessary protecting group manipulation and/or oxidation/reduction protocols, the coupling products were elaborated easily to afford the corresponding natural products. Therefore, the synthetic focal point is the preparation of those stereochemically rich and highly oxygenated 2-iodo epoxycyclohexene derivatives.
Scheme 2.1

In the past two decades, many synthetic approaches have been developed successfully to 2-halocyclohexene derivatives using the chiral pool of readily available natural products as the starting materials; utilizing enzymatic resolution of racemic mixtures, and so forth.

In 1996, Ogasawara and Kamikubo utilized the tricyclic monoacetate 2-24, derivated from enzymatic desymmetrisation of the meso-enediol precursor, as a chiral synthon of 1,4-
dihydroxy-cyclohexa-2,5-diene (Scheme 2.2). After TBDMS protection, the acetyl group was deprotected and oxidized to the enone 2-25. Stereoselective epoxidation of 2-25 using 30% hydrogen peroxide in the presence of Triton B (Trimethylbenzylammonium hydroxide) provided exo-epoxide 2-26 as a single isomer. Heating 2-26 in boiling diphenyl ether resulted in a retro Diels-Alder reaction, which recovered the alkene functionality to form the epoxycyclohexenone (−)-2-27. Treatment of (−)-2-27 with iodine and pyridine mixture in CH₂Cl₂ provided 2-iodocyclohexenone (−)-2-13. Because ketone functionality inhibited the Sonogashira coupling reaction, vinyl iodide (−)-2-13 was reduced under the Luche condition to form the iodocyclohexene 2-10 for cross coupling reaction.

Scheme 2.2. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 88%; (b) K₂CO₃, MeOH; (c) PDC, CH₂Cl₂, 87% in two steps; (d) 30% H₂O₂, Triton B, THF, 0 °C, 88%; (e) PhOPh, reflux, 93%; (f) I₂, pyridine, CH₂Cl₂, 0 °C, 89%; (g) NaBH₄, CeCl₃·7H₂O, 0 °C, 100%.

Taylor and coworkers prepared bromoxone derivative 2-30 from 1-bromo-2,5-dimethoxybenzene 2-28 in 3 steps involving an anodic oxidation and applied it to Sonogashira coupling reaction with 2-methyl-1-buten-3-yne 2-14. However, the yield of cross coupling reaction was disappointingly low (41%). By exchanging bromo- to iodo-substituent, a better yield (62%) was obtained (Scheme 2.3). In 2010, they updated their synthesis by employing a double oxidation of 2-33 with hypervalent iodine reagent in methanol followed by asymmetric epoxidation, which was converted into the natural product, (−)-harveynone.
Scheme 2.3. Reagents and conditions: (a) Anodic oxidation, KOH/MeOH, 87%; (b) AcOH, acetone, 71%; (c) tBuOOH, KH, THF, -50 °C, 46%; (d) nBuLi then I₂, 90%; (e) aq. AcOH, 95%; (f) H₂O₂, NaOH, 51%; (g) PhI(OAc)₂, MeOH, rt, 56%; (h) TrOOH, NaHMDS, L-DIPT, PhMe, -65 °C, 84%, 93:7 er.

In 1997, Johnson and Miller reported enantioselective syntheses of (+)/(−)-harveynone and (−)-tricholomenyn A.⁸⁰ Synthesis of chiral iodoenone (+)-2-13 commenced with bromination of p-quinone 2-34 followed by reduction with NaBH₄ to generate dibromo diallylic alcohol 2-35. In turn, (±)-2-35 was converted to diacetate and submitted to the enzymatic resolution condition to afford enantiomerically enriched allylic alcohol (+)-2-35 (90% ee). Monoprotection with TBDMS group followed by a stereoselective epoxidation provided hydroxyepoxide 2-38, which was exposed to zinc in refluxing methanol to generate 2-39. Alcohol 2-39 was oxidized by PCC and then the resulting enone (+)-2-27 was treated with I₂ and pyridine in CCl₄ to deliver 2-iodocyclohexenone (+)-2-13.

Negishi et al. synthesized racemic 2-13 using a similar route and subjected it to a Pd-catalyzed coupling reaction with organozincs 2-19 and 2-20 to achieve the synthesis of harveynone and tricholomenyn A.⁸¹
Scheme 2.4. Reagents and conditions: (a) Br₂; (b) NaBH₄, 62%; (c) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 72%; (d) Amano PS-30, pH = 8, 50 °C, 47%, 90% ee; (e) TBDMSOTf, Et₃N, 45%; (f) CF₃CO₂H, Na₂HPO₄, CH₂Cl₂, 84%; (g) Zn, MeOH, 81%; (h) PCC, 82%; (i) I₂, pyridine, CCl₄, 77%.

Maycock and coworkers utilized a chiral pool, in the form of the abundant metabolite (−)-quinic acid 2-40 as a framework for the first synthesis of (−)-asperpentyn.82 (−)-Quinic acid was converted to 4,5-<i>O</i>-isopropylidene lactone in 80% yield. Reduction and subsequent oxidative cleavage of the resulting vicinal diol by sodium periodate gave cyclohexanone 2-42 in 92% yield in two steps. TBDMS protection product of 2-42 followed by 0.5 N NaOH treatment generated a mixture of 1:1 desired product 2-43 and its constitutional isomer 2-44 resulting from silyl migration. Stereocontrolled epoxidation of the mixture of the enones by 30% H₂O₂ under a basic condition afforded a mixture of the epoxides 2-45 and 2-46, in which stereochemical outcome could result from the directing effect of the nearby hydroxyl group. Acetylation of both the epoxides only led to the subsequent elimination of one of the resulting acetates to form the enone 2-48, which was converted to iodocyclohexenone (⁺)-2-13 under standard iodination condition.
Scheme 2.5. **Reagents and conditions:** (a) 2,2-dimethoxypropane, (+)-CSA, benzene, 80%; (b) NaBH₄, EtOH; (c) NaIO₄, CH₂Cl₂/H₂O, 92% in two steps; (d) TBDMSCl, imidazole, DMF, 98%; (e) 0.5 N NaOH, THF, 0 °C, 82%, 2-43:2-44 = 1:1; (f) 30% H₂O₂, Triton B, THF, 0 °C, 89%; (g) Ac₂O, DIPEA, DMAP, CH₂Cl₂, 0 °C, 44% (2-47), 42% (2-48); (h) I₂, DMAP, pyridine, CCl₄, 0 °C to rt, 93%.

Recently, Banwell and coworkers employed *cis*-1,2-dihydrocatechols, which are readily available from the enzymatic dihydroxylation of the corresponding halobenzene,⁸³ as starting material to synthesize the 2-iodo epoxycyclohexenone 2-22.⁸⁴ Treatment of halodiene 2-49 with NBS and water in THF at room temperature selectively afforded bromohydrin 2-50 in 66% yield. Epoxide 2-51 formed smoothly by exposure 2-50 to freshly prepared NaOMe in THF. Under Mitsunobu reaction conditions, monoacetate 2-52 was generated probably due to the presence of the iodine, which induced steric difference between two hydroxyl groups. Oxidation of 2-52 with PDC provided the corresponding 2-iodoenone 2-22 for Stille cross coupling reaction.

Scheme 2.6. **Reagents and conditions:** (a) NBS, H₂O, THF, 0.5 h, 66%; (b) NaOMe, THF, 1 h, 79%; (c) (t-BuOCON)₂, PPh₃, CICH₂CO₂H, THF, 15 min, 77%; (d) PDC, AcOH, CH₂Cl₂, 1 h, 75%.
2.2.2. Mehta’s synthetic approach

In 2012, Mehta et al. reported a novel norbornyl-based synthetic approach toward (+)-harveynone and (–)-asperpentyn that does not involve the 2-halocyclohexenone intermediate (Schemes 2.7 & 2.8). The synthesis started with epoxidation of readily available tricyclic endo-adduct 2-53 with H₂O₂ under basic condition followed by a stereocontrolled aldol reaction with formalin solution in the presence of catalytic amount of DBU to generate α-hydroxymethylated product 2-55. Subsequent TBDMS-protection and stereoselective reduction with NaBH₄ resulted in the formation of racemic alcohol 2-56. Exposure of (±)-2-56 to lipase PS-D in vinyl acetate solvent and termination of the reaction at nearly 50% transesterification led to the isolation of enantiomerically pure (–)-2-57 and (+)-2-58.

Scheme 2.7. Reagents and conditions: (a) 30% H₂O₂, 10% Na₂CO₃, acetone, 0 °C, 96%; (b) DBU (10 mol%), 40% formalin, THF, 0 °C, 95%; (c) TBDMSCl, imidazole, DMAP, DMF, rt, 92%; (d) NaBH₄, MeOH, -15 °C, 81%; (e) Lipase PS-D (Amano), vinyl acetate, rt, 28 h, (–)-2-57, 45%, (+)-2-58, 46%.

With 2-57 in hand, a retro-Diels-Alder reaction was performed to generate the functionalized epoxyquinone 2-59. Protection of the secondary hydroxyl group with a more robust TBDMS group followed by selective deprotection of the primary TBDMS yielded 2-61. Stereoselective carbonyl reduction with DIBAL-H and regioselective primary allylic oxidation of the resultant diol 2-62 with manganese dioxide delivered 2-63. Wittig olefination of 2-63 furnished a mixture of Z-, E-chloroolefins 2-64, which was exposed to n-butyl lithium to provide the alkyne 2-65. At last, Pd-catalyzed Sonogashira coupling with 2-bromopropene followed by a Dess-Martin periodinane oxidation and TBDMS
deprotection gave the natural product (+)-harveynone. (–)-Asperpentyn was obtained from deprotection of the coupling product (+)-2-15.

**Scheme 2.8. Reagents and conditions:** (a) Ph₂O, 230 °C, 20 min, 83%; (b) LiOH, MeOH, 0 °C; (c) TBDMSOTf, 2,6-lutidine, 0 °C, 88%; (d) PPTS, MeOH, 75%; (e) DIBAL-H, -78 °C, 73%; (f) MnO₂, CH₂Cl₂, 93%; (g) ClCH₂PPh₃Cl, nBuLi, THF/HMPA, 0-25 °C, 72%; (h) nBuLi, THF, -78 °C, 77%; (i) 2-bromopropene, PdCl₂(PPh₃)₂, iPr₂NH, CuI, THF, 41%; (j) DMP, CH₂Cl₂, 90%; (k) 40% HF, CH₃CN, 92% for (+)-harveynone or 20% HF, CH₃CN, 95% for (–)-asperpentyn.

2.3. Total Synthesis of (+)-asperpentyn, (–)-harveynone and (–)-tricholomenyn A*

2.3.1. Retrosynthetic analysis

On the basis of our experience and achievements in metathesis chemistry, we envisioned a conceptually new strategy relying on enyne metathesis-based construction of the cyclohexene core with concomitant installation of the 1,3-enyne moiety starting from the corresponding acyclic precursors (Figure 2.2). This new approach will harness a streamlined sequence of enyne ring-closing metathesis

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*This work was performed on the basis of preliminary study by Reagen L. Miller and Sang Ho Park, two former graduate students of Professor Daesung Lee.
followed by metallotropic [1,3]-shift, whereby the 1,5-dien-3-yne moiety will be directly installed on the incipient epoxy cyclohexene ring.\(^{88}\)

![Figure 2.2](image)

**Figure 2.2**

Retrosynthetically, cyclohexene derivative \(2-66\) with an appropriate R substituent would serve as a common advanced intermediate for all three natural product targets (+)-asperpentyn, (−)-harveynone and (−)-tricholomenyn A (Figure 2.3). A direct precursor of \(2-66\) would be an acyclic 1,3-diyne-containing compound \(2-67\) or its simpler variant lacking the relay device. The pivotal metathesis substrate \(2-67\) would be prepared through fluoride-catalyzed addition of silylated 1,3-diyne to epoxy aldehyde \(2-68\), which in turn would be derived from aldehyde \(2-70\)\(^{89}\) and allyl propargyl ether \(2-71\).

![Figure 2.3](image)

**Figure 2.3**

### 2.3.2. Preliminary results\(^{†}\)

To test the feasibility of the key step, alkene-tethered 1,3-diyne \(2-77\) was prepared from commercially available cis-2-buten-1,4-diol \(2-72\) in 8 steps (Scheme 2.9).\(^{90}\) Following the known procedure involving the Sharpless asymmetric epoxidation,\(^{91}\) cis-2-buten-1,4-diol \(2-72\) was elaborated to

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\(^{†}\) This work was performed by Reagen L. Miller, a former graduate student of Professor Daesung Lee.
epoxide 2-73. Oxidation of the primary alcohol with PCC followed by addition of vinyl magnesium bromide to the corresponding aldehyde, MOM-protection of the resultant secondary alcohol 2-74 (1:1 mixture) and removal of the TBS group afforded primary alcohol 2-75. After Dess-Martin oxidation\textsuperscript{92} of the primary alcohol, a lithiated diyne derived from 2-76 was added to provide an RCM substrate 2-77. Disappointedly, however, treatment of 2-77 with Grubb second-generation catalyst did not promote the ring closure to generate 2-78. We assumed that the initiation was hindered by the steric congestion around the vinyl group.\textsuperscript{93}

\begin{equation*}
\text{Scheme 2.9. Reagents and conditions: (a) TBDMSCl, Et}_3\text{N, CH}_2\text{Cl}_2; (b) (+)-DET, Ti(O^{'Pr})_4, TBHP, 4 \text{ Å MS, CH}_2\text{Cl}_2, -20 ^\circ\text{C}; (c) PCC, 4 \text{ Å MS, CH}_2\text{Cl}_2; (d) VinylMgBr, THF (e) MOMCl, Et}_2\text{N}^{'Pr, CH}_2\text{Cl}_2; (f) HF-pyr, THF, 0 ^\circ\text{C}; (g) DMP, CH}_2\text{Cl}_2; (h) nBuLi, 2-76, THF; (i) Grubbs second-generation catalyst, CH}_2\text{Cl}_2.}
\end{equation*}

2.3.3. Synthesis of epoxyaldehyde 2-82\textsuperscript{1}

To overcome this hindered initiation, a relay metathesis strategy was adopted, which entails the preparation of more elaborated RCM substrate containing the relay device.\textsuperscript{94} Along this modified plan, the first goal is to synthesize a common intermediate that can branch off to different target molecules, which is aldehyde 2-82 (Scheme 2.10). The synthesis of 2-82 was commenced with the addition of acetylhydride derived from allyl propargyl ether 2-71 to an aldehyde derived from alcohol 2-73, providing separable diastereomeric alcohols 2-79 and 2-80 in 1:2 ratio. The desired β-epimer 2-79 was easily

\textsuperscript{1} This work was performed based on the dissertation of Sang Ho Park, a former graduate student of Professor Daesung Lee.
elaborated to acetate 2-81 via controlled partial hydrogenation\textsuperscript{11} (H\textsubscript{2}, Pd/CaCO\textsubscript{3}, Pb(OAc)\textsubscript{4}, quinoline, hexanes/EtOAc 1:1) and acetylation (Ac\textsubscript{2}O, py, DMSO, CH\textsubscript{2}Cl\textsubscript{2}). It should be noted that a significant amount of overreduced product from hydrogenation of the terminal alkene was obtained when commercially available Lindlar catalyst was used without further poisoning. For a more practical material throughput, without separation the mixture of two epimers 2-79 and 2-80 was subjected to a four-step sequence to convert to 2-81, which involves Dess-Martin oxidation of the secondary alcohols, \((R)\)-Me-CBS mediated reduction, partial hydrogenation of the triple bond, and Mitsunobu reaction with acetic acid.\textsuperscript{95} Several attempts had been carried out to optimize the asymmetric reduction. By using 2 equiv \((S)-(\textendash )\)-Me-CBS reagent, the ratio of \(\alpha : \beta\) was increased slightly from 1:2 to 1:3, whereas higher stereoselectivity was observed when 2 equiv of \((R)-(\textendash )\)-Me-CBS was used, the \(\alpha\)-isomer having the opposite stereochemistry at C4 was the major product and the ratio of \(\alpha : \beta\) was up to 10:1. Most Recently, Meyer and Cossy found that the Noyori transfer hydrogenation of \(\alpha,\beta\)-epoxy ynones could lead to the corresponding \(\alpha,\beta\)-epoxy propargylic alcohols in high reagent-controlled diastereoselectivity.\textsuperscript{96} Removal of the TBS group from 2-81 followed by oxidation of the corresponding primary alcohol gave the aldehyde 2-82. Several attempts had been carried out to optimize the asymmetric reduction.

2.3.4. Key tandem metathesis reaction

For the synthesis of asperpetyne and harveynone, aldehyde 2-82 was reacted with triethylsilyl-1,3-pepadiyne 2-84\textsuperscript{97} and catalytic amount of anhydrous fluoride source tetrabutylammonium difluorotriphenylsilicate (TBAT),\textsuperscript{98} providing enyne RCM substrate 2-85 after silyl concomitant protection of the secondary alcohol (Scheme 2.11). TES-protected pentadiyne 2-84 was prepared from the ketone 2-83 by Colvin’s rearrangement.\textsuperscript{99} Alternatively, 2-84 could be prepared by coupling of bromopropyne and commercially available triethylsilylacetylene under the Cadiot-Chodkiewicz protol.\textsuperscript{100} Treatment of 2-85 with Grubbs second-generation catalyst in dilute solution of CH\textsubscript{2}Cl\textsubscript{2}, mixture of epimer 2-90 and 2-91 was isolated in 62% yield along with unidentified byproduct.
Scheme 2.10. Reagents and conditions: (a) PCC, 4 Å MS, CH₂Cl₂; (b) nBuLi, 2-71, THF, 90%; (c) DMP, 83%; (d) (R)-Me-CBS, BH₃•SMe₂, 81%; (e) H₂, Pd/BaSO₄, Pb(OAc)₄, quinoline, 83%; (f) DIAD, PPh₃, AcOH, 90%; (g) H₂, Pd/BaSO₄, Pb(OAc)₄, quinoline, 83%; (h) Ac₂O, pyr, 99%; (i) HF, pyr, 80%; (j) DMP, 88%.

Based on the level of our understanding, we believe, the overall metathesis process started from the terminal alkene of the allyl ether relay device to form 2-86 initially, which then delivers the ruthenium moiety intramolecularly to the cis-alkene to generate a new propagating alkylidene 2-87. Subsequent enyne RCM generating alkynyl Ru-alkylidene 2-88 would induce facile metallotropic [1,3]-shift to generate fully conjugated alkylidene 2-89. The termination at the sterically least hindered carbon through 2-89 would ultimately deliver the final products 2-90 and 2-91, thereby establishing 1,5-diene-3-yne substructure.¹¹
Scheme 2.11. Reagents and conditions: (a) nBuLi, trimethylsilyldiazomethane, THF, -78 °C, 67%; (b) TBAT (5 mol%), THF/CH2Cl2, 73%; (c) Grubbs second-generation catalyst, CH2Cl2, 62%.

2.3.5. Completion of natural products

After separation, the C1-β-epimer of 2-90 was elaborated to (+)-asperpentyn through the removal of both the C1-TES group and C4-acetate in one step (KCN, EtOH 95%) (Scheme 2.12). Also, the TES-group on C1-α-epimer 2-91 was selectively deprotected to generate an alcohol (HF·pyr, pyr, CH2Cl2, 0 °C), which was then oxidized to acetylated harveynone 2-92. Unfortunately, under a variety of conditions, the C4-acetyl group of 2-92 could not be removed probably due to the instability of the compound toward basic/nucleophilic conditions. To address this problematic deprotection under basic conditions, the C4-acetyl group of α-epimer 2-91 was first converted to a TIPS group generating 2-93. The selective removal of the C1-TES group of 2-93 (HF·pyr, pyr, CH2Cl2), followed by oxidation (MnO2, CHCl3) afforded TIPS-protected form of harveynone 2-95, which was successfully converted to (−)-harveynone after removal of the C4-TIPS group (HF·pyr, pyr, CHCl3).
Scheme 2.12. Reagents and conditions: (a) KCN, EtOH, 87%; (b) HF•pyr, pyr, 78%; (c) MnO₂, CHCl₃, 92%; (d) KCN, EtOH, 95%; (e) TIPSOTf, Et₃N, 88%; (f) HF•pyr, pyr, 78%; (g) MnO₂, CHCl₃, 92%; (h) HF•pyr, pyr, CH₃CN, 81%.

The total synthesis of (−)-tricholomenyn A was commenced with the addition of triethylsilyl-1,3-diyne anion derived from 2-98 to a common intermediate aldehyde 2-82 (Scheme 2.13). Silylated 1,3-diyne 2-98 was prepared via Colvin’s rearrangement from ketone 2-97, which is in turn can be prepared in a straightforward manner starting from known aldehyde 2-96. The reaction between aldehyde 2-82 and silyl-1,3-diyne catalyzed by tetrabutylammonium difluorotriphenylsilicate (TBAT), provided silylated adduct 2-99 (1:1 epimeric mixture), which was subjected to RCM to generate 2-100 as a separable mixture of epimers. The removal of the TES- protecting group from 2-100 (HF•pyr) followed by oxidation (MnO₂, CHCl₃) delivered the target natural product (−)-tricholomenyn A in good yield.
Scheme 2.13. Reagents and conditions: (a) nBuLi, triethylsilylacetylene 2-98, THF, -78 °C; (b) MnO₂, CHCl₃, 80% in two steps; (c) nBuLi, trimethylsilyldiazomethane, THF, 90%; (d) TBAT (5 mol%), THF/CH₂Cl₂, 65%; (e) Grubbs second-generation catalyst, CH₂Cl₂, 58%; (f) HF•pyr, pyr, 89%; (g) MnO₂, CHCl₃, 92%.

2.3.6. Summary

In summary, we have developed a novel strategy to synthesize epoxyquinone natural products bearing a 1,5-diene-3-yne moiety via a tandem sequence of relay metathesis-induced ring-closing enyne metathesis and metallotropic [1,3]-shift. By using this strategy, we have accomplished the total syntheses of (+)-asperpentyn, (-)-harveynone and (-)-tricholomenyn A.
2.4. Synthesis of panepophenanthrin from other groups

As we mentioned before in 2.1, the more complex epoxyquinoid panepophenanthrin (2-7) is the first known inhibitor of the ubiquitin-activating enzyme (E1), which has a pivotal role in activating the ubiquitin-proteasome pathway (UPP). UPP is known to involve in the regulation of a number of cellular functions through the degradation or processing of target proteins. Therefore, the discovery and study of such E1 inhibitor was of great biological promise.

Due to this important biological activity as well as its novel structural features, panepophenanthrin (2-7) has drawn significant attention from the synthetic community since it was isolated in 2002. Since panepophenanthrin (2-7) could be derived from a biomimetic approach involving Diels-Alder dimerization of structurally simpler monomeric epoxyquinols, therefore, all the syntheses or synthetic efforts focus on efficient construction of the basic monomer 2-101 (Figure 2.4).102

![Figure 2.4](image)

In 2003, the research groups of Porco103 and Baldwin104 independently accomplished total syntheses using a highly stereoselective Diels-Alder reaction of epoxyquinol monomer 2 or its TES-protected form (Scheme 2.14). In the following years, Mehta, Wood, Hayashi and Banwell groups developed different routes to Diels-Alder precursor 2-101, thereby realizing the total synthesis of panepophenanthrin 2-7.105 Among them, most groups utilized Pd-catalyzed Stille or Heck cross coupling reactions between the preformed bromoxone derivatives 2-102-2-103, 2-109 or its iodo analogues (−)-2-13 and 2-22 and 2-methyl-3-buten-2-ol or its derivative 2-107 as key step (Scheme 2.14). One exception is from Mehta group (Scheme 2.15). On the basis of their norbornyl-based approach, Mehta’s synthesis started from the readily available tricyclic Diels-Alder adduct 2-53 of cyclopentadiene and p-
benzoquinone, which was further manipulated to the chiral α,β-epoxyketone 2-111 involving lipase-mediated dsymmetrization of meso-diol. Base-mediated hydroxymethylation of 2-111 led to (−)-2-112, which installed the side arm in 2-101. Monocyte 2-113 from a retro Diels-Alder reaction of 2-112 was exposed to a sequence of reduction, oxidation and Wittig olefination in order to extend the side chain. Addition of an excess of methyl lithium to E-α,β-unsaturated ester 2-114 followed by oxidation and removal of TBDMS group provided the monomer 2-101 with iso-pentenyl side chain in good yield. Under neat condition, (−)-2-101 was spontaneously dimerized to (+)-panepophenanthin 2-7.

Scheme 2.14
Scheme 2.15. Reagents and conditions: (a) DBU, formalin, 85%; (b) Ph$_2$O, 240 °C; 85%; (c) DIBAl-H, THF, -78 °C, 80%; (d) O$_2$, TEMPO, CuCl, DMF, 96%; (e) Ph$_3$P=CHCO$_2$Me, benzene, 91%; (f) MeLi, THF, 0 °C, 56%; (g) MnO$_2$, CH$_2$Cl$_2$, 74%; (h) HF•py, THF, quant; (i) neat, 24 h, 74%.

Porco and coworkers investigated systematically the mechanism of the stereospecific intermolecular Diels-Alder dimerization. They proposed two possible pathways for the biomimetic dimerization, differentiating from which reaction, Diels-Alder dimerization or hemiacetal formation, occurs first (Scheme 2.16). In one case, hemiacetal formation occurs first, and then an intramolecular, inverse-demand Diels-Alder reaction affords the dimeric natural product. In the other case, a pseudo-transannular normal Diels-Alder reaction occurs first, subsequent formation of five-membered ring hemiacetal leads to the natural product. To gain more insight, they modified the epoxyquinol monomer by replacing a tertiary hydroxyl group with a methyl group. As a result, they found that tertiary hydroxyl group is not essential for dimerization, which rules out the pathway a to some extent. Also, they utilized high level DFT calculations to further confirm that the route b involving intermolecular cycloaddition and subsequent hemiacetal formation is about 15 kcal/mol more favorable.
2.5. Total synthesis of (+)-panepophenanthrin

2.5.1. Retrosynthetic analysis of (+)-panepophenanthrin

To further demonstrate the powerful capability of tandem enyne metathesis process in the formation many bonds in one operation and continue our effort in the epxyquinoid natural product synthesis, we envisioned an efficient and novel approach to 2-101 from a linear substrate 2-116 via tandem enyne metathesis, specifically involving tandem relay metathesis-induced enyne ring-closing metathesis (RCM) followed by cross metathesis with appropriate alkenols, further leading to total synthesis of (+)-panepophenanthrin 2-7.

Retrosynthetically, epoxyquinol diene monomer (−)-2-101 may be obtained from precursor 2-115, which in turn would be generated via a tandem metathesis from enyne 2-116 (Figure 2.5). This metathesis substrate 2-116 could be prepared through fluoride-mediated addition of triethylsilyl acetylene to the known epoxy aldehyde 2-82.

Figure 2.5
2.5.2. Key tandem metathesis reaction

Previously, we prepared chiral aldehyde 2-82 from cis-2-butene-1,4-diol in ten steps (Scheme 2.10 in 2.3.3). Fluoride-catalyzed addition of triethylsilyl acetylene to aldehyde 2-82 afforded a mixture of epimeric silyl ethers 2-116. The merit of this acetylide addition is its mild reaction conditions as well as the direct installation of the silyl ether.

With the metathesis substrate 2-116 in hand, initially we chose 2-methyl-3-buten-2-ol as the alkene partner of cross metathesis, however, the cross metathesis was unsuccessful as expected using Grubbs second-generation catalyst (G-II). Then we employed 3-buten-2-ol as the alkene partner of cross metathesis. Treatment of 2-116 and 2-buten-3-ol in CH₂Cl₂ with Grubbs second-generation catalyst (G-II) afforded the desired 1,3-diene-containing cyclohexene derivative 2-115 in 51% yield. To further improve the yield, various conditions with several different combinations of alkene partners and catalysts were tried as shown in Scheme 2.17. However, no improvement could be made. It was surprising that allyl alcohol did not afford any expected CM product. Also, employment of internal racemic alkene hex-3-ene-2,5-diol¹⁰⁶ to minimize the unproductive degenerate cross metathesis did not give any

![Scheme 2.17](image)

Scheme 2.17. Reagents and conditions: (a) Triethylsilyl acetylene, TBAT (6 mol%), CH₂Cl₂, 62%; (b) 3-buten-2-ol, G-II (10 mol%), CH₂Cl₂, 51%. 
improvement, providing 32% yield when the reaction was carried out at an elevated temperature (90 °C) in toluene. Furthermore, electron-deficient alkenes such as acrolein and methyl acrylate showed much lower reactivity, giving only marginal yields of the corresponding cross metathesis products even with high catalyst loading.

For these processes, mechanistically we believe that the initiation occurred from the terminal alkene of the relay device to form Ru-alkylidene 2-117, which undergoes an RCM to release 2,5-dihydrofuran, generating a new alkylidene 2-118 (Mechanism A in Scheme 2.18). Subsequent RCM of 2-118 with the tethered terminal alkyne delivers a cyclohexenyl ruthenium-alkylidene 2-119. The cross metathesis of 2-119 with alkene cross metathesis partner then generates the observed product 2-115. We surmised that the most problematic step in the catalytic cyclic should be the cross metathesis between 2-119 and 3-buten-2-ol, thereby giving only marginal yield. Searching for further improvement led us to consider an intermolecular union of an allylic alcohol with an alkyne moiety of an appropriate enyne substrate in the first step followed by a subsequent RCM sequence (Mechanism B in Scheme 2.18). We hypothesized that the cross metathesis between an incipient alkylidene 2-120 with the tethered terminal alkene should be more efficient than that between the sterically hindered and conjugated

![Scheme 2.18](image-url)
alkylidene 2-119 and 3-buten-2-ol. Another merit of this strategy is that the relay device is not necessary any more, thus a simpler substrate such as 2-121 can be used. We were disappointed to find out that, however, only low yields of 2-115 were obtained from reactions of 2-121 with different allylic alcohols due to the formation of multiple by-products (Scheme 2.19). One notable observation is that the diastereomeric ratios of the product from these two different manifolds of reactions were substantially different from each other. This is another line of evidence that suggests different intermediates such as 2-118 and 2-120 are involved in the ring closure step in mechanisms A and B.

Scheme 2.19

2.5.3. Completion of (+)-panepophenanthrin

With 2-115 in hand, the corresponding tertiary alcohol 2-122 was prepared without difficulties via an oxidation of allylic alcohol (MnO₂, CHCl₃) followed by methyl group addition. Apparently, acetate 2-123 should be a straightforward precursor to the epoxyquinol diene 2-101 (Scheme 2.20). However, the C4-acetate of 2-123 could not be removed under a variety of basic and/or nucleophilic conditions. Under neat conditions, enone 2-123 smoothly dimerized to form acetatylated form of paneophenanthrin 2-124, which was also unable to be deacetylated due to its instability under basic conditions.

Scheme 2.20. Reagents and conditions: (a) MnO₂, CHCl₃, rt, 95%; (b) MeMgBr, THF, 0 °C, 74%; (c) TBAF, THF; (d) MnO₂, CHCl₃, 66% in two steps; (e) neat, rt.
To address this problematic protecting group manipulation, the C4-acetate in 2-122 was first converted to a TBDMS ether 2-125 (Scheme 2.21). The selective removal of the triethylsilyl group at C1 (HF-pyr, CH₂Cl₂, pyr) followed by an oxidation (MnO₂, CHCl₃) afforded enone 2-126 with C4 TBDMS ether, which is an advanced intermediate in Mehta¹⁰⁵a and Hayashi¹⁰⁵d’s total synthesis of (+)-panepophenanthrin. After several attempts, TBS group was successfully removed using NH₄F, providing monomer enone (−)-2-101 in good yield. A highly stereoselective intermolecular Diels-Alder reaction of (−)-2-101 under neat condition afforded (+)-panepophenanthrin (2-7).

Scheme 2.21. Reagents and conditions: (a) KCN, 95% EtOH, 0 °C; (b) TBDMSCl, imidazole, DMAP (cat.), CH₂Cl₂, 0 °C to rt, 51% in two steps; (c) HF-pyridine, pyridine, MeCN, 0 °C, 82%; (d) MnO₂, CHCl₃, 86%; (e) NH₄F, MeOH, overnight, 77%; (f) neat, 30 °C, quantitative.

2.5.4. Summary

In summary, we have described a novel enantioselective total synthesis of (+)-panepophenanthrin from a linear substrate via a tandem metathesis reaction involving a relay metathesis-induced enyne ring-closing metathesis followed by a cross metathesis. Although the key relay metathesis-based tandem RCM and CM sequence did not provide high efficiency, this approach clearly demonstrated the powerful nature of enyne metathesis process for the formation many bonds in a single operation.
Chapter 3

Diastereoselective ring-rearrangement metathesis to set a stereogenic all-carbon quaternary center

3.1. Introduction and background

Construction of all-carbon quaternary carbon centers is a significant challenge in organic chemistry. To address this issue, various methods have been developed, yet truly effective and general as well as readily executable user-friendly methods are still in demand.

Recently, gold complex-catalyzed reactions have emerged as a powerful tool in organic synthesis since gold complexes are potential carbophilic Lewis acids that activate alkynes to generate cationic or carbenoid intermediates depending on the functional groups within the molecules containing the alkyne and these reactive intermediates are known to undergo an array of transformations to engender diverse carbon frameworks. On the basis of previous study in gold catalysis, we envisioned a gold-catalyzed cycloisomerization/allylation of 3-hydroxy-1-hexen-5-yne allylsilyl ethers to set an all-carbon quaternary stereogenic center.

In 2007, Kirsch et al. reported a relevant gold chemistry in which 1-hexen-5-yn-3-ols or their silyl ethers were converted to cyclopentene carboxaldehydes (Scheme 3.1). It is believed to proceed through the intermediate arising from a nucleophlic attack of the alkene to the gold-activited alkynyl functionality in a 6-endo-dig carbocyclization mode, which then undergoes an irreversible pinacol-type rearrangement to another intermediate followed by loss of a proton or a silyl group, yielding 3-4. We conceived that if the carbocationic intermediate could be intercepted by an allylsilane, before it undergoes a skeletal rearrangement to 3-3, to generate a [5.4.0]bicyclic intermediate 3-5, then 3-5 would undergo C–Si bond cleavage to deliver a cyclohexene derivative containing an all-carbon quaternary stereogenic center. On the other hand, if the formation of rearranged oxonium intermediate still takes precedence over the direct trapping of 3-2 by the allyl group, an alternative carbocationic intermediate 3-7 would arise. Finally, the C–Si bond cleavage next to the carbocationic center would lead to a cyclopentene derivative 3-8.
As described in chapter 1, ring-rearrangement metathesis (RRM) is a very useful tactic among many subsets of olefin metathesis.\textsuperscript{18} It involves one or more ring-closing and ring-opening steps that convert one cyclic structure to a new cyclic product. RRM reaction is unique in its capacity to make connectivity change in carbon-based molecular frameworks, which is not possible by any other bond-breaking and bond-forming processes. Therefore, even if the formation of rearranged oxonium intermediate 3-3 is faster than the allyl trapping event, resulting in the formation of cyclopentene derivatives 3-8, which don’t have quaternary stereogenic center, it is still possible to generate 3-6 via the RRM of 3-8. Virtually, the RRM of 3-8 to 3-6 reverse the connectivity change ensued in the ring contraction of cyclohexenyl cation 1 to the corresponding cyclopentenyl oxonium species 3-3 (Scheme 3.1).\textsuperscript{115} As such, this RRM process indirectly overrides the kinetically-driven connectivity change of 3-2 to 3-3 by the counteraction of a thermodynamically-driven metathesis process.

Although RRM is a powerful and straightforward transformation, it has significant limitations. Due to the equilibrium nature of the reaction, shifting the equilibrium completely toward the product side is not always attainable. We assumed that the higher reactivity in the ring opening of cyclopentenes compared to that of cyclohexenes by Grubbs-type ruthenium alkylidenes would be extrapolated to the
systems of concern. This reactivity difference would favourably affects the ring opening of cyclopentene moiety relative to the cyclohexene moiety, thereby accumulating the cyclohexene product 3-6 during the course of reaction (Scheme 3.2). Therefore, under an appropriate reaction conditions full conversion of the starting material should be achievable.

Scheme 3.2

3.2. Gold(I)-catalyzed cycloisomerization/allylation

To examine the behavior of the carbocationic intermediates toward trapping with allylsilane moiety, 2-methylhex-1-en-5-yn-3-yloxy allyldimethylsilyl ether 3-10a was prepared via propargylation of methacrolein (propargyl bromide, Zn, aq NH₄Cl–DMF) followed by silylation. Unfortunately, with cationic gold complex 3-9 (1 mol%), reaction of 3-10a in the presence of tert-butanol (1.1 equiv) in dichloromethane did not provide desired cyclohexene product containing a quaternary stereogenic center. Instead, cyclopentene derivative 3-11a was obtained as major product in 86% yield combined with nonnegligible amount of cyclopentene carboxaldehyde (3-4) (entry 1 in Table 3.1).

To minimize the formation of cyclopentene carboxaldehyde byproduct, it was found that the combined use of allyldiphenylsilyl ether and phenol as opposed to allyldimethylsilyl ether and tert-butanol is effective. Under the optimized conditions, various enyne substrates 3-10b–f afforded homoallylic siloxane 3-11b–f in good yields. Compound 3-11c–e derived from internal alkynes 3-10c–e provided mixtures of diastereomers (entries 3–5), but products 3-11b and 3-11f derived from terminal

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5 This experiment was performed in collaboration with Xiaoguang Liu, who was a graduate student of Professor Daesung Lee, currently works with Professor Justin Mohr.
alkyne are single diastereomers because the quaternary carbon center is not stereogenic (entries 2). Similarly, relatively complex substrate 3-12 containing an aromatic moiety with oxygen substituents afforded 3-13 in good yield (76%) without complication.

Table 3.1

<table>
<thead>
<tr>
<th>entry</th>
<th>enyne</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-10a</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>3-11a</td>
<td>86c</td>
</tr>
<tr>
<td>2</td>
<td>3-10b</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>3-11b</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>3-10c</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>3-11c</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>3-10d</td>
<td>Ph</td>
<td>Me</td>
<td>Br</td>
<td>3-11d</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>3-10e</td>
<td>Ph</td>
<td>Me</td>
<td>allyl</td>
<td>3-11e</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>3-10f</td>
<td>Ph</td>
<td>(CH2)3OPiv</td>
<td>H</td>
<td>3-11f</td>
<td>76</td>
</tr>
</tbody>
</table>

Unambiguous cyclopentene structural determination was realized by an X-ray crystallographic analysis of the p-nitrobenzoate 3-17 derived from 3-15, which is the product of the reaction of enyne 3-14 containing an allyl-transfering silyl ether moiety (Scheme 3.3).

Scheme 3.3
3.3. Diastereoselective ring-rearrangement metathesis (dRRM)

As we proposed before, a ring-rearrangement metathesis of cyclopentene derivatives 3-8 would construct the corresponding cyclohexenes 3-6 having an all-carbon quaternary stereogenic center (Scheme 3.1). More importantly, the stereochemistry of the all-carbon quaternary center may be established during the metathesis process by the influence of the stereogenic center at the next carbon connecting to an oxygen substituent. Since the quaternary center in the cyclopentene is nonstereogenic due to its symmetrical nature, this diastereoselective RRM reaction can also be considered a desymmetrization of cyclopentene. If this highly diastereoselective RRM of symmetric cyclopentene is achieved, conceptually, it will complement the state of the art technology currently available for the construction of quaternary carbon-containing cyclohexane-based molecular structures, one of whose is the palladium-catalyzed allylation reaction developed independently by Trost$^{120}$ and Stoltz$^{121}$ (Eq 1 in Scheme 3.4). And this dRRM has an additional merit in terms of installing two consecutive stereogenic centres and one extra manipulatable unsaturation compared to that in Eq 1. The prowess of this approach would readily allow the synthesis of natural products such as nitramine and glanthamine (Scheme 3.4).

Scheme 3.4
On the other hand, this diastereoselective RRM (dRRM) would be an unprecedented one to create a stereogenic all-carbon quaternary center. Although many variants of RRM have been reported in the literature, construction of a stereogenic all-carbon quaternary center by using RRM is rare. In their insightful application of RRM, Koreeda and coworkers converted functionalized norbonene derivatives to a tricyclic system containing a quaternary carbon center. An excellent example of RRM to form cyclohexene derivatives containing a silyloxy-substituted quaternary center has been reported by Hoveyda using a chiral Mo-alkylidene complex, however, the corresponding RRM to establish an all-carbon quaternary center is not reported.

### 3.3.1. Preliminary study of diastereoselective ring-rearrangement metathesis (dRRM)

**Table 3.2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>P</th>
<th>Product</th>
<th>Selectivity</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-21a</td>
<td>H</td>
<td>3-22a</td>
<td>1 : 1</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>3-21b</td>
<td>Ac</td>
<td>3-22b</td>
<td>1.3 : 1</td>
<td>86%</td>
</tr>
<tr>
<td>3</td>
<td>3-21c</td>
<td>Et</td>
<td>3-22c</td>
<td>5 : 1</td>
<td>77%</td>
</tr>
<tr>
<td>4</td>
<td>3-21d</td>
<td>iPr</td>
<td>3-22d</td>
<td>8 : 1</td>
<td>&gt;95% *a</td>
</tr>
<tr>
<td>5</td>
<td>3-21e</td>
<td>SiMe₃</td>
<td>3-22e</td>
<td>2.5 : 1</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>6</td>
<td>3-21f</td>
<td>SiMe₂OPh</td>
<td>3-22f</td>
<td>2.7 : 1</td>
<td>90%</td>
</tr>
<tr>
<td>7</td>
<td>3-21g</td>
<td>SiEt₃</td>
<td>3-22g</td>
<td>8 : 1</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>8</td>
<td>3-21h</td>
<td>SiMe₂Bu</td>
<td>3-22h</td>
<td>≥10 : 1</td>
<td>&gt;95% *b</td>
</tr>
</tbody>
</table>

* *a*65% isolated yield. *b*89% isolated yield.

To explore the dRRM as a means to transform a cyclopentene derivative to the corresponding allyl-containing cyclohexene, phenoxydimethylsilyl protected cyclopentene 3-21f was chosen as an initial test substrate because this compound could be easily prepared via gold-catalyzed isomerisation of the corresponding dimethylallylsilyl ether of 2-methyl-1-hexen-5-yn-3-ol followed by an intramolecular allyl trapping event. When 3-21f was treated with a catalytic amount (5 mol%) of Grubbs second-generation catalyst in dichloromethane under ethylene gas, a smooth transformation of 3-21f to
cyclohexene derivative 3-22f occurred with a marginal level of diastereocntrol and good conversion (Table 3.2, entry 6). We suspected that a right choice of hydroxy-protecting group would be important to achieve optimal conversion and diastereoselectivity. To establish a general trend, the protecting groups on cyclopentene derivatives 3-21 were systematically varied. First, the parent compound 3-21a without protecting group was examined but low selectivity and conversion to 3-22a was observed (entry 1). Acetate derivative 3-21b behaved similarly but with a slightly increased selectivity of 3-22b (entry 2). Considering that the strong chelation of the hydroxyl (3-21a), acetoxy (3-21b) and phenoxy (3-21f) group to the propagating ruthenium alkylidene species might be the cause of the low selectivity, simpler alkyl and silyl group-containing substrates were explored (3-21c–e, 3-21g, 3-21h). Gratifyingly, complete conversion was achieved with these substrates except 3-21c (entries 3–5, 7 and 8). The conversion and diastereoselectivity seem to depend on the size of the protecting groups on the oxygen such that the higher conversion and selectivity was achieved with sterically larger alkyl and silyl group. Among the tried, tert-butyldimethylsilyl group was found to be the optimal protecting group that yielded cyclohexene product 3-22h in ≥10:1 diastereomeric ratio with complete conversion (entry 8).125

3.3.2. Substrate scope of diastereoselective ring-rearrangement metathesis (dRRM)

Next, we examined the substrate scope of this diastereoselective ring-rearrangement metathesis (dRRM) with different substituents at the quaternary carbon center (Table 3.3). With substrates 3-23a–j containing more functionalized alkyl and aryl substituents compared to methyl in 3-21a–h, good to excellent yields and diastereoselectivities for various cyclohexene derivatives 3-24a–j were realized. Notably, higher diastereoselectivity was observed from substrates that contain an aryl group at the quaternary carbon (3-24f–i). In case of spirocyclic substrate 3-23j with a fused aromatic moiety, only the cis-ring junction isomer 3-24j was obtained in an excellent yield, which is the carbon backbone of many natural products including galanthamine (See 3.6). One salient feature of these processes is the lack of metathetic dimer formation once the products are generated.
Table 3.3

The RRM behavior of substrates containing multiple stereogenic centers was also examined (Scheme 3.5). For the diastereomeric substrates 3-23k and 3-23l, the RRM of the former provided a sole product 3-24k in 80% yield whereas that of 3-23l afforded 3-24l in quantitative yield but with only 2.5:1 diastereoselectivity. Bicyclic substrates 3-23m and 3-23n with the relative 1,2-stereochemistry similar to that of 3-23l underwent a smooth metathesis at room temperature to yield 3-24m and 3-24n in high yields with moderate diastereoselectivities. It is worthy of mentioning the reactivity difference of 3-23k/3-23l versus 3-23m/3-23n, where the former requires much harsher conditions (90 °C in toluene) than the latter (room temperature in CH₂Cl₂).
3.3.3. Mechanism and diastereoselectivity

We propose that the current RRM catalytic cycle commences with the formation of a propagating ruthenium alkylidene intermediate 3-25 (Scheme 3.6). A ring-closing and ring-opening metathesis of the alkylidene moiety of 3-25 with the symmetrical endocyclic double bond would generate a structurally reorganized new ruthenium alkylidene 3-26. The diastereotopic facial differentiation of the double bond is made via the formation of metallacyclobutane intermediates exo-3-23-Int and endo-3-23-Int.

Scheme 3.6
The main difference between these two intermediates is the orientation of the alkoxy substituent, which would suffer from a greater steric strain in the \textit{endo-3-23-Int} intermediate relative to that in the \textit{exo-3-23-Int}. This rationale corroborates the observed selectivity trend where the sterically larger alkoxy group provided higher diastereoselectivity. Once formed, intermediate \textit{3-26} would undergo an alkylidene exchange with another substrate, delivering the final product \textit{3-24}, and the catalyst reinitiates a new catalytic cycle.

In case when there are two substituents in the alkenyl tether such as in substrates \textit{3-23k–n}, the relative 1,2-stereochemistry could be reinforcing or interfering. For example, substrate \textit{3-23k} leads to intermediates \textit{exo-3-23k-Int} more favorably than \textit{endo-3-23k-Int}, because the former has both the alkoxy and methyl substituents in sterically less congested \textit{exo}-face as opposed to both in more congested endo face in the latter. Therefore, the final product \textit{3-24k} should be engendered via only the energetically more favorable intermediate \textit{exo-3-23k-Int}. On the other hand, substrate \textit{3-23l} will lead to both \textit{exo-3-23l-Int} and \textit{endo-3-23l-Int}, where one of the substituents is in \textit{exo} and the other in \textit{endo}. The energy difference between these two intermediates would not be so substantial that product \textit{3-24l} formed only in 2.5:1 ratio of diastereomers. Although the 1,2-stereochemical relationships in \textit{3-23m} and \textit{3-23n} is identical to that of \textit{3-23l}, the cyclic nature of the 1,2-vicinal substituents could make more pronounced differentiation between the energy of the \textit{endo} and \textit{exo} intermediates, leading to increased selectivity in \textit{3-24m} and \textit{3-24n}.

In 2006, Blechert and coworkers reported a related RRM process of cyclopentene derivative \textit{3-27} with a tertiary carbon centre at the branch point of the alkenyl group (\textit{Figure 3.1}). Although the RRM product was obtained from this substrate (P = TBDMS) in excellent yield, the diastereoselectivity was low (2:1).\textsuperscript{5a} To justify these outcome, the authors proposed that the metathesis was initiated both at the pendant alkene and endocyclic double bond in \textit{3-27}.\textsuperscript{5b}

It is quite surprising that the RRM of \textit{3-27} and \textit{3-23} shows such a stark difference in its diastereoselectivity despite their structural similarity. To reconcile these perplexing behaviours, we hypothesized that R group at the quaternary carbon center in \textit{3-23} should play a crucial role for the observed high diastereoselectivity. As opposed to the two possible initiation events with Blechert
substrate 3-27, leading to both the low and high-selectivity intermediates, the sterically demanding R
group in substrate 3-23 prevents the initiation at the endocyclic double bond, rendering only the initiation
at the pendant alkene possible, which ultimately lead to the high-selectivity intermediate (exo-3-23-Int).
It is obvious that the energy difference between the two bicyclic diastereomeric intermediates 3-28
derived from the initiation at the endocyclic double bond will be smaller compared to that between the
two intermediates exo-Int and endo-Int originated from the initiation at the pendant alkene. Currently,
we don’t have any evidence to completely rule out the possibility of initiation from the endocyclic
double. However, even with this initiation event, the final outcome will not be altered because the
incipient alkeylidene species would undergo ring-closing metathesis to regenerate the cyclopentene
much faster than to form cyclohexene product.126

Figure 3.1

3.3.4. Desymmetrizing metathesis of acyclic substrates containing three terminal alkenes

To further elucidate the origin of the observed diastereoselectivity with substrate 3-23, ring-
closing metathesis (RCM) of the corresponding acyclic counterpart 3-29 was investigated (Scheme 3.7).
Not surprisingly, when 3-29g, 3-29i, 3-29o, and 3-29p were subjected to the typical metathesis
conditions product 3-24g, 3-24i, 3-24o, and 3-24p were obtained with the same level of efficiency and
selectivity as the corresponding RRM of substrate 3-23. A careful monitoring of the metathesis process
of 3-29g by $^1$H NMR revealed the accumulation of an intermediate at the early stage, which then slowly disappeared while the product steadily increased. The characteristic $^1$H NMR signature of the intermediate could be assigned to that of 3-23g.

Scheme 3.7

On the basis of this observation, we formulated an overall mechanistic picture as depicted in Scheme 3.8. We surmise that the initiation of ring-closing metathesis starts with any one of the three terminal alkenes in 3-29 with equal probability to form 3-30 as well as two diastereomeric intermediates 3-31, and 3-32. While these initially formed intermediates are in an equilibrium of rapid alkylidene exchanges ($k_1, k_{-1} > k_2, k_3 >> k_4$), the kinetically favorable ring-closure to form 5-membered ring occurs much faster over the 6-membered counterpart ($k_2 >> k_3, k_4$), draining the equilibrium down to the observed steady intermediate 3-23. Once the concentration of 3-23 reached to a certain level, the high diastereoselectivity path starts to kick in to convert 3-23 to the final product 3-24.
3.4. Application to total synthesis of (±)-nitramine

The construction of cyclopentene derivatives followed by their RRM to cyclohexene derivatives containing contiguous stereogenic centers and a quaternary carbon provided a general and versatile platform for the synthesis of diverse natural products, such as nitramine and glanthamine (Scheme 3.9). Both of these two natural products share three common characters: 1) They possess two neighboring stereogenic centers in which one of them is an all-carbon quaternary center and the other is secondary oxygen substituent; 2) Those two stereogenic centers have a certain relative stereochemistry, which could be expressed perfectly in the dRRM reactions; 3) The pendant terminal allyl groups could be modified to form the resultant spirocycles in the natural products with another substituents at the newly-formed quaternary center.

Scheme 3.8
We initially aimed at the synthesis of structurally simple natural product nitramine using $d$RRM reaction. Nitramine is a naturally occurring spiropiperidine alkaloid isolated from plants of the *Nitraria* genus. It has a 2-azaspiro-[5,5]-undecanol structure.\(^\text{127,128}\) Its structure closely resembles the molecular framework of the neurophysiologically important histriomicotxin alkaloids.\(^\text{129}\) One of the main challenges in the synthesis of nitramine is the installation of quaternary carbon center with a correct stereochemistry relative to the secondary hydroxyl group at the next carbon.

Our synthesis commenced with LAH reduction of commercially available dimethyl cyclopent-3-ene-1,1-dicarboxylate followed by monoprotection and a sequential Swern oxidation,\(^\text{130}\) allylation and TBDMS protection, providing the RRM substrate 3-36. As expected, the desymmetrization under metathesis condition smoothly afforded the desired diastereomer 3-37 in 95% yield and high diastereoselectivity (>20:1) (Scheme 3.10). Subsequent hydroboration-oxidation\(^\text{131}\) afforded advanced intermediate 3-38. Several ring-closure strategies including $S_N$2, double $S_N$2 and double reductive amination, were not fruitful. Alternatively, 3-38 was transformed to the corresponding azide 3-39 under Mitsunobu reaction condition,\(^\text{132}\) which was then subjected to hydrogenation conditions to delivered 3-40 in almost quantitative yield after Boc protection. Oxidation of the primary hydroxyl group of 3-40 with Dess-Martin periodinane induced a spontaneous cyclization with concomitant incorporation of acetoxy group, providing bicyclic intermediate 3-41. Treatment of 3-41 with TFA resulted in a cyclic imine 3-42, which was reduced and desilylated to deliver the target natural product nitramine.
Scheme 3.10. Reagents and conditions: (a) Grubbs second-generation catalyst (4 mol%), CH₂Cl₂, H₂C=CH₂, rt, 95%; (b) 9-BBN, then NaOH/H₂O₂, 64%; (c) DEAD, PPh₃, DPPA, THF, 93%; (d) 10% Pd/C, H₂, (Boc)₂O, EtOAc, >95%; (e) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂; (f) TFA, CH₂Cl₂; (g) NaBH₄, MeOH; (h) NH₄F, MeOH, 82% over four steps.

3.5. Application to synthesis of galanthamine

3.5.1. Introduction and background

Galanthamine was isolated from the Caucasian snow-drop (*Galanthus woronowii*) and the bulbs of different species of the *Amaryllidaceae* family. It possesses acetylcholinesterase (AChE) inhibitory and neuronal nicotinic receptor allosteric modulating effect. Currently this natural alkaloid has been approved for symptomatic treatment of mild to moderate Alzheimer’s disease (AD) and various other memory impairments, in particular those of vascular origin.

Due to the scarce supplies of natural sources and expensive isolation from natural sources, many synthetic approaches have been developed for the total synthesis of galantamine. Key synthetic issues that organic chemists addressed in their syntheses are how to efficiently build the tricyclic benzofuran core having a sterically congested quaternary center and how to construct the allylic hydroxyl moiety which is essential for its bioactivity.¹³³ Among the known synthetic routes, most of them rely on two key transformations to make tricyclic benzofuran core, one is the biomimetic approach via the oxidative phenol coupling reaction; the other is the intramolecular Heck reaction.¹³⁴
3.5.2. Previous syntheses

3.5.2.1. Previous syntheses based on oxidative phenol coupling reactions

Figure 3.2.

Barton and Kirby was the first to recognize that *Amaryllidaceae* alkaloids, including galanthamine 3-45, could be derived from norbelladine 3-43 via intramolecular oxidative phenol coupling reaction (Figure 3.2). In 1962, they accomplished the first total synthesis of racemic galanthamine, although the key step yield was very poor (1.4%) (Scheme 3.11). The preparation of norbelladine derivative 3-49 started from the condensation of the acyl chloride 3-46 and the *N*-methylamine 3-47 to generate the amide 3-48, which was then reduced with LAH followed by deprotection of benzyl group to afford the oxidative phenol coupling reaction substrate 3-49.

Scheme 3.11. Reagents and conditions: (a) benzene, rt, 2 h, 85%; (b) i) LiAlH₄, Et₂O, reflux, 2 h, 88%; ii) H₂, 10% Pd/C, MeOH, rt, 2 h, 76%; (c) K₂Fe(CN)₆, NaHCO₃, H₂O, rt, 2.5 h, 1.4%; (d) LiAlH₄, Et₂O, reflux, 2 h, 61%.
Kametani et al. utilized diphenol 3-51 as the substrate of oxidative phenol coupling to obtain a narwedine derived product in 40% yield (Scheme 3.12).\textsuperscript{136} They believed that the improved yield is the consequence of the presence of a para-bromine atom to the hydroxyl group that prevents the competing reaction at the para position. Later, Carroll and coworkers also applied para-bromo-substituted phenols 3-54 to their oxidative coupling reaction.\textsuperscript{137}

\begin{equation}
\text{Kita et al. used trimethylsilyl group to protect the para position to promote the desired ortho coupling reaction (Scheme 3.13).}\textsuperscript{138} \text{ More importantly, they used PIFA as a suitable oxidant instead of iron reagent. The use of trifluoroethanol as solvent was also critical for this transformation.}
\end{equation}

\begin{figure}
\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme_3.12}
\end{center}
\end{figure}

\textbf{Scheme 3.12}

Similarly, Kita et al. used trimethylsilyl group to protect the para position to promote the desired ortho coupling reaction (Scheme 3.13).\textsuperscript{138} More importantly, they used PIFA as a suitable oxidant instead of iron reagent. The use of trifluoroethanol as solvent was also critical for this transformation.

\begin{figure}
\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme_3.13}
\end{center}
\end{figure}

\textbf{Scheme 3.13. Reagents and conditions:} (a) PIFA, CF\textsubscript{3}OH, 36%; (b) CF\textsubscript{3}CO\textsubscript{2}H, rt, 30 min; (c) K\textsubscript{2}CO\textsubscript{3}, Me\textsubscript{2}SO\textsubscript{4}, quantitative yield in two steps.

In 2001, Node et al. reported a PIFA-promoted oxidative coupling reaction of N-formamide 3-60 in trifluoroethanol to afford the tricyclic dienone 3-61 in high yield (85%).\textsuperscript{139} Then the reaction of 3-61
with boron trichloride at low temperature afforded the desired narwedine-type compound, on which the extra hydroxyl group was reduced to generate 3-62 by its conversion to a triflate group followed with a palladium(0)-catalyzed reduction with formic acid. Then 3-62 was converted to galanthamine (Scheme 3.14). In 2004, Node and coworkers reported an asymmetric synthesis of (−)-galanthamine through remote asymmetric induction with a chiral imidazolidinone auxiliary derived from phenylalanine.140

Scheme 3.14. Reagents and conditions: (a) PIFA, CF₃CH₂OH, 85%; (b) BCl₃, CH₂Cl₂, -78 °C, 95%; (c) i. Tf₂O, pyridine, 99%; ii. Pd(OAc)₂, PPh₃, Et₃N, HCO₂H, 97%.

In 1978, on the basis of predecessors’ work, Koga and coworkers finished the first asymmetric synthesis of (+)- and (−)-galanthamine 3-45 using L-tyrosine methyl ester as the chiral pool.141 In 1998, Jordis and coworkers made a great contribution to the studies of galanthamine by reporting a kilogram-scale asymmetric synthesis. (Scheme 3.15)142 The synthetic sequence includes the known process related to Carroll’s to narwedine and a spontaneous resolution method of racemic narwedine developed by Shieh and Carlson.143 Once chiral narwedines were obtained, L-selectride reduction led to the high-yielding of galanthamine in enantiomerically pure form. The spontaneous resolution of racemic narwedine 3-44 is usually achieved by the addition of a small amount of a foreign substance (such as enantiomerically pure (−)-narwedine 3-44 or (−)-galanthamine 3-45) in ethanol/Et₃N (9:1) and then crystallization at 40 °C. The whole synthetic route requires neither low-temperature reactions nor chromatographic purifications. Currently, commercial supplies of galanthamine from Sanochemia AG are based on this route in nine steps from 3,4-dimethoxybenzaldehyde and 12% overall yield.
Scheme 3.15. **Reagents and conditions**: (a) EtOH/Et$_3$N, cat (–)-narwedine 3-44, cooled at 40 °C, 80%; (b) L-selectride, 99%.

### 3.5.2.2. Previous syntheses based on intramolecular Heck reactions

In 2000, Fels group reported a stereoselective approach toward the galanthamine ring system based on the intramolecular Heck reaction (Scheme 3.16). They treated the ether substrate 3-63 with palladium(0) catalyst in the presence of base, affording the compounds 3-64 in good yield. Then 3-64 were transformed to tetracyclic product 3-75. One year later, Parsons *et al.* demonstrated a similar approach to compound 3-75. However, interestingly, both of them did not finish the total synthesis of galanthamine.

Scheme 3.16

In 2000, Trost and Toste successfully used this strategy to finish the total synthesis of (–)-galanthamine (Scheme 3.17). They used the palladium-catalyzed asymmetric allylic alkylation (AAA) reaction to generate the substrates for the Heck reaction. However, Heck reactions are not straightforward. Finally, they found bidentate alkylphosphine ligands, especially depe (1,2-bis(dicyclohexylphosphino)ethane) would suppress side reactions, such as olefin isomerization and phenol ionization reaction. Benzofuran 3-68 along with monodeprotected product 3-67 was obtained in 69% yield. Since attempts to convert 3-69 to (–)-galanthamine by direct allylic oxidation were unsuccessful, alternatively, they resorted to a tedious four-step protocol. Epoxidation of 3-69 to form 3-
followed by regioselective ring opening with sodium phenylselenide produced \( \alpha \)-hydroxy selenide intermediate, which was converted to isogalanthamine 3-71 by treating with sodium periodate and heating to 80 °C. Reaction of 3-71 with Osborn’s rhenium catalyst delivered (–)-galanthamine.

Scheme 3.17. Reagents and conditions: (a) Pd(OAc)$_2$ (20 mol%), dcpe (18 mol%), Proton sponge, DMA, 80 °C, P = TBDMS, 50% and P = H, 19%; (b) i. TsOH; ii. DMDO, acetone; iii. DBU, CH$_2$Cl$_2$, 45%; (c) PhSeSePh, NaBH$_4$, EtOH, 80 °C; (d) NaIO$_4$, then 80 °C, 64%; (e) Ph$_3$SiOReO$_3$, TsOH, PhH, 60 °C, 50%.

A shorter and more efficient synthesis was reported two years later (Scheme 3.18).$^{148}$ In this version, Trost and Tang used nitrile 3-72 as the substrate to perform Heck reaction, which resulted in high yielding of benzofuran 3-73. Allylic oxidation using SeO$_2$ yielded the compound 3-74 in moderate yield but with good diastereoselectivity (10:1). The mixture was submitted to a one-pot reaction involving reductive amination, reduction of nitrile to aldehyde and formation of the hemiaminal, which was reduced with NaCNBH$_3$ to afford (–)-galanthamine.
Scheme 3.18. Reagents and conditions: (a) Pd(OAc)$_2$ (15 mol%), dpdp (15 mol%), Ag$_2$CO$_3$, PhCH$_3$, 107 °C, 91%; (b) SeO$_2$, NaH$_2$PO$_4$, 150 °C, dr = 10 : 1, 64%; (c) i. MeNH$_2$; ii. DIBAL-H; iii. NaCNBH$_3$, 62% (−)-3-45 and 6% (−)-epi-3-45.

In 2001, Guillou et al. reported a total synthesis of racemic glanthamine using the intramolecular Heck reaction to generate the spiro quaternary carbon center as a key step (Scheme 3.19).$^{149}$ Heck cyclization of 3-75 was accomplished in the presence of Pd$_2$(dba)$_3$, dppe and thallium acetate in acetonitrile with 67% yield. Deprotection of the dioxolane group followed by a nonclassical dehydrogenation reaction provided the key intermediate spirocyclohexadienone 3-77, which was converted to (±)-oxonarwedine 3-79 through a sequence of aminolysis, Michael addition and Pictet-Spengler reaction. Reduction of the enone and amide functionality led to (±)-galanthamine.

Scheme 3.19. Reagents and conditions: (a) Pd$_2$(dba)$_3$ (10 mol%), dppe [1,2-bis(diphenylphosphanyl)ethane] (20 mol%), TIOAc (1.2 equiv.), CH$_3$CN, 67%; (b) Ph$_3$CBF$_4$, CH$_2$Cl$_2$, 100%; (c) (PhSeO)$_2$O, CH$_2$Cl$_2$, 50%; (d) 40% aq MeNH$_2$, THF, 100%; (e) (CH$_3$O)$_n$, TFA, DCE, 60 °C, 63%; (f) L-selectride, THF, -78 °C, 93%; (g) LAH, DME, 50 °C, 80%.
Very recently, Zhou and coworkers reported an enantioselective synthesis of (–)-galanthamine by using a highly efficient palladium-catalyzed intramolecular reductive Heck reaction (Scheme 3.20).\textsuperscript{150} Employing sodium formate as a reducing reagent and the iodinated substrate 3-81 was crucial.

Scheme 3.20

3.5.2.3. Other syntheses

Except oxidative phenol coupling and intramolecular Heck reaction, there are some other synthetic strategies used to construct the tricyclic benzofuran core, such as, radical cyclization,\textsuperscript{151} intermolecular alkylation,\textsuperscript{152} semipinacol rearrangement\textsuperscript{153} and intramolecular oxa-Michael addition\textsuperscript{154} etc. Herein only one example is briefly introduced.

In 2009, Magnus et al. completed a concise synthesis of (–)-galanthamine via racemic narwedine intermediate (Scheme 3.21).\textsuperscript{155} It involves eight steps with an overall yield of 63%, which is approximately five times the yield of the current commercial process. The synthesis commenced with a Suzuki coupling between tris(p-tert-butyldimethylsilyloxy)phenyl-2,4,6-trioxatriborinane 3-89 and commercially available 3-83 to afford diaryl compound 3-84. Treatment of 3-84 with ethylvinyl ether and bromine resulted in the formation of ether 3-85. Key intramolecular phenol alkylation was carried out in DMF at 130 °C in the presence of 3 equivalents of CsF, leading to 3-86. Refluxing of 3-86 in 2 M HCl in dioxane generated 3-87, which was reductively aminated to form 3-88. The complex 3-88 was converted to (±)-narwedine 3-44 by the treatment with 1 M MeSO\textsubscript{3}H. (±)-narwedine could be converted to (–)-galanthamine by spontaneous resolution followed by L-Selectride reduction in virtually quantitative yield.
Scheme 3.21. Reagents and conditions: (a) boronic acid trisanhydride 3-89, Pd$_2$(dba)$_3$, PCy$_3$, BHT, K$_2$CO$_3$, dioxane/H$_2$O, 80 °C, 99%; (b) ethyl vinyl ether, bromine, $^t$Pr$_2$NEt, CH$_2$Cl$_2$, 0 °C, 99%; (c) CsF, DMF, 130 °C, 1.5 h, 96%; (d) 2 M HCl, dioxane, reflux; (e) MeNH$_3$Cl, $^t$Pr$_2$NEt, NaCNBH$_3$, AcOH, dioxane, 93%; (f) MeSO$_3$H, dioxane, reflux, 72% in two steps.

3.5.3. Retrosynthetic analysis

To further demonstrate the prowess of the aRRM in the total synthesis of natural products, we chose galanthamine as the next target molecule. We envisioned that a aRRM of 3-35 would construct the tricyclic benzofuran core with a correct relative stereochemistry (Scheme 3.9). More importantly, the two newly-formed double bonds might be further elaborated to the corresponding moieties in galanthamine. Thus this would be a conceptually distinct strategy from the previous ones.

Retrosynthetically, the tetracyclic galanthamine could be appended onto a preformed tricyclic benzofuran 3-90 since a Pictet-Spengler reaction of 3-90 with para-formaldehyde will be reliable for the seven-membered ring closure (Figure 3.3). A regioselective allylic alcohol formation from epoxide opening of 3-91 would be expected through phenyl selenide axial attack to form 3-93 followed by selenoxide elimination, leading to the penultimate intermediate 3-90. The favored axial attack results from the formation of the energetically stable chair-like transition state during the epoxide opening. 3-91 could be obtained by functional group transformations from the terminal alkene to the methylamine via ozonolysis and reductive amination. The stereoselective epoxidation of the aRRM product 3-24j from
the sterically more hindered side might be achieved via a saponification of formyloxy iodide by the treatment with I₂ and formic acid in a basic condition.

![Chemical Structures](image)

**Figure 3.3**

The spiro tricyclic dRRM substrate 3-35 may be obtained from 3-94 by a Mitsunobu reaction following deprotections (Figure 3.4). The transformation of 3-96 to 3-95 would be realized via a gold-catalyzed formation of oxonium ions from the silyl ether of 1,5-enyn-3-ol followed by an intramolecular allyl trapping event described previously. Enyne 3-96 could be traced back to arylacrolein 3-97 via a Barbier reaction with propargyl bromide. Stille cross-coupling reaction between aryl iodide 3-98 and stannylacrylate 3-99 should lead to arylacrolein 3-97 after reducing the ester functional group to aldehyde.
3.5.4. Results and discussion

3.5.4.1. Synthesis of dRRM substrate 3-35

3.5.4.1.1. Synthesis of dRRM substrate 3-35 based on Stille coupling reaction

Synthesis of dRRM substrate 3-35 commenced with the protection of guaiacol 3-100 as a MOM ether and the ortho metallation directed by MOM group followed by trapping with iodine to give aryl iodide 3-102 in 82% yield (Scheme 3.22). Stille cross coupling of 3-102 with ethyl 2-(tributylstanny1) acrylate afforded the arylacrylate 103 in 90% yield. Not surprisingly, DIBAl-H reduction of ester 3-103 to aldehyde 3-104 at low temperature failed. Instead, a mixture of aldehyde 3-104 and the corresponding alcohol were obtained; so oxidation using Dess-Martin periodinane was applied to the mixture to give the aldehyde 3-104 in 65% yield. Barbier reaction installed the propargyl group, generating 1-hexen-2-aryl-5-yn-3-ol 3-105 in 50–70% yield. Two serious problems regarding the Barbier reaction should be noted are 1) most of the time the Barbier reaction was not that clean and it always accompanied with substantial amount of allene byproduct, which affected the isolation of the desired propargylic alcohol 3-105; 2) sometimes a significant amount of isomeric byproduct was detected due to the MOM group transfer.
Scheme 3.22. Reagents and conditions: (a) MOMCl, DIPEA, CH₂Cl₂, reflux; (b) nBuLi (2.2 equiv.), 0°C then I₂, 82% in two steps; (c) ethyl 2-(tributylstannyl) acrylate (1.2 equiv.), Pd(PPh₃)₄ (10 mol%), LiCl (6 equiv.), CuCl (5 equiv.), DMF, 60 °C, 90%; (d) DIBAl-H, PhMe, -78 °C; (e) Dess-Martin Periodinane, NaHCO₃, CH₂Cl₂, 65% in two steps; (f) propargyl bromide, Zn, DMF, aq. NH₄Cl, 50–70%.

Then the alcohol 3-105 was converted under standard protection condition to its diphenylallylsilyl ether 3-106, which is the substrate for generating the homoallylic substituted cyclopentene 3-107 in the next step using our gold-catalyzed cycloisomerization/allylation cascade described previously (Scheme 3.23). Unfortunately, treatment of 3-106 with gold catalyst 3-9 and phenol in CH₂Cl₂ did not give the desired product 3-107. Instead an acetal product 3-110 was obtained, which is probably the consequence of the participation of the neighboring oxygen atom on the benzene ring to form 3-109 followed by the loss of MOM group and protiodeauration. 3-110 was subjected to a standard metathesis condition, which leaves the starting material untouched as we had expected.
Scheme 3.23. Reagents and conditions: (a) Au(SMe₂)Cl (1 mol%), xantphos (1 mol%), allyldiphenylsilane, DMF, 90 °C, 91%; (b) Au cat. 3-9 (2 mol%), PhOH (1.2 equiv.), CH₂Cl₂, 83%.

To solve this problem, we then examined the possibility of forming the tetrahydrofuran ring prior to the generation of cyclopentene (Scheme 3.24). Deprotection of the resulting alcohol 3-105 led to 1,4-diol 3-111. Treatment of 3-111 with triphenyl phosphine and DIAD in THF delivered Mitsunobu reaction product dihydrobenzofuran 3-339. On the basis of our previous study,¹¹⁵ exposure of 3-112 to the gold catalyst 3-9, allyltrimethylsilane and isopropanol in CH₂Cl₂ should induce an intermolecular allylic trapping of the in-situ formed oxonium 3-113 to produce 3-35. However, surprisingly, no desired product 3-35 was obtained. Based on the NMR analysis, a dibenzo[b,d]furan 3-115 was the exclusive product, resulting presumably from E1 elimination.
Scheme 3.24. Reagents and conditions: (a) conc. HCl (cat.), iPrOH or TFA, CH$_2$Cl$_2$, 0 °C; (b) PPh$_3$, DIAD, THF, 0 °C, 90% yield in two steps; (c) Au cat. 3-9 (2 mol%), allyltrimethylsilane, iPrOH (1.2 equiv), CH$_2$Cl$_2$, quantitative yield.

Next, to avoid the formation of the undesired product resulting from the neighboring oxygen participation, we switched the protecting group from MOM to a sterically hindered TIPS or TBDMS group (Scheme 3.25). Although the yields were much lower than before, the Stille coupling of bulky silyl group protected aryl iodides still provided the enough amounts of materials for further study. TBDMS protected coupling product 3-117 reacted with diphenylallylsilane under gold-catalyzed hydrosilylation condition to generate the allylsilyl ether 3-12.$^{117}$ Gratifyingly, neighboring oxygen participation was suppressed by the presence of TBDMS group during the course of gold-catalyzed cycloisomerization. The resultant cyclopentene product 3-13 was obtained in an excellent yield. Treatment of 3-13 with TBAF followed by a Mitsunobu reaction resulted in the desired $d$RRM substrate 3-35. However, when TIPS-protected coupling product 3-116 was considered for the cycloisomerization/allylation sequence, however, disappointingly, it could not generate the corresponding allylsilyl ether. Alternatively, without diphenylallylsilyl group, a carboxaldehyde 3-118 formation followed by allylation via Grignard reaction and globe deprotection delivered the diol 3-94. Similarly 3-94 was converted to the spiro $d$RRM substrate 3-35 by Mitsunobu reaction.
**Scheme 3.25.** Reagents and conditions: (a) Au(SMe₂)Cl (1 mol%), xantphos (1 mol%), allyldiphenylsilane, DMF, 90 °C, 79%; (b) Au cat. PhOH (1.2 equiv.), CH₂Cl₂, 93%; (c) TBAF, THF; (d) PPh₃, DIAD, THF, 88% in two steps; (e) Au cat. 3-9 (2 mol%), CH₂Cl₂, rt, 85%; (f) allylMgBr, THF, 0 °C, 67%; (g) TBAF, THF, 95%.

Instead of preventing it from occurring, we utilized the neighboring oxygen participation wisely to shorten the synthetic route of generating diol 3-94 (**Scheme 3.26**). Removal of MOM group of 3-105 followed by a gold-catalyzed cycloisomerization involving an oxygen participating event provided 3-119. Hemiacetal 3-119 was converted to the spiro dRRM substrate 3-35 as previously described in **Scheme 3.25** with an overall 60% yield. Without deprotection, 3-105 could be converted to a MOM protected hemiacetal 3-120. However, all the attempts, such as, TMSOTf or I₂ catalyzed allylation or direct allylation using allyl Grignard reagent, failed to generate 3-35 as the major product.
**Scheme 3.26.** *Reagents and conditions:* (a) 2M HCl, \(^i\)PrOH, THF, 89%; (b) Au cat. 3-9 (2 mol%), CH\(_2\)Cl\(_2\), 90% (from 3-111 to 3-119), 95% (from 3-105 to 3-120); (c) allylMgBr, Et\(_2\)O, 0 °C, 83%; (d) PPh\(_3\) (1.1 equiv.), DIAD (1.1 equiv.), THF, 91%.

Although the \(d\)RRM substrate 3-35 had been obtained, the yield is pretty low and variable according to the linear synthesis of 3-105 outlined in **Scheme 3.22.** To improve it, we envisioned a more divergent route by employing stannyl-substituted enynes 3-124 as Stille coupling partners. The preparation of 3-124 began with a reduction of ethyl 2-(tributylstannyl) acrylate 3-99 to the corresponding aldehyde 3-122 followed by Barbier reaction to form 2-stannyl-hexenyn-3-ol 3-123, which was protected with TES group to give 3-124 (**Scheme 3.27**).
Scheme 3.27. Reagents and conditions: (a) DIBAl-H, THF, 0 °C, 66%; (b) TPAP (7 mol%), NMO (1.6 equiv.), 4Å MS, CH₂Cl₂, 70%; (c) propargyl bromide, Zn, DMF, aq. NH₄Cl, 61%; (d) TESCl, imidazole, DMAP (cat.), CH₂Cl₂, 93%; (e) Pd(PPh₃)₄ (10 mol%), CuCl (5 equiv.), LiCl (6 equiv.), DMSO, 65 °C, 2 d, 41% (from 3-124 to 3-125); overnight, 20% (from 3-127 to 3-128).

Initial attempt of Stille coupling was performed between the iodide 3-102 and stannane 3-124 (Scheme 3.27). However, no desired product was detected instead 3-355 was isolated as major product with recovery of some stannane starting material. To inhibit the undesired C(sp)–C(sp²) coupling, a TES-substituted stannane 3-127 derived from 3-124 was applied. As a result, only about 20% desired product 3-128 was obtained after stirring at 65 °C overnight.

3.5.4.1.2. Synthesis of spiro dRRM substrate 3-35 based on Suzuki coupling reaction

With the disappointing Stille coupling results, we resorted to Suzuki coupling (Scheme 3.28). Similarly, 2-bromo-3-siloxyl-hexenyn 3-130 having a terminal alkyne group underwent a faster undesired C(sp)–C(sp²) coupling with the aryl pinacol boronic ester 3-129 rather than the desired Suzuki coupling when a catalytic amount of PdCl₂(PhCN)₂, triphenylarsine and silver oxide (1.6 equiv.) was used. When the terminal alkyne was protected with a TES group, a dimerization of the aryl pinacol...
boronic ester occurred to generate 3-134. When 20 mol% palladium tetrakis and a mixture of benzene and methanol as solvent was used, a moderate yielding (47%) of 3-135 was obtained.

\[
\text{OMe} \quad \text{OMOM} \quad + \quad \text{Br} \quad \text{OTES} \quad \text{PdCl}_2(\text{PhCN})_2(10 \text{ mol})\% \quad \text{AsPh}_3(20 \text{ mol})\% \quad \text{Ag}_2\text{O} \quad \text{THF}/\text{MeOH} (8:1), \text{rt} \\
\text{3-129} \quad \text{3-130} \quad \text{3-131} \quad \text{3-132} \quad \text{3-133} \quad \text{3-134} \quad \text{3-135}
\]

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<td>PdCl₂(PhCN)₂ (10 mol%), AsPh₃ (20 mol%), Ag₂O (1,6 equiv.), THF/MeOH (8:1), rt</td>
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<td>dimer 3-134 (major)</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄ (20 mol%), 2M Na₂CO₃, benzene/MeOH, 80 °C</td>
<td>47% 3-135</td>
</tr>
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Scheme 3.28

3.5.4.2. dRRM and epoxidation

With the spirocyclic substrate 3-35 in hand, a standard dRRM condition gave a cis-ring junction isomer 3-24j in an excellent yield (90–95%), which is exactly the carbon backbone of galanthamine. Several epoxidation procedures were attempted including saponification of formyloxy iodide, mCPBA as well as oxone in acetone, however, none of them gave desired epoxide 3-136, either with the recovering of the starting material 3-24j or ending up with a messy mixture. (Table 3.4).
In addition to epoxidation, dihydroxylation was also examined under the condition of a catalytic amount of OsO\(_4\) in the presence of NMO in acetone/H\(_2\)O mixed solvent (Scheme 3.29). The reaction selectively occurred at the internal double bond to form the diol 3-137, leaving the terminal double bond intact. Although treatment of the diol 3-137 with excessive amount of NaH (4 equiv.) and one equivalent of tert-butyldimethylsilyl chloride only afforded a mixture of 3-138 and 3-139 in a ratio of 1:1, they could be separated by column chromatography.

**Scheme 3.29.** Reagents and conditions: (a) OsO\(_4\) (cat.), NMO, acetone/H\(_2\)O (4:1), 90%; (b) NaH (4 equiv.), TBDMSCl (1 equiv.), THF, -78 °C, 3-138, 42% and 3-139, 44%.

### 3.5.4.3. Functionalization of terminal double bond

Next, we turned our attention to examining the feasibility of functionalization of terminal double bond prior to that of internal double bond (Scheme 3.30). It was envisioned that the terminal double bond could be transformed to a primary hydroxyl group via hydroboration-oxidation sequence. Once the primary alcohol 3-140 is available, it could be converted to a primary amide 3-141, which would be further converted to the corresponding one-carbon shorter amine 3-142 via Hofmann rearrangement.
However, the terminal double bond proved to be unexpectedly difficult to functionalize. Two typical hydroboration-oxidation conditions failed to give any positive results (entries 1 and 2 in Scheme 3.31). We then intended to use a cross metathesis (CM) of 3-24j to functionalize the terminal double bond. Unfortunately, the CM reaction under variable reaction temperature and metathesis partners led to the recovery of starting materials (entries 3-5). Hydrosilylation using platinum catalyst 3-144 was also fruitless (entry 6). A tandem metathesis of 3-35 involving RRM and CM only resulted in 3-146 based on the $^1$H NMR analysis. The poor reactivity of the terminal double bond is probably due to the steric hindrance resulting from the rigid tricyclic skeleton.

**Scheme 3.30**

**Scheme 3.31**

<table>
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<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i. 9-BBN, THF, 0 °C, ii. NaBO$_3$ or NaOH, H$_2$O$_2$</td>
<td>3-24j + unknown</td>
</tr>
<tr>
<td>2</td>
<td>i. BH$_3$SMe$_2$, -20 °C, ii. NaOH H$_2$O$_2$</td>
<td>complicated</td>
</tr>
<tr>
<td>3</td>
<td>G-II (cat.), 3-143, benzoquinone, DCM, 40 °C</td>
<td>recover 3-24j</td>
</tr>
<tr>
<td>4</td>
<td>G-II (cat.), 3-143, benzoquinone, toluene, 80 °C</td>
<td>recover 3-24j</td>
</tr>
<tr>
<td>5</td>
<td>G-II, ethyl vinyl ether, toluene, 80 °C</td>
<td>recover 3-24j</td>
</tr>
<tr>
<td>6</td>
<td>3-144 (cat), PF$_3$, PHMe$_2$SiH, CH$_2$CN, 80 °C</td>
<td>complicated</td>
</tr>
</tbody>
</table>
3.5.4.4. C–O coupling based strategy

With the failure of functionalization of the terminal double bond, we deduced that cleavage of a C–O bond in the benzofuran to make the σ-bond connecting the aromatic ring and cyclohexene moiety free rotatable might reduce the steric congestion around the allyl group. Therefore, we examined the reactivity of the terminal double bond in 3-152, which was obtained from dRRM of the cyclopentene 3-151 without a spiro structure. The synthesis of 3-151 was outlined in Scheme 3.32. After extensive experimentation, we found a Suzuki coupling between 3-methoxyphenyl boronic acid and the vinyl bromide 3-147 smoothly generated the enyne 3-148. Removal of TES group and protection of secondary alcohol with diphenylallylsilyl group provided 3-150, which afforded the cyclopentene 3-151 under the previously described gold(I)-catalyzed cycloisomerization/intramolecular allylation condition.

![Scheme 3.32](image)

**Scheme 3.32. Reagents and conditions:** (a) boronic acid (3.5 equiv.), Pd(PPh3)4 (10 mol%), 2 M Na2CO3, MeOH/benzene (1:5), 87%; (b) TBAF, CH2Cl2, 87%; (c) dimethylallylsilane, AuCl(SMe2) (1 mol%), xantphos (1 mol%), DMF, 90 °C, 80%; (d) Au cat. 3-9 (2 mol%), PhOH, CH2Cl2, rt, 88%.

As expected, metathesis of 3-151 afforded the desired desymmetrization product 3-152 in 84% yield (Scheme 3.33). Treatment of 3-152 with 9-BBN at room temperature followed by H2O2 in sodium hydroxide solution resulted in the formation of primary alcohol 3-153 in 45% yield. Oxidation of 3-153 with Dess-Martin periodinane gave an obvious aldehyde signal in the crude 1H NMR but the desired carboxylic acid wasn’t isolated after the following Pinnick oxidation.159
Scheme 3.33. Reagents and conditions: (a) G-II (5 mol%), CH₂Cl₂, 84%, +dr = 8:1; (b) i. 9-BBN (3 equiv.), THF, rt; ii. NaOH, H₂O₂, 45%; (c) Dess-Martin periodinane, CH₂Cl₂; (d) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, THF/H₂O.

Alternatively, a sequence of epoxidation followed by ozonolysis was examined (Scheme 3.34). Due to the preciousness of the cyclohexene 3-152, we carried out a model study by using an easily accessible substance 3-24a. Deprotection of 3-24a led to the secondary alcohol 3-156, which underwent a facial stereoselective epoxidation directed by the free hydroxyl group at the homoallylic position to give the epoxide 3-157. Reprotection of the free alcohol with TES group followed by exposure of the epoxide 3-158 to a saturated ozone solution in dichloromethane provided the aldehyde 3-159. Subjection of 3-159 to bistrimethylsilyl methylamine in methanol in the presence of magnesium sulfate afforded an imine intermediate, which was further reduced to the primary amine 3-160 by NaBH₄. We envisioned that the lithium amide generated from the secondary amine by a suitable alkyl lithium reagent might induce an intramolecular elimination to open the epoxide and form the desired allylic hydroxyl moiety in 3-161. However, the conditions using nBuLi under variable temperatures and solvents failed to give any positive results.
Scheme 3.34. Reagents and conditions: (a) 6 M HCl, MeOH, 95%; (b) VO(acac)₂, tBuOOH, CH₂Cl₂, rt, 92%; (c) TESOTf, Et₃N, DMAP (cat.), DMF, 80 °C, 93%; (d) O₃, CH₂Cl₂, MeOH then Me₂S; (e) MeN(TMS)₂, MeOH, MgSO₄; (f) NaBH₄, 59% in three steps.

While the model studies were underway, we started to examine the requisite dihydrobenzofuran ring closure (Scheme 3.35). Originally, we planned to utilize the Pd(II)-catalyzed hydroxyl directed C–H activation/C–O cyclization reaction developed in Yu’s lab. Soon, we realized that, although it is a powerful method for constructing dihydrobenzofurans, the method was limited to tertiary alcohol substrates. The cyclization of secondary alcohol gave substantially lower yield due to the competitive oxidation of the alcohol to ketone via β-hydride elimination. In order to improve the furan ring closure efficiency of the secondary alcohol, a traditional C–O cyclization through Pd(0) or Cu(I) catalysis may be reliable by introducing a halogen substituent (X) ortho to the methoxy and the cyclohexenyl. Therefore, a series of regioselective bromination conditions based on the heteroatom directed ortho-metallation were tried (Scheme 3.35). Unfortunately, no desired brominated product 3-164 was observed.
With the failure of all above strategies, we made another detour (Figure 3.5). We planned to start the synthesis with a substrate having a 2-bromo-3-methoxy phenyl group. Also, this time, a
desymmetrization of triene 3-167 was chosen instead of previous dRRM reaction due to the ready availability of 3-167 compared to that of the corresponding cyclopentene substrate.

The synthesis of the cyclohexene 3-166 commenced with a regioselective bromination of 3-hydroxybenzaldehyde\textsuperscript{162} followed by methylation to give 2-bromo-3-methoxybenzaldehyde 3-171 (Scheme 3.36). Treatment of 3-171 with the deprotonated methyl methylysulfinylmethyl sulfide at 50 °C resulted in the formation of 1-methylsulfinyl-1-thiomethyl alkene, which was exposed to HCl in ethanol to generate the ethyl aryl acetate 3-168. Diallylation of 3-168 followed by a standard reduction and oxidation sequence delivered the diallyl aryl carboxaldehyde 3-173. After the third allyl was installed using allylmagnesium bromide, a TBDMS protection afforded the desymmetrization substrate 3-167.

Unexpectedly, under the standard dRRM condition, the cyclohexene 3-174 was formed in a mixture of two diastereomers with 4 : 1, which is in sharp contrast with the previous observed general high diastereoselectivity.

\textbf{Scheme 3.36. Reagents and conditions:} (a) Fe powder (cat.), NaOAc (2 equiv.), HOAc, then Br\textsubscript{2} (1.1 equiv.), 44%; (b) MeI, DMF, K\textsubscript{2}CO\textsubscript{3}, 93%; (c) methyl methylysulfinylmethyl sulfide, NaH, THF, rt to 50 °C, overnight; (d) HCl (2 M in Et\textsubscript{2}O), EtOH, 60 °C, overnight, 81% in two steps; (e) NaH, TBAI (cat.), allyl bromide; (f) LDA, HMPA, allyl bromide, TBAI (cat.), 80% in two steps; (g) LAH, THF; (h) (COCl\textsubscript{2}, DMSO, -78 °C, then Et\textsubscript{3}N, 89% over two steps; (i) allylMgBr, THF, 0 °C; (j) TBDMSOTf, DMF, Et\textsubscript{3}N, DMAP (cat.), 74% over two steps; (k) Grubbs second-generation catalyst (4 mol%), H\textsubscript{2}C=CH\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, \textit{dr} = 4:1, 90%.
3.5.5. Future work

At this point, the key remaining problem is to selectively open the epoxide, further constructing the allylic hydroxyl moiety. According to the original plan in Figure 3.3, a regioselective epoxide-opening would be expected through phenyl selenide axial attack followed by selenoxide elimination to form 3-175 (Scheme 3.37). With 3-175 in hand, deprotection followed by C–O cross coupling would generate the penultimate intermediate 3-90. A Pictet-Spengler reaction of 3-90 with para-formaldehyde is expected to deliver the natural product galanthamine 3-45.

Scheme 3.37

Because of the limited supplies from natural sources, a number of synthetic strategies towards galanthamine or its analogues have been developed including some highly efficient ones. However, this does not render the search for other novel and efficient total synthesis. Different from the known approaches, our synthetic route features a novel diastereoselective ring closing metathesis of tirene to not only set an all-carbon quaternary stereogenic center but also define the stereochemical relationship of two contiguous stereogenic centers. Also, our synthetic route may provide access to a broad range of analogues, which could possess potential bioactivities and further advance the understanding towards Amaryllidaceae family natural products.
3.6. Application to synthesis of caribenol A

3.6.1. Introduction and background

Caribenol A, a novel norditerpene with an unprecedented tricarbocyclic skeleton, was isolated by Rodríguez and coworkers in 2007 from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* (Figure 3.6). It has strong inhibitory activity against *Mycobacterium tuberculosis* (H37Rv).163

![Caribenol A and Caribenol B](image)

**Figure 3.6**

The interesting molecular structure and promising biological activities of caribenol A has attracted significant attention from synthetic chemists. In 2010, Yang and coworkers164 reported the first and the only total synthesis, which featured intramolecular Diels-Alder reaction (IMDA) and biomimetic oxidation reactions. The authors assembled IMDA precursor 3-178 efficiently from three building blocks: chiral enone 3-179, methyl propiolate and dienyl iodide 3-180 (Figure 3.7). However, interestingly, seemingly reactive precursor 3-178 did not provide the expected IMDA product with various Lewis acid or under higher temperature. After many attempts, the authors found 2,6-di-tert-butyl-4-methylphenol (BHT) could serve as active catalyst to generate the desired IMDA product 3-181 in 92% yield (Scheme 3.38). Then 3-181 was converted to 3-182 through a sequence of hydrogenation, deprotection, esterification following reduction. Oxidation of allylic alcohol and hydrogenation afforded intermediate 3-183. Treatment of 3-183 with KHMDS delivered vinyl triflate after trapping with Comins reagent [N-(5-chloro-2-pyridyl) triflimide], which underwent a Negishi coupling reaction with ZnMe₂ to form a reduced caribenol A 3-184. In order to finish the total synthesis, the authors screened a variety of oxidative methods to oxidize C–H bond at C-5 position. Finally, the caribenol A was achieved by treatment of compound 3-184 with oxygen gas in the presence P(OEt)₃ under basic conditions in 66% yield.
Scheme 3.38. Reagents and conditions: (a) BHT, toluene, 120 °C, 24 h, 92%; (b) Rh(PPh3)3Cl, H2, PhH, 66 °C, 95%; (c) HF/Pyr, THF, rt, 91%; (d) NaBH4, CeCl3•7H2O, EtOH, 0 °C, 92%; (e) TPAP, NMO, 4 Å MS, CH2Cl2, rt, 92%; (f) Pd/C, H2, THF, 93%; (g) KHMDS, THF, Commins reagent [N-(5-chloro-2-pyridyl) triflimide], -78 °C, 92%; (h) Pd(PPh3)4, Me2Zn, THF, rt, 84%; (i) O2, DMF, K2CO3, P(OEt)3, 60 °C, 80 h, 66%

3.6.2. Retrosynthetic analysis

A careful examination of the structure of caribenol A reveals that the molecule contains two contiguous stereogenic centers with one all-carbon quaternary stereogenic center on the central seven-membered ring. This structural feature reminded us of the capability of the dRRM methodology we described in 3.4. We envisioned the dRRM could set those two neighboring stereogenic centers and the central seven-membered ring could be achieved by ring expansion from cyclohexene (Figure 3.8).

Retrosynthetically, disconnection of C–O bond of butenolide in the caribenol A (3-176) would generate the reduced form of the carboxylic acid 3-185, which should be accessible from 3-186 by one-carbon homologation. Tricyclic intermediate 3-186 was proposed to arise through an intramolecular
Aldol condensation of keto aldehyde 3-187, which can be formed from 3-188 through a ring expansion of six-membered ring followed by deprotection and oxidation of primary alcohol to aldehyde. Bicyclic intermediate ketone 3-188 was generated by alkylation of 3-189, which could be traced back to the methyl ketone 3-190 via an alkylidene carbene insertion into allylic C–H bond to produce cis-fused bicyclic ring followed by a double bond migration and a Michael addition. A Wacker oxidation of RRM product 3-22 was expected to afford compound 3-190. dRRM substrate cyclopentene 3-21 was readily available according to the previous described procedure.

Figure 3.8

3.6.3. Results and discussion

3.6.3.1. Synthesis of cis-fused bicyclic enone 3-195

To test the feasibility of the synthetic route shown in Figure 3.8, a successful preparation of the requisite cis-fused bicyclic enone 3-195 was highly needed (Scheme 3.29).

We initially aimed at a racemic synthesis of 3-195, which commenced with dimethylallylsilyl ether 3-10a formation followed by a tandem gold-catalyzed cycloisomerization–intramolecular allylation to generate symmetric cyclopentene 3-11a, which was directly subjected to the standard dRRM condition without further purification, resulting in the formation of cyclohexene 3-22f in 90% overall yield.
Although a low diastereoselectivity was obtained in this metathesis, it wasn’t our concern at this stage since the stereogenic center connected to the siloxy group will be oxidized eventually for the completion of the total synthesis. For a successful execution of a regioselective alkylidene carbene insertion, a protecting group switching from silyl to pivaloyl was required. Typical protection procedure using pivaloyl chloride and triethylamine in the presence of catalytic amount of $N,N$-dimethylaminopyridine at high temperature (120 °C) afforded 3-193, but a nonnegligible triene byproduct was also detected, which was probably the consequence of the E2-elimination of the pivalate under the harsh condition. However, using excessive amount of pivaloyl chloride and pyridine as solvent at 60 °C could avoid the side-reaction, thus a substantial improvement of the yield was achieved. Treatment of 3-193 with a catalytic amount of palladium chloride and 1.5 equivalents of copper(I) chloride in the oxygen atmosphere for 20 hours led to a methyl ketone 3-190. Highly regioselective insertion of the alkylidene carbene derived from 3-190 into the allylic C–H bond delivered cis-fused bicyclic diene 3-194 exclusively, which presumably was the consequence of the deactivation of the tertiary C–H by the electron-withdrawing pivaloyl group. Deprotection of pivaloyl using DIBAI hydride followed by oxidation of the resultant secondary alcohol with PCC followed by a double bond migration afforded cyclohexenone 3-195.

Scheme 3.39. Reagents and conditions: (a) $\text{H}_2\text{C}=\text{CHCH}_2(\text{CH}_3)_2\text{SiCl}$, imidazole, DMAP (cat.), $\text{CH}_2\text{Cl}_2$, 96%; (b) $\text{Au(PPh}_3\text{)Cl/AgSbF}_6$ (2 mol%), PhOH (1.1 equiv.) $\text{CH}_2\text{Cl}_2$, 0 °C to rt, then filter through silica
gel; (c) G-II (5 mol%), CH$_2$Cl$_2$, H$_2$C=CH$_2$, rt to 40 °C, overnight, 90%, $dr = 2.7 : 1$; (d) TBAF (1.0 M), CH$_2$Cl$_2$, 90% or 2M HCl, MeOH, 92%; (e) PiVCl, Et$_3$N, DMAP (cat.), DMF, 120 °C, 1 h, 65% or PiVCl, pyridine, 60 °C, 12 h, 90%; (f) PdCl$_2$ (15 mol%), CuCl (1.5 equiv.), O$_2$, H$_2$O/DMF, 20 h, 84%; (g) TMSC(Li)N$_2$, THF, -78 °C to rt, 79%; (h) DIBAl-H, CH$_2$Cl$_2$, 77%; (i) DMP, CH$_2$Cl$_2$, then DBU 86%.

Concurrent with racemic synthesis, an enantioselective synthesis was also explored. A chiral $d$RRM substrate could be derived from a chiral cyclopentenyl homoallylic alcohol. Gratifyingly, an asymmetric allylation of methylecyclopentenylcarbaldehyde 3-196 using Leighton’s reagent ($S$, $S$)-3-197$^{165}$ afforded a ($S$)-3-198 in 90% yield and >95% ee (Scheme 3.40).

![Scheme 3.40](image)

### 3.6.3.2. Alkylation of ketone 3-419

Having establishing a reliable for the preparation of enone 3-195, we begin to explore the following reactions in the synthetic plan shown in Figure 3.8 (Scheme 3.41). A Michael addition was examined first using Gilman reagent in diethyl ether at low temperature, affording the addition product in 70% yield but a low diastereoselectivity ($dr = 1.5 : 1$). Switching the solvent from diethyl ether to THF resulted in a lower yield (50%) and significant improvement of the diasteromeric ratio. A mixed solvent of THF and diethyl ether (THF/Et$_2$O = 2:1) gave a better yield and a little bit improved diastereomeric ratio.

![Scheme 3.41](image)
Direct trapping of the enolate from the Michael addition with TMSCl provided the silyl enol ether 3-199 (Scheme 3.42). Treatment of 3-199 with methyl lithium followed by the addition of iodide 3-200 failed to afford the desired α-alkylation product 3-201. The linear iodide 3-200 was used rather than the requisite branched (R)-2-methyl-3-iodopropanol tert-butyldimethylsilyl ether in order to avoid the unnecessarily troublesome handling of diastereomers. Then we tried LDA as the base at varied temperatures along with the addition of HMPA, but, all the attempts were not successful until we used nBuLi combined with HMPA, a desired α-alkylation took place, accompanied with the nucleophilic addition of the n-butyl lithium.

![Scheme 3.42](image)

### Scheme 3.42

#### 3.6.3.3. Ring expansion

With cyclohexanone 3-201 in hand, we were ready for the examination of the feasibility of the ring expansion to 3-202. Clearly, a direct lithiated trimethylsilyldiazomethane addition to the carbonyl group followed by pinacol-type displacement of nitrogen recently developed in our group, would be ideal.\(^{166}\) However, the congested environment around the carbonyl group makes it rather challenging. As shown in Scheme 3.43, we initially screened both of basic condition developed in our lab and Lewis acidic-promoted condition\(^{167}\) using substrate 3-201, but unfortunately all of these attempts failed. To reduce the steric hinderance around the carbonyl group, we decided to use 3-189, the precursor of α-alkylation
product, for the ring expansion, although this reaction sequence switching might bring up some new problems such as the selective installation of a \( \alpha \)-alkyl group adjacent to the existing methyl group in a 7-membered ring in a later stage. Although Sc(OTf)\(_3\)-catalyzed and \( \text{tBuOK} \)-induced conditions did generate some ring expansion products based on NMR and mass spectroscopy data, the products could not be isolated due to the same polarity with that of the unreacted cyclohexanone starting material. Moreover, the regioselectivity is not clear due to the possibility of two different alkyl group migration events.

![Scheme 3.43](image)

**Scheme 3.43**

To facilitate the carbonyl addition, we envisioned that a switch of the intermolecular addition to an intramolecular addition could be achieved by employing the keto aldehyde 3-204 (Scheme 3.44). According to our plan, lithiated trimethylsilyldiazomethane would react with the aldehyde group first to generate the intermediate 3-206. A brook rearrangement converted 3-206 to lithiated diazoalkane 3-207, which would add to the carbonyl group of the cyclohexanone intramolecularly to produce 3-208. The intermediate 3-208 would undergo a pinacol-type rearrangement to deliver the ring expansion product 3-205. In fact, if this reaction is realized, it not only expands the ring size but also constructs the tricyclic skeleton in a single step. However, treatment of 3-204 with 1.2 equivalent of lithiated trimethylsilyldiazomethane at -78 °C did not give any positive results. Probably this is due to the difficulty in the formation of a seven-membered ring to generate the intermediate 3-208.
Scheme 3.44. Reagents and conditions: (a) TBAF, THF; (b) DMP, CH₂Cl₂, NaHCO₃, 76%; (c) TMSC(Li)N₂ (1.2 equiv.), THF, -78 °C to rt.

Alternative strategy based on the ring opening of a strained cyclopropane, via either heterolysis or homolysis of the shared bond, in [4.1.0] bicyclic ring system could also lead to the seven-membered ring. Exposure of 3-189 to LDA followed by quenching with trimethylsilyl chloride afforded silyl enol ether 3-199, which was treated with diethyl zinc and diiodomethane under Simmons-Simth cyclopropanation condition to generate 3-209. Then we resorted to FeCl₃-promoted ring opening of 3-209. Thus the cyclopropane 3-209 was treated with anhydrous FeCl₃ dissolved in dry DMF in the presence of triethylamine. However, a complex reaction mixture was obtained (Scheme 3.45).

Scheme 3.45. Reagents and conditions: (a) LDA, TMSCl, 70%; (b) Et₂Zn, CH₂I₂, toluene, rt; (c) i. FeCl₃ (4 equiv.), DMF, Et₃N, ii, NaOAc, MeOH.

Due to the preciousness of the advanced intermediate 3-189, we planned to use 3-210 as a synthetic analogue to 3-189 (Scheme 3.46). Compound 3-210 and 3-189 are structurally very similar to each other and the only difference is an extra methyl substituent on the cyclic double bond in 3-189, which should not affect the following ring expansion testing. A concise synthesis of 3-210 started with a
Michael addition\textsuperscript{169} between \textit{tert}-butyl propionylacetate 3-211 and crotonaldehyde 3-212 followed by a intramolecular Knoevenagel condensation to form the cyclic intermediate 3-213. \textit{tert}-Butyl propionylacetate 3-211 is commercially available or could be easily prepared from \textit{tert}-butyl acetoacetate.\textsuperscript{170} Under thermal and acidic condition, decarboxylation of 3-213 led to the formation of cyclic enone 3-214. Propargylation of 3-214 with Grignard reagent resulted in the formation of a single isomer 3-215, which was subjected to the Kirsch’s procedure\textsuperscript{112} to induce a cycloisomerization followed by a pinacol-type rearrangement to form 3-210. Overall, ketone 3-210 was obtained in four steps with 55% yield. The ready availability of compound 3-210 greatly facilitates the model study.

\textbf{Scheme 3.46. Reagents and conditions:} (a) \textit{t}BuOK (5 mol%), \textit{t}BuOH, 0 °C, 30 min then \textit{t}BuOK (20 mol%), reflux, 17 h; (b) \textit{p}-TSA (20 mol%), toluene, 80 °C, 76% in two steps; (c) propargyl bromide, Mg, Et\textsubscript{2}O, 81%; (d) Au cat. 3-9, CH\textsubscript{2}Cl\textsubscript{2}, 90%.

With 3-210 in hand, cyclopropane 3-220 was prepared according to the previous procedure. At this time, a different cyclopropane ring opening condition [NaI (1 equiv.), CAN (2 equiv.), CH\textsubscript{3}CN/H\textsubscript{2}O (8 : 1)] was employed to effect the ring expansion (\textbf{Scheme 3.47}).\textsuperscript{171} To our delight, treatment of 3-220 with above condition at room temperature generated a desired \(\beta\)-iodo cycloheptanone 3-221 which was treated with DBU to form the cycloheptenone 3-222. To install an alkyl group selectively at \(\beta\)-position of the carbonyl, initially, we exposed 3-222 to Michael addition, which, surprisingly, resulted in the formation
of a single diastereoisomer 3-223 exclusively. This is quite unusual considering the poor
distereoselectivity control on a seven-membered ring due to its ill-defined conformation.

![Scheme 3.47](image)

**Scheme 3.47. Reagents and conditions:** (a) TMSOTf, Et$_3$N, 0 °C, THF; (b) Et$_2$Zn, CH$_2$I$_2$, toluene, 0 °C to rt, overnight, 80% in two steps; (c) NaI (1 equiv.), CAN (2 equiv.), CH$_3$CN/H$_2$O (8 : 1); (d) DBU, CH$_2$Cl$_2$, 40 °C, 65% in two steps; (e) EtMgBr, CuI, THF, -78 °C, 95%.

3.6.3.4. Model study of one carbon homologation

Additionally, another key step as we planned in Figure 3.8 was also explored. The one carbon homologation of enone 3-185 is based on a synthetic method of β-cyano-α-amino ketone developed in our group,\(^{172}\) we envisioned the β-cyano-α-amino ketone could be further methylated to a tetraalkylammonium salt and then Hofmann elimination would lead to β-cyano substituted enone 3-224 (Scheme 3.48). We initially used (R)-carvone 3-225 for the model study. Formal cycloaddition of trimethylsilyldiazomethane with electron-deficient double bond in 3-225 followed by N-methylation and N-N bond cleavage of the resultant pyrazoline cycloadduct to generate the β-cyano-α-amino ketone 3-226. Quaternary amination using a sequence of reductive amination [(CH$_2$O)$_n$, NaBH(OAc)$_3$] and direct methyl displacement via Meerwein’s salt (Me$_3$OBF$_4$) provided the Hofmann elimination precursor 3-227, which was treated with a concentrated aqueous KOH in toluene, leading to the formation of desired one carbon homologation product 3-228.
Scheme 3.48. **Reagents and conditions:** (a) Trimethylsilyl diazomethane, TBAT (cat.), CH$_2$Cl$_2$, 90%; (b) i. (CH$_2$O)$_n$, NaBH(OAc)$_3$, ii. p-TsOH, 83% in two steps; (c) (CH$_2$O)$_n$, NaBH(OAc)$_3$, 67%; (d) Me$_3$OBF$_4$, CH$_2$Cl$_2$, 50 °C; (e) KOH, toluene/H$_2$O, 70% in two steps.

3.6.4. **Future work**

Based on the above promising results, an enantioselective total synthesis of caribenol A would be expected (Scheme 3.49). This synthetic route features a novel diastereoselective RRM to set an all-carbon quaternary stereogenic center and two lithiated trimethylsilyldiazomethane based methodologies to achieve cyclopentene formation and β-cyano homologation, respectively.

Scheme 3.49

3.7. **Summary**

In summary, we have developed a highly diastereoselective ring-rearrangement metathesis of cyclopentene derivatives. This metathesis-based desymmetrization strategy to set up the stereochemistry
at a non-stereogenic quaternary carbon center provides an efficient entry to the synthesis of cyclohexene skeleton containing an all carbon quaternary stereogenic center. We also found that the same cyclohexene skeleton could be constructed through an alternative metathesis process starting from acyclic trienes.

More importantly, the $d$RRM reaction also provided a general and versatile platform for the synthesis of diverse natural products, which has been illustrated in a concise stereocontrolled total synthesis of (±)-nitramine and the synthetic efforts towards the natural products galanthamine and (−)-caribenol A.
Chapter 4. Experimental details for part I

4.1. General information

All non-aqueous reactions were carried out under an inert nitrogen atmosphere in the flasks which were oven-dried overnight and cooled under a stream of nitrogen unless otherwise indicated. Flash chromatography was performed using silica gel 60 Å (32-63 mesh) purchased from Sorbent Technologies or Silicycle Inc. Analytical thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel 60 (particle size 0.040-0.063 mm). Visualization was accomplished by UV light and TLC stains including iodine, p-anisaldehyde, vanillin, ninhydrin and potassium permanganate solution. Yields refer to chromatographically and/or spectrographically pure compounds, unless otherwise noted.

All reagents were purchased from Aldrich, TCI, Acros, Fisher, Alfa Aesar or Strem and used without further purification unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et2O) were freshly distilled from sodium/benzophenone under nitrogen. Dichloromethane (CH2Cl2), toluene (PhCH3), triethylamine (Et3N) and diisopropylamine (iPr2NH) were distilled from calcium hydride under nitrogen. Anhydrous N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and hexanes was purchased from Aldrich.

1H NMR and 13C NMR spectra were recorded on a Bruker DRX-500 spectrometer. 1H and 13C chemical shifts were referenced to internal solvent resonances and reported relative to tetramethylsilane (SiMe4); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad). 1H NMR signals that fall within a ca. 0.3 ppm range are generally reported as a multiplet, with a single chemical shift value corresponding to the center of the peak. Coupling constants, J, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer in the University of Wisconsin at Madison or on a Waters Micromass Q-Tof Ultima in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra were obtained using a Micromass AutoSpecTM or a Micromass 70-VSE. Chemical ionization (CI) mass spectra were obtained using a Micromass 70-VSE. Fast atom bombardment (FAB)
mass spectra were taken at the Mass Spectrometry Laboratory in the University of Illinois at Urbana-Champaign, using a Micromass 70-VS-4F and 70-VSE. IR spectra were recorded using ATI Mattson, Genesis series FTIR or using JASCO FT-IR-4100 with GLADiATR™ Attenuated Total Reflectance (ATR) FT-IR accessory. Optical rotations were measured on a JASCO DIP-370 digital polarimeter.

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### 4.2. Total Syntheses of (+)-asperpentyn, (–)-harveynone and (–)-tricholomenyn A

![Reaction Scheme](image)

To a stirred solution of trimethylsilyl diazomethane (2.0 M in hexanes, 2.75 mL, 5.5 mmol) in THF (30 mL) was added n-BuLi (2.5 M in hexanes, 2.4 mL, 6.0 mmol) at -78 °C and stirred for 30 min. A solution of the known ketone 4-(triethylsilyl)but-3-yn-2-one\textsuperscript{173} 2-83 (0.91 g, 5.0 mmol) in THF (10 mL) was added slowly to the solution above at -78 °C and the mixture was then stirred while allowing to warm to room temperature over 1 h. The mixture was filtered through a pad of silica gel and washed with ether. After drying over anhydrous MgSO\textsubscript{4}, the filtrate was concentrated under reduced pressure. The residue was purified using flash chromatography (hexane) to afford diyne 2-84 (0.59 g, 3.35 mmol, 67%). Colorless Oil; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 1.93 (s, 1H), 0.98 (t, \(J = 5.3\) Hz, 9H), 0.61 (q, \(J = 5.9\) Hz, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 89.42, 80.44, 75.00, 64.94, 7.36, 4.24.
To a stirred solution of (triethylsilyl)acetylene (2.05 g, 14.65 mmol) in THF (100 mL) was added \textit{n}-BuLi (2.5 M in hexanes, 5.6 mL, 14.0 mmol) at -78 °C and stirred for 30 min. A solution of known aldehyde 5-methylhex-4-enal\textsuperscript{174} 2-96 (1.32 g, 11.7 mmol) in THF (5 mL) was added slowly to the mixture above at -78 °C and the mixture was then stirred while allowing to warm to 0 °C over 1 h. The reaction was quenched by adding saturated NH\textsubscript{4}Cl solution and then was extracted by Et\textsubscript{2}O (3 x 100 mL). After concentration of the organic layer in vacuum, the colorless oil residue (2.73 g, 10.8 mmol, 92\%) was used without further purification. To a homogenous solution of 2-iodoxybenzoic acid\textsuperscript{175} (4.9 g, 17.5 mmol) in DMSO (14 mL) was added the above product (2.73 g, 10.8 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (50 mL) at room temperature. After stirring for 20 min, white precipitates formed and TLC showed the completion of reaction. Then the reaction mixture was filtered and the filtrate was added into water (20 mL) then extracted with ether (3 x 40 mL). The organic layer was concentrated under reduced pressure. The residue was purified using flash chromatography (hexane) to afford 2-97 (2.35 g, 9.37 mmol, 87\%). Colorless Oil; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 5.07 (t, \( J = 7.1 \) Hz, 1H), 2.57 (t, \( J = 5.0 \) Hz, 2H), 2.35 (q, \( J = 7.4 \) Hz, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.00 (t, \( J = 5.3 \) Hz, 9H), 0.66 (q, \( J = 5.9 \) Hz, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 187.56, 133.20, 122.02, 103.26, 96.08, 45.65, 25.65, 22.85, 17.66, 7.29, 3.83; HRMS (FAB) calc. for C\textsubscript{16}H\textsubscript{27}OSi 251.1831, found 251.1831.

To a stirred solution of trimethylsilyldiazo methane (2.0 M in diethyl ether, 1.65 mL) in THF (15 mL) was added \textit{n}-BuLi (2.5 M in hexanes, 1.44 mL) at -78 °C and stirred for 30 min. A solution of ketone 2-97 (0.75 g, 3.0 mmol) in THF (3 mL) was added slowly to the solution above at -78 °C and the
mixture was then stirred while allowing to warm to room temperature over 1 h. The mixture was filtered through a pad of silica gel and washed with ether. The filtrate was concentrated under reduced pressure. The residue was purified using flash chromatography (hexane) to afford 2-98 (0.66 g, 2.7 mmol, 90%). Colorless Oil; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.14 (t, \(J = 6.7\) Hz, 1H), 2.27 (t, \(J = 6.9\) Hz, 2H), 2.22 (dt, \(J = 7.2, 6.7\) Hz, 2H), 1.70 (s, 3H), 1.61 (s, 3H), 0.99 (ddd, \(J = 5.3\) Hz, 9H), 0.61 (q, \(J = 5.9\) Hz, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 133.54, 122.19, 89.47, 81.03, 79.18, 65.69, 26.93, 25.65, 19.81, 17.73, 7.35, 4.26; HRMS (FAB) calc. for C\(_{16}\)H\(_{27}\)Si 247.18821, found 247.18820.

To a solution of allylpropargyl ether 2-71 (1.06 g, 11.0 mmol) in THF (10 mL), was added \(n\)-BuLi (2.5 M in hexanes, 4.2 mL, 10.5 mmol) dropwise at -78 °C. After stirring of 1 h at the same temperature, was added a solution of the known aldehyde 4-1 (2R,3R)-3-((tert-butyldimethylsilyloxy)methyl)oxirane-2-carbaldehyde\(^{176}\) in THF (2.16 g, 10.0 mmol) for 10 min. at -78 °C. The reaction mixture was slowly warmed to ambient temperature, quenched with saturated NH\(_4\)Cl solution, extracted with Et\(_2\)O, dried over anhydrous MgSO\(_4\), and concentrated to yield 2.81 g (9.0 mmol, 90%) of mixture of alcohols 2-79 and 2-80. Each diastereomer was separated via silica gel chromatography (ether:pentane = 1:20−1:10). Colorless Oil; Compound 2-79: \([\alpha]_D = +47.0\) (CHCl\(_3\), \(c = 1.0, 22 \^\circ\)C). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.90 (ddt, \(J = 17.2, 10.4, 5.7\) Hz, 1H), 5.31 (dq, \(J = 17.3, 1.6\) Hz, 1H), 5.22 (dq, \(J = 10.4, 1.2\) Hz, 1H), 4.40 (ddt, \(J = 6.9, 5.0, 1.7\) Hz, 1H), 4.20 (d, \(J = 1.8\) Hz, 2H), 4.05 (dt, \(J = 5.9, 1.2\) Hz, 2H), 3.95 (dd, \(J = 12.0, 3.7\) Hz, 1H), 3.78 (dd, \(J = 12.2, 5.7\) Hz, 1H), 3.20−3.28 (m, 2H), 2.24 (d, \(J = 5.2\) Hz, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 134.01, 118.22, 83.22, 83.17, 70.99, 61.64, 61.46, 59.42, 57.67, 57.50, 26.04, 18.50, −5.09, −5.19; HRMS (ESI) calc. for C\(_{16}\)H\(_{28}\)O\(_4\)SiNa [M+Na]\(^+\) 335.1655, found 335.1670.
Palladium catalyst (1.00 g, 10:1 mixture of 5% Pd/CaCO\(_3\) and Pb(OAc)\(_4\)) was added to a solution of the alcohol 2-79 (1.00 g, 3.20 mmol) and quinoline (0.62 g, 4.8 mmol) in 100 mL 1:1 mixture of ethyl acetate and hexanes. The reaction was stirred under the atmospheric pressure of hydrogen gas. The reaction mixture was washed with 100 mL 1N HCl solution, 100 mL saturated NaHCO\(_3\), and 100 mL brine. After the solvent was removed in vacuum, 0.83 g (2.65 mmol, 83% yield) of dienol 4-2 was isolated from silica gel chromatography (EtOAc:hexanes = 1:10−1:3). Colorless Oil; \([\alpha]_D = +2.0\) (CHCl\(_3\), \(c = 1.1, 21^\circ\)C). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.90 (ddt, \(J = 17.2, 10.3, 5.7\) Hz, 1H), 5.77 (dtd, \(J = 11.4, 5.8, 0.8\) Hz, 1H), 5.67 (ddt, \(J = 11.3, 7.7, 1.3\) Hz, 1H), 5.28 (dq, \(J = 17.2, 1.6\) Hz, 1H), 5.20 (ddt, \(J = 10.4, 1.7, 1.2\) Hz, 1H), 4.33 (td, \(J = 7.5, 2.5\) Hz, 1H), 4.10 (AB of ABX, \(J_{AB} = 13.0\) Hz, \(J_{AX} = 6.0\) Hz, \(J_{BX} = 5.5\) Hz, 2H), 3.99 (app. dq, \(J = 5.6, 1.2\) Hz, 2H), 3.79 (AB of ABX, \(J_{AB} = 11.9\) Hz, \(J_{AX} = 4.3\) Hz, \(J_{BX} = 5.9\) Hz, 2H), 3.17 (dt, \(J = 6.0, 4.4\) Hz, 1H), 3.08 (dd, \(J = 7.3, 4.3\) Hz, 1H), 2.73 (d, \(J = 3.2\) Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 134.46, 130.48, 130.38, 117.86, 71.80, 66.97, 66.34, 61.80, 59.64, 57.90, 26.06, 18.51, -5.02, -5.14; HRMS (ESI) calc. for C\(_{16}\)H\(_{30}\)O\(_4\)SiNa [M+Na]\(^+\) 337.1811, found 337.1806.

To a solution of the diene alcohol 4-2 (0.54 g, 1.72 mmol) and pyridine (1.0 ml, 12.4 mmol) in dichloromethane (25 mL), was added 4-dimethylaminopyridine (37 mg) and acetic anhydride (0.7 mL, 7.4 mmol) with stirring at 0 °C. Then the ice bath was removed. After stirred 2 h, the reaction mixture was concentrated under reduced pressure and the residue was purified using flash column chromatography (silica gel, hexane : ether = 10:1−5:1) to afford 606 mg (1.70 mmol, 99%) desired...
product 2-81. Colorless Oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.90 (ddt, $J = 16.1, 10.5, 5.7$ Hz, 1H), 5.80 (A of ABXY, dt, $J = 11.6, 6.1$ Hz, 1H), 5.50 (B of ABXY, ddt, $J = 11.1, 9.6, 1.7$ Hz, 1H), 5.34 (dd, $J = 9.0, 8.8$ Hz, 1H), 5.28 (dq, $J = 17.2, 1.6$ Hz, 1H), 5.19 (dq, $J = 10.4, 1.4$ Hz, 1H), 4.18 (X of ABXY, $J = 12.9, 6.5, 1.6$ Hz, 1H), 4.12 (Y of ABXY, $J = 12.9, 5.8, 1.8$ Hz, 1H), 3.98 (m, 2H), 3.88 (A of ABX, dd, $J = 12.1, 3.6$ Hz, 1H), 3.69 (B of ABX, dd, $J = 12.1, 6.1$ Hz, 1H), 3.18 (X of ABX, dd, $J = 12.6, 4.5$ Hz, 1H), 3.16 (m, 1H), 2.07 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.80, 134.51, 133.01, 124.97, 117.35, 71.66, 69.40, 66.21, 61.55, 57.19, 56.69, 25.88, 21.13, 18.34, -5.20, -5.31.

To a solution of a mixture of the alcohols 2-79 and 2-80 (1.87 g, 6.0 mmol) in dichloromethane (30 mL), was added DMP$^{177}$ (1.85 g, 6.6 mmol) at room temperature. After stirred for 3 h, the reaction mixture was flushed over a plug of cotton, the filtrate was then poured into water and extracted with Et$_2$O. The solution was dried over MgSO$_4$, and concentrated in vacuum. Purification by silica gel chromatography gave 1.65 g (5.2 mmol, 83 % yield) of the ketone 4-3. Colorless Oil; $[\alpha]_D^{20} = +18.8$ (CHCl$_3$, $c = 1.1, 24$ °C). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.88 (ddt, $J = 17.3, 10.4, 5.8$ Hz, 1H), 5.31 (dq, $J = 17.3, 1.6$ Hz, 1H), 5.23–5.28 (m, 1H), 4.34 (s, 2H), 4.08 (dt, $J = 5.8, 1.3$ Hz, 2H), 3.88 (dd, $J = 11.9, 5.6$ Hz, 1H), 3.75 (d, $J = 6.7$ Hz, 1H), 3.73 (dd, $J = 11.9, 4.9$ Hz, 1H), 3.44 (q, $J = 5.1$ Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 181.09, 133.46, 118.82, 92.58, 84.27, 71.35, 60.46, 59.46, 58.81, 57.09, 25.98, 18.46, -5.17, -5.29; HRMS (ESI) calc. for C$_{16}$H$_{26}$O$_4$SiNa [M+Na]$^+$ 333.1498, found 333.1488.
To a flame dried round-bottom flask was added the ketone 4-3 (1.55 g, 5.0 mmol) and Me-CBS reagent (2.77 g, 10.0 mmol) in 30 mL THF. The solution was cooled to -25 °C under the nitrogen environment. 2.0 M borane-ether complex solution in THF (12.5 mL, 25.0 mmol) was then added dropwise for 5 min at -25 °C, and the reaction stirred at the temperature for 4 h. The reaction mixture was poured carefully to saturated NH₄Cl solution at 0 °C, and extracted with Et₂O. The solvent was removed in vacuo and the residue purified by silica gel chromatography (20:1-10:1 pentane:ether) giving 1.14 g (3.65 mmol, 73 %) of the desired α-epimer 2-80 along with 0.11g (0.35 mmol, 7%) of β-epimer 2-79. Colorless Oil; [α]D = -29.9 (CHCl₃, c = 1.1, 24 °C). ¹H NMR (300 MHz, CDCl₃) δ 5.90 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 5.31 (dq, J = 17.3, 1.6 Hz, 1H), 5.22 (ddt, J = 10.4, 1.8, 1.2 Hz, 1H), 4.41 (ddt, J = 7.3, 3.5, 1.7 Hz, 1H), 4.23 (d, J = 1.7 Hz, 2H), 4.04−4.09 (overlap m, 3H), 3.79 (dd, J = 11.9, 5.7 Hz, 1H), 3.28 (dd, J = 7.2, 4.3 Hz, 1H), 3.21 (td, J = 5.4, 4.3 Hz, 1H), 2.97 (d, J = 3.4 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 134.06, 118.11, 84.26, 82.56, 70.84, 61.79, 61.36, 58.47, 57.51, 56.38, 25.98, 18.42, -5.16, -5.31; HRMS (ESI) calc. for C₁₆H₂₈O₄SiNa [M+Na]+ 335.1655, found 335.1648.

Palladium catalyst (1.14 g, 10:1 mixture of 5 % Pd/CaCO₃ and Pb(OAc)₄ was added to a solution of the alcohol 2-80 (1.14 g, 3.65 mmol) and quinoline (0.71 g, 4.8 mmol) in 100 mL 1:1 mixture of ethyl acetate and hexanes. The reaction was stirred under the atmospheric pressure of hydrogen gas. The reaction mixture was washed with 100 mL 1N HCl solution, 100 mL saturated NaHCO₃, and 100 mL brine. After the solvent was removed in vacuo, 0.93 g (2.96 mmol, 81 % yield) of diene alcohol 4-4
was isolated from silica gel chromatography (EtOAc:hexanes = 1:10–1:3). Colorless Oil; \(\alpha\)_D = -23.2 (CHCl₃, c = 1.0, 21 °C). \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 5.92 (ddt, \(J\) = 17.4, 10.4, 5.7 Hz, 1H), 5.77 (br. dt, \(J\) = 11.5, 6.0 Hz, 1H), 5.72 (ddt, \(J\) = 11.3, 7.5, 1.4 Hz, 1H), 5.28 (dq, \(J\) = 17.2, 1.6 Hz, 1H), 5.19 (ddt, \(J\) = 10.4, 1.9, 1.4 Hz, 1H), 4.37 (td, \(J\) = 7.3, 2.2 Hz, 1H), 4.01–4.19 (overlapped AB of ABX, 2H), 4.06 (dd, \(J\) = 11.7, 5.7 Hz, 1H), 4.00 (dm, \(J\) = 5.9 Hz, 2H), 3.80 (dd, \(J\) = 11.7, 6.1 Hz, 1H), 3.20 (td, \(J\) = 5.9, 4.2 Hz, 1H), 3.05 (dd, \(J\) = 7.6, 4.3 Hz, 1H), 2.95 (d, \(J\) = 2.1 Hz, 1H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 134.76, 131.89, 130.39, 117.51, 71.46, 66.82, 66.32, 62.23, 48.77, 56.37, 26.04, 18.46, -5.08, -5.24; HRMS (ESI) calc. for C₁₆H₃ₒ₃O₅SiNa [M+Na]⁺ 337.1811, found 337.1815.

\[
\begin{align*}
\text{O} & \quad \	ext{DiAD, PPh₃, AcOH} \\ 4-4 & \quad \rightarrow \\ & \quad \text{2-81}
\end{align*}
\]

To a flame-dried round-bottom flask, was added the alcohol 4-4 (0.629 g, 2.0 mmol), triphenylphosphine (0.577 g, 2.2 mmol), and acetic acid (0.132 g, 2.2 mmol). The reaction was cooled to 0 °C, and then DIAD (0.471 g, 2.2 mmol) was added in one portion. The reaction was stirred for 2 h and then quenched with water, extracted with Et₂O. The ether solution was dried over anhydrous MgSO₄, and concentrated in vacuum Column chromatography of the residue provided 641 mg (1.8 mmol, 90 % yield) of diene ester 2-81. Colorless Oil; \(\alpha\)_D = +8.3 (CHCl₃, c = 1.0, 22 °C). \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 5.92 (ddt, \(J\) = 16.0, 10.6, 5.6 Hz, 1H), 5.83 (br. dt, \(J\) = 11.5, 6.1 Hz, 1H), 5.52 (ddt, \(J\) = 9.2, 7.9 Hz, 1H), 5.28 (dq, \(J\) = 17.3, 1.7 Hz, 1H), 5.20 (dm, \(J\) = 10.4 Hz, 1H), 4.16 (AB of ABX, \(J_{AB} = 12.9\) Hz, \(J_{AX} = 6.3\) Hz, \(J_{BX} = 6.0\) Hz, 2H), 3.99 (m, 2H), 3.87 (dd, \(J\) = 12.6, 3.6 Hz, 1H), 3.71 (dd, \(J\) = 12.0, 6.1 Hz, 1H), 3.18 (overlapped m, 2H), 2.08 (s, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 170.00, 134.72, 133.22, 125.17, 117.53, 71.85, 69.59, 66.41, 61.74, 57.39, 56.89, 26.05, 21.30, 18.52, -5.03, -5.13; HRMS (ESI) calc. for C₁₈H₃₂O₅SiNa [M+Na]⁺ 379.1917, found 379.1910.
To a solution of the diene ester 2-81 (0.356 g, 1.0 mmol) and pyridine (0.356 ml) in 15 mL dichloromethane, was added 0.356 mL hydrofluoride-pyridine at 0 °C. After stirred 4 h, the reaction was flushed through a pad of silica gel (ether: pentane = 1:5~2:1) to afford 215 mg (0.89 mmol, 89 % yield) desired alcohol 4-5. Colorless Oil; [α] D = +29.3 (CHCl3, c = 1.0, 22 °C). 1H NMR (300 MHz, CDCl3) δ 5.86-5.99 (overlapped, 2H), 5.52-5.67 (overlapped, 2H), 5.30 (dq, J =17.4, 1.5 Hz, 1H), 5.25 (ddt, J = 10.3, 2.2, 1.1 Hz, 1H), 4.31 (ddd, J = 11.7, 7.7, 1.5 Hz, 1H), 4.04 (dt, J = 5.8, 1.5 Hz, 2H), 3.99 (ddd, J = 11.8, 7.3, 0.8 Hz, 1H), 3.85–3.93 (br. m, 1H), 3.65-3.74 (br. m, 1H), 3.21–3.27 (overlapped, 2H), 2.85 (br. t, J = 2.85 Hz, 1H), 2.09 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 170.20, 134.08, 131.56, 127.34, 119.47, 72.30, 69.19, 65.82, 59.92, 57.50, 56.36, 21.29; HRMS (ESI) calc. for C12H18O5SiNa [M+Na]+ 265.1052, found 265.1056.

Dess-Martin periodinane (0.45 g, 1.06 mmol) was added portion-wise to a solution of alcohol 4-5 (0.218 g, 0.9 mmol) in dichloromethane at 0 °C. The reaction was warmed to room temperature over 1 h. The reaction was quenched with 3 mL saturated sodium bicarbonate and 3 mL saturated sodium thiosulfate. Ether was added and the layers separated and then the ether layer was dried over anhydrous magnesium sulfate. The residue was purified by silica gel chromatography to afford 190 mg (0.79 mmol, 88 % yield) desired aldehyde 2-82. Colorless Oil; [α] D = -43.3 (CHCl3, c = 1.1, 21 °C). 1H NMR (300 MHz, CDCl3) δ 9.49 (d, J = 4.7 Hz, 1H), 5.81–5.98 (overlapped m, 2H), 5.75 (ddd, J = 9.6, 6.7, 0.8 Hz, 1H), 5.53 (dt, J = 9.6, 1.7 Hz, 1H), 5.30 (dq, J = 17.3, 1.4 Hz, 1H), 5.21 (ddt, J = 10.2, 3.0, 1.1 Hz, 1H), 4.07 (dd, J = 5.9, 1.6 Hz, 2H), 3.97 (dt, J = 5.7, 1.4 Hz, 2H), 3.51 (dd, J =
4.7, 7.2 Hz, 1H), 3.45 (t, J = 4.9 Hz, 1H), 2.09 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 197.07, 169.54, 134.48, 133.50, 124.70, 117.65, 71.84, 67.89, 66.26, 59.94, 57.79, 21.09; HRMS (ESI) calc. for C₁₂H₁₆O₅SiNa [M+Na]⁺ 263.0895, found 263.0907.

To a solution of the diyne 2-84 (137 mg, 0.77 mmol) and the aldehyde 2-82 (154 mg, 0.64 mmol) in dichloromethane (3 mL) was added Tetrabutylammonium triphenyldifluoro-silicate (TBAT) (17 mg, 0.03 mmol) with stirring at -78 °C. Then the reaction mixture was warmed up slowly to room temperature. A maroon solution was formed at about 0 °C. After stirring at room temperature for 30 min, the solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (florisil, hexane:ether = 10:1) to afford 156 mg (0.37 mmol, 58 %) desired products 2-85 and some TES-unprotected products as minor products, which were protected using TESOTf under basic condition to afford 39 mg (0.09 mmol, 15 %) desired products 2-85.

To a solution of the Grubbs 2nd generation catalyst (15 mg, 0.02 mmol) was added dropwise using a addition funnel a solution of 2-85 (82 mg, 0.19 mmol) in CH₂Cl₂ (50 mL) under nitrogen. During the addition, the reaction was stirred under reflux for 6 h, and then concentrated in vacuum. Purification by silica gel chromatography (10:1 pentane:ether) gave the cyclized products 2-90 and 2-91 (41 mg, 0.12 mmol, 62 % yield). Colorless Oil; Compound 2-90: [α]D = -54.0 (CHCl₃, c = 0.9, 20 °C). 1H NMR (300 MHz, CDCl₃) δ 5.97 (dd, J = 5.1, 1.6 Hz, 1H), 5.56 (m, 1H), 5.31 (s, 1H), 5.27 (t, J = 1.6 Hz, 1H), 4.49 (s, 1H), 3.26–3.28 (overlapped, 2H), 2.11 (s, 3H), 1.90 (s, 3H), 1.01 (t, J = 8.0 Hz, 9H), 0.73 (dq, J = 7.5, 2.0 Hz, 6H); 13C NMR (75 MHz, CDCl₃) δ 170.26, 126.94, 126.42, 124.80, 122.72,
92.03, 87.66, 65.57, 64.31, 53.27, 49.92, 23.17, 20.98, 6.85, 5.00; HRMS (ESI) calc. for C$_{19}$H$_{28}$O$_4$SiNa [M+Na]$^+$ 371.1655, found 371.1654. Compound 2-91: HRMS (ESI) calc. for C$_{19}$H$_{28}$O$_4$SiNa [M+Na]$^+$ 371.1648, found 371.1655.

To a solution of KCN (10 mg, 0.15 mmol) in 95% EtOH, was added 2-90 (16 mg, 0.046 mmol) at room temperature. The reaction was stirred overnight, then quenched with saturated NH$_4$Cl, and extracted with CH$_2$Cl$_2$. The solution was dried over anhydrous MgSO$_4$, and then concentrated in vacuum. Silica gel column chromatography afforded 7.8 mg (0.04 mmol, 87 % yield) natural compound (+)-asperpentyn. Colorless Oil; $[\alpha]_D^\circ = +24.2$ (CHCl$_3$, $c = 0.5$, 20 °C). $^1$H NMR (300 MHz, CDCl$_3$) δ 6.08 (dd, $J = 5.2, 1.3$ Hz, 1H), 5.36 (s, 1H), 5.31 (s, 1H), 4.51 (overlapped, 2H), 3.42 (s, 1H), 3.35 (s, 1H), 3.21 (br.s, 1H), 3.04 (br. s, 1H), 1.92 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 131.54, 126.41, 123.43, 122.72, 111.75, 111.70, 92.56, 86.93, 65.87, 63.05, 52.43, 51.72, 23.46; HRMS (ESI) calc. for C$_{11}$H$_{12}$O$_3$SiNa [M+Na]$^+$ 215.0684, found 215.0686.

To a solution of the TES-protected diol 2-90 (14 mg, 0.04 mmol) in THF (2 mL) was added etrbutylammonium triphenyldifluorosilicate (TBAT, 43 mg, 0.08 mmol) at room temperature. After stirring for about 4 hr, the mixture was flushed through a pad of silica gel. The filtrate was concentrated under reduced pressure and purified using flash chromatography to afford 7.9 mg (0.034 mmol, 84% yield) desired alcohol 4-6. Colorless Oil; $[\alpha]_D^\circ = -30.3$ (CHCl$_3$, $c = 0.4$, 19 °C). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.96 (dd, $J = 5.0, 1.7$ Hz, 1H), 5.47 (dq, $J = 4.9, 1.8$ Hz, 1H), 5.49 (d, $J = 1.8$ Hz, 1H),
5.30–5.32 (m, 1H), 5.07-5.13 (m, 1H), 4.48 (s, 1H), 3.46-3.48 (m, 1H), 3.30–3.33 (dtd, $J = 3.5, 1.9, 1.1$ Hz, 1H), 2.19–2.22 (overlapped, 4H), 2.11 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.47, 132.66, 130.99, 126.74, 124.99, 123.32, 122.90, 92.51, 87.42, 65.64, 65.56, 52.84, 49.92, 37.35, 26.97, 25.90, 21.24, 17.99; HRMS (ESI) calc. for C$_{18}$H$_{22}$O$_4$Na $[M+Na]^+$ 325.1416, found 325.1410.

Manganese oxide (0.02 g, 0.2 mmol) was added to a solution of the alcohol 4-6 (5 mg, 0.02 mmol) in chloroform. The reaction was stirred overnight at ambient temperature, and then filtered through a pad of celite. The concentration of the residue afforded 4 mg (0.016 mmol, 78 % yield) of the ketone 2-92. Colorless Oil; $[\alpha]_D = -156.5$ (CHCl$_3$, $c = 0.4$, 20 °C). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.78 (dd, $J = 5.2, 2.5$ Hz, 1H), 5.83 (ddd, $J = 5.3, 1.6, 1.1$ Hz, 1H), 5.43 (dq, $J = 2.0, 1.0$ Hz, 1H), 5.34 (p, $J = 1.7$ Hz, 1H), 3.75 (ddd, $J = 4.0, 2.5, 1.5$ Hz, 1H), 3.61 (dd, $J = 3.7, 1.0$ Hz, 1H), 2.14 (s, 3H), 1.94 (dd, $J = 1.6, 1.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 189.76, 169.87, 140.77, 126.15, 125.28, 124.43, 111.88, 96.82, 81.29, 64.45, 53.20, 23.22, 20.85; LRMS (ESI) calc. for C$_{13}$H$_{12}$O$_4$SiNa $[M+Na]^+$ 255.0634, found 255.0632.

To a solution of KCN (1.5 mg, 0.022 mmol) in 95% EtOH, was added 2-91 (7.6 mg, 0.022 mmol) at 0 °C. The reaction was stirred for 2 h at the temperature, quenched with saturated NH$_4$Cl solution, and extracted with CH$_2$Cl$_2$. The solution was dried over anhydrous MgSO$_4$, and then concentrated in vacuum. Silica gel column chromatography afforded 5.9 mg (0.019 mmol, 88 % yield) of the desired alcohol 4-7; Colorless oil; $[\alpha]_D = +14.9$ (CHCl$_3$, $c = 0.3$, 27 °C); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 6.02 (d, $J = 4.5$ Hz, 1H), 5.30 (s, 1H), 5.25 (m, 1H), 4.61 (s, $J = 1.1$ Hz, 1H), 4.53 (t, $J = 6.2$ Hz, 1H), 3.42 (s, 2H), 1.90 (s, 3H), 1.62 (d, $J = 7.5$ Hz, 1H), 1.02 (t, $J = 7.8$ Hz, 9H), 0.73 (q, $J = 7.7$ Hz, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 131.39, 126.64, 124.38, 122.35, 92.11, 86.72, 66.03, 63.13,
54.68, 54.42, 29.74, 23.27, 6.89, 5.08; HRMS (ESI) calc. for C$_{17}$H$_{26}$O$_{3}$SiNa [M+Na]$^+$ 329.1549, found 329.1549.

To a solution of the secondary alcohol 4-7 (7.9 mg, 0.026 mmol) and triethyl amine (12 drops) in dichloromethane (2 mL), was added triisoproplysilyl trifluoromethanesulfonate (neat, 3 drops) and N,N-dimethylaminopyridine (DMAP, 6 mg) at 0 °C. Then the ice bath was removed. After stirring for about 5 min, TLC showed the completion of the reaction. The mixture was concentrated under reduced pressure and purified using flash column chromatography (silica gel, hexane : ether = 10 : 1) to afford 11.2 mg (0.024 mmol, 95 % yield) of 2-93; Colorless oil; [α]$_D$ = -19.5 (CHCl$_3$, c = 1.0, 27 °C); $^1$H NMR (500 MHz, CDCl$_3$) δ = 6.03 (d, J = 5.0 Hz, 1H), 5.30 (s, 1H), 5.26 (t, J = 1.5 Hz, 1H), 4.62 (s, 1H), 4.53 (d, J = 5.2 Hz, 1H), 3.42 (s, 2H), 1.90 (s, 3H), 1.03 (t, J = 7.9 Hz, 9H), 0.74 (q, J = 7.9 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 132.42, 126.86, 122.80, 121.99, 91.32, 87.21, 66.04, 63.70, 55.59, 54.72, 23.36, 18.06, 18.02, 12.33, 6.90, 5.09; HRMS (ESI) calc. for C$_{26}$H$_{46}$O$_{3}$Si$_{2}$Na [M+Na]$^+$ 485.2875, found 485.2883.

To a solution of the protected diol 2-93 (5.6 mg, 0.012 mmol) and pyridine (4 drops) in acetonitrile (1.5 mL), was added hydrogen fluoride-pyridine complex (neat, 1 drop) at 0 °C. After stirring at 0 °C for about 10 min, TLC showed the completion of the reaction. The mixture was flushed through a pad of silica gel. The filtrate was concentrated under reduced pressure and purified using flash chromatography (hexane : EtOAc = 4 : 1) to afford 3.2 mg (0.009 mmol, 78 % yield) colorless oil 2-94. [α]$_D$ = +28.1 (CHCl$_3$, c = 0.3, 27 °C); $^1$H NMR (500 MHz, CDCl$_3$) δ = 5.96 (m, 1H), 5.36 (s, 1H), 5.29 (m, 1H), 4.60 (d, J = 4.7 Hz, 1H), 4.50 (d, J = 6.2 Hz, 1H), 3.59 (t, J = 3.4 Hz, 1H), 3.44 (m, 1H), 2.22 (d, J = 7.7 Hz, 1H), 1.92 (s, 3H), 1.09 (m, 3H), 1.08 (d, J = 5.2 Hz, 18H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 132.37, 126.34, 122.93, 122.08, 92.63, 85.53, 65.34, 63.65, 56.05, 53.80, 23.36, 18.05, 18.01, 12.34; HRMS (ESI) calc. for C$_{20}$H$_{32}$O$_{3}$SiNa [M+Na]$^+$ 371.2004, found 371.2018.
Manganese oxide (124 mg, 1.4 mmol) was added to a solution of the alcohol 2-94 (5.0 mg, 0.014 mmol) in chloroform. The reaction was stirred for 2 hrs at room temperature, and then filtered through a pad of celite. The concentration of the residue afforded 4.6 mg (0.013 mmol, 93 % yield) of the ketone 2-95. Colorless Oil; [α]_D = -90.5 (CHCl₃, c = 0.46, 27 °C); ^1^H NMR (500 MHz, CDCl₃) δ = 6.76 (dd, J = 5.2, 2.5 Hz, 1H), 5.83 (dd, J = 5.3, 1.6, 1.1 Hz, 1H), 5.43 (dq, J = 2.0, 1.0 Hz, 1H), 5.34 (p, J = 1.7 Hz, 1H), 3.75 (dd, J = 4.0, 2.5, 1.5 Hz, 1H), 3.61 (dd, J = 3.7, 1.0 Hz, 1H), 2.14 (s, 3H), 1.94 (dd, J = 1.6, 1.0 Hz, 3H); ^1^C NMR (125 MHz, CDCl₃): δ = 190.23, 145.73, 126.14, 123.74, 122.34, 95.19, 81.60, 63.89, 58.04, 53.42, 23.17, 18.00, 17.96, 12.33; HRMS (ESI) calc. for C_{20}H_{30}O_{3}SiNa a [M+Na]^+ 369.1874, found 369.1862.

To a solution of the TIPS-protected alcohol 2-95 (7.3 mg, 0.02 mmol) and pyridine (4 drops) in acetonitrile (2 mL) in a plastic bottle was added hydrogen fluoride-pyridine complex (neat, 25 drops) at room temperature. After stirring for about 2 hr, TLC showed the completion of the reaction. The mixture was quenched by saturated sodium bicarbonate solution (5 mL) and washed with copper sulfate solution (5 mL) twice, then remove the solvent under vacuum. The residue was purified using flash chromatography (hexane : EtOAc = 4 : 1) to afford 3.2 mg (0.016 mmol, 81 % yield) natural product (–)-harveynone. Colorless oil; [α]_D = -207.4 (MeOH, c = 0.2, 27 °C) {lit^80: [α]_D = -208 (MeOH, c = 0.45, 20 °C)}; ^1^H NMR (500 MHz, CDCl₃) δ = 6.85 (dd, J = 5.1, 2.5 Hz, 1H), 5.43 (m, 1H), 5.35 (t, J = 1.6 Hz, 1H), 4.78 (dd, J = 8.2, 5.1 Hz, 1H), 3.82 (dd, J = 3.7, 2.5, 1.3 Hz, 1H), 3.59 (dd, J = 3.6, 1.0 Hz, 1H), 2.03 (d, J = 8.6 Hz, 1H), 1.94 (t, J = 1.2 Hz, 3H); ^1^C NMR (125 MHz, CDCl₃): δ =
To a solution of the diyne 2-98 (87 mg, 0.35 mmol) and the aldehyde 2-82 (77 mg, 0.32 mmol) in dichloromethane (1.5 mL) was added Tetrabutylammonium triphenyldifluorosilicate (TBAT) (17 mg, 0.032 mmol) with stirring at -78 °C. Then the reaction mixture was warmed up slowly to room temperature. A maroon solution was formed at about 0 °C. After stirring at room temperature for 30 min, the solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (florisil, hexane : ether = 10 : 1) to afford 64 mg (65 % brsm) desired products 2-99 and 30 mg recovered diyne 2-98.

To a solution of the Grubbs second-generation catalyst (11.2 mg, 0.013 mmol) was added dropwise using a addition funnel a solution of 2-99 (64 mg, 0.13 mmol) in CH₂Cl₂ (50 mL) under nitrogen. During the addition, the reaction was stirred under reflux for 6 h, and then concentrated in vacuum. Purification by silica gel chromatography (10:1 pentane:ether) gave the cyclized products 2-100. Colorless Oil (58 % yield); Compound 2-100-β: ¹H NMR (500 MHz, CDCl₃) δ 5.97 (dd, J = 5.2, 1.5 Hz, 1H), 5.57 (dq, J = 4.8, 1.5 Hz, 1H), 5.34 (d, J = 1.7 Hz, 1H), 5.27-5.28 (m, 1H), 5.05-5.11 (m, 1H), 4.50 (q, J = 1.4 Hz, 1H), 3.26-3.30 (m, 1H), 3.22 (br. s, 4H), 2.11 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.01 (t, J = 7.9 Hz, 9H), 0.73 (q, J = 7.8 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 170.46, 132.53, 131.29, 127.11, 125.12, 123.39, 122.20, 91.60, 88.62, 65.85, 64.55, 53.46, 50.10, 37.37, 27.01, 25.90, 21.15, 17.99, 7.03, 5.22; HRMS (ESI) calc. for C₂₄H₃₆O₄SiNa [M+Na]⁺ 439.2281, found 439.2277.
To a solution of the dienyne 2-100-β (6.6 mg, 0.015 mmol) and pyridine (10 mg, 0.13 mmol) in acetonitrile (1 mL) in a plastic bottle was added hydrogen fluoride-pyridine complex (neat, 2 drops) at 0 °C. After stirring at 0 °C for about 30 min, the mixture was flushed through a pad of silica gel. The filtrate was concentrated under reduced pressure and purified using flash chromatography to afford 4.2 mg (0.013 mmol, 89% yield) desired product 4-8. Colorless Oil; [α]D = -47.8 (CHCl3, c = 0.37, 27 °C). 1H NMR (500 MHz, CDCl3) δ 5.96 (dd, J = 5.0, 1.7 Hz, 1H), 5.47 (dq, J = 4.9, 1.8 Hz, 1H), 5.49 (d, J = 1.8 Hz, 1H), 5.30–5.32 (m, 1H), 5.07-5.13 (m, 1H), 4.48 (s, 1H), 3.46-3.48 (m, 1H), 3.30–3.33 (dtd, J = 3.5, 1.9, 1.1 Hz, 1H), 2.19–2.22 (overlapped, 4H), 2.11 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 169.96, 132.51, 130.72, 127.38, 125.45, 123.07, 122.81, 93.39, 85.57, 65.33, 64.66, 53.33, 52.84, 37.14, 26.75, 25.72, 20.87, 17.80; HRMS (ESI) calc. for C18H22O4Na [M+Na]+ 325.1405, found 325.1416.

Manganese oxide (0.02 g, 0.2 mmol) was added to a solution of the alcohol 4-8 (3.5 mg, 0.01 mmol) in chloroform. The reaction was stirred for 6 hrs at ambient temperature, and then filtered through a pad of celite. The concentration of the residue afforded 3.0 mg (0.009 mmol, 86 % yield) of the natural product (−)-tricholomenyn A. Colorless Oil; [α]D = -228.0 (CH2Cl2, c = 0.1, 27 °C); {lit60; [α]D = -237 (CH2Cl2, c = 0.6, 20 °C)}; 1H NMR (500 MHz, CDCl3) δ 6.76 (dd, J = 5.2, 2.5 Hz, 1H), 5.82 (dt, J = 5.2, 1.2 Hz, 1H), 5.45 (d, J = 1.6 Hz, 1H), 5.35 (m, 1H), 5.09 (m, 1H), 3.75 (dd, J = 3.8, 2.5, 1.5 Hz, 1H), 3.61 (dd, J = 3.6, 1.0 Hz, 1H), 2.22 (overlapped, 4H), 2.14 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 189.48, 169.69, 140.35, 132.49, 130.59, 125.12, 123.54, 123.55.
123.10, 96.02, 81.95, 64.23, 54.79, 53.00, 37.04, 26.71, 25.74, 20.70, 17.80; HRMS (ESI) calc. for C_{18}H_{20}O_{4}Na [M+Na]^+ 323.1261, found 323.1259.

4.3. Total synthesis of (+)-panepophenantrin

\[
\begin{align*}
\text{O} & \quad \rightarrow \\
\text{O} & \quad \text{OAc} \\
\text{O} & \quad \text{Et}_3\text{Si} \\
\text{Ph}_3\text{SiF}_2\text{NBu}_4 & \\
2-82 & \quad \text{OTES} \\
\rightarrow & \\
\text{OTES} & \quad \text{O} \\
\text{OAc} & \quad \text{O} \\
2-116 & \\
\end{align*}
\]

To a solution of the TES acetylene (221 mg, 1.56 mmol) and the known aldehyde 2-82 (290 mg, 1.20 mmol) in dichloromethane (2.5 mL) was added Tetrabutylammonium triphenyldifluorosilicate (TBAT) (38 mg, 0.072 mmol) slowly with stirring at room temperature. A maroon solution was formed after stirring for 30 min. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (florisil, hexane : ether=10 : 1) to afford 196 mg (0.51 mmol, 43%, d.r.=1 : 1) desired products 2-116 and 82 mg (0.31 mmol, 26%) TES-unprotected product as minor product, which was protected using TESOTf under basic condition to afford desired products 2-116 (86 mg, 0.23 mmol, 73%); colorless oil.

\[
\begin{align*}
\text{OTES} & \quad \rightarrow \\
\text{OH} & \quad \text{G-II} (10 \text{ mol%}) \\
\text{CH}_2\text{Cl}_2, \text{reflux} & \\
2-116 & \quad \rightarrow \\
\text{OTES} & \quad \text{OH} \\
2-115 & \\
\end{align*}
\]

To a solution of 2-116 (80 mg, 0.21 mmol) and but-3-ene-2-ol (38 mg, 0.52 mmol) in dichloromethane (3 mL) was added a solution of the Grubbs 2nd generation catalyst (18 mg, 0.02 mmol) in dichloromethane (2 mL) under nitrogen atmosphere. Then the Schlenk tube was placed in the 50 °C oil bath. The reaction was stirred under reflux for 4 h, and then concentrated in vacuum. Purification by silica gel chromatography gave the cyclized products 2-115 (38 mg, 0.11 mmol, 51% yield, d.r.= 2 : 1); colorless oil.
To a solution of 2-121 (62 mg, 0.20 mmol) and but-3-ene-2-ol (43 mg, 0.60 mmol) in dichloromethane was added a solution of the Grubbs 2nd generation catalyst (12 mg, 0.014 mmol) in dichloromethane (4 mL) under ethylene atmosphere. Then the Schlenk tube was placed in the 50 °C oil bath. The reaction was stirred under reflux for 6 hrs, and then concentrated in vacuum. Purification by silica gel chromatography gave the cyclized products 2-115 (20 mg, 0.056 mmol, 28% yield, d.r.=1 : 5); colorless oil.

Manganese oxide (235 mg, 2.7 mmol) was added to a solution of the alcohol 2-115 (32 mg, 0.09 mmol) in chloroform. The reaction was stirred at ambient temperature for 20 minutes, and then filtered through a pad of celite. The concentration of the filtrate afforded 30 mg (0.085 mmol, 95% yield, d.r.=1 : 1) of the corresponding enones 4-9. One isomer: 1H NMR (500 MHz, CDCl₃) δ 7.10 (d, J = 16.3 Hz, 1H), 6.48 (d, J = 16.3 Hz, 1H), 6.01 (m, 1H), 5.60 (d, J = 4.7 Hz, 1H), 4.86 (s, 1H), 3.50 (t, J = 3.2 Hz, 1H), 3.42 (m, 1H), 2.27 (s, 3H), 2.09 (s, 3H), 1.01 (t, J = 7.9 Hz, 9H), 0.73 (q, J = 8.2 Hz, 6H); the other isomer: 1H NMR (500 MHz, CDCl₃) δ 7.01 (d, J = 16.3 Hz, 1H), 6.39 (d, J = 16.3 Hz, 1H), 6.03 (d, J = 5.0 Hz, 1H), 5.63 (m, 1H), 4.82 (s, 1H), 3.38 (m, 1H), 3.35 (m, 1H), 2.29 (s, 3H), 2.12 (s, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.68 (q, J = 8.2 Hz, 6H); 13C NMR (125 MHz, CDCl₃) δ 198.06, 197.94, 170.17, 169.92, 142.60, 141.31, 137.37, 136.54, 130.16, 128.95, 127.54, 125.06, 65.82, 64.86, 64.48, 63.22, 54.28, 53.15, 52.99, 50.32, 27.57, 27.48, 20.89, 6.90, 6.86, 5.47, 5.33; HRMS (ESI) calc. for [M+Na]⁺ C₁₈H₂₈O₅SiNa: 375.1604, found 375.1599.

To a solution of the corresponding enones 4-9 (17.9 mg, 0.05 mmol) in dry THF (1 mL) was added slowly methylmagnesium bromide solution (3.0 M in Et₂O, 0.10 mmol) in dry ether at 0 °C. The mixture
was stirred for 10 mins, and quenched with sat. NH₄Cl solution. Extraction with ether (3 x 2 mL), drying
the combined extract with MgSO₄ and removing solvent by rotavapor gave the crude product. The
mixture was purified using flash chromatography to afford 13.6 mg (0.037 mmol, 74% yield) desired
tertiary alcohol 2-122.

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\text{OTES} \quad O
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\[
\text{OAc}
\]

\[
\text{OH}
\]

1. KCN, MeOH
2. TBSCl, Et₃N
(51%)

To a solution of KCN (2.9 mg, 0.045 mmol) in 95% EtOH, was added the tertiary alcohol 2-122
(15.4 mg, 0.042 mmol) at 0 °C. The reaction was stirred for 4 h at this temperature, quenched with
saturated NH₄Cl solution, and extracted with CH₂Cl₂. The solution was dried over anhydrous MgSO₄,
and then concentrated in vacuum. Silica gel column chromatography afforded the desired diol; To a
solution of the diol and imidazole (15 mg, 0.22 mmol) in dichloromethane (2 mL), was added tert-
butyldimethylsilyl chloride (12 mg, 0.08 mmol) and N,N-dimethylaminopyridine (DMAP, 4 mg) at 0 °C.
Then the ice bath was removed. After stirring for about 5 min, TLC showed the completion of the
reaction. The mixture was was concentrated under reduced pressure and purified using flash column
chromatography to afford 9.4 mg 2-125 (0.021 mmol, 51 % yield for two steps); Colorless oil; major
diastereomer: ¹H NMR (500 MHz, CDCl₃) δ 6.16 (d, \( J = 16 \) Hz, 1H), 6.10 (d, \( J = 16 \) Hz, 1H), 5.61 (m,
1H), 4.77 (m, 1H), 4.51 (d, \( J = 4.4 \) Hz, 1H), 3.43 (t, \( J = 3.4 \) Hz, 1H), 3.32 (ddd, \( J = 1.3, 2.2, 3.7 \) Hz, 1H),
1.34 (s, 6H), 1.01 (t, \( J = 7.9 \) Hz, 9H), 0.91 (s, 9H), 0.72 (q, \( J = 7.9 \) Hz, 6H), 0.14 (s, 3H), 0.12 (s, 3H);
¹³C NMR (125 MHz, CDCl₃) δ 139.05, 134.81, 125.41, 123.95, 70.98, 66.27, 64.12, 56.50, 55.03, 29.78,
29.74, 25.91, 18.35, 6.99, 5.37, -4.40, -4.58.

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\text{OTES} \quad O
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\text{OTBDMS}
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2-125

1. HF\textsuperscript{+}pyr, pyr
2. MnO₂
(71%)

To a solution of the protected diol 2-125 (8.1 mg, 0.018 mmol) and pyridine (4 drops) in
acetonitrile (1.5 mL), was added hydrogen fluoride-pyridine complex (neat, 1 drop) at 0 °C. After stirring
at 0 °C for about 10 min, TLC showed the completion of the reaction. The mixture was flushed through a pad of silica gel. The filtrate was concentrated under reduced pressure and purified using flash chromatography (hexane : EtOAc=4 : 1) to afford 4.8 mg (0.015 mmol, 82% yield) secondary alcohols (colorless oil). Major diastereomer (--)-isomer 4-12: [α]D = -25.8 (CHCl3, c = 0.48, 27 °C); 1H NMR (500 MHz, CDCl3) δ 6.27 (d, J = 16.1 Hz, 1H), 6.13 (d, J = 16.1 Hz, 1H), 5.57 (s, 1H), 4.64 (dd, J = 3.4, 10.9 Hz, 1H), 4.49 (d, J = 4.2 Hz, 1H), 3.61 (t, J = 3.7 Hz, 1H), 3.44 (ddd, J = 1.1, 2.2, 3.6 Hz, 1H), 1.84 (d, 1H), 1.46 (d, 1H), 1.36 (s, 3H), 1.35 (s, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 140.08, 133.91, 126.57, 125.46, 71.02, 64.02, 63.85, 58.06, 54.96, 29.98, 29.87, 25.86, 18.31, -4.44, -4.60; HRMS (ESI) calc. for C17H30O4SiNa [M+Na]+ 349.1811, found 349.1801.

Manganese oxide (0.02 g, 0.2 mmol) was added to a solution of the corresponding secondary alcohols (4.8 mg, 0.015 mmol) in chloroform. The reaction was stirred at ambient temperature, and then filtered through a pad of celite. The concentration of the residue afforded 4.1 mg (0.013 mmol, 86% yield) of the ketone (--)-2-126. [α]D = -176.0 (CHCl3, c = 0.41, 27 °C) 1H NMR (500 MHz, CDCl3) δ 6.43 (d, J = 16.0 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 6.30 (d, J = 16.1 Hz, 1H), 4.74 (d, J = 5.1 Hz, , 1H), 3.65 (ddd, J = 1.3, 2.5, 3.7 Hz, 1H), 3.54 (dd, J = 1.0, 3.7 Hz, 1H), 1.45 (s, 1H), 1.36 (2 s, 6H), 0.92 (s, 9H), 0.15 (2 s, 6H); 13C NMR (125 MHz, CDCl3) δ 193.35, 142.40, 138.16, 132.95, 119.93, 71.11, 64.28, 58.06, 54.32, 29.74, 25.75, 18.20, -4.28, -4.51; HRMS (ESI) calc. for C17H28O4SiNa [M+Na]+ 347.1655, found 347.1660.

To a solution of the TBS-protected alcohol (--)-2-126 (4.1 mg, 0.013 mmol) in methanol (0.5 mL) was added ammonium fluoride (2 mg, 0.05 mmol) at room temperature. After stirring overnight, TLC showed the completion of the reaction. The mixture was flushed through a pad of silica gel. The filtrate was concentrated under reduced pressure and purified using flash chromatography (hexane : EtOAc=2 : 1) to afford 2.1 mg (0.010 mmol, 77% yield) colorless oil 2-101. 1H NMR (500 MHz, CDCl3) δ 6.59
(dd, J = 5.2, 2.4 Hz, 1H), 6.46 (d, J = 16.1 Hz, 1H), 6.32 (dd, J = 16.1 Hz, 1H), 4.77 (dd, J = 6.9, 6.2 Hz, 1H), 3.81 (m, 1H), 3.57 (d, J = 3.7 Hz, 1H), 1.89 (d, J = 8.5 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 193.16, 143.11, 136.92, 134.04, 119.46, 71.12, 63.73, 57.31, 54.20, 29.80, 29.73.

The monomer 2-101 (2.1 mg, 0.01 mmol) was concentrated and placed in the 30 °C oil bath for 30 h. Purification using flash chromatography afforded natural product (+)-panepophenanthrin; white solid. $^1$H NMR (500 MHz, CD$_3$OD) δ 6.81 (dd, J = 4.9, 3.1 Hz, 1H), 5.99 (d, J = 16.3 Hz, 1H), 5.68 (d, J = 16.3 Hz, 1H), 4.55 (d, J = 1.9 Hz, 1H), 4.35 (d, J = 1.6 Hz, 1H), 3.83 (m, 1H), 3.63 (s, 1H), 3.50 (m, 1H), 3.42 (d, J = 4.0 Hz, 1H), 3.35 (m, 1H), 3.31 (overlapped with solvent, 1H), 2.32 (d, J = 9.9 Hz, 1H), 2.03 (d, J = 9.9 Hz, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H) 1.16 (s, 3H); HRMS (ESI) calc. for C$_{22}$H$_{28}$O$_8$Na [M+Na]$^+$ 443.1682, found 443.1680.

4.4. Gold(I)-catalyzed cycloisomerization/intramolecular allylation

4.4.1. Representative procedure

To a solution of 3-allylsilyloxy-1,5-enzyme 3-10b (60.1 mg, 0.18 mmol) and phenol (18.8 mg, 0.20 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added the Au(I) catalyst 3-9 (1 mol%). The resulting solution was stirred at room temperature for 1 hour, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column
chromatography with hexane and ethyl acetate (30:1) to give the desired cyclopentene product 3-11b (colorless oil, 73.7 mg, 96% yield).

4.4.2. Characterization data

![Image 1](image1.png)

Colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.78 (m, 1H), 4.96 (s, 1H), 4.86 (m, 3H), 4.22 (t, 1H, $J = 6.6$ Hz), 2.39 (m, 2H), 1.97 (t, 1H, $J = 2.6$ Hz), 1.70 (s, 3H), 1.63 (d, 2H, $J = 8.1$ Hz), 0.12 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 145.9, 134.4, 113.6, 112.1, 81.5, 75.4, 69.8, 26.7, 24.8, 16.9, -2.0, -2.1.

![Image 2](image2.png)

Colorless oil (86% yield): $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.93 (m, 1H), 5.59 (s, 2H), 5.04 (dd, 1H, $J = 0.7$ Hz, $J = 17.1$ Hz), 5.00 (dd, 1H, $J = 1.0$ Hz, $J = 10.1$ Hz), 3.66 (dd, 1H, $J = 3.4$, 8.1 Hz), 2.39 (m, 2H), 2.20 (m, 2H), 1.92 (m, 2H), 1.28 (s, 9H), 1.01 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 137.5, 129.2, 128.8, 115.8, 79.8, 72.7, 47.2, 44.4, 43.6, 38.6, 31.9, 23.4, 1.0.

![Image 3](image3.png)

Colorless oil: IR (ATR diamond crystal, cm$^{-1}$) 3300, 3068, 2918, 1634, 1428, 1070; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.64 (m, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 5.84 (m, 1H), 4.93 (m, 3H), 4.86 (s, 1H), 4.35 (m, 1H), 2.47 (m, 2H), 2.24 (m, 2H), 1.96 (s, 1H), 1.73 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 145.1, 135.0, 134.9, 134.4, 133.0, 130.0, 129.9, 127.8, 127.7, 115.2, 112.9, 81.1, 70.1, 26.5, 22.2, 17.0; HRMS (Cl) calcd for C$_{22}$H$_{24}$OSi [M+1]$^+$ 333.1674, found 333.1666.

![Image 4](image4.png)

Colorless oil (78% yield): IR (ATR diamond crystal, cm$^{-1}$) 3052, 2961, 1598, 1493, 1091, 913; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.72 (m, 2H), 7.43 (m, 2H), 7.37 (m, 4H), 7.15 (m, 3H), 6.91 (m, 4H), 5.77 (m, 1H), 5.53 (m, 2H), 4.92 (d, 1H, $J = 17.1$ Hz) ppm 4.90 (d, 1H, $J = 10.7$ Hz), 3.79 (m, 1H), 2.39 (m, 2H), 2.26 (m, 2H), 1.94 (m, 2H), 1.07 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 152.1, 136.3, 135.3, 130.4, 129.2, 128.6, 127.7, 121.3, 119.6, 116.7, 81.5, 47.3, 44.5, 43.8, 38.6, 23.3; HRMS (Cl) calcd for C$_{28}$H$_{30}$O$_2$Si [M+1]$^+$ 427.2093, found 427.2113.
Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3068, 3052, 2963, 2328, 1628, 1428, 1064; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.63 (m, 4H), 7.41 (m, 2H), 7.34 (m, 6H), 7.26 (m, 3H), 5.83 (m, 1H), 1H-NMR (501 MHz), 4.90 (m, 3H), 4.85 (s, 1H), 4.41 (t, 1H, \(J = 6.4\) Hz), 2.67 (m, 2H), 2.24 (m, 2H), 1.75 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 147.1, 135.0, 134.9, 133.1, 129.9, 129.8, 128.1, 127.7, 127.69, 127.64, 124.5, 115.1, 87.1, 82.2, 27.6, 22.2, 17.1; HRMS (EI) calcd for C\(_{28}\)H\(_{28}\)OSi [M\(^+\)] 408.1909, found 408.1897.

Colorless oil (81% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 3052, 2915, 2835, 1591, 1487, 1118, 921, 695; Major: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.79 (m, 4H), 7.47 (m, 2H), 7.40 (m, 4H), 7.32 (m, 3H), 7.24 (m, 2H), 7.19 (m, 2H), 6.99 (m, 2H), 6.94 (m, 1H), 6.03 (s, 1H), 5.82 (m, 1H), 4.98 (m, 2H), 3.93 (s, 1H), 2.73 (m, 2H), 2.41 (m, 2H), 2.31 (m, 2H), 1.19 (d, 3H, \(J = 9.7\) Hz); Minor: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.79 (m, 4H), 7.47 (m, 2H), 7.40 (m, 4H), 7.32 (m, 3H), 7.24 (m, 2H), 7.19 (m, 2H), 6.99 (m, 2H), 6.94 (m, 1H), 6.03 (s, 1H), 5.82 (m, 1H), 4.98 (m, 2H), 3.52 (q, 1H, \(J = 7.0\) Hz), 2.70 (m, 2H), 2.41 (m, 2H), 2.10 (m, 2H), 1.19 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 154.5, 140.1, 136.7, 135.5, 132.4, 130.5, 129.3, 128.2, 127.8, 126.9, 125.5, 124.5, 123.6, 121.4, 119.7, 116.9, 81.4, 47.4, 45.0, 44.5, 44.3, 38.6, 23.6, 23.1; HRMS (CI) calcd for C\(_{34}\)H\(_{34}\)O\(_2\)Si [M\(^+\)] 502.2328, found 502.2333.

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3071, 3052, 2966, 2328, 1628, 1428, 1064; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.62 (m, 4H), 7.46 (m, 2H), 7.40 (dd, 4H, \(J = 4.0, 10.5\) Hz), 5.85 (m, 1H), 4.95 (m, 3H), 4.86 (s, 1H), 4.34 (t, 1H, \(J = 6.4\) Hz), 2.49 (m, 2H), 2.25 (m, 2H), 1.72 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 145.3, 135.1, 134.4, 133.1, 130.0, 127.8, 115.2, 112.8, 77.3, 75.7, 39.9, 27.8, 22.2, 17.1.
Colorless oil (69% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 3071, 2928, 1591, 1428, 1067, 916; \(^1\)H NMR (CDCl\(_3\), 500 MHz) diastereomer A: \(\delta\) 7.71 (m, 4H), 7.46 (m, 2H), 7.39 (m, 4H), 7.16 (m, 2H), 6.91 (m, 3H), 5.75 (m, 1H), 5.71 (s, 1H), 4.93 (m, 2H), 3.78 (m, 1H), 1.8-3.0 (m, 6H), 1.13 (s, 3H); diastereomer B: \(\delta\) 7.71 (m, 4H), 7.46 (m, 2H), 7.39 (m, 4H), 7.16 (m, 2H), 6.91 (m, 3H), 5.75 (m, 1H), 5.63 (s, 1H), 4.93 (m, 2H), 3.78 (m, 1H), 1.8-3.0 (m, 6H), 1.13 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 154.4, 135.6, 132.2, 130.6, 129.7, 129.3, 127.9, 121.5, 119.6, 118.9, 118.2, 117.1, 80.5, 50.4, 48.0, 44.6, 38.4, 24.0; HRMS (CI) calced for C\(_{28}\)H\(_{29}\)BrO\(_2\)Si \([M+1]^+\) 505.1198, found 505.1179.

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3068, 3046, 2978, 1631, 1428, 1070; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.63 (m, 4H), 7.43 (m, 2H), 7.38 (m, 4H), 5.81 (m, 2H), 5.30 (dd, 1H, \(J = 1.8, 17.0\) Hz), 5.08 (dd, 1H, \(J = 1.7, 10.0\) Hz), 4.92 (m, 3H) ppm 4.83 (s, 1H), 4.33 (t, 1H, \(J = 6.6\) Hz), 2.90 (m, 2H), 2.49 (m, 2H), 2.23 (m, 2H), 1.73 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 163.9, 145.6, 136.0, 134.9, 134.6, 133.1, 129.9, 127.7, 115.8, 112.6, 79.4, 78.5, 76.4, 27.0, 23.2, 22.2, 17.1; HRMS (CI) calced for C\(_{25}\)H\(_{28}\)OSi \([M+1]^+\) 373.1987, found 373.1976.

Colorless oil (78% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 3071, 2910, 1643, 1490, 1070, 913; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.71 (m, 4H), 7.43 (m, 2H), 7.36 (m, 4H), 7.14 (t, 2H, \(J = 7.8\) Hz), 6.90 (m, 3H), 5.76 (m, 2H), 5.19 (s, 1H), 4.94 (m, 4H), 3.76 (dd, 1H, \(J = 3.3, 7.9\) Hz), 2.69 (m, 2H), 2.26 (m, 2H), 1.6-2.6 (m, 4H), 1.06 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 154.5, 140.5, 136.3, 136.1, 135.3, 130.3, 129.2, 127.7, 122.8, 121.3, 119.6, 116.7, 116.6, 115.5, 81.5, 47.5, 46.2, 44.2, 38.5, 35.8, 23.5; HRMS (EI) calced for C\(_{31}\)H\(_{34}\)O\(_2\)Si \([M]^+\) 466.2328, found 466.2334.
Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3291, 3071, 2918, 1726, 1634, 1425, 1070; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.59 (m, 4H), 7.42 (m, 2H), 7.36 (m, 4H), 5.80 (m, 1H), 5.04 (s, 1H), 4.90 (m, 3H), 4.34 (t, 1H, \(J = 6.4\) Hz), 4.01 (t, 2H, \(J = 6.5\) Hz), 2.45 (m, 2H), 2.22 (m, 2H), 2.08 (m, 2H) ppm 1.92 (m, 1H) ppm 1.70 (m, 1H), 1.93 (t, 1H, \(J = 2.6\) Hz), 1.68 (m, 2H), 1.19 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 178.5, 148.2, 135.0, 134.2, 132.9, 130.0, 127.8, 115.2, 111.9, 80.9, 75.5, 70.2, 63.9, 38.7, 27.2, 26.9, 26.7, 26.5, 22.1; HRMS (EI) calcd for C\(_{29}\)H\(_{36}\)O\(_3\)Si [M+Na]\(^+\) 483.2, found 483.2.

Colorless oil (81% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 3073, 2904, 1726, 1591, 1490, 1070, 916; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.70 (m, 4H), 7.44 (m, 2H), 7.36 (m, 4H), 7.15 (m, 2H), 6.90 (m, 3H), 5.74 (m, 1H), 5.54 (m, 2H), 4.90 (m, 2H), 3.95 (t, 2H, \(J = 6.4\) Hz), 3.83 (dd, 1H, \(J = 3.7, 7.1\) Hz), 2.45 (m, 2H), 2.30 (m, 2H), 2.03 (m, 2H), 1.60 (m, 1H), 1.50 (m, 2H), 1.40 (m, 1H), 1.19 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 178.5, 154.4, 136.2, 135.3, 132.4, 132.3, 130.4, 129.4, 127.8, 127.7, 121.4, 119.6, 116.7, 80.6, 65.1, 49.3, 41.3, 38.7, 38.2, 30.6, 27.2, 23.6; HRMS (CI) calcd for C\(_{35}\)H\(_{42}\)O\(_4\)Si [M+1]\(^+\) 555.2930, found 555.2948.

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3309, 3068, 3052, 2954, 1631, 1470, 1055, 910; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.68 (m, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 6.79 (m, 2H), 6.66 (m, 1H), 5.87 (m, 1H), 5.73 (s, 1H), 5.25 (s, 1H), 4.93 (m, 3H), 3.78 (s, 3H), 2.42 (dd, 1H, \(J = 2.7, 4.1\) Hz), 2.38 (m, 2H), 2.27 (m, 2H), 1.93 (s, 1H), 0.94 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 150.2, 147.4, 142.1, 135.3, 134.6, 133.3, 132.4, 129.9, 127.6, 122.8, 120.8, 115.9, 115.1, 110.5, 81.7, 73.2, 70.4, 54.7, 26.5, 22.6, 18.8, -3.4, -3.8; HRMS (EI) calcd for C\(_{34}\)H\(_{42}\)O\(_3\)Si\(_2\) [M+1]\(^+\) 555.2751, found 555.2756.
Colorless oil (76% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 3073, 3049, 2931, 2853, 1951, 1457, 1070, 733, 692; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.56 (m, 4H), 7.45 (m, 2H), 7.37 (m, 4H), 7.10 (m, 2H), 6.86 (m, 4H), 6.68 (m, 2H), 5.62 (m, 2H), 4.73 (m, 2H), 4.63 (s, 1H), 3.72 (s, 3H), 3.07 (m, 2H), 2.77 (m, 2H), 2.30 (m, 1H), 2.13 (m, 1H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 156.2, 149.1, 144.3, 136.4, 135.4, 133.1, 130.1, 129.0, 127.5, 122.5, 121.1, 119.2, 116.3, 108.8, 78.0, 55.3, 54.1, 38.7, 27.1, 19.7, 1.0, -1.5; HRMS (EI) calcd for C\(_{40}\)H\(_{48}\)O\(_4\)Si\(_2\) [M]+ 648.3091, found 648.3071.

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3306, 3088, 2937, 1711, 1482, 1028; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.68 (m, 4H), 7.45 (m, 2H), 7.39 (m, 4H), 7.26 (m, 5H), 5.87 (m, 1H), 5.45 (s, 1H), 5.32 (s, 1H), 4.96 (dd, 1H, \(J = 1.5, 17.0\) Hz), 4.90 (d, 1H, \(J = 10.1\) Hz), 4.82 (t, 1H, \(J = 5.8\) Hz), 2.41 (m, 2H), 2.29 (m, 1H), 1.92 (t, 1H, \(J = 2.6\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 149.1, 139.1, 135.1, 133.0, 130.0, 128.2, 127.7, 127.6, 127.2, 115.3, 115.0, 81.3, 74.2, 70.2, 27.3, 22.3; HRMS (EI) calcd for C\(_{27}\)H\(_{26}\)OSi [M]+ 394.3631, found 394.3613.

Colorless oil (85% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 3071, 2910, 1601, 1493, 1070, 916; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.63 (m, 4H), 7.43 (m, 2H), 7.37 (m, 4H), 7.24 (m, 4H), 7.17 (m, 3H), 6.89 (m, 3H), 5.65 (m, 1H), 5.58 (m, 2H), 4.75 (m, 2H), 4.11 (dd, 1H, \(J = 2.8, 7.8\) Hz), 2.91 (m, 2H), 2.66 (m, 2H), 2.10 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 154.4, 146.7, 136.2, 135.4, 134.5, 132.3, 130.4, 129.2, 129.1, 129.0, 128.0, 127.7, 125.8, 121.4, 119.7, 116.6, 80.0, 56.1, 42.2, 41.0, 38.8; HRMS (CI) calcd for C\(_{33}\)H\(_{32}\)O\(_2\)Si [M+1]+ 489.2249, found 489.2236.

Compound 3-16 was obtained from desilylation of compound 3-15 using TBAF. Colorless oil: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.32 (m, 2H), 7.23 (m, 3H), 5.80 (m, 1H), 5.75 (s, 2H), 5.04 (m, 2H), 3.64 (dd, 1H, \(J = 2.0\)H, 4.3, 10.4 Hz), 2.85(m, 2H), 2.76 (m, 2H), 2.27 (m, 1H), 1.78 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 146.7, 136.4, 129.5, 129.3, 128.2, 127.9, 126.1, 117.2, 77.0, 54.9, 41.6, 40.7, 37.2.
4.5. Diastereoselective ring-rearrangement metathesis

4.5.1. Preparation of ring-rearrangement metathesis substrates

4.5.1.1. Preparation of ring-rearrangement metathesis substrates 3-21a-h and 3-23a, 3-23d and 3-23f

Scheme 4.1

The substrates 3-21a-h and 3-23a, 3-23d and 3-23f were prepared from allylation and protection of the corresponding cyclopentyl carboaldehydes, which were synthesized according to the reported gold catalyzed isomerization of 3-hydroxy 1,5-enynes (Scheme 4.1). The 3-hydroxy 1,5-enynes were prepared from Barbier-type propargylation of 2-aryl- or 2-alkyl acroleins. To a solution of carboaldehydes (1.0 mmol, 1.0 equiv.) in 5 mL of THF was added allyl magnesium bromide solution (1.2 mmol, 1.0 M, 1.2 equiv.) slowly at 0 °C. The reaction was slowly warmed up to room temperature and monitored by TLC. Upon reaction completion, saturated NH₄Cl solution was added at 0 °C to quench the reaction. Then the reaction mixture was separated and the aqueous layer was extracted by Et₂O (10 mL x 3). The extract was combined with the organic layer and then was washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated to obtain the crude product which was purified by column chromatography to afford the pure alcohols.

To a solution of the secondary alcohols (0.5 mmol, 1.0 equiv.) and triethylamine (3.0 equiv.) in DMF (2 mL), was added tert-butyldimethylsilyl triflate (1.0 equiv.) and catalytic amount of N,N-dimethylaminopyridine (DMAP) at 0 °C. Then the ice bath was removed. After stirring at 80 °C for several hours, TLC showed the completion of the reaction. The mixture was quenched by saturated NH₄Cl solution and extracted with Et₂O, then dried over MgSO₄, concentrated under reduced pressure and purified using flash column chromatography to afford the RRM substrates 3-21a-h and 3-23a, 3-23d and 3-23f.
4.5.1.2. Preparation of ring-rearrangement metathesis substrates 3-23c, 3-23e and 3-23h

![Scheme 4.2]

The substrates 3-23c, 3-23e and 3-23h were prepared according to the reported gold catalyzed isomerization of 3-siloxy 1,5-enynes followed by intramolecular allyl trapping (Scheme 4.2).115

4.5.1.3. Preparation of ring-rearrangement metathesis substrates 3-23g and 3-23i

![Scheme 4.3]

The substrates 3-23g and 3-23i were also prepared from allylation and protection of the corresponding cyclopentyl carboaldehydes. Different from the previous synthetic routes, the cyclopentyl carboaldehydes were synthesized based on strategy of diallylation and ring-closing metathesis (Scheme 4.3).

To a stirred solution of 2-arylacetic acid (5 g) in dry MeOH was added sulfuric acid (0.5 mL) dropwise and heated to reflux. Stirring was then continued for 2 hours. The reaction mixture was then cooled and poured into saturated aqueous NaHCO₃ and extracted with EtOAc. The combined organic
fractions were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield the corresponding methyl 2-arylacetate, which was used for next step without further purification.

A solution of methyl 2-arylacetate (1.0 equiv.), allyl bromide (1.5 equiv.) and tetrabutylammonium iodide (0.05 equiv.) in tetrahydrofuran (0.5 M) at 0°C was treated portionwise with sodium hydride (60% in oil, 1.0 equiv.). The solution was allowed to warm to 25°C and heated at reflux for 1 hour. The mixture was cooled to 0°C, treated with saturated ammonium chloride solution. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium bicarbonate solution and brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was used for next step without further purification.

To a stirring solution of diisopropylamine (1.2 equiv.) in THF (1 M) at -78°C was added nBuLi (2.5 M in hexanes, 1.1 equiv.). This solution was allowed to stir at -78°C for 1 h. Methyl 2-aryl, 2-allylacetate (1.0 equiv.) in THF was added dropwise over 30 min. After the solution stirred at -78°C for an additional 15 min, allyl bromide (1.5 equiv.) was added dropwise over 10 min. The reaction was allowed to warm up to rt, stirred for 4 h, and quenched by addition of 3 M HCl. The aqueous layer was extracted with Et₂O. The combined organics were washed with brine, dried over MgSO₄, and concentrated. The crude residue was purified by silica gel chromatography to provide the intermediate ester as colorless oil.

To a stirring solution of 2, 2-diallyl ester in CH₂Cl₂ was added Grubbs 1st generation catalyst (3 mol%). The RCM reaction was monitored by TLC until the completion of the reaction. Then the reaction solution was concentrated by rotavap and purified by silica gel column chromatography to give colorless oil.

To a stirring solution of cyclopentyl carboxylate (1.0 equiv.) in mixed solvents (hexanes : Et₂O = 3:1) was added DIBAL (1.0 M in hexanes, 1.0 equiv.) solution at -78°C. After 30 min, the reaction was quenched with MeOH and saturated aqueous potassium sodium tartrate (Rochelle’s salt) solution. After stirring for 30 min, the aqueous layer was extracted with Et₂O. The extracted organic layers were dried over MgSO₄, filtered and concentrated by rotary evaporation. The product was isolated by flash
chromatography as colorless oil. Sometimes overreduction cannot be avoided. In those cases, a Swern-type oxidation was adopted to reoxidize the corresponding primary alcohol to the aldehyde.

4.5.1.4. Preparation of ring-rearrangement metathesis substrates 3-23k and 3-23l

Scheme 4.4

Potassium crotyltrifluoroborates were prepared according to the reported procedures. 178 Crotylation was carried out according to Batey’s procedure (Scheme 4.4) 179: To a solution of the aldehyde (1.0 mmol) and tetrabutylammonium iodide (36.9 mg, 0.1 mmol) in CH2Cl2 (3 mL) was added the corresponding crotyltrifluoroborate (174 mg, 1.10 mmol) and water (3 mL). The biphasic reaction mixture was vigorously stirred for 15 min at rt. The reaction mixture was then diluted with CH2Cl2 (5 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 x 5 mL). The combined organic extracts were dried (MgSO4), filtered and concentrated
to afford a clear, colorless oil. This material was passed through a short plug of silica gel using EtOAc as the eluent. The resulting eluate was concentrated in vacuo to afford the desired homoallylic alcohols. Substrates 3-23k and 3-23l were prepared according to the previously described protection of the homoallylic alcohols.

4.5.2. Representative procedure of ring-rearrangement metathesis

To a solution of the Grubbs 2nd generation catalyst (5 mol%) under ethylene atmosphere was added slowly a solution of 3-23 (1.0 equiv.) in CH2Cl2 (0.1 M). Then the reaction was warmed up to 40 °C. The reaction was monitored by TLC or 1H NMR until completion of the reaction. Then the reaction solution
was concentrated by rotavap and purified by silica gel column chromatography to give the ring-
rearrangement metathesis products 3-24.

4.5.3. Diastereoselective ring-closing metathesis of acyclic trienes

4.5.3.1. Preparation of acyclic trienes 3-29g, 3-29i, 3-29o and 3-29p

![Scheme 4.5](image)

Acyclic trienes 3-29g, 3-29i, 3-29o and 3-29p were prepared from allylation and protection of 2-
allyl-2-arylpent-4-enals, which were synthesized according to the previously described procedures in

4.5.1.3.

4.5.3.2. General procedure of diastereoselective ring-closing metathesis

To a solution of the Grubbs 2nd generation catalyst (5 mol%) under ethylene atmosphere was added
slowly a solution of 3-29 (1.0 equiv.) in CH₂Cl₂ (0.1 M). Then the reaction was warmed up to 40 °C. The
reaction was monitored by TLC or ¹H NMR until completion of the reaction. Then the reaction solution
was concentrated by rotavap and purified by silica gel column chromatography to give the ring-
rearrangement metathesis products 3-24.

4.5.4. Characterization data

Known compound 3-21d was prepared according to the literature.¹b 3-22d, colorless oil,
65% yield; ¹H NMR (CDCl₃, 500 MHz) δ  5.86 (tdd, J = 15.2, 10.8, 7.5 Hz, 1H), 5.55 (m, 2H), 5.03 (d, J = 10.0 Hz, 1H), 5.03 (d, J = 16.5 Hz, 1H), 3.62 (septet, J = 6.2 Hz, 1H), 3.22 (dd, J = 7.5, 5.3 Hz, 1H), 2.35-2.25 (m, 1H), 2.18 (dd, J = 13.5, 7.8 Hz, 1H), 2.00 (dd, J = 13.2, 7.3 Hz, 2H), 1.94-1.79 (m, 2H), 1.12 (t, J = 6.2 Hz, 6H), 0.88 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 135.35,
125.73, 123.92, 117.06, 77.72, 70.34, 43.77, 36.21, 29.65, 23.62, 22.27, 18.82; LRMS (Cl) calcd for C_{13}H_{22}O [M] 194.1, found 194.1.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.87 (tdd, $J$ = 17.2, 10.0, 7.2 Hz, 1H), 5.60 (m, 2H), 5.04 (d, $J$ = 17.2 Hz, 1H), 5.00 (d, $J$ = 10.6 Hz, 1H), 3.58 (dd, $J$ = 7.5, 3.6 Hz, 1H), 2.44-2.28 (m, 2H), 2.28-2.10 (m, 2H), 1.92 (m, 2H), 0.99 (s, 3H), 0.95 (t, $J$ = 7.9 Hz, 9H), 0.60 (q, $J$ = 7.9 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 137.24, 129.30, 128.85, 116.05, 79.69, 47.50, 44.48, 43.83, 39.21, 23.24, 7.12, 5.66; HRMS (EI) calcd for C$_{16}$H$_{29}$OSi [M-1] 265.1988, found 265.1991.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.84 (tdd, $J$ = 17.4, 10.3, 7.5 Hz, 1H), 5.60-5.45 (m, 2H), 5.03 (d, $J$ = 10.3 Hz, 1H), 5.02 (d, $J$ = 16.8 Hz, 1H), 3.60 (dd, $J$ = 8.0, 5.4 Hz, 1H), 2.26-2.13 (m, 2H), 2.07-1.93 (m, 2H), 1.92-1.78 (m, 2H), 0.97 (t, $J$ = 7.9 Hz, 9H), 0.85 (s, 3H), 0.60 (q, $J$ = 8.1 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 136.36, 125.72, 123.80, 117.04, 73.18, 43.94, 37.14, 35.94, 32.57, 17.75, 7.02, 5.34; HRMS (Cl) calcd for C$_{16}$H$_{29}$OSi [M-1] 265.1988, found 265.1982.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.88 (tdd, $J$ = 17.2, 10.1, 7.2 Hz, 1H), 5.58 (m, 2H), 5.03 (dd, $J$ = 17.2, 1.6 Hz, 1H), 4.99 (dd, $J$ = 10.2, 0.8 Hz, 1H), 3.58 (dd, $J$ = 6.3, 4.2 Hz, 1H), 2.44-2.25 (m, 3H), 2.25-2.15 (m, 1H), 1.92 (m, 2H), 1.01 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 137.22, 129.37, 128.74, 115.93, 79.38, 47.66, 44.76, 44.00, 39.38, 26.08, 23.36, 18.33, -3.13, -4.24; HRMS (EI) calcd for C$_{16}$H$_{29}$OSi [M-1] 265.1988, found 265.1993.

Colorless oil; 89% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.82 (ddt, $J$ = 15.2, 10.2, 7.8 Hz, 1H), 5.52 (m, 2H), 5.03 (d, $J$ = 10.1 Hz, 1H), 5.02 (d, $J$ = 16.8 Hz, 1H), 3.57 (dd, $J$ = 7.9, 5.5 Hz, 1H), 2.27-2.09 (m, 2H), 1.99 (m, 2H), 1.84 (m, 2H), 0.89 (s, 9H), 0.85 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 135.29, 125.68, 123.77, 117.12, 73.06,
Colorless oil; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.28-7.22 (m, 2H), 7.22-7.18 (m, 3H), 5.94 (dtt, \(J = 14.0\) 7.2, 4.0 Hz, 1H), 5.39 (s, 2H), 5.09 (d, \(J = 17.3\) Hz, 1H), 5.06 (d, \(J = 11.3\) Hz, 1H), 3.74 (dd, \(J = 6.3, 3.9\) Hz, 1H), 2.81 (m, 2H), 2.52-2.43 (m, 1H), 2.42-2.25 (m, 5H), 0.96 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 139.68, 137.32, 130.52, 129.42, 129.10, 127.68, 125.74, 116.12, 79.28, 51.69, 41.90, 41.57, 40.42, 39.16, 26.20, 18.45, -2.92, -4.21; HRMS (El) calcd for C\(_{16}\)H\(_{29}\)OSi [M-1] 265.1988, found 265.1993.

Colorless oil; 96% yield; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.33 (t, \(J = 7.3\) Hz, 2H), 7.26 (t, \(J = 7.3\) Hz, 1H), 7.22 (d, \(J = 7.1\) Hz, 2H), 5.97-5.82 (m, 1H), 5.68 (m, 2H), 5.11 (d, \(J = 10.2\) Hz, 1H), 5.04 (d, \(J = 16.9\) Hz, 1H), 3.93 (dd, \(J = 6.9, 5.6\) Hz, 1H), 2.82 (m, 2H), 2.45-2.29 (m, 2H), 2.21 (m, 1H), 2.01 (m, 1H), 1.87 (m, 1H), 1.80 (m, 1H), 1.03 (s, 9H), 0.19 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 139.16, 134.83, 131.15, 127.78, 125.92, 125.83, 124.02, 117.87, 71.25, 40.78, 38.74, 37.51, 32.43, 31.37, 26.08, 18.31, -3.31, -4.70; HRMS (Cl) calcd for C\(_{17}\)H\(_{21}\)O \([M+1]^+\) 343.2457 found 343.2458.

Colorless oil; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.38-7.32 (m, 4H), 7.31-7.27 (m, 1H), 5.90 (tdd, \(J = 14.6, 10.2, 7.2\) Hz, 1H), 5.58 (m, 2H), 5.02 (d, \(J = 15.3\) Hz, 1H), 5.00 (d, \(J = 8.7\) Hz, 1H), 4.50 (m, 2H), 3.93 (dd, \(J = 6.9, 3.5\) Hz, 1H), 3.37 (m, 2H), 2.49-2.28 (m, 3H), 2.26-2.04 (m, 3H), 0.96 (t, \(J = 7.9\) Hz, 9H), 0.61 (q, \(J = 8.0\) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 138.83, 137.38, 129.42, 129.17, 128.27, 127.58, 127.39, 115.98, 75.45, 75.06, 73.22, 51.15, 38.93, 38.61, 38.49, 7.12, 5.64; HRMS (Cl) calcd for C\(_{22}\)H\(_{34}\)OSi \([M-1]\) 371.2406, found 371.2401.
Colorless oil; 95% yield, $\text{dr} \geq 10 : 1$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.38 (m, 4H), 7.31 (m, 1H), 5.95-5.84 (m, 1H), 5.69-5.62 (m, 1H), 5.59-5.52 (m, 1H), 5.07 (d, $J = 16.0$ Hz, 1H), 5.07 (d, $J = 11.1$ Hz, 1H), 4.51 (m, 2H), 3.93 (t, $J = 4.0$ Hz, 1H), 3.54 (d, $J = 8.6$ Hz, 1H), 3.30 (d, $J = 8.6$ Hz, 1H), 2.29 (m, 1H), 2.22 (m, 2H), 2.09-1.98 (m, 2H), 1.86-1.75 (m, 1H), 0.99 (t, $J = 8.0$ Hz, 9H), 0.64 (q, $J = 8.0$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 139.07, 135.26, 128.25, 127.56, 127.34, 125.41, 123.12, 117.34, 73.33, 72.30, 69.27, 41.19, 36.84, 31.51, 28.30, 7.08, 5.32; HRMS (CI) calcd for C$_{23}$H$_{35}$O$_2$Si [M-1] 371.2406, found 371.2413.

Colorless oil; 94% yield, $\text{dr} = 15 : 1$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.71 (t, $J = 7.1$ Hz, 4H), 7.49-7.33 (m, 6H), 7.15 (t, $J = 7.7$ Hz, 2H), 6.92 (d, $J = 7.8$ Hz, 3H), 5.70 (td, $J = 16.7, 7.6$ Hz, 1H), 5.56 (m, 1H), 5.40 (m, 1H), 4.98 (m, 2H), 3.95 (t, $J = 5.1$ Hz, 1H), 3.91 (m, 2H), 2.27-2.11 (m, 2H), 2.07 (m, 2H), 1.92 (m, 2H), 1.64-1.47 (m, 3H), 1.37 (m, 1H), 1.17 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 178.55, 154.47, 135.05, 134.99, 134.18, 132.64, 132.49, 130.57, 130.50, 129.34, 127.94, 125.52, 123.32, 121.61, 119.65, 117.70, 73.38, 65.14, 39.09, 38.74, 38.18, 32.94, 31.49, 29.11, 27.26, 22.60; HRMS (CI) calcd for C$_{35}$H$_{43}$O$_4$Si [M+1]$^+$ 555.2931, found 555.2924.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.91 (tdd, $J = 17.2, 10.0, 7.2$ Hz, 1H), 5.53 (s, 2H), 5.02 (dd, $J = 19.2, 1.5$ Hz, 1H), 4.99 (d, $J = 10.8$ Hz, 1H), 3.80 (t, $J = 4.6$ Hz, 1H), 2.45-2.31 (m, 2H), 2.29-2.12 (m, 3H), 1.99 (d, $J = 17.1$ Hz, 1H), 1.78-1.61 (m, 4H), 1.60-1.51 (m, 1H), 1.40 (t, $J = 11.7$ Hz, 1H), 1.25-1.07 (m, 3H), 1.03-0.93 (m, 2H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 137.49, 129.97, 129.78, 115.71, 76.34, 52.30, 44.12, 38.73, 38.51, 37.78, 27.41, 26.92, 26.82, 26.78, 26.04, 25.74, 18.35, -3.00, -4.46; HRMS (CI) calcd for C$_{21}$H$_{37}$OSi [M-1] 333.2614, found 333.2608.
Colorless oil; 82% yield; $^1$H NMR (CDCl$_3$, 500 MHz) δ 5.96-5.85 (m, 1H), 5.62-5.55 (m, 1H), 5.48 (m, 1H), 4.98 (d, $J = 16.8$ Hz, 1H), 4.95 (dd, $J = 9.0$, 0.9 Hz, 1H), 3.90 (t, $J = 4.3$ Hz, 1H), 2.25 (m, 1H), 2.17-1.99 (m, 3H), 1.94 (m, 2H), 1.79 (m, 3H), 1.64 (m, 3H), 1.23-1.05 (m, 5H), 0.87 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 136.93, 126.33, 122.94, 116.11, 70.33, 42.09, 41.61, 36.33, 32.02, 31.92, 27.93, 27.84, 27.80, 27.43, 27.11, 25.90, 18.16, -3.78, -4.80; HRMS (CI) calcd for C$_{21}$H$_{37}$OSi [M-1] 333.2614, found 333.2622.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.22 (m, overlapped, $J = 7.6$ Hz, 3H), 6.96 (t, $J = 7.4$ Hz, 1H), 6.91-6.85 (m, overlapped, 4H), 6.75 (dd, $J = 8.1$, 2.3 Hz, 1H), 5.80 (tdd, $J = 11.5$, 9.2, 7.1 Hz, 1H), 5.70 (2s, 2H), 4.94 (d, $J = 15.5$ Hz, 1H), 4.93 (d, $J = 12.0$ Hz, 1H), 3.97 (dd, $J = 9.1$, 2.1 Hz, 1H), 3.79 (s, 3H), 2.93 (m, 1H), 2.85-2.64 (m, overlapped, 3H), 2.23 (dd, $J = 14.8$, 6.6 Hz, 1H), 1.98-1.88 (m, 1H), 0.12 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 159.14, 149.02, 136.85, 129.59, 129.37, 129.10, 128.60, 121.39, 120.76, 119.89, 116.76, 114.86, 110.66, 80.14, 55.84, 55.18, 41.79, 41.04, 38.49, -1.77, -2.14; LRMS (CI) calcd for C$_{24}$H$_{30}$O$_3$Si [M] 394.20, found 394.20.

Colorless oil; 84% yield, $dr = 8 : 1$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.25-7.13 (m, 3H), 7.02 (m, 2H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.84 (m, 2H), 6.76 (dd, $J = 8.1$, 1.8 Hz, 1H), 5.77 (d, $J = 9.8$ Hz, 1H), 5.54-5.46 (m, 1H), 5.39 (dddd, $J = 16.9$, 10.0, 8.6, 5.8 Hz, 1H), 4.96 (d, $J = 17.0$ Hz, 1H), 4.90 (d, $J = 9.4$ Hz, 1H), 4.22 (dd, $J = 7.6$, 4.6 Hz, 1H), 3.78 (s, 3H), 2.80 (m, 1H), 2.65 (m, 1H), 2.31-2.13 (m, 3H), 1.81 (m, 1H), 0.20 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 161.56, 154.57, 144.65, 134.79, 129.39, 128.25, 125.85, 124.43, 121.54, 120.82, 119.88, 117.23, 114.69, 110.92, 75.07, 55.08, 45.12, 43.46, 33.16, 32.47, -1.89, -2.31; HRMS (CI) calcd for C$_{24}$H$_{30}$O$_3$Si [M] 394.1964, found 394.1972.
Colorless oil; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.37-7.33 (m, 1H), 7.32 (d, \(J = 7.4\) Hz, 1H), 7.25-7.18 (m, 2H), 5.71 (m, 3H), 5.27 (m, 2H), 4.89 (d, \(J = 15.6\) Hz, 1H), 4.89 (d, \(J = 11.5\) Hz, 1H), 3.89 (t, \(J = 5.1\) Hz, 1H), 2.97 (m, 2H), 2.78 (m, 2H), 2.39-2.25 (m, 1H), 2.03 (m, 1H), 1.24 (s, 9H), 0.84 (s, 9H), -0.04 (s, 3H), -0.40 (s, 3H); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 178.34, 146.73, 136.81, 135.03, 131.09, 130.42, 129.59, 128.91, 127.46, 126.25, 115.96, 77.84, 65.34, 57.06, 42.49, 39.28, 27.27, 26.17, 18.21, -3.72, -5.03; HRMS (Cl) calcd for C\(_{27}\)H\(_{43}\)O\(_3\)Si \([\text{M}+1]^+\) 443.2982, found 443.2955.

Colorless oil; 92% yield; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.40-7.35 (m, 1H), 7.32 (m, 1H), 7.23 (m, 2H), 5.77 (s, 1H), 5.59 (m, 1H), 5.40 (m, 2H), 5.27 (m, 1H), 4.91 (d, \(J = 17.0\) Hz, 1H), 4.82 (d, \(J = 10.0\) Hz, 1H), 4.30 (s, 1H), 2.88 (d, \(J = 16.3\) Hz, 1H), 2.65 (d, \(J = 11.1\) Hz, 1H), 2.48-2.29 (m, 1H), 2.23-2.13 (m, 1H), 2.00 (d, \(J = 17.7\) Hz, 1H), 1.23 (s, 9H), 0.67 (s, 9H), -0.07 (s, 3H), -0.46 (s, 3H); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 178.49, 142.85, 135.16, 134.48, 131.13, 129.32, 127.60, 126.32, 126.17, 123.11, 116.79, 72.65, 65.22, 46.79, 38.88, 32.54, 27.26, 25.64, 17.86, -4.62, -5.46; HRMS (Cl) calcd for C\(_{27}\)H\(_{41}\)O\(_3\)Si \([\text{M}-1]\) 441.2825, found 441.2817.

Colorless oil; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.34 (d, \(J = 7.7\) Hz, 2H), 7.29 (t, \(J = 7.6\) Hz, 2H), 7.19 (t, \(J = 7.2\) Hz, 1H), 5.74-5.64 (m, 3H), 4.96-4.80 (m, 2H), 3.90-3.84 (m, 1H), 2.96 (d, \(J = 16.6\) Hz, 1H), 2.81-2.68 (m, 2H), 2.63 (d, \(J = 16.5\) Hz, 1H), 2.27-2.18 (m, 1H), 1.96-1.88 (m, 1H), 0.91 (s, 9H), 0.02 (s, 3H), -0.11 (s, 3H); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 147.43, 137.14, 129.35, 129.26, 128.18, 127.66, 125.73, 115.85, 78.06, 56.43, 41.86, 41.34, 39.50, 26.27, 26.17, 18.33, -3.20, -4.75; HRMS (Cl) calcd for C\(_{21}\)H\(_{35}\)OSi \([\text{M}+1]^+\) 329.2301, found 329.2305.
Colorless oil; 95% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.44 (d, $J = 7.4$ Hz, 2H), 7.27 (t, $J = 7.6$ Hz, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 5.85-5.70 (m, 1H), 5.56-5.46 (m, 1H), 5.36 (dd, $J = 16.8$, 10.0, 8.6, 5.9 Hz, 1H), 4.95 (d, $J = 17.0$ Hz, 1H), 4.89 (d, $J = 10.2$ Hz, 1H), 3.99 (dd, $J = 8.0$, 4.6 Hz, 1H), 2.87 (dd, $J = 13.6$, 5.7 Hz, 1H), 2.71-2.60 (m, 1H), 2.25-2.10 (m, 3H), 1.72-1.59 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), -0.04 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 142.95, 135.11, 128.44, 127.30, 125.92, 125.84, 124.64, 116.93, 74.74, 45.35, 43.97, 33.51, 32.88, 25.88, 18.08, -4.08, -4.98; HRMS (CI) calcd for C$_{21}$H$_{33}$OSi [M+1]$^+$ 329.2301, found 329.2308.

Colorless oil; 94% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.62-7.55 (m, 2H), 7.52 (d, $J = 7.4$ Hz, 1H), 7.48-7.33 (m, 7H), 7.33-7.26 (m, 4H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.11 (t, $J = 7.8$ Hz, 2H), 6.96-6.75 (m, 3H), 5.80-5.68 (m, 1H), 5.40 (m, 1H), 5.37-5.25 (m, 1H), 4.88 (m, 1H), 4.85 (d, $J = 10.53$ Hz, 1H), 4.30 (dd, $J = 6.3$, 4.5 Hz, 1H), 2.72 (m, 2H), 2.21 (m, 3H), 1.90 (m, 1H), 1.37-1.22 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 154.45, 143.26, 135.08, 134.96, 134.64, 130.47, 130.36, 129.27, 127.97, 127.87, 127.80, 127.64, 126.00, 125.75, 123.98, 121.52, 119.69, 117.23, 75.41, 45.01, 42.92, 32.35, 32.17; HRMS (CI) calcd for C$_{33}$H$_{33}$O$_2$Si [M+1]$^+$ 489.2250, found 489.2259.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.93 (d, $J = 2.0$ Hz, 1H), 6.83 (dd, $J = 8.4$, 2.0 Hz, 1H), 6.78 (d, $J = 8.4$ Hz, 1H), 5.72-5.64 (m, 3H), 4.88 (d, $J = 8.3$ Hz, 1H), 4.87 (d, $J = 17.0$ Hz, 1H), 3.88 (s, 1H), 3.86 (s, 1H), 3.81 (dd, $J = 5.6$, 4.8 Hz, 1H), 2.96 (d, $J = 16.3$ Hz, 1H), 2.68 (m, 2H), 2.55 (d, $J = 16.5$ Hz, 1H), 2.27-2.11 (m, 1H), 1.98-1.79 (m, 1H), 0.91 (s, 9H), 0.03 (s, 3H), -0.05 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 148.20, 147.21, 139.83, 137.12, 129.39, 129.24, 120.09, 115.83, 112.28, 110.33, 78.04, 56.14, 55.96, 55.85, 42.05, 41.99, 39.64, 26.16, 18.30, -3.24, -4.61; HRMS (EI) calcd for C$_{23}$H$_{36}$O$_3$Si [M] 388.2434, found 388.2428.
Colorless oil; 93% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.14 (d, $J = 1.8$ Hz, 1H), 6.87 (dd, $J = 8.5$, 2.0 Hz, 1H), 6.75 (d, $J = 8.5$ Hz, 1H), 5.81-5.69 (b, 1H), 5.48 (b, 1H), 5.42-5.32 (m, 1H), 4.94 (d, $J = 17.0$ Hz, 1H), 4.89 (d, $J = 10.2$ Hz, 1H), 3.94 (dd, $J = 8.7$, 4.6 Hz, 1H), 3.85 (s, overlapped, 6H), 2.88 (dd, $J = 13.6$, 5.5 Hz, 1H), 2.60 (dd, $J = 17.9$, 3.4 Hz, 1H), 2.13 (m, 3H), 1.66 (m, 1H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 147.88, 147.17, 135.16, 125.84, 125.06, 120.76, 116.87, 112.45, 109.85, 75.36, 55.93, 55.68, 45.16, 44.56, 32.98, 25.97, 18.11, -4.05, -4.90; HRMS (EI) calcd for C$_{23}$H$_{36}$O$_3$Si [M] 388.2434, found 388.2443.

Colorless oil; 90% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.81 (t, $J = 7.8$ Hz, 1H), 6.71 (d, $J = 7.3$ Hz, 1H), 6.69 (d, $J = 7.3$ Hz, 1H), 5.84 (s, 2H), 5.75-5.62 (m, 1H), 5.09 (d, $J = 16.0$ Hz, 1H), 5.08 (d, $J = 11.5$ Hz, 1H), 4.83 (t, $J = 4.3$ Hz, 1H), 3.85 (s, 3H), 2.62 (dt, $J = 15.5$, 3.9 Hz, 1H), 2.46 (m, 2H), 2.33 (dd, $J = 15.5$, 4.4 Hz, 1H), 2.28 (m, overlapped, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 148.12, 144.04, 135.70, 133.93, 128.21, 125.82, 120.84, 118.49, 115.24, 110.80, 87.27, 55.75, 49.41, 45.31, 34.37, 28.88; HRMS (EI) calcd for C$_{16}$H$_{18}$O$_2$ [M] 242.1307, found 242.1316.

Colorless oil; 80% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.28 (m, 4H), 7.21-7.14 (m, 1H), 5.73-5.62 (m, 2H), 5.56-5.49 (m, 1H), 4.72 (dd, $J = 10.3$, 1.8 Hz, 1H), 4.62 (dd, $J = 17.4$, 2.0 Hz, 1H), 3.93 (s, 1H), 2.92-2.76 (m, 2H), 2.62 (m, 2H), 2.15 (p, $J = 7.2$ Hz, 1H), 0.98 (t, $J = 7.9$ Hz, 9H), 0.94, (d, $J = 7.0$ Hz, 3H), 0.62 (q, $J = 7.8$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 147.76, 140.74, 129.75, 128.28, 127.81, 127.62, 125.69, 113.13, 82.49, 57.05, 44.26, 40.43, 38.83, 21.49, 7.21, 5.79; HRMS (EI) calcd for C$_{22}$H$_{34}$OSi [M] 342.2379, found 342.2388.
(q, J = 7.69 Hz, 3H), 0.15 (m, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 145.45, 135.03, 129.86, 127.76, 127.55, 125.86, 124.38, 116.88, 78.00, 45.56, 42.28, 34.54, 29.24, 16.14, 7.17, 5.08; HRMS (EI) calcd for C$_{22}$H$_{34}$OSi [M] 342.2379, found 342.2375.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.35 (d, J = 7.4 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 5.87-5.71 (m, 2H), 5.69-5.63 (m, 1H), 4.89 (d, J = 10.3 Hz, 1H), 4.85 (d, J = 17.2 Hz, 1H), 3.95 (d, J = 1.43 Hz, 1H), 3.12-2.98 (m, 1H), 2.80-2.67 (m, 2H), 2.66-2.58 (m, 1H), 2.29-2.17 (m, 1H), 1.00 (t, J = 8.0 Hz, 9H), 0.63 (q, J = 8.0 Hz, 6H), 0.50 (d, J = 6.80 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 147.06, 145.04, 129.68, 128.67, 127.98, 127.69, 125.75, 112.60, 80.57, 56.94, 42.92, 40.64, 39.85, 13.45, 7.21, 5.67; HRMS (EI) calcd for C$_{22}$H$_{34}$OSi [M] 342.2379, found 342.2388.

Colorless oil; 95% yield, $dr = 2.5 : 1$; Major isomer: $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.47 (d, J = 7.3 Hz, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 5.70 (tdd, J = 9.8, 4.9, 2.4 Hz, 1H), 5.39-5.25 (m, 2H), 4.94 (d, J = 17.0 Hz, 1H), 4.88 (d, J = 10.1 Hz, 1H), 3.59 (d, J = 8.9 Hz, 1H), 3.04 (dd, J = 13.4, 5.6 Hz, 1H), 2.64 (m, 1H), 2.13-2.04 (m, 2H), 1.66-1.55 (m, 1H), 1.03 (t, J = 7.9 Hz, 9H), 0.98 (d, J = 7.2 Hz, 3H), 0.73 (q, J = 7.9 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 142.44, 135.10, 132.48, 128.84, 127.15, 125.85, 124.32, 116.83, 82.74, 45.91, 45.84, 36.86, 35.79, 18.84, 7.27, 5.70; HRMS (EI) calcd for C$_{22}$H$_{34}$OSi [M] 342.2348, found 342.2386.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) δ 5.66 (td, J = 17.1, 9.8 Hz, 1H), 5.58 (b, 2H), 5.01 (dd, J = 17.1, 1.6 Hz, 1H), 4.89 (dd, J = 10.2, 1.9 Hz, 1H), 3.16-3.05 (m, 1H), 2.97 (d, J = 9.5 Hz, 1H), 2.46 (m, 1H), 2.25-2.15 (m, 2H), 1.97 (m, 2H), 1.73-1.55 (m, 2H), 1.51-1.35 (m, 3H), 1.29-1.16 (m, 1H), 1.00 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 141.47, 128.97, 128.87, 113.61, 88.37, 79.19, 46.96, 46.21, 45.98, 44.59, 32.36, 31.26, 29.41, 22.53, 10.30; HRMS (EI) calcd for C$_{15}$H$_{24}$O [M] 220.1827, found 220.1832.
Colorless oil; 94% yield, \( dr = 5 : 1 \); Major isomer: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 5.91-5.76 (m, 1H), 5.49 (ddd, \( J = 9.5, 4.6, 2.2 \) Hz, 1H), 5.33-5.27 (m, 1H), 5.07-4.99 (m, 2H), 3.21-3.09 (m, 1H), 2.83 (d, \( J = 9.2 \) Hz, 1H), 2.27-1.90 (m, 4H), 1.91-1.83 (m, 1H), 1.66 (m, 2H), 1.54-1.47 (m, 1H), 1.46-1.38 (m, 1H), 1.32-1.18 (m, 2H), 0.98-0.92 (m, 3H), 0.90 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 135.51, 128.66, 125.40, 117.13, 83.60, 79.74, 43.91, 37.57, 36.36, 32.27, 30.30, 29.40, 19.01, 10.41; HRMS (EI) calcd for C\(_{15}\)H\(_{25}\)O \([M] \) 220.1827, found 220.1833.

Colorless oil; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 5.66 (td, \( J = 17.1, 9.8 \) Hz, 1H), 5.58 (b, 2H), 5.02 (dd, \( J = 17.1, 1.3 \) Hz, 1H), 4.90 (dd, \( J = 10.2, 1.9 \) Hz, 1H), 3.99 (tdd, \( J = 11.5, 4.2, 1.6 \) Hz, 1H), 3.35 (dt, \( J = 12.0, 2.5 \) Hz, 1H), 2.97 (d, \( J = 9.6 \) Hz, 1H), 2.32 (m, 2H), 1.96 (m, 2H), 1.85 (m, 2H), 1.63 (m, 2H), 1.64 (ddt, \( J = 8.7, 8.5, 4.2 \) Hz, 1H), 1.01 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 141.32, 128.84, 113.70, 88.99, 68.64, 46.75, 46.18, 44.89, 32.17, 25.96, 22.45; HRMS (EI) calcd for C\(_{13}\)H\(_{20}\)O \([M]^+ \) 192.1514, found 192.1521.

Colorless oil; 93% yield, \( dr = 4.7 : 1 \); Major isomer: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 5.90-5.77 (m, 1H), 5.49 (ddd, \( J = 9.7, 4.9, 2.5 \) Hz, 1H), 5.28 (ddd, \( J = 9.9, 1.1 \) Hz, 1H), 5.07-5.01 (m, 2H), 4.06-3.99 (m, 1H), 3.40 (m, 1H), 2.83 (d, \( J = 9.2 \) Hz, 1H), 2.19-1.99 (m, 3H), 1.89 (dd, \( J = 12.7, 1.5 \) Hz, 1H), 1.77-1.51 (m, 3H), 1.29-1.21 (m, 2H), 0.91 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 135.14, 128.68, 125.33, 117.38, 84.65, 69.08, 44.00, 37.63, 36.70, 30.21, 26.99, 24.43, 18.73; HRMS (EI) calcd for C\(_{13}\)H\(_{20}\)O \([M]^+ \) 192.1514, found 192.1512.

Colorless oil; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 7.43 (d, \( J = 8.1 \) Hz, 2H), 7.30 (t, \( J = 7.6 \) Hz, 2H), 7.21 (t, \( J = 7.2 \) Hz, 1H), 5.78-5.54 (m, 3H), 5.05 (m, 3H), 4.96 (d, \( J = 9.4 \) Hz, 1H), 4.87 (d, \( J = 9.1 \) Hz, 1H), 4.84 (d, \( J = 16.7 \) Hz, 1H), 3.93 (dd, \( J = 6.2, 4.0 \) Hz, 1H), 2.79 (dd, \( J = 14.3, 6.5 \) Hz, 1H), 2.70 (dd, \( J = 14.2, 8.3 \) Hz, 1H), 2.56 (dd, \( J = 14.3, 6.9 \) Hz, 2H), 2.17 (ddd, \( J = 8.9, 5.2, 2.6 \) Hz, 1H), 1.89 (td, \( J = 14.0, 6.9 \) Hz, 1H), 0.95 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 143.87, 137.01, 136.10, 134.83, 127.99, 127.68, 125.94, 117.85,
116.58, 115.96, 78.73, 48.70, 38.90, 38.83, 26.24, 18.42, -3.31, -4.02; HRMS (ESI) calcd for C$_{23}$H$_{36}$O$_3$Si [M] 356.2536, found 356.2528.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.08 (d, $J = 1.8$ Hz, 1H), 6.87 (dd, $J = 8.5$, 2.0 Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 5.83-5.70 (m, 1H), 5.61 (m, 2H), 5.12-4.91 (m, 4H), 4.86 (d, $J = 8.8$ Hz, 1H), 4.83 (d, $J = 16.4$ Hz, 1H), 3.90 (dd, $J = 6.2$, 4.1 Hz, 1H), 3.87 (s, 6H), 2.77 (m, $J = 14.2$, 6.1 Hz, 1H), 2.56 (dq, $J = 14.2$, 7.2 Hz, 2H), 2.45 (dd, $J = 14.3$, 8.0 Hz, 1H), 2.20-2.09 (m, 1H), 1.94-1.81 (m, 1H), 0.94 (s, 9H), 0.10 (s, 6H), 0.06 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 148.19, 147.24, 136.99, 136.57, 135.99, 134.78, 119.97, 117.99, 116.64, 115.95, 111.95, 110.11, 78.27, 55.98, 55.71, 48.25, 39.54, 38.95, 38.75, 26.24, 18.39, -3.31, -4.07; HRMS (EI) calcd for C$_{25}$H$_{40}$O$_3$Si [M] 416.2747, found 416.2744.

Colorless oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.25 (d, $J = 7.7$ Hz, 1H), 7.23 (t, $J = 7.0$ Hz, 1H), 6.91 (t, $J = 7.6$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.15 (m, 1H), 5.61 (m, 1H), 5.46 (m, 1H), 5.07 (d, $J = 17.1$ Hz, 1H), 5.00 (d, $J = 10.1$ Hz, 1H), 4.93 (d, $J = 17.0$ Hz, 1H), 4.82 (m, 3H), 4.62 (t, $J = 5.3$ Hz, 1H), 3.83 (s, 3H), 3.02 (dd, $J = 14.1$, 6.3 Hz, 1H), 2.77 (m, 1H), 2.66 (m, 1H), 2.19-2.13 (m, 2H), 0.94 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 158.00, 137.77, 136.95, 132.23, 129.54, 127.63, 120.50, 115.84, 115.71, 115.46, 111.38, 54.90, 49.99, 39.39, 38.48, 37.93, 26.26, 18.41, -3.28, -4.16; HRMS (EI) calcd for C$_{24}$H$_{38}$O$_2$Si [M] 386.2641, found 386.2645.

Colorless oil; 88% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.20-7.15 (m, 1H), 7.12 (d, $J = 7.8$ Hz, 1H), 6.87 (t, $J = 7.5$ Hz, 1H), 6.83 (t, $J = 7.9$ Hz, 1H), 5.81-5.73 (m, 1H), 5.63-5.53 (m, 1H), 5.29-5.16 (m, 1H), 4.84 (d, $J = 17.0$ Hz, 1H), 4.74 (m, 2H), 3.83 (s, 3H), 3.00-2.90 (m, 1H), 2.76 (d, $J = 16.2$ Hz, 1H), 2.38 (m, 1H), 2.25 (dd, $J = 13.2$, 8.5 Hz, 1H), 2.12-1.98 (m, 2H), 0.63 (s, 9H), -0.12 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 158.04, 136.36, 132.91,
129.38, 127.08, 125.83, 122.81, 120.18, 115.62, 110.65, 69.15, 54.67, 45.36, 35.75, 32.26, 28.46, 25.63, 17.81, -4.64, -5.85; HRMS (Cl) calcd for C_{23}H_{35}O_2Si [M+1]^+ 359.2406, found 359.2411.

Colorless oil; ^1H NMR (CDCl_3, 500 MHz) δ 7.43 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 5.74 (dtd, J = 14.6, 8.5, 6.5 Hz, 1H), 5.68-5.54 (m, 2H), 5.09 (m, 2H), 5.02 (d, J = 17.0 Hz, 1H), 4.97 (d, J = 10.2 Hz, 1H), 4.88 (d, J = 9.3 Hz, 1H), 4.86 (d, J = 16.9 Hz, 1H), 3.89 (dd, J = 6.2, 4.1 Hz, 1H), 2.77 (m, 1H), 2.64 (dd, J = 14.18, 8.26 Hz, 1H), 2.58-2.44 (m, 2H), 2.20-2.10 (m, 1H), 1.91-1.82 (m, 1H), 0.95 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^13C NMR (CDCl_3, 125 MHz) δ 142.85, 136.60, 135.36, 134.21, 130.70, 129.96, 120.11, 118.35, 117.14, 116.22, 77.95, 48.54, 39.18, 38.84, 38.38, 26.23, 18.41, -3.33, -4.02; HRMS (EI) calcd for C_{23}H_{34}OBrSi [M-1] 433.1562, found 433.1554.

Colorless oil; 91% yield, dr = 13 : 1; ^1H NMR (CDCl_3, 500 MHz) δ 7.38 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 5.78-5.70 (m, 1H), 5.48 (dd, J = 9.4, 1.8 Hz, 1H), 5.35 (ddd, J = 16.4, 8.7, 6.1 Hz, 1H), 4.95 (d, J = 17.1 Hz, 1H), 4.90 (d, J = 10.4 Hz, 1H), 3.94 (dd, J = 8.6, 4.7 Hz, 1H), 2.86 (dd, J = 13.7, 5.8 Hz, 1H), 2.58 (dd, J = 18.1, 3.2 Hz, 1H), 2.19-2.09 (m, 3H), 1.58 (ddd, J = 14.1, 7.1, 3.9 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^13C NMR (CDCl_3, 125 MHz) δ 141.71, 134.54, 130.49, 130.33, 125.62, 125.02, 119.95, 117.37, 74.68, 45.31, 44.23, 34.11, 32.88, 25.89, 18.09, -4.04, -4.90; HRMS (Cl) calcd for C_{21}H_{32}OBrSi [M+1]^+ 407.1406, found 407.1410.

**4.6. Total synthesis of (±)-nitramine**

To a suspension of LiAlH_4 (2.2 g, 57.9 mmol, 3.0 equiv) in 50 mL of THF stirred at 0 °C under N_2 atmosphere, a solution of dimethyl cyclopent-3-ene-1,1-dicarboxylate 4-10 (3.55 g, 19.3 mmol) in 20 mL
of diethyl ether was added dropwise. The mixture was stirred for 1 h at room temperature. Then, at 0 °C, water (2 mL), an aqueous solution 3 N in NaOH (4 mL) and water (6 mL) were successively added dropwise and stirring was continued for 15 min more. The resulting mixture was then filtered over Celite and rinsed several times with diethyl ether. The organic layer was separated, dried on anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford cyclopent-3-ene-1,1-diyldimethanol as a white solid, which was used directly for next step without further purification.

According to the known procedure reported by Kubota¹⁸⁰, to a solution of the above diol in THF (60 mL) was added NaH (60% dispersion in mineral oil, 656 mg, 1.0 equiv.) slowly at 0 °C. After stirring at room temperature for 1 h, benzyl bromide (1.95 mL, 1.0 equiv.) and a catalytic amount of tetrabutylammonium iodide (TBAI) were added and stirred at room temperature for 12 h. The reaction mixture was extracted with ethyl acetate and saturated NH₄Cl. The organic solvent was washed with brine, dried over MgSO₄, and concentrated. Purification on a silica gel column with hexane-ethyl acetate gave (1-(benzyloxymethyl)cyclopent-3-enyl)methanol 4-11 (2.82 g, yield 67% over two steps) and recovered diol (315 mg, 13% over two steps). ¹H NMR (CDCl₃, 500 MHz) δ 7.39-7.28 (m, 5H), 5.60 (s, 2H), 4.53 (s, 2H), 3.61 (s, 2H), 3.52 (s, 2H), 2.23 (m, 4H).

A dry DMSO (1.45 mL, 2.2 equiv.) was slowly added over a stirred oxalyl chloride (1.32g, 1.1 equiv.) in dry dichloromethane (0.5 M) at -78 °C. After the evolution of gas ceased, a solution of (1-(benzyloxymethyl)cyclopent-3-enyl)methanol 4-11 (2.02 g, 9.25 mmol) in dry dichloromethane was slowly added to the resulting solution of activated DMSO at -78 °C. After 60 min, triethylamine (5 equiv.) was added. After 30 min, the reaction was slowly warmed up to room temperature. The reaction was quenched by the addition of 10% NH₄Cl solution. The mixture was washed by dichloromethane for three times and the collected organic phases were dried over anhydrous MgSO₄ followed by concentration to give crude product, which was used directly without further purification. ¹H NMR (CDCl₃, 500 MHz) δ 9.66 (s, 1H), 7.63-6.98 (m, 5H), 5.80-5.41 (m, 2H), 4.53 (s, 2H), 3.63 (s, 2H), 2.79-
2.66 (m, 2H), 2.35 (td, J = 12.6, 2.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 203.23, 138.02, 128.44, 128.38, 127.73, 127.60, 73.44, 73.20, 57.41, 36.93.

An allyl magnesium bromide solution (1.0M, 12 mL) in diethyl ether was added slowly to the above aldehyde solution in THF at 0 °C. After addition, the reaction solution was slowly warmed up to room temperature. Once TLC indicated the reaction was completed, a saturated NH$_4$Cl solution was added to quench the reaction. Then the reaction solution was extracted with diethyl ether for three times and washed by brine. The collected organic phase was dried over anhydrous MgSO$_4$ followed by concentration to afford crude alcohol, which was further purified by column chromatograph to give allylic alcohol (2.15 g, yield 90% in two steps).

To a solution of the allylic alcohol (2.03 g, 7.86 mmol), triethylamine (2.1 mL, 15 mmol) and catalytic amount 4-dimethylaminopyridine in anhydrous DMF was added slowly tert-butyldimethylsilyl triflate (1.8 mL, 7.86 mmol) at 0 °C. Then the reaction was heated up to 80 °C until completion. Then the reaction was quenched by the addition of 1N HCl, extracted with diethyl ether, dried over anhydrous MgSO$_4$ and concentrated under vacuum to afford crude oil, which was purified by column chromatograph to give the metathesis substrate 3-36 (2.75 g, yield 94%); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.37 (m, 4H), 7.34-7.28 (m, 1H), 5.93 (tdd, J = 17.1, 10.1, 7.2 Hz, 1H), 5.65-5.54 (m, 2H), 5.01 (d, J = 17.2 Hz, 1H), 4.99 (d, J = 9.5 Hz, 1H), 4.51 (m, 2H), 3.97-3.93 (m, 1H), 3.38 (m, 2H), 2.51-2.36 (m, 3H), 2.29-2.18 (m, 2H), 2.13-2.03 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 138.82, 137.32, 129.35, 129.26, 128.31, 127.63, 127.44, 115.82, 75.12, 75.02, 73.22, 51.29, 38.96, 38.88, 38.83, 26.10, 18.33, -3.16, -4.48; HRMS (CI) calcd for C$_{25}$H$_{35}$O$_2$Si [M-1] 371.2406, found 371.2405.

To a solution of the Grubbs 2nd generation catalyst (100 mg, 0.04 equiv.) under ethylene atmosphere was slowly added a solution of 3-36 (1.11 g, 2.98 mmol) in CH$_2$Cl$_2$ (80 mL). The reaction
was monitored by TLC or $^1$HNMR until completion of the reaction. Then the reaction solution was concentrated by rotavap and purified by silica gel column chromatography to give the ring-rearrangement metathesis product 3-37 (1.05 g, yield 95%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.35 (m, 4H), 7.29 (dd, $J = 8.4$, 4.1 Hz, 1H), 5.91-5.78 (tdd, $J = 16.3$, 11.2, 7.5 Hz, 1H), 5.64-5.47 (m, 2H), 5.03 (d, $J = 15.6$ Hz, 1H), 5.03 (d, $J = 11.5$ Hz, 1H), 4.47 (m, 2H), 3.86 (t, $J = 4.0$ Hz, 1H), 3.37 (m, 2H), 2.30-2.10 (m, 3H), 1.98 (m, 2H), 1.76 (m, 1H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 139.02, 135.19, 128.24, 127.53, 127.32, 125.28, 123.00, 117.35, 73.25, 72.28, 69.08, 41.15, 36.69, 31.34, 28.16, 25.88, 18.09, -4.04, -4.96; HRMS (CI) calcd for C$_{23}$H$_{37}$O$_2$Si [M+1]$^+$ 373.2563, found 373.2534.

To a solution of diene 3-37 (1.54 g, 4.12 mmol) in THF (10 mL) was added a THF solution of 9-BBN (0.5 M, 14 mL, 7.0 mmol) slowly at 0 °C and the reaction mixture was stirred for 7 h at that temperature. After the addition of 3M NaOH (7.35 mL, 22.1 mmol) solution and H$_2$O$_2$ solution (30%, 7.35 mL, 77.2 mmol), the reaction mixture was stirred for 30 minutes. Organic materials were extracted with ethyl acetate two times and the combined organic extracts were washed with brine two times and dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo after filtration. Purification by silica gel column chromatography gave the primary alcohol 3-38 (1.03 g) in 64% yield. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.34-7.31 (m, 4H), 7.28 (td, $J = 7.9$, 2.2 Hz, 1H), 5.61-5.44 (m, 2H), 4.45 (m, 2H), 3.86 (t, $J = 4.0$ Hz, 1H), 3.57 (t, $J = 6.6$ Hz, 2H), 3.48 (d, $J = 8.7$ Hz, 1H), 3.25 (d, $J = 8.7$ Hz, 1H), 2.27-2.18 (m, 1H), 2.04-1.91 (m, 2H), 1.82 (m, 1H), 1.75-1.62 (m, 2H), 1.57-1.46 (m, 2H), 1.46-1.35 (m, 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 138.86, 128.26, 127.58, 127.40, 125.24, 123.04, 73.26, 72.24, 69.37, 63.88, 40.41, 31.37, 28.57, 28.07, 25.86, 22.71, 18.08, -4.07, -4.97; HRMS (CI) calcd for C$_{23}$H$_{38}$O$_3$Si [M+1]$^+$ 391.2669, found 391.2660.
To a solution of alcohol 3-38 (321 mg, 0.82 mmol) in THF (3 mL) was added triphenylphosphine (865 mg, 3.30 mmol), diphenyl phosphorazidate (355 μL, 1.65 mmol) and diethyl azodicarboxylate (575 mg, 3.30 mmol) at 0°C. Then the reaction was stirred for 30 minutes at room temperature. The mixture was concentrated and purified the residue by column chromatography to afford the azide 3-39 (317 mg, yield 93%). ¹H NMR (CDCl₃, 500 MHz) δ 7.38-7.30 (m, 4H), 7.30-7.27 (m, 1H), 5.63-5.44 (m, 2H), 4.45 (m, 2H), 3.85 (t, J = 4.2 Hz, 1H), 3.46 (d, J = 8.8 Hz, 1H), 3.24 (d, J = 8.8 Hz, 1H), 3.22-3.17 (dt, J = 7.0, 2.3 Hz, 2H), 2.21 (dd, J = 17.9, 1.9 Hz, 1H), 2.07-1.90 (m, 2H), 1.70 (d, J = 17.4 Hz, 1H), 1.62-1.53 (m, 3H), 1.51-1.34 (m, 2H), 0.86 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 138.81, 128.28, 127.57, 127.43, 125.13, 123.14, 73.28, 71.99, 69.46, 52.42, 40.50, 31.41, 29.68, 28.61, 25.84, 23.19, 18.07, -4.05, -4.98; HRMS (EI) calcd for C₂₃H₃₇O₂N₃Si [M] 415.2655, found 415.2648.

A solution of the azide 3-39 (440 mg, 1.05 mmol) in ethyl acetate was added to a solution of 10% palladium/charcoal (300 mg) and di-tert-butyl dicarbonate (231 mg, 1.1 equiv.) in ethyl acetate (11 mL). The palladium catalyst was washed by ethyl acetate for several times before use in order to avoid side reaction (mainly deprotonation of silyl group). Then the reaction mixture was flushed by hydrogen gas for three times and stirred under atmospheric pressure of hydrogen gas at room temperature for 24 hrs. Once TLC indicated the completion of reaction, the reaction was filtered through a pad of celite, concentrated and purified by silica gel column chromatography to give the primary alcohol 3-40 (401 mg, yield 95%). ¹H NMR (CDCl₃, 500 MHz) δ 4.61 (s, 1H), 4.16 (d, J = 10.4 Hz, 1H), 3.55 (dd, J = 9.9, 4.2 Hz, 1H), 3.28 (d, J = 10.5 Hz, 2H), 3.11 (td, J = 12.7, 6.2 Hz, 2H), 1.98-1.85 (m, 1H), 1.71 (m, 3H), 1.54-1.40 (m, 13H), 1.28-1.17 (m, 2H), 1.19-1.01 (m, 2H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C
NMR (CDCl₃, 125 MHz) δ 155.99, 79.42, 78.94, 85.00, 41.40, 40.87, 32.70, 32.22, 31.08, 28.46, 25.83, 24.40, 23.16, 20.99, 17.92, -4.12, -5.03; HRMS (Cl) calcd for C₁₉H₂₅O₄SiN [M-1] 400.2883, found 400.2877.

To a solution of the primary alcohol 3-40 (129 mg, 0.32 mmol) in dichloromethane (3 mL) was added Dess-Martin Periodinane (204 g, 1.5 equiv.) followed by sodium bicarbonate (3 equiv.) at room temperature. After stirred for 2 h, the reaction mixture was flushed over a plug of cotton; the filtrate was then poured into a mixture of Na₂S₂O₅ and NaHCO₃ solution and extracted with diethyl ether. The solution was dried over anhydrous MgSO₄, and concentrated in vacuum to provide a residue, whose ¹H NMR showed a formation of cyclic product 3-41 incorporating acetoxy group. Treatment of the cyclized intermediate 3-41 in dichloromethane with trifluoroacetic acid at room temperature for 30 min followed by basic workup yielded a crude aldimine 3-42. ¹H NMR (CDCl₃, 500 MHz) δ 7.95 (s, 1H), 3.62 (d, J = 17.0 Hz, 1H), 3.52 (m, 1H), 3.48-3.37 (m, 1H), 1.93 (ddd, J = 13.1, 8.8, 3.9 Hz, 1H), 1.76-1.56 (m, 5H), 1.55-1.41 (m, 4H), 1.38 (m, 1H), 1.21-1.11 (m, 1H), 0.89 (s, 9H), 0.03 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 169.86, 74.53, 49.51, 41.02, 31.69, 29.66, 28.99, 25.87, 25.80, 21.48, 20.62, 19.13, 18.09, -4.09, -5.04; HRMS (EI) calcd for C₁₆H₃₂NOSi [M+1]⁺ 282.2253, found 282.2243.

The aldimine 3-42 solution in MeOH was carefully treated with NaBH₄ (12 mg, 0.32 mmol). The reaction mixture was stirred for 10 min and quenched with 1 M NaOH. The product was extracted with ether. The ether extract was washed with saturated aqueous NaCl and dried over MgSO₄. The solvent was evaporated to give the crude protected nitramine as colorless oil. To a solution of the protected
nitramine in methanol was added ammonium fluoride (37 mg, 1 mmol) at 50 °C. After stirring overnight, TLC showed the completion of the reaction. The mixture was flushed through a pad of silica gel. The filtrate was concentrated under reduced pressure and purified using silica gel column chromatography to deliver the nature product (±)-nitramine (44 mg, 82% yield over four steps from 10). \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 4.28 (b, 1H), 3.59 (dd, \(J = 9.8, 3.8\) Hz, 1H), 3.49 (d, \(J = 11.9\) Hz, 1H), 3.04 (d, \(J = 11.1\) Hz, 1H), 2.63 (dt, \(J = 11.3, 3.2\) Hz, 1H), 2.40 (d, \(J = 11.9\) Hz, 1H), 2.19-2.03 (m, 1H), 1.90-1.80 (m, 1H), 1.76 (m, 1H), 1.67 (m, 1H), 1.63-1.48 (m, 2H), 1.38 (m, 2H), 1.27 (m, 4H), 1.05 (m, 1H); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 76.78, 52.15, 46.67, 37.91, 36.88, 35.97, 32.29, 24.02, 23.31, 21.08; HRMS (Cl) calcd for C\(_{10}\)H\(_{20}\)NO [M] 170.1545, found 170.1551.
4.7. Synthetic studies on (±)-galanthamine

Ethyl 2-(tributylstannyl) acrylate 3-99 was prepared according to Tanner’s procedure.\textsuperscript{156} To a cooled (0 °C) solution of ethyl propiolate (6.08, 62 mmol) in degassed THF (100 mL) was added bis(triphenylphosphine)-palladium(II)chloride (435 mg, 1 mol%). With stirring tributyltin hydride (19.9 g, 68 mmol) was added dropwise at the same temperature. Then the reaction was warmed to room temperature and stirred for 10 min during, which time the originally light-yellow solution turned orange-brown. The solvent was quickly removed by rotary evaporation. The obtained residue was dissolved in pentane, and washed with CH$_3$CN, water and brine. The organic phase was isolated, dried over MgSO$_4$, filtered and concentrate to afford the compound 3-99 in 95% yield (22.9 g); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.91 (d, $J = 2.7$ Hz, 1H), 5.91 (d, $J = 2.7$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 1.55-1.42 (m, 6H), 1.37-1.24 (m, 6H), 1.00-0.95 (m, 6H), 0.88 (m, 12H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 170.56, 146.19, 139.75, 60.61, 28.96, 27.30, 14.33, 13.71, 10.14.

To a solution of guaiacol 3-100 (2.95 g, 23.8 mmol) in anhydrous DCM (40 mL) were added diisopropylethylamine (DIPEA) (5.2 g, 40.0 mmol). Then the mixture was stirred and cooled to 0 °C. After adding MOMCl (2.10 g, 26.2 mmol), the ice-bath was removed and the mixture was refluxed until the TLC showed the completion of the reaction. The reaction mixture was then diluted with EtOAc, and washed with 1N HCl solution. The organic layer were washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuum to afford 3.95 g (23.5 mmol, 99 % yield) crude product 3-101, which was used directly for next step without further purification.

To a solution of the compound 3-101 (2.13 g, 12.6 mmol) in anhydrous diethyl ether (30 mL) were added nBuLi solution in hexanes (2.5 M, 11.1 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. Then
iodine (19.0 g) solution in THF was added to the above mixture and the resulting solution was stirred at
room temperature overnight. Once the reaction was completed, the reaction was quenched by adding
Na₂S₂O₃ solution and extracted with Et₂O. The organic layer were washed with brine, dried over MgSO₄,
filtered, and concentrated in vacuum. Purification by silica gel column chromatography gave 3.08 g
(10.5 mmol, 82 % yield in two steps) of the desired compound 3-102. ¹H NMR (CDCl₃, 500 MHz) δ7.36
(dd, J = 8.0, 1.3 Hz, 1H), 6.87 (dd, J = 8.2, 1.2 Hz, 1H), 6.78 (t, J = 8.1 Hz, 1H), 5.16 (s, 2H), 3.81 (s,
3H), 3.67 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 152.49, 145.92, 131.03, 126.00, 112.86, 98.73, 92.74,
58.43, 56.00.

A Schlenck tube was charged with LiCl (2.03 mg, 6.0 equiv.) and flame dried under high vacuum.
Upon cooling, Pd(PPh₃)₄ (921 mg, 0.8 mmol) and CuCl (3.94 mg, 5.0 equiv.) were added, and the
mixture was degassed (4 times) under high vacuum with an N₂ purge. DMSO (64 mL) was introduced
with concomitant stirring, followed by the addition of aryl iodide 3-102 (2.34 g, 7.9 mmol) and vinyltin
compound 3-99 (3.72 g, 1.2 equiv.). The resulting mixture was rigorously degassed (4 times) by the
freeze-thaw process (-78 to 25 °C, N₂). The reaction mixture was stirred at room temperature for 1 h,
then heated to 60 °C for more than 40 h. Following completion of the coupling as monitored by TLC, the
reaction mixture was cooled, diluted with Et₂O, and washed with a mixture of brine and 5% aqueous
NH₄OH. The aqueous layer was further extracted with Et₂O, and the combined organic layers were
washed with water then brine, dried over MgSO₄, and concentrated to a residue that was purified by
column chromatography to give 1.91 g (90% yield) desired coupling product 3-103; ¹H NMR (CDCl₃,
500 MHz) δ 7.05 (t, J = 7.9 Hz, 1H), 6.91 (dd, J = 8.2, 1.3 Hz, 1H), 6.84 (dd, J = 7.6, 1.4 Hz, 1H), 6.34
(d, J = 1.4 Hz, 1H), 5.77 (d, J = 1.4 Hz, 1H), 5.02 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.47 (s,
3H), 1.26 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 167.20, 152.09, 143.38, 140.07, 132.74,
126.90, 124.19, 122.20, 112.69, 98.48, 61.05, 57.50, 55.86, 14.21.
To a stirred solution of the ester 3-103 (706 mg, 2.8 mmol) in toluene was added DIBAL (1.0 M in hexanes, 5.6 mL) solution at -78 °C. Then the reaction was warmed up to room temperature. After 30 min, the reaction was quenched with ethyl acetate and saturated aqueous potassium sodium tartrate solution. After stirring for 1 h, the aqueous layer was extracted with Et₂O. The extracted organic layers were dried over MgSO₄, filtered and concentrated by rotary evaporation. Purification by silica gel column chromatography gave a crude product, which was treated with Dess-Martin reagent (1.5 equiv.) in the presence of NaHCO₃ (2.0 equiv.) in DCM at room temperature. After stirred for 2 h, the reaction mixture was flushed over a plug of cotton; the filtrate was then poured into a mixture of Na₂S₂O₃ and NaHCO₃ solution and extracted with diethyl ether. The solution was dried over anhydrous MgSO₄, and concentrated in vacuum to provide a residue, which was purified by column chromatography to afford 404 mg (18.2 mmol, 65 % yield in two steps) of the desired compound 3-104.

\[
\begin{align*}
\text{OMe} & \quad \text{OMOM} \quad \text{OEt} \\
3-103 & \quad \overset{\text{i. DIBALH}}{\longrightarrow} \quad \text{OMe} \quad \text{OMOM} \quad \text{H} \\
& \quad \overset{\text{ii. DMP}}{\longrightarrow} \quad \text{OMe} \quad \text{OMOM} \\
3-104 & 
\end{align*}
\]

\[\delta 9.72 (s, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.92 (dd, J = 8.2, 1.3 Hz, 1H), 6.77 (dd, J = 7.7, 1.4 Hz, 1H), 6.38-6.29 (m, 2H), 4.98 (s, 2H), 3.82 (s, 3H), 3.39 (s, 3H);\]

\[\text{13C NMR (CDCl₃, 125 MHz)} \quad \delta 192.25, 152.32, 146.68, 143.50, 133.94, 129.92, 124.39, 122.23, 112.94, 98.58, 57.47, 55.84.\]

To a stirred solution of aldehyde 3-104 (515 mg, 2.3 mmol) in DMF (15 mL) was added propargyl bromide (1.6 equiv.) and zinc powder (181 mg, 1.2 equiv.) at room temperature. Then the reaction mixture was cooled to 0 °C and 1-2 drops of saturated NH₄Cl solution were added carefully. After the addition, the reaction was slowly warmed up to room temperature for 30 min. Following completion of the reaction as monitored by TLC, the reaction was diluted with Et₂O and water, extracted with Et₂O, then washed with brine and dried over MgSO₄. Concentration and purification by column chromatography afforded 251 mg (94 % yield) of the desired product 3-105.
chromatography gave the homoallylic alcohol **3-105** in 70% yield (422 mg). **1H NMR (CDCl₃, 500 MHz)**

δ 7.03 (t, \( J = 7.9 \text{ Hz}, 1\text{H} \)), 6.87 (dd, \( J = 8.2, 1.3 \text{ Hz}, 1\text{H} \)), 6.78 (dd, \( J = 7.6, 1.4 \text{ Hz}, 1\text{H} \)), 5.56 (s, 1H), 5.23 (s, 1H), 5.05 (m, 1H), 4.75 (q, \( J = 5.7 \text{ Hz}, 1\text{H} \)), 3.83 (s, 3H), 3.51 (s, 3H), 3.25 (d, \( J = 5.3 \text{ Hz}, 1\text{H} \)), 2.37 (m, 1H), 2.01 (t, \( J = 2.6 \text{ Hz}, 1\text{H} \)); **13C NMR (CDCl₃, 125 MHz)** δ 152.22, 148.26, 142.80, 134.84, 124.66, 124.46, 122.76, 122.70, 116.36, 111.97, 98.98, 80.81, 72.45, 70.66, 57.70, 55.82, 26.38.

**3-105**

**3-106**

AuCl(SMe₂) (1.5 mg, 0.005 mmol) and xantphos ligand (3.0 mg, 0.005 mmol) were placed in the reaction vial under argon atmosphere. Then dry dichloroethane (0.5 mL) was added and stirred. After stirring for 1 h at room temperature, the solvent was removed under reduced pressure and refilled with argon again. Dry DMF (2 mL) was added to dissolve the resultant solid followed by the addition of the alcohol **3-105** (146, 0.56 mmol) and allyldiphenylsilane (124 mg, 0.56 mmol). The reaction mixture was heated up to 90 °C and stirred for 8 h. Following completion of the reaction as monitored by TLC, the reaction was diluted with Et₂O and water, extracted with Et₂O, then washed with brine and dried over MgSO₄. Concentration and purification by column chromatography gave the desired product **3-106** in 91% yield (244 mg). **1H NMR (CDCl₃, 500 MHz)** δ 7.68 (dd, \( J = 9.2, 3.6 \text{ Hz}, 4\text{H} \)), 7.43 (d, \( J = 7.3 \text{ Hz}, 2\text{H} \)), 7.38 (t, \( J = 7.2 \text{ Hz}, 4\text{H} \)), 6.99 (t, \( J = 7.9 \text{ Hz}, 1\text{H} \)), 6.84 (d, \( J = 8.1 \text{ Hz}, 1\text{H} \)), 6.73 (dd, \( J = 7.7, 1.1 \text{ Hz}, 1\text{H} \)), 5.87 (qd, \( J = 9.9, 7.8 \text{ Hz}, 1\text{H} \)), 5.74 (s, 1H), 5.27 (s, 1H), 5.03 (t, \( J = 4.8 \text{ Hz}, 1\text{H} \)), 4.98-4.87 (m, 2H), 4.84 (m, 2H), 3.83 (s, 3H), 3.39 (s, 3H), 2.39-2.14 (m, 4H), 1.92 (t, \( J = 2.5 \text{ Hz}, 1\text{H} \)); **13C NMR (CDCl₃, 125 MHz)** δ 152.42, 147.96, 142.84, 135.20, 135.11, 135.06, 135.00, 134.50, 133.18, 129.98, 127.74, 124.34, 123.00, 115.68, 115.25, 111.74, 98.54, 81.23, 72.41, 70.24, 57.47, 55.80, 26.78, 22.35.
According to the gold-catalyzed cycloisomerization/allylation procedure described in section 4.4.1, the acetal 3-110 was obtained in 83% yield. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.63 (d, $J = 7.9$ Hz, 2H), 7.58 (d, $J = 7.9$ Hz, 2H), 7.46-7.30 (m, 6H), 6.86 (d, $J = 7.7$ Hz, 1H), 6.80 (d, $J = 7.4$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 5.88-5.83 (m, 1H), 5.75 (m, 1H), 5.68 (s, 1H), 5.66-5.62 (m, 1H), 4.86 (dd, $J = 17.0$, 1.5 Hz, 1H), 4.82 (d, $J = 10.1$ Hz, 1H), 3.82 (s, 3H), 3.30-3.22 (m, 1H), 2.72-2.62 (m, 1H), 2.41 (m, 2H), 2.30 (d, $J = 7.8$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 145.24, 144.60, 136.49, 135.07, 134.91, 133.83, 132.85, 130.51, 130.05, 129.93, 128.01, 127.79, 127.67, 122.01, 115.19, 114.74, 111.97, 108.99, 57.26, 56.16, 45.96, 37.99, 22.38.

To a flame-dried flask was added the diol 3-111 (44 mg, 0.2 mmol), and triphenylphosphine (57 mg, 0.2 mmol). The reaction was cooled to 0 °C, and then DIAD (47 mg, 0.2 mmol) was added in one portion. The reaction was stirred for 2 h and then quenched with water, extracted with Et$_2$O. The ether solution was dried over anhydrous MgSO$_4$, and concentrated in vacuum. Purification of column chromatography of the residue provided 37 mg (92 % yield) of the ether 3-112. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.02 (d, $J = 7.6$ Hz, 1H), 6.87 (t, $J = 7.8$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 5.47 (d, $J = 2.8$ Hz, 1H), 5.30 (m, 1H), 5.18 (d, $J = 2.3$ Hz, 1H), 3.89 (s, 3H), 2.74 (m, 2H), 2.01 (t, $J = 2.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 150.74, 146.42, 145.13, 126.72, 121.60, 113.15, 112.98, 101.78, 83.33, 79.08, 70.77, 56.05, 26.01.
To a solution of enyne 3-112 (26 mg, 0.13 mmol), isopropanol (9.4 mg, 0.16 mmol) and allyl trimethylsilane (37 mg, 0.33 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added the Au(I) catalyst 3-9 (1 mol%). The resulting solution was stirred at room temperature for 2 hour, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column chromatography to give the product 3-115 (26 mg, quantitative yield). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.14 (t, $J = 7.8$ Hz, 1H), 7.04 (d, $J = 7.7$ Hz, 1H), 6.78 (d, $J = 7.9$ Hz, 1H), 5.93 (m, 2H), 4.01 (s, 3H), 3.41 (m, 4H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 151.27, 145.11, 143.30, 129.71, 124.60, 123.06, 122.83, 111.22, 110.62, 105.86, 56.03, 24.99, 23.75.

Following the previous procedures, 3-116 and 3-117 were prepared from the corresponding iodides 4-13 and 4-14 in four steps involving Stille coupling with 3-99, reduction, Swern-type oxidation and Barbier reaction with propargyl bromide. Compound 3-116, colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.86 (t, $J = 7.8$ Hz, 1H), 6.80 (dd, $J = 8.1$, 1.5 Hz, 1H), 6.70 (dd, $J = 7.5$, 1.6 Hz, 1H), 5.50 (s, 1H), 5.15 (s, 1H), 4.77 (m, 1H), 3.78 (s, 3H), 2.87-2.76 (m, 1H), 2.36 (m, 2H), 2.03 (t, $J = 2.5$ Hz, 1H), 1.23 (q, $J = 7.5$ Hz, 3H), 1.05 (d, $J = 7.3$ Hz, 18H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 149.75, 148.97, 142.61, 131.64, 122.87, 120.94, 114.92, 110.75, 80.96, 72.37, 70.54, 54.68, 26.40, 18.16, 14.10. Compound 3-117, colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.89 (t, $J = 7.8$ Hz, 1H), 6.81 (dd, $J = 8.1$, 1.6 Hz, 1H), 6.72 (dd, $J = 7.5$, 1.6 Hz, 1H), 5.51 (t, $J = 1.4$ Hz, 1H), 5.17 (s, 1H), 4.81-4.76 (m, 1H), 3.79 (s, 3H), 2.89 (d, $J = 5.0$ Hz, 1H), 2.33 (m, 1H), 2.03 (t, $J = 2.6$ Hz, 1H), 0.97 (s, 9H), 0.15 (s, 3H),
0.12 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 150.26, 148.91, 141.88, 132.26, 122.99, 121.56, 115.47, 111.06, 80.86, 72.21, 70.68, 54.86, 26.50, 26.09, 18.78, -3.90, -4.03.

Aldehyde 3-118 was prepared based on Kirsch’s procedure.$^{111}$ To a solution of enyne 3-116 (65 mg, 0.17 mmol), in CH$_2$Cl$_2$ (0.5 mL) was added the Au(I) catalyst 3-9 (1 mol%). The resulting solution was stirred at room temperature for 2 hour, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column chromatography to give the aldehyde 3-118 (57 mg, 89% yield). $^1$H NMR (CDCl$_3$, 500 MHz) δ 9.72 (s, 1H), 6.88 (d, $J = 7.5$ Hz, 1H), 6.83 (m, 2H), 3.79 (s, 3H), 3.11 (m, 2H), 2.74 (m, 2H), 1.35-1.25 (m, 3H), 1.09 (d, $J = 7.5$ Hz, 18H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 201.39, 149.21, 143.56, 134.29, 128.36, 127.95, 120.25, 120.20, 110.41, 54.56, 53.46, 40.80, 18.25, 14.95.

To a solution of enyne 3-111 (191 mg, 0.88 mmol), in CH$_2$Cl$_2$ (1.5 mL) was added the Au(I) catalyst 3-9 (1 mol%). The resulting solution was stirred at room temperature for 2 hour, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column chromatography to give the aldehyde 3-119 (173 mg, 90% yield). $^1$H NMR (CDCl$_3$, 500 MHz) δ 6.89 (t, $J = 7.8$ Hz, 1H), 6.81 (d, $J = 7.5$ Hz, 1H), 6.78 (d, $J = 8.0$ Hz, 1H), 5.89-5.84 (m, 1H), 5.70 (m, 2H), 3.89 (s, 3H), 3.17-3.09 (m, 1H), 3.05 (d, $J = 4.1$ Hz, 1H), 2.74-2.67 (m, 1H), 2.65-2.57 (m, 1H), 2.45 (m, 1H), 1.56 (s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 144.56, 136.05, 130.36, 127.93, 122.24, 114.77, 111.40, 108.59, 62.12, 56.00, 46.37, 37.46.
To a stirred cooled (0 °C) solution of hemiacetal 3-119 (209 mg, 0.96 mmol) in diethyl ether (4 mL) was added the allylmagnesium bromide (1.0 M in diethyl ether, 2.5 mL) solution slowly. After the addition, the resulting solution was stirred at room temperature for 30 min, at which point TLC indicated the consumption of the starting material. The reaction mixture was quenched with saturated NH₄Cl solution, extracted with Et₂O, dried over MgSO₄. Concentration and purification by column chromatography gave the diol 3-94 (207 mg, 83% yield). ¹H NMR (CDCl₃, 500 MHz) δ 7.09 (s, 1H), 6.85-6.76 (m, 3H), 5.81 (m, 1H), 5.73 (s, 1H), 5.05 (d, J = 10.4 Hz, 1H), 5.04 (d, J = 16.8 Hz, 1H), 3.90 (s, 1H), 3.88 (s, 3H), 3.21 (m, 1H), 2.92 (m, 1H), 2.80-2.67 (m, 2H), 2.46 (s, 1H), 2.36-2.19 (m, 1H), 1.80 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 148.02, 144.45, 136.50, 131.60, 129.48, 128.92, 121.83, 119.21, 117.47, 109.38, 75.79, 56.08, 54.43, 41.02, 40.92, 37.67.

To a flame-dried round-bottom flask was added the diol 3-94 (94 mg, 0.36 mmol), and triphenylphosphine (105 mg, 0.40 mmol) and THF (2 mL). The reaction was cooled to 0 °C, and then DIAD (81 mg, 0.40 mmol) was added in one portion. The reaction was stirred for 2 h and then quenched with water, extracted with Et₂O. The ether solution was dried over anhydrous MgSO₄, and concentrated in vacuum. Purification of column chromatography of the residue provided 79 mg (91 % yield) of the ether 3-35, colorless oil; ¹H NMR (CDCl₃, 500 MHz) δ 6.85-6.78 (m, 2H), 6.77-6.72 (m, 1H), 5.98 (tdd, J = 17.0, 10.3, 6.8 Hz, 1H), 5.82-5.67 (m, 2H), 5.19 (d, J = 17.0 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.50 (dd, J = 8.5, 4.8 Hz, 1H), 3.88 (s, 3H), 2.88 (m, 2H), 2.66 (td, J = 14.5, 7.2 Hz, 1H), 2.59-2.45 (m, 2H), 2.25 (d, J = 16.8 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 146.21, 144.36, 138.98,
134.59, 129.23, 128.91, 121.54, 117.39, 114.32, 111.14, 92.32, 55.97, 54.27, 46.29, 40.77, 35.39; LRMS (EI) calcd for C₁₆H₁₈O₂ [M] 242.13, found 242.13.

To a solution of enyne 3-105 (34 mg, 0.13 mmol), in CH₂Cl₂ (0.5 mL) was added the Au(I) catalyst 3-9 (1 mol%). The resulting solution was stirred at room temperature for 2 hour, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column chromatography to give the aldehyde 3-120 (32 mg, 95% yield). ¹H NMR (CDCl₃, 500 MHz) δ 6.90-6.85 (m, 1H), 6.80 (dd, J = 7.5, 1.2 Hz, 1H), 6.77 (dd, J = 8.0, 1.0 Hz, 1H), 5.91-5.81 (m, 1H), 5.72-5.67 (m, 1H), 5.60 (s, 1H), 5.14 (d, J = 6.6 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 3.88 (s, 3H), 3.39 (s, 3H), 3.20-3.10 (m, 1H), 2.76-2.69 (m, 1H), 2.66-2.60 (m, 1H), 2.45 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 144.60, 130.37, 128.01, 127.95, 122.16, 114.53, 111.76, 111.71, 109.84, 94.06, 56.11, 56.00, 46.39, 37.67.

To a stirred solution of the ester 3-99 (4.68 g, 12.0 mmol) in THF was added DIBAL (1.0 M in THF, 26.5 mL) solution at 0 °C. Then the reaction was warmed up to room temperature. After 30 min, the reaction was quenched with ethyl acetate and saturated aqueous potassium sodium tartrate solution. After stirring for 1 h, the aqueous layer was extracted with Et₂O. The extracted organic layers were dried over MgSO₄, filtered and concentrated by rotary evaporation. Purification by silica gel column chromatography gave a crude product, which was used for next step without further purification.

To a flame-dried flask was added freshly activated 4 Å molecular sieves (7 g), dichloromethane (20 mL), N-methyl morpholine N-oxide (NMO, 409 mg, 1.6 equiv.), and the above alcohol (735 mg, 2.1 mmol). The solution was stirred for 10 min, then tetra-n-propylammonium perruthenate (TPAP,
54 mg, 7 mol%) was added in one portion. The reaction mixture was stirred overnight, by which time the solution had become brown, and TLC showed a complete conversion of the alcohol into one product. The reaction mixture was slightly concentrated and then directly applied to column chromatography to give the product 3-122 (512 mg, 70%) as a light brown oil; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 9.66 (s, 1H), 6.85 (d, $J = 2.1$ Hz, 1H), 6.69 (d, $J = 2.0$ Hz, 1H), 1.53-1.43 (m, 6H), 1.34-1.24 (m, 6H), 1.02-0.97 (m, 6H), 0.87 (d, $J = 7.3$ Hz, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 199.26, 156.45, 148.06, 29.00, 28.92, 27.24, 13.66, 9.64.

![Chemical structure](image)

Following the procedure described previously for compound 3-103, compound 3-125 was generated in 41% yield from the Suzuki coupling of iodide 3-102 and vinyl stannane 3-124 and some of the iodide 3-102 was recovered. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.02 (t, $J = 7.9$ Hz, 1H), 6.96-6.94 (m, 2H), 6.88-6.81 (m, 3H), 5.66 (s, 1H), 5.22 (s, 1H), 5.21 (s, 1H), 5.06 (m, 2H), 4.98 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.58 (s, 3H), 3.52 (s, 3H), 2.62 (m, 1H), 2.42 (m, 1H), 1.00 (t, $J = 7.9$ Hz, 9H), 0.70 (q, $J = 7.8$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 149.17, 135.50, 125.51, 124.37, 123.85, 123.11, 114.85, 112.06, 111.72, 98.75, 98.53, 72.09, 57.62, 57.37, 55.91, 55.81, 28.47, 6.99, 4.99.

![Chemical structure](image)

To a stirred and cooled ($-78^\circ$C) solution of acrolein (3.3 mL, 50 mmol) in CH$_2$Cl$_2$ (75 mL) was added Br$_2$ (2.6 mL, 50 mmol) over 10 min. After an additional 30 min at $-78^\circ$C, Et$_3$N (6.9 mL, 50 mmol) was added and the mixture was warmed to room temperature over 2 h. The reaction was then quenched by the addition of H$_2$O, the layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined aqueous layers were washed with a mixture of brine and 1 M HCl (9:1), dried with MgSO$_4$, filtered and carefully concentrated at room temperature under low vacuum due its high
volatility.

To a solution of the bromoacrolein (3.48 g, 25.79 mmol) in DMF (25 mL) was added Zn powder (1.85 g, 28.36 mmol) and propargyl bromide (7.76 g, 51.57 mmol) at 0 °C. Then a solution of the saturated aqueous NH₄Cl (1 mL) was added dropwise to ensure the temperature of the reaction solution at about 0 °C. Upon finishing the addition, the reaction mixture was slowly warmed up to room temperature and quenched by adding 50 mL H₂O and the solution was extracted with CH₂Cl₂ (3 X 50 mL). The combined organic layers were washed with brine, dried with MgSO₄ and concentrated give the colorless oil, which was directly used for the next step with further purification. A following TES protection was conducted according to the previous procedure to give compound 3-130 in 48% yield over 3 steps. ^1H NMR (CDCl₃, 500 MHz) δ 5.94 (m, 1H), 5.58 (d, J = 1.6 Hz, 1H), 4.28 (t, J = 6.0 Hz, 1H), 2.54 (m, 2H), 1.99 (t, J = 2.6 Hz, 1H), 0.97 (t, J = 7.9 Hz, 9H), 0.64 (q, J = 8.0 Hz, 6H); ^13C NMR (CDCl₃, 125 MHz) δ 135.44, 117.40, 80.33, 75.28, 70.41, 27.11, 6.77, 4.74.

A solution of compound 3-130 (273 mg, 1 mmol) in 5 mL THF was slowly treated with a solution of MeLi in ether (1.6 M, 0.63 mL, 1.1 mmol) at −78 °C and the solution was slowly warmed up to 0 °C in 30 min and a solution of TESCl (166 mg, 1.2 mmol) in 5 mL of THF was slowly added. Then the reaction was warmed up to room temperature in 30 min and quenched with 10 mL of H₂O. The solution was then extracted with diethyl ether (3 X 20 mL). The combined organic layers were washed with brine, dried with MgSO₄ and concentrated give the crude compound 3-133, which was purified by column chromatography to give the pure 3-133 of 331 mg, 82% yield. ^1H NMR (CDCl₃, 500 MHz) δ 5.91 (s, 1H), 5.55 (d, J = 1.4 Hz, 1H), 4.27 (t, J = 6.0 Hz, 1H), 2.59 (m, 2H), 0.97 (t, J = 7.9 Hz, 2x9H), 0.64 (q, J = 8.0 Hz, 6H), 0.57 (q, J = 7.9 Hz, 6H).

To a solution of vinyl bromide 3-133 (133 mg, 0.33 mmol) in toluene (3 mL) was added sequentially at room temperature with i-PrNEt₂ (21 mg, 0.5 equiv), hexamethylditin (249 mg, 1.3 equiv),
and Pd(PPh₃)₄ (36 mg, 0.1 equiv). The resultant yellow-orange solution was degassed with bubbling nitrogen for 30 min, and the reaction mixture were heated at 80 °C for 3 h. Upon completion, the reaction mixture was cooled to room temperature, poured into H₂O, and extracted with EtOAc. The combined organic layers were then washed with H₂O and brine, dried over MgSO₄, and concentrated. The resultant residue was purified by flash column chromatography to give vinyl stannane 3-127 (178 mg, 88% yield). ¹H NMR (CDCl₃, 500 MHz) δ 5.76 (d, J = 1.2 Hz, 1H), 5.17 (d, J = 1.4 Hz, 1H), 4.28 (t, J = 6.6 Hz, 1H), 2.34 (m, 2H), 1.53-1.45 (m, 6H), 1.36-1.27 (m, 6H), 1.00-0.85 (m, 33H), 0.58 (q, Hz, 12H); ¹³C NMR (CDCl₃, 125 MHz) δ 157.51, 124.66, 105.20, 83.49, 79.64, 30.65, 29.09, 27.49, 13.69, 10.23, 7.45, 6.92, 4.98, 4.52.

A reaction tube charged with the vinyl bromide 3-130 (324 mg), Pd(PhCN)₂Cl₂ (42 mg), AsPh₃ (66 mg) and Ag₂O (401 mg) was evacuated under vacuum and backfilled with N₂ for 3 times. A THF solution of boronic ester 3-129 (294 mg, 1 mmol) was added and an additional THF was added to ensure the concentration to be 0.06 M. The reaction was stirred at room temperature for 4 h and quenched by the addition of 10 mL of aqueous NH₄Cl and filtered with a plug of celite. The resultant solution was exacted with ethyl acetate for 3 times, dried over MgSO₄ and concentrated under vacuum. The residue was purified by column chromatography to give the coupling product 3-131 of 296 mg (65% yield). ¹H NMR (CDCl₃, 500 MHz) δ 6.97 (m, 2H), 6.89-6.82 (m, 1H), 5.98 (s, 1H), 5.60 (d, J = 1.4 Hz, 1H), 5.21 (s, 2H), 4.36 (t, J = 6.0 Hz, 1H), 3.83 (s, 3H), 3.63 (s, 3H), 2.90-2.69 (m, 2H), 0.97 (t, J = 7.9 Hz, 9H), 0.65 (q, J = 7.9 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 152.66, 135.73, 125.42, 123.99, 118.73, 117.57, 112.42, 98.52, 90.06, 79.07, 75.50, 57.45, 55.91, 28.31, 6.80, 4.77.
The boronic ester 3-129 (198 mg, 0.67 mmol) was dissolved in a mixed solvent of benzene and MeOH (5:1, 12 mL), and the solution was added vinyl bromide 3-133 (325 mg, 1.2 equiv.) followed by 2 M aqueous Na₂CO₃ solution (1.2 mL). A stream of N₂ was bubbled through the reaction mixture for 5 minutes and Pd(PPh₃)₄ (154 mg, 0.2 mol%) was added in one portion. The resulting mixture was heated to reflux (80 °C) and maintained for 90 min, after which TLC indicated the reaction was complete. The mixture was allowed to cool to room temperature and Na₂SO₄ was added. The mixture allowed to stand for 10 min and then filtered through Celite. The filtrate was concentrated and the resulting crude product was purified by column chromatography to provide 3-135 (155 mg, 47 %). ¹H NMR (CDCl₃, 500 MHz) δ 7.01 (t, J = 7.9 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.80 (dd, J = 7.7, 1.2 Hz, 1H), 5.62 (s, 1H), 5.18 (s, 1H), 5.05 (m, 1H), 4.89-4.85 (m, 1H), 3.84 (s, 3H), 3.52 (s, 3H), 2.32 (m, 2H), 1.05-0.94 (m, 18H), 0.70 (q, J = 7.5 Hz, 6H), 0.56 (q, J = 7.9 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 152.44, 149.05, 142.79, 135.51, 124.32, 123.03, 114.71, 111.59, 105.43, 98.72, 83.08, 71.99, 57.58, 55.74, 28.70, 24.82, 7.44, 6.99, 5.07, 4.55.

To a solution of compound 3-24j (48 mg, 0.2 mmol) in a mixed solvent of acetone and H₂O (10:1, 1.5 mL) was added NMO (27 mg, 1.2 equiv) at room temperature followed by the addition of 1 drop of the aqueous solution of the OsO₄ (0.05 M). Then the reaction solution was stirred at room temperature until the TLC indicated the full consumption of the starting material. Acetone was removed under vacuum and the resulting solution was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried with MgSO₄ and concentrated give the crude 3-137, which was purified by column
chromatography to give the pure 3-137 of 49 mg, 90% yield. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.90-6.83 (m, 1H), 6.76 (m, 2H), 5.81-5.64 (m, 1H), 5.06 (d, $J = 9.3$ Hz, 1H), 5.03 (d, $J = 16.8$ Hz, 1H), 4.70 (t, $J = 5.8$ Hz, 1H), 4.00 (m, 1H), 3.87 (s, 3H), 3.78-3.68 (m, 1H), 2.45 (m, 2H), 2.28-1.86 (m, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 146.25, 145.30, 135.31, 133.79, 121.38, 118.51, 115.28, 111.42, 85.37, 68.30, 67.86, 55.91, 47.63, 44.04, 35.48, 31.67.

To a stirred suspension of NaH (29 mg, 60% pure, 0.72 mmol) in THF (0.5 mL) was added a solution of compound 3-137 (49 mg, 0.18 mmol) in THF at 0 °C and the reaction was kept at that temperature for 30 min followed by the addition a TBDMSCl (27 mg, 0.18 mmol). The reaction was slowly warmed to room temperature in 1 hour and quenched by adding the aqueous NH$_4$Cl and diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried with MgSO$_4$, filtered and concentrated under vacuum to give a mixture of compound 3-138 and 3-139, which could be separated by column chromatography to give the pure 3-138 of 30 mg (42% yield) and 3-139 of 31 mg (44% yield) respectively. 3-138: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.87 (t, $J = 7.7$ Hz, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 6.72 (d, $J = 7.4$ Hz, 1H), 5.68 (tdd, $J = 17.3, 9.9, 7.3$ Hz, 1H), 5.05 (dd, $J = 10.2, 1.0$ Hz, 1H), 5.00 (d, $J = 17.0$ Hz, 1H), 4.76-4.69 (m, 1H), 3.87 (s, 3H), 3.85 (m, 1H), 3.64 (td, $J = 9.8, 3.7$ Hz, 1H), 2.36 (m, 2H), 2.25 (d, $J = 5.1$ Hz, 1H), 2.22 (t, $J = 5.7$ Hz, 1H), 1.97 (m, 1H), 1.86 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). 3-139: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.85 (t, $J = 7.7$ Hz, 1H), 6.81-6.73 (m, 2H), 5.80-5.65 (m, 1H), 5.09-5.00 (m, 2H), 4.68-4.62 (m, 1H), 3.98 (td, $J = 7.1, 3.4$ Hz, 1H), 3.87 (s, 3H), 3.64-3.55 (m, 1H), 2.46 (m, 2H), 2.14 (m, 1H), 2.06 (d, $J = 6.4$ Hz, 1H), 1.99 (m, 1H), 1.95-1.86 (m, 2H), 0.92 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H).
To a stirred solution of TES protected alcohol 3-133 (1.61 g, 4.0 mmol) in THF (2 mL) was added 2N HCl solution (2.5 mL) and methanol (3 mL). The resultant solution was stirred at room temperature until the completion of the reaction, which was monitored by TLC. The reaction was diluted with ethyl acetate and washed with water, extracted with ethyl acetate and then dried over MgSO4. Concentration and column chromatography gave the alcohol 3-147 (1.08 g, mmol, 93% yield); 1H NMR (CDCl3, 500 MHz) δ 5.97 (s, 1H), 5.61 (d, J = 1.8 Hz, 1H), 4.28 (t, J = 6.0 Hz, 1H), 2.75-2.62 (m, 2H), 2.60-2.22 (b, 1H), 0.97 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 7.9 Hz, 6H); 13C NMR (CDCl3, 125 MHz) δ 134.15, 117.84, 102.12, 86.03, 73.95, 27.68, 7.46, 4.42.

Following the procedure described previously for the synthesis of 3-135, the compound 3-148 was prepared from the Suzuki coupling reaction between 3-methoxyphenylboronic acid and vinyl bromide 3-147. 1H NMR (CDCl3, 500 MHz) δ 7.38-7.14 (m, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.92-6.89 (m, 1H), 6.84 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H), 5.44 (s, 1H), 5.34 (s, 1H), 4.74 (t, J = 5.5 Hz, 1H), 3.81 (s, 3H), 2.51 (m, 3H), 0.98 (t, J = 7.9 Hz, 9H), 0.59 (p, J = 7.9 Hz, 6H); 13C NMR (CDCl3, 125 MHz) δ 159.57, 149.47, 141.09, 129.42, 119.45, 113.62, 113.05, 112.96, 103.46, 85.54, 71.40, 55.23, 28.28, 7.51, 4.48.
To a stirred solution of alcohol **3-148** (283 mg, 0.9 mmol) in CH$_2$Cl$_2$ (2 mL) was added TBAF solution (1.0 M, 1 mL) at room temperature. Following the completion of the reaction monitored by TLC, the reaction was diluted with ethyl acetate and saturated NH$_4$Cl solution, extracted with ethyl acetate and then dried over MgSO$_4$. Concentration and column chromatography gave the alcohol **3-147** (158 mg, 87% yield); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.25 (t, $J = 7.9$ Hz, 1H), 6.95 (d, $J = 7.6$ Hz, 1H), 6.93-6.89 (m, 1H), 6.85 (dd, $J = 8.2$, 2.6 Hz, 1H), 5.45 (s, 1H), 5.37 (s, 1H), 4.78 (dd, $J = 7.0$, 4.4 Hz, 1H), 3.81 (s, 1H), 2.54 (m, 1H), 2.37 (m, 2H), 2.07 (t, $J = 2.6$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.61, 149.54, 140.86, 129.52, 119.37, 113.70, 113.15, 112.94, 80.54, 71.36, 71.17, 55.28, 26.70.

Following the procedure previously described for the synthesis of compound **3-106**, compound **3-150** was prepared in 80% yield. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.25 (t, $J = 7.9$ Hz, 1H), 6.96 (d, $J = 7.7$ Hz, 1H), 6.94 (d, $J = 2.2$ Hz, 1H), 6.84 (dd, $J = 8.2$, 2.4 Hz, 1H), 5.84 (m, 1H), 5.41 (s, 1H), 5.32 (s, 1H), 4.92 (dd, $J = 17.0$, 1.4 Hz, 1H), 4.90-4.86 (m, 1H), 4.74 (dd, $J = 7.4$, 4.5 Hz, 1H), 3.82 (s, 3H), 2.35 (m, 2H), 1.97 (t, $J = 2.6$ Hz, 1H), 1.71 (d, $J = 8.1$ Hz, 2H), 0.20 (d, $J = 2.9$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 159.49, 149.97, 140.86, 134.13, 129.36, 119.58, 114.35, 113.82, 113.15, 112.90, 81.79, 73.73, 69.86, 55.25, 27.60, 24.95, -1.93.
To a solution of 3-allylsilyloxy-1,5-enyne 3-150 (21 mg, 0.07 mmol) and phenol (9 mg, 1.4 equiv.) in CH₂Cl₂ (0.4 mL) was added the Au(I) catalyst 3-9 (1 mol%). The resulting solution was stirred at room temperature for 1 hour, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column chromatography to give the desired cyclopentene product 3-151 (colorless oil, 24 mg, 88% yield). ¹H NMR (CDCl₃, 500 MHz) δ 7.22 (m, overlapped, J = 7.6 Hz, 3H), 6.96 (t, J = 7.4 Hz, 1H), 6.91-6.85 (m, overlapped, 4H), 6.75 (dd, J = 8.1, 2.3 Hz, 1H), 5.80 (tdd, J = 11.5, 9.2, 7.1 Hz, 1H), 5.70 (2s, 2H), 4.94 (d, J = 15.5 Hz, 1H), 4.93 (d, J = 12.0 Hz, 1H), 3.97 (dd, J = 9.1, 2.1 Hz, 1H), 3.79 (s, 3H), 2.93 (m, 1H), 2.85-2.64 (m, overlapped, 3H), 2.23 (dd, J = 14.8, 6.6 Hz, 1H), 1.98-1.88 (m, 1H), 0.12 (s, 3H), 0.06 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.14, 149.02, 136.85, 129.59, 129.37, 129.10, 128.60, 121.39, 120.76, 119.89, 116.76, 114.86, 110.66, 80.14, 55.84, 55.18, 41.79, 41.04, 38.49, -1.77, -2.14; LRMS (CI) calcd for C₂₄H₃₀O₃Si [M] 394.20, found 394.20.

Then 3-151 was treated with RRM standard condition to afford the cyclohexene 3-152. 84% yield, dr = 8 : 1; ¹H NMR (CDCl₃, 500 MHz) δ 7.25-7.13 (m, 3H), 7.02 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.84 (m, 2H), 6.76 (dd, J = 8.1, 1.8 Hz, 1H), 5.77 (d, J = 9.8 Hz, 1H), 5.54-5.46 (m, 1H), 5.39 (dddd, J = 16.9, 10.0, 8.6, 5.8 Hz, 1H), 4.96 (d, J = 17.0 Hz, 1H), 4.90 (d, J = 9.4 Hz, 1H), 4.22 (dd, J = 7.6, 4.6 Hz, 1H), 3.78 (s, 3H), 2.80 (m, 1H), 2.65 (m, 1H), 2.31-2.13 (m, 3H), 1.81 (m, 1H), 0.20 (s, 3H), 0.15 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 161.56, 154.57, 144.65, 134.79, 129.39, 128.25, 125.85, 124.43, 121.54, 120.82, 119.88, 117.23, 114.69, 110.92, 75.07, 55.08, 45.12, 43.46, 33.16, 32.47, -1.89, -2.31; HRMS (CI) calcd for C₂₄H₃₀O₃Si [M] 394.1964, found 394.1972.
To a stirred solution of TBS protected alcohol 3-24a (250 mg, 0.73 mmol) in THF (1 mL) was added 6 M HCl solution (1 mL) and methanol (2 mL). The resultant solution was stirred at 50 °C until the completion of the reaction, which was monitored by TLC. The reaction was diluted with ethyl acetate and washed with water, extracted with ethyl acetate and then dried over MgSO₄. Concentration and column chromatography gave the alcohol 3-156 (158 mg, 0.69 mmol); To a stirred solution of VO(acac)₂ (1.5 mol%) and the alkenol 3-156 (123 mg, 0.54 mmol) in CH₂Cl₂ was added TBHP (1.5 equiv, 5.5 M in hexane). The reaction was carried out at room temperature. Following the completion of the reaction, saturated aqueous Na₂S₂O₃ was added and the mixture was extracted with ethyl acetate. The combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography to afford product 3-157 (122 mg, 0.50 mmol, 92% yield). ¹H NMR (CDCl₃, 500 MHz) δ 7.31-7.25 (m, 2H), 7.22 (m, 3H), 5.93 (m, 1H), 5.17 (d, J = 10.0 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 3.41 (d, J = 10.6 Hz, 1H), 3.33 (d, J = 0.8 Hz, 1H), 3.25-3.18 (m, 1H), 2.92 (d, J = 10.7 Hz, 1H), 2.78 (s, 2H), 2.33-2.10 (m, 2H), 2.08-1.98 (m, 2H), 1.88 (m, 1H), 1.65 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 137.84, 134.02, 130.87, 127.99, 126.15, 118.48, 69.88, 53.43, 51.63, 40.88, 39.40, 38.31, 30.70, 27.66.

To a stirred solution of epoxy alcohol 3-157 (122 mg, 0.5 mmol) in CH₂Cl₂ (5 mL) was added sequentially imidazole (68 mg, 1.0 mmol), a catalytic amount of DMAP (4 mg) and TESCl (83 mg, 0.55 mmol). Following the completion of the reaction monitored by TLC, the reaction was diluted with ether and washed with saturated NH₄Cl solution, extracted with hexane and then dried over MgSO₄. Concentration and column chromatography gave the TES protected alcohol (166 mg, 93% yield). ¹H
NMR (CDCl₃, 500 MHz) δ 7.31-7.24 (m, 4H), 7.22 (m, 1H), 5.78 (m, 1H), 5.07 (d, J = 10.1 Hz, 1H), 4.98 (d, J = 17.0 Hz, 1H), 3.73 (t, J = 7.4 Hz, 1H), 3.13 (m, 3H), 2.61 (m, 1H), 2.24 (m, 1H), 2.20-2.14 (m, 2H), 1.97 (m, 1H), 1.73 (m, 1H), 1.50 (m, 1H), 1.03 (t, J = 7.9 Hz, 9H), 0.66 (m, 6H).

A stream of ozone gas was bubbled in a stirred and cooled (-78 °C) CH₂Cl₂ (30 mL) to form a saturated ozone solution. The approximate concentration (0.02 M) was measured by reaction with simple alkene. To a solution of the above TES protected alkenol (166 mg, 0.46 mmol) in MeOH was added saturated ozone solution (40 mL) portionwise until the reaction solution turned pale blue. Then nitrogen was passed through the solution for 15 min followed by addition of Me₂S with stirring for 2 h. Concentration and column chromatography purification afforded the aldehyde 3-159.

To a stirred solution of the above aldehyde 3-159 in anhydrous methanol was added sequentially MgSO₄ and MeN(TMS)₂ (0.55 mL, 5 equiv.). After the reaction mixture was stirred at room temperature for 1 hour, NaBH₄ (19 mg, 0.5 mmol) was added and the reaction was stirred for another 1 hour. Then the reaction was quenched by the addition of the saturated aqueous NaHCO₃ solution and the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried with MgSO₄ and concentrated give the crude 3-160, which was purified by column chromatography to give the pure 3-160 of 102 mg (59% yield in three steps). ¹H NMR (CDCl₃, 500 MHz) δ 7.26 (t, J = 7.4 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 7.0 Hz, 2H), 3.88 (s, 1H), 3.70 (s, 1H), 3.39 (d, J = 9.5 Hz, 1H), 3.00 (d, J = 12.9 Hz, 1H), 2.83 (d, J = 1.7 Hz, 1H), 2.57-2.47 (m, 2H), 2.33 (s, 3H), 2.20 (d, J = 12.9 Hz, 1H), 2.17-2.09 (m, 1H), 2.02 (m, 1H), 1.83 (m, 1H), 1.03 (t, J = 7.9 Hz, 9H), 0.71 (m, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 137.76, 131.12, 127.82, 126.03, 76.75, 65.96, 59.82, 48.68, 45.52, 43.70, 36.75, 36.49, 31.59, 29.16, 24.54, 6.98, 5.08.

To a stirred solution of the compound 3-152 (316 mg, 0.80 mmol) in THF was slowly added to tetrabutylammonium fluoride (1 M, 1 mL) solution at 0 °C. After addition, the reaction was warmed to
room temperature and stirred for 30 min. Following the completion of the reaction monitored by TLC, the reaction was diluted with saturated NH₄Cl and ethyl acetate, extracted with ethyl acetate, dried over MgSO₄. Concentration and purification by column chromatography gave the alcohol 3-163 (176 mg, 90% yield). ¹H NMR (CDCl₃, 500 MHz) δ 7.27 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.98-6.95 (m, 1H), 6.79 (dd, J = 8.1, 2.4 Hz, 1H), 5.85-5.74 (m, 1H), 5.66-5.58 (m, 1H), 5.43-5.28 (m, 1H), 4.96 (d, J = 17.1 Hz, 1H), 4.91 (d, J = 10.1 Hz, 1H), 4.12 (t, J = 4.5 Hz, 1H), 3.80 (s, 3H), 2.57 (m, 2H), 2.41 (m, 1H), 2.34-2.25 (m, 2H), 2.00 (m, 1H), 1.60 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.67, 145.13, 134.35, 129.27, 125.54, 123.47, 119.59, 117.54, 113.99, 111.03, 71.94, 55.18, 44.80, 42.24, 31.06.

To a dried flask was added 3-hydroxybenzaldehyde 3-169 (16.1 g, 132 mmol), iron powder (560 mg, 10 mmol), anhydrous sodium acetate (21.3 g, 260 mmol) and glacial acetic acid (120 mL). The suspension was warmed until a clear solution was obtained, and then allowed slowly to cool to room temperature. To the mixture was added dropwise, over 15 min, a solution of bromine (24.0 g, 150 mmol) in glacial acetic acid (25 mL). The reaction temperature was not allowed to rise above room temperature. One hour after the completion of the addition, the reaction mixture was poured into ice-water (800 mL), and extracted with CH₂Cl₂ (3 times, 200 mL). The combined organic extracts were dried (MgSO₄) and filtered through a pad of silica gel (CH₂Cl₂). Concentration and crystallization from CH₂Cl₂ (20 mL) afforded 7.9 g (39.3 mmol, 30%) 2-bromo-3-hydroxybenzaldehyde 3-170. Column chromatography of the mother liquor afforded another 3.7 g (18.4 mmol, 14%) of the desired product 3-170; ¹H NMR (CDCl₃, 500 MHz) δ 10.28 (s, 1H), 7.50 (dd, J = 7.5, 1.5 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.28 (dd, J = 8.0, 1.6 Hz, 1H), 6.01 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 191.25, 153.02, 133.88, 131.97, 128.89, 122.79, 121.74.
2-bromo-3-hydroxybenzaldehyde 3-170 (2.23 g, 11.09 mmol) was dissolved in DMF (20 mL). Then methyl iodide (2.36 g, 16.6 mmol) and potassium carbonate (1.69 g, 12.2 mmol) were added to it at 0 °C. After stirring at room temperature for 4 h, the reaction was quenched by 1N HCl aqueous solution and extracted with dichloromethane. Concentration and purification by column chromatography afforded a white solid 3-171 (2.22 g, 10.3 mmol, 93% yield). \[^1\]H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 10.31 (s, 1H), 7.38 (dd, \(J = 7.7, 1.4 \text{ Hz}, 1\text{H})\), 7.27 (t, \(J = 7.90 \text{ Hz}, 1\text{H})\), 7.03 (dd, \(J = 8.1, 1.0 \text{ Hz}, 1\text{H})\), 3.85 (s, 3H); \[^{13}\]C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 192.04, 156.20, 134.67, 128.33, 121.27, 116.99, 116.93, 56.63.

To a solution of methyl methylsulfinylmethyl sulfide (1.58 mL, 15.1 mmol) in dry THF (20 mL) was added sodium hydride (635 mg, 15.9 mmol) at 0 °C, and resulting solution was stirred at room temperature for 30 min. Then a solution of 2-bromo-3-methoxybenzaldehyde 3-171 (3.58 g, 16.6 mmol) in THF (15mL) was added dropwise, and the resulting mixture was heated to 50 °C and stirred at the same temperature overnight. Once the reaction is completed, it was neutralized with 4N HCl to pH=2 and extracted with ether. The combined extracts were washed with water, and dried with MgSO\textsubscript{4}. Concentration and column chromatography gave the corresponding intermediate 4-17; \[^1\]H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 7.79 (s, 1H), 7.34 (d, \(J = 7.62 \text{ Hz}, 1\text{H})\), 7.28 (t, \(J = 7.99, 7.99 \text{ Hz}, 1\text{H})\), 6.86 (d, \(J = 8.12 \text{ Hz}, 1\text{H})\), 3.87 (s, 3H), 2.77 (s, 3H), 2.16 (s, 3H); \(^{13}\)C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 156.14, 144.76, 135.90, 135.60, 127.88, 122.19, 113.80, 111.89, 56.43, 40.45, 17.95.

Under stirring, HCl (2 M in Et\textsubscript{2}O) was added into a solution of 4-17 in anhydrous ethanol. After stirring at 60 °C for overnight, the reaction mixture was poured into ice-water and extracted with ether. The combined ether was washed with water, dried with MgSO\textsubscript{4}. Concentration and column
chromatography gave 3-168 (3.67 g, 81% yield); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.21 (t, \(J = 7.92, 7.92\) Hz, 1H), 6.89 (d, \(J = 7.00\) Hz, 1H), 6.80 (d, \(J = 7.94\) Hz, 1H), 4.16 (q, \(J = 7.10, 7.10, 7.08\) Hz, 2H), 3.85 (s, 3H), 3.79 (s, 2H), 1.24 (t, \(J = 7.12, 7.12\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 170.52, 156.20, 136.09, 127.95, 123.43, 114.62, 110.69, 60.99, 56.36, 42.07, 14.22.

According to the procedures described in 4.5.1.3, ethyl arylacetate 3-168 was diallylated to 3-172 in 80% yield in two steps; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.24 (t, \(J = 8.1\) Hz, 1H), 6.89 (d, \(J = 7.9\) Hz, 1H), 6.84 (d, \(J = 8.0\) Hz, 1H), 5.45 (dt, \(J = 16.9, 8.0\) Hz, 2H), 5.03 (d, \(J = 17.0\) Hz, 2H), 5.00 (d, \(J = 10.1\) Hz, 2H), 4.12 (q, \(J = 7.1\) Hz, 2H), 3.86 (s, 3H), 3.00 (m, 2H), 2.71 (m, 2H), 1.18 (q, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 174.28, 156.29, 142.40, 133.28, 127.42, 121.22, 118.48, 113.88, 110.60, 60.99, 56.52, 38.46, 14.17.

According to the procedures described in 4.5.1.3 and 4.5.3.1, diallyl ester 3-172 was converted to the corresponding triallyl TBDMS protected alcohol 3-167 in 66% yield through a four-step sequence involving LAH reduction, Swern oxidation, allylation and TBDMS protection. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.21 (t, \(J = 8.1\) Hz, 1H), 7.05 (d, \(J = 7.8\) Hz, 1H), 6.82 (d, \(J = 7.9\) Hz, 1H), 6.23-5.92 (m, 1H), 5.65 (dd, \(J = 16.0, 8.6\) Hz, 1H), 5.52 (m, 1H), 5.13-4.97 (m, 4H), 4.86 (dd, \(J = 16.4, 8.5\) Hz, 3H), 3.88 (s, 3H), 3.45 (m, 1H), 2.89 (m, 1H), 2.86-2.60 (m, 2H), 2.17 (s, 2H), 0.91 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 156.51, 144.37, 137.14, 137.03, 136.07, 127.47, 123.74, 116.62, 116.36, 116.07, 113.59, 110.41, 75.52, 56.63, 51.81, 39.30, 38.61, 37.80, 26.22, 18.34, -3.30, -3.70.
4.8. Synthetic studies on caribenol A

![Chemical structure of caribenol A](image)

To a solution of the acrolein (2.27 g, 80% pure, 25.9 mmol) in DMF (20 mL) was added Zn powder (2.02 g, 1.2 equiv.) and propargyl bromide (4.8 g, 1.5 equiv.) at 0 °C. Then a solution of the saturated aqueous NH₄Cl (1 mL) was added dropwise to ensure the temperature of the reaction solution at about 0 °C. Upon finishing the addition, the reaction mixture was slowly warmed up to room temperature and quenched by adding water and the solution was extracted with CH₂Cl². The combined organic layers were washed with brine, dried with MgSO₄ and concentrated to afford the alcohol 3-191 (1.91 g, 67% yield). ¹H NMR (CDCl₃, 500 MHz) δ 5.02 (s, 1H), 4.90 (d, J = 1.3 Hz, 1H), 4.21 (m, 1H), 2.53-2.37 (m, 2H), 2.30-2.25 (m, 1H), 2.04 (dd, J = 5.3, 2.6 Hz, 1H), 1.73 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 145.44, 111.94, 80.65, 73.44, 70.80, 25.90, 17.96. A following silyl protection was conducted according to the previously described standard procedure to give compound 3-10a (96% yield).

According to the gold-catalyzed cycloisomerization/allylation and RRM procedure described previously in 3.2. and 3.3., enyne 3-10a was converted to a mixture of diastereomeric cyclohexenes 3-22f (dr = 2.7 : 1) in 90% yield over two steps. Then the mixture was further treated with 2 M HCl in methanol to generate the alcohols in 92% yield. To a solution of the alcohols (620 mg, 4.1 mmol) in pyridine (20 mL) was added PivCl (3 mL, 24.4 mmol) and DMAP (497 mg, 4.1 mmol) at room temperature. Then the reaction solution was stirred at 60 º for 12 hours. The reaction mixture was cooled to room temperature and 1 M HCl was added carefully and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried with MgSO₄ and concentrated to
give the crude product, which was purified by column chromatography to give the pivolate 3-193 (866 mg, 90% yield). \( ^1 \)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 5.78 (m, 1H), 5.58 (m, 1H), 5.55-5.47 (m, 1H), 5.05 (d, \( J = 10.1 \) Hz, 1H), 5.01 (dd, \( J = 17.0, 1.3 \) Hz, 1H), 4.74 (t, \( J = 6.0 \) Hz, 1H), 2.43-2.33 (m, 1H), 2.00 (m, 4H), 1.87 (m, 1H), 1.35 (s, 9H), 0.94 (s, 3H).

Palladium chloride (60 mg, 0.3 mmol) and copper (I) chloride (320 mg, 3.0 mmol) in a 6 : 1 mixture of DMF and H\(_2\)O (12 mL) were stirred for 4 hours under an oxygen atmosphere. A solution of alkene (472 mg, 2.0 mmol) in DMF (1 mL) was introduced, and the mixture was stirred for overnight prior to filtration through celite. Saturated NH\(_4\)Cl solution was added and the separated aqueous phase was extracted with ethyl acetate. The combined extracts were washed with diluted ammonium hydroxide solution until blue color was gone then dried with MgSO\(_4\) and concentrated give the crude product, which was purified by column chromatography to give the pure 3-190 (424 mg, 84% yield). \( ^1 \)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 5.64-5.56 (m, 1H), 5.55-5.47 (m, 1H), 4.90 (dd, \( J = 6.8, 5.4 \) Hz, 1H), 2.42 (m, 3H), 2.38-2.29 (m, 1H), 2.17 (m, 2H), 2.11 (s, 3H), 2.08-1.97 (m, 1H), 1.22 (s, 9H), 1.06 (s, 3H); \( ^{13} \)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 207.81, 177.80, 125.35, 122.86, 73.85, 50.42, 39.03, 35.72, 35.36, 32.49, 28.13, 27.01, 19.42.

To a stirred solution of the trimethylsilyldiazomethane (2.0 M, 2.2 mL, 4.4 mmol) in THF at -78 °C was added nBuLi (2.5 M in hexanes, 1.9 mL) solution. After stirring at this temperature for 30 min, a solution of the methyl ketone 3-190 (953 mg, 3.77 mmol) was added slowly. Then the reaction continued to stir at -78 °C for 1h followed by slowly warmed up to 0 °C. Following the completion of the reaction monitored by TLC, the reaction was quenched with saturated aqueous NH\(_4\)Cl solution. Then the aqueous layer was extracted with Et\(_2\)O. The extracted organic layers were dried over MgSO\(_4\), filtered and
concentrated by rotary evaporation. Purification by silica gel column chromatography gave bicyclic product 3-194 (739 mg, 79% yield). $^1$H NMR (CDCl$_3$, 500 MHz) δ 5.69 (m, 1H), 5.56-5.47 (m, 1H), 5.19 (s, 1H), 4.82 (dd, $J = 8.6$, 5.0 Hz, 1H), 2.98 (d, $J = 1.3$ Hz, 1H), 2.35-2.27 (m, 1H), 2.14 (m, 1H), 2.08-1.96 (m, 2H), 1.65 (d, $J = 1.1$ Hz, 3H), 1.21 (s, 9H), 1.14 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 178.12, 137.24, 128.61, 126.67, 121.67, 72.96, 54.32, 47.54, 44.44, 27.21, 27.05, 20.81, 16.84.

To a stirred solution of the pivolate 3-194 (739 mg, 3.0 mmol) in THF was added DIBAL (1.0 M in THF, 7 mL) solution at 0 °C. Then the reaction was warmed up to room temperature. After 30 min, the reaction was quenched with ethyl acetate and saturated aqueous potassium sodium tartrate solution. After stirring for 1 h, the aqueous layer was extracted with Et$_2$O. The extracted organic layers were dried over MgSO$_4$, filtered and concentrated by rotary evaporation. Purification by silica gel column chromatography gave the alcohol 4-17 in 77% yield (379 mg); $^1$H NMR (CDCl$_3$, 500 MHz) δ 5.74-5.65 (m, 1H), 5.54 (dtd, $J = 7.6$, 4.8, 2.4 Hz, 1H), 5.18 (s, 1H), 3.68 (dd, $J = 8.5$, 4.8 Hz, 1H), 2.97 (d, $J = 1.7$ Hz, 1H), 2.43 (m, 1H), 2.28 (m, 1H), 2.13-2.02 (m, 2H), 1.67 (d, $J = 1.0$ Hz, 3H), 1.48 (s, 1H), 1.10 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 137.37, 129.09, 126.76, 122.08, 70.70, 54.13, 47.69, 45.56, 30.67, 20.11, 16.92.

To a stirred solution of the above homoallylic alcohol 4-17 (379 mg, 2.31 mmol) in dichloromethane was added sodium bicarbonate (500 mg). Then Dess-Martin periodinane (1.27 g, 1.3 equiv.) was added slowly. After 1 h, the reaction was quenched with saturated sodium bicarbonate and saturated sodium thiosulfate. Then the mixture was extracted with diethyl ether and dried over anhydrous magnesium sulfate. The residue was purified by silica gel chromatography to afford a crude product, which was dissolved in dichloromethane then treated with DBU (3 drops) for 1 h. Following the completion of the reaction monitored by TLC, the reaction was quenched with saturated NH$_4$Cl solution, extracted with Et$_2$O and then dried over MgSO$_4$. Concentration and purification by silica gel column
chromatography gave the enone **3-195** (322 mg, 86% yield); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 6.87-6.62 (m, 1H), 5.98 (dd, \(J = 10.0, 1.3\) Hz, 1H), 5.12 (s, 1H), 2.93 (m, 1H), 2.80 (m, 1H), 2.63-2.50 (m, 1H), 2.45-2.34 (m, 1H), 2.14 (m, 1H), 1.65 (s, 3H), 1.22 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 204.67, 146.35, 141.24, 129.28, 128.06, 53.52, 49.14, 48.02, 29.71, 26.24, 22.12, 16.86.

![Reaction Scheme](image)

To a cooled (-10 °C) solution of (S, S)-**3-197** (265 mg, 1.5 equiv.) in toluene (3 mL) was added the aldehyde (74 mg, 0.66 mmol). The reaction mixture was stirred at -10 °C for 2 h. Following the completion of the reaction monitored by TLC, 1N HCl and EtOAc were added to quench the reaction. Then the reaction mixture was extracted with EtOAc. The extracted organic layers were dried over MgSO\(_4\), filtered and concentrated by rotary evaporation. Purification by silica gel column chromatography gave the chiral alcohol **3-198** (90 mg, 90% yield, >95% ee, measured by \(^1\)H NMR using chemical shift reagent); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 5.87 (dddd, \(J = 16.0, 10.2, 8.5, 5.7\) Hz, 1H), 5.67-5.55 (m, 2H), 5.22-5.11 (m, 2H), 3.51-3.42 (m, 1H), 2.44 (m, 2H), 2.37-2.27 (m, 1H), 2.01 (m, 3H), 1.66 (d, \(J = 3.4\) Hz, 1H), 1.04 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 136.22, 129.22, 128.91, 117.94, 45.82, 43.54, 37.64, 23.39.

![Reaction Scheme](image)

To a stirred suspension of copper(I) iodide (278 mg, 3.0 equiv.) in THF (2 mL) was added methyl lithium (1.6 M, 1.8 mL, 6.0 equiv.) slowly at -78 °C. Then the mixture was stirred at -40 °C for 30 min and cooled back to -78 °C before adding the enone **3-195** (79 mg, 0.48 mmol). After addition, the reaction was warmed up to -40 °C and stirred at this temperature for 1 h. Following the completion of the reaction monitored by TLC, the reaction was quenched with saturated NH\(_4\)Cl solution, then warmed up to room temperature, extracted with Et\(_2\)O and dried over MgSO\(_4\). Concentration and purification by
silica gel column chromatography gave the addition product **3-189** (43 mg, 50%, $dr = 14:1$); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.08 (s, 1H), 2.91-2.78 (m, 2H), 2.41-2.30 (m, 1H), 2.04-1.85 (m, 3H), 1.78-1.70 (m, 1H), 1.66 (s, 3H), 1.50-1.38 (m, 1H), 1.19 (s, 3H), 0.95 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 216.50, 140.49, 128.00, 54.74, 53.15, 47.34, 46.93, 34.89, 28.20, 23.27, 22.01, 16.69.

To a stirred cooled (-78 °C) solution of the ketone **3-189** (37 mg, 0.21 mmol) and HMPA (5.0 equiv.) in THF (1 mL) was added $n$BuLi (2.5 M, 0.18 mL, 2.2 equiv.) slowly. Then the reaction was stirred at this temperature for 10 min and at 0 °C for 5 min. After that, the reaction was cooled back to -78 °C and the iodide **3-200** (3.0 equiv.) was added. The reaction was slowly warmed up to room temperature and monitored by TLC. Following the completion of the reaction, the reaction was quenched with saturated NH$_4$Cl solution, extracted with Et$_2$O and then dried over MgSO$_4$. Concentration and purification by silica gel column chromatography gave **3-201** (37 mg, 48% yield) and the addition product in 25% yield; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.10 (s, 1H), 3.68-3.53 (m, 2H), 3.34 (m, 1H), 2.85 (m, 1H), 2.78 (s, 1H), 2.07-1.96 (m, 1H), 1.92 (m, 1H), 1.67 (s, 3H), 1.60-1.44 (m, 7H), 1.31 (m, 2H), 1.20 (s, 3H), 1.03 (d, $J = 6.6$ Hz, 2H), 0.88 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 217.62, 140.29, 127.34, 63.20, 55.33, 53.39, 52.27, 46.32, 35.10, 33.25, 33.17, 27.61, 26.01, 24.37, 23.74, 21.00, 18.39, 18.76, -5.22.

To a stirred solution of iPr$_2$NH (52 mg, 0.52 mmol) in THF (4 mL) at -78 °C was added $n$BuLi (2.5 M in hexanes, 0.19 mL, 0.47 mmol). The resulting mixture was stirred for 1 h before the compound **3-189** (77 mg, 0.43 mmol) was added. The resulting reaction mixture was stirred for 30 min and then warmed up to 0 °C and stirred at 0 °C for 30 min before trimethylsilyl chloride (52 mg, 1.1 equiv.) was
added. The resulting mixture was stirred for 1 h and then quenched with saturated NaHCO₃ solution, extracted with ether, washed with brine and dried over MgSO₄. Concentration gave crude silyl enol ether 3-199 (75 mg, 70% yield); ¹H NMR (CDCl₃, 500 MHz) ṽ 5.15 (s, 1H), 4.63 (d, J = 2.8 Hz, 1H), 2.64 (s, 1H), 2.45 (m, 1H), 2.20-2.09 (m, 1H), 2.05 (m, 1H), 1.66 (s, 3H), 1.61 (m, 1H), 1.21 (m, 1H), 1.17 (s, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.19 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) ṽ 155.09, 138.84, 127.59, 108.96, 51.21, 48.24, 46.00, 32.99, 29.74, 27.49, 25.28, 22.14, 16.99, 0.51.

To a solution of sodium hydride (1.05 equiv.) in dry THF was added tert-butyl acetoacetate (1.0 equiv.) at room temperature. After stirring at room temperature for 10 min, the resulting solution was cooled to 0 °C. Then a solution of nBuLi (1.15 equiv.) was added rapidly at 0 °C and stirred at the same temperature for 10 min. After that, methyl iodide (1.15 equiv.) was added to the reaction mixture in one portion and stirred at 0 °C for 5 min followed by room temperature for 10 min. Once the reaction is completed, it was quenched by 10% HCl and extracted with ether. Concentration of the combined extracts and the following purification by column chromatography gave the desired 3-211; To a solution of β-keto ester 3-211 (834 mg, 4.84 mmol) and conjugate aldehyde 3-212 (339 mg, 4.84 mmol) in tert-butanol was added a catalytic amount of potassium tert-butoxide (27 mg, 0.24 mmol) at 0 °C under nitrogen atmosphere and the resulting solution was stirred at this temperature for 30 min. Then more potassium tert-butoxide (108 mg, 0.96 mmol) was added to the reaction mixture and stirred at reflux for 17 h. Upon cooling to room temperature, the mixture was quenched with 1 M HCl solution and then diluted with ether, washed by 1 M NaOH solution and brine. The combined organic layers were concentrated to provide a residue, which was treated with p-TsOH (0.96 mmol) in toluene. The reaction mixture was heated at 80°C for 17 h, cooled to 25°C, diluted with ether, and washed with saturated NaHCO₃, 1 M aqueous HCl, and brine, dried over MgSO₄. Concentration under reduced pressure gave crude cyclic enone 3-214 in 76% yield (457 mg, 3.68 mmol), which was used directly for next step without further purification. ¹H NMR (CDCl₃, 500 MHz) ṽ 6.67 (d, J = 0.9 Hz, 1H), 2.45 (m, 1H), 2.40-
2.26 (m, 1H), 2.21-1.91 (m, 3H), 1.73 (s, 3H), 1.02 (d, \( J = 6.4 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 200.13, 144.79, 135.36, 46.45, 34.38, 30.83, 21.24, 15.75.

To a suspension of Mg (76 mg, 3.16 mmol) in diethyl ether (7 mL) was added a catalytic amount of Hg(OAc)\(_2\) and propargylic bromide (6.32 mmol). The resulting mixture was stirred at 0 °C for 2 h until the magnesium disappeared. Then the cyclohexane 3-214 (302 mg, 2.43 mmol) was added. After stirring for 30 min, the reaction was quenched with saturated NH\(_4\)Cl solution, extracted with ether and dried over MgSO\(_4\). Careful concentration and column chromatography gave 3-215 (347 mg, 87% yield); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 5.46 (s, 1H), 2.66 (m, 1H), 2.42 (m, 1H), 2.22 (m, 1H), 2.10-2.03 (m, 2H), 1.96 (s, 1H), 1.73 (s, 3H), 1.83-1.81 (m, 2H), 1.80-1.52 (m, 1H), 1.31 (t, \( J = 12.7 \) Hz, 1H), 0.98 (d, \( J = 6.4 \) Hz, 3H).

Ketone 3-210 was prepared according to the Kirsch’s procedure\(^{111}\). Although the TLC looked dirty, the crude \(^1\)H NMR is pretty clean. Therefore, the crude material (90% yield from 3-215) was used directly for next step without further purification. To a stirred solution of ketone 3-210 (164 mg, 1.0 mmol) in THF (2 mL) was added triethylamine (5 equiv.). Then the reaction was cooled to 0 °C and trimethylsilyl triflate (1.5 equiv.) was added slowly. After addition, the reaction was warmed up to room temperature until the reaction was completed. The solvent and volatiles were carefully removed by reduced vacuum. The Simmons-Smith cyclopropanation was carried out according to the procedure described for the synthesis of 3-209. Cyclopropane 3-220 was obtained in 80% yield (200 mg) in two steps. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 5.62-5.58 (m, 1H), 5.43 (dd, \( J = 5.3, 2.3 \) Hz, 1H), 2.58 (m, 1H), 2.32-2.21 (m, 2H), 2.06-1.97 (m, 1H), 1.34 (ddd, \( J = 13.9, 5.5, 2.4 \) Hz, 1H), 1.31-1.26 (m, 1H), 1.22 (s, 3H), 1.16 (d, \( J = 7.0 \) Hz, 3H), 0.90 (dt, \( J = 13.3, 4.4 \) Hz, 1H), 0.66 (dd, \( J = 10.2, 6.0 \) Hz, 1H), 0.42 (t, \( J = 7.0 \) Hz, 3H).
= 6.0 Hz, 1H), 0.12 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 133.35, 128.30, 63.82, 47.86, 47.41, 43.06, 31.47, 30.05, 29.00, 28.27, 21.25, 15.39, 1.67.

To a stirred solution of cyclopropane 3-220 (290 mg, 1.16 mmol) and sodium iodide (173 mg, 1.16 mmol) in MeCN/H$_2$O (8:1, 12 mL) at 0 °C was added a solution of CAN (1.27 g, 2.32 mmol) in H$_2$O (1 mL) slowly. The resulting mixture was stirred for 1 h. Then the reaction was diluted with water, extracted with ethyl acetate, washed with brine and dried over MgSO$_4$. Concentration and purification by column chromatography afforded $\beta$-iodo ketone 3-221, which was treated with DBU (3 drops) in CH$_2$Cl$_2$ (2 mL) and heated at 40 °C. Following the completion of the reaction monitored by TLC, the reaction was quenched with saturated NH$_4$Cl solution, extracted with Et$_2$O and dried over MgSO$_4$. Concentration and purification by column chromatography gave cycloheptenone 3-222 (colorless oil, 133 mg, 65%); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.11 (dd, $J = 12.3, 2.5$ Hz, 1H), 5.81 (dd, $J = 12.3, 2.1$ Hz, 1H), 5.77-5.69 (m, 1H), 5.44 (d, $J = 2.6$ Hz, 1H), 2.96 (m, 1H), 2.72 (s, 1H), 2.64-2.52 (m, 1H), 2.04 (m, 1H), 1.65 (m, 2H), 1.22 (s, 3H), 1.07 (d, $J = 7.39$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 208.11, 147.84, 132.19, 130.00, 128.33, 59.01, 52.75, 44.65, 37.30, 33.25, 26.69, 21.12.

To a stirred solution of CuI (120 mg, 0.64 mmol) in THF (1 mL) at -10 °C was added ethylmagnesium bromide (0.64 mmol). The resulting mixture was stirred for 1 h and cooled to -78 °C before a solution of enone 3-222 (27 mg, 0.16 mmol) in THF (0.5 mL) was added slowly. After stirring for 1 h at -78 °C, the reaction mixture was quenched with saturated NH$_4$Cl, diluted with ethyl acetate, extracted with ethyl acetate, dried over MgSO$_4$. Concentration and column chromatography gave the
product 3-223 (31 mg, 95% yield). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.62 (dt, $J$ = 4.2, 2.0 Hz, 1H), 5.54 (dd, $J$ = 5.7, 2.2 Hz, 1H), 2.82 (m, 1H), 2.77-2.67 (m, 1H), 2.55 (dd, $J$ = 12.0, 2.7 Hz, 1H), 2.39 (dd, $J$ = 11.9, 9.5 Hz, 1H), 2.16 (m, 1H), 1.70-1.64 (m, 1H), 1.63-1.55 (m, 1H), 1.49-1.38 (m, 1H), 1.37-1.24 (m, 4H), 1.22 (s, 3H), 1.00 (d, $J$ = 6.9 Hz, 3H), 0.88 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 214.70, 134.01, 127.94, 56.81, 50.89, 43.82, 42.83, 41.57, 36.18, 33.92, 26.39, 25.50, 20.32, 10.91.

To a stirred solution of $n$-BuLi (0.22 mL, 2.5 M in hexanes, 0.55 mmol) in anhydrous THF (2 mL) under an atmosphere of nitrogen and at –78 °C was added trimethylsilyl diazomethane (0.55 mmol, 2.0 M in Ether, 0.28 mL) dropwise over 5 minutes. The solution went pale yellow and was allowed to stir for an additional 30 minutes at –78°C. (R)-carvone 3-225 (75 mg, 0.5 mmol) in THF (2 mL) was then added dropwise and the reaction allowed to stir for a further 30 minutes until TLC showed the complete consumption of the starting material. The reaction mixture was warmed up to 0°C and several drops of saturated aqueous solution of NH$_4$Cl were added followed the addition of MgSO$_4$. The drying reagent was filtered and solvent was removed under reduced pressure to give the crude pyrazoline. Subsequent purification using flash chromatography with gradient elution afforded a pyrazoline (118 mg, 90% yield).

A solution of the above pyrazoline (264 mg, 1 mmol), formaldehyde (60 mg, 2 mmol) and NaBH(OAc)$_3$ (424 mg, 2 mmol) in ClCH$_2$CH$_2$Cl (4 mL) was stirred at 40 °C until the TLC indicated the full consumption of the starting material. The solution was allowed to cool to room temperature and washed with water. The aqueous solution was extracted with CH$_2$Cl$_2$. The combined organic layer was dried over MgSO$_4$ and concentrated to give the crude product. A subsequent purification using flash column chromatography gave the pure methylated pyrazoline.

To a stirred solution of the above methylated pyrazoline (139 mg, 0.5 mmol) in CH$_2$Cl$_2$ (1 mL) was added TsOH (0.6 mmol). Then the reaction was heated to reflux. Following the complete
consumption of the starting material monitored by TLC, the reaction was allowed to cool to room
temperature and treated with saturated aqueous NaHCO₃. The aqueous solution was extracted with
CH₂Cl₂. The combined organic layer was dried over MgSO₄. Concentration and a subsequent
purification using flash column chromatography afforded the α-amino ketone 3-226 (83% yield in two
steps). ¹H NMR (500 MHz, CDCl₃) δ 4.89 (s, 1H), 4.76 (s, 1H), 3.15 (dd, J = 6.3, 4.0 Hz, 1H), 2.77 (dd,
J = 9.4, 4.8 Hz, 1H), 2.67 (m, 1H), 2.56 (dd, J = 14.1, 9.6 Hz, 1H), 2.37-2.31 (m, 4H), 2.04 (m, 1H), 1.93
(bs, 1H), 1.76 (s, 3H), 1.37 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 208.26, 145.15, 118.88, 112.21,
63.19, 41.79, 41.67, 39.46, 28.81, 28.59, 21.16, 19.82; HRMS (ESI) calc. for C₁₂H₁₉N₂O [M+H]⁺
207.1497, found 207.1492.

![Chemical structure of 3-226 and 3-227](image)

To a stirred solution of the α-amino ketone 3-226 (51 mg, 0.25 mmol) in ClCH₂CH₂Cl (1 mL) was
added formaldehyde (15 mg, 0.5 mmol) and NaBH(OAc)₃ (106 mg, 0.5 mmol). Then the reaction was
stirred at 40 °C until the TLC indicated the full consumption of the starting material. The solution was
allowed to cool to room temperature and treated with saturated aqueous NaHCO₃. The aqueous solution
was extracted with CH₂Cl₂. The combined organic layer was dried over MgSO₄. Concentration and a
subsequent purification using flash column chromatography afforded the α-dimethylamino ketone 3-227
(37 mg, 67% yield). ¹H NMR (CDCl₃, 500 MHz) δ 4.92 (s, 1H), 4.77 (s, 1H), 3.12 (m, 1H), 2.78 (s, 1H),
2.71-2.63 (m, 2H), 2.43 (m, 1H), 2.25 (s, 6H), 2.02-1.92 (m, 1H), 1.73 (s, 3H), 1.14 (s, 3H); ¹³C NMR
(CDCl₃, 125 MHz) δ 209.56, 145.19, 119.99, 113.68, 67.71, 40.86, 40.43, 39.19, 34.89, 26.04, 22.34,
9.46.
To a solution of amine 3-227 (30 mg, 0.14 mmol) in dichloromethane (1 mL) was added trimethylloxonium tetrafluoroborate (30 mg, 0.20 mmol) and the resulting mixture was heated to 50 °C for 4 h. Then the reaction was cooled to room temperature and the solvent was evaporated to give a residue, which was treated with potassium hydroxide (20% aqueous solution, 0.3 mL) and toluene (2 mL). The suspension was heated to 70 °C and stirred at this temperature for 6 h. After cooling to room temperature, the reaction mixture was neutralized with NH₄Cl solution, extracted with ether and dried over MgSO₄. Concentration and column chromatography gave the product 3-228 (17 mg, 70% yield in two steps). $^1$H NMR (CDCl₃, 500 MHz) δ 4.89 (s, 1H), 4.78 (s, 1H), 2.76 (m, 1H), 2.72-2.61 (m, 2H), 2.58-2.48 (m, 1H), 2.43 (m, 1H), 2.09 (d, $J = 1.4$ Hz, 3H), 1.76 (s, 3H); $^{13}$C NMR (CDCl₃, 125 MHz) δ 196.66, 146.37, 144.76, 124.60, 116.98, 111.90, 42.66, 41.31, 33.13, 20.44, 14.89.
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PART II

SYNTHESIS OF CYCLOPROPENES AND THEIR REARRANGEMENTS
Chapter 5. Cyclopropenation via alkylidene carbene insertion into C–Si bond††

5.1. Alkylidene carbene

5.1.1. Introduction

Carbenes have long been recognized as a very important and fundamental intermediate in organic chemistry. Usually, carbene is a divalent carbon species linked to two adjacent groups by a covalent bond. It possesses two non-bonding electrons. Most of carbenes have short lifetimes and high reactivity due to their electron-deficient nature. As one type of the unsaturated carbenes, alkylidene carbene (5-1), also known as alkenylidene and vinylidene, has its electron-deficient carbene carbon on an unsaturated double bond.

Similar to normal saturated carbene, an alkylidene carbene is in one of three following energy states depicted in Figure 5.1: singlet state $S_0$, where one carbon orbital is empty and the other contains two spin-paired electrons, singlet state $S_1$, where both orbitals are singly occupied with spins anti-parallel and triplet state $T_1$, where two electrons with parallel spins singly occupy two carbon orbitals. Theoretical calculations showed a singlet ground state ($S_0$) for alkylidene carbene has 20-46 kcal/mol lower energy than triplet state ($T_1$). Ab initio calculations employing a 6-31 G** basis set indicate that methylidene carbene is a singlet carbene, which is essentially $sp$-hybridized: the HOMO extends linearly as an alkyne, and the LUMO is the empty $p$-orbital. Experimentally, Gilbert and Ohira further supported singlet state by confirming C–H insertion into a stereochemically defined methine with retention of absolute configuration.

![Figure 5.1](image)

There are three major species regarding encumbrance of alkylidene carbenes (Figure 5.2). Species 5-2 is basically an organometallic compound where the metal and halogen are essentially

†† This work was performed in collaboration with Chunrui Sun, a graduate student of Professor Daesung Lee.
covalently bound to carbon. Therefore, 5-2 are nucleophilic. Usually they are formed using vinyl halides and alkyl metal species at low temperature and can be readily trapped with CO₂, CH₃I etc. Upon warming, they may easily react with olefin and other nucleophile via 5-3 or 5-4. Species 5-3 is a carbenoid in which either the leaving group or the metal, or both, is associated with the carbene intermediate. The existence of alkylidene carbenoids was proven by Köbrich through chemical trapping⁴ and later by Seebach through ¹³C NMR spectroscopy.⁵ Species 5-4 is a free carbene, which is implied by identical chemical behavior under a variety of conditions. In contrast to 5-2, carbenoid 5-3 and/or free carbene 5-4 show the usual electrophilic characters.

![Figure 5.2](image)

### 5.1.2. Generation of alkylidene carbenes

The most commonly used method for the formation of alkylidene carbenes is the α-elimination of vinyl halides (Eq. 1). In the past several decades, extrusion of nitrogen from diazoalkenes (Eq. 2) and many other methods have been developed including retro 1,2-shift of alkynes (Eq. 3),⁶ retro [1,3]-C–H insertion of cyclopropenes,⁷ exo-cyclization of alkynyllithiums 5-13 (Eq. 4),⁸ decomposition of N-nitrosooxazolidinones 5-15⁹ decomposition of tetrazole derivatives 5-16¹⁰ and decomposition of α,β-epoxy-N-aziridinylimines 5-17¹¹ (Scheme 5.1).
Among $\alpha$-eliminations, the reactions between 1-halogenated alkenes and alkyl lithium or similar bases are the most widely investigated method for the generation of alkylidene carbenes. For example, treatment of vinyl chloride 5-18 with a strong base resulted in the formation of alkylidene carbenoids 5-19 by deprotonation. The metal is usually Li, Na, K or Mg. Intermediate 5-19 could be converted to alkyliden carbene 5-20 by $\alpha$-elimination of KCl. Alternatively, lithium-halogen exchange between 1,1-
dihaloalkenes and alkyllithiums also forms similar intermediate 5-23, which then undergoes α-elimination to provide the corresponding alkylidene carbene 5-24 (Scheme 5.2).

\[
\begin{align*}
\text{5-18} & \xrightarrow{\text{KHMDS}} \begin{cases} 
\text{5-19} \\
\text{5-20}
\end{cases} \\
\text{5-21} & \xrightarrow{n-BuLi \text{, } -78 \text{ to } -40 ^\circ C} \begin{cases} 
\text{5-22} \\
\text{5-23} \\
\text{5-24}
\end{cases}
\end{align*}
\]

\( R = \text{CO(OCH}_3)_2\text{CH}_3 \)

Scheme 5.2

Usually, it is believed that the α-elimination of 1-halo or 1,1-haloalkenes results in the formation of alkylidene carbenoids, while active species generated from vinyl triflates are free alkylidene carbenes. This is partially because triflate is known to be a much better leaving group than halides, which indicates the α-elimination from vinyl triflates is a concerted process.\(^{12}\)

Alkynyliodonium salts could also serve as convenient precursors to alkylidene carbenes via the addition of nucleophiles to alkynyliodonium salts followed by α-elimination (Scheme 5.3).\(^{13}\) The general and mild approach to the preparation of alkynyliodonium salts is the reaction of alkynylstannanes with cyano(phenyl)iodonium triflate (Stang’s reagent, 5-26). In 2006, Wardrop and Fritz utilized this alkynyliodonium-based method to develop a novel methodology for the preparation of 3-phenylsulfonyl-2,5-dihydrofurans 5-31 by [1,5]-C–H insertion of arylsulfone-substituted alkylidene carbenes 5-30\(^{14}\). Furthermore, via its application, they accomplished the first total synthesis of (±)-magnofargesin.\(^{15}\)
Scheme 5.3

Alkylidene carbenes could also be generated by extrusion of nitrogen from diazoalkylidenes 5-34 (Scheme 5.4). A general protocol for the synthesis of diazoalkylidenes involves olefination of carbonyl compounds 5-9 (aldehydes or ketones) with deprotonated trimethylsilyl via 5-32 by Peterson elimination\(^\text{16}\) or with dialkylphosphonyl diazomethane derivatives via 5-33 by the Wittig-Horner method\(^\text{17}\), generating free alkylidene carbenes 5-1 by spontaneous extrusion of one molecule of nitrogen.\(^\text{18,19}\)

Scheme 5.4

5.1.3. Reactivity of alkylidene carbenes

Similar to saturated carbenes, alkylidene carbenes could undergo a range of characteristic bond-forming processes, such as, cyclopropanation,\(^\text{20}\) 1,2-rearrangement,\(^\text{21}\) electrophilic addition\(^\text{22}\) and various \(\sigma\)-bond insertion\(^\text{23}\) including C–H insertion (Scheme 4.5). All these reactions seem to originate with an interaction between the empty \(p\)-orbital at the terminus of the electrophilic carbene and the source of electron density in the reacting counterparts (e.g., C–C, C–C, C–H, or H–X bond or lone pair on heteroatom).\(^\text{24}\)
Scheme 5.5

Among these reaction categories, the C–H insertion has gained more attention due to its unique feature to generate five- or six-membered carbocyclic or heterocyclic systems with a stereochemically defined carbon center. In 1974, Köbrich disclosed α-elimination of terminal vinyl chlorides with nBuLi at -10 to -60 °C afforded cyclopentenes in moderate yields, showing the insertion occurs exclusively at C-5.25 Wolinsky and Gilbert have extensively examined the reactivity order of C–H bonds towards alkylidene carbene insertion to be tertiary > secondary (benzylic) > secondary >> primary.26 Recently, Lee and coworkers conducted a systematic study with variously substituted and conformationally constrained substrates, which shed light on the inherent selectivity of intramolecular C–H bond insertions of alkylidene carbenes.27 They found that an endo-cyclic oxygen drastically activates the adjacent C–H bond (Eq. 1 and 2 in Scheme 5.6). In contrast, insertion with 5-44 affording a mixture of 5-45 and 5-46 in a 10:1 ratio shows a less pronounced effect of the exocyclic oxygen than the endocyclic oxygen (Eq. 3). The lack of the competing insertion into the relatively more reactive benzylic C–Hb on 5-47 as opposed to the participation of the less reactive C–Hb in 5-49 is another piece of evidence supporting this trend (Eq. 4 and 5 in Scheme 5.6). They also examined pyran-containing substrates, which revealed a strong stereoelectronic effect of oxygen (Scheme 5.7). The axial C–H adjacent to the oxygen in the ring of 5-52 is more electron-rich due to the interaction of lone pair on the oxygen with C–H σ* (Eq. 1 in Scheme 5.7). In contrast, the equatorial C–H at the same position in 5-54 is deactivated because of the electron-withdrawing effect of the oxygen (Eq. 2 in Scheme 5.7).
taking advantage of this stereoelectronic effect, the tetracyclic core of platensimycin 5-58 was obtained via a regioselective C–H insertion reaction (Scheme 5.7).

Scheme 5.6

Scheme 5.7
5.2. Discovery of cyclopropenation via alkylidene carbene insertion into C–Si bond

Insertion of alkylidene carbenes into a C–H bond is a powerful tool to construct carbocycles containing quaternary carbon centers with defined stereochemistry. We envisioned that the prowess of this C–H insertion reaction can be extended to the silyl-substituted alkylidene carbene 5-59, which should constitute an effective entry into the stereoselective synthesis of functionalized cyclopentene derivatives 5-60 (Scheme 5.8). Then the resultant allylic silane 5-60 could be further elaborated to highly substituted methylidenecyclopropane 5-61.

Scheme 5.8

5.2.1. Preparation of α-silyl ketones‡‡

Our investigation was commenced with searching for an efficient method for the preparation of α-silyl ketones. Generally, α-silyl ketones can be synthesized through several methods including condensation of esters or acyl halides with α-silylated organolithium or organomagnesium, or reaction of α-silyl esters with Grignard reagents, oxidation of vinylsilanes followed by rearrangement and deprotonation-silylation of corresponding hydrazones. Although some of these are versatile methods available, more mild and efficient methods are highly needed.

Many homologation reactions of cyclic ketones with diazoalkane and its derivatives have been recorded in the literature but the homologation of aldehyde with trimethylsilyldiazomethane to generate α-silyl ketones is rare because they are prone to rearrange to the corresponding silyl enol ether. After screening a variety of Lewis acids, we found that indium(III) chloride could serve as a uniquely effective catalyst in the reaction of trimethylsilyldiazomethane and aldehydes to form α-silyl ketones. In this reaction, indium(III) chloride serves as Lewis-acid to activate aldehyde A, which would undergo a

‡‡ This methodology was developed in collaboration with graduate student Chunrui Sun and undergraduate student Silviya Demerzhan in the group of Professor Daesung Lee.
nucleophilic addition by trimethylsilyldiazomethyl carbon in B to afford diazonium intermediate C. This intermediate then will undergo a 1,2-hydride shift with a concomitant extrusion of nitrogen gas to form the desired α-silyl ketone product and regenerate the catalyst (Scheme 5.9). More importantly, this method could suppress the latent side reactions, maximizing the yield of α-silyl ketones. Those side reactions include formation of the corresponding silyl enol ethers, either through 1,2-H shift of carbene intermediate E or through Lewis acid catalyzed isomerization of α-silyl ketones, and formation of methyl ketones from protodesilylation of α-silyl ketones. The α-silyl ketones prepared with a catalytic amount of indium chloride is quite pure, thus purification was unnecessary for subsequent use.

Scheme 5.9

5.2.2. Discovery of cyclopropenation via alkylidene carbene insertion into C–Si bond

With securing a method for the preparation of α-silyl ketones, citronellal 5-67a was converted into 5-62, which was then treated with lithiated trimethylsilyldiazomethane37 without purification, delivering a product in 77% yield. To our surprise, the identity of this compound was established to be silylcyclopropene 5-68a38 and the expected cyclopentene derivative 5-60 was not detected (Scheme 5.10).
Scheme 5.10

This is probably due to a more favorable interaction between the empty \( p \)-orbital of the carbenic carbon and the C–Si bond in proximity compared to that with a rather remote C\( \gamma \)--H bond (Scheme 5.11).

A related alkylidene carbene insertion into C\( \alpha \)--H bond starting from a ketone was reported by Taber and coworkers in 1997 in their synthesis of \( \alpha \)-necrodol (Scheme 5.12).\(^{39}\) Treatment of ketone 5-63 with lithiated trimethylsilyldiazomethane solution in DME resulted in unusual low yields of benzyl protected \( \alpha \)-necrodol 5-64 (29%) and its \textit{cis}-diastereomer 5-65 (12%) accompanied with an unexpected
byproduct, cyclopropene 5-66, in 41% yield. They attributed the unusual cyclopropenation to more reactive methine C\(\alpha\)–H bond and deactivated C\(\gamma\)–H bond by a \(\beta\)-oxygen.

Scheme 5.12

5.3. Study of cyclopropenation via alkylidene carbene insertion into C–Si bond

Since cyclopropenes are unusual yet versatile substrate for a variety of synthetic transformations,\(^{40}\) the development of this unprecedented and efficient method for their preparation is highly desirable. Although there are many known synthetic approaches to cyclopropenes,\(^ {41}\) most of them could fall into three categories (Scheme 5.13). The first category is through carbene or carbenoid insertion into an alkyne (Eq. 1 in Scheme 5.13).\(^ {42}\) Carbene or carbenoids are generated by the thermal, photochemical or transition-metal catalyzed decomposition of alpha-diazoacetates. In metal-catalyzed reactions of diazo compounds with alkynes, copper and rhodium are widely investigated as catalysts. The dirhodium catalyzed cyclopropenations have largely supplanted the copper-catalyzed reactions nowadays due to their lower catalyst loading, higher reactivity and higher potentials in asymmetric cyclopropenations. However, a major limitation is that simple \(\alpha\)-alkyl-\(\alpha\)-diazoacetates were not viable except Me, Et, and benzyl due to lack of selectivity over \(\beta\)-hydride elimination. A few successful exceptions were reported by Müller and Padwa, respectively.\(^ {43}\) In addition, when this method is applied to synthesize \(\alpha\)-silylated cyclopropenes using silylated alkyne, only moderate efficiency is obtained.\(^ {44}\) The second category is through 1,2-elimination (Eq. 2 in Scheme 5.13). Treatment of monohalogenated cyclopropanes with strong base or fluoride anion leads to the corresponding cyclopropenes. This method requires at least two steps from commercially available olefins via addition of dihalocarbenes to olefins\(^ {45}\) followed by partial reduction of dihalocyclopropanes.\(^ {46}\) Although this method has been known for a long time, no reliable scaled-up procedures have been developed. It should be mentioned that strong basic and nucleophilic reagents employed in this method limit its functional group tolerance. The third category is the pyrolysis
of hydrazone derivatives under basic condition to form vinylecarbenes, which cyclize to cyclopropenes (Eq. 3 in Scheme 5.13). This procedure is always plagued by low yields due to the formation of undesired isomerization products.47

Encouraged by the preliminary results of cyclopropene formation via Ca–Si insertion, the generality was further examined with a variety of aldehydes carrying γ,δ-unsaturation (5-67b–5-67i) and branched chains (5-67j–5-67m) with electronic and steric variation (Table 5.1). Both cis- and trans-dodecenal 5-67b and 5-67c afforded cyclopropenes 5-68b and 5-68c in 81 and 78% yields (entries 1 and 2). Symmetrical cis-dialdehyde48 5-67d also gave the corresponding bis-cyclopropene 5-68d in good yield (entry 3). Aldehydes 5-67e–5-67g with trisubstituted γ,δ-double bonds behave similarly, affording cyclopropenes 5-68e–5-68g in good yields (entries 4–6). An alkyne or aromatic substituent at this position in 5-67h and 5-67i did not interfere with the Ca–Si insertion, providing 5-68h and 5-68i in 54 and 65% yield, respectively. Although the addition of alkylidene carbene to γ,δ-double bond is well preceded,49 the addition reaction was not observed with these systems. The selectivity of insertion between the Cγ–H and Ca–Si bonds was also examined with aldehyde 5-67j–5-67m50 that contain methylene and methine protons as well as oxygen atom at Cγ-position (Table 5.2). Quite surprisingly, no
competing insertion into the Cγ-H protons or oxygen moiety was observed, and only cyclopropenes 5-68j–5-68m were isolated in good yields.

Table 5.1

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>cyclopropene</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="5-67b" alt="" /></td>
<td><img src="5-68b" alt="" /></td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td><img src="5-67c" alt="" /></td>
<td><img src="5-68c" alt="" /></td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td><img src="5-67d" alt="" /></td>
<td><img src="5-68d" alt="" /></td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td><img src="5-67e" alt="" /></td>
<td><img src="5-68e" alt="" /></td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td><img src="5-67f" alt="" /></td>
<td><img src="5-68f" alt="" /></td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td><img src="5-67g" alt="" /></td>
<td><img src="5-68g" alt="" /></td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td><img src="5-67h" alt="" /></td>
<td><img src="5-68h" alt="" /></td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td><img src="5-67i" alt="" /></td>
<td><img src="5-68i" alt="" /></td>
<td>65</td>
</tr>
</tbody>
</table>

Conditions A and B are shown in Scheme 5.10. Isolated yields
Next, a variety of substrates carrying more activated Cα–H bonds were explored (Table 5.3). Due to an especially strong activating role of the α-oxygen in the tether for Cγ–H insertion, the formation of both cyclopropane 5-68 via Cα–Si bond insertion and dihydrofurane 5-69 via Cγ–H insertion were expected. When subjected to Conditions A followed by Condition B, aldehyde 5-67n with Cγ–methylene protons provided a mixture of cyclopropane 5-68n and allylic silane-containing dihydrofuran 5-69n in 1.2:1 ratio in 75% yield (entry 1). Similarly, aldehydes 5-67p and 5-67q afforded a mixture of cyclopropene 5-68p/q and C–H insertion product 5-69p/q with slightly higher ratios and yields (entries 3 and 4). Surprisingly, aldehyde 5-67o with allylic methylene protons yielded cyclopropane 5-68o and C–H insertion product 5-69o only in 2:1 ratio albeit the allylic C–H bonds are generally more activated toward carbene insertion (entry 3). An effect of an alkyl substituent was examined with a methine proton-containing substrate 5-67r, which, contrary to our expectation, provided even higher ratio (3.2:1) of cyclopropene 5-68r to C–H insertion product 5-69r (entry 5). Substrate 5-67s containing methine proton on a six-membered ring provided cyclopropane 5-68s and slightly increased ratio (1.5:1) of insertion product 5-69s in 69% yield (entry 6).
Table 5.3

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>cyclopropane / insertion product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-67n</td>
<td>5-68n, 1.2 : 1</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>5-67o</td>
<td>5-68o, 2 : 1</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>5-67p, R = H</td>
<td>5-68p, R = H, 2.4 : 1</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>5-67q, R = Me</td>
<td>5-68q, R = Me, 3.0 : 1</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>5-67r</td>
<td>5-68r, 3.2 : 1</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>5-67s</td>
<td>5-68s, 1.5 : 1</td>
<td>69</td>
</tr>
</tbody>
</table>

*Conditions A and B are shown in Scheme 5.10. *Ratio determined by 1H NMR analysis of the crude products.
*Combined isolated yields of products 5-68 and 5-69. *A pure sample of 5-69r could be obtained for full characterization.

5.4. Summary

In conclusion, we developed a new cyclopropenation reaction involving Cα–Si bond insertion of alkylidene carbenes derived from α-silyl ketones. This unprecedented alkylidene carbene reactivity features an excellent selectivity for Cα–Si bond insertion over Cγ–H bond as well as addition to the γ,δ-double and triple bonds. The selectivity trend in Table 5.3 clearly indicates that the α-oxygen in the tether significantly promotes Cγ–H insertion although the Cα–Si bond insertion still competes effectively.
It is worth to note that the reactivity of C–H bond toward carbene insertion depends intricately on the electronic and steric factors, which cannot be predicted by simple additive effect of contributing factors.
Chapter 6. Metal-catalyzed rearrangement of cyclopropene to allenes§§

6.1. Metal-catalyzed opening of cyclopropenes

6.1.1. Introduction

Three-membered ring systems have an important position in organic chemistry due to their versatility, along with their unique structural and electronic properties. Cyclopropene, the simplest isolable unsaturated cyclic molecule, is the most attractive one among them. It attracts a wide range of attention from both theoretical and experimental chemists. The ring strain of cyclopropene is about 55 kcal/mol. On the basis of Allen’s study, the vinylic carbon atoms of cyclopropene has $sp^{2.68}$-hybridized orbitals in the ring $\sigma$-framework and $sp^{1.19}$-hybridized orbitals in bonding with substituents.

It is well known that cyclopropenes can serve as good ligands to coordinate with various $\pi$-philic transition metals due to their electron-rich double bonds and highly strained character. Donation of filled $\pi$-orbital electrons from cyclopropenes to the hybridized $spd$-orbitals of the metals will release the ring strains of cyclopropenes. Typically this coordination is along with the corresponding $\pi$-back-donation from the metals to the $\pi^*$-orbital of cyclopropenes. Once coordinated, the intermediate 6-2 may result in the formation of zwitterions 6-3, which then opens the cyclopropane ring through a C–C bond migration to form a reactive organometallic species that can be viewed as a hybrid between a vinyl metal carbene 6-5 and a metal-stablized allylic carbocation 6-6. (Scheme 6.1). Alternatively, organometallic species 6-5 or/and 6-6 could also be generated from the metallacyclobutene 6-4, which is formed from the insertion of the metal into one of the C–C bonds, followed by ring opening.

§§ This work was performed in collaboration with graduate student Chunrui Sun and undergraduate student Silviya Demerzhan in the group of Professor Daesung Lee.
In 2008, Fürstner and coworkers tried to take advantage of the ring-opening of 3,3-disubstituted cyclopropenes to investigate the nature of organogold species (Scheme 6.2). The cyclopropenone acetal 6-7 gave organogold species upon treatment with Gagosz’s complex [(Ph₃P)AuNTf₂] (CD₂Cl₂, -78 °C), whose NMR spectroscopic data corresponds to the carbocationic structures (Z)-6-8. Upon warming up, organogold (Z)-6-8 isomerized to its isomer (E)-6-8. Relying on the density functional theory (DFT), Toste and coworkers calculated the rotational barriers for (Z)-6-8 and the results were found to be in agreement with Fürstners’ experiment results. They also studied the effect of the ligand on the structure of gold-substituted 3,3-dimethyl allyl cations of 6-9. They found that strong π-acidic ligands such as phosphites favor the organogold species having more carbocation character due to decreased π-back donation from gold to carbon, whereas the ligands that increase π-back donation will also increase the carbene-like reactivity of the organogold species.

Scheme 6.2

Through metal carbene 6-5 and/or metal-stablized allylic carbocation 6-6, ring-opening of cyclopropenes may lead to various end products, including polyene or carbo- and heterocycles via different reaction profiles. In addition, ring-opening of cyclopropenes could generate very useful metal
complexes. For example, 3,3-diphenylcyclopropene 6-10 has been well-known to be a precursor of the ruthenium vinyl alkylidene 6-11, which is the early Grubbs-type catalyst for metathesis (Scheme 6.3).\textsuperscript{56}

![Scheme 6.3](image)

### 6.1.2. Reactivity of vinyl metal carbenes and/or metal-stabilized allylic carbocations

#### 6.1.2.1. 1,2-Shift

In 1972, Leftin and Gil-Av demonstrated that methyl cyclopropene carboxylate 6-12 were isomerized to diene 6-14 via vinyl silver carbenoid 6-13 followed by hydride 1,2-shift (Scheme 6.4).\textsuperscript{57}

![Scheme 6.4](image)

In 2010, Wang and coworkers disclosed a cycloisomerization of cyclopropene-ynes 6-15 to generate phenols and their derivatives 6-19 in good to excellent yields (Scheme 6.5).\textsuperscript{58} The scope of this reaction is quite broad. The authors proposed a mechanistic scenario involving an initial chemoselective activation of the alkyne by the gold catalyst followed by intramolecular nucleophilic attack of the cyclopropene olefin to generate the intermediate 6-17, which, with a subsequent ring opening and a 1,2-shift of the R\textsuperscript{1} group in 6-18, leads to the substituted 4,5-diphenylphenols.
Scheme 6.5

6.1.2.2. Olefin cyclopropanation

In 1981, Padwa and coworkers reported the first examples of intramolecular olefin cyclopropanation promoted by a silver carbenoid generated from ring-opening of cyclopropenes,\(^5^9\) in which 1,2-diphenylcyclopropenes, substituted with allyl, methallyl, crotly groups at C-3, rearranged to the corresponding 1,2-diphenylbicyclo[3.1.0]hex-2-enes upon treatment with stoichiometric amount of AgClO\(_4\) in refluxing benzene or methanol.

Based on their calculation results, Toste group examined the different reactivity of cationic species versus carbene-like species on intermolecular cyclopropanation (Scheme 6.6).\(^5^5\) In the presence of an olefin and cationic gold(I) catalyst, cyclopropene acetal 6-7 did not provide any cyclopropanation product, which is consistent with Fürstner’s assertion that the organogold species generated from ring-opening of 6-7 is a gold-stabilized carbocation. In contrast to 6-7, cyclopropene 6-21 reacted with (Z)-stilbene in the presence of gold catalyst, although the yields and diastereoselectivities were highly dependent on the ligand. π-acidic phosphites such as P(OMe)\(_3\) gave none of the cyclopropanation product 6-23. Phosphine ligands gave moderate results while N-heterocyclic carbene IPr gave the highest yield of 6-23 with good diastereoselectivity due to its ability as a strong σ-donor and weak π-acceptor.
Scheme 6.6

In 2010, Meyer and Cossy et al. reported gold(I)-catalyzed cycloisomerization of allyl cyclopropenylcarbiny1 ethers or sulfonamides 6-24, which leads to 5-isopropylidene-3-oxa- and 3-azabicyclo[4.1.0]heptanes 6-25 in good yields and high diastereoselectivities (Scheme 6.7). The formation of bicyclic products was proposed to be generated via a vinyl gold carbene 6-26 trapped by an intramolecular alkenes. More recently, they reported a similar reaction, which features rhodium-catalyzed cycloisomerization to access to carbocyclic or heterocyclic scaffolds 6-28 containing a [6.1.0] bicyclic system fused on an aromatic ring.

Scheme 6.7
6.1.2.3. C–H insertion

Doyle and Müller\(^{62}\) studied extensively the Rh(II)-catalyzed ring-opening of the substituted cyclopropene carboxylates. They found that three different products, furans, diene, or methylidenecyclopentanes, depending upon the substituents of the cyclopropenes, could be generated. Among them, the formation of methylidenecyclopentanes is particularly interesting since it is a typical product of a carbene insertion into a C–H bond. In the presence of rhodium perfluorobutyrate dimer, the cyclopropene 6-29 was heated in refluxing benzene to deliver the cyclopentylidene derivative 6-33 in 30-35% yield (Scheme 6.8). Mechanistically, they suggested a preferential electrophilic attack by the bulky Rh(II) catalyst \textit{trans} to the ketone moiety, generating the more substituted cyclopropyl cation 6-31. Then a disrotatory ring opening leads to the carbene complex \((E)-6-32\), which undergoes an intramolecular C–H bond insertion at C-5 to form 6-33.

Scheme 6.8

6.1.2.4. Intramolecular Friedel-Crafts reaction

In 1981, Padwa group reported a silver-catalyzed rearrangement of the unsymmetrical cyclopropene 6-34 to generate the indene 6-35 (Scheme 6.9).\(^{63}\) The silver-catalyzed reaction has a different regioselective outcome from the photolysis of cyclopropene 6-34.\(^{64}\) They believed that the regioselectivity of bond \(a\) cleavage in the silver-mediated reaction strongly relied on the relative stability of benzylic metallo carbocation 6-37, which undergoes intramolecular Friedel-Crafts reaction to generate 6-35. Under photolytic condition, however, 6-36 was obtained via free carbene 6-38. One possibility to
account for the preferential bond \textit{b} cleavage under photolysis is that the incipient vinyl radical could be inductively stabilized by the attached methyl group.

\textbf{Scheme 6.9}

In 2008, Shi and coworkers developed a cycloisomerization of vinylcyclopropenyl benzenes catalyzed by a gold(I) catalyst to furnish 2-vinyl-1H-indenes (\textbf{Scheme 6.10}). This chemistry has a different selectivity from the one in their previously reported \textit{Cu(OTf)\textsubscript{2}}-catalyzed rearrangement reaction. With a gold catalyst, the formation of indene \textit{6-40} indicates that the bond \textit{b} cleavage occurs favorably to afford the gold-stabilized allylic cation \textit{6-43}, which undergoes a Friedel-Crafts reaction with a subsequent protodeauration to form \textit{6-40}. In the \textit{Cu(II)}-catalyzed reaction, Shi and coworkers suggested the bond \textit{a} cleavage occurs preferentially to avoid the repulsion of the rather bulky \textit{Cu(OTf)\textsubscript{2}} with the aryl group. They also found that naphthalenes \textit{6-41} were formed when a catalytic amount of \textit{BF\textsubscript{3}}•\textit{OEt\textsubscript{2}} was used. Reaction of \textit{BF\textsubscript{3}}•\textit{OEt\textsubscript{2}} with trace amounts of water in the system generates a Brønsted acid, which induces the ring opening through a more stable cyclopropyl cation \textit{6-45} followed by a Friedel-Crafts reaction. It is noted that this Friedel-Crafts reaction under Brønsted acid condition occurred with a different phenyl group from that in the gold-catalyzed reaction.
Scheme 6.10

6.1.2.5. Nucleophilic addition

Metal carbene 6-5 and/or metal-stabilized allylic carbocation 6-6 generated by the ring-opening of cyclopropenes can also participate in the nucleophilic addition by the oxygen atoms in the carbonyl or hydroxyl groups. In 1991, Padaw group demonstrated a rhodium-catalyzed ring-opening reaction of cyclopropene ketone 6-46 (Scheme 6.11). Treatment of 6-46 with catalytic amount of rhodium acetate dimer \([\text{Rh}_2(\text{OAc})_4]\) afforded furan 6-49, whereas replacement of \(\text{Rh}_2(\text{OAc})_4\) with a rhodium(I) catalyst resulted in a pronounced alternation in the ratio of isomers. In the Rh(II)-catalyzed transformation, a rhodium carbene 6-48 may be involved followed by a nucleophilic attack of carbonyl oxygen. In the Rh(I)-catalyzed reaction, they suggested that a metallocyclobutene intermediate 6-50 is formed initially by oxidative insertion. The equilibration of 6-50 with thermodynamically more stable isomer 6-52 proceeds via a cycloreversion-cycloaddition sequence. Then the rhodium migration from carbon to oxygen to form the intermediate 6-53 followed by reductive elimination produces the furan 6-47. Probably, this divergent reactivity is due to the fact that the formal oxidation from Rh(I) to Rh(III) is much more facile than that from Rh(II) to Rh(IV).
In 2003, Ma and Zhang discovered a regioselective cycloisomerization of cyclopropene ketones 6-54 to form 2,3,5-trisubstituted furans 6-56 using a catalytic amount of PdCl$_2$(CH$_3$CN)$_2$. In contrast to these results, in the presence of CuI, the other regioisomer 2,3,4-trisubstituted furans 6-55 predominately formed. The authors proposed the regioselective chloropalladation of the C=C bond of the cyclopropene played a crucial role (Scheme 6.12).

In 2007, Gevorgyan and Chuprakov reported the first example of a regiodivergent metal-catalyzed rearrangement of 3-iminocyclopropenes 6-57 into N-fused heterocycles (Scheme 6.13). They proposed that cyclopropene 6-57 undergoes ring opening to form the most substituted carbenoid in the presence of Rh(I) complex to form 6-58, whereas the formation of less substituted carbenoid is preferred to generate 6-59 when Cu(I) is used.
In 2008, Lee and coworkers described the first examples of gold-catalyzed solvolysis of simple 3,3-dialkyl substituted cyclopropenes with a series of alcohols and water, via nucleophilic attack at C-3, yielding the corresponding tert-allylic ethers (Scheme 6.14).\(^7\) Excess alcohol is needed to ensure good regioselectivity as it retards subsequent isomerization of the tert-allylic ether to the primary allylic ethers.\(^7\) They proposed that gold(I) catalyzed the ring opening of cyclopropenes to form the intermediate gold vinyl carbenoid 6-67 and/or cationic species 6-65 and 6-66, which were trapped by different nucleophiles. Depending on the identity of the nucleophiles, different regioselectivity was observed. When oxidant Ph\(_2\)SO was used, a mixture of 6-62 was formed via exclusive attack at C-1. When styrene was used, an intermolecular olefin cyclopropanation took place, showing the carbenoid nature of the intermediate (Scheme 6.8).

\[
\text{Octyl} \quad \text{PPh}_3\text{AuNTf}_2 \quad (5 \text{ mol\%}) \quad \text{ROH}, \text{DCM, rt} \quad 34-88\%
\]

\[
\text{Octyl} \quad \text{PPh}_3\text{AuCl}/\text{AgSbF}_6 \quad (5 \text{ mol\%}) \quad \text{Ph}_2\text{SO}, \text{DCM, rt} \quad 66\%
\]

\[
\text{Octyl} \quad \text{PPh}_3\text{AuNTf}_2 \quad (5 \text{ mol\%}) \quad \text{styrene}, \text{DCM, rt} \quad 72\%
\]

\[
\text{Scheme 6.14}
\]

In 2010, Ariafard and coworkers investigated the gold-catalyzed reactivity of cyclopropenylmethyl acetates, which underwent a rapid and stereoselective rearrangement to form Z-acetoxydienes\(^7\) (Scheme 6.15). On the basis of the density functional theory (DFT) calculations, they preferred a ring-opening followed by 1,2-migration mechanism via the attack of the pendant acetate at C-1.
6.1.3. Ring-opening of cyclopropenes through other intermediates

Cyclopropenes could also be opened by metal-mediated CO insertion, nucleophilic addition or metathesis reaction, etc. In 1987, Liebeskind and Cho disclosed a rhodium-catalyzed carbonylation of cyclopropenyl esters and ketones 6-71 at 1 atm of CO to provide α-pyrones 6-72 via η²-vinyl ketene metal complex intermediate 6-75 (Scheme 6.16). When vinyl cyclopropenes were applied to the reaction conditions, phenols 6-73 were afforded as the major products. In the same year, Semmelhack et al. employed the similar idea to finish metal carbonyl promoted rearrangement of 3-arylsubstituted cyclopropenes to naphthol. Recently, Wang group investigated Rh(I)-catalyzed carbonylative carbocyclization of nitrogen- or oxygen-tethered ene- or yne-cyclopropene systems, providing bicyclohexenones and phenols.
In their examination of the behavior of cyclopropene-1,\(n\)-ynes, Wang and coworkers found that the treatment of sulfonamide 6-81 containing a 1,7-enzyme subunit with in situ-generated [(\text{JohnPhos})\text{AuSbF}_6] afforded a tricyclic compound 6-84 incorporating a seven-membered heterocycle (Scheme 6.17).\(^{58}\) In this reaction, nucleophilic attack of cyclopropene to the chemoselectively activated alkyne in a 6-\(exo\)-dig manner to form 6-82 followed by a ring-opening generated gold species 6-83. It is noted that this gold species is generated from alkyne group not cyclopropene. A subsequent Friedel-Crafts cyclization delivered the formation of the product 6-84. Interestingly, if the alkyne was replaced by an alkene or an allene, only the cyclopropene unit reacted directly with gold catalyst to form 6-87/6-88, keeping the alkene and allene untouched.

**Scheme 6.17**

Significant exothermicity that accompanies the ring opening of strained cyclopropoenes implicates the metathesis reaction to be a facile and efficient process. Schrock group reported a living ring-opening metathesis polymerization (ROMP) of cyclopropenes. \(3,3\) disubstituted cyclopropenes 6-90 were treated with molybdenum initiators 6-89 to produce the corresponding polymers 6-91 in high yields and selectivity, although the polymers were not highly tactic (Scheme 6.18).\(^{77}\)
Hoveyda group showed that metathesis of the prochiral cyclopropene 6-90 proceeded with remarkable diastereoselectivity to assemble enantiomerically pure alkylated quaternary stereogenic centers. Their studies indicated that the intramolecular hydrogen-bonding interactions could significantly increase the reaction rate and levels of stereocontrol in this ring-opening/cross metathesis reaction (Scheme 6.19).

6.2. Hypothesis about metal-catalyzed opening of silylated cyclopropenes

Having in hand a convenient method for the synthesis of silylated cyclopropenes (Chapter 5), we want to explore their reactivity under transition metal condition. We surmised that the metal carbenoids derived from opening of silylated cyclopropenes 6-95 would take a different reaction course to generate new end products. As depicted in Figure 6.1, firstly, the \(\pi\)-philic transition metal coordinates with this double bond. Then, due to the \(\beta\)-cation-stabilizing effect of silicon, the formation of the intermediate 6-98 will be favored. To relieve the ring strain, the C-C bond shift will generate the well-known metal vinyl alkylene 6-100. But, because of the preference of silyl group migration, it is equally possible to form this cyclopropyl metal carbene complex 6-99, which is less-explored intermediate, may lead to a new product.
6.3. Preliminary result

To verify our hypothesis, we treated silylated cyclopropenes 6-101 and 6-103 with a catalytic amount of platinum dichloride (5 mol%) in dichloromethane at 50 °C. Not surprisingly, new rearrangement products, allenes 6-102 and 6-104 were afforded in good yields (Scheme 6.20). To our knowledge, the corresponding metal-catalyzed reaction is virtually unprecedented. To examine the importance of silyl group, we compared the reaction of silylated cyclopropenes 6-101 and 6-103 with that of the corresponding unsilylated cyclopropenes 6-105 and 6-106. We found that the corresponding unsubstituted cyclopropenes 6-105 and 6-106 provided only intractable material without any sign of allenes 6-107 and 6-108. This clearly indicates that the silyl substituent is required for the rearrangement of cyclopropenes to the corresponding allenes.
**Scheme 6.20**

Actually, the rearrangement of cyclopropenes to allenes under thermal and photochemical conditions has been documented extensively, especially for silylated cyclopropenes (Scheme 6.21). However, the photolytic reorganization of cyclopropenes usually gave low selectivity to allenes. Thermal reorganization required elevated temperature, usually in excess of 150 °C, despite the fact that the cyclopropene ring system possesses remarkably high strain energy.

**Scheme 6.21**

6.4. Reaction Scope

To further define the structural requirements for this rearrangement of cyclopropenes to allenes, we examined the behavior of 3,3-diphenyl silyl-substituted cyclopropene 6-113 (Scheme 6.22). When 6-113 was treated with the same reaction condition, only silylated indene 6-115 was generated, presumably via the formation of vinyl platinum carbenoid 6-114 followed by C–H insertion. However, interestingly,
silylated cyclopropene 6-116 containing a benzyl group led to exclusive formation of allene 6-119 without observing any indene 6-118.

Scheme 6.22

We also examined other conditions and different catalysts (Table 6.1). As opposed to the formation of allene 6-102 in 95% yield from cyclopropene 6-101 with platinum chloride (entry 1), thermal conditions alone were not effective in a 50–110 °C range, and 6-101 was recovered intact (entry 2). A cationic gold complex, although not effective at room temperature (entry 3), provided the desired allene 6-102 at an elevated temperature in 65% yield along with unidentified by-products (entry 4). Other metal complexes such as Rh$_2$(O$_2$CCF$_3$)$_4$, PtCl$_2$(PPh$_3$)$_2$, and RuCl$_2$(PPh$_3$)$_3$ were virtually inert towards the substrate and the starting material was recovered un consumed (entries 5–7). It is noted that the reaction under CO did not show much difference in terms of reaction rate and yield.
Table 6.1

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst / conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCl₂(CH₂Cl₂, 50 °C)</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>No catalyst, DMF, 110 °C</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6-120, CH₂Cl₂, rt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>6-120, CH₂Cl₂, 50 °C</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(OC₂CCF₃)₃, CH₂Cl₂, 50 °C</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>cis-Rh₂(PPPh₃)₂(CH₂Cl₂, 50 °C</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>cis-Rh₂(PPPh₃)₂(CH₂Cl₂, 50 °C</td>
<td>0</td>
</tr>
</tbody>
</table>

The relatively readily preparation and better reaction profiles of C3-unsubstituted silylated cyclopropenes compared to other cyclopropenes prompted us to choose them as the substrate platform to further explore the rearrangement of cyclopropenes to allenes. Relying on our method, we prepared a variety of silylated cyclopropenes 6-121a–j and examined their conversion to the corresponding allenes (Table 6.2). A simple alkyl chain-substituted cyclopropene 6-121a afforded allene 6-122a in excellent yield (entry 1) but the reaction of 3-butenyl substituted cis- and trans-isomers of 6-121b was not satisfactory (entry 2). One of the major by-products from cis-6-121b was identified as a cyclopropanated material derived from a putative carbenoid, such as 6-124. The ¹H and ¹³C NMR signals of this material are identical to those of the cyclopropanated product of cis-6-121b catalyzed by the cationic gold complex 6-120 used in Table 6.1. In addition, a mass spectroscopic (MALDI) analysis of the products derived from both cis- and trans-6-121b showed clusters of high molecular masses in the range of 300 up to 1233, implicating the formation of oligomers associated with a platinum metal. Similarly, several by-products were formed from a geranyl moiety-containing cyclopropene 6-121c, although the desired allene was also generated (entry 3). Formation of at least three inseparable by-products precludes the unambiguous identification of their structures. These results suggest that the double bond near the reaction center might interfere with the rearrangement.
Table 6.2

<table>
<thead>
<tr>
<th>entry</th>
<th>cyclopropene</th>
<th>time (h)</th>
<th>allene</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₁₃</td>
<td>12</td>
<td>C₆H₁₃</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>C₅H₁₁</td>
<td>20</td>
<td>C₅H₁₁</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>10</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>10</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>10</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>14</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>10</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>18</td>
<td></td>
<td>85</td>
</tr>
</tbody>
</table>

To explore the compatibility of unsaturation, we introduced structural variations to the unsaturated moiety, and found that cyclic alkenes are tolerant. Thus, cyclopropanes 6-121d–f all rearranged to allenes 6-122d–f in good yields (entries 4–6). However, 6-121g with a tetrasubstituted exocyclic double
bond did not provide desired allene 6-122g (entry 7). Alkenyl and alkynyl substituents at the remote site are tolerant, thus cyclopropenes 6-121h–j provided allenes 6-122h–j in excellent yields (entries 8–10). Notably, the terminal alkynyl substituted substrate corresponding to 6-121j generated complex product mixture. The expected allene product was identified in the NMR but it was too unstable to be isolated via purification on silica gel.

It was observed that a proximal alkene functionality such as in 6-121b interfered with the reaction. We surmised that this is the consequence of a putative interaction between Lewis acidic platinum in 6-123 or 6-124 and the alkene during the reaction. If this is indeed the case, other basic functionalities, such as ether, would interfere with the process in a similar manner. To verify this hypothesis, we prepared cyclopropenes 6-121k–o that contain an ether linkage with varying distance from the cyclopropene moiety and examined their rearrangement (Table 6.3). Except for α-alkoxy substituted substrate 6-121k (entry 1), all other alkoxy substituted substrates 6-121l–o afforded allenes 6-122l–o in good yields (entries 2–5).

Table 6.3

<table>
<thead>
<tr>
<th>entry</th>
<th>cyclopropene</th>
<th>time (h)</th>
<th>allene</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-121k</td>
<td>12</td>
<td>6-122k</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6-121l</td>
<td>10</td>
<td>6-122l</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>6-121m</td>
<td>17</td>
<td>6-122m</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>6-121n</td>
<td>10</td>
<td>6-122n</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>6-121o</td>
<td>10</td>
<td>6-122o</td>
<td>82</td>
</tr>
</tbody>
</table>
To further demonstrate the synthetic utility and effectiveness of the current allene synthesis, a three-step procedure without purifying intermediates was developed (Scheme 6.23). With this protocol, hydrocinnamaldehyde 6-125 could be transformed to the corresponding allene 6-102 in 57% overall yield with only one column purification at last step.

![Scheme 6.23](image)

We also examined the stereospecificity of this rearrangement reaction using chiral silylated cyclopropene 6-126, which was prepared by Fox’s method followed by silylation (Scheme 6.24). Unfortunately, after the rearrangement and deprotection of TBDMS group, Mosher’s ester of the corresponding alcohol 6-128 only gave a 2:1 diastereomeric ratio.

![Scheme 6.24](image)

Scheme 6.24. Reagents and conditions: (a) PtCl₂ (5 mol%), CH₂Cl₂, 50 °C, 72%; (b) p-TsOH, CH₃OH, THF, 74%; (c) (S)-Mosher’s acid, DCC, DMAP, CH₂Cl₂.

To gain further insight into the reactivity difference between platinum- and gold-based catalysts, we treated those problematic substrates 6-121b and 6-121i with gold catalyst 6-120 (Scheme 6.25). Not surprisingly, this pair of Z/E isomers efficiently delivered the corresponding diasteromeric [3.1.0] bicyclic compounds 6-130 and 6-131 via vinyl gold carbenoid 6-134 insertion into double bonds. With the same condition, the substrate 6-121i gave 6-132 and 6-133 in a ratio of 1:1 in high yield, which shows a totally different reactivity from platinum chloride. Formation of 6-133 could be consequence of electrophilic addition of double bond to electron-deficient carbenoid 6-135 followed by protiodeauration.
In light of the known carbophilic Lewis acidity of the platinum complex, several plausible mechanistic pathways can be proposed (Scheme 6.26). The β-cation-stabilizing effect of a silyl group favors the formation of intermediate 6-98, which is doomed to follow three different structural reorganization processes. We surmised that the formation of 6-136 from 6-98 via a C–C bond migration should be quite reasonable because of the relief of ring strain. A subsequent [1,2]-alkyl shift with 6-136 would provide the observed allene products. Alternatively, a C–Si bond migration leading to 6-137 followed by a [1,2]-C–C bond shift is quite plausible. In another pathway, the formation of a regioisomeric intermediate 6-139 via the cycloreversion of 6-138 followed by a [1,2]-silyl shift is equally possible. The insertion of the metal catalyst into one of the C–C bonds to form metallacyclobutene followed by its electrocyclic ring opening is another pathway leading to 6-136 and 6-139.
Scheme 6.26

To gain more insight into the reaction mechanism, isotopically labeled cyclopropane 6-142 was prepared from the commercially available $^{13}$C-labeled palmitic acid 6-140 and subjected to the reaction conditions that form an allene (Scheme 6.27). Under these conditions, $^{13}$C-labeled allene 6-143 was obtained exclusively, where the alkyl group remains connected to the original $^{13}$C-labeled carbon. This clearly rules out the possibility of a [1,2]-alkyl shift involving intermediate 6-136, and supports the other pathways with intermediates 6-137 and 6-139. Unfortunately, the current experiment with $^{13}$C-labeled cyclopropane 6-140 cannot distinguish the remaining two pathways, however, the pathway involving a 1,2-silyl migration followed by C–C bond shift is preferred energetically over the other one having a highly strained [1.1.0] bicyclic intermediate 6-138.

Most recently, Fang et al. investigated the mechanism of this PtCl$_2$-catalyzed rearrangement of cyclopropenes to allenes using density functional theory calculations carried out at the B3LYP/6-31G(d,p) (LANL2TZ(f) for Pt) level of theory. Their calculations suggested that the major pathway should be the one which involves an initial [1,2]-silyl shift to form cyclopropyl carbenoid intermediate followed by a subsequent [1,2]-C–C bond shift to lead to allenes, which is consistent with our opinion. Through the calculations, they found that the failure of the rearrangement to allene for $\alpha$-alkoxy-substituted cyclopropenes might stem from the interaction between the Lewis acidic platinum and the
initially formed allene, which induced the formation of cyclic intermediate, which could easily transformed to other products due to its instability.

\[
\begin{align*}
\text{CH}_3\text{(CH}_2\text{)}_{14}\text{SiMe}_3 & \xrightarrow{1. \text{LiAlH}_4, \text{THF, rt}} \text{CH}_3\text{(CH}_2\text{)}_{14}\text{O} \\
\text{6-140} & \xrightarrow{2. \text{DMP, CH}_2\text{Cl}_2} \text{CH}_3\text{(CH}_2\text{)}_{14}\text{OH} \\
\text{6-141} & \xrightarrow{1. \text{InCl}_2 \text{(cat), N}_2\text{CTMS, THF, }-78^\circ \text{C}} \text{CH}_3\text{(CH}_2\text{)}_{14}\text{SiMe}_3 \\
\text{6-142} & \xrightarrow{\text{PtCl}_2, \text{CH}_2\text{Cl}_2} \text{CH}_3\text{(CH}_2\text{)}_{14}\text{SiMe}_3 \\
\text{6-143} & \xrightarrow{1. \text{InCl}_2 \text{(cat), N}_2\text{CTMS, THF, }-78^\circ \text{C}} \text{CH}_3\text{(CH}_2\text{)}_{14}\text{O} \\
\text{6-141} & \xrightarrow{2. \text{LiC(N}_2\text{)TMS, THF, }-78^\circ \text{C}} \text{CH}_3\text{(CH}_2\text{)}_{14}\text{SiMe}_3 \\
\text{6-144} & \text{not observed}
\end{align*}
\]

Scheme 6.27

At the almost same time, Zhang and coworkers reported a novel mechanism based on their calculation results, in which, they believe, a PtCl\textsubscript{2}-allene complex 6-149 with the metal center coordinated with the external double bond forms and serves as the real catalyst during the reaction (Scheme 6.28).\textsuperscript{91} Firstly, PtCl\textsubscript{2} coordinates with cyclopropene 6-101 to form a PtCl\textsubscript{2}-cyclopropene complex 6-145, in which PtCl\textsubscript{2} is fixed appropriately to form a linear Cl–Pt–Cl disposition. They think, due to this linear disposition, the Pt center in 6-145 could use its \(d\pi\)-orbital to interact with the \(\pi^*\)-orbital of the C\textsubscript{2} atom in a second reactant, thereby promoting the cleavage of the C\textsubscript{2}-C\textsubscript{3} bond of the second molecule of 6-101. After simultaneous expulsion of the initial reactant molecule, a Pt(IV) complex 6-146 is formed. Subsequently, one of the chlorine ligands transfers to the C\textsubscript{2} atom from Pt, affording the
intermediate **6-147**, which is followed by the silyl migration to furnish the PtCl2-allene complex **6-149**. Instead of dissociating into the allene product, PtCl2-allene complex **6-149** reacts with cyclopropene to form an allene-PtCl2-allene sandwich compound **6-152** as the most stable structure on the potential energy surface, which dissociates directly to form allene product **6-102** and regenerate the catalyst PtCl2-allene complex **6-149**. Although this mechanism based on computational study has a certain degree of the reasonableness, we are skeptical about the formation of the intermediate **6-151** from the perspective of organic chemistry.

![Scheme 6.28](image_url)
6.6. PtCl₂-catalyzed dimerization of cyclopropenes

6.6.1. Introduction

Conjugated trienes are important structural motifs in many biologically important natural products such as antifungal macrolides and anticancer retinoids, as well as π-extended materials. However, current approaches towards functionalized, substituted trienes often require several iterative steps and/or stoichiometric reagents.92

In 1964, Stechl observed the Cu(I)-catalyzed dimerization of tri- and tetramethylcyclopropene to a triene product (Scheme 6.29).93 He proposed a mechanism, in which the coordination of two cyclopropenes to copper followed by the ring-opening leads to the formation of two vinyl copper carbenoid species 6-154. The metal carbenoid 6-154 dimerizes to form the product 6-155.

Scheme 6.29

In 1986, Condé-Petiniot and coworkers found that the cyclopropene carboxylate 6-152 afforded a conjugated triene 6-153 having Z,E,Z-configurations when stirred at room temperature in the presence of copper triflate in toluene (Eq.1 in Scheme 6.30).94 They thought the dimerization follows the same mechanism proposed by Stechl and the stereoselectivity in favor of the trans isomer is controlled by the geometric and steric requirements imposed by the metal. In 1987, Shapiro and coworkers reported a similar dimerization of 6-154 with improved yield (Eq.2 in Scheme 6.30).95 Also, in the study of proton donor addition to 1-alkylcyclopropene 3-carboxylates, they observed the formation of the triene 6-158 in 15% yield as a byproduct (Eq.3 in Scheme 6.30).96 In 1995, in their investigation of rhodium-catalyzed rearrangement of cyclopropenes, Müller and coworkers identified small amounts of dimers 6-162 and 6-163, which have different configurations from those in the previous reports (Eq.4 in Scheme 6.30).97 The configurations were determined by comparison of ¹H NMR spectra with those of similar trienes in the
literature. They proposed that the dimmers originated from attack of a vinyl rhodium carbenoid on unreacted cyclopropene to form a bicyclobutane, which then breaks down to the trienes.

\[
\text{CO}_2\text{Me} \quad \text{nBu} \\
\text{H} \quad \text{Cu(OTf)}_2 \\
\text{Toluene, rt} \\
\text{6-152} \quad \text{(15%)} \\
\rightarrow \\
\text{MeO}_2\text{C} \quad \text{nBu} \\
\text{Z} \quad \text{Z} \\
\text{E} \quad \text{Z} \\
\text{H} \quad \text{CO}_2\text{Me} \\
\text{6-153} \\
\]

(Eq.1)

\[
\text{CO}_2\text{Me} \quad \text{nPent} \\
\text{H} \quad \text{CuCl \cdot 2MeCCTMS} \\
\text{Benzene} \\
\text{6-154} \quad \text{(50%)} \\
\rightarrow \\
\text{MeO}_2\text{C} \quad \text{nPent} \\
\text{nPent} \quad \text{nPent} \quad \text{nPent} \\
\text{Z} \quad \text{Z} \\
\text{Z} \quad \text{CO}_2\text{Me} \\
\text{6-155} \quad \text{6-156} \quad \text{(10%)} \\
\text{(Eq.2)}
\]

\[
\text{CO}_2\text{Me} \quad \text{H}_2\text{C} \quad \text{H} \\
\text{H} \quad \text{CuCl \cdot 2MeCCTMS} \\
\text{DCM, rt} \\
\text{6-157} \quad \text{(15%)} \\
\rightarrow \\
\text{MeO}_2\text{C} \quad \text{E} \\
\text{H}_2\text{C} \quad \text{H} \\
\text{H} \quad \text{R} = \text{Cl} \quad \text{(45%, 67:33)} \\
\text{R} = \text{OC}_6\text{H}_4(\text{p}-\text{NO}_2) \quad \text{(30%, 17:83)} \\
\text{6-158} \quad \text{6-159} \\
\text{6-160} \\
\text{(Eq.3)}
\]

\[
\text{CO}_2\text{Et} \quad \text{nBu} \quad \text{CH}_3 \\
\text{E} \quad \text{Ru(II)} \\
\text{Benzene} \\
\text{6-161} \quad \text{(7%)} \\
\rightarrow \\
\text{MeO}_2\text{C} \quad \text{nBu} \\
\text{E} \quad \text{E} \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{E} \quad \text{H}_3\text{C} \quad \text{nBu} \\
\text{6-162} \quad \text{6-163} \quad \text{6-164} \quad \text{(55%)} \\
\text{(Eq.4)}
\]

Scheme 6.30

Recently, Hadfield and Lee reported a method by gold(I)-catalyzed reaction of cyclopropenes with furans (Scheme 6.31).

In the presence of 2-methylfuran, a variety of 3,3-disubstituted cyclopropenes 6-165 led to a mixture of geometric triene isomers 6-170, which was isomerized by treatment with a catalytic amount of iodine. Presumably, this reaction involves an initial cyclopropanation of the less hindered double bond in 2-methylfuran with the organogold species 6-166 and/or 6-167, followed by a ring-opening of the resulting 6-168 and/or 6-169. Usually the symmetric trisubstituted cyclopropenes normally require harsher conditions.
6.6.2. Results and discussion

During the study of PtCl₂-catalyzed rearrangement of cyclopropenes to allenes, we found that PtCl₂ could also induce the dimerization of 1-alkylcyclopropene 3-carboxylates, which were prepared from rhodium(II)-catalyzed cyclopropenation of terminal alkynes with ethyl diazoacetate. In the presence of a catalytic amount of PtCl₂, the cyclopropene 6-171 was heated in refluxing CH₂Cl₂ for 12 h to generate a mixture of trienes (6:1) in 78% yield (Scheme 6.32). Based on the chemical shifts and signal pattern in the ¹H NMR spectrum, the triene 6-172 with all-E configurations was temporarily assigned as the major product. Similarly, we assumed the all-E configurated triene 6-175 should be the major product in the dimerization of the cyclopropene 6-174. However, an X-ray analysis of a crystal from the reaction revealed the unambiguous structure of the major product from dimerization of 6-174 is the triene 6-176 with Z,E,E-configuration, which is totally different from the previous observations in the copper or rhodium-mediated dimerization (Figure 6.2).
To better understand this novel PtCl₂-catalyzed dimerization, other 1-alkylcyclopropene carboxylate substrates were prepared and subjected to the conditions (Figure 6.3). β-benzyloxy substituted substrate 6-177 and cyclopropanyl substituted substrate 6-178 reacted smoothly to generate the desired Z,E,E-configurated trienes, although the unambiguous yields and ratios were not obtained. Methyl substituted 6-177 derivative 6-179 did not provide any product under typical conditions. A higher reaction temperature led to formation of a complicated mixture. This could be explained by the nature of 1,2-disubstituted cyclopropene as well as the position of oxygen atom since 1,2-dialkyl substituted cyclopropenes have always a low regioselectivity of ring-opening to form two isomeric metal vinyl carbenoids, further increasing the possibility of side reactions. α-Silyloxy substituted substrate 6-180 did not give the dimerization product either, even in an extended reaction time.

6.7. Summary

In summary, we have developed an efficient metal-catalyzed rearrangement of silylated cyclopropenes to the corresponding allenes. Both the electronic effect of a silyl substituent on the cyclopropene and the presence of platinum catalyst are proven to be essential for this reaction. The mild
reaction conditions are in stark contrast to those of thermal or photochemical reactions. Good overall functional group tolerance was also recognized except for several cases where alkene and oxygen substituents interfered with the reaction. In some cases, platinum dichloride was found to be an effective catalyst for the rearrangement reaction whereas gold-based complexes primarily provided cyclopropanated products. In addition, we discovered a novel PtCl₂-catalyzed dimerization of 1-alkylcyclopropene 3-carboxylates to form conjugated trienes.
Chapter 7. Experiment details for part II

7.1. General information (see chapter 4)

7.2. Cyclopropenation via alkylidene carbene insertion into C–Si bond

7.2.1. Preparation of aldehydes 5-67 for cyclopropenation

7.2.1.1. Preparation of aldehyde 5-67d, 5-67f, 5-67h, 5-67j and 5-67l

To a solution of alkene, (10.0 mmol, 1.0 equiv) in 30 mL of dichloromethane was added meta-Chloroperoxybenzoic acid (15.0 mmol, 1.5 equiv) slowly at -78 °C. The reaction was slowly warmed up to room temperature and monitored by TLC. Upon reaction completion, sodium thiosulfate aqueous solution was added at 0 °C to quench the reaction. Then the reaction mixture was separated and the aqueous layer was extracted by Et2O (25 mL x 3). The extract was combined with the organic layer and then was washed with brine, dried over anhydrous MgSO4, filtered, and concentrated to obtain the crude product which was purified by column chromatography to afford the pure epoxide.

To finely powered sodium periodate (3.0 mmol, 3 equiv) in a round-bottom flask was added a mixture of CH3CN and water (20 mL, 2:1) and stirred for five minutes. The epoxide (1.0 mmol, 1 equiv) was then added and the reaction mixture was stirred at room temperature. Upon reaction completion, as monitored by TLC, the white precipitate was filtered away and washed by Et2O. The aqueous layer was extracted by Et2O (20 mL x 2) and washed by brine, then combined with the organic layer, dried over MgSO4, filtered and concentrated under reduced pressure to afford the crude aldehyde, which was further purified by column chromatography on silica gel.
5-67d (colorless oil): IR (ATR diamond crystal, cm\(^{-1}\)) 3011, 2900, 2822, 2729, 1720, 1408, 1392, 1054, 914, 728, 651; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 9.74 (d, 2H, \(J = 1.6\) Hz), 5.35 (t, 2H, \(J = 4.4\) Hz), 2.48 (t, 4H, \(J = 7.1\) Hz), 2.35 (dd, 4H, \(J = 6.2, 12.0\) Hz); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 201.84, 128.88, 43.52, 19.95; HRMS (ESI) calcd for C\(_8\)H\(_{12}\)O\(_2\)Na, [M+Na]\(^+\) 163.0735, found 163.0730.

The precursor 7-2 was prepared from protection of geraniol using pivaloyl chloride. 5-67f (colorless oil) IR (ATR diamond crystal, cm\(^{-1}\)) 2966, 2930, 2874, 2819, 2722, 1724, 1476, 1395, 1284, 1148, 953, 862; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 9.73 (t, \(J = 1.56\) Hz, 1H), 5.30 (ddd, \(J = 1.26, 2.53, 6.83\) Hz, 1H), 4.52 (d, \(J = 6.84\) Hz, 2H), 2.53 (dt, \(J = 1.44, 7.44, 7.83\) Hz, 2H), 2.33 (t, \(J = 7.46\) Hz, 2H), 1.68 (s, 3H), 1.14 (s, 9H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 201.74, 178.46, 139.47, 119.72, 60.99, 41.75, 38.69, 31.44, 27.16, 16.58; HRMS (ESI) calcd for C\(_{12}\)H\(_{20}\)O\(_3\)Na [M+Na]\(^+\) 235.1310, found 235.1310.

The precursor 7-3 was prepared according to the procedure described in 4.3. 5-67h (colorless oil): IR (ATR diamond crystal, cm\(^{-1}\)) 3018, 2969, 2952, 2974, 2227, 2104, 1739, 1454, 1421, 1372, 1232, 1009, 722, 524; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 9.78 (s, 1H), 2.72 (t, \(J = 6.96\) Hz, 2H), 2.60 (t, \(J = 7.06\) Hz, 2H), 0.98 (dt, \(J = 7.84, 0.93\) Hz, 9H), 0.61 (q, \(J = 7.88\) Hz, 6H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 199.42, 88.89, 82.20, 76.61, 66.56, 41.93, 12.43, 7.38, 4.21.
5-67j (colorless oil) IR (ATR diamond crystal, cm⁻¹) 2956, 2921, 2862, 2715, 1720, 1454, 1360, 1092, 1024, 735, 699; \(^1\)H NMR (CDCl₃, 500 MHz) \(\delta\) 9.75 (m, 1H), 7.34 (m, 4H), 7.28 (m, 1H), 4.50 (s, 2H), 3.51 (m, 2H), 2.43 (m, 2H), 1.67 (m, 2H), 1.46 (m, 2H), 0.90 (d, 2H, \(J = 6.5\) Hz); \(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta\) 202.77, 138.56, 128.39, 127.66, 127.57, 73.00, 68.29, 41.63, 36.48, 29.55, 28.89, 19.34; HRMS (ESI) calcd for C₁₄H₂₀O₂Na [M+Na]^+ 243.1361, found 243.1361.

5-67l (colorless oil): IR (ATR diamond crystal, cm⁻¹) 2973, 2930, 2865, 2722, 1720, 1454, 1379, 1336, 1099, 1057, 739, 696; \(^1\)H NMR (CDCl₃, 500 MHz) \(\delta\) 9.74 (s, 1H), 7.34 (m, 5H), 4.56 (d, 1H, \(J = 11.6\) Hz), 4.40 (d, 1H, \(J = 11.6\) Hz), 3.55 (dq, 1H, \(J = 6.1, 11.9\) Hz), 2.53 (m, 2H), 1.84 (m, 2H), 1.22 (d, 3H, \(J = 6.1\) Hz); \(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta\) 202.49, 138.64, 128.40, 127.76, 127.58, 73.81, 70.44, 40.19, 29.18, 19.49; HRMS (EI) calcd for C₁₂H₁₇O₂ [M+1]^+ 193.12286, found 193.12369.

7.2.1.2. Preparation of aldehydes 5-67e and 5-67g

Scheme 7.2

Aldehyde 5-67e was prepared from vinyl Grignard reagent addition of citronella followed by Claisen rearrangement in ethyl vinyl ether in the presence of mercuric acetate (Scheme 7.2).\(^{99}\) 5-67e (colorless oil): IR (ATR diamond crystal, cm⁻¹) 2963, 2914, 2859, 2715, 1730, 1450, 1386, 1190, 1076, 829; \(^1\)H NMR (CDCl₃, 500 MHz): \(\delta\) 9.75 (t, \(J = 1.78\) Hz, 1H), 5.17 (t, \(J = 7.27\) Hz, 1H), 5.08 (t, \(J = 7.08\) Hz, 1H), 4.79 (s, 1H), 4.40 (s, 1H), 3.72 (s, 1H), 3.50 (s, 1H), 1.78 (m, 2H), 1.32 (m, 2H), 0.90 (d, 2H, \(J = 6.7\) Hz); \(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta\) 202.77, 138.56, 128.39, 127.66, 127.57, 73.00, 68.29, 41.63, 36.48, 29.55, 28.89, 19.34; HRMS (ESI) calcd for C₁₄H₂₀O₂Na [M+Na]^+ 243.1361, found 243.1361.
Hz, 1H), 2.51 (dt, \( J = 7.78, 7.49, 1.81 \text{ Hz}, 2H \)), 2.33 (t, \( J = 7.44 \text{ Hz}, 2H \)), 2.03-1.88 (m, 4H), 1.81 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.44 (dt, \( J = 6.69, 13.14 \text{ Hz}, 1H \)), 1.35-1.27 (m, 1H), 1.12 (ddddd, \( J = 6.05, 7.87, 9.38, 13.57 \text{ Hz}, 1H \)), 0.84 (d, \( J = 6.68 \text{ Hz}, 3H \)); \(^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 202.69, 133.47, 131.09, 124.90, 124.56, 42.25, 36.80, 35.15, 33.21, 32.07, 25.75, 25.69, 19.48, 17.65, 16.25 \text{ HRMS (CI) calcd for C}_{15}\text{H}_{27}\text{O} [\text{M}+1]^+ 223.20620, \text{found 223.20665}."

**Scheme 7.3**

Aldehyde 5-67g was prepared using the same strategy as aldehyde 5-67e (Scheme 7.3). 5-67g (colorless oil): \(^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 9.72 (d, \( J = 1.73 \text{ Hz}, 1H \)), 4.98 (t, \( J = 7.25 \text{ Hz}, 1H \)), 2.78 (s, 1H), 2.41 (t, \( J = 7.00 \text{ Hz}, 2H \)), 2.34-2.23 (m, 3H), 1.90 (s, 2H), 1.87-1.75 (m, 6H), 1.71-1.64 (m, 4H); \(^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 202.74, 149.26, 113.72, 44.48, 40.45, 39.74, 38.85, 37.17, 32.11, 28.54, 19.59; \text{HRMS (CI) calcd for C}_{14}\text{H}_{19}\text{O} [\text{M-1}]^+ 203.14360, \text{found 203.14451}."

**7.2.1.3. Preparation of aldehyde 5-67k, 5-67m and 5-67r**

**Scheme 7.4**

Alcohols 7-6, 7-7 and 7-8 was prepared according to the reported procedure (Scheme 7.4). To a mixture of benzaldehyde (1.06 g, 10 mmol, 1 equiv) in 20 mL of THF and 40 mL of saturated NH\(_4\)Cl solution was added Zn dust (1.30 g, 20 mmol, 2 equiv) and allyl bromide (2.42 g, 20 mmol, 2 equiv).
After the mixture was stirred for 30 min, it was extracted with diethyl ether for 3 times, the combined organic layer was dried over MgSO\_4 and diethyl ether and excess amount of allyl bromide was removed under reduced pressure to afford 1-phenyl-3-butenol of colorless oil which was subjected to the next step without further purification.

To a solution of the crude secondary alcohol (296 mg, 2 mmol, 1 equiv) in 10 mL of the corresponding diol, PdCl\_2 (36 mg, 0.2 mmol, 0.2 equiv) was added. Thereafter the reaction was heated at 40 °C under air overnight, water and diethyl ether were added. The organic layer was separated, and the aqueous portion was extracted with ether for 3 times. The combined organic layers were washed with water and brine, dried over MgSO\_4, filtered, and concentrated to obtain the crude product which was purified by column chromatography (Hexane : Ethyl acetate = 6:1) to afford the pure primary alcohol 7-6, 7-7, or 7-8.

To a solution of the primary alcohol (1 equiv) in 5 mL of dichloromethane, Dess-Martin periodinane (1.3 equiv) and NaHCO\_3 (1.3 equiv) was added. Upon complete consumption of the starting material in 2 hrs, diethyl ether was added and white precipitate was formed. Filtering through a short plug of silica gel and concentrating under reduced pressure afforded the crude product which was purified by column chromatography using Hexane : Ether = 10:1 to give the pure aldehyde 7-9, 5-67m, or 5-67k.

7-9 (colorless oil, 62% over two steps): \(^1\)H NMR (CDCl\_3, 500 MHz) \(\delta\) 9.73 (s, 1H), 7.39 (d, \(J = 7.30\) Hz, 2H), 7.33 (t, \(J = 7.54\) Hz, 2H), 7.27 (t, \(J = 7.22\) Hz, 1H), 6.54 (d, \(J = 15.95\) Hz, 1H), 6.08 (dd, \(J = 15.95, 8.02\) Hz, 1H), 4.11 (m, 3H), 1.43 (d, \(J = 6.30\) Hz, 3H); \(^13\)C NMR (CDCl\_3, 125 MHz) \(\delta\) 201.03, 136.11, 132.75, 130.01, 128.69, 128.09, 126.59, 78.01, 73.84, 21.56.

5-67r was obtained quantitatively by hydrogenation of 1r' using H\_2 in the presence of Pd/C in EtOAc. 5-67r (colorless oil) IR (ATR diamond crystal, cm\(^{-1}\)) 2926, 2865, 1730, 1606, 1496, 1454, 1116, 1024, 914, 744, 699; \(^1\)H NMR (CDCl\_3, 500 MHz): \(\delta\) 9.74 (s, 1H), 7.30 (t, \(J = 7.46\) Hz, 2H), 7.21 (d, \(J = 7.09\) Hz, 3H), 4.06 (m, 2H), 3.51 (qt, \(J = 6.01\) Hz,
1H), 2.97-2.56 (m, 2H), 2.03-1.87 (m, 1H), 1.80 (m, 1H), 1.23 (d, J = 6.10 Hz, 3H); 13C NMR (CDCl3, 125 MHz) δ 201.48, 141.96, 128.45, 125.91, 76.14, 74.16, 38.13, 31.72, 19.42; HRMS (ESI) calcd for C12H19O2 [M+H]+ 195.1385, found 195.1381.

5-67m (colorless oil, 56% over two steps): 1H NMR (CDCl3, 500 MHz) δ 9.80 (s, 1H), 7.40 (d, 1H, J = 7.8 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.25 (t, 1H, J = 7.3 Hz), 6.54 (d, 1H, J = 15.9 Hz), 6.10 (dd, 1H, J = 7.7, 15.9 Hz), 4.03 (p, 1H, J = 6.4 Hz), 3.79 (m, 2H), 2.67 (dt, 2H, J = 1.8, 6.1 Hz), 1.33 (d, 3H, J = 6.4 Hz); 13C NMR (CDCl3, 125 MHz) δ 201.49, 136.49, 131.31, 128.63, 128.48, 127.79, 126.51, 77.15, 61.96, 44.06, 21.63.

5-67k (colorless oil, 67% over two steps): 1H NMR (CDCl3, 500 MHz) δ 9.75 (s, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 6.50 (d, J = 15.95 Hz, 1H), 6.09 (ddd, J = 15.95, 7.59, 1.31 Hz, 1H), 3.96 (q, J = 6.59 Hz, 1H), 3.59-3.44 (m, 1H), 3.44-3.29 (m, 1H), 2.49 (m, 2H), 1.90 (q, 2H), 1.31 (d, J = 6.36 Hz, 3H); 13C NMR (CDCl3, 125 MHz) δ 202.33, 136.62, 131.75, 131.09, 128.62, 127.70, 126.49, 76.69, 41.10, 22.83, 21.64.

7.2.1.4. Preparation of aldehyde 5-67n, 5-67o, 5-67p, 5-67q and 5-67s

Scheme 7.5

To a solution of alcohol (10.0 mmol, 1.0 equiv) in 30 mL of dimethylformamide was added sodium hydride (60% in oil, 15.0 mmol, 1.5 equiv) and tetrabutylammonium iodide (0.1 mmol, 0.01 equiv.). After the solution was stirred at room temperature for 30 minutes, bromoacetaldehyde diethyl acetal (20.0 mmol, 2.0 equiv) was added into the reaction at 0 °C slowly. Then the reaction was heated to 40 °C and stirred overnight. The reaction was quenched by adding water and diethyl ether. The organic layer was separated, and the aqueous portion was extracted with ether for 3 times. The combined
organic layers were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated to obtain the crude product which was purified by column chromatography to afford the pure acetal;

To a solution of the corresponding acetal (1.0 mmol, 1.0 equiv) in acetone (3 mL) was added concentrated HCl solution (0.2 mmol, 0.2 equiv). The reaction was monitored by TLC carefully. Upon formation of quite amount of desired aldehyde, the reaction was quenched immediately by adding sodium bicarbonate solution slowly and extracted by Et₂O. Long reaction time will lead to decomposition of desired aldehyde to starting alcohol. The extract was dried over MgSO₄ and concentrated under reduced pressure to afford a crude oil, which was purified by column chromatography to generate the corresponding α-alkoxy aldehydes 5-67n-5-67q and 5-67s, which were used for cyclopropenation without storage.

5-67n (colorless oil): IR (ATR diamond crystal, cm⁻¹) 2959, 2917, 2869, 1750, 1720, 1450, 1379, 1252, 1109, 979, 836, 741; ¹H NMR (CDCl₃, 500 MHz) δ 9.72 (s, 1H), 5.07 (t, J = 7.1 Hz, 1H), 4.04 (s, 2H), 3.55 (dt, J = 7.01, 1.54 Hz, 2H), 2.12-1.87 (m, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.42 (m, 1H), 1.38-1.27 (m, 1H), 1.16 (dd, J = 13.53, 9.28, 7.76, 6.15 Hz, 1H), 0.89 (d, J = 6.62 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 201.15, 131.27, 124.80, 124.65, 76.34, 70.47, 37.15, 36.45, 29.41, 25.71, 25.43, 19.49, 17.63.

5-67o (colorless oil): IR (ATR diamond crystal, cm⁻¹) 2917, 1737, 1464, 1369, 1268, 1090, 1009, 957, 803, 683; ¹H NMR (CDCl₃, 500 MHz) δ 9.68 (d, J = 4.27 Hz, 1H), 5.50 (s, 1H), 3.97 (d, J = 4.27 Hz, 1H), 3.91 (s, 1H), 2.41-2.33 (m, 1H), 2.25 (dd, J = 39.24, 18.69 Hz, 1H), 2.20-2.15 (m, 1H), 2.07 (s, 1H), 1.26 (d, J = 3.27 Hz, 1H), 1.24 (d, J = 16.19 Hz, 1H), 1.11 (dd, J = 8.66, 3.04 Hz, 1H), 0.86-0.81 (m, 1H), 0.79 (d, J = 3.06 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 201.06, 144.32, 121.69, 74.85, 74.51, 43.21, 40.80, 38.02, 31.49, 31.31, 26.12, 21.07; HRMS (ESI) calcd for C₁₂H₁₉O₂ [M+1]⁺ 195.1385, found 195.1381.
5-67p (colorless oil) IR (ATR diamond crystal, cm⁻¹) 3005, 2933, 2859, 1734, 1460, 1376, 1304, 1116, 1076, 709; ¹H NMR (CDCl₃, 500 MHz) δ 9.71 (d, J = 2.75 Hz, 1H), 5.32 (m, 2H), 4.04 (d, J = 2.32 Hz, 2H), 3.51 (dt, J = 6.63, 2.18 Hz, 2H), 2.01 (m, 4H), 1.70-1.50 (m, 2H), 1.46-1.17 (m, 4H), 0.93 (dt, J = 7.54, 2.20 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 201.13, 131.80, 128.90, 76.31, 72.14, 29.50, 29.44, 26.96, 25.59, 20.51, 14.37; LRMS (CI) calcd for C₁₁H₂₁O₂ [M+1]+ 185.2, found 185.2.

5-67q (colorless oil): IR (ATR diamond crystal, cm⁻¹) 2936, 2933, 2862, 1727, 1457, 1379, 1090, 1070, 1035, 725, 692; ¹H NMR (CDCl₃, 500 MHz) δ 9.73 (s, 1H), 5.33 (ddt, J = 17.9, 10.8, 7.1 Hz, 2H), 4.05 (dq, J = 0.98, 17.8 Hz, 2H), 3.47 (qd, J = 6.2, 12.1 Hz, 1H), 2.02 (q, J = 6.8 Hz, 4H), 1.65-1.52 (m, 1H), 1.49-1.38 (m, 1H), 1.41-1.27 (m, 4H), 1.17 (d, J = 6.1 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 201.85, 131.83, 128.92, 74.13, 36.27, 29.78, 27.01, 25.09, 20.53, 19.41, 14.40; LRMS (CI) calcd for C₁₂H₂₃O₂ [M+1]+ 199.2, found 199.2.

5-67s (colorless oil): IR (ATR diamond crystal, cm⁻¹) 2907, 2826, 1739, 1473, 1454, 1372, 1102, 985, 923; ¹H NMR (CDCl₃, 500 MHz) δ 9.74 (d, J = 0.98 Hz, 1H), 4.05 (m, 2H), 3.68 (dt, J = 9.02, 4.73 Hz, 1H), 2.46-2.35 (m, 1H), 2.32 (dtd, J = 8.35, 6.18, 2.11 Hz, 1H), 2.14-2.00 (m, 1H), 1.99-1.87 (m, 1H), 1.78 (dd, J = 9.75, 6.53, 3.98 Hz, 2H), 1.19 (s, 3H), 1.12 (d, J = 7.43 Hz, 3H), 1.04 (d, J = 9.80 Hz, 1H), 0.87 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 201.76, 80.31, 74.45, 47.52, 44.37, 41.31, 38.40, 35.30, 33.39, 27.47, 23.77, 21.35.

7.2.2. General procedures for cyclopropenation

In a fume hood, a vial equipped with a Teflon-coated stir bar was charged with aldehyde (1 mmol, 1.0 equiv) and 1 mL of anhydrous dichloromethane. Trimethylsilyl diazomethane (2.0 M in diethyl ether, 0.6 mL, 1.2 mmol, 1.2 equiv) was added by syringe at room temperature followed by InCl₃ (4.4 mg, 0.02 mmol, 0.02 equiv) added at once and vigorous bubbling was observed. The reaction was stirred in the air at room temperature for 10 to 20 min, at which point TLC indicated the consumption of the starting
material. Dichloromethane and the excess amount of trimethylsilyldiazomethane was removed under reduced pressure and the crude α-TMS ketone was subjected to the next step without further purification.

To a cooled (-78 °C) solution of TMS diazomethane (2.0 M in diethyl ether, 0.6 mL, 1.2 mmol, 1.2 equiv) in THF (2 mL) was added n-BuLi (2.5 M in hexane, 0.52 mL, 1.3 equiv) dropwise under N₂ atmosphere. After the mixture was stirred at -78 °C for 30 minutes, a solution of the crude α-TMS ketone in THF (1.0 mL) was added into the mixture dropwise. Then the reaction was stirred at -78 °C for 10 minutes. The reaction mixture was warmed up to room temperature by removing dry ice-acetone bath and quenched by adding several drops of an aqueous saturated NH₄Cl solution and the mixture was directly dried over MgSO₄, filtered through a short plug of silica gel and concentrated under reduced pressure to afford the crude oil. Purification by column chromatography gave the desired product 5-68a-5-68s and 5-69n-5-69s.

7.2.3. Characterization data

5-68a (colorless oil, 77%): IR (ATR diamond crystal, cm⁻¹) 2966, 2922, 2877, 1739, 1717, 1452, 1363, 1245, 1158, 838, 671; ¹H NMR (CDCl₃, 500 MHz) δ 5.14-5.08 (m, 1H), 2.55 (dd, J = 5.45, 15.84 Hz, 1H), 2.42 (dd, J = 7.46, 15.85 Hz, 1H), 2.10-1.94 (m, 1H), 1.82 (dt, J = 6.74, 13.41 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.46-1.35 (m, 1H), 1.29-1.17 (m, 1H), 0.94 (dd, J = 0.68, 6.68Hz, 3H), 0.72 (d, J = 0.88 Hz, 1H), 0.17 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 134.18, 131.19, 124.72, 105.46, 36.87, 35.63, 31.48, 25.72, 25.62, 19.88, 17.64, 6.32, -1.38.

5-68b (colorless oil, 81%): IR (ATR diamond crystal, cm⁻¹) 3008, 2956, 2926, 2871, 1801, 1739, 1457, 1372, 1246, 1223, 992, 839, 758, 634; ¹H NMR (CDCl₃, 500 MHz) δ 5.39 (t, J = 4.93 Hz, 2H), 2.59 (t, J = 7.50 Hz, 2H), 2.32 (td, J = 6.41, 12.43 Hz, 2H), 2.04 (dd, J = 6.91, 12.64 Hz, 2H), 1.39-1.24 (m, 6H), 0.89 (t, J = 6.92 Hz, 3H), 0.75 (s, 2H), 0.17 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 134.86, 130.69, 128.72, 105.46, 36.87, 35.63, 31.48, 25.72, 25.62, 19.88, 17.64, 6.32, -1.31; HRMS (CI) calcd for C₁₅H₂₇Si [M-1]⁺ 235.1882, found 235.1879.
5-68c (colorless oil, 78%): IR (ATR diamond crystal, cm\(^{-1}\)) 2960, 2925, 2871, 2852, 1796, 1460, 968, 832, 759; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 5.45 (td, \(J = 3.69, 5.16\) Hz, 2H), 2.60 (t, \(J = 7.38\) Hz, 2H), 2.28 (td, \(J = 12.65, 6.31\) Hz, 2H), 2.00-1.94 (m, 2H), 1.41-1.19 (m, 6H), 0.89 (t, \(J = 6.98\) Hz, 3H), 0.74 (s, 2H), 0.16 (s, 9H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 134.86, 131.07, 129.17, 105.40, 32.57, 31.41, 30.32, 29.25, 28.87, 22.57, 14.08, 6.36, -1.31; HRMS (CI) calced for C\(_{15}\)H\(_{29}\)Si \([M+1]^+\) 237.20, found 237.1648.

5-68d (colorless oil, 71%): IR (ATR diamond crystal, cm\(^{-1}\)) 2959, 2916, 2876, 1796, 1730, 1444, 1376, 1244, 994, 837, 758, 636; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 5.43 (t, \(J = 4.9\) Hz, 1H), 2.60 (t, \(J = 7.5\) Hz, 2H), 2.35 (dd, \(J = 7.4, 12.7\) Hz, 2H), 0.76 (s, 2H), 0.17 (s, 9H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 134.72, 129.48, 105.89, 28.77, 25.24, 6.46, -1.31; HRMS (CI) calced for C\(_{18}\)H\(_{31}\)Si\(_2\) \([M-1]^+\) 303.19644, found 303.19618.

5-68e (colorless oil, 69%): \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 5.17 (t, \(J = 6.69\) Hz, 1H), 5.10 (t, \(J = 7.10\) Hz, 1H), 2.68-2.63 (m, 2H), 2.28 (t, \(J = 7.60\) Hz, 2H), 2.05-1.90 (m, 3H), 1.88-1.78 (m, 1H), 1.69 (s, 3H), 1.61 (d, \(J = 5.61\) Hz, 6H), 1.50-1.40 (m, 1H), 1.39-1.29 (m, 1H), 1.14 (dddd, \(J = 5.99, 7.73, 9.44, 13.51\) Hz, 1H), 0.85 (d, \(J = 6.66\) Hz, 3H), 0.74 (s, 2H), 0.16 (s, 9H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 135.15, 134.84, 131.02, 125.00, 123.62, 105.25, 37.35, 36.83, 35.16, 35.07, 33.30, 27.49, 25.73, 19.53, 17.65, 16.13, 6.32, -1.29; HRMS (CI) calced for C\(_{20}\)H\(_{35}\)Si \([M-1]^+\) 303.25081, found 303.25064.

5-68f (colorless oil, 75%): IR (ATR diamond crystal, cm\(^{-1}\)) 2966, 2906, 2849, 1796, 1448, 1246, 1907, 993, 835, 753; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 5.34 (ddt, \(J = 1.2, 2.5, 6.8\) Hz, 1H), 4.57 (d, \(J = 6.9\) Hz, 2H), 2.67 (t, \(J = 7.7\) Hz, 2H), 2.32 (t, \(J = 7.7\) Hz, 2H), 1.72 (s, 3H), 1.19 (s, 9H), 0.73 (s, 2H), 0.15 (s, 9H); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 178.61, 140.84, 134.56, 119.00, 105.80, 61.27, 38.75, 36.97, 27.22, 26.96, 16.47, 6.40, -1.31.
5-68g (colorless, 81%): IR (ATR diamond crystal, cm⁻¹) 2953, 2906, 2849, 1796, 1448, 1246, 1907, 993, 835, 753; 1H NMR (CDCl₃, 500 MHz) δ 5.07 (t, J = 7.2 Hz, 1H), 2.81 (s, 1H), 2.57 (t, J = 7.5 Hz, 2H), 2.32 (s, 1H), 2.27 (q, J = 7.3 Hz, 1H), 1.95 (s, 1H), 1.86, (ddd, J = 2.7, 6.3, 11.9 Hz, 6H), 1.82 (s, 1H), 1.76 (d, J = 11.7 Hz, 2H), 1.70 (d, J = 11.8 Hz, 2H), 0.76 (s, 2H), 0.17 (s, 9H); 13C NMR (CDCl₃, 125 MHz) δ 148.16, 135.15, 115.36, 105.46, 40.49, 39.85, 38.98, 37.34, 32.14, 29.60, 28.67, 24.49, 6.44, -1.27; HRMS (EI) calcd for C₁₉H₃₀Si [M]+ 286.21168, found 286.21278.

5-68h (colorless, 54%): IR (ATR diamond crystal, cm⁻¹) 3014, 2956, 2914, 2878, 2224, 2107, 1798, 1739, 1460, 121, 129, 1229, 1004, 839, 725, 634; 1H NMR (CDCl₃, 500 MHz) δ 2.79 (t, J = 7.17 Hz, 2H), 2.54 (t, J = 7.17 Hz, 2H), 0.89 (t, J = 7.91 Hz, 9H), 0.78 (s, 1H), 0.61 (q, J = 7.92 Hz, 6H), 0.18 (s, 9H); 13C NMR (CDCl₃, 125 MHz) δ 132.69, 107.65, 89.34, 81.45, 78.19, 66.17, 27.85, 17.75, 7.35, 6.68, 4.24, -1.43; HRMS (EI) calcd for C₁₈H₂₉Si₂ [M-1]+ 301.18079, found 301.18034.

5-68i (colorless, 65%): IR (ATR diamond crystal, cm⁻¹) 3028, 2952, 2874, 1798, 1739, 1496, 1454, 1369, 1246, 995, 832, 744, 696, 631; 1H NMR (CDCl₃, 500 MHz) δ 7.32 (t, J = 7.7 Hz, 2H), 7.23 (d, J = 7.2 Hz, 3H), 2.93 (m, 4H), 0.83 (s, 2H), 0.17 (s, 9H); 13C NMR (CDCl₃, 125 MHz) δ 141.71, 134.48, 128.36, 125.97, 106.31, 33.56, 30.48, 6.56, -1.35; HRMS (CI+) calcd for C₁₄H₁₉Si [M-1]+ 215.1256, found 215.1257.

5-68j (colorless, 51%): IR (ATR diamond crystal, cm⁻¹) 2956, 2928, 2871, 1796, 1455, 1366, 1246, 1101, 993, 838, 736, 699; 1H NMR (CDCl₃, 500 MHz) δ 7.35 (d, J = 4.18 Hz, 4H), 7.32-7.27 (m, 1H), 4.51 (d, J = 1.67 Hz, 2H), 3.58-3.48 (m, 2H), 2.64-2.50 (m, 2H), 1.76-1.60 (m, 3H), 1.52-1.41 (m, 2H), 0.93 (d, J = 6.31 Hz, 3H), 0.74 (s, 2H), 0.16 (s, 9H); 13C NMR (CDCl₃, 125 MHz) δ 138.68, 135.30, 128.37, 127.62, 127.50, 105.06, 72.95, 68.64,
5-68k (colorless oil, 82%): IR (ATR diamond crystal, cm$^{-1}$) 3031, 2956, 2868, 1791, 1739, 1447, 1369, 1245, 1148, 1096, 966, 832, 748, 692, 637; $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.41 (d, $J = 7.24$ Hz, 2H), 7.34 (t, $J = 7.59$ Hz, 2H), 7.26 (t, $J = 7.29$ Hz, 1H), 6.53 (d, $J = 15.95$ Hz, 1H), 6.14 (dd, $J = 7.55$, 15.95 Hz, 1H), 4.04-3.98 (m, 1H), 3.59 (td, $J = 6.58$, 9.26 Hz, 1H), 3.42 (td, $J = 6.52$, 9.28 Hz, 1H), 2.67 (dt, $J = 2.00$, 7.16 Hz, 2H), 1.91 (p, $J = 6.84$ Hz, 2H), 1.36 (d, $J = 6.37$ Hz, 3H), 0.76 (s, 2H), 0.17 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 136.73, 134.77, 132.10, 130.89, 128.60, 127.63, 126.48, 105.43, 76.66, 67.73, 27.80, 25.40, 21.75, 6.41, -1.28; HRMS (CI) calcd for C$_{19}$H$_{27}$OSi [M-1]$^+$ 299.18313, found 299.18400.

5-68l (colorless oil, 71%): IR (ATR diamond crystal, cm$^{-1}$) 3018, 2969, 2950, 2869, 1743, 1447, 1369, 1216, 1090, 1064, 836, 735, 692, 526; $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.38-7.33 (m, 4H), 7.30-7.26 (m, 1H), 4.59 (d, $J = 11.68$ Hz, 1H), 4.45 (d, $J = 11.68$ Hz, 1H), 3.62-3.53 (m, 1H), 2.66 (t, $J = 7.48$ Hz, 2H), 1.89 (dt, $J = 7.38$, 14.28 Hz, 1H), 1.76 (dtd, $J = 5.03$, 7.62, 7.83, 13.01 Hz, 1H), 1.24 (d, $J = 6.14$ Hz, 3H), 0.72 (s, 2H), 0.16 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 138.97, 134.90, 128.35, 127.67, 127.46, 105.21, 74.16, 70.51, 34.37, 24.72, 19.58, 6.33, -1.29; LRMS (CI) calcd for C$_{17}$H$_{25}$OSi [M-1]$^+$ 273.2, found 273.2.

5-68m (colorless oil, 75%): IR (ATR diamond crystal, cm$^{-1}$) 3028, 2956, 2871, 1795, 1739, 1443, 1366, 1249, 1148, 1092, 972, 836, 748, 692, 637; $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.41 (d, $J = 7.72$ Hz, 2H), 7.34 (t, $J = 7.59$ Hz, 2H), 7.26 (t, $J = 7.27$ Hz, 1H), 6.56 (d, $J = 15.94$ Hz, 1H), 6.15 (dd, $J = 7.61$, 15.94 Hz, 1H), 4.10-4.03 (m, 1H), 3.81-3.74 (m, 1H), 3.65-3.59 (m, 1H), 2.91-2.85 (m, 2H), 1.37 (d, $J = 6.35$ Hz, 3H), 0.78 (s, 2H), 0.18 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 136.71, 132.10, 131.88, 131.12, 128.60, 127.67, 126.50, 106.84, 76.78, 66.20, 29.54, 21.75, 6.02, -1.36; HRMS (ESI) calcd for C$_{18}$H$_{26}$ONaSi [M+Na]$^+$ 309.1651, found 309.1640.
5-68n (colorless oil, 41%): IR (ATR diamond crystal, cm⁻¹) 3014, 2972, 2921, 2852, 1739, 1678, 1454, 1372, 1232, 1154, 1096, 832, 761, 6926; ¹H NMR (CDCl₃, 500 MHz) δ 5.10 (t, J = 6.47 Hz, 1H), 4.55 (s, 2H), 3.59-3.47 (m, 2H), 2.07-1.90 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.43 (td, J = 6.74, 13.43 Hz, 1H), 1.37-1.30 (m, 1H), 1.17 (td, J = 8.35, 13.60 Hz, 1H), 0.90 (d, J = 6.65 Hz, 3H), 0.88 (s, 2H), 0.18 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 131.34, 131.15, 124.81, 108.38, 69.11, 68.02, 37.31, 36.74, 29.64, 25.73, 25.50, 19.60, 17.64, 6.71, -1.50; HRMS (Cl) calcd for C₉H₁₈OSi [M⁻1]⁺ 279.2144, found 279.2146.

5-69n (colorless oil, 34%): ¹H NMR (CDCl₃, 500 MHz) δ 5.21 (d, J = 16.05 Hz, 1H), 5.10 (ddd, J = 1.31, 5.85, 7.06 Hz, 1H), 4.87 (s, 1H), 4.50-4.36 (m, 2H), 2.08-1.88 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.52 (d, J = 4.31 Hz, 2H), 1.48-1.29 (m, 3H), 1.25 (ddd, J = 4.34, 8.94, 13.48 Hz, 1H), 1.16 (ddddd, J = 2.81, 9.91, 5.64, 11.71 Hz, 1H), 0.93 (dd, J = 1.91, 6.63 Hz, 3H), 0.04 (s, 9H) ¹³C NMR (CDCl₃, 125 MHz) δ 138.02, 124.89, 121.54, 121.24, 85.45, 85.08, 77.61, 44.13, 37.87, 37.31, 29.87, 29.51, 25.75, 25.45, 20.24, 19.54, 17.66, 17.11, -1.43.

5-68o (colorless oil, 55%): IR (ATR diamond crystal, cm⁻¹) 2982, 2950, 2913, 2836, 1737, 1678, 1464, 1360, 1246, 1083, 843, 758; ¹H NMR (CDCl₃, 500 MHz) δ 5.51-5.49 (m, 1H), 4.53 (s, 2H), 3.93-3.89 (m, 1H), 2.40 (td, J = 5.61, 8.61 Hz, 1H), 2.28 (dd, J = 17.81, 38.15 Hz, 2H), 2.20 (dt, J = 1.22, 5.71 Hz, 1H), 2.10 (ddd, J = 2.35, 3.61, 6.89 Hz, 1H), 1.29 (s, 3H), 1.18 (d, J = 8.63 Hz, 1H), 0.86 (d, J = 15.62 Hz, 3H), 0.18 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 145.15, 131.22, 120.09, 108.35, 73.22, 66.85, 43.35, 40.90, 38.01, 31.58, 31.31, 26.20, 21.08, 6.70, -1.45; HRMS (Cl) calcd for C₁₇H₂₈OSi [M⁺] 276.19095, found 276.19088.

5-69o (colorless oil, 28%): IR (ATR diamond crystal, cm⁻¹) 2950, 1743, 1457, 1369, 1249, 1213, 1038, 825, 677; ¹H NMR (CDCl₃, 500 MHz) δ 1H NMR 5.45 (s, 1H), 5.18 (s, 1H), 4.98 (s, 1H), 4.51-4.40 (m, 2H), 2.40 (td, J = 5.62, 8.57 Hz, 1H), 2.32 (td, J = 2.86, 17.79 Hz, 1H), 2.19 (td, J = 2.58, 17.80 Hz, 1H), 2.12 (t, J = 5.45 Hz, 1H), 2.06 (s, 1H), 1.62 (d, J = 13.95 Hz,
1H), 1.45 (d, \(J = 13.97 \text{ Hz}, 1\text{H}\)), 1.26 (s, 3H), 1.22 (d, \(J = 8.63 \text{ Hz}, 1\text{H}\)), 0.79 (s, 3H), 0.05 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 148.8, 139.09, 119.21, 118.86, 89.94, 78.73, 41.22, 40.97, 37.83, 31.78, 31.23, 26.14, 21.24, 17.25, -1.34\); LRMS (Cl) calcd for C\(_{17}\)H\(_{29}\)OSi [M-1]\(^+\) 275.2, found 275.2.

**5-68p** (colorless oil, 60%): IR (ATR diamond crystal, cm\(^{-1}\)) 3004, 2937, 2852, 1739, 1678, 1450, 1369, 1220, 1076, 1102, 839, 754; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta 5.40-5.28 \text{ (m, 2H)}, 4.55 \text{ (s, 2H)}, 3.49 \text{ (t, } J = 6.71 \text{ Hz, 2H)}, 2.03 \text{ (p, } J = 7.10 \text{ Hz, 4H)}, 1.66-1.58 \text{ (m, 2H)}, 1.37 \text{ (dd, } J = 3.46, 7.04 \text{ Hz, 4H)}, 0.95 \text{ (t, } J = 7.54 \text{ Hz, 3H)}, 0.88 \text{ (s, 2H)}, 0.18 \text{ (s, 9H); } ^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 148.8, 139.09, 119.21, 118.86, 89.94, 78.73, 41.22, 40.97, 37.83, 31.78, 31.23, 26.14, 21.24, 17.25, -1.34\); HRMS (Cl) calcd for C\(_{16}\)H\(_{31}\)OSi [M+1]\(^+\) 267.21443, found 267.21369.

**5-69p** (colorless oil, 24%): IR (ATR diamond crystal, cm\(^{-1}\)) 3004, 2955, 2936, 2860, 1743, 1652, 1454, 1369, 1251, 1064, 968, 844, 695; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta 5.39-5.28 \text{ (m, 2H)}, 5.19 \text{ (s, 1H)}, 4.80 \text{ (s, 1H)}, 4.44 \text{ (td, } J = 8.72, 20.75 \text{ Hz, 2H)}, 2.09-1.95 \text{ (m, 4H)}, 1.54-1.46 \text{ (m, 4H)}, 1.36 \text{ (m, 4H)}, 0.95 \text{ (t, } J = 7.53 \text{ Hz, 3H)}, 0.03 \text{ (s, 9H); } ^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 137.61, 131.65, 129.14, 120.81, 86.90, 77.93, 36.60, 29.94, 27.12, 24.94, 20.52, 17.11, 14.41, -1.42\); HRMS (Cl) calcd for C\(_{16}\)H\(_{29}\)OSi [M-1]\(^+\) 265.19878, found 265.19907.

**5-68q** (colorless oil, 40%): IR (ATR diamond crystal, cm\(^{-1}\)) 3002, 2969, 2933, 2859, 1743, 1450, 1369, 1450, 1216, 1128, 1073, 832, 754, 692; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta 5.39-5.28 \text{ (m, 2H)}, 4.55 \text{ (q, } J = 15.78 \text{ Hz, 2H)}, 3.52 \text{ (se, } J = 6.0 \text{ Hz, 1H)}, 2.07-1.99 \text{ (m, 4H)}, 1.63-1.56 \text{ (m, 1H)}, 1.47-1.28 \text{ (m, 5H)}, 1.16 \text{ (d, } J = 6.1 \text{ Hz, 3H)}, 0.95 \text{ (t, } J = 7.6 \text{ Hz, 3H)}, 0.88 \text{ (s, 3H)}, 0.18 \text{ (s, 9H); } ^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 141.71, 134.48, 128.36, 125.97, 106.31, 33.56, 30.48, 6.56, -1.35\); HRMS (Cl) calcd for C\(_{17}\)H\(_{31}\)OSi [M-1]\(^+\) 279.2144, found 279.2148.
5-69q (colorless oil, 13%): IR (ATR diamond crystal, cm⁻¹): 3008, 2966, 2933, 2862, 1739, 1447, 1369, 1216, 1050, 846, 692; ¹H NMR (CDCl₃, 500 MHz) δ 5.55-5.23 (m, 2H), 5.10 (s, 1H), 4.48-4.38 (m, 2H), 2.02 (m, 4H), 1.54-1.46 (m, 4H), 1.37-1.27 (m, 4H), 1.24 (s, 3H), 0.95 (t, J = 7.51 Hz, 3H), 0.04 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 136.44, 131.57, 129.24, 124.95, 90.97, 77.62, 41.49, 30.29, 27.19, 27.10, 24.40, 20.51, 16.98, 14.41, -1.40; HRMS (CI) calcd for C₁₇H₃₁OSi [M-1]⁺ 279.2144, found 279.2146.

5-68r (colorless oil, 57%): IR (ATR diamond crystal, cm⁻¹) 2966, 2952, 1739, 1652, 1447, 1366, 1249, 1066, 969, 843, 748, 689; ¹H NMR (CDCl₃, 500 MHz) δ 7.28 (dd, J = 4.88, 12.40 Hz, 2H), 7.19 (dd, J = 2.57, 7.91 Hz, 3H), 4.62 (d, J = 15.68 Hz, 1H), 4.52 (d, J = 15.68 Hz, 1H), 3.56 (dd, J = 6.09, 12.12 Hz, 1H), 2.79-2.65 (m, 2H), 1.96-1.85 (m, 1H), 1.80-1.71 (m, 1H), 1.22 (d, J = 6.12 Hz, 3H), 0.90 (s, 2H), 0.20 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 142.41, 131.75, 128.44, 128.35, 125.72, 108.62, 74.47, 65.43, 38.44, 31.75, 19.45, 6.89, -1.41; HRMS (CI) calcd for C₁₇H₂₅OSi [M-1]⁺ 273.1675, found 273.1669.

5-68s (colorless oil, 41%): IR (ATR diamond crystal, cm⁻¹) 2956, 2904, 1678, 1469, 1447, 1366, 1245, 1076, 836, 758, 703; ¹H NMR (CDCl₃, 500 MHz) δ 4.57 (q, J = 15.62 Hz, 2H), 3.74 (td, J = 9.06, 4.52 Hz, 1H), 2.46-2.36 (m, 1H), 2.36-2.28 (m, 1H), 2.13-2.05 (m, 1H), 1.94 (tt, J = 3.10, 5.81 Hz, 1H), 1.88-1.81 (m, 1H), 1.79 (dt, J = 1.97, 5.91 Hz, 1H), 1.21 (s, 3H), 1.11 (d, J = 7.41 Hz, 3H), 0.92 (s, 2H), 0.90 (s, 3H), 0.19 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 131.92, 109.02, 78.39, 65.46, 47.69, 44.47, 41.42, 38.42, 35.60, 33.28, 27.54, 23.76, 21.52, 6.99, -1.39; HRMS (CI) calcd for C₁₇H₂₅OSi [M-1]⁺ 277.19878, found 277.19812.

5-69s (colorless oil, 28%): IR (ATR diamond crystal, cm⁻¹) 2952, 2904, 1739, 1656, 1450, 1369, 1249, 1216, 1154, 1047, 839, 787, 696; ¹H NMR (CDCl₃, 500 MHz) δ 5.32 (s, 1H), 4.37 (s, 2H), 2.38 (dq, J = 2.62, 7.91 Hz, 1H), 2.29-2.20 (m, 1H), 2.14 (dd, J = 3.80, 14.86 Hz, 1H), 2.06-2.01 (m, 1H), 1.87-1.81 (m, 1H), 1.58 (d, J = 13.95 Hz, 1H), 1.54-
1.47 (m, 2H), 1.20 (s, 3H), 1.01 (d, J = 8.01 Hz, 3H), 0.90 (s, 3H), 0.05 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 136.08, 125.24, 90.95, 75.84, 48.69, 46.92, 41.97, 40.14, 37.98, 29.34, 27.60, 22.90, 18.12, 17.03, -1.36; HRMS (CI) calcd for C\(_{17}\)H\(_{29}\)OSi [M-1]\(^+\) 277.1988, found 277.1982.

7.3. PtCl\(_2\)-catalyzed rearrangement of cyclopropenes to allenes

7.3.1. Representative procedure

![Catalyst diagram](attachment:reaction_diagram.png)

To silylated cyclopropene 6-101 (39 mg, 0.18 mmol) in CH\(_2\)Cl\(_2\) (0.5 mL) was added PtCl\(_2\) (5 mol%, 2.4 mg). The resulting yellow suspension was stirred in 50 °C sand bath for 10 hours, at which point TLC indicated the consumption of the starting material. The suspension was filtrated through a plug of silica gel to remove the solid. The filtrate was concentrated to afford the crude product, which was purified by column chromatography with hexane to give the desired allene product 6-102 (colorless oil, 37 mg, 95% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 3064, 3028, 2955, 2903, 1930, 1251, 830, 813, 751, 702; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.29 (t, J = 7.44 Hz, 2H), 7.20 (m, 3H), 4.40 (t, J = 3.38 Hz, 2H), 2.81–2.74 (m, 2H), 2.28–2.19 (m, 2H), 0.11 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 208.36, 142.52, 128.50, 128.40, 125.79, 94.41, 69.60, 35.42, 30.61, –1.69; HRMS (EI) calcd for C\(_{14}\)H\(_{20}\)Si [M]\(^+\) 216.1334, found 216.1340.

7.3.2. Characterization data

![Characterized compound](attachment:characterization.png)

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 2956, 2921, 2852, 1801, 1457, 1249, 1102, 839, 741, 696; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.41–7.33 (m, 4H), 7.29 (m, 1H), 4.58–4.47 (m, 1H), 3.46 (m, J = 9.8, 5.1 Hz, 1H), 3.27 (dd, J = 9.7, 5.5 Hz, 1H), 2.57 (t, J = 6.9 Hz, 2H), 1.68–1.57 (m, 3H), 1.36 (m, 7H), 0.93 (t, J = 6.8 Hz, 3H), 0.20 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 139.57, 139.22, 128.28, 127.62, 127.29, 110.83, 79.09, 72.40, 31.71, 29.10,
28.15, 27.49, 22.70, 19.34, 14.16, -0.94. HRMS (EI) calcd for C_{20}H_{31}OSi [M-1]^+ 315.2144, found 315.2133.

Colorless oil (74% yield): IR (ATR diamond crystal, cm\(^{-1}\)) 2952, 2926, 2855, 1931, 1454, 1249, 1090, 836, 732, 689; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.39-7.31 (m, 4H), 7.31-7.24 (m, 1H), 5.00 (m, 1H), 4.55 (q, \(J = 11.7\) Hz, 2H), 4.06 (dq, \(J = 11.3, 7.2\) Hz, 2H), 2.07-1.90 (m, 2H), 1.47 (m, 2H), 1.32 (m, 6H), 0.89 (t, \(J = 6.7\) Hz, 3H), 0.11 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 205.56, 138.65, 128.36, 127.73, 127.48, 97.29, 83.24, 71.35, 69.17, 31.78, 29.26, 29.08, 22.71, 14.13, -1.41. HRMS (EI) calcd for C_{20}H_{32}OSi [M]^+ 316.2222, found 316.2231.

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3021, 2959, 2874, 1775, 1603, 1496, 1450, 1024, 744, 692; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.32 (t, \(J = 7.47\) Hz, 2H), 7.24 (m, 3H), 6.50 (s, 1H), 2.94 (t, \(J = 7.5\) Hz, 2H), 2.84 (t, \(J = 7.6\) Hz, 2H), 0.96 (d, \(J = 1.7\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 141.60, 128.45, 128.39, 126.04, 120.01, 98.76, 33.35, 28.71, 5.49. HRMS (EI) calcd for C_{11}H_{11} [M-1]^+ 143.0861, found 143.0855.

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 2923, 2857, 1730, 1454, 1362, 1238, 1093, 1073, 1024, 725, 692; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.41-7.31 (m, 4H), 7.30-7.27 (m, 1H), 6.63 (s, 1H), 4.52 (s, 2H), 3.37 (ddd, \(J = 29.83, 9.84, 5.10\) Hz, 2H), 2.47 (t, \(J = 7.1\) Hz, 2H), 1.71 (dt, \(J = 5.1, 1.4\) Hz, 1H), 1.56 (m, 2H), 1.40-1.22 (m, 5H), 0.89 (t, \(J = 6.7\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 138.97, 128.29, 127.66, 127.37, 125.53, 102.43, 78.12, 72.46, 31.60, 29.94, 27.12, 26.32, 22.58, 17.84, 14.07. HRMS (EI) calcd for C_{11}H_{23}O [M]^+ 244.1827, found 244.1844.

Colorless oil: IR (ATR diamond crystal, cm\(^{-1}\)) 3029, 2958, 2874, 1795, 1495, 1248, 993, 833, 749, 695; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.35–7.29 (m, 2H), 7.24 (m, 3H),
3.89 (s, 2H), 0.87 (s, 2H), 0.05 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 138.49, 134.37, 128.83, 128.41, 126.32, 106.90, 35.21, 7.27, −1.46; HRMS (EI) calcd for C$_{13}$H$_{18}$Si [M]$^+$ 202.1178, found 202.1168.

Colorless oil (93% yield): IR (ATR diamond crystal, cm$^{-1}$) 3063, 3031, 2956, 2898, 1926, 1255, 846, 817, 699; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.28 (t, $J$ = 7.5 Hz, 2H), 7.19 (m, 3H), 4.33 (t, $J$ = 2.6 Hz, 2H), 3.34 (t, $J$ = 2.4 Hz, 2H), 0.03 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 209.88, 140.56, 128.94, 128.08, 126.03, 94.49, 68.86, 36.28, −1.50; HRMS (EI) calcd for C$_{13}$H$_{17}$Si [M−1]$^+$ 201.1100, found 201.1088.

Colorless oil: IR (ATR diamond crystal, cm$^{-1}$) 2956, 2926, 2871, 2859, 1795, 1464, 1246, 839; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.54 (t, $J$ = 7.2 Hz, 2H), 1.59 (qn, $J$ = 7.2 Hz, 2H), 1.38−1.21 (m, 8H), 0.89 (t, $J$ = 6.8 Hz, 3H), 0.73 (s, 2H), 0.16 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 135.37, 104.93, 31.89, 29.35, 29.15, 28.55, 27.32, 22.69, 14.11, 6.25, −1.31. HRMS (EI) calcd for C$_{13}$H$_{26}$Si [M]$^+$ 210.1804, found 210.1785.

Colorless oil (95% yield): IR (ATR diamond crystal, cm$^{-1}$) 2963, 2924, 2859, 1926, 1252, 839, 810; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 4.32 (t, $J$ = 3.2 Hz, 2H), 1.93 (m, 2H), 1.44 (qn, $J$ = 7.0 Hz, 2H), 1.29 (m, 8H), 0.88 (t, $J$ = 6.7 Hz, 3H), 0.09 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 208.29, 94.63, 88.70, 31.92, 29.40, 29.20, 29.11, 28.80, 22.70, 14.13, −1.62. HRMS (EI) calcd for C$_{13}$H$_{26}$Si [M]$^+$ 210.1804, found 210.1787.

Colorless oil: IR (ATR diamond crystal, cm$^{-1}$) 2962, 2917, 2873, 1794, 1248, 991, 835; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.18 (dd, $J$ = 6.9, 6.0 Hz, 1H), 5.11 (t, $J$ = 6.8 Hz, 1H), 2.59 (t, $J$ = 7.5 Hz, 2H), 2.29 (q, $J$ = 7.2 Hz, 2H), 2.08 (m, 2H), 2.02−1.97 (m, 2H), 1.69 (s, 3H), 1.62 (d, $J$ = 7.4 Hz, 6H), 0.76 (s, 2H), 0.17 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 135.62, 135.13, 131.32, 124.35, 123.70, 105.56, 39.73, 28.95, 26.76, 25.91, 25.71, 17.69, 16.08, 6.48, −1.30; HRMS (EI) calcd for C$_{17}$H$_{30}$Si [M]$^+$ 262.2117, found 262.2126.
Colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.17 (s, 1H), 2.62 (q, $J = 6.1$ Hz, 2H), 2.51 (m, 1H), 2.20 (td, $J = 8.8, 5.6$ Hz, 1H), 1.98 (d, $J = 4.3$ Hz, 2H), 1.68 (s, 3H), 1.30 (s, 3H), 1.18 (d, $J = 8.8$ Hz, 1H), 0.89 (s, Hz, 3H), 0.74 (s, 2H), 0.17 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 145.02, 134.33, 120.21, 105.28, 47.79, 45.11, 40.83, 38.67, 32.63, 27.95, 26.54, 22.93, 20.53, 6.37, −1.29; HRMS (EI) calcd for C$_{17}$H$_{28}$Si [M]$^+$ 260.1960, found 260.1949.

Colorless oil (68% yield): IR (ATR diamond crystal, cm$^{-1}$) 2979, 2947, 2917, 1926, 1249, 846, 817, 754; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.17 (s, 1H), 4.32 (t, $J = 3.0$ Hz, 2H), 2.52–2.40 (m, 1H), 2.16 (td, $J = 8.8, 5.6$ Hz, 1H), 2.08–2.00 (m, 1H), 1.97 (m, 2H), 1.92–1.82 (m, 1H), 1.66 (s, 3H), 1.28 (s, 3H), 1.14 (d, $J = 8.7$ Hz, 1H), 0.85 (s, 3H), 0.09 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 208.50, 144.55, 120.66, 93.04, 68.70, 47.87, 44.91, 39.51, 32.36, 27.94, 26.63, 22.95, 20.50, −1.60; HRMS (EI) calcd for C$_{17}$H$_{28}$Si [M]$^+$ 260.1956, found 260.1956.

Colorless oil: IR (ATR diamond crystal, cm$^{-1}$) 3081, 2962, 2916, 2873, 1792, 1448, 1248, 889, 834, 755; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.52–5.41 (m, 1H), 4.74–4.65 (m, 2H), 2.84 (m, 1H), 2.58 (m, 1H), 2.50 (s, 1H), 2.24–2.13 (m, 1H), 2.06 (d, 1H), 1.94–1.80 (m, 2H), 1.72 (s, 3H), 1.71 (s, 3H), 1.28 (m, 1H), 0.72 (s, 2H), 0.16 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 150.10, 136.80, 133.59, 123.16, 108.44, 106.19, 77.27, 77.02, 76.76, 41.63, 38.72, 35.26, 32.36, 31.30, 31.17, 21.17, 20.70, 6.43, −1.36; HRMS (EI) calcd for C$_{17}$H$_{28}$Si [M$+1]^+$ 261.2039, found 261.2057.

Colorless oil (92% yield): IR (ATR diamond crystal, cm$^{-1}$) 3077, 2959, 2911, 2855, 1926, 1252, 888, 843, 813, 751; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 5.46 (s, 1H), 4.70 (s, 2H), 4.33 (dd, $J = 3.7, 2.3$ Hz, 2H), 2.44 (m, 1H), 2.33 (d, $J = 3.3$ Hz, 1H), 2.13 (t, $J = 10.8$ Hz, 1H), 2.03 (m, 2H), 1.94–1.82 (m, 1H), 1.73 (s, 3H), 1.72–1.69 (m, 1H), 1.68 (s, 3H), 1.11 (m, 1H), 0.11 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 208.44, 150.43, 136.52, 122.99, 108.28, 92.83, 68.94, 41.63, 39.62, 35.44, 31.36, 21.38, 20.82, −1.54; HRMS (EI) calcd for C$_{17}$H$_{28}$Si [M$+1]^+$ 260.1960, found 260.1964.
Colorless oil: IR (ATR diamond crystal, cm⁻¹) 2956, 2930, 2874, 1795, 1249, 992, 832, 761; ¹H NMR (CDCl₃, 500 MHz) δ 5.31 (s, 1H), 2.51 (d, J = 6.8 Hz, 2H), 2.40 (s, 1H), 1.89 (s, 2H), 1.78–1.70 (m, 2H), 1.65 (s, 3H), 1.60–1.48 (m, 2H), 1.19 (m, 1H), 0.73 (s, 2H), 0.17 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 134.42, 134.09, 125.60, 105.71, 35.32, 34.16, 30.18, 28.99, 23.89, 21.72, 6.28, –1.34; HRMS (EI) calcd for C₁₄H₂₄Si [M]⁺ 220.1647, found 220.1642.

Colorless oil (78% yield): IR (ATR diamond crystal, cm⁻¹) 2956, 2917, 2859, 1926, 1441, 1249, 832, 806, 754; ¹H NMR (CDCl₃, 500 MHz) δ 5.33 (s, 1H), 4.33 (t, J = 3.0 Hz, 2H), 2.25 (s, 1H), 1.95–1.83 (m, 4H), 1.80–1.69 (m, 2H), 1.65 (s, 3H), 1.57–1.45 (m, 1H), 1.18–1.09 (m, 1H), 0.10 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 208.53, 134.17, 126.03, 92.89, 68.62, 35.60, 34.99, 30.37, 28.90, 23.96, 21.72, –1.61.

Colorless oil: IR (ATR diamond crystal, cm⁻¹) 2952, 2911, 2871, 1789, 1252, 839, 754; ¹H NMR (CDCl₃, 500 MHz) δ 2.90–2.86 (m, 2H), 2.80 (m, 1H), 2.68 (m, 1H), 2.35–2.25 (m, 1H), 2.07–1.99 (m, 1H), 1.98–1.92 (m, 1H), 1.69 (s, 3H), 1.68 (m, 1H), 1.60 (s 3H), 1.37 (d, J = 10.0 Hz, 1H), 1.26 (s, 3H), 0.77 (m, 2H), 0.64 (s, 3H), 0.19 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 137.95, 134.67, 122.82, 105.69, 45.98, 41.23, 41.02, 40.30, 31.65, 30.69, 26.87, 26.15, 21.27, 20.44, 19.76, 6.55, –1.25; HRMS (EI) calcd for C₁₉H₃₂Si [M]⁺ 288.2273, found 288.2254.

Colorless oil: IR (ATR diamond crystal, cm⁻¹) 3005, 2952, 2929, 2876, 1799, 1244, 844, 758; ¹H NMR (CDCl₃, 500 MHz) δ 5.42–5.28 (m, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.05 (m, 4H), 1.61 (qn, J = 7.3 Hz, 2H), 1.45–1.36 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H), 0.73 (s, 2H), 0.16 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 135.18, 131.79, 128.95, 105.06, 77.27, 77.02, 76.76, 29.44, 28.43, 26.93, 20.55, 14.40, 6.27, –1.31; HRMS (EI) calcd for C₁₄H₂₆Si [M]⁺ 222.1804, found 222.1818.
Colorless oil (87% yield): IR (ATR diamond crystal, cm⁻¹) 3002, 2959, 2930, 2855, 1928, 1249, 832, 810, 751; ¹H NMR (CDCl₃, 500 MHz) δ 5.44–5.24 (m, 2H), 4.32 (t, J = 3.2 Hz, 2H), 2.09–1.98 (m, 4H), 1.97–1.89 (m, 2H), 1.51–1.42 (m, 2H), 1.38 (qn, J = 7.0 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H), 0.09 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 208.30, 131.66, 129.19, 94.51, 68.80, 29.49, 28.69, 29.15, 14.42, −1.61; HRMS (EI) calcd for C₁₄H₂₆Si [M]⁺ 222.1804, found 222.1791.

Colorless oil (74% yield): IR (ATR diamond crystal, cm⁻¹) 2955, 2920, 2850, 1924, 1248, 837, 800, 755; ¹H NMR (CDCl₃, 500 MHz) δ 5.11 (tt, J = 7.1, 1.3 Hz, 1H), 4.30 (td, J = 2.9, 0.9 Hz, 2H), 2.06–1.89 (m, 3H), 1.80–1.71 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.40 (dddd, J = 13.4, 9.8, 6.3, 5.2 Hz, 1H), 1.26 (s, 1H), 1.14 (dddd, J = 13.5, 9.5, 8.0, 5.8 Hz, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.09 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 208.69, 131.05, 125.01, 93.25, 68.24, 36.98, 36.78, 32.34, 25.74, 25.60, 19.74, 17.66, −1.55; HRMS (EI) calcd for C₁₅H₂₈Si [M]⁺ 236.1960, found 236.1955.

Colorless oil: IR (ATR diamond crystal, cm⁻¹) 3307, 2959, 2897, 2873, 1796, 1254, 991, 830, 755, 627; ¹H NMR (CDCl₃, 500 MHz) δ 2.67 (t, J = 7.2 Hz, 2H), 2.24 (dt, J = 7.1, 2.6 Hz, 2H), 1.96 (t, J = 2.6 Hz, 1H), 1.83 (qn, J = 7.2 Hz, 2H), 0.73 (s, 2H), 0.16 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 134.08, 106.14, 84.02, 77.27, 77.02, 76.76, 68.56, 27.45, 26.22, 18.03, 6.21, −1.35; HRMS (EI) calcd for C₁₁H₁₇Si [M-1]⁺ 177.1100, found 177.1095.

Colorless oil: IR (ATR diamond crystal, cm⁻¹) 2955, 2904, 2874, 2172, 1795, 1245, 1044, 1010, 839, 749, 719; ¹H NMR (CDCl₃, 500 MHz) δ 2.67 (t, J = 7.2 Hz, 2H), 2.29 (t, J = 7.1 Hz, 2H), 1.82 (dd, J = 7.1, 7.12 Hz, 2H), 0.98 (t, J = 7.9 Hz, 9H), 0.73 (s, 2H), 0.57 (q, J = 7.9 Hz, 6H), 0.16 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 134.31, 108.00,
106.00, 81.99, 27.45, 26.55, 19.50, 7.51, 6.25, 4.57, -1.33; HRMS (EI) calcd for $C_{17}H_{32}Si_2 [M]^+$ 292.2043, found 292.2026.

Colorless oil (85% yield): IR (ATR diamond crystal, cm$^{-1}$) 2950, 2911, 2878, 2172, 1928, 1242, 843, 817, 718; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 4.34 (t, $J = 3.2$ Hz, 2H), 2.29 (t, $J = 6.9$ Hz, 2H), 2.13–2.04 (tt, $J = 3.2$, 6.9 Hz, 2H), 1.73–1.65 (qn, $J = 7.2$ Hz, 2H), 0.98 (t, $J = 7.9$ Hz, 9H), 0.57 (q, $J = 7.9$ Hz, 6H), 0.10 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 208.24, 108.39, 93.96, 81.79, 69.17, 27.99, 27.48, 19.49, 7.50, 4.60, -1.70; HRMS (EI) calcd for $C_{17}H_{32}Si_2 [M]^+$ 292.2043, found 292.2026.

Colorless oil: IR (ATR diamond crystal, cm$^{-1}$) 2956, 2874, 2852, 1798, 1675, 1249, 1096, 1080, 832; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.40–7.33 (m, 4H), 7.29 (m, 1H), 4.62 (s, 2H), 4.60 (s, 2H), 0.92 (s, 2H), 0.20 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 138.14, 131.02, 128.39, 127.74, 127.65, 109.04, 72.32, 67.18, 6.76, -1.44. HRMS (EI) calcd for $C_{14}H_{19}OSi [M-1]^+$ 231.1205, found 231.1215.

Colorless oil: IR (ATR diamond crystal, cm$^{-1}$) 2955, 2867, 1799, 1248, 1106, 994, 834, 755, 735, 695; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.35 (m, 4H), 7.32–7.27 (m, 1H), 4.55 (s, 2H), 3.73 (t, $J = 6.9$ Hz, 2H), 2.90 (t, $J = 6.9$ Hz, 2H), 0.76 (s, 2H), 0.17 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 138.39, 132.01, 128.40, 127.73, 127.61, 106.99, 73.02, 68.19, 29.36, 5.99, -1.39. HRMS (EI) calcd for $C_{15}H_{21}OSi [M-1]^+$ 245.1362, found 245.1349.

Colorless oil (74% yield): IR (ATR diamond crystal, cm$^{-1}$) 3064, 3031, 2955, 2857, 1928, 1248, 1093, 1024, 837, 741, 695; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.35 (m, 4H), 7.29 (m, 1H), 4.53 (s, 2H), 4.34 (t, $J = 3.2$ Hz, 1H), 3.60 (t, $J = 7.4$ Hz, 2H), 2.28 (tt,
$J = 7.1, 3.2 \text{ Hz, } 2\text{H}, 0.10 \text{ (s, } 9\text{H}); ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 208.45, 138.59, 128.36, 127.71, 127.52, 91.12, 73.00, 69.94, 69.06, 28.72, -1.74. \text{ HRMS (EI) calcd for } C_{13}H_{22}OSi [M]^+ 246.1440, \text{ found 246.1426.}$

Colorless oil (90% yield): IR (ATR diamond crystal, cm$^{-1}$) 3031, 2949, 2895, 2855, 1928, 1255, 1090, 1080, 966, 839, 820, 744, 692; $^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 7.39 \text{ (d, } J = 7.3 \text{ Hz, } 2\text{H}), 7.32 \text{ (t, } J = 7.6 \text{ Hz, } 2\text{H}), 7.24 \text{ (td, } J = 7.3, 1.3 \text{ Hz, } 1\text{H}), 6.52 \text{ (d, } J = 15.9 \text{ Hz, } 1\text{H}), 6.12 \text{ (dd, } J = 15.9, 7.5 \text{ Hz, } 1\text{H}), 4.33 \text{ (t, } J = 3.4 \text{ Hz, } 2\text{H}), 3.99 \text{ (q, } J = 6.5 \text{ Hz, } 1\text{H}), 3.54 \text{ (td, } J = 9.3, 6.7 \text{ Hz, } 1\text{H}), 3.39 \text{ (td, } J = 9.3, 6.6 \text{ Hz, } 1\text{H}), 2.02 \text{ (tt, } J = 8.9, 3.3 \text{ Hz, } 2\text{H}), 1.82-1.71 \text{ (m, } 2\text{H}), 1.33 \text{ (d, } J = 6.4 \text{ Hz, } 4\text{H}), 0.10 \text{ (s, } 9\text{H}); ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 208.18, 136.82, 132.28, 130.72, 128.58, 127.57, 126.46, 94.22, 69.31, 67.93, 29.21, 25.11, 21.73, -1.66; \text{ HRMS (EI) calcd for } C_{19}H_{28}OSi [M]^+ 300.1909, \text{ found 300.1926.}$

Colorless oil (81% yield): IR (ATR diamond crystal, cm$^{-1}$) 3031, 2949, 2895, 2855, 1928, 1255, 1090, 1080, 966, 839, 820, 744, 692; $^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 7.38-7.31 \text{ (m, } 4\text{H}), 7.30-7.25 \text{ (m, } 1\text{H}), 4.58 \text{ (d, } J = 11.8 \text{ Hz, } 1\text{H}), 4.47 \text{ (d, } J = 11.8 \text{ Hz, } 1\text{H}), 4.34 \text{ (t, } J = 3.34 \text{ Hz, } 2\text{H}), 3.63-3.55 \text{ (m, } 1\text{H}), 2.15-1.94 \text{ (m, } 2\text{H}), 1.79 \text{ (m, } 1\text{H}), 1.64 \text{ (td, } J = 14.87, 9.52, 5.74 \text{ Hz, } 1\text{H}), 1.22 \text{ (d, } J = 6.13 \text{ Hz, } 3\text{H}), 0.11 \text{ (s, } 9\text{H}); ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 208.17, 139.19, 128.32, 127.68, 127.39, 94.40, 74.42, 70.40, 69.31, 35.72, 24.42, 19.64, -1.64; \text{ HRMS (EI) calcd for } C_{17}H_{26}OSi [M]^+ 274.1753, \text{ found 274.1772.}$

Colorless oil (82% yield): IR (ATR diamond crystal, cm$^{-1}$) 3008, 2956, 2924, 2859, 1928, 1249, 1099, 836, 817, 696; $^1\text{H NMR (CDCl}_3, 500 \text{ MHz}) 7.34 \text{ (d, } J = 4.2 \text{ Hz, } 4\text{H}), 7.30-7.27 \text{ (m, } 1\text{H}), 4.50 \text{ (d, } J = 2.4 \text{ Hz, } 2\text{H}), 4.31 \text{ (t, } J = 3.1 \text{ Hz, } 2\text{H}), 3.51 \text{ (m, } 2\text{H}), 2.05-1.87 \text{ (m, } 2\text{H}), 1.75-1.58 \text{ (m, } 1\text{H}), 1.52-1.38 \text{ (m, } 2\text{H}), 1.36-1.23 \text{ (m, } 2\text{H}), 0.90 \text{ (d, } J = 6.5 \text{ Hz, } 3\text{H}), 0.09 \text{ (s, } 9\text{H}); ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 208.27, 138.74, 128.36, 127.83, 127.48, 94.69, 72.94, 68.97,
68.80, 36.73, 36.41, 29.74, 26.15, 19.64, −1.60; HRMS (EI) calcd for C_{19}H_{30}OSi [M]^+ 302.2066, found 302.2081.

7.3.3. PtCl₂-catalyzed Isomerization of Cyclopropene 6-113 to Indene 6-115

To cyclopropene 6-113 (15 mg, 0.053 mmol) in CH₂Cl₂ (0.2 mL) was added PtCl₂ (5 mol%, 0.8 mg). The resulting yellow suspension was stirred at 50 °C (sand bath) for 2 hours, at which point TLC indicated the consumption of the starting material. The suspension was filtrated through a plug of silica gel to remove the solid. The filtrate was concentrated to afford the pure indene product 6-115.

\[
\text{White solid: } \text{IR (ATR diamond crystal, cm}^{-1}\text{)} 3057, 3025, 2952, 1792, 1594, 1248, 836, 794; \text{ } ^1\text{H NMR (CDCl}_3\text{, 500 MHz) } \delta 7.26 (t, J = 7.6 \text{ Hz, 4H}), 7.17–7.11 (m, 6H), 2.31 (s, 3H), 0.18 (s, 9H); \text{ } ^{13}\text{C NMR (CDCl}_3\text{, 125 MHz) } \delta 147.95, 132.93, 128.06, 127.93, 124.91, 114.39, 35.86, 11.09, −0.42; \text{HRMS (EI) calcd for C}_{19}\text{H}_{22}\text{Si [M]^+ 278.1491, found 278.1500.}
\]

\[
\text{White solid (99% yield): } \text{IR (ATR diamond crystal, cm}^{-1}\text{)} 3054, 2959, 2911, 1454, 1246, 826, 758, 692; \text{ } ^1\text{H NMR (CDCl}_3\text{, 500 MHz) } \delta 7.45 (d, J = 7.6 \text{ Hz, 1H}), 7.31–7.25 (m, 2H), 7.22 (t, J = 7.3 \text{ Hz, 2H}), 7.12 (d, J = 7.3 \text{ Hz, 1H}), 7.04 (t, J = 7.4 \text{ Hz, 1H}), 7.00 (d, J = 7.5 \text{ Hz, 2H}), 4.31 (s, 1H), 1.99 (s, 3H), 0.41 (s, 9H); \text{ } ^{13}\text{C NMR (CDCl}_3\text{, 125 MHz) } \delta 159.23, 149.03, 148.74, 140.27, 135.84, 128.68, 128.38, 126.66, 126.49, 123.89, 123.66, 121.34, 62.65, 15.99, 0.71; \text{HRMS (EI) calcd for C}_{19}\text{H}_{22}\text{Si [M]^+ 278.1491, found 278.1481.}
\]
7.3.4. A three-step procedure from aldehyde 6-125 to allene 6-102

In a fume hood, a vial equipped with a Teflon-coated stir bar was charged with hydrocinnamaldehyde 6-125 (285 mg, 2.12 mmol) and 2 mL of anhydrous dichloromethane. Trimethylsilyl diazomethane (2.0 M in diethyl ether, 1.25 mL, 2.5 mmol) was added by syringe at room temperature followed by InCl₃ (9.4 mg, 0.04 mmol) added at once and vigorous bubbling was observed. The reaction was stirred in the air at room temperature for 10 to 20 min, at which point TLC indicated the consumption of the starting material. Dichloromethane and the excess amount of trimethylsilyldiazomethane were removed under reduced pressure and the crude α-TMS ketone was subjected to the cyclopropenation step without further purification. To a cooled (-78 °C) solution of TMS diazomethane (2.0 M in diethyl ether, 1.25 mL, 2.5 mmol) in THF (5 mL) was added n-BuLi (2.5 M in hexane, 1.1 mL) dropwise under N₂ atmosphere. After the mixture was stirred at -78 °C for 30 minutes, a solution of the crude α-TMS ketone in THF (2.0 mL) was added into the mixture dropwise. Then the reaction was stirred at -78 °C for 30 minutes. The reaction mixture was warmed up to room temperature by removing dry ice-acetone bath and quenched by adding several drops of an aqueous saturated NH₄Cl solution and the mixture was directly dried over MgSO₄, filtered through a short plug of silica gel, washed by diethyl ether and hexanes and concentrated under reduced pressure to afford the crude oil, which was subjected to the allene formation step without further purification.

To the crude silylated cyclopropene in CH₂Cl₂ (1 mL) was added PtCl₂ (5 mol%, 28 mg). The resulting yellow suspension was stirred in 50 °C sand bath for 10 hours, at which point TLC indicated the consumption of the starting material. The suspension was filtrated through a plug of silica gel to remove the solid. The filtrate was concentrated to afford the crude product, which was purified by column chromatography with hexane to give the desired allene product 6-102 (colorless oil, 261 mg, 1.21 mmol, 57% yield).
7.3.5. Experiment for stereospecificity study

Scheme 7.6

Following Fox’s protocol\textsuperscript{85}, chiral (S)-cyclopropene 7-16 was synthesized from the resolution of cyclopropene 3-carboxylic acid 7-12 via diastereomeric N-acyloxazolidines prepared from enantiomerically pure (S)-benzyloxazolidinone. After protection with TBDMS group, cyclopropene 7-16 was treated with tert-butyl lithium in THF at -78 °C followed by quenching with TMSCl to provide silylated cyclopropene 6-126. Under standard PtCl\textsubscript{2}-catalyzed condition, cyclopropene 6-126 was converted the corresponding allene 6-127.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) δ 6.30 (d, J = 1.2 Hz, 1H), 2.49 (t, J = 7.3 Hz, 2H), 2.10 (d, J = 1.3 Hz, 1H), 1.58 (tqt, J = 13.8, 6.9, 6.2 Hz, 2H), 1.39-1.30 (m, 2H), 1.30-1.23 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) δ 183.50, 115.24, 93.45, 31.46, 28.79, 26.56, 24.93, 22.52, 19.52, 14.01.
1H NMR (CDCl₃, 500 MHz) δ 7.30 (t, J = 7.3 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.19 (d, J = 7.2 Hz, 2H), 6.29 (d, J = 1.0 Hz, 1H), 4.65 (dq, J = 7.3, 3.1 Hz, 1H), 4.22-4.09 (m, 2H), 3.45 (s, 1H), 3.28 (dd, J = 13.3, 3.0 Hz, 1H), 2.75 (dd, J = 13.3, 9.7 Hz, 1H), 2.57-2.43 (m, 2H), 1.66-1.52 (m, 2H), 1.40-1.15 (m, 7H), 0.87 (t, J = 6.8 Hz, 3H); 13C NMR (CDCl₃, 125 MHz) δ 177.01, 154.02, 135.64, 129.47, 128.90, 127.22, 114.21, 92.23, 66.31, 55.67, 38.04, 31.49, 28.82, 26.77, 24.93, 22.55, 20.03, 14.07.

1H NMR (CDCl₃, 500 MHz) δ 3.43 (m, 2H), 2.52 (t, J = 7.3 Hz, 2H), 1.65-1.52 (m, 2H), 1.50 (t, J = 5.0 Hz, 1H), 1.33 (m, 6H), 0.90 (m, 12H), 0.15 (s, 9H), 0.03 (s, 6H); 13C NMR (CDCl₃, 125 MHz) δ 140.01, 111.21, 71.22, 31.69, 29.08, 28.10, 27.51, 26.08, 22.66, 22.12, 18.40, 14.11, -0.93, -5.08.

1H NMR (CDCl₃, 500 MHz) δ 5.01-4.88 (m, 1H), 4.20-4.07 (m, 2H), 2.01-1.89 (m, 2H), 1.48-1.38 (m, 2H), 1.36-1.21 (m, 6H), 0.94-0.84 (m, 12H), 0.08 (s, 9H), 0.07 (s, 6H); 13C NMR (CDCl₃, 125 MHz) δ 204.44, 97.76, 86.53, 62.20, 31.77, 29.30, 29.09, 25.98, 22.69, 18.39, 14.12, -1.42, -5.02, -5.07.

7.3.6. Gold-catalyzed cycloisomerization of cyclopropenes

1H NMR (CDCl₃, 500 MHz) δ 4.79 (s, 1H), 4.73 (s, 1H), 2.30-2.09 (m, 2H), 1.87-1.74 (m, 1H), 1.62-1.50 (m, 1H), 1.44-1.35 (m, 2H), 1.34-1.16 (m, 6H), 0.92-0.84 (m, 3H), 0.10 (m, 10H), 0.08-0.03 (m, 1H); 13C NMR (CDCl₃, 125 MHz) δ 157.96, 103.35, 34.67, 31.89, 31.74, 31.61, 30.29, 30.01, 26.91, 22.72, 14.12, 0.56.

1H NMR (CDCl₃, 500 MHz) δ 4.83 (d, J = 1.2 Hz, 1H), 4.78 (s, 1H), 2.59 (m, 1H), 2.19 (m, 1H), 1.96-1.83 (m, 1H), 1.61 (m, 2H), 1.41-1.18 (m, 8H), 1.16-1.05 (m, 1H), 0.96 (m, 1H), 0.88 (m, 3H), 0.07 (m, 1H), -0.01 (m, 10H); 13C NMR (CDCl₃, 125 MHz) δ 154.84,
105.26, 38.25, 31.93, 29.17, 27.62, 24.81, 23.03, 22.73, 14.12, -2.22.

\[ ^1\text{H NMR (CDCl}_3, 500 \text{ MHz)} \delta 4.74 \text{ (s, 1H)}, 4.69 \text{ (d, } J = 1.1 \text{ Hz, 1H)}, 2.29-2.10 \text{ (m, 3H)}, 2.10-1.95 \text{ (m, 2H)}, 1.67 \text{ (dt, } J = 13.0, 6.5 \text{ Hz, 1H)}, 1.59 \text{ (tdd, } J = 12.4, 10.0, 6.0 \text{ Hz, 1H)}, 1.38-1.24 \text{ (m, 1H)}, \]
\[ 1.04 \text{ (d, } J = 1.1 \text{ Hz, 3H)}, 1.02 \text{ (d, } J = 1.1 \text{ Hz, 3H)}, 0.99 \text{ (d, } J = 6.6 \text{ Hz, 3H)}, 0.15 \text{ (s, 9H)}; \]
\[ ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)} \delta 151.85, 106.37, 34.52, 33.68, 32.40, 31.89, 27.18, 21.93, 19.53, 0.20. \]

\[ ^1\text{H NMR (CDCl}_3, 500 \text{ MHz)} \delta 5.23 \text{ (s, 1H)}, 4.68 \text{ (s, 1H)}, 4.64 \text{ (s, 1H)}, 2.52 \text{ (dd, } J = 13.1, 4.4 \text{ Hz, 1H)}, 2.39 \text{ (d, } J = 8.4 \text{ Hz, 1H)}, 2.20-2.14 \text{ (m, 1H)}, 1.82 \text{ (dd, } J = 13.0, 10.5 \text{ Hz, 1H)}, 1.71 \text{ (s, 3H)}, 1.66-1.55 \text{ (m, 5H)}, 0.95 \text{ (d, } J = 6.6 \text{ Hz, 3H), 0.90 (m, 1H), 0.09 (s, 9H); \]
\[ ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)} \delta 158.76, 151.28, 125.28, 108.23, 47.20, 46.72, 44.16, 33.60, 33.41, 29.52, 23.05, 20.78, 0.39. \]

7.3.7. Experiment for the transformation from \(^{13}\text{C-labeled palmitaldehyde to allene 6-143}

\[
\begin{align*}
\text{CH}_3\big(CH_2\big)_{34}\text{O} & \quad \text{1. LiAlH}_4, \text{THF, rt} \quad \text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 \quad \text{2. DMP, CH}_2\text{Cl}_2 \quad (89\%) \quad \text{CH}_3\big(CH_2\big)_{34}\text{CH}\quad \text{1. InCl}_2(\text{cat}), N_2\text{CHTMS} \quad \text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 \quad \text{2. LiCl(N}_2\text{)TMS, THF, -78°C} \quad (58\%) \\
\text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 & \quad \text{CH}_3\big(CH_2\big)_{34}\text{O} \quad \text{1. LiAlH}_4, \text{THF, rt} \quad \text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 \quad \text{2. DMP, CH}_2\text{Cl}_2 \quad (89\%) \quad \text{CH}_3\big(CH_2\big)_{34}\text{CH}\quad \text{1. InCl}_2(\text{cat}), N_2\text{CHTMS} \quad \text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 \quad \text{2. LiCl(N}_2\text{)TMS, THF, -78°C} \quad (58\%) \\
\text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 & \quad \text{CH}_3\big(CH_2\big)_{34}\text{O} \quad \text{1. LiAlH}_4, \text{THF, rt} \quad \text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 \quad \text{2. DMP, CH}_2\text{Cl}_2 \quad (89\%) \quad \text{CH}_3\big(CH_2\big)_{34}\text{CH}\quad \text{1. InCl}_2(\text{cat}), N_2\text{CHTMS} \quad \text{CH}_3\big(CH_2\big)_{34}\text{SiMe}_3 \quad \text{2. LiCl(N}_2\text{)TMS, THF, -78°C} \quad (58\%) \\
\end{align*}
\]

Scheme 7.7

A solution of palmitic acid 6-140 (248 mg, 0.96 mmol) in dry THF (2 mL) was added dropwise to an ice-cooled and stirred suspension of LiAlH\(_4\) (57 mg, 1.50 mmol) in dry THF (3 mL). The mixture was
stirred at room temperature and monitored by TLC. Upon reaction completion, the reaction was quenched by slowly adding water (60 µL) then 10% sodium hydroxide solution (120 µL) followed by water (180 µL) mixture. The mixture was dried directly by anhydrous MgSO₄ and filtered through a pressed plug of Celite to give crude primary alcohol as a white solid; To a stirring solution of the crude alcohol in CH₂Cl₂ was added Dess-Martin periodinane (637 mg, 1.5 mmol) followed by addition of NaHCO₃ (378 mg, 4.5 mmol) at 0 °C. Then the ice-bath was removed and the reaction was stirred at room temperature and monitored by TLC. Upon reaction completion, diethyl ether and an aqueous solution containing Na₂S₂O₃ and NaHCO₃ were added. The resulting solution is stirred for 15 min. The organic phase is separated, dried (MgSO₄) and concentrated, giving a residue, which was further purified by column chromatography to give white ¹³C-labeled palmitaldehyde 6-141 (218 mg, 0.85 mmol, yield 89% in two steps). ¹H NMR (CDCl₃, 500 MHz) δ 9.72 (d, J = 169.70 Hz, 1H), 2.38 (dd, J = 13.3, 6.2 Hz, 2H), 1.66-1.53 (m, 2H), 1.25 (m, 24H), 0.85 (t, J = 6.8 Hz, 3H), ¹³C NMR (CDCl₃, 125 MHz) δ 202.63, 64.59, 44.03, 43.72, 31.92, 29.66, 29.58, 29.52, 29.43, 29.35, 29.15, 22.67, 22.07, 14.06.

In a fume hood, a vial equipped with a Teflon-coated stir bar was charged with ¹³C-labeling palmitaldehyde 6-141 (125 mg, 0.51 mmol) and 0.6 mL of anhydrous dichloromethane. Trimethylsilyl diazomethane (2.0 M in diethyl ether, 0.3 mL, 0.6 mmol) was added by syringe at room temperature followed by InCl₃ (2.2 mg, 0.01 mmol) added at once and vigorous bubbling was observed. The reaction was stirred in the air at room temperature for 10 to 20 min, at which point TLC indicated the consumption of the starting material. Dichloromethane and the excess amount of trimethylsilyldiazomethane were removed under reduced pressure and the crude α-TMS ketone was subjected to the cyclopropenation step without further purification. To a cooled (-78 °C) solution of TMS diazomethane (2.0 M in diethyl ether, 0.3 mL, 0.6 mmol) in THF (2 mL) was added n-BuLi (2.5 M in hexane, 0.26 mL) dropwise under N₂ atmosphere. After the mixture was stirred at -78 °C for 30 minutes, a solution of the crude α-TMS ketone in THF (1.0 mL) was added into the mixture dropwise. Then the reaction was stirred at -78 °C for 10 minutes. The reaction mixture was warmed up to room temperature by removing dry ice-acetone bath and quenched by adding several drops of an aqueous saturated NH₄Cl solution and the mixture was directly dried over MgSO₄, filtered through a short plug of
silica gel and concentrated under reduced pressure to afford the crude oil, which was purified by column chromatography to give 6-142 (96 mg, 0.30 mmol, yield 58% in two steps). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.54 (dd, $J = 15.95$, 7.37 Hz, 2H), 1.58 (qd, $J = 13.8$, 7.0 Hz, 2H), 1.29 (m, 24H), 0.89 (t, $J = 6.9$ Hz, 1H), 0.72 (d, $J = 2.2$ Hz, 2H), 0.16 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 135.37, 105.09, 104.70, 31.97, 29.73, 29.47, 29.40, 28.76, 28.32, 27.32, 27.73, 14.14, 6.30, 6.20–1.32; Compound 7-19: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 2.54 (t, $J = 7.2$ Hz, 2H), 1.53 (m, $J = 1.6$ Hz, 2H), 1.29 (m, 24H), 0.88 (t, $J = 6.8$ Hz, 3H), 0.72 (s, 2H), 0.16 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 135.38, 104.94, 31.97, 29.73, 29.47, 29.39, 28.55, 27.32, 22.73, 14.14, 6.26, -1.30.

To silylated cyclopropene 6-142 (49 mg, 0.15 mmol) in CH$_2$Cl$_2$ (0.3 mL) was added PtCl$_2$ (5 mol%, 2.0 mg). The resulting yellow suspension was stirred in 50 °C sand bath for 16 hours, at which point TLC indicated the consumption of the starting material. The suspension was filtrated through a plug of silica gel to remove the solid. The filtrate was concentrated to afford the crude product, which was purified by column chromatography with hexane to give the desired allene product 6-143 (colorless oil, 44 mg, 90% yield): $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 4.31 (m, 2H), 1.93 (s, 2H), 1.45 (s, 2H), 1.26 (m, 24H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.09 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 208.63, 207.93, 94.88, 94.64, 94.40, 88.72, 88.67, 31.96, 29.73, 29.53, 29.39, 29.12, 28.94, 28.65, 27.73, 14.14, -1.60; Compound 7-20: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 4.32 (d, $J = 2.6$ Hz, 2H), 2.01-1.88 (m, 2H), 1.50-1.40 (m, 2H), 1.26 (s, 24H), 0.88 (t, $J = 6.7$ Hz, 2H), 0.09 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 208.29, 94.64, 68.68, 31.94, 29.70, 29.68, 29.51, 29.42, 29.37, 29.09, 28.78, 22.70, 14.12, -1.64.

7.4. PtCl$_2$-catalyzed dimerization of 1-alkycyclopropene 3-carboxylates

![Scheme 7.8](image)

1-alkycyclopropene 3-carboxylates were prepared according to the following procedure: To a flame-dried flask was added a catalytic amount of [Rh$_2$(OAc)$_4$] (22.0 mg, 0.05 mmol, 1.0 mol %)
followed by dissolving it in CH₂Cl₂ (5.0 mL). And then alkyne solution (5 mmol) in CH₂Cl₂ (50 mL) was added. With stirring, ethyl 2-diazoacetate (0.7 g, 6 mmol) CH₂Cl₂ (20 mL) was added to the reaction flask through a syringe pump at a rate of 2.0 mL/h. Upon completion of addition, the reaction solution was passed through a plug of celite, and the solvent was removed under reduced pressure. The resulting solid material was purified by flash chromatography on to provide the desired cyclopropenes.

To a solution of 1-alkylcyclopropene 3-carboxylate 6-171 (104 mg, 0.4 mmol) in CH₂Cl₂ (1 mL) was added PtCl₂ (5 mol%, 5 mg). The resulting yellow suspension was stirred at 50 °C (sand bath) for 12 hours, at which point TLC indicated the consumption of the starting material. The suspension was filtrated through a plug of silica gel to remove the solid. The filtrate was concentrated to afford the crude product, which was purified by column chromatography to give a mixture of 6-172 and 6-173.

Colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.36-7.31 (m, 4H), 7.30-7.25 (m, 1H), 6.33 (s, 1H), 4.50 (s, 1H), 4.18-4.04 (m, 2H), 3.59-3.48 (m, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.13 (s, 1H), 1.90 (p, J = 6.7, 6.6 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 176.51, 138.45, 128.40, 127.65, 127.61, 115.12, 94.56, 72.99, 69.08, 60.21, 27.03, 21.92, 19.79, 14.42.

Colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.13 (d, J = 16.4 Hz, 1H), 7.39-7.27 (m, 10H), 6.54 (d, J = 16.4 Hz, 1H), 5.87 (s, 1H), 5.79 (s, 1H), 4.51 (d, J = 7.4 Hz, 4H), 4.16 (qd, J = 14.5, 7.26, 7.3 Hz, 4H), 3.58 (t, J = 6.7 Hz, 2H), 3.50 (p, J = 6.4 Hz, 2H), 2.99-2.92 (m, 2H), 2.53-2.46 (m, 2H), 1.93-1.77 (m, 4H), 1.28 (dt, J = 7.1, 1.8 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 166.28, 156.32, 153.29, 136.45, 130.12, 128.44, 128.38, 128.27, 127.64, 127.34, 121.67, 119.52, 73.03, 72.73, 70.36, 69.27, 60.02, 59.93, 30.57, 29.51, 29.30, 24.52, 14.33.

Colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.29 (t, J = 7.5 Hz, 2H), 7.21 (d, J = 7.2 Hz, 3H), 6.36 (s, 1H), 4.17-4.09 (m, 2H), 2.92 (t, J = 7.7 Hz, 2H), 2.86-2.80 (m, 2H), 2.15 (d, J = 1.2 Hz,
1H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 176.42, 140.71, 128.47, 128.34, 126.26, 114.94, 94.96, 60.24, 32.91, 26.78, 19.90, 14.41.

White solid: $^{1}$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.25 (d, $J = 16.4$ Hz, 1H), 7.38 (d, $J = 7.2$ Hz, 2H), 7.31 (td, $J = 13.0$, 7.5 Hz, 4H), 7.21 (qd, $J = 14.7$, 7.5, 7.4 Hz, 4H), 6.54 (d, $J = 16.4$ Hz, 1H), 5.91 (s, 1H), 5.81 (s, 1H), 4.27-4.15 (m, 4H), 3.17 (dd, $J = 9.8$, 6.8 Hz, 2H), 2.88-2.78 (m, 4H), 2.68 (dd, $J = 9.7$, 6.4 Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 166.20, 166.04, 155.60, 152.74, 141.82, 141.02, 136.10, 130.23, 128.78, 128.61, 128.48, 128.32, 126.35, 125.92, 121.97, 119.67, 60.11, 60.02, 35.92, 35.87, 35.53, 30.38, 14.37.

Colorless oil: $^{1}$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.34 (m, 4H), 7.31-7.25 (m, 1H), 6.44 (s, 1H), 4.52 (s, 2H), 4.18-4.02 (m, 2H), 3.73-3.64 (m, 2H), 2.88-2.75 (m, 2H), 2.17 (s, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 176.38, 138.12, 128.43, 127.70, 113.03, 95.73, 73.08, 67.08, 60.25, 25.98, 19.58, 14.40.

Colorless oil: $^{1}$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.19 (d, $J = 1.4$ Hz, 1H), 4.13-4.00 (m, 2H), 2.00 (d, $J = 1.4$ Hz, 1H), 1.85-1.76 (m, 1H), 1.20 (t, $J = 7.1$ Hz, 3H), 0.94-0.84 (m, 2H), 0.83-0.74 (m, 1H), 0.58 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 176.18, 117.50, 91.74, 60.13, 18.67, 14.35, 6.90, 5.95, 5.86.

Colorless oil: $^{1}$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.36-7.31 (m, 4H), 7.30-7.24 (m, 1H), 4.52 (s, 2H), 4.10 (dq, $J = 7.1$, 1.2 Hz, 2H), 3.71-3.61 (m, 2H), 2.72 (m, 2H), 2.06 (s, 1H), 2.04 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 176.66, 138.22, 128.41, 127.72, 127.66, 103.70, 103.61, 73.06, 67.48, 59.90, 25.42, 22.53, 14.46, 9.86.
Colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.52 (s, 1H), 4.72-4.56 (m, 2H), 4.18-4.04 (m, 2H), 2.31-2.21 (m, 1H), 1.29-1.17 (m, 3H), 0.91-0.87 (m, 9H), 0.08 (m, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 175.57, 114.71, 95.98, 60.26, 58.00, 25.84, 25.75, 20.65, 18.29, 14.34, 14.18, -5.29, -5.39.
CITED LITERATURE II


APPENDICES I: Selected NMR spectra

Et₃Si - - - - - - - -

2-84
(+)-Asperpentyn
(−)-Harveynone
(-)-Tricholomenyn A
2-125 (single isomer)
(+)-Panepophenanthenrin
(in CD$_3$OD)
3-11c (d.r. = 5:3)
3-14
3-22d
3-23b
3-24c
OMe

3-23e

ppm (f1)

ppm (f1)
OSiPh₂OPh

3-24h
3-23k
Ph
\[\text{OSiEt}_3\]

3-24k

ppm (f1)

ppm (f1)
3-24I-major
3-24n (dr 4.7:1)
\[ \text{3-29i, } \text{Ar} = 3,4\text{-dimethoxyphenyl} \]
3-29a, Ar = 2-methoxyphenyl
3-29p, Ar = 4-bromophenyl
3-37

ppm (f1)

ppm (f1)
Nitramine
3-103

ppm (H1)

ppm (F1)
3-110

OMe

Ph₂

ppm (f1)

10.0
5.0
0.0

ppm (f1)

200
150
100
50
0
3-116
3-119
3-168

ppm (f1)

ppm (f1)
3-198
5-68a
Me$_3$Si

5-68b
Me₃Si

5-68c

ppm (f1)
$\text{Me}_3\text{Si}$

$\text{SiMe}_3$

$5-68d$

$\text{ppm (f1)}$

$0.0$

$5.0$

$10.0$

$0$

$50$

$100$

$150$

$200$
H\text{\textsubscript{3}}\text{SiEt\textsubscript{3}}

5-67h
Me₃Si\(\text{O}\)\(\text{Ph}\)

5-68m

ppm (f1)
Me₃Si
5-68n
Me₃Si

5-69n

ppm (f1)

ppm (f1)
SiMe₃

5-69o

ppm (f1)

ppm (f1)
Me₃Si

5-69p

ppm (f1)

ppm (f1)
7-9
SiMe$_3$
6-121f

ppm (H)
6-126, 99% e.e.
byproducts containing $^{13}$C-enriched carbon
$^{13}$C NMR comparison of 6-143 (top, $^{13}$C-labeled allene) and 7-20 (bottom)
APPENDICES II: X-ray crystal information

1. Information for crystal 3-17

1.1. Crystal data

\[
\begin{align*}
\text{C}_{22}\text{H}_{21}\text{NO}_{4} & \quad F(000) = 768 \\
M_r & = 363.40 \quad D_x = 1.269 \text{ Mg m}^{-3} \\
\text{Monoclinic, } P2_1/n & \quad \text{Mo Kα radiation, } \lambda = 0.71073 \text{ Å} \\
a & = 16.759 (3) \text{ Å} & \theta = 2.5–21.1° \\
b & = 6.0204 (10) \text{ Å} & \mu = 0.09 \text{ mm}^{-1} \\
c & = 19.032 (3) \text{ Å} & \beta = 97.771 (3)° \\
\beta & = 97.771 (3)° & T = 100 \text{ K} \\
V & = 1902.7 (5) \text{ Å}^3 & \text{Rod, Colourless}
\end{align*}
\]
$Z = 4 \quad 0.3 \times 0.1 \times 0.1 \text{ mm}$

1.2. Data collection

CCD diffractometer

1968 reflections with $I > 2\sigma(I)$

Radiation source: fine-focus sealed tube $R_{int} = 0.153$

Graphite monochromator $\theta_{\text{max}} = 27.5^\circ, \theta_{\text{min}} = 1.5^\circ$

$\omega$ scan $h = -21 \rightarrow 21$

21284 measured reflections $k = -7 \rightarrow 7$

4331 independent reflections $l = -24 \rightarrow 24$

1.3. Refinement

Refinement on $F^2$ Primary atom site location: Structure-invariant direct methods

Least-squares matrix: Full Secondary atom site location: Difference Fourier map

$R[F^2 > 2\sigma(F^2)] = 0.053$ Hydrogen site location: Inferred from neighbouring sites

$wR(F^2) = 0.157$ H atoms treated by a mixture of independent and constrained refinement

$S = 0.83$ $w = 1/[\sigma^2(F_o^2) + (0.0767P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$

4331 reflections $(\Delta\sigma)_{\text{max}} = 0.003$

247 parameters $\Delta\rho_{\text{max}} = 0.20 \text{ e Å}^{-3}$

0 restraints $\Delta\rho_{\text{min}} = -0.20 \text{ e Å}^{-3}$

1.4. Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the
full covariance matrix. The cell esds are taken into account individually in the estimation of esds in
distances, angles and torsion angles; correlations between esds in cell parameters are only used when
they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for
estimating esds involving l.s. planes.

Refinement. Refinement of $F^2$ against ALL reflections. The weighted R-factor wR and goodness of fit S
are based on $F^2$, conventional R-factors R are based on F, with F set to zero for negative $F^2$. The
threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant
to the choice of reflections for refinement. R-factors based on $F^2$ are statistically about twice as large as
those based on F, and R- factors based on ALL data will be even larger.

1.5. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters
(Å$^2$)

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### 1.6. Atomic displacement parameters (Å²)

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2. Information for crystal 6-176

2.1. Crystal data

C_{28}H_{32}O_{4} \quad V = 1206.4 (12) \, \text{Å}^3

M_r = 432.54 \quad Z = 2

a = 9.799 (6) \, \text{Å} \quad D_a = 1.191 \, \text{Mg m}^{-3}

b = 11.237 (6) \, \text{Å} \quad \text{Mo } \text{Ka radiation, } \lambda = 0.71073 \, \text{Å}
\[ c = 11.623 \ (7) \ \text{Å} \quad m = 0.08 \ \text{mm}^{-1} \]
\[ a = 85.572 \ (11)^\circ \quad T = 293 \ \text{K} \]
\[ b = 79.133 \ (11)^\circ \]
\[ g = 73.78 \ (1)^\circ \]

### 2.2. Data collection

Radiation source: fine-focus sealed tube

\( R_{int} = 0.231 \)

graphite

\( q_{\text{max}} = 23.2^\circ, q_{\text{min}} = 1.8^\circ \)

7262 measured reflections

\( h = -10 \ldots 10 \)

3416 independent reflections

\( k = -12 \ldots 12 \)

1466 reflections with \( I > 2s(I) \)

\( l = -11 \ldots 12 \)

### 2.3. Refinement

Refinement on \( F^2 \)

Primary atom site location: structure-invariant direct methods

Least-squares matrix: full

Secondary atom site location: difference Fourier map

\( R[F^2 > 2s(F^2)] = 0.106 \)

Hydrogen site location: inferred from neighbouring sites

\( wR(F^2) = 0.350 \)

H atoms treated by a mixture of independent and constrained refinement

\( S = 0.86 \)

\[ w = \frac{1}{[s^2(F_o^2) + (0.2P)^2 + 0.1644P]} \]

where \( P = (F_o^2 + 2F_c^2)/3 \)

3416 reflections

\( (D/s)_{\text{max}} = 0.005 \)

291 parameters

\( Dp_{\text{max}} = 0.41 \ \text{e} \ \text{Å}^{-3} \)

0 restraints

\( Dp_{\text{min}} = -0.24 \ \text{e} \ \text{Å}^{-3} \)
2.4. Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. Refinement of $F^2$ against ALL reflections. The weighted $R$-factor $wR$ and goodness of fit $S$ are based on $F^2$, conventional $R$-factors $R$ are based on $F$, with $F$ set to zero for negative $F^2$. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating $R$-factors(gt) etc. and is not relevant to the choice of reflections for refinement. $R$-factors based on $F^2$ are statistically about twice as large as those based on $F$, and $R$-factors based on ALL data will be even larger.

2.5. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{Å}^2$)

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M.S., Physical Chemistry, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, China, 2004
M.S., Inorganic Chemistry, University of New Hampshire, Durham, NH, 2007

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10th Zhang Shu-Min Fellowship, 1999-2000
Haizheng Scholarship, 1999-2000
2nd Tier Lanzhou University Scholarship, 1999–2000
Winner Award in Lanzhou University Analytical Chemistry Contest, 1999
3rd Tier Lanzhou University Scholarship, 1998–1999
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PROFESSIONAL MEMBERSHIP: American Chemical Society


Jingwei Li, Xiaoguang Liu, Daesung Lee, Gold-catalyzed formation of


**PRESENTATIONS:**

- **Jingwei Li, Daesung Lee,** Desymmetrization of nonstereogenic all-carbon quaternary centers via ring-rearrangement metathesis. Abstracts of Papers, Poster Presentation, 4th Chicago Organic Symposium, Chicago, IL, United States, April 30, 2012. (poster)

- **Chunrui Sun, Jingwei Li, Daesung Lee,** C–H amination of cyclopropenes. Abstracts of Papers, Poster Presentation, 4th Chicago Organic Symposium, Chicago, IL, United States, April 30, 2012. (poster)

- **Jingwei Li, Chunrui Sun, Daesung Lee,** Synthesis of silylated cyclopropenes and their rearrangement to allenes. Abstracts of Papers, Oral Presentation, 242nd ACS National Meeting, Denver, CO, United States, August 28-September 1, 2011. (oral)

- **Daesung Lee,** Sang Young Yun, Jingwei Li, Kung-Pern Wang, Enyne Metathesis for the Synthesis of Molecules with Multiple Unsaturation. 18th International Symposium on Olefin Metathesis and Related Chemistry, Leipzig, Germany, August 2-7, 2009. (oral)